

UMC Utrecht

Research

Evaluation

2013-2018

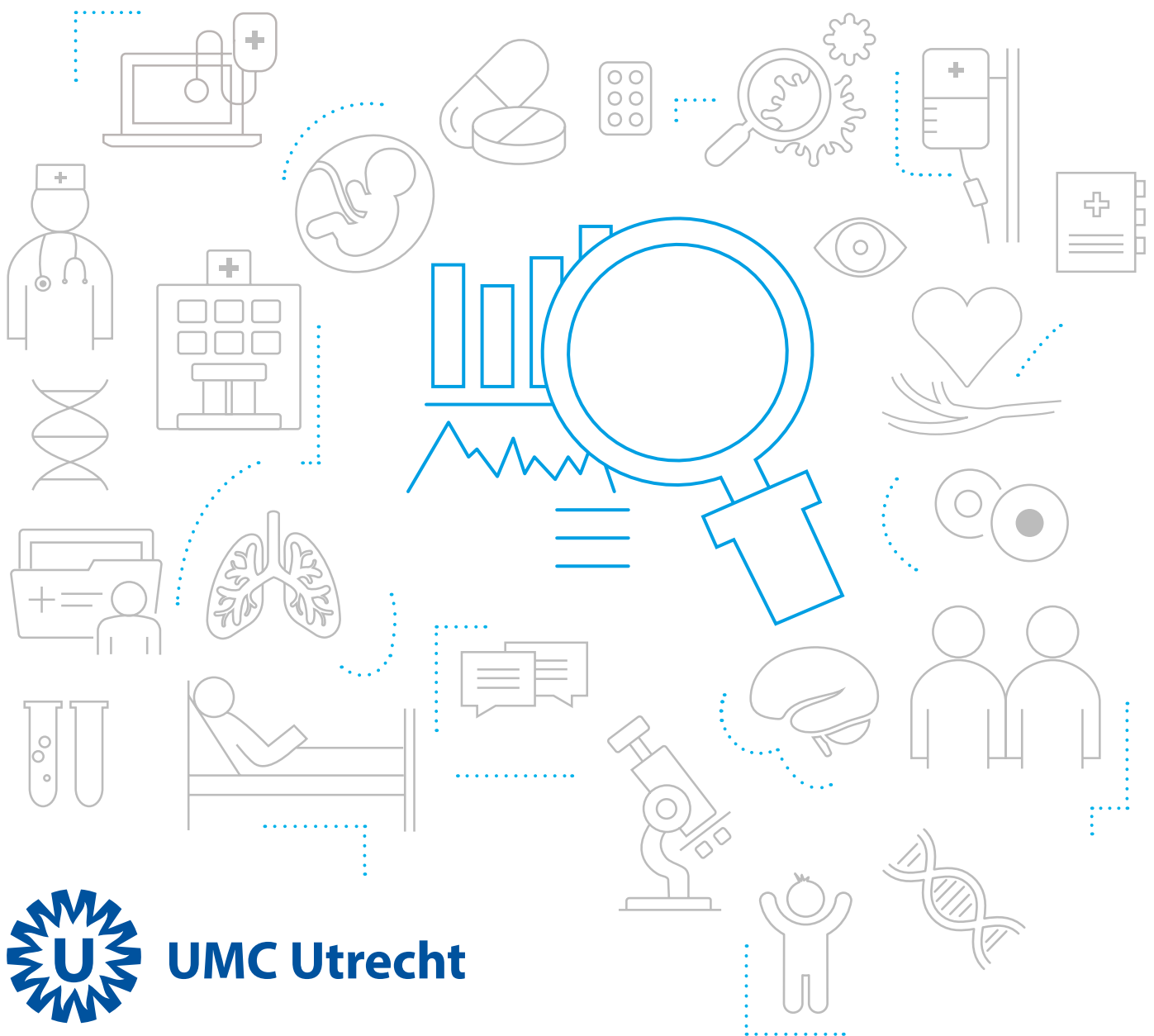
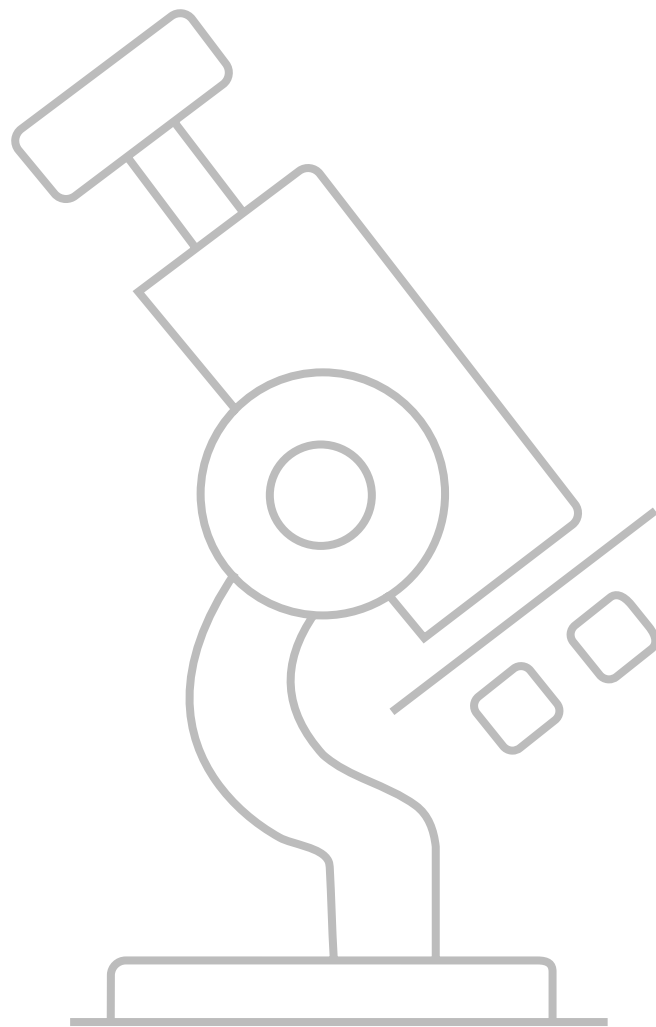


Table of contents

UMC Utrecht research Self-evaluation report	3
Self-evaluation strategic research program Brain	33
Self-evaluation report strategic research program Cancer	82
Self-evaluation report strategic research program Child Health	150
Self-evaluation report strategic research program Circulatory Health	218
Self-evaluation report strategic research program Infection & Immunity	294
Self-evaluation report strategic research program Regenerative Medicine & Stem Cells	352



UMC Utrecht research Self-evaluation report (2013-2018)





Foreword	5
1. Mission, strategy & general organisation	6
1.1 Mission	6
1.2 Strategy 2015-2020 'Connecting U'	6
1.3 Executive Board	6
1.4 Supervisory Board	6
1.5 Organisation	7
1.6 Governance developments	7
1.7 Patient and public involvement	7
1.8 Educational Research	8
2. Research organisation & key figures	9
2.1 Strategic research programs	9
2.2 Management and responsibilities	10
2.3 Research FTE	11
2.4 Professorships	11
2.5 Diversity	11
2.6 Funding and earning capacity	12
2.7 Facilities	14
2.8 Partners and collaborations	14
3. Research policy & support	17
3.1 Research Office	17
3.2 Support for innovation and funding	17
3.3 Compliance and quality management of clinical research	18
3.4 Integrity	18
3.5 Data management	19
3.6 Open Science	19
3.7 Benchmark: Research evaluation practices at the UMC Utrecht	20
4. PhD programs: Graduate School of Life Sciences	22
4.1 Recruitment, selection & admission	22
4.2 PhD enrolment	22
4.3 PhD training	23
4.4 Supervision	24
4.5 Governance	24
5. SWOT analysis & future perspectives	26
5.1 Future perspectives	27
Appendix 1. Funding and earning capacity	28
Appendix 2. Funding from European Union	30



Foreword

The threefold mission of university medical centers in the Netherlands can be hard to pin down. How to combine research, education and healthcare in one organization, while ensuring the quality and impact we strive for? This cannot be achieved by just maintaining and optimizing international excellence in a few selected research areas. Neither are UMC's just hospitals that deliver 'last resort' healthcare. In my view, university medical centers can best be seen as *responsive* research, education and healthcare organisations that are well-equipped to adapt to the ever changing scientific and healthcare landscape. And I believe the UMC Utrecht is doing a great job at that, as this self-evaluation report shows.

For a start, responsiveness means having the freedom to pursue curiosity-driven research to explore new, promising research areas. For example, in the field of organoids we are at the forefront of new discoveries. Some clinical applications, such as targeted treatment of cystic fibrosis patients, have already been developed, but this technology is obviously not yet fully exploited. UMC Utrecht devotes significant research efforts to this field, building on collaborations at Utrecht Science Park, a global hub in the development of stem cell-derived organoids. Another example of a discovery that we are still exploring further, while already being applied in clinical practice, is MRI-guided radiotherapy (MR-Linac).

Responsiveness to research developments also implies we identify and capitalize on breakthroughs in *other* scientific domains. For example, in the coming years we will try to translate the much-anticipated developments in artificial intelligence and data sciences into tangible benefits for biomedical research and healthcare, including prevention. An example of the latter is *exposome sciences*, a field where scientists from several faculties at Utrecht University closely collaborate. They recently received a Gravity award from the Dutch Research Council.

Finally, responsiveness means that our center is in continuous dialogue with stakeholders to align ourselves with societal expectations. This dialogue takes place at many different levels and time scales and involves patient organisations, hospitals, primary care organisations, municipal authorities, research institutes, research funders, health insurers and other stakeholders. A recent manifestation is the agreement between UMCs and the minister of Healthcare that UMCs will develop a shared research agenda with regional partners with ample attention to prevention of disease.

Of course this doesn't imply our research should be 'regional' in a limitational sense of geography, knowledge and relevance. On the contrary, it recognizes that successful and efficient healthcare innovation requires multidisciplinary collaboration across networks that bring together real-world questions and world-class academic problem-solving capacity. The region seems an appropriate scale for a 'living lab', from which valuable, generalizable lessons can be learned. The availability of several successful networks and collaborations in the Utrecht region, such as the Health Hub, the elderly care network NUZO and the primary care network Julius Health Care Centers, will be instrumental in these endeavours.

We owe our responsiveness in great part to the curiosity, dedication and ambition of our employees. Every day, researchers, doctors, nurses and others go to great lengths, sometimes in the face of big pressures, to deliver the best possible care today and create the care of tomorrow.

The way we organise and evaluate our research also enhances our responsiveness. Our current strategy 'Connecting U', aiming for connection with patients and increasing our societal impact, already made that very explicit. One of the major governance changes in the UMC Utrecht has been the formation of six strategic research programs (focus areas) in 2010. These horizontal, division-spanning programs provide the strategic direction for our research efforts. They bring together the different phases of what we call the 'innovation loop': basic, translational and clinical/applied, research, with basic knowledge being translated to clinical application and with clinical questions shaping basic research. The strategic research programs have matured steadily in dynamic interaction with our ten divisions and continue to further focus their research efforts to increase their impact. Currently, our strategic research programs are of crucial importance in defining the research topics where the UMC Utrecht wants to make a difference in the next strategic period (2021-2025). In addition, they are in the lead in the process of establishing new (research) chairs.

During the past years we also brought our evaluation guidelines in line with our goal of being a responsive research, education and healthcare organisation, emphasizing the societal impact of research. Science in Transition, a 2013 UMC Utrecht initiative that focuses on the 'real' impact of research, certainly changed the way we evaluate our scientists. This is strongly related to very similar policy changes announced this year by Dutch research funders, the association of universities (VSNU) and the Royal Academy of Sciences, recognizing the frontrunning role of UMC Utrecht in research evaluation. We are very much supported by Utrecht University and their support for Open Science and responsible research evaluation.

Obviously, there is room for improvement. We critically evaluated the previous SEP report and, for example, took measures to increase our clinical trial activities in our strategic research programs. We have work to do in focusing our research efforts even more and in streamlining research support, which will take center stage in our next strategy. But all in all, I believe the UMC Utrecht is well-equipped and robustly organised to create positive impact in research and healthcare in the Utrecht region, in the Netherlands and in the world.

Prof. Arno Hoes
Dean and vice-chairman of the executive board, UMC Utrecht



1. Mission, strategy & general organisation

1.1 Mission

UMC Utrecht is a leading international university medical center generating, testing, sharing, and applying knowledge on health, illness, and health care for the benefit of patients and society. UMC Utrecht was created in 2000 by merging the Academic Hospital Utrecht (founded 1875), Wilhelmina Children's Hospital (founded 1888) and the Medical Faculty of Utrecht University (founded 1636). The merger of an academic hospital and the faculty of medicine into a new organisation with a single governance (university medical center) is a typical Dutch development which started around 20 years ago and is internationally unique. UMC Utrecht is, thus, separate from but also closely intertwined with Utrecht University, for example in the development of strategic research programs and in the appointment of professors. Binding agreements about collaboration and responsibilities are defined in a formal cooperation agreement.

1.2 Strategy 2015-2020 'Connecting U'

UMC Utrecht launched its "Connecting U" strategy in January 2015. This strategy elaborates on the previous strategic period "3.0" in which UMC Utrecht opted for a selected number of strategic research programs. Connecting U is all about connection: connection with patients, with general practitioners, with researchers, with each other, and connection with society. To achieve its ambitions, UMC Utrecht has formulated the following two strategic objectives:

- To further increase its social impact with an emphasis on the strategic research programs
- To further strengthen the connection with our patients and other stakeholders (including students, citizens and other healthcare providers).

1.3 Executive Board

The Executive Board stands at the head of the daily management of the UMC Utrecht. The Executive Board determines the general policy of the UMC Utrecht. It also determines the policy and general strategy, tasks and functions, and mission and goals of the UMC Utrecht in relation to social, political and financial developments. The Executive Board represents UMC Utrecht to government, funders, the scientific and educational world, and in the media.

The Executive Board of the UMC Utrecht consists of:

Professor Margriet M.E. Schneider, MD, PhD, president

Mirjam H. van Velthuisen-Lormans, MSc, member

Anouk Vermeer, MA, BA, member (since 1/10/2018) (*)

Professor Arno W. Hoes, dean and vice-president of the board (since 1/6/2019)(**)

* In 2018 the executive board was expanded to four members as part of a larger organisational change

** During the period under review professor Frank Miedema was dean and vice-president of the board (2008-2019)

1.4 Supervisory Board

The Supervisory Board of UMC Utrecht is appointed by the Ministry of Education, Culture and Science, and consists of the following members:

Mrs. C.E. Princen, MSc, president

Mr. P.C.J. Leijh, PhD, vice-president

Mr. L.A.M. van den Nieuwenhuijzen, MSc RA, member

Mrs. Prof. M. de Visser, MD PhD, member

Mr. prof. G. van der Wal, MD PhD, member

Mr. A. Kregting, MSc MBA, member



1.5 Organisation

UMC Utrecht is organised in ten divisions, mostly centered around healthcare.

Imaging & Oncology	Neurosciences	Heart and Lungs	Woman and Baby	Anesthesiology, Intensive Care and Emergency Medicine
Surgical Specialties	Julius Center for Health Sciences and Primary Care	Pediatrics	Laboratories, Pharmacy & Biomedical Genetics (*)	Internal Medicine and Dermatology

* Divisions resulting from mergers in 2018

1.6 Governance developments

In 2017, following extensive internal and external debate about leadership and culture, a range of governance changes were implemented at UMC Utrecht. This included the reduction of the number of divisions from 12 to 10. Also, divisional management teams were reduced from four to two members, and were complemented with a 'leadership team', consisting of, amongst others, a manager of research and a manager of education. In the new situation, the two-person division management carries the integral responsibility for research, care and education, with a dedicated research manager being part of the broader 'leadership team'.

An important feature of the change agenda is an institutional program for 'continuous improvement' called "Samen voor de patiënt", where 'improvement teams' visit all departments for a couple of months to introduce a new, bottom up process to increase input from all employees with the aim to improve efficiency and customer excellence. Part of this new way of working are day or week starts, where groups or departments in a non-hierarchical way decide about local priorities and try to solve bottlenecks.

1.7 Patient and public involvement

Following Strategy 'Connecting U' 2015-2020 where connection with patients and other stakeholders is central, a myriad of initiatives can be discerned in the UMC Utrecht in terms of patient and public involvement. Structural strategic embedding started in December 2018 with the Patient and Public involvement program. This stimulates new initiatives, brings together best practices and provides essential support.

The mission of the Patient and Public involvement program is to cooperate with patients and the public in a structural manner in care, education and research. Only this way we can work in a meaningful way and provide the care that supports meaningful life.

The mission is articulated in the following goals:

- The experience of each patient will be the starting point of meaningful care.
- Patient and public involvement is part of the culture of the UMC Utrecht. Healthcare professionals, teachers and researchers are facilitated to work in a way in which they profit from the expertise and experience of patients and the public.
- Care, education and research are shaped using a multi-expertise model of health and disease.
- Patient and public involvement is developed as an area for research. The methods for good and effective involvement are studied in the UMC Utrecht.

The program consists of two leaders (a professor in medical ethics and a professor of psychiatry), an advisor patient involvement and a project leader.



1.8 Educational Research

Educational Research at UMC Utrecht encompasses high quality educational research in (bio)medical and health science disciplines. The program aims to carry out educational research with impact and rigor that contributes to the development of state-of-the-art professionals who are thoughtful; are creative problem solvers; take responsibility for patients, self and society; are skilled in communication and societal debates; know how to use innovative technological solutions; collaborate interprofessionally and interdisciplinary. Consequently, the program's aim is linked to quality and innovations in education at Ba, Ma, Postgraduate and PhD level as well as continuous education of professionals by translating research to learning.

Examples are research with high local and international impact regarding the field of *Entrustable Professional Activities* by Ten Cate, which innovates curricula and competency based assessments at worldwide level. Other examples are projects concerning monitoring of students' progress in order to improve their well-being (EU project Ofla and the Utrecht project Thermos). These projects innovate the current quality of education at international and local level by means of Learning Analytics.

Research in the Education Center is of multidisciplinary nature, based on the vision of Science in Transition, and uses and contributes to integrative educational theories and methodologies for health professions education. Examples of multidisciplinary are the collaboration humanities and arts in the program 'De Nieuwe Utrechtse School', and the board membership of the Utrecht University's Focus areas Professional Performance and Higher Education. The program encloses several interconnected themes on research of learning in health professions education (HPE) from a socioconstructivist translational perspective, i.e: Diversity and inclusion, Interprofessional learning and feedback, Teachers' professional development, Continuous education, participation of patients in education, Teaching in the Sciences and Resilience.

The program is driven by a close collaboration between (educational) chairs at UMC Utrecht, appointed to the Education Center as well as to several divisions (see table below). Strong international research collaborations exists, a.o. with University of California UCSF, University of Toronto, the League of European Research Universities (LERU) and several other North- and South-American, European and Asian faculties.

At the moment more than 30 PhD students participate in the program. Several research grants were recently received from the EU, NWO, Ministry of Education/Surf, Utrecht University. Last years output contained >300 peer-reviewed international journal articles on health professional education and many contributions to international conferences, and courses.

Current education chairs at UMC Utrecht

Research and Development of Medical Education	Education Center	Prof. Th.J. ten Cate, PhD
Immunology and pediatrics	Education Center	Prof. B. Prakken, PhD
Interprofessional Education	Education Center	Prof. T. Westerveld, PhD
Undergraduate medical education	Division Laboratories, Pharmacy and Biomedical Genetics	Prof. M.R. van Dijk, PhD
Biomedical sciences education and educational technology	Education Center	Prof. H. van Rijen, PhD
Radiology education and training	Imaging & Oncology	Prof. J.P.M. van Schaik, PhD
Education in perioperative, intensive and emergency care	Division of Vital Functions	Prof. R.G. Hoff, PhD
Patient and Family Centered Education	Division of Child Health	Prof. J. Frenkel, PhD
Education to connect science and professional practice	Education Center	Prof. M. Kluijtmans, PhD
Nursing Science	Education Center	Prof. M. Schuurmans, PhD
Research and Development of Health Professions Education	Education Center	Prof. M. van der Schaaf, PhD



2. Research organisation & key figures

2.1 Strategic research programs

In the UMC Utrecht strategic research governance is since 2010 assigned to six strategic research programs with each a limited number of disease targets. These six programs were developed and chosen through an extensive bottom up process, building on past performance and critical mass but also on innovation, patient-centeredness and future perspectives. The research programs together with the divisions form a matrix structure, where most divisions are involved in several (or even all) strategic research programs.













Patient care is integrated in these programs, ensuring close collaboration between clinical and pre-clinical research. A multidisciplinary approach guarantees that patients benefit from the latest available expertise and innovative technological solutions. The programs are in the lead regarding research strategy, whereas divisions facilitate both research and healthcare. Hierarchical management of the research line and funding remain the responsibility of the divisions.

For the period 2015-2020, the strategic research programs receive an annual budget of 267,000 euro each for a chair person, a program manager and other support. This includes a 'programming' budget for the organisation of program-specific tasks such as community building (eg interaction with clinicians and researchers, seminars with international speakers), outreach (eg development and organisation of patient-stakeholder interaction), and education (eg development and coordination of program specific bachelor and master courses, education tools for patients).

Strategic research program	Chair
Brain	Prof. R.J. Pasterkamp, PhD
Cancer	Prof. E. van der Wall, MD PhD
Child Health	Prof. C.K. van der Ent, MD PhD
Circulatory Health	Prof. D.E. Grobbee, MD PhD (Prof. F.W. Asselbergs, MD PhD, per 1-8-2019)
Infection & Immunity	Prof. M.J.M. Bonten, MD PhD
Regenerative Medicine & Stem Cells	Prof. M.C. Verhaar, MD PhD

Every strategic research program focuses on a limited number of research themes as outlined in the program-specific chapters. There is also substantial collaboration between the six strategic research programs, as is visualized in the matrix below.



	 Circulatory health	 Brain	 Regenerative medicine & stem cells	 Child health	 Cancer	 Infection & immunity
 Circulatory health	<ul style="list-style-type: none"> high risk hypertension diabetes woman specific 	<ul style="list-style-type: none"> cerebral ischemia 	<ul style="list-style-type: none"> heart failure aneurysm chronic kidney disease peripheral arterial diseases 	<ul style="list-style-type: none"> congenital heart disorders 	<ul style="list-style-type: none"> cardio-oncology focus cardio-toxicity after treatment risk factors 	
 Brain		<ul style="list-style-type: none"> stroke epilepsy developmental disorders precision psychiatry neuromuscular disorders neuro-oncology 	<ul style="list-style-type: none"> brain, stem cells and organoids 	<ul style="list-style-type: none"> fertility, ante- and perinatal damage child rehabilitation 	<ul style="list-style-type: none"> neuro-oncology expertise center gliomas phase I/II research imaging 	
 Regenerative medicine & stem cells	<ul style="list-style-type: none"> heart failure aneurysm chronic kidney disease peripheral arterial diseases 	<ul style="list-style-type: none"> brain, stem cells and organoids 	<ul style="list-style-type: none"> bone & cartilage chronic kidney diseases peripheral arterial diseases organ disorders 	<ul style="list-style-type: none"> organoids congenital and hereditary disorders (cystic fibrosis, liver, kidney, metabolic) 	<ul style="list-style-type: none"> organoids stem cells 	<ul style="list-style-type: none"> cell therapy immune defects immunology wound healing & tissue regeneration
 Child health	<ul style="list-style-type: none"> congenital heart disorders 	<ul style="list-style-type: none"> fertility, ante- and perinatal damage child rehabilitation 	<ul style="list-style-type: none"> organoids congenital and hereditary disorders (cystic fibrosis, liver, kidney, metabolic) 	<ul style="list-style-type: none"> lifecycle medicine from child- until adulthood physical and mental social medicine ethics 	<ul style="list-style-type: none"> hereditary tumors 	<ul style="list-style-type: none"> severe inflammatory disorders (juvenile idiopathic arthritis, cystic fibrosis, respiratory infections)
 Cancer	<ul style="list-style-type: none"> cardio-oncology focus cardio-toxicity after treatment risk factors 	<ul style="list-style-type: none"> neuro-oncology expertise center gliomas phase I/II research imaging 	<ul style="list-style-type: none"> organoids stem cells 	<ul style="list-style-type: none"> hereditary tumors 	<ul style="list-style-type: none"> biology of cancer risk factors early diagnosis innovative trials and treatments survivorship 	<ul style="list-style-type: none"> immune therapy, CAR-T cells, checkpoint inhibitors innovation bone marrow transplantation
 Infection & immunity			<ul style="list-style-type: none"> cell therapy immune defects immunology wound healing & tissue regeneration 	<ul style="list-style-type: none"> severe inflammatory disorders (juvenile idiopathic arthritis, cystic fibrosis, respiratory infections) 	<ul style="list-style-type: none"> immune therapy, CAR-T cells, checkpoint inhibitors innovation bone marrow transplantation 	<ul style="list-style-type: none"> antimicrobial resistance inflammation host-pathogen interactions immune-mediated therapy & prevention

2.2 Management and responsibilities

Research Board

Frequency: every month

Present: dean and the ten research managers from divisions

Topics: research policy and management

Function: research managers inform and advise the dean about research policy and management

Strategic Board

Frequency: every month

Present: executive board, chairs of divisions, directors of support departments, chairs of strategic research programs

Topics: UMC Utrecht strategic issues

Function: development of UMC Utrecht strategic directions, advise executive board

Management contracts with divisions

Annual agreement between executive board and divisions

Topic: priority setting by executive board, strategic research programs provide crucial input.

Strategic plans of strategic research programs

Strategic research programs made strategic plans during their launch in 2010 and updated these in 2015. The current research evaluation will provide input for the next strategic cycle of both the strategic research programs as for the entire UMC Utrecht strategy.

UMC Utrecht and Utrecht University

The Executive Board is accountable to Utrecht University regarding the faculty of medicine. The executive boards of UMC and university meet at least twice a year to discuss budget, administrative agenda and realization of earlier agreements.



2.3 Research FTE

Research FTE and composition UMC Utrecht

	2018		2017		2016		2015		2014		2013	
	#	FTE	#	FTE	#	FTE	#	FTE	#	FTE	#	FTE
Scientific staff (1)	882	302	757	321	833	280	833	282	856	245	859	228
Post-docs (2)	340	163	331	198	525	279	562	283	391	133	417	138
PhD students (3)	962	552	662	410	403	256	463	275	855	384	870	375
Total research staff	2183	1017	1750	929	1761	815	1858	840	2102	761	2146	740
Other tenured staff	190	91	262	151	NA	NA	NA	NA	261	118	270	125
Total Staff	2374	1108	2012	1081	1761	815	1858	840	2363	879	2416	866

Note 1: Comparable with WOPI categories HGL, UHD and UD; tenured and non-tenured staff

Note 2: Comparable with WOPI category Onderzoeker

Note 3: Standard PhD (employed) and Contract PhDs (externally or internally funded but not employed)

Research FTE of Strategic Research Programs (2018)

Total UMC Utrecht (*)	Brain	Cancer	Child Health	Circulatory Health	I&I	RMSC	Other (**)
1108	206	253	72	223	244	92	19

*other staff included

**researchers outside strategic research programs

2.4 Professorships

Until 2016 the UMC Utrecht adhered to a (university imposed) maximum of 150 professorships. After the release of that 'cap', the number of professors has increased to a little over 200 at the end of 2018. This steep increase is expected to level off in the coming years.

Almost 40 professorships are shared chairs with strategic partners like the Hubrecht Institute, the Princess Maxima Center for Pediatric Oncology and the National Institute for Public Health and the Environment. Current numbers are broadly in line with other university medical centers in The Netherlands.

Traditionally, divisions have been in the lead for formally suggesting new chairs. As of 2019 the initiative rests with strategic research programs, who obviously have to engage divisions in their choices.

2.5 Diversity

UMC Utrecht has defined a policy and targets on Diversity and Inclusion for the period 2016-2020. As a basis for this policy, the following statement, aligned with the UU Diversity statement, applies: "Within the UMC Utrecht, we work on an inclusive environment and culture, with employees that represent the society we live in. UMC Utrecht strives to be an organisation where patients, staff and students feel recognized. Factors like gender, origin, sexual orientation, religion and physical or mental limitations should not stand in the way."

Gender diversity has been a specific goal for over ten years. UMC Utrecht joined the Charter Talent for the Top in 2009, aiming to have more female full professors and a good balance on leadership at all levels. Since then, the percentage of female professors has increased from 16% in 2010 to 28.6% on December 31st, 2018 and is still increasing. In 2018 UMC Utrecht appointed 8 female professors and 7 male professors. The executive board consists of three women and one man.



Actions have been:

- organizing bias training and selection training to decision makers in recruitment processes;
- make sure selection committees for recruitment of new professors always have at least one female professor as a member (typically there are more than one present);
- yearly report on progression made towards targets;
- insight in intern talents and potential candidates for professorship;
- support program for female research talent (Steyn Parvé program) in 2012, 2017 & 2018 for 75 participants.

Since 2015 the scope of Diversity has been enlarged to Diversity & Inclusion, aiming for an inclusive organisation environment. UMC Utrecht only has diversity targets on gender, as it is the only registered characteristic of diversity in the UMC Utrecht, based on Dutch legislation.

<i>% female staff per category:</i>	2010	2016	2018	Target end of 2020
Full professors	16%	24%	28%	35%
Associate professors	38%	39%	39%	50%
Assistant professors	unknown	55%	58%	>50%
Program directors ('Opleiders')	22%	33%	38%	50%
Deputy program directors ('Plaatsvervangend opleiders')	13%	39%	35%	50%
Medisch specialist & fellow	unknown	49%	53%	50%
Management incl. directors & MD's	33%	44%	47%	50%
Management incl. subtop	unknown	unknown	56%	>50%
Executive board (RvB)	0%	67%	75%	>30%
Supervisory board (RvT)	unknown	29%	29%	>30%

At the moment we are investigating how cultural diversity could be targeted, registered and measured. However, this needs further examination and specific measures are expected to be taken in 2020.

In order to achieve the targets, the following measures apply:

- 1) training of chairs of selection committees (BAC) on how to select and avoid bias;
- 2) selection committees exist of at least one female professor and a female advisor from HR;
- 3) written explanation if no female candidate has been taken into account or proposed for the position;
- 4) other academic hospitals asked for their input on a professor position are asked explicitly to propose female candidates;
- 5) as long as the diversity stimulation fund Aspasia exists (on hold as of 2018), the Steyn parvé program for female research talent is being executed (1 final program in 2020 is expected);
- 6) diversity and inclusion will be part of new leadership programs;
- 7) annual reporting on (gender) diversity in relation to targets.

2.6 Funding and earning capacity

The UMC Utrecht as a whole is annually financed by insurance companies (care/cure related production), The Ministry of Education, Cultural Affairs and Science, Ministry of Health, Welfare and Sports, Utrecht University and several other external funding organisations. The total UMC Utrecht budget for 2018 was 1,193 billion euro and the number of employees 11,500.

The UMC Utrecht research budget consists of two main sources:

- First, there is governmental block funding through three different channels. Direct funding from Utrecht University amounts to 32 mln euro. In addition there is funding from the Ministry of Health, Welfare and Sports which is meant for top clinical care (4,8 mln euro) and for research (15 mln euro). Together this constitutes the so-called 'first money flow' of roughly 50 mln euro per year.



- Second, the UMC Utrecht obtains competitive or external research funding from national and international research funders (NWO, ZonMw, KNAW, EU) and also from health charities and industry which amounts to about 102 mln euro in 2018.

Specifically, the topsector Lifesciences and Health has become an increasingly important research funder by supporting large public private research programs like Oncode and RegMedXB, and by providing direct funding of public private projects. The annual amount of funding which is available for public private projects for UMC Utrecht research projects has increased from just over 600k€ in 2016, to 1,45 mln€ in 2017 to 4,45 mln€ in 2018.

UMC Utrecht research funding by source

UMC Utrecht

	2018	2017	2016	2015	2014	2013
Direct Funding (1)	€ 51,400,000	€ 52,100,000	€ 56,300,000	€ 53,900,000	€ 53,900,000	€ 47,100,000
National grants (2)	€ 15,341,707	€ 28,393,113	€ 23,877,213	€ 17,062,423	€ 18,503,039	€ 21,491,913
External grants (3)	€ 66,227,511	€ 58,307,101	€ 47,150,283	€ 58,853,910	€ 56,101,803	€ 53,266,936
Contract research (4)	€ 20,421,442	€ 24,210,959	€ 19,834,387	€ 17,885,006	€ 13,427,912	€ 13,670,862
Total Funding	€ 153,390,660	€ 163,011,173	€ 147,161,883	€ 147,701,339	€ 141,932,754	€ 135,529,711

Direct Funding (1)	Block funding from government
National grants (2)	Competitive grants from Dutch national research funders (e.g. NWO, ZonMw, KNAW)
External grants (3)	Grants from external, not-for-profit parties (e.g. European Commission and health charities)
Contract research (4)	Grants from industry

See Appendix 1 for further details about funding capacity of strategic research programs.

Developments

Earning capacity is generally constant and satisfactory. UMC Utrecht is relatively stronger in obtaining collaborative and consortium grants than in obtaining personal grants. The importance of collaborative funding from the European Commission is increasing rapidly (see paragraph Research Office). The budget for the UMC Utrecht as a whole is under pressure, as health insurers are tightening their reimbursement policies following a macroeconomic 'ceiling' on the national healthcare budget. This may affect research activities, but the scope is unclear at present. Dedicated funding from both the Health ministry for top clinical care and from the Science ministry for research and teaching is under scrutiny. There is a growing argument that topclinical hospitals in the Netherlands should be able to vie for a share of the budget that is now reserved solely for UMCs. The background is a longstanding policy push for transparency that requires UMCs to be increasingly explicit about their 'added value'. The partly inherent and partly perceived lack of financial transparency in UMCs due to the close interconnectness of the three missions - research, teaching and care - is increasingly discussed.



2.7 Facilities

Academic contract research organisation Julius Clinical	Expertise in designing and executing clinical trials worldwide.
Animal laboratory facility	Expertise in setting up and conducting responsible animal experimental research
Biobank facility	Facilitates the processing, storage and release of human body material in accordance with the UMC Utrecht Framework Regulations.
Cellular Therapy Facility	GMP-compliant production of cellular treatments
Data science facility	Facilitating that scientific research is conducted in accordance with the FAIR principles; data must be 'Findable, Accessible, Interoperable and Re-usable'
Microscopy facility	For the application of standardized and specialized light microscopic (LM) and electron microscopic (EM) methods.
Omics facilities	State-of-the-art measurement methods (innovative, high throughput) for DNA / RNA, protein and metabolites for fundamental, translational and clinical research
Organoid platform (U-Port)	Stimulating organoid technology in fundamental and translational research
Phase I / II research facility	Facilitating GCP-compliant human-related phase I / II research
Radionuclide facility	GMP-compliant production of radioactive compounds
Research clinic	Implementation of broad informed consent of all patients and registration at the source with basic set of patient data.
Translational laboratory facilities (e.g. LTO, LTI, CIS, Regenerative Medicine Center Utrecht)	Support to apply insights from fundamental research for the development and testing of new strategies for diagnosis and treatment. Proof-of-concept for feasibility of such new strategies in pre-clinical model systems and small patient groups (first-in-men).
Trial facility (U-Trial)	Expertise in setting up and conducting clinical trials that should change daily clinical practice (advice, quality control, training, monitoring etc) in close collaboration with UMC Utrecht's academic contract research organisation (CRO) Julius Clinical.

2.8 Partners and collaborations

2.8.1 Utrecht Science Park

Utrecht University

Utrecht University (UU) was founded in 1636 and has a long history and rich tradition. Utrecht University is a modern and leading institution with a growing international reputation. UU has seven faculties of which one is the Faculty of Medicine at UMC Utrecht. With the merger of the faculty of medicine with the academic hospital a special relation was created which is formalized in a cooperation agreement (last updated in 2007). The Faculty of Medicine has remained part of UU in an administrative sense, and has become part of UMC Utrecht in an organisational sense. The university tasks of the Faculty of Medicine include the education of medicine and biomedical sciences, and (bio)medical research. The execution and organisation of these tasks lies with UMC Utrecht.

UMC Utrecht has close ties with many faculties in research and teaching, specifically the Science faculty and the Veterinary faculty. In 'Utrecht Life Sciences' and in the Graduate School of Life Sciences UMC Utrecht collaborates closely with those faculties. But there are also many collaborations in the field of geosciences; law, economics and governance; and social and behavioural sciences. Utrecht University and UMC Utrecht for example collaborate in multiple large-scale grants, like the 'gravitation grants' (NWO Zwaartekracht) into cancer genomics and individual development.



Other main research partners on Utrecht Science Park

Hubrecht Institute

The Hubrecht Institute is a research institute of the Royal Netherlands Academy of Arts and Sciences (KNAW). In 2008 the KNAW and UMC Utrecht decided to join forces to develop the Hubrecht Institute into an internationally renowned institute in the area of biomedical research. Besides the funding from the KNAW, UMC Utrecht provides additional financial support. Research at the Hubrecht Institute focuses on developmental biology and stem cells at the organismal, cellular, genetic, genomic and proteomic level. Basic insight into development and into stem cells will provide insight into (human) disease, such as cancer.

University of applied sciences of Utrecht

The University of applied sciences of Utrecht offers a wide range of higher professional education programs for students and professionals in the field of health care, biology and medical laboratory research. This makes it an important partner for education, research and collaboration in the field of healthcare and life sciences.

Princess Maxima Center for Pediatric Oncology

This brand new hospital, built adjacent to the Wilhemina's Children Hospital of UMC Utrecht, since 2018 treats all children in the Netherlands with cancer. The Princess Maxima Center also hosts a substantial research organisation, with nearly 30 independent research groups performing pre-clinical and clinical research on childhood cancer. Between UMC Utrecht and PMC extensive and still deepening research ties exist.

National Institute for Public Health and the Environment (RIVM)

The National Institute for Public Health and the Environment (RIVM) works to prevent and control outbreaks of infectious diseases. RIVM promotes public health and consumer safety, and helps to protect the quality of the environment. UMC Utrecht and RIVM are working together in the field of infectious diseases, toxicology, epidemiology and preventives.

National 'Medicines evaluation board'

The national 'Medicines evaluation board' ('College ter Beoordeling van Geneesmiddelen', CBG) will move to the Utrecht campus in 2021.

Industry partners

Located at Utrecht Science Park are also Danone/Nutricia Research, focused on early life and medical nutrition, and Genmab, an international biotechnology company specializing in the creation and development of differentiated antibody therapeutics for the treatment of cancer.

Utrecht Life Sciences

Utrecht Life Sciences (ULS) is an open innovation network, which unites authorities, business and knowledge institutions. ULS works on intensifying collaboration in the areas of education, research and innovation for example by providing state of the art shared infrastructures, scouting and educating talented people, creating access to scarce expertise and databases, and increasing access to funds for its partners. ULS is an initiative of Utrecht University, HU University of Applied Sciences Utrecht, Danone Research and UMC Utrecht. ULS aims to become a leading Biomedical Center in Europe.

2.8.2 Main research partners on the national level

Eindhoven University of Technology

In 2011, Eindhoven University of Technology (TU/e), Utrecht University and UMC Utrecht started a strategic alliance. With this partnership UMC Utrecht wants to promote innovation in research, education and patient care. UMC Utrecht is working more closely with TU/e on mainly two themes: medical imaging and regenerative medicine including stem cells.

TU/e has the technical knowledge for developing medical equipment, but needs UMC Utrecht for studying whether it is of any benefit to the patients. Conversely, the specialists at UMC Utrecht need the knowledge and the research facilities of TU/e for practical implementation of their ideas about new treatment methods.



Intensifying cooperation between UMC Utrecht, Utrecht University, Wageningen University & Research, and Eindhoven University of Technology

Utrecht University, Wageningen University & Research, Eindhoven University of Technology and the UMC Utrecht, have the ambition to enter into a more intensive cooperation in thematic areas. The institutes find each other in complementary expertise in scientific fields – for example medicine, food, technology, social sciences – and will enter in cross-disciplinary cooperation.

2.8.3 International collaboration

The UMC Utrecht believes that internationalisation is instrumental in realising its mission. International collaboration is needed to solve global health challenges and it will facilitate the exchange of ideas and data. A global perspective is also needed to attract talent and to expand funding options.

UMC Utrecht researchers engage in a wide range of international collaborations. The result sections of this self-evaluation report bear witness to that, as does the increasing amount of European Commission funding obtained in collaborative grants. In addition, we maintain a series of strategic collaborations with research institutes that include relations at the level of the executive board.

Investing in these strategic networks is important for UMC Utrecht. It results in joint research projects, joint publications, joint PhD training and student exchanges. With a number of organisations there is an intensive collaboration focused on research and innovation. These collaborations manifest themselves through joint appointments, collaborative EU grants, visiting professors and exchange of PhD candidates and students.

Currently, our strategic partners are:

- University College London (United Kingdom)
- KU Leuven (Belgium)
- University of Toronto (Canada)
- Chinese University of Hong Kong (China)

2.8.4 Innovation and knowledge transfer

Utrecht Holdings is the Knowledge Transfer Office (KTO) of Utrecht University and UMC Utrecht. Utrecht Holdings focuses on the knowledge utilisation and commercialisation of academic research and supports researchers in developing, protecting, marketing and creating spin-offs of innovations, particularly in the field of biotech, medtech, education and ICT. An examples of a spin-off company is Gadeta B.V., which was established in 2015 and develops innovative immuno-therapies for cancer (more information about Gadeta in the chapters about Cancer and Infection & Immunity).

Pontes Medical is embedded in the UMC Utrecht, VUmc and AMC and is an innovation partner for doctors, nurses, researchers and companies for the development, investment and marketing of medical devices. In collaboration with the business community, Pontes realizes innovations for affordable care, safer care and actually brings products to the patient. Examples of products and spin-off companies of Pontes Medical are Artrosave, which brings a solution to patients to avoid knee joint prothesis and Prolira, which markets the first delirium monitor.

The Healthcare Innovation Center, THINC., is part of the Julius Center. In 2016 THINC was stabled with the aim to improve the potential impact of healthcare innovations. THINC services UMC Utrecht researchers but mostly external parties such as start-ups, SME's and larger companies. THINC offers rigorous, fast, scientific research to healthcare innovators as part of their R&D. This paves the way for smooth market access.

Through our extensive network in the UMC Utrecht, we have access to patient groups, test environments, scientific expertise, healthcare professionals, healthcare costs, healthcare data. We provide short, efficient, customized research based on knowledge of HTA (Health Technology Assessment), Clinical Epidemiology, Public Health, Ethics, primary care and implementation. We focus on different types of innovations including e-health, medical apps, med-tech, medical devices, (international) care pathways and triage systems.

With the company Wind Tales, THINC has performed a usability and feasibility study to achieve an optimal fit for the serious game Wind Tales with their users. Windtales is a breath-training game for children with Cystic Fibrosis, where breath is the interface in the game. Windtales is the 2015 winner of the UREKA Mega Challenge, an innovation challenge organized by the Research Office.



3. Research policy & support

3.1 Research Office

Staff advisors from the Research Office (19 employees) translate internal and external developments into institutional research policies that contribute to research with impact. Strategic partnerships, state-of-the-art infrastructure, and appropriate incentives and rewards are instrumental to that aim. The Research Office also provides direct support for researchers through a range of activities, including support for internationalisation; innovation and valorisation; and grant applications and project management. As of 2017 Dries Hettinga PhD is head of the Research Office, he succeeded Susanne van Weelden PhD (2011-2017).

3.2 Support for innovation and funding

Support for international grants is the core task of the Research Support Office, which is part of the Research Office. For the UMC Utrecht, participation in internationally funded research projects and in particular in the Horizon2020 program is important in both financial and strategic terms. In addition to the financial aspects, international visibility, the connection with European networks and strategic alliances with key players are important. The income from research funding programs from international sources rose sharply in the 2014-2018 period (see Appendix 2 for tables with breakdown of earning capacity in specific sources).

UMC Utrecht started the project "Stimulating European Research" (SEO project) in Q2 2016. Three goals have been defined:

1. Stimulate new grant applications by implementing H2020 strategic plan
2. Establish central support and advice for divisions for the Post-Award phase of EU-funded research projects
3. "Capacity building" of researchers as well as support offices, staff members and the central Research Support Office by offering course, lectures, seminars and training events.

Part of the Stimulating European Research project is for example funding for hiring external consultants / grant writers for both H2020 applications (max 25k €) as well as for national subsidies (max 10 k €) such as Zwaartekracht, NWA-ORC, NWO Cross-over grants. This support is carried out by implementing an internal grant called 'Proposal development grants'.

The UMC Utrecht performs well in Horizon2020 proposals. Thanks to the targeted support from the SEO project and the strategic choice for new 'collaborative actions', a clear increase can be distinguished in the allocation of non-individual grants (see Figure 5). With over € 30 million, the UMC Utrecht is currently receiving more grants from the Societal Challenges than the entire University of Utrecht (€ 24 million). In addition, the individual grants received also show a stable picture.

Room for improvement

On 1 January 2018 a start was made with centrally offering project management services for coordination of European grant projects. The reason is a strong need for support from researchers on the one hand and a need to mitigate financial and legal risks. The project management capacity is partly paid for from the SEO funds and for the most part from the project funding itself. The centrally appointed project managers are seconded to the relevant divisions as the responsibility lies with the divisions at all times. The range of project management services will be further developed in the years ahead.

The visibility and recognition of the strategic research programs of the UMC Utrecht can still be improved internationally. Increased participation in the prestigious Horizon2020 program (of which the ERC and the Marie Skłodowska-Curie programs are an integral part) can increase this visibility.

The support towards national funding schemes is very limited due to a lack of capacity. There is no dedicated, proactive support for national funding opportunities. UMC Utrecht just participates in the Utrecht University support programs for personal grants.



An increase of capacity for (pro-) active support and expertise on national funding schemes might increase the revenues from this source (for example 69 VICI grants have been awarded in 2016 but none have been awarded to the UMC Utrecht and in the period 2014-2018 434 VIDJ grants have been awarded and only 7 (1,6%) were awarded to the UMC Utrecht).

Also, the support for public private partnerships other than within the context of the topsector LSH, receive limited support. Primarily because the Knowledge transfer office of the UMC Utrecht (Utrecht Holdings) plays a very limited role due to their strong focus on IP, IP licencing and startup creation. Rather than a more integral approach of knowledge transfer, assumed by many other UMC's, where also research collaboration is considered knowledge transfer.

3.3 Compliance and quality management of clinical research

The Executive Board is responsible for all human subject-related research that is carried out at UMC Utrecht and has delegated this responsibility to the division management. Within the division, the (medical) department head is primarily responsible for the quality of the research. The (central) principal investigator is responsible for the design, implementation and completion of the research.

All scientific research that meets the criteria of the Medical Research Act with human subjects (WMO) is assessed by a review committee and can only be carried out with the consent of the Executive Board. The UMC Utrecht Research Code describes the principles and rules relating to scientific integrity in order to promote sound and honest scientific behavior.

The Research Office holds the responsibility for *Quality of research* with the following tasks: Quality Assurance, Training, Expertise Centre and UMC-wide procedures and policies. Part of the quality system is the mandatory monitoring for all research subject to WMO. In addition, the UMC Utrecht has an internal audit program, which is conducted in the form of tracers. There are tracers on the research itself and tracer on leadership. Through research tracers, the implementation of the UMC-wide research policies is checked. The tracer on leadership focuses primarily on the organisation of the research over the whole division and on the management and support processes.

Critical findings from monitoring and tracers are reported by the department head to the division management. The division management escalates critical findings to the Executive Board. In addition, critical findings are reported to the Research Office and the review committee.

All divisions have dedicated research quality coordinators who report to division management. The research quality coordinator has a facilitating, advising and controlling task to promote quality and safety. The research quality coordinator performs quality checks on the non-scientific aspects of a research file before it can be submitted to the review committee.

The UMC Utrecht quality system is consistent with the Directive on Quality Assurance for Human Research which has been prepared by the Dutch Federation of University Medical Centers (NFU).

In June 2019 UMC Utrecht was accredited for the third time by the Joint Commission International in the domains of healthcare, education and research.

3.4 Integrity

Research integrity plays a vital role in allowing scientific research to function properly. The reputation and the reliability of scientific research depend on the individual actions of every researcher. Every researcher is responsible for research integrity. UMC Utrecht has developed its own (new!) Research Code.

This Research Code 1) helps to ensure that researchers can and will adhere to the standards for good research practices, as stated in the Dutch Code of Conduct for Scientific Integrity (VSNU), 2) indicates clearly what to do in the event of any integrity dilemmas and offers possibilities for reporting (suspicions) of scientific misconduct, 3) offers support to the researcher and provides insight into what good research practice implies within the discipline(s) and institution, including a brief explanation of and reference to existing UMC policy.

Scientific integrity (and the Research Code) needs to become a more commonly talked about subject between researchers than it is today. It should be normal to regularly discuss (and practice) research dilemmas among researchers, both planned (for instance with the dilemma game) and spontaneously. At the start of (clinical) research, extra attention needs to be given to the subject of research integrity as well as during annual interviews. For this, an implementation plan is being developed.



Also, together with the UU, and as part of a European grant, a Bachelor and Master program for Research Integrity is currently being developed.

The research office also played a coordinating role in developing a policy outline for academic entrepreneurship, involving Utrecht Holdings, the Legal and Human Resources department. The aim of the policy outline is to guide involved researchers, departments and the board of directors in facilitating this important route to create impact of research but on the other hand maintain the integrity of research.

3.5 Data management

Data management in scientific research is fundamental to high quality research and academic integrity. Research Data Management (RDM) covers the entire process of data collection, processing, validation, cleaning, preparation for analysis, archiving and sharing data. An adequate interpretation of data management ensures that the data be used in research comply with privacy laws remain accessible, reliable, traceable, usable and reusable. UMC Utrecht has therefore updated its [RDM policy](#), which comes into effect in stages: starting February 1st 2019 for WMO compulsory research and from July 1st 2019 for other scientific research. Every researcher is responsible for good research data management, also as part of research integrity. Each study requires a [Data Management Plan](#) that describes how research data are collected, how data are processed and stored during research and how data are made accessible for others once the study is completed. The aim of a Data Management Plan is to ensure that good scientific practice is followed according to the FAIR principles; data should be made 'Findable, Accessible, Interoperable and Re-usable'. UMC Utrecht offers a DMP-template to the researchers with guidance and examples of suitable and available IT infrastructure. Advise and support is available in every division in the form of division datamanagers.

3.6 Open Science

"Open Science is the ongoing transition in how research is performed and how knowledge is shared. It represents a new approach to the scientific process based on cooperative work and new ways of knowledge distribution using digital technologies and new collaborative tools. In practice, Open Science can make science more: credible (addressing scientific integrity); reliable (better and transparent verification of data); efficient (avoiding duplication of resources); and responsive to societal challenges (helping find answers to some of the major concerns of our time)."

The above perspective of the European Commission has in The Netherlands been translated into a National Plan Open Science and at Utrecht University into the Open Science Platform. The UMC Utrecht operationalizes Open Science in three domains: stakeholder involvement, data sharing and Open Access publications. Incentives and rewards for researchers should be in line with these goals (see paragraph above about evaluation practices).

At the UMC Utrecht we stimulate stakeholder involvement in priority setting in research, especially patient organisations, to make research responsive to societal challenges. Numerous examples in the program-specific chapters illustrate this. The strategic research program 'Patient participation' accelerates and professionalizes this long-standing practice.

We facilitate data sharing practices, with the aim of making research data FAIR available to other researchers, to speed up the process of scientific discovery.

The governance for research data, including technical infrastructure and dedicated personnel, is expanding rapidly (see paragraph 'Data management policies' for policy).

Finally, we stimulate publication of research findings in Open Access journals and on preprint servers to make publicly funded research indeed publicly available. UMC Utrecht researchers can apply for financial support at the Utrecht University Open Access fund that partly reimburses article processing charges. Despite this partial reimbursement, we realize that the upfront costs for Open Access publishing effectively imply a shift from institution-funded subscriptions to researcher-paid fees.

That is why our institutional policies should be put in perspective to (inter)national developments, like the making of 'Big Deals' between scientific publishers and all Dutch universities. The Netherlands are a frontrunner in the 'opening up' of scientific publishing, as is demonstrated for example by the so-called 'Taverne pilot' that legally enables researchers to publish their paper after a reasonable time in an open access repository, regardless of publisher's restrictions. In a case of leading by example, The most recent scientific articles from the Rectores Magnifici of Dutch universities will soon be available online to the general, international public for free. Further reading: www.openaccess.nl/en.



UMC Utrecht Open Access publications 2016-2018

	Gold	Hybrid	Green	Closed	Sum
2016	681	1248	67	1904	3900
2017	675	1115	260	1898	3948
2018	904	1014	222	1707	3847

Gold: the article was published in a Full OA journal

Hybrid: the article was published in a hybrid journal (subscription journal with separate OA articles)

Green: the article was NOT published in an OA journal, but an Open Access copy is available in a repository

Closed: the article is not available in any OA form

This classification is maintained by the Dutch Association of Universities

3.7 Benchmark: Research evaluation practices at the UMC Utrecht

The UMC Utrecht can be considered a frontrunner in the domain of research evaluation, both as contributor to the worldwide debate and as organisation where new forms of evaluation, focusing explicitly on societal impact, are being developed and implemented.

In the global debate about the science system research evaluation practices are routinely linked to reproducibility issues and lack of relevance ('research waste'). Rewarding researchers mainly for publications in high impact journals is increasingly being seen as detrimental to the progress of science (witness the San Francisco Declaration on Research Assessment (DORA), the [Leiden Manifesto for Research Metrics](#), the Lancet series '[Increasing value, reduce waste](#)' and much of the work of prof. [John Ioannidis](#)). In response, funders and institutions worldwide are moving towards responsible research practices, although these practices are still very much under construction.

In The Netherlands this debate profoundly influenced research policy. For example, 'productivity' was scrapped as stand alone criterium from the Dutch Standard Evaluation Protocol (2014). The government initiated the National Research Agenda where Dutch citizens submitted close to 12,000 questions to science. This has been translated into different 'routes' with associated funding (2015 onwards). And in 2017 the [National Plan Open Science](#) was launched with ambitions for openness of the research agenda, open data, open access publishing; and associated changes in incentives and rewards for researchers.

For the biomedical domain urgency was added by a Health Council report (2016) about UMCs. The council concludes that "their main focus is on fundamental medical-biological, translational and medical-specialist (curative-oriented) research and less on research into common diseases, keeping the population healthy for longer and coping with impairments". The Health Council links this to "assessments of the functioning of departments and individual researchers largely on the basis of bibliometric data such as citation scores".

As of 2018, these developments culminated in a joint statement by Dutch research funders (NWO and ZonMW), the federation of UMCs (NFU), the Royal Academy of Arts and Sciences (KNAW) and the association of universities (VSNU) where they signed DORA and announced principal changes in research evaluation at both institutions and funders, e.g. removing references to H-indexes and Journal Impact Factors from grant application forms.

The UMC Utrecht played a significant role in this debate, as the previous dean (2011-2019), prof. Frank Miedema, was one of the initiators of [Science in Transition](#). This group of academics pointed towards 'perverse incentives' in science and made an argument for structurally involving society in research agenda setting. Much of the Science in Transition critique, formulated in 2013, has become mainstream.

The UMC Utrecht has been at the forefront of responsible research practices ('[Fewer numbers, better science](#)', [Nature, 2016](#)) regarding SEP-based evaluations and academic promotion procedures. Already in 2012 we defined a valorisation profile for associate professors, explicitly valuing public private collaboration with dedicated criteria, broadening up career options for researchers. We took an even larger step in 2016, when we started asking all applicants for associate professors and professors to submit a portfolio covering multiple domains: science, teaching, clinical activities, leadership, impact, and innovation. Candidates are required to present themselves in an inclusive way, with narratives about the impact and goals of their research (See addendum: "UMC Utrecht qualification portfolio"). Parallel to this development, multiple UMC Utrecht divisions and departments are using 'broader' evaluation methods for researchers, taking into account a wider array of activities during annual assessments.



In the SEP-based evaluations we involve societal stakeholders. We did so for the first time in 2014, we build and extend on that experience with the current evaluation where stakeholders review patient participation and societal impact. Also, we developed 'indicators for impact' that form an important building block of the current self-evaluation reports. Strategic research programs are asked to explain how they arrived at their main research questions, how their research fits with existing knowledge, and how their findings are brought to 'the next step', for example to advance clinical applications.



4. PhD programs: Graduate School of Life Sciences

Doctoral education within UMC Utrecht is organised by the Graduate School of Life Sciences (GSLS). The GSLS is an interfaculty School in which also the faculties of Science and Veterinary Medicine of Utrecht University participate. It is probably among the largest Graduate Schools in Europe to which \pm 1,750 PhD candidates have registered.

The GSLS of Utrecht University aims that PhD candidates:

- conduct research according to the prevailing standards;
- are enabled to develop their research skills as well as personal competences in an inspiring and passionate/energetic environment;
- take responsibility towards the scientific community and society as a whole;
- obtain a position after their PhD as a highly qualified and integer knowledge worker, be it within or outside academia;
- are supervised by a team that effectively facilitates to reach these goals.

4.1 Recruitment, selection & admission

4.2 Most PhD candidates are employed on research grants obtained by one of our researchers. Thus, recruitment and selection are done by that supervisor. This holds also true for candidates on a scholarship. Once hired, the PhD track starts with admission of the candidate to the track by the Board for the Conferral of Doctoral Degrees after registration in the online tool MyPhD and ends with approval of the thesis by the reading committee and successful public defence of the thesis.

4.2 PhD enrolment

Enrolment	Success rates														
			#	%	#	%	#	%	#	%	#	%	#	%	
Starting year	Male	Female	Total	Graduated in year 4 or earlier	Graduated in year 5 or earlier	Graduated in year 6 or earlier	Graduated in year 7 or earlier	Not yet finished	Discontinued						
T-8 2010	101	149	250	124 49,60%	47 18,80%	29 11,60%	23 9,20%	11 4,40%	16 6,40%						
T-7 2011	111	150	261	146 55,94%	49 18,77%	31 11,88%	7 2,68%	17 6,51%	11 4,21%						
T-6 2012	83	138	221	118 53,39%	34 15,38%	24 10,86%	3 1,36%	29 13,12%	13 5,88%						
T-5 2013	120	141	261	128 49,04%	51 19,54%	18 6,90%	0 0,00%	47 18,01%	17 6,51%						
T-4 2014	117	171	288	140 48,61%	32 11,11%	0 0,00%	0 0,00%	102 35,42%	14 4,86%						
Total	532	749	1281	656 51,21%	213 16,63%	102 7,96%	33 2,58%	206 16,08%	71 5,54%						



4.3 PhD training

Funding for PhD training

For the period 2019-2023 the deans have allocated roughly € 1,000 per PhD per year for funding of the PhD programmes and the PhD Course Centre.

PhD programmes

Approx. 90% of our PhD candidates fit into any one of the 14 thematic PhD programs. The programmes provide a spectrum of activities, such as an introduction to the programme for new PhD candidates, thematic courses, seminars, masterclasses, symposia, PhD evenings and/or an annual retreat (PhDs only). PhDs are permitted to attend courses of other PhD programmes, and even Master's programmes, free of charge, if space permits.

From the beginning in 2009 we aimed for an active participation of PhD candidates in the GSLS: each PhD programme is run by a programme committee which includes PhD representatives. In addition, each programme is represented in the PhD Council.

PhD programs of the Graduate School of Life Sciences

- Biomembranes
- Cancer, Stem Cells & Developmental Biology
- Cardiovascular Research
- Clinical & Experimental Neuroscience
- Clinical & Translational Oncology
- Computational Life Sciences
- Drug Innovation
- Environmental Biology
- Epidemiology
- Infection & Immunity
- Medical Imaging
- Molecular Life Sciences
- Regenerative Medicine
- Toxicology & Environmental Health

PhD Course Centre

To provide general courses focussed on professional and personal development we established the PhD Course Centre in 2015. The number of course editions and participants is steadily increasing (see table below). In 2015-2017 we were able to offer the courses free of charge to PhD candidates, but in 2018 we were forced to ask a modest fee, which led to a decrease in course participation. From 2019 onward we are able to offer the courses free of charge again, which has led to a boost in applications. The course agenda can be found online and PhD candidates can subscribe to a biweekly Course Update to which we currently have 1,129 subscribers.

Number of participants of PhD course center per faculty

Faculty	2015	2016	2017	2018
Faculty of Veterinary Medicine	62	102	112	54
Faculty of Science	111	172	166	135
UMC Utrecht	167	342	411	282
Hubrecht Institute		13	12	8
Princess Máxima Centre				5
Westerdijk Institute				1
Other	6	11	21	21
Total	346	640	722	506



PhD Competence Model

In 2017, in collaboration with the other UMC's, the core competences for development of PhD's were defined in a PhD Competence Model. The core competences are: Research Skills & Knowledge, Scientific Integrity, Communication, Teaching, Personal Effectiveness, Professional development, and Leadership & Management. The model serves as a framework for structured organisation of our courses. The model comes with a self-assessment form, to be used by PhD candidates for structuring their scientific and personal development. We have organised the courses offered by the PhD Course Centre accordingly.

Career services

For several years, we have organised career events in which alumni, generally graduated < 10 years ago, told their stories about their career after graduation, the choices they made, how they handled work-life balance. These stories were evaluated invariably very well, but managed to attract only a small audience. Therefore, we will scale up this approach to provide a comprehensive programme of workshops and events for career orientation, offered at different levels (PhD programme – GSLS – UU – national). This initiative was greatly helped by the recent decision of the LS deans to invest an additional €30,000 per annum for career services.

4.4 Supervision

Each PhD candidate has at least one supervisor and one co-supervisor. The latter is responsible for daily supervision. In addition, each PhD candidate has a Supervisory Committee ('aio-begeleidingscommissie'): 1-2 researchers not involved in the candidate's research project.

In accordance with the Collective Labour Agreement (most PhDs are employees), candidates have an annual assessment interview with their (co-)supervisor(s). In addition, candidates may meet with their Supervisory Committee. Preferably once per year, or more often if needed.

Since PhD candidates generally are employees, information regarding go/no go decisions, (confidential) assessment interviews, consultation of the supervisory committee and time to degree is the responsibility of the faculty, i.e. the UMC divisions.

In January 2019 a new online PhD registration tool, MyPhD, was launched. Compared to the former registration tool Hora Est, MyPhD will contain all relevant information on training, supervision and progression, accessible to faculties and School.

To better support our supervisors we have started a training for young supervisors in 2018 and aim to organize informational and inspirational events on a regular basis, starting June 2019. The aim is to create an atmosphere in which good supervision is a skill which can be learned and is a joy

We expect our supervisors not only to be excellent scientists, but also take a supportive role towards personal development and career orientation of their PhD candidates. The PhD candidates embrace this view, organizing a Supervisor of the Year election each year.

4.5 Governance

Board of Studies

Together, the deans of UMC Utrecht and the faculties of Science and Veterinary Medicine constitute the Board of Studies. While they are collectively responsible for the educational programme, they are individually responsible for the quality of supervision and research of PhD candidates supervised by a professor from their faculty.

Director of doctoral education

In 2019 the Life Sciences deans have given an important boost to doctoral education at the GSLS: The appointment of the first Director of Doctoral Education and simultaneous approval of the budget for PhD programmes and PhD Course Centre until 2023.



PhD Council

The PhD Council consists of representatives of the PhD programmes and cares for the interests of PhD candidates, addresses programme-overarching issues in the Board of Studies, evaluates the PhD programmes each year and organizes events, such as an annual PhD Day, election of the (co-) supervisor of the year. The Council is represented in the Board of Studies by its chair. The MD-PhD sensor group is part of the PhD Council and represents the interests of medical PhDs. They organize events every 6 months.



5. SWOT analysis & future perspectives

(Internal)

Strengths

- Unique positioning at Utrecht Science Park with Utrecht Life Sciences cluster (consisting of UMC Utrecht, Veterinary Faculty and Science Faculty), industry (e.g. Danone, Genmab) and complementary research institutions (Hubrecht Institute, National Institute for Public Health and the Environment, Princess Maxima Center for Pediatric Oncology).
- With six disease-oriented strategic research programs (each covering basic, translational and clinical research) the UMC Utrecht has initiated a profiling process that facilitates strategic decision making. The scientific research of the selected areas is of very high quality.
- Innovation cycle – technology development and translation towards clinic – with a strong fundamental and technical scientific core and availability of large patients (and population-based) cohorts linked to biobanked patient materials.
- Strategic alliances at a regional, national and international level. Specifically, the newly developed alliance with UU, TU-Eindhoven and University Wageningen.
- High quality scores of education at all levels.
- UMC Utrecht leadership in Open Science/responsible research evaluation.
- Start of U-Trial, a centralized trial team in collaboration with Julius Clinical Academic CRO, gives opportunities for acquisition of international clinical trials.

Weaknesses

- Research support for grant applications (including for pre- and post- award activities), innovation and valorisation, and also for regulatory compliance, has been professionalizing and expanding, but is still hard-to-navigate, fragmented and understaffed. There is no proactive support for personal grants (Veni, Vidi, Vici scheme of NWO).
- Research governance is divided between budget-responsible divisions and strategic research programs. One implication is that ‘horizontal’ research topics, that are not specific for any of the strategic research program, are difficult to address.
- Dedicated time for research and teaching is limited, especially for clinicians.
- Lack of a centralized talent policy and programs in the UMC Utrecht and unclear career perspective for senior post-docs and assistant professors.
- MDs pursuing a PhD (the majority of PhD candidates) mainly to get into residency training is seen by many as a factor contributing to opportunistic research practices.
- No structural plan to implement data science expertise and infrastructure.
- Diversity of cultural backgrounds is low in almost all levels of the organisation.
- Limited external visibility of research expertise due to lack of communication strategy.
- Lack of structural support of the Cell Therapy Facility and Good Manufacturing Practice of compounds as key facilities for clinical trials.

(external)

Opportunities

- Push from Health minister to engage in research priority setting with regional actors.
- Brexit will create more room for Netherlands/UMC Utrecht to assume leadership roles in EU consortium grants. Also, we expect stronger collaboration with the EMA, following the move to Amsterdam.
- Well positioned in network with community-based and other academic hospitals.

Threats

- Researchers feel increasingly burdened by regulatory pressure, especially when initiating clinical trials.
- Tighter reimbursement policies by health insurers put pressure on UMC Utrecht budget as a whole, affecting the not always clearly demarcated time and funding for research.
- New policies from main Dutch research funder (‘Inbeddingsgarantie’, NWO) and government (WNRA) limit hiring practices with temporary contracts that are the norm in academia.
- Smaller government funding for ‘academic’ tasks of UMC, as topclinical hospitals will be allowed to claim part of that budget.
- Lack of (support) personnel, including nursing staff, to perform clinical research.



5.1 Future perspectives

UMC Utrecht will continue to capitalize on combination of research, healthcare and teaching in one organisation, with the strategic research programs providing the direction of our research. The focus for the next years will be on improving research support in the broadest sense, from compliance and data management to grant support and Open Science.

Aims for relevance and quality of research

- Development of UMC Utrecht strategy 2021-2025, with focus on data science and prevention.
- Further develop evaluation practices / Open Science, anticipating and building on (inter)national changes.
- Following recommendations from the Health Council and the Health minister, all Dutch UMCs have committed themselves to developing knowledge agendas with regional actors like hospitals, primary care providers and citizens.

Aims for support and infrastructure

- Integration and professionalisation of research support.
- New research building, with integration of laboratories and methodological support (eg statistics, ethics, health technology assessment, epidemiology etc).



Appendix 1. Funding and earning capacity

Brain						
	2018	2017	2016	2015	2014	2013
National grants (2)	2,645,472	€ 5,958,121	3,515,560	€ 5,353,261	€ 4,785,538	€ 6,248,458
External grants (3)	14,806,416	€ 9,693,711	5,226,790	€ 14,107,627	€ 18,288,026	€ 8,877,901
Contract research (4)	1,624,360	€ 1,863,042	862,107	€ 1,014,745	€ 943,207	€ 1,244,316
Total Funding	€ 19,076,248	€ 17,514,874	€ 9,604,457	€ 20,475,633	€ 24,016,771	€ 16,370,675

Cancer						
	2018	2017	2016	2015	2014	2013
National grants (2)	€ 5,648,771	€ 6,724,746	€ 9,572,216	€ 3,372,687	€ 4,455,670	€ 6,727,638
External grants (3)	€ 17,575,440	€ 14,711,525	€ 10,874,190	€ 14,460,948	€ 13,049,223	€ 14,998,057
Contract research (4)	€ 7,537,376	€ 1,110,919	€ 7,041,862	€ 2,150,060	€ 1,942,630	€ 2,984,618
Total Funding	€ 30,761,587	€ 22,547,190	€ 27,488,268	€ 19,983,695	€ 19,447,523	€ 24,710,313

Child health						
	2018	2017	2016	2015	2014	2013
National grants (2)	1,894,871	€ 3,529,020	2,168,355	€ 1,579,184	€ 1,031,585	€ 1,144,430
External grants (3)	4,599,053	€ 5,711,599	7,337,379	€ 2,268,385	€ 3,287,500	€ 3,808,356
Contract research (4)	1,627,640	€ 2,207,749	1,243,258	€ 969,618	€ 1,891,163	€ 624,306
Total Funding	€ 8,121,564	€ 11,448,368	€ 10,748,992	€ 4,817,187	€ 6,210,248	€ 5,577,092

Circulatory Health						
	2018	2017	2016	2015	2014	2013
National grants (2)	2,275,897	€ 4,168,455	2,920,090	€ 1,120,351	€ 1,743,250	€ 841,440
External grants (3)	4,762,502	€ 8,529,722	8,380,920	€ 3,953,706	€ 4,240,854	€ 6,281,845
Contract research (4)	2,997,926	€ 3,154,502	3,302,322	€ 3,407,703	€ 3,476,394	€ 2,408,798
Total Funding	€ 10,036,326	€ 15,852,679	€ 14,603,332	€ 8,481,760	€ 9,460,498	€ 9,532,083

Infection & Immunity						
	2018	2017	2016	2015	2014	2013
National grants (2)	€ 1,311,570	€ 3,814,841	€ 2,344,361	€ 3,842,218	€ 3,701,705	€ 3,562,295
External grants (3)	€ 17,481,309	€ 12,963,928	€ 6,500,119	€ 16,586,142	€ 11,688,963	€ 14,265,786
Contract research (4)	€ 3,921,197	€ 14,143,464	€ 5,426,932	€ 7,942,817	€ 3,773,936	€ 3,949,428
Total Funding	€ 22,714,076	€ 30,922,233	€ 14,271,412	€ 28,371,177	€ 19,164,604	€ 21,777,509



Regenerative Medicine & Stem Cells

	2018	2017	2016	2015	2014	2013
National grants (2)	1,186,422	€ 2,716,089	€ 1,036,860	€ 1,775,286	€ 2,197,318	€ 2,556,106
External grants (3)	€ 4,259,474	€ 3,383,714	€ 6,633,557	€ 5,070,750	€ 4,726,931	€ 3,714,171
Contract research (4)	€ 2,429,617	€ 1,364,728	€ 1,445,325	€ 2,206,997	€ 1,021,052	€ 2,075,567
Total Funding	€ 7,875,513	€ 7,464,531	€ 9,115,742	€ 9,053,033	€ 7,945,301	€ 8,345,844

Other Research

	2018	2017	2016	2015	2014	2013
National grants (2)	€ 378,704	€ 1,481,842	2,319,773	€ 19,438	€ 587,974	€ 411,547
External grants (3)	€ 2,743,316	€ 3,312,903	€ 2,197,330	€ 2,406,354	€ 820,307	€ 1,320,820
Contract research (4)	€ 283,326	€ 366,556	512,582	€ 193,066	€ 379,531	€ 383,830
Total Funding	€ 3,405,346	€ 5,161,301	€ 5,029,685	€ 2,618,858	€ 1,787,812	€ 2,116,197

Direct Funding (1)	Block funding from government
National grants (2)	Competitive grants from Dutch national research funders (e.g. NWO, ZonMw, KNAW)
External grants (3)	Grants from external, not-for-profit parties (e.g. European Commission and health charities)
Contract research (4)	Grants from industry



Appendix 2. Funding from European Union

Overview Horizon2020 coordinated projects UMC Utrecht (2013-2018)

Programme and acronym	Coordinator	Start of the project	Total project sum
H2020 CSA (GCOF)	Terry Vrijenhoek	2015	€ 1,195,106
H2020 RIA (PRECIOUS)	Bart van der Worp	2015	€ 5,994,000
H2020 PCP project (NIGHTINGALE)	Cor Kalkman	2016	€ 5,351,667
H2020 RIA (WEAKID)	Karin Gerritsen	2017	€ 3,306,750
H2020 RIA (B-SMART)	Raymond Schiffelers	2017	€ 5,998,303
H2020 COFUND (3M€) Regenerative Medicine (RESCUE)	Paul Coffey	2018	€ 6,069,120
H2020 RIA (HIT-CF)	Kors van der Ent	2018	€ 8,753,615
H2020 RIA (CONVINCE)	Peter Blankestijn	2018	€ 6,865,425
H2020 FET (NICI)	Dennis Klomp	2018	€ 3,146,973
H2020 RIA (FURTHER)	Lenny Verkooijen	2019*	€ 3,998,125
H2020 RIA (PREFERABLE)	Anne May	2019*	€ 4,066,743
H2020 CSA (ECRAID-PLAN)	Marc Bonten	2019*	€ 2,994,560
H2020 RIA (EXPERT)	Raymond Schiffelers	2019*	€ 15,010,088

*Projects are awarded in 2018 but will start in 2019

Overview IMI and Erasmus+ coordinated projects UMC Utrecht (2013-2018):

Programme and acronym	Coordinator	Start of the project	Total project sum
IMI1-6 (COMBACTE-NET)	Marc Bonten	2013	€ 207,148,429
IMI1-7 (GETREAL)	Rick Grobbee	2013	€ 16,952,280
IMI1-11 (APPROACH)	Harry Weinans	2015	€ 17,550,008
IMI1-9 (COMBACTE-CARE)	Marc Bonten	2015	€ 85,113,336
IMI1-11 (COMBACTE-MAGNET)	Marc Bonten	2015	€ 168,658,670
H2020-JTI-IMI2-2015-07-two-stage (BigData@Heart)	Rick Grobbee	2017	€ 19,398,970
H2020-JTI-IMI2-2016-09-two-stage (COMBACTE-CDI)	Marc Bonten	2017	€ 4,582,218
ERASMUS+ KA2 (GROWTH)	Rick Grobbee	2017	€ 889,960
ERASMUS+ KA2 (Health-I)	Rick Grobbee	2017	€ 916,479
ERASMUS+ KA2 (PATHWAY)	Berent Prakken	2017	€ 415,117
H2020-JTI-IMI2-2017-11-single-stage (GetReal Initiative)	Rick Grobbee	2018	€ 3,100,688
H2020-JTI-IMI2-2017-12-two-stage (VITAL)	Debbie van Baarle	2018	€ 12,390,572



MSCA-ITN participations (no coordinated projects in 2013-2018)

Acronym	MSCA programme	EU project contribution
BonePain	H2020-MSCA-ITN-2014	€ 255,374
TargetCaRe	H2020-MSCA-ITN-2014	€ 255,374
DISSection	H2020-MSCA-ITN-2015	€ 510,749
EDGE	H2020-MSCA-ITN-2015	€ 510,749
RELEVANCE	H2020-MSCA-ITN-2015	€ 255,374
IMforFUTURE	H2020-MSCA-ITN-2016	€ 255,374
circRTrain	H2020-MSCA-ITN-2016	€ 510,749
TRAIN	H2020-MSCA-ITN-2016	€ 510,749
QuanTII	H2020-MSCA-ITN-2017	€ 510,749
BonePainII	H2020-MSCA-ITN-2018	€ 531,240
INFANS	H2020-MSCA-ITN-2018	€ 531,240
HOPE	H2020-MSCA-RISE-2018	€ 13,800

Awarded ERC grants (2013-2018)

Acronym	MSCA programme	EU project contribution	
3D-JOINT	ERC-2014-CoG	€ 1,901,871	Jos Malda
HEARTOFSTROKE	ERC-2014-STG	€ 1,499,450	Jeroen Hendrikse
IXSI3D	ERC-2014-CoG	€ 1,999,000	Hugo de Jong
ComBact	ERC-2014-STG	€ 1,497,290	Suzan Rooijackers
iGOLDD	ERC-2015-PoC	€ 150,000	Chrit Moonen
MIRASYS	ERC-2015-PoC	€ 149,190	Inge de Wit
NeMoFoil	ERC-2015-PoC	€ 149,060	Nick Ramsey
EVICARE	ERC-2016-COG	€ 1,997,298	Joost Sluiter
EScORIAL	ERC-2017-COG	€ 1,980,434	Jan Veldink
ASSYSt	ERC-2017-PoC	€ 150,000	Timothy Radstake
SELMA	ERC-2018-PoC	€ 149,979	Jacobus Jan Marinus Zwanenburg
ReCoDE	ERC-2018-STG	€ 1,499,966	Frank Meye
IntratumoralNiche	ERC-2018-STG	€ 1,500,000	Boudewijn Burgering
Epilepsy_Core	ERC-2018-STG	€ 1,500,000	Maeike Zijlmans



Awarded MSCA individual fellowship grants (2013-2018)

Acronym	MSCA programme	EU project contribution
ISSVS	H2020-MSCA-IF-2014	€ 177,599
CR-PHAGOCYTOSIS	H2020-MSCA-IF-2014	€ 165,599
WntTraffic	H2020-MSCA-IF-2014	€ 177,599
PREVENT	H2020-MSCA-IF-2014	€ 228,422
NEUTRO-LILR	H2020-MSCA-IF-2015	€ 165,599
CAMEOS	H2020-MSCA-IF-2015	€ 260,930
gdTCR-Ligand	H2020-MSCA-IF-2016	€ 177,599
PGXOME	H2020-MSCA-IF-2016	€ 82,799
PRE-PSYCH	H2020-MSCA-IF-2016	€ 242,930
mABSPN	H2020-MSCA-IF-2017	€ 165,599
BEAT	H2020-MSCA-IF-2017	€ 260,930
HGB-StIC	H2020-MSCA-IF-2017	€ 260,930



Self-evaluation strategic research program **Brain**





1. Self-evaluation strategic research program Brain	35
1.1 The mission, strategy & organisation	35
1.2 Composition and Funding	39
1.3 SWOT analysis	39
1.4 Evaluation practices	40
1.5 Patient involvement	41
1.6 Master and PhD education	42
2. UMC Utrecht Brain Center – Developmental disorders	43
2.1 Mission, strategy, and organisation	43
2.2 Research projects with patient involvement	44
2.3 Key publications	44
2.4 Most important contributions to society	45
3. UMC Utrecht Brain Center – Epilepsy	50
3.1 Mission, strategy, and organisation	50
3.2 Research projects with patient involvement	50
3.3 Key publications	51
3.4 Most important contributions to society	52
4. UMC Utrecht Brain Center – Neuromuscular disorders	57
4.1 Mission, strategy, and organisation	57
4.2 Research projects with patient involvement	58
4.3 Key publications	59
4.4 Most important contributions to society	60
5. UMC Utrecht Brain Center – Psychotic disorders	65
5.1 Mission, strategy, and organisation	65
5.2 Research projects with patient involvement	66
5.3 Key publications	67
5.4 Most important contributions to society	68
6. UMC Utrecht Brain Center – Stroke	73
6.1 Mission, strategy, and organisation	73
6.2 Research projects with patient involvement	73
6.3 Key publications	74
6.4 Most important contributions to society	74
Appendix: Organisational structure of the UMC Utrecht Brain Center from 2019 onwards	77
Appendix: program X-talks 2016-2017	78



1. Self-evaluation strategic research program Brain

1.1 The mission, strategy & organisation

Mission

The strategic research program Brain is named UMC Utrecht Brain Center in external communication. In this document UMC Utrecht Brain Center is used. The UMC Utrecht Brain Center is an internationally recognized, leading research center in clinical and experimental neuroscience, where the latest insights in the development and function of the nervous system in health and disease are generated, applied in clinical care and disseminated to a broad audience, in an open dialogue with relevant stakeholders.

The last years we have focused on five disease areas:

- Epilepsy
- Neuromuscular disorders
- Developmental disorders
- Psychotic disorders
- Stroke

Within all five disease areas we aim to translate basic science and patient-driven research questions into clinically applicable diagnostic methods, prediction tools, and novel treatment options. In the area of **Epilepsy**, we aim to improve the health of patients – particularly children – with refractory, complex, and rare epilepsies. **Neuromuscular disorders** provides excellent clinical care for patients with all forms of neuromuscular disease and performs outstanding research on motor neuron disease and neuropathy. Within **Developmental disorders** new treatments and biomarkers are developed by understanding which neurobiological aspects are affected by genetic or idiopathic changes in the brain. Additionally, we aim to understand the developmental trajectory and underlying mechanisms of **Psychotic disorders** and investigate the efficacy of new interventions to treat or prevent them. Finally, **Stroke** focuses on patients with cerebrovascular disease, including those with stroke, unruptured intracranial vascular malformations, or vascular cognitive impairment, and neonates with hypoxic-ischemic brain damage.

Since January 2019 we are developing a sixth disease area, **neuro-oncology**. Both within the UMC Utrecht Brain Center and Utrecht Science Park in general (e.g. Prinses Maxima Center), research and care related to different brain tumours have intensified. These efforts will converge into one disease area, in collaboration with the strategic research program Cancer. A very successful kick-off meeting was organized in June 2019.

Patient care and the scientific landscape within the focus areas 'Psychotic disorders' and 'Developmental disorders' have changed during the past years (e.g. due to the departure of principal investigators (PIs)). Both areas have recently been evaluated and are currently being reorganized. Kick-off meetings are expected for the end of the summer.

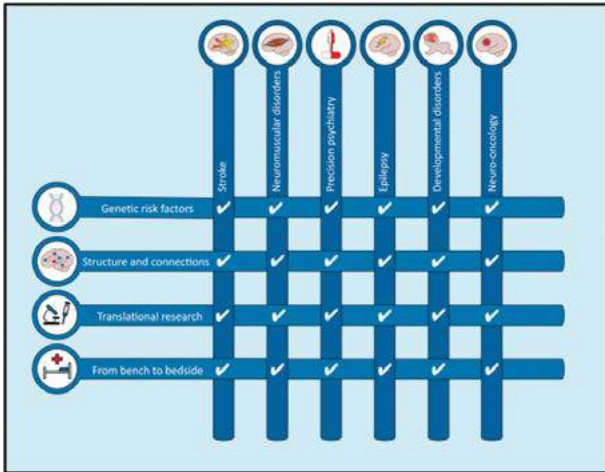
The above listed disease areas share and convene along common research themes:

- Genetic risk factors.
- Environmental risk factors, in interaction with the genetic background.
- Their impact on the structure and connections of the nervous system.
- The use of translational models to unravel disease mechanisms and guide treatment options.
- Testing new treatment options in clinical trials and implementing research findings in the daily practice of patient care.

Because of changes in research focus and future developments, we will refocus the research theme environmental factors towards prevention research and data science.



From 2019 onwards the UMC Utrecht Brain Center will be structured as follows:



Three research facilities have been implemented in the UMC Utrecht Brain Center and are financially supported by the center: a facility for neurogenetics research, a facility for induced pluripotent stem cell (iPSC) and other stem cell studies, and a facility for human brain imaging. The **neurogenetics** facility is a collaboration between the departments of neurology, psychiatry, and translational neuroscience and facilitates all research related to genetics, including biobanking, DNA shipment, and experimental support. The **iPSC** facility is part of the MIND facility for human brain models and imaging which is situated in the department of translational neuroscience. It is a training facility for researchers who want to learn to generate iPSCs from human material, who want to perform experiments with existing cells or who want to test new protocols for human tissue culture. The facility is equipped to generate iPSCs, to differentiate them into neural cells or brain organoids, and to subsequently analyse those cells and tissues at the cellular and molecular level. The **imaging** facility represents a brain image acquisition and high-performance computing imaging processing facility with algorithms required for state-of-the-art studies on structural and functional brain imaging. These different facilities are used by many researchers from different divisions and improve collaborations within the UMC Utrecht Brain Center and the UMC Utrecht. The performance of each facility is evaluated on a yearly basis.

Overall ambitions



1. Scientifically we belong to the top-3 of Europe within our five disease areas.
Groundbreaking insights are acquired through state-of-the-art approaches that are shared among the focus areas, from basic neuroscience to evidence-based clinical research.
2. New knowledge and insights are transferred to the clinical setting.
3. With this knowledge we aim to be (regional or national) market leader in and provider of high-quality clinical care in the disease areas.
4. We operate through an open dialogue, both in an academic setting and with relevant health care, societal, and industrial stakeholders.
5. Strong focus on collaborations: internal (within the divisions of the UMC Utrecht and between the six strategic research programs) and external (campus, regional, national and international).
6. Foster talents via active talent management measures.



Some highlights of actions we have taken to achieve our ambitions:

- Monthly meetings across the center (X-talks) to bring together basic and clinical neuroscience, to provide an opportunity for staff, junior scientist and students to frequently meet, and to learn from each other's research approaches and techniques. Quarterly bulletin and weekly newsletter (as of September 2019) on research, patient care, talents etc.
- Performed an internal evaluation of our center in 2017 and adjusted our goals and ambitions accordingly ('Bridging the future').
- Close contact with our international partners - Institute of Psychiatry London, Edinburgh Neuroscience, Neuroscience Campus Munich, University of Leuven - (organisation of several international institute meetings, reciprocal participation in activities such as courses and summer schools) to combine our strengths and efforts, and to apply for joint funding.
- Strengthened the interplay between the six strategic research programs of the UMC Utrecht via monthly meetings, an overarching strategy on general topics like prevention, data-science, strategic research program laboratories and clinical scientists.
- Awarding UMC Utrecht Brain Center fellowships for talented young researchers (Rudolf Magnus Young Investigator award; 1-2 per year). Awarding yearly prizes for best thesis, publication, and outreach activity. The winners of the Rudolf Magnus Young investigator award of the previous years can be found in table below.
- Organisation of annual research day (in November) and Utrecht Brain Conference (in December) to stimulate collaboration between neuroscience academia and industry at Utrecht Science Park.
- Stimulated the generation and execution of clinical trials by appointing one of our senior clinical researchers as a clinical trial generator (U-TRIAL, 0.6 fte).
- Invested in our MSc and PhD program and enlarged our visibility in all other academic programs in the UMC Utrecht by renewing educational programs within the MSc and the PhD curricula to bring them in line with the research performed within the UMC Utrecht Brain Center. Furthermore, we acted as advisors in a series of election courses on the topic of neuroscience with the other academic programs (clinical and biomedical programs) and an online course for international students at the advanced bachelor level.

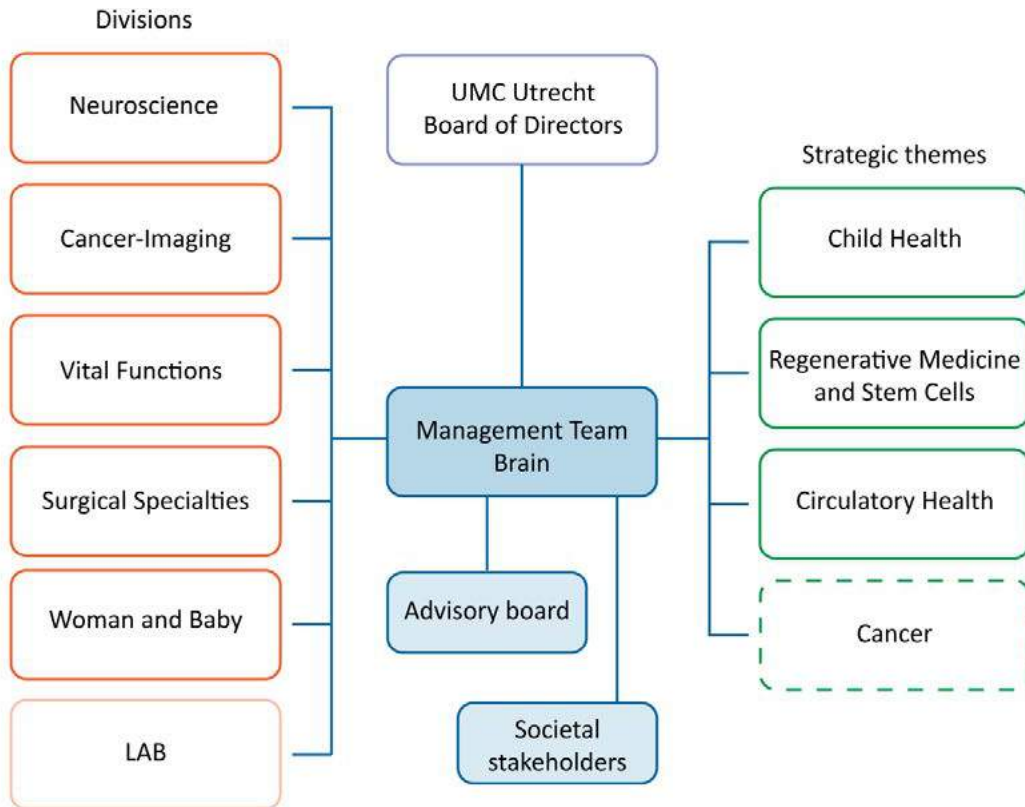
Winners Rudolf Magnus Young Talent Fellowships

2010	Ynte Ruigrok	Martijn van den Heuvel
2011	Michael van Es	Lot de Witte
2012	Maeike Zijlmans	
2013	Jacoba Greeving	Christiaan Vinkers
2014	Jurjen Luijkx	
2016	Yeal Reijmer	Mathijs Bossong



Organisation

This figure is a schematic overview of the organisational structure of the UMC Utrecht Brain Center.



The management team

- The management team is the decisive structure of the center: decisions about strategy; investment; selection procedures etc. are made by this team.
- Consists of the chair, six members (representatives of the participating divisions), a communication officer and a program manager. This provides a structural link to the divisions.
- The members have specific portfolios: i.e. education, research, valorisation, communication, patient care. Each member meets with representatives from the different divisions for their specific portfolios (e.g. with the Manager Research or Manager Education).
- The team meets every month in person, and has further contact via email, Skype etc.

Advisory board

- Advises the management team on strategy, focus areas, nominations for prizes etc.
- Has a leading role in the organisation of X-talks, the UMC Utrecht Brain Center research day, masterclasses, summer schools etc. Mostly composed of mid-career, talented group leaders.
- Consists of the coordinators of the disease areas and research themes.
- The advisory board meets twice a year with the chair and the program manager.
- The chair sends regular updates to members of the advisory board.

Advisory Board of Societal Stakeholders

- Advises the UMC Utrecht Brain Center on issues related to societal relevance (e.g. outreach to lay public or health professionals; interaction with patients or industrial partners).
- Consists of representatives of clinical (regional) partners, business/industry, charities, politics, patient organisations, and media.
- Meets once a year with the chair and program manager.



Interaction with Divisions

- The following divisions participate in the UMC Utrecht Brain Center: Neuroscience, Cancer-Imaging, Vital Functions, Woman and Baby, Surgical Specialties, and LAB.
- With each of these divisions a collaboration agreement has been signed (2016-2020), which delineates specific goals or agreements. It also specifies the financial contribution of each of the divisions to the center. [N.B. The agreement with Cancer-Imaging is reviewed on a yearly basis and the contribution of LAB will end after 2019].
- Each year the chair and the program manager of the center meet with the management team of each of the participating divisions, to evaluate the past year and discuss goals/potential threats and opportunities for the coming year.
- In preparation of the management letter of the Board of Directors, members of the center's management team responsible for patient care, research and education obtain input from the participating divisions.
- Management teams of the divisions are regularly updated by email.
- Any matter that emerges and which logically should involve divisions (e.g. selection of candidates for UMC Utrecht stimulation programs) are dealt with on an ad hoc basis.

Interaction with Strategic research programs

There is a strong collaboration with other strategic research programs. In the past five years, the UMC Utrecht Brain Center closely collaborated with Child Health, Regenerative Medicine and Stem Cells, and Circulatory Health. In 2019, we will set up a collaboration with Cancer within the neuro-oncology disease theme.

1.2 Composition and Funding

Researchers from the junior (PhD) to the most senior (professor) level participate in the UMC Utrecht Brain Center. They work in divisions affiliated with the UMC Utrecht Brain Center and have their research focus in one or more of the research areas (disease- or theme-related). The UMC Utrecht Brain Center houses about 350 researchers (clinical and preclinical). We have a constant basis of around 200 PhD students (50-50 clinical and preclinical students), 36 full professors, around 22 associate professors, 45 assistant professors and 50 postdocs. This number is relatively constant throughout the years.

Most of our research is funded by external funding bodies such as the government, Europe and US funding, societal funds (collectebus), and private funding (crowd funding and patient donations). We have a stable success rate with a yearly income of external funding between 10 -15 million Euro. Researchers of the institute have obtained prestigious individual grants (e.g. ERC Starting and Advanced grants or grants within the VENI-VIDI-VICI scheme) and participate in and coordinate large national (e.g. NWO Gravitation) and international consortia (e.g. H2020 projects).

Tables 1 and 2 in the UMC Utrecht part of this evaluation protocol give an estimate of our fte and external funding over the last six years.

1.3 SWOT analysis

STRENGTHS

1. Patient care and research in the UMC Utrecht Brain Center are focused on a restricted number of diseases, without losing the flexibility to re-evaluate and adjust to new developments and needs in the field. This makes the strategic research program coherent and easy to recognize (both to our own researchers and to scientists outside the UMC Utrecht). Substantial patient cohorts have been 'generated' in these fields, with excellent possibilities for research, (PhD) education, and excellent patient care.
2. The combination of psychiatry, neurology, neurosurgery, rehabilitation, translational neuroscience, neonatology, epidemiology, physics, human genetics, and psychology in one program is very rare and has led to cross-over between disciplines and between clinical and preclinical approaches.
3. The scientific research of the selected areas is of very high quality. Both with respect to the number and quality of our scientific publications, as well as in securing funding (national and international).
4. The research infrastructure of the UMC Utrecht Brain Center is excellent, due to our continued investments in facilities for neurogenetics, neuroimaging, and translational neuroscience research.
5. Active collaborations at all different levels (from large international networks to individual collaborations at the institutional level).



WEAKNESSES

1. The collaboration between clinical departments and clinicians in different divisions has started but can be reinforced to optimize patientcare, incorporating new knowledge provided from our research.
 2. Brain (the UMC Utrecht Brain Center) has not yet succeeded in becoming a unique label in Utrecht Science Park (University Utrecht (UU)). Visibility within the UU priority theme Life Sciences is limited.
 3. Interactions between various research groups within the center have improved. However, many opportunities for sharing knowledge, expertise, and infrastructure could still be exploited. Similarly, knowledge transfer to clinical practice and societal/industrial partners is increasingly explored and performed, but not yet to its full potential.
 4. Career possibilities for highly talented young investigators are rate-limiting factors, especially in basic and translational neuroscience.
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OPPORTUNITIES

1. The leading principle is that for sizeable patient-cohorts, patient care and research are combined. This facilitates research from bench to bedside, and vice versa. The potential for translational research and knowledge transfer to the patient and to societal/industrial partners is very high.
 2. Two topics that are expected to be part of the new UMC Utrecht strategy (2020-2030; prevention and data-science) provide an opportunity to further strengthen and actively use our expertise in these areas.
 3. Development of strategic research program laboratories (Laboratory of Translational Neuroscience). This will strengthen collaboration between researchers in the center and allow for sharing research infrastructure, personnel and knowledge.
 4. U-trial facility: an in house core facility for trial development provides us with an opportunity to enlarge our expertise in and the number of clinical trials.
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THREATS

1. Research funding is at a critical stage. Funding rates of national and EU agencies have dropped (often below 10%) and the remuneration for research for Dutch academic medical centers has been substantially reduced.
 2. For clinical scientists it is challenging to perform research at a competitive international level, because of a plethora of other tasks in addition to performing research (i.e. teaching, management, patient care).
 3. Large budget cuts in the UMC Utrecht disproportionately and negatively impact research and researchers.
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1.4 Evaluation practices

Within the UMC Utrecht Brain Center we have a few of standard annual evaluation points. Furthermore, we performed an extensive internal evaluation in 2017.

Standard evaluation points encompass

- An annual progress report and budget evaluation is requested from our three research facilities (neurogenetics, iPSC, and imaging). These reports are evaluated by the chair, program manager and members of the management team. This evaluation focuses on the budget (keeping within budget), productivity within the center, width of activities, and visibility within the center.
- An annual evaluation with the management teams of the participating divisions. This evaluation focuses on research output, talent management, facilities, and teaching.
- Twice a year the chair meets with the Dean to discuss progress and potential issues.

Internal evaluation 2017

In 2017, the new chair of the UMC Utrecht Brain Center, professor R.J. Pasterkamp, initiated an internal evaluation of the center. The aim of this evaluation was to critically evaluate the focus areas and our goals with respect to research, teaching, outreach etc. The report (written in Dutch) called 'Bridging the future' is available as a separate document.

The main conclusions were:

- The matrix of selected disease areas and methods and approaches is still valid and provides the right focus;
- 'The patient' should play an even more prominent role;
- Expand and intensify collaborations at all levels (from local to international);
- More emphasis on talent management is needed;
- Enhance multidisciplinary and emphasize innovation.



Open Science activities

Openness of the research agenda & stakeholder involvement

The UMC Utrecht Brain Center has many stakeholders, such as other UMCs and regional hospitals, patient organisations and companies. Please find below a couple of examples of our stakeholders:

- Dutch Epilepsy Fund
- Spieren voor Spieren
- ALS Stichting
- Hersenstichting
- SAFE (Stroke Alliance For Europe)
- SEIN
- Patient organisations (Balans, Ypsilon, Anoiksis)
- InteRNA
- Mimetas
- Nutricia
- Phillips

Openness of data and protocols

The researchers of the center are following the guidelines and policy of the UMC Utrecht on data management. This means that:

- For all research involving patients a data management plan is generated and discussed with data managers of the division the researcher is employed at. From September 2019 onwards, this will also hold true for all research without patient involvement.
- All data is stored according to FAIR principles (starting July 2019 an EDC system is in place for the UMC Utrecht to further improve data storage).

We stimulate the registration of protocols for clinical trials (clinicaltrials.gov, trialregister.nl, clinicaltrialsregister.eu). Awareness of this kind of registration is heightened in collaboration with the quality officers of the participating divisions. Results of clinical trials will always (if possible) be published in journals. To be able to publish the results a trial needs to be registered.

Open Access publications

We encourage open access publishing and point researchers to available funding opportunities to facilitate this. While it is important that all data (including scientific publications) becomes available as soon as possible, the center notices that the costs of open access publications are high and mostly not covered in grants etc. Therefore it is important that the UMC Utrecht plays a (national) role in making open access publishing more affordable.

1.5 Patient involvement

Several disease areas are very actively involving patients in different aspects of patient care, research, and teaching. Since other areas are still developing their patient involvement programs, the center has initiated a central patient participation program. We have interviewed several key researchers of the center to obtain their point of view on patient involvement: what do you do, what works and what doesn't, and what do you need to improve patient involvement. The main conclusions of these interviews were:

- the importance of patient involvement is a priority for all;
- the degree to which patients are involved differs, from letting patients co-determine research questions and raising funds with the patients via crowd funding to informing them during lay speeches at meetings of patient groups/associations (see for examples the individual parts of the disease areas);
- knowing what drives patients and what they need helps to focus research;
- it is necessary to arrange central support, e.g. for communication and expectation management with patients (groups/associations);
- for (almost) all granting agencies proving that patients are involved in the research process is a requirement;
- learn from each other, i.e. provide a list of best practices.



The outcome of the interviews will be discussed within the center with a few relevant patient associations to establish a general minimal approach (and best practice sharing) of patient involvement. The use of the approach will be monitored during the yearly evaluations with the management teams of the divisions and the bi-annual meetings with the advisory board.

1.6 Master and PhD education

The UMC Utrecht Brain Center is involved in the master program Neuroscience and Cognition (www.neuroscience-cognition.org/, www.UMC Utrechtrecht.nl/en/Research/Strategic-themes/Brain-Center/Education-and-career/Masters-program-and-internships). Additionally, the UMC Utrecht Brain Center encompasses the PhD program Clinical and Experimental Neuroscience (www.UMC Utrechtrecht.nl/en/Research/Strategic-themes/Brain-Center/Education-and-career/PhD-program-en). Both are part of the Graduate School of Life Sciences of Utrecht University. In total these programs contain 250 students (55 master students and around 200 PhD students).

The master program Neuroscience and Cognition is a two year, interdisciplinary research master program, combining experimental/clinical and cognitive neuroscience. The program starts with a 10 week introductory course Fundamentals in Neuroscience and Cognition, in which all departments of the UMC Utrecht Brain Center participate. Thereafter, the master students perform two internships (nine and six months). The major internship (nine months) mainly takes place in the departments of the UMC Utrecht Brain Center and the minor internship (six months) in the UMC Utrecht Brain Center or in other research labs (Utrecht, outside Utrecht, outside the Netherlands). Most of these labs are collaborators of PIs of the UMC Utrecht Brain Center. Finally, the master thesis (writing assignment) of a large number of master students enrolled in this program is written under supervision of PIs of the UMC Utrecht Brain Center.

The PhD program Clinical & Experimental Neuroscience combines preclinical and clinical neuroscience. The teaching activities in this program in which the UMC Utrecht Brain Center is involved, include the Clinical and Experimental Neuroscience Summer School, the Current Issues in Clinical Neuroscience course, and several disciplinary courses (e.g. Neurodevelopment). PhD students also actively participate in de X-talks and the annual UMC Utrecht Brain Center research day.



2. UMC Utrecht Brain Center – Developmental disorders

2.1 Mission, strategy, and organisation

Mission

There is an unmet need for new treatments and biomarkers for developmental disorders. We are developing research and care programs to address individual patient needs from our youngest patients to adults. By involving patients and their families we focus on the aspects of developmental disorders that matter most. By understanding which neurobiological aspects are affected by genetic or idiopathic changes in the brain, and how they interact with behavior, we can discuss with patients how their condition affects their everyday life. By having this dialogue we can help empower patients to regain control of their lives.

Understanding the development of the healthy brain will improve our understanding of the causes and consequences of developmental disorders and can be used to optimize the care we provide for children and their care-givers. To this end, we aim to conduct excellent and collaborative research unraveling the neurobiological and behavioral aspects of developmental disorders. Understanding these links will permit us to improve treatment options and strategies. We focus on mechanisms, rather than on symptoms. We focus on individuals, and on variation between individuals, rather than on diagnostic categories.

Strategy

Over the last years, investigators from the UMC Utrecht Departments of Psychiatry (e.g. dr. Bruining, prof. dr. Durston, prof. dr. Kemner, dr. Oranje), Pediatric Neurology (e.g. dr. Dudink), and Neonatology (e.g. prof. dr. Benders, prof. dr. Hoebeek) have worked together in the disease area Developmental Disorders. In our research, we have addressed the direct and indirect consequences of genetic disorders, early life events and early brain injury, such as hypoxia, ischemia and encephalopathy of prematurity, as well as autism spectrum disorders (ASD), attention-deficit hyperactivity disorder (ADHD), and pediatric epilepsy. The research scope has encompassed multidisciplinary collaboration from fundamental neurobiology to clinical sciences. We have included various patient populations in longitudinal follow-up studies, and several thousands of patients are tracked in our clinics to monitor their brain activity, structure and behavior over development. Importantly, we have completed several state-of-the-art intervention studies with the aim to repurpose off-label medications for developmental disorders and to develop prognostic markers to optimize treatment allocation and prognosis. We collaborate widely within the UU and this multi-disciplinary research forms an important pillar of the UU strategic theme Dynamics of Youth.

Future developments

In the years to come, the Developmental Disorders disease area will continue to invest in multi-disciplinary approaches to aid the investigation of causes, consequences and cures of and for developmental disorders. Our involvement in the *KinderKennisCentrum* as well as the 'labelling' and '1001 critical days' programs with Dynamics of Youth underlines our continued focus on autism spectrum disorders, ADHD and pediatric epilepsy. In addition, we are adding new expertise from within the UMC Utrecht Brain Center: we will focus on the consequences of adverse early life events (e.g. brain injury, stress, pain, impaired sleep) on long-term brain development. Furthermore, we are now collaborating with investigators of the department of Rehabilitation to identify the optimal rehabilitation strategies for common behavioral, cognitive, learning, sensory, and motor problems seen in specific groups of children. Likewise we will explore future collaborations that will support patients with developmental disorders who have undergone neurosurgical interventions (e.g. cochlear implants, neurostimulation). Already we are including fundamental and translational research experts from the departments of Translational Neuroscience and Developmental origins of disease (DIDOD) in our team. These investigators have already developed various pre-clinical models including *ex-vivo*, *in-vivo* and *in-vitro* preparations (e.g., brain organoids from induced pluripotent stem cells and rodent models for encephalopathy of prematurity) that are fine-tuned to investigate causes, consequences and cures for a range of developmental disorders.

Organisational structure

Our structure is designed to facilitate collaboration across all focus areas. We are horizontally organized, with two PIs in the lead (prof. dr. Hoebeek & dr. Dudink), who facilitate the exchange of ideas and collaboration through a series of formal and more informal meetings (e.g., of disciplinary teams around EEG, animal models, clinical instruments, brain organoids), joint research proposals (e.g., AIMS), and joint masterclasses to address topics of broad interest.



We will meet in larger format once a month and there is a lively network of smaller meetings, enabling the integration of translation and clinical research with care programs.

An example of such interdepartmental collaboration is the Sensory Processing (SP) Program. This program takes an integrative 'trans-diagnostic' approach to the triage of developmental disorders across DSM nosology and comorbidities and has developed novel (patented) EEG biomarkers to support rational treatment allocations. The program closely collaborates with the department of Neurology and Neonatology to include a wide range of pediatric patients that suffer from sensory and cognitive information processing problems. A second example is our strategic research program that focusses on neuro-protective and -regenerative strategies (e.g., stem cell transplantation) and that has become a multi-disciplinary endeavor by combining research efforts of the departments for Developmental Origins of Disease, Translational Neuroscience and Neonatology, which has been recognized as the NFU expertise center for neonatal neurology. These examples underline that the collaborative efforts of clinical disciplines and biomedical research is imperative to the success of the developmental disorders research and care programs of the UMC Utrecht Brain Center.

2.2 Research projects with patient involvement

Sensory Patient Report Outcome Measure (PROM)

This project is a co-production between patients, caregivers, the Julius Centre, and the sensory processing (SP) program. With the possible advent of novel treatments, the need arises for good outcomes from the perspective of patients and/or caregivers themselves. Due to limitations in our current tools and questionnaires for ASD, we have developed a prototype patient-reported outcome measure (PROM) for problems arising from sensory difficulties and neural imbalances from the caregivers' perspective. The most important step in developing the prototype PROM was to ensure that the content represents the perspective of the respondents, in this case the parents or caregivers of children with ASD. For this purpose, we interviewed five focus groups of four parents/caregivers of children with ASD each to extract relevant topics for the PROM. We transformed into a pool of items and response options, leading to the pilot version of the PROM. To individualize the PROM, we asked the focus group respondents to prioritize the items into a restricted number of areas.

Reducing early life stress to optimize brain development

After preterm birth, infants spend a critical period for brain development in the neonatal intensive care unit (NICU) and are exposed to many stressful stimuli, which result in significant neurobiological changes: affecting brain volume, DNA methylation and the hypothalamic-pituitary-adrenal-axis. To study these effects we collaborate with local and (inter-) national colleagues, but also depend on parental involvement. We have set up a program to empower parents, called 'the VOICE' program. The parents are (1) educated, (2) trained in 'shared care' and (3) shared decision making. Parents are being structurally interviewed to get feedback on our care and research. Also, a neonatal 'parent board' has been created who provides input on new studies. Based on this input we are now conducting several studies with our national (Hippo-trial) and international research partners on how stress (e.g. painful procedures) and stress relievers (e.g. skin-to-skin care, sleep) influence brain connectivity. This research is complemented by animal models of early life stress embedded in the translational neuroscience and developmental origins of disease departments.

2.3 Key publications

1. [Ambrosino et al. What can Cortical Development in Attention-Deficit/Hyperactivity Disorder teach us about the Early Developmental Mechanisms Involved? *Cereb Cortex* 2017;27\(9\):4624-4634.](#)

This paper uses longitudinal structural MR data to compare brain development between children with and without ADHD. Different dimensions of cortical morphology, such as surface area and thickness, relate to different neurodevelopmental mechanisms. We found that subjects with ADHD had smaller overall cortical volume, predominantly driven by decreases in frontal lobe volume associated with reduced surface area and gyrification. Nearly all decreases were stable across development. These results suggest that ADHD is associated with developmentally persistent reductions in frontal cortical volume, surface area, and gyrification and implicate early neurodevelopmental mechanisms regulating cortical expansion and convolution in ADHD.



2. Bruining et al. Genetic Mapping in Mice Reveals the Involvement of Pcdh9 in Long-Term Social and Object Recognition and Sensorimotor Development. *Biol Psychiatry* 2015;78(7):485-95.

This paper is the results from an elaborate Dutch/Japanese collaborative project in which we reversed the traditional line of gene-to-behavior experimentation and performed a forward quantitative genetic analysis of elementary social behaviors in mice. Our aim was to identify the impact of ASD candidate genes on specific components of behavior and social functioning. We used a mouse genetic reference panel to detect quantitative loci affecting social recognition. We found that a gene, Protocadherin 9 (Pcdh9), is specifically needed for long-term social and object recognition. Through further functional, morphological, and behavioral studies across different developmental stages, we revealed that the Pcdh9 related recognition defects were not associated with memory problems but emerged with higher order sensory processing deficits.

3. Sarabdjitsingh et al. Ultradian corticosterone pulses balance glutamatergic transmission and synaptic plasticity. *Proc Natl Acad Sci U S A*. 2014;111(39):14265-70.

The adrenal hormone corticosterone is known to change hippocampal glutamate transmission for many hours. Corticosterone is normally released in hourly pulses, with steeply rising amplitudes just before awakening. This paper addressed how organisms can be prepared for imminent danger if the first high-amplitude corticosterone pulse lastingly changes glutamate transmission, thus potentially deadlocking the system. We showed that exposure of hippocampal cells to a second high amplitude corticosterone pulse completely normalizes all aspects of glutamate transmission (including synaptic plasticity), thus lifting the potential deadlock caused by a first pulse. This ensures full system responsiveness to any stressful event that requires encoding of information, an important principle that promotes survival of individuals.

4. Van Campen et al. Relation between stress-precipitated seizures and the stress response in childhood epilepsy. *Brain* 2015;138(Pt 8):2234-2248.

In this paper, we report how children with epilepsy and healthy controls were exposed to a standardized acute psychosocial stressor. We demonstrated an altered regulation of the hormonal stress response in children with stress sensitive epilepsy with a decreased cortisol response to stress compared to children without stress sensitive seizures and healthy controls. This suggests that seizure precipitating effects of stress are associated with dysregulation of the HPA axis and alterations of neurotransmitter balance and adds significantly to unraveling the biological basis for stress sensitivity of seizures.

5. Burbach. AUTISM. Unraveling a pathway to autism. *Science* 2016;351(6278):1153-1154.

This paper addresses the problem in research on autism spectrum disorders that genetic studies have pointed to hundreds of causative or susceptibility genes, making it difficult to find common underlying pathogenic mechanisms. Careful dissection of molecular and cellular mechanisms is needed to define the molecular targets that can translate into therapeutic strategies. The discussed study identifies a new pathway leading to autistic symptoms and develops a compound that is able to reverse symptoms in an animal model for (Shank3 deletion) through modulation of this pathway.

6. van Tilborg et al. Combined fetal inflammation and postnatal hypoxia causes myelin deficits and autism-like behavior in a rat model of diffuse white matter injury. *Glia* 2018;66(1):78-93.

This paper is the result of a long-term collaboration between the departments for Developmental origins of disease, Neonatology, and the division of Behavioral Neuroscience of the UU veterinary medicine faculty and describes the characterisation of a novel rat model for diffuse white matter injury (WMI) in preterm infants. The aim was to set up clinically relevant animal models to study diffuse WMI in the preterm brain. In the novel model, a double-hit of fetal inflammation and postnatal hypoxia was used and molecular, histological, and behavioral assessments revealed that the model mimics myelin deficits and behavioral aberrations, including autism-like behavior, commonly seen in preterm patients. This study opened a new pipeline of translational research for effectively testing therapeutic innovations for this patient group.

2.4 Most important contributions to society

Improvement of sleep for babies on the NICU

The main brain activity of babies is sleep. Sleep plays a major role in health early brain development and is often severely compromised in infants admitted to the intensive care. Their sleep stages are thought to be an important driver of brain development. The preterm newborn spends most of its time in 'active sleep' (REM sleep), which coincides with heightened synaptogenesis and brain plasticity. Furthermore sleep deficiency has major implications for older children with brain injury; contributing to the development or exacerbation of neurodevelopmental impairments and yet (as in vulnerable infants admitted on the NICU) it is an underemphasized aspect of health and development.



There is very little research evidence to guide the management of sleep disorders in children with cerebral palsy, a common neurodevelopmental disability of childhood. We set out to improve sleep for babies on the NICU, children in the hospital and children with cerebral palsy in the rehabilitation centers. Working together with several departments, parent organisations (e.g. BOSK) and grants (including a grant from ZonMW) we have set up a sleep awareness and improvement program.

We have been giving workshops and lectures for parents (Public information talks), have made patient materials (posters, website, programs), an online video (www.onlinedocu.nl), won the Dutch Hacking Health 2019 best Innovation Award and have been invited to the Dutch ministry of health to discuss public health guidelines on Sleep management. (www.kcrutrecht.nl/project/voeding-slaap-en-beweging/)

Labelling project

The practice of 'labelling' our children, giving children diagnostic classifications, such as ADHD and autism, is subject to controversy and public debate. On the one hand are researchers and clinicians pointing to the biomedical research literature to prove that such disorders are real and should be considered within the biomedical model, and on the other are clinicians and other stakeholders arguing that these are best considered social problems and we are medicalizing our youth by applying labels. The stakes are high, as such classifications are common and many children receive such a classification at some time during their development. Furthermore, the prevalence of these disorders is on the rise and the societal costs are huge. The 'labelling project' is a collaboration between researchers of the UMC Utrecht, other parties (Social Sciences, Humanities) within the UU Strategic Theme Dynamics of Youth and societal partners, such as youth health care institutions, local councils (who are charged with organizing the mental health care system for youth) and other stakeholders. It aims to place itself at the midst of the controversy and investigate what the connotations, both positive and negative, are of the practice of labelling our youth, depending on the goal, context and user of the label. In addition to aiming to ground this debate in science, we participate actively in it, by organizing focus groups for stake holders, giving public lectures for patient organisations and other special interest groups and publishing in the popular media. (www.uu.nl/en/research/dynamics-of-youth/research/interdisciplinary-themes/developmental-labels-the-good-the-bad-and-the-contested)

Table 3: Suggested research process indicators

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment

Mission

We aim for full understanding of child development, both typical and atypical, from inherent curiosity in order to improve care for children and their care-givers. To this end, we aim to conduct excellent and collaborative research on behavioral control and social competence, as well as on the developmental origins of disease. We focus on mechanisms, rather than on symptoms. Additionally, we focus on individuals and variation between individuals rather than on diagnostic categories.

Research questions

There is an unmet need for new treatments for developmental disorders, such as ADHD and autism, and for biomarkers. In response to this need, we are (1) running state-of-the-art imaging and clinical monitoring programs including follow-up studies to detect the earliest forms of abnormal brain development and its consequences at the National neonatal neurology expertise center; (2) we are developing programs to address the need for biomarkers and target treatments to individual problems, including in the Sensory Perception Program for autism in the department of psychiatry and the AIMS international consortium; (3) we are conducting fundamental and translational research to help to understand the causes and consequences of early life brain damage to direct the development and improvement of rehabilitation, neuro-regenerative and -protective cures in the translational neuroscience and developmental origins of disease departments.

3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

Throughout all departments involved in the developmental disorders disease area, the strategic research programs were designed partially based on systemic literature reviews and patient experiences. All departments and research teams have long-term collaborations with patient organisations (NVA, Balans, BOSK, VOC) and have attracted funding from societal funders (ZonMW, Hersenstichting and charity funds). For instance, the department of psychiatry created a '**research agenda**' or roadmap for developmental psychiatry focusing on sensory processing, 22q11DS, selective mutism, young children with behavioral problems. Sensory processing problems in children was listed in the top 10 of most urgent themes indicated in the national knowledge agenda of the Dutch Psychiatry Association. In addition, our research teams have frequently conducted systematic reviews on causes, consequences and potential cures of adverse early life events (e.g., Van Tilborg et al., 2016). Another example of how our research relates to existing knowledge and has societal impact is the **collaborative ZonMW** grant awarded to the department of Neonatology, in collaboration with rehabilitation experts from the Hoogstraat and patient organisation BOSK. This project will investigate which targets should be added to our outpatient follow-up program (e.g., sleep problems, eating disorders, physical activity).



3.3. Stakeholders are involved in formulating the main research questions

Stake holders are very important to our research. For example, in the AIMS consortium, half the budget comes from industrial and societal partners. In Dynamics of Youth, we rely on contacts with patient and caregiving organisations, as well as other societal stakeholders. For example, the parent organisation Balans is an advisor on the project and we are using focus groups to consult stakeholders. Patient groups were also consulted in formulating the research questions for AIMS2 (IMI) and for the National registry for tuberous sclerosis complex. In addition, various strategic research programs in the departments for Developmental origins of disease and Neonatology are funded by pharmaceutical companies (Chiesi, Nutricia), and tech-industry (ANT-Neuro, Phillips, Artinis, Eemagine)

3.4. The research questions are feasible and are pursued using optimal and efficient design

- We have strong statistical and methodological scientists within our teams, including world experts in the areas of machine learning, EEG and network analyses, as well as epidemiologists.
- We collaborate widely within international consortia where a wide range of expertise is available, including in AIMS (IMI), ENIGMA, TACTICS (FP7) and CID (NWO Gravitation Program).
- We consult with the UMC Utrecht Julius center if necessary, and three neonatology team members are qualified clinical epidemiologists and can be consulted for statistical and methodological support. The division Woman & Baby sponsored a position for a professor in the Julius Center for many years who provided extensive, top of the range bio-statistical support to our researchers.
- We have research office team members and data managers in our departments to ensure that our research is conducted according to the highest scientific standards. This includes according to European Privacy Laws.
- Investigators from developmental disorders are supported by U-TRIAL and the UMC Utrecht Trial and Data Center.

3.5. What is 'the next step' if the project delivers positive results

Users of research findings

We collaborate extensively with pharmaceutical companies, including Roche, Chiesi, Nutricia/Danone, Phillips, Eemagine, Artinis and Lundbeck and with clinical partners including nurses, rehabilitation experts (Hoogstraat expertise center) and yoga therapists, as well as practitioners within and outside the UMC Utrecht

Support for innovation and valorisation

For our business development, we collaborate with dedicated partners within the UMC Utrecht, such as the THINK initiative at the Julius Center. In addition we are supported by the startup incubator UtrechtInc.

Funding

We are funded by the Dutch governmental institutions, including NWO and ZonMW, the European Union (in H2020, FP7 and IMI programs), charities such as the Brain Foundation (Hersenstichting) and research contracts with private parties (companies like Chiesi, Nutricia/Danone).

Memberships

- We are member of a number of guideline committees and working groups, including the Dutch working group on postmortem examination, the Dutch working group on extremely preterm birth, the Dutch working group on post term birth, and the working group on benchmarking of Neonatology; various ILAE taskforces and committees (Epilepsy).
 - We underscore the importance of dissemination to a broad range of possible users, for each project there is a combination of strategies including as mentioned above.
 - We are involved in clinical (inter)national guidelines and benchmarking, such as NVOG, N3 and EFCNI and regularly invited for discussions with Dutch policymakers and EU panel discussions with EU research officers.
 - Our work is covered approximately 20 times a year in the general media or grey literature, such as in newspapers (Volkskrant, NRC), or by talk programs on television or radio.
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Table 4: Suggested output indicators

4.1 Research products for peers	1) Key publications <ul style="list-style-type: none">We have contributed to textbooks and published in top-tier journals, including in <i>J Pediatrics</i> (Weeke et al., 2018), <i>Neuron</i> (Schmidt et al., 2014, Kong et al., 2016), <i>Developmental Cell</i> (Van Erp, 2015), <i>Nature Communications</i> (Van Battum et al., 2014; Jongbloets et al., 2017), <i>Science</i> (Burbach, 2016), <i>Cer Cortex</i> (Benders et al., 2015, Ambrosino et al., 2017), <i>Glia</i> (van Tilborg et al., 2017, 2018), <i>Biol Psychiatry</i> (Bruining et al., 2015, Casey & Durston, 2014), <i>Brain</i> (Campen et al., 2015) & PNAS (Sarabdjitsingh et al., 2014) 2) Databases and clinical models <ul style="list-style-type: none">We have built a database of MR, genetic and cognitive data on close to 1000 subjects with ADHD, ASD and typically developing controls (prof. dr. Durston & the NICHE lab) as well as a unique deep-phenotyped cohort of more than 300 autistic children, some of which ex-prematurely born, with or without epilepsy (dr. Bruining, dr. Jansen, dr. Oranje, prof. dr. Benders) that will continue to participate in follow up studies and trials.Various pre-clinical models have been developed in the department for Developmental origins of disease (Nijboer). Various treatment options for grey and white matter damage in the developing brain have been investigated, a selection of which are now being tested in clinical trials led by the neonatology department (e.g., IGF-1 and stem cell treatments). 3) Dissertations <p>In total 21 dissertation were completed in the last five years: 2015 (3), 2016 (8), 2017 (5), 2018 (5).</p>
4.2 Research products for societal target groups	<ol style="list-style-type: none">We have contributed to national guidelines on the use of therapeutic hypothermia for hypoxic-ischemic encephalopathy and international neonatal brain MRI and ultrasound guidelines (e.g. Dutch Neonatal neuroimaging guideline, European Standards of Care for Newborn Health (EFCNI))We have given numerous public lectures, including a keynote address for <i>Balans</i>, parent organisation for children with developmental disorders and at the Dutch public health meeting and for other patient organisations and we have contributed columns to a major newspaper (Volkskrant) and our research has been used for arts exhibitions (BioComputation Robots https://annadumitriu.tumblr.com/robotics) and cinema documentaries (including 'are you there').We have provided an online dataset (https://phenome.jax.org/projects/Kas1), an online database mining tool to run tailor-made meta-analyses (https://vbonapersona.shinyapps.io/MaBapp/) and prediction tools to predict epilepsy and seizure recurrence (http://epilepsypredictiontools.info).
4.3 Use of research products by peers	<ol style="list-style-type: none">We have co-developed monitor analysis software called "SignalBase" and "BedBase" which allows time linked recording of multimodal monitoring data (e.g. EEG recordings, NIRS data, Heart rate, Oxygen Saturation etc). Using deep learning algorithms these time-linked recordings can be analysed in SignalBase (e.g. to use early biomarkers to predict long-term neurodevelopmental outcome of children born preterm). This is now being used by our researchers (including our researcher in the ADAM project). The software package is being acquired by other departments of the UMC Utrecht and by other Academic Medical Centers.We co-developed EEG tasks for a large European consortium (EU-AIMS) consortium and supervised their assessmentsOur research is widely cited by peers, with our top-researchers having h-indexes > 40 (prof. dr. Benders, prof. dr. Burbach, prof. dr. Pasterkamp, prof. dr. Durston, prof. dr. Joëls).
4.4 Use of research products by societal groups	<ol style="list-style-type: none">New guidelines for drug administration during therapeutic hypothermia were developed based on results of the "PharmaCool" study and the results of our pharmacokinetic analysis of sedatives and anticonvulsants have been adopted as new guidelines in the Kinderformularium (www.Kinderformularium.nl).The medical ethical committee (METC) of the UMC Utrecht provisionally accepted the use of EEG in clinical care for autism, representing a major step forward in bringing what was previously mostly a research tool towards clinical use.For pediatric epilepsy, we participated in developing a new classification of seizure types (dr. Jansen as member of the ILAE consortium 2017).



4.5 Marks of recognition from peers

- 1) **Multiple awards** (selection)
 - prof. dr. Durston was awarded the Golestan fellowship at the Netherlands Institute for Advanced Study in 2016/2017
 - dr. Bos was awarded the 2018 Samuel W. Perry III, MD Distinguished Award in Psychiatry Medicine by Cornell and Columbia Universities in New York City, where she did a fellowship
 - prof. dr. De Vries was awarded an honorary award of the German speaking society of child neurology (GNP)
 - prof dr. Joëls won the European Medal 2017 from the British Endocrinology Society. Joëls was the president of the federation of European neuroscience societies (FENS) from 2012-2014
- 2) We hold various (vice) chair positions in national and European neonatal (European Brain Club), neurology (ILAE), neuroscience (FENS, SFN) psychiatry (NVvP) and pediatric (ESPR) societies, underscoring our leading role in the developmental disorders fields
- 3) The neonatology department has recognized as a NFU (Dutch federation of universities) neonatal neurology expertise center.

4.6 Marks of recognition from societal groups

- 1) Prof. dr. Scheepers is a member of the Health Council (Gezondheidsraad) and prof. dr. Durston and prof. dr. Braun were members of the Gezondheidsraad committee on alcohol and brain development (2018/2019)
 - 2) Dr. Bruining is chair of the National Research Committee of the Dutch Association for Psychiatry (NVVP)
 - 3) Several of our PIs regularly participate in reviewing and advisory bodies that distribute societal funding.
-



3. UMC Utrecht Brain Center – Epilepsy

3.1 Mission, strategy, and organisation

Mission

Through internationally recognized and societally well-embedded translational research, our center adds to the improvement of the health of patients – particularly children – with refractory, complex, and rare epilepsies. We hope to be recognized as one of the leading European centers that combines excellent academic epilepsy care – in its broadest sense – with a comprehensive and well-integrated strategic research program. We aim to translate both basic science and patient-driven research questions into clinically applicable diagnostic methods, prediction tools, and novel treatment options.

Strategy

As a nationally (NFU) and internationally (ERN EpiCARE) endorsed center of expertise for rare and complex epilepsies, our strength lies in the multidisciplinary collaboration between basic/translational scientists and clinical epileptologists. We have a clinical focus on refractory epilepsy in the context of epilepsy surgery (for which the UMC Utrecht serves as the largest and oldest Dutch center, with national exclusivity for children) and on rare genetic pediatric epilepsies (with a longstanding and national expertise in the field of epilepsy genetics).

Within the program our focus lays on focal structural epilepsy (in particular focal cortical dysplasia) and monogenic epilepsy syndromes. The different methodological approaches that are used in the strategic research program are: 1) multicenter data collection; 2) outcome prediction modeling; 3) advanced EEG analysis, in particular networks and HFOs; 4) epilepsy surgery & presurgical diagnostics; and 5) (epi)genetics. Via these methodological areas of expertise we aim to improvement patient counselling and outcome prediction, presurgical decision making and patient selection, optimizing AED policies and personalized treatment, and developing novel therapies.

Organisation

The epilepsy research program is embedded in the UMC Utrecht Brain Center, in which the division of Neurosciences collaborates with different other divisions (in particular Pediatrics, Biomedical Genetics, Woman and Baby, Imaging). Researchers are working in several departments and groups: Child Neurology, Neurosurgery, Neurology, Neurophysiology, Medical Genetics, Center for Molecular Medicine, Translational Neuroscience, Psychiatry, Neonatology, Radiology, Biomedical MR imaging and spectroscopy, and Neuropsychology. The strategic research program is coordinated by prof. dr. Braun (Child Neurology), together with the thematic research group leaders; dr. Koeleman (Genetics), dr. Leijten (Neurophysiology), dr. Zijlmans (high frequency oscillations (HFOs)), prof. dr. Pasterkamp (Translational Neuroscience), and prof. dr. Benders (Neonatal Neurology).

3.2 Research projects with patient involvement

NightWatch®

NightWatch® is a medical device for home detection and alarming of nocturnal motor seizures, developed in the Netherlands from direct patients' needs. We started out with a consortium encompassing the whole epilepsy field, i.e. the epilepsy centers, the UMC Utrecht, and patients' and caregivers' representatives from three national patient's associations, institutions, and the Epilepsy Foundation. In the early phase of the design we had several rounds defining the different needs and expectations, with all parties involved (technical, medical, commercial, patients, caregivers, authorities). We published on this method of value-sensitive design (PlosOne 2015;10:e0121446) to provide an example to others. NightWatch was recently commercially released on the market and already in a few months, 500 have been sold. Currently we perform studies into the effect on wellbeing of the device with questionnaires that were developed together with users.

Clinical trial electrode implantation

At the moment we are preparing a clinical therapeutic trial for a relatively rare group of people with focal seizures arising from the primary motor cortex. These patients experience nasty motor seizures with limb jerking that are medically intractable and cannot be treated surgically without functional loss. We will test if responsive neural stimulation is a therapy, which includes implantation of electrodes directly on the brain and a pacemaker. People with this type



of epilepsy often have their own view on what constitutes 'function' of their involved limb and balance therapeutic risks in a way that is not predictable by neurologists. We published on our experience with these patients (Epilepsy Res 2017;130:37-46) to illustrate this. The project proposal and follow-up of the clinical trial has been designed, and will be evaluated, by a patient board consisting of three such patients who underwent unsuccessful epilepsy surgery.

3.3 Key publications

- 1) [Stevellino, Koeleman et al. ILAE Consortium on Complex Epilepsies; genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies. *Nat Commun* 2018;9:5269.](#)
The genome-wide association study performed by key analysts from our epilepsy genetics group and the "International League Against Epilepsy Consortium on Complex Epilepsies" uncovered 16 chromosomal risk regions for common epilepsies, leading to a set of candidate epilepsy genes that included current and potentially novel drug targets. The researchers found that the association signals clustered in regions containing known epilepsy genes and implicated regulatory sequences important for brain-specific gene expression. These findings provide important biological insights and possible avenues to develop personalised and precision therapies for patients with difficult and complex epilepsy.
- 2) [Lamberink, Otte, Braun et al. Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. *Lancet Neurol* 2017;16:523-531.](#)
Until recently, counselling patients who became seizure-free on medical treatment about the risk of seizure-recurrence after AED withdrawal was based on average risks from mixed populations (~34%). A total of 25 possible predictors of relapse had been reported before, but not systematically or simultaneously studied in a sufficiently large cohort. How these predictors would contribute to the recurrence risk in a single individual was unknown. With an IPD (Individual Participant Data) meta-analysis, based on data of 1769 patients from 10 previously published studies, we created nomograms for the individualized prediction of relapse risk and seizure-freedom after AED withdrawal, and made a calculation tool available online.
- 3) [Vangoor, Pasterkamp et al. Antagonizing increased miR-135a levels at the chronic stage of experimental TLE reduces spontaneous recurrent seizures. *J Neurosci* 2019 Apr 23. pii: 3014-18.](#)
miRNAs are post-transcriptional regulators of gene expression with roles in the pathogenesis of epilepsy. However, the precise mechanism-of-action and therapeutic potential of epilepsy-associated miRNAs remain poorly understood. Our study revealed dramatic upregulation of the key neuronal miRNA miR-135a in both experimental and human mTLE. Silencing miR-135a in experimental TLE reduced seizure activity at the spontaneous recurrent seizure stage. These data support the exciting possibility that miRNAs can be targeted to combat seizures after spontaneous seizure activity has been established. Further, by using unbiased approaches novel neuronal targets of miR-135a are identified that begin to explain how deregulation of miR-135a may contribute to epilepsy. The finding that miRNAs are targets to control seizure activity has been patented in collaboration with industry (InteRNA) and we are currently negotiating with industry for follow-up towards clinical application.
- 4) [van t Klooster, Leijten, Braun, Zijlmans et al. Tailoring epilepsy surgery with fast ripples in the intraoperative electrocorticogram. *Ann Neurol* 2017;81:664-676.](#)
This study shows that new biomarkers for epilepsy, 'fast ripples', recorded during surgery with intra-operative electrocorticography, predict post-surgical seizure outcome. Nine out of twelve patients, in whom fast ripples remained after the resection, had persistent seizures. These findings hold great promise for the use of HFO-based electrocorticography to tailor resective epilepsy surgery. They form the basis for the UMC Utrecht initiated HFO trial, comparing tailoring based on HFOs versus spikes.
- 5) [van Campen, Jansen, Otte, Joels, Braun et al. Relation between stress-precipitated seizures and the stress response in childhood epilepsy. *Brain* 2015;138:2234-2248.](#)
In this paper we report how children with epilepsy and healthy controls were exposed to a standardized acute psychosocial stressor. We demonstrated an altered regulation of the hormonal stress response in children with stress sensitive epilepsy with a decreased cortisol response to stress compared to children without stress sensitive seizures and healthy controls. This suggests that seizure precipitating effects of stress are associated with dysregulation of the HPA axis and alterations of neurotransmitter balance and adds significantly to unravelling the biological basis for stress sensitivity of seizures.



3.4 Most important contributions to society

Seizure relapse prediction tool (www.EpilepsyPredictionTools.info)

About two-thirds of people (children and adults) with epilepsy reach seizure control with antiepileptic drugs (AEDs). At some point most of them wish to know if – and when – discontinuation of AEDs is an option. In a subset of children, who have so-called benign-course epilepsy, the disorder will subside when reaching adulthood, but for many others it remains uncertain if AEDs are still needed after having been seizure-free for a certain period of time. When counselling these patients, the possible risks of AED discontinuation should be carefully balanced against the benefits of withdrawal. Particularly in adults, a seizure recurrence can have detrimental effects on professional and driving abilities. On the other hand, successful discontinuation of AEDs will “cure” them from epilepsy, which improves their quality of life. In children, withdrawal-associated recurrences probably have less psychosocial impact and drug-withdrawal has been proven to improve cognitive abilities. Until recently, the only way to counsel patients was to provide them with group-averaged cumulative relapse risks over time (around 35%). Although many possible predictors of relapse had been reported in the literature, how each of these independently contributed to the risk in an individual patient remained unknown, hampering precise informing of patients on their individual relapse risks.

After approaching authors of previously published cohort studies on recurrence following AED withdrawal, we were able to collect data of 1769 patients from 10 studies, which allowed a so-called “Individualized Participant Data” (IPD) meta-analysis, to determine the independent predictive value of previously reported outcome determinants, and to produce nomograms for the calculation of an individualized risk in a single patient. This prediction model was published in *Lancet Neurology* (2017), and a calculation tool was made available online, with free access for medical doctors and all others interested in the topic. With this simple tool, each patient who considers AED withdrawal can be informed on his or her individualized relapse risk and eventual chance of being seizure-free, which allows a much better balanced decision making process. For all neurologists who treat and follow people with epilepsy, this tool can be useful in everyday clinical practice. After its publication, the tool has been accessed >12.000 times in two years. Many international journals have positively commented on the prediction model, and we have received invitations to present this work at several European and worldwide epilepsy congresses. Since the development of this model, we have published two other epilepsy prediction models, both also available on the same website, to predict individualized risks of seizure relapse following postoperative AED reduction in children, and the chance of have the diagnosis “epilepsy” after a first event in children.

NightWatch®

NightWatch® is a medical device for home detection and alarming of nocturnal motor seizures, developed from direct patients’ needs. The idea was to use non-EEG sensors which can be easily applied by parents or caregivers at home. The device was developed with all parties involved in epilepsy in the Netherlands. After extensive clinical testing in the hospital, we ended up with a small device that can be worn around the upper arm during the night that contains motion detectors and detects heart rate. The device has been tested outside the hospital and is now the most reliable device for seizure detection. A commercial firm (LivAssured) was founded after a few years to develop a prototype for commercial use. Private investors and hedge funds have invested 20 M euro to earn CE and take it in production. Successful crowd funding has ensured the first home trial users to be able to keep the first version of NightWatch. NightWatch was recently commercially released on the market and already in a few months, 500 have been sold. Currently we perform studies using NightWatch in young children and special groups. We are also developing new seizure detection methods, based on automated video-frame and audiological analysis as an alternative, especially when wearing a device on the body constitutes a problem. NightWatch will soon be launched on the German market and we are preparing FDA approval. In the meantime, we await the outcome of an application to have NightWatch re-imbursed by Dutch health insurance.



Table 3: Suggested research process indicators

<p>3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment</p>	<p>Mission Through internationally recognized and societally well-embedded translational research, our unit adds to the improvement of the health of patients – particularly children – with refractory, complex, and rare epilepsies.</p> <p>Research questions As a nationally (NFU) and internationally (ERN EpiCARE) endorsed center for rare epilepsies, the UMC Utrecht epilepsy unit aims to:</p> <ul style="list-style-type: none"> • unravel genetic and epigenetic causes of epilepsy; • develop novel therapeutic targets; • find biomarkers and predictors of outcome; • improve presurgical evaluation and decision-making. <p>The UMC Utrecht has national exclusivity in – and is one of the largest European centers for – pediatric epilepsy surgery, and is the only Dutch ERN EpiCARE center. The unique collaboration between basic scientists and clinical epileptologists – together with the affiliated epilepsy center SEIN – ensures a translational research program that is directly driven by healthcare-related needs, in order to improve diagnosis and treatment of epilepsy.</p>
<p>3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made</p>	<p>Members of the UMC Utrecht epilepsy team have initiated – or contributed to – several recent international systematic review projects and meta-analysis studies, and are well aware of existing scientific knowledge (gaps) and of all up-to-date clinical diagnostic and treatment options. As a core center of the ERN EpiCARE and member of its steering committee, we participate in the harmonisation and dissemination of current best practices in epilepsy care. Our team members are frequently invited plenary and session speakers at international conferences and courses.</p> <p>Our participation in large EU-funded research projects and our large clinical experience in epileptology, both guarantee a research program that is driven by clinical needs, and aimed at improving clinical care. Being a key partner in several European and world-wide research consortia, we closely follow – and contribute to – the international epilepsy research agenda.</p>
<p>3.3. Stakeholders are involved in formulating the main research questions</p>	<ul style="list-style-type: none"> • Members of our clinical and research team regularly meet with the Dutch patient representatives organisation (EVN), the Dutch Epilepsy Fund, the Dutch Tuberosus Sclerosis Foundation, the Dutch Dravet society, the “Zie” foundation. We annually meet with parents who have donated to part of our research resources. • Our group members regularly teach and present at national patient information and education conferences, e.g. a yearly empowerment meeting for patients and parents who are evaluated for epilepsy surgery. • In the “NightWatch” project, patients and caregivers have been closely involved in the development of a user-friendly and reliable nocturnal seizure detection system (a product that is now on the market). • In almost all recently funded research projects, patients were involved in formulating the questions and design of the study. Furthermore, projects funded by the Epilepsy Foundation were evaluated and commented on by an expert patient panel, before being granted. <p>Apart from patients/parents and patient organisations, four examples of other stakeholders that are closely involved in our projects:</p> <ol style="list-style-type: none"> 1) SEIN (Stichting Epilepsie Instellingen Nederland) one of the two large Dutch epilepsy centers, closely collaborating in epilepsy and epilepsy surgery care, and in epilepsy research, with the UMC Utrecht 2) the SME “LivAssured” (created specifically for the valorisation of the NightWatch seizure detection system) 3) “Inomed”, a German neuromonitoring SME, and the medical industrial design company; “Productzaken”, involved in the development of “EpiSign” a per-operative online signal detection and evaluation system to guide the localisation of the epileptogenic zone during epilepsy surgery 4) “InterNA” is a technological company to develop miRNA therapeutics
<p>3.4. The research questions are feasible and are pursued using optimal and efficient design</p>	<ul style="list-style-type: none"> • We have a structural collaboration with an epidemiologist / methodologist, who assists in data-analysis of our epilepsy projects and supervises the development of prediction models. In addition, our researchers have easy access to the expertise of the Julius Center in the UMC Utrecht. • Our RESCUE ESES trial has received extensive methodological and financial support from ECRIN (European Clinical Research Infrastructure Network). • Quality and safety control, ethical approval submission, study monitoring, and general research support is provided by research staff members of the UMC Utrecht Brain Center.



3.5. What is 'the next step' if the project delivers positive results

Users of research findings

- SME "LivAssured" is a close collaborator in the Nightwatch project (product development, valorisation, commercialisation)
- the clinical epilepsy prediction models (for epilepsy diagnosis after a first seizure, for seizure relapse after AED withdrawal, and for outcome following postoperative AED withdrawal) are made available as online tools at: www.epilepsypredictiontool.org for users (epileptologists worldwide). The AED withdrawal tool has been visited 12.000 times in the past 2 years.
- "InterNA technologies" is a company that uses miRNA-based therapeutics to find treatments for epilepsy, in collaboration with Pasterkamp.
- Medtronic is involved in our intracranial closed-loop stimulation system for central lobe epilepsy

Support for innovation and valorisation, see above and:

- LivAssured
- InterNA
- Medtronic
- Inomed
- Productzaken

Funding

Our projects have received funding from a broad range of national and international, public and private funds (e.g. the Dutch Epilepsy Fund, ERC, ZonMW/NWO, Brain Foundation, EU funded E-PILEPSY / EpiCARE (ERN), FP7 projects [EpiStop, EpiMiRNA], Marie-Curie ITN [circRTrain], private patients' donations, crowd-funding projects, etc.)

Memberships

Members of our team are (or have been) members of:

- ILAE committees and task forces (e.g. seizure classification, evidence-based epilepsy surgery, big-data, EpilepsyDiagnosis.org, and the next generation task force)
- a panel of European experts to produce recommendations for epilepsy treatment in tuberous sclerosis complex
- scientific advisory boards (e.g. Dutch Epilepsy Fund, WKZ Fund)
- steering committees of international consortia (and taskforce leaders), e.g. ERN
- Epicare, pilot-ERN E-PILEPSY, EpiStop, EpiMiRNA
- The Dutch Health Council (Gezondheidsraad)

Our work has been covered in general **media**:

- Newspapers ("de Telegraaf", intelligence improves after postoperative AED withdrawal, 28-9-2015, Braun; "de Telegraaf", epilepsy surgery in children, 28-6-2014; "de Volkskrant" 15-7-2017, van Eijnsden)
- National radio ("Met het oog op morgen", 7-2-2016, Braun; BNR radio, "epilepsy gene discovery", 10-12-2018, Stevelink; BNR radio, "Betere medicinale behandeling epilepsie" 11-2-2019, Koeleman)
- National television ("Geef om je hersenen" [care about your brain], 27-3-2019, van Eijnsden/Zijlmans)

Epilepsy research results are regularly presented during invited (plenary and platform) talks at national and international professional congresses, such as IEC, ECE, EPNS, ICNA, AES, and during many teaching courses.

Our team members regularly present at national patient-organisation's teaching/educational symposia (e.g. yearly EVN epilepsy surgery meeting)

A recent PR campaign about the UMC Utrecht epilepsy work (clinical and research), including infographs, interviews, talks, has been linked to the website of the Dutch Epilepsy Patients' Society (EVN)



Table 4: Suggested output indicators

4.1 Research products for peers

1) Key publications:

- Stevelink, Koeleman et al. ILAE Consortium on Complex Epilepsies; genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies. *Nat Commun.* 2018;9:5269.
- Lamberink, Otte, Braun et al. Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. *Lancet Neurol.* 2017;16:523-531.
- Vangoor, Pasterkamp et al. Antagonizing increased miR-135a levels at the chronic stage of experimental TLE reduces spontaneous recurrent seizures. *J Neurosci.* 2019 Apr 23. pii: 3014-18.
- van t Klooster, Leijten, Braun, Zijlmans et al. Tailoring epilepsy surgery with fast ripples in the intraoperative electrocorticogram. *Ann Neurol.* 2017;81:664-676.
- van Campen, Jansen, Otte, Joels, Braun et al. Relation between stress-precipitated seizures and the stress response in childhood epilepsy. *Brain* 2015;138:2234-2248.

2) development of three clinical epilepsy prediction models

The prediction tools have been made available as online calculation tools (www.epilepsypredictiontools.info). Furthermore, Pasterkamp's group has a patent related to a miRNA molecule relevant in the diagnosis/treatment of epilepsy.

3) 12 dissertations in the field of epilepsy during the last 5 years

(Peeters, van Campen, van Diessen, Boshuisen, van Schooneveld, Meekes, Braams, van t Klooster, de Lange, Verbeek, van Klink, van Erp). The coming year, another five dissertations are expected.

4.2 Research products for societal target groups

- 1) The **Nightwatch** has been developed by a multicenter Dutch consortium that involved members of our team (Leijten). This wearable nocturnal seizure detector is user-friendly and reliable, and has become a CE-marketed commercially available product that has been sold over 500 times.
- 2) We have produced several **systematic literature reviews** for the E-PILEPSY European pilot reference network, aimed to harmonize presurgical evaluation and increase access to epilepsy surgery throughout Europe. These reviews, as well as several published E-PILEPSY surveys, will form the basis for the development of future recommendations (topics: EEG/MEG source localisation, high-field MR imaging and MR sequences, long-term video-EEG monitoring, language/memory function lateralisation, invasive monitoring), and they are used for policymaking throughout Europe. Furthermore, being member of the steering-committee of ERN **EpiCARE**, part of our activities are aimed at improving diagnosis and treatment for Dutch patients with rare and complex epilepsies, through national and international care networks.
- 3) Several of our researchers have been invited to report on their activities in **national television and radio** broadcast programs (see table 3.5). We also regularly lecture at **patients' organisation** (advocacy groups) **educational meetings** (e.g. EVN epilepsy surgery days, tuberous sclerosis complex expert network meetings). In addition, Dr. Jansen is a member of BRES (broad signaling consultation and partnership epilepsy), the Netherlands knowledge center for pharmacotherapy in children, and of the Dutch TSC expert network. Prof. Braun has served as a member of the Dutch League Against Epilepsy board. Prof. Pasterkamp and prof. Braun were members (and chair) of the scientific advisory board of the Dutch Epilepsy Fund. Prof. Pasterkamp and Dr Zijlmans are members of the scientific advisory board of the foundation "Friends of the UMC Utrecht".

4.3 Use of research products by peers

- 1) Our **online seizure recurrence calculation tool**, to predict individualized recurrence risks after AED withdrawal, has been used worldwide over 12.000 times over the last 2 years (~25 times per day)
- 2) The unique concept and design of the **UMC Utrecht HFO trial**, comparing the use of spikes versus HFOs for tailoring of resective epilepsy surgery, and the large UMC Utrecht experience in the field of HFO analysis, has led to the participation in an international trial, initiated by UCLA, and in an European MEG HFO study
- 3) Since its publication, the relapse **risk prediction model** has been requested to be used in order to be validated in 2 other large patient cohorts (Italy, China)

4.4 Use of research products by societal groups

- 1) The new insights regarding **safety and benefits of early postoperative AED withdrawal in children** – provided by our European TimeToStop studies (*Lancet Neurol* 2012, *Ann Neurol* 2015) – have led to an important change in drug withdrawal policies worldwide, particularly in Europe. Parents and doctors start withdrawal much earlier than the previously recommended 2 years after surgery.
- 2) New knowledge, based on studies we participated in, has been (or will be) implemented in the **update of existing epilepsy guidelines** (e.g. the new ILAE classification is included in the Dutch Society of Neurology guidelines on epilepsy, and the results of the EpiStop trial will be included in the TSC guidelines).
- 3) The development of the **NightWatch** seizure detection device has enabled the design of clinical trials using domotics, in which the entire Dutch epilepsy field can participate.



4.5 Marks of recognition from peers

- 1) large research grants:
 - 1.5 M euro ERC grant for Dr. Zijlmans
 - 0.5 M euro ZonMW grant for Dr. Koeleman and Prof. Braun
 - 1.5 M euro VICI grant to Prof Pasterkamp
- 2) invited lectures at large international meetings; several of our researchers are regularly invited to present their results at plenary, platform or teaching sessions of (epilepsy-related) meetings, e.g. European Congress of Epileptology, International Epilepsy Congress, European Paediatric Neurology Society meeting, International Child Neurology Congress, American Epilepsy Society
- 3) Our researchers are (and have been) members of several scientific committees (scientific advisory board Dutch epilepsy fund, WKZ research fund, Friends of UMC fund, ZonMW), and of editorial boards (Epilepsia Open, Epileptic Disorders)

4.6 Marks of recognition from societal groups

- 1) Public prizes**
 - Dr. Boshuisen has received the Harry Meinardi best thesis prize of the Dutch Epilepsy Foundation
 - Dr. van Campen received the Jacobus Willemse prize of the Dutch Paediatric Neurology Society
 - Drs. Hulshof was granted the Linda de Meirleir award by the European Paediatric Neurology Society
 - 2) Funding**
 - Parents of 2 children with epilepsy donated 1.3 M euro to prof. Braun's team to fund epilepsy genetics research.
 - The ESES and TSC epilepsy projects received additional funding from parents' initiatives through the "Friends of the UMC Utrecht" fund
 - The NightWatch project received additional funding by means of crowdfunding
 - 3) Advisory bodies**
 - Prof Braun was member of the Health Council (Gezondheidsraad) committee on alcohol and the developing brain
-



4. UMC Utrecht Brain Center – Neuromuscular disorders

4.1 Mission, strategy, and organisation

Mission

Our mission is to provide excellent clinical care for patients with all forms of neuromuscular disease (in all age groups) and perform outstanding research (Top 5% in Europe) on motor neuron disease and neuropathy.

Our research focusses on 2 topics in particular: 1) motor neuron disease and 2) neuropathy. Motor neuron diseases are a heterogeneous collection of disorders that may affect patients of all ages. In childhood, spinal muscular atrophy (SMA) is the most common disease and is one of the main areas of focus within our group. In adult patients, we focus on amyotrophic lateral sclerosis (ALS), which is the most frequent type of MND as well as primary lateral sclerosis (PLS) and progressive spinal muscular atrophy (PMA) which appears to be closely related. The SMA and ALS groups both perform research on a wide range of topics that are in line with the mission of the UMC Utrecht Brain Center, including genetics, molecular biology, clinical studies, biomarker research, neuroimaging, clinical trials and quality of life. Within the neuropathy group the focus is predominantly on immune-mediated forms of the disease, such as multifocal motor neuropathy (MMN) and IgM M-protein associated neuropathies. Here, the focus lies on improving diagnostics using novel electromyography and imaging techniques. There is also a focus on unravelling the etiology of axonal neuropathies of unknown cause, designated as chronic idiopathic axonal neuropath (CIAP).

Strategy

We believe that patients are the best model of any disease. All research is therefore based on patient-derived data and patient material. Furthermore, we believe that the outcome of our research projects should always benefit patients and thus there is a strong emphasis on translation, clinical implementation, and valorisation. As our research is patient-centered, seeing patients is crucial to our success. In order to attract the patients within our areas of focus, it is necessary to provide high-level clinical care to patients with all forms of neuromuscular disease. Only by doing so, have we managed to have the largest clinical databases worldwide on SMA, PLS, PMA, ALS, MMN, MGUS, and CIAP. Furthermore, we believe that the quest for effective treatments for these disorders can only be achieved by collaboration. We therefore have extensive collaborations with other groups within our institution as well as internationally.

Organisation

The organisation of the disease area Neuromuscular Disorders aligns with our strategy. We are organized in a number of main pillars; clinical care for all neuromuscular diseases, allowing the collection of large cohorts of patients within our areas of focus (separate research pillars for ALS, neuropathy and SMA). As patient collaboration is crucial, we closely interact with numerous patient organisations. We have extensive and highly fruitful collaborations with our rehabilitation physicians as well as the department of neuro-imaging. We are a part of Neuromuscular Disease Netherlands (national collaboration of neuromuscular disease centers) and we are part of multiple, international consortia (Project MinE, Euro motor, TRICALS, etc.). Many of these consortia are also led by our group.

The disease area Neuromuscular Disorders has multiple PIs on different topics and in different divisions of the UMC Utrecht and (inter)national collaborations:

Department of Neurology & Neurosurgery

dr. Ludo van der Pol (SMA, inflammatory neuropathies, MMN), co-PI: dr. Wadman (SMA), dr. Groen (SMA), Prof. dr. van den Berg (director of National ALS center, inflammatory neuropathies, MMN), Prof. dr. Veldink (genetics and epidemiology, ALS), dr. van Es (genetics, cognition, clinical trials ALS), dr. Peters (epidemiology ALS), Prof. dr. Notermans (CIAP, IgM M-protein associated neuropathy), dr. Goedee (neuro-imaging neuropathy), and dr. Vrancken (TTR amyloidosis).

Department of Translational Neuroscience

Prof. dr. R.J. Pasterkamp (ALS), co-PI: dr. Zelina (translational research ALS), dr. Pasteuning (stem cell modeling ALS).

Department of Rehabilitation

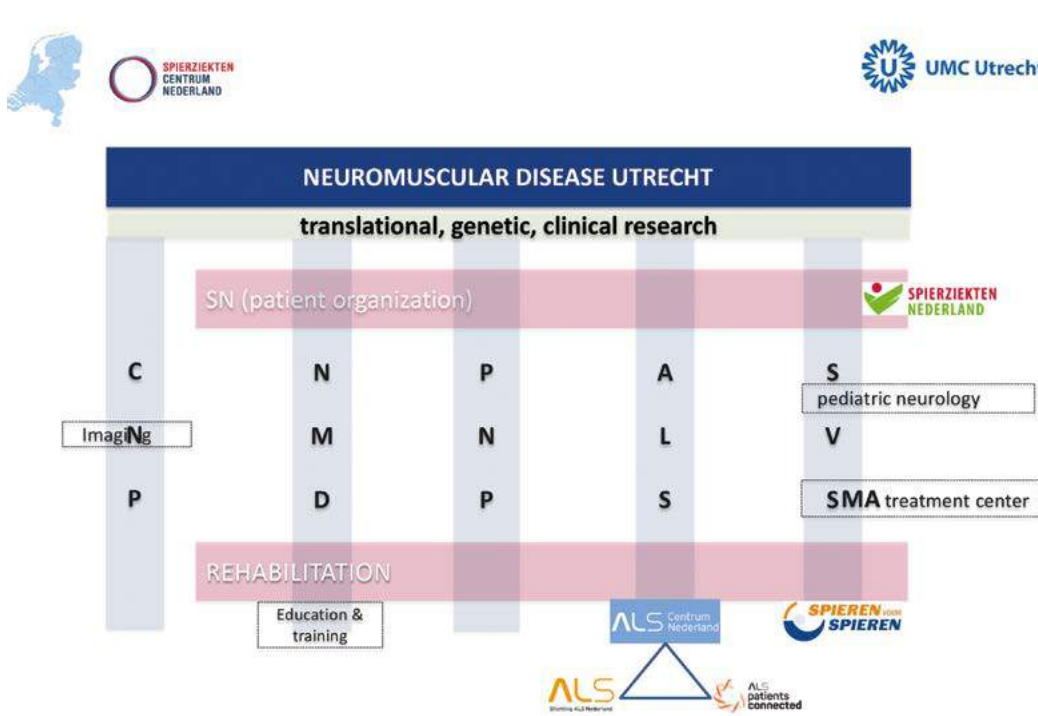
Prof. dr. Visser-Meily, dr. Beelen, and dr. Kruitwagen (e-health, clinimetrics, quality of life, care innovation).



Collaborations

- ALS: epidemiology with IRAS (prof. dr. Vermeulen), imaging with the department of Radiology UMC Utrecht and VUMC (dr. van den Heuvel and prof. dr. Hendrikse, 7T MRI group). Internationally with King's college London, SiTRAN Sheffield UK, Trinity College Dublin, Ireland; University of Turin, Italy; multiple groups in Milan, Italy; University of Tours, France; University of Oxford, UK; VIB Leuven, Belgium; and several groups in the US (Umass, NIH, UCSD), Consortia: Project MinE, TRICALS, Euomotor, TOTALS, RNA-NEURO, MAXOMOD, INTEGRALS, RESCUE.
- Neuropathy: IgM M-protein-associated neuropathy with MUMC (Perionoms) and inflammatory neuropathies (AMC, Erasmus MC).

A graphical overview of our organisational structure and collaborators is provided below.



CNP: clinical neurophysiology, NMD: neuromuscular disease, PNP: polyneuropathy, ALS: amyotrophic lateral sclerosis, SVS: Spieren voor Spieren, which is the pediatric neuromuscular clinic, SMA: spinal muscular atrophy, SN: Spierziekten Nederland, which is the national patient organisation for all neuromuscular diseases.

4.2 Research projects with patient involvement

Patients are involved in all research within the disease area Neuromuscular Disorders. There are regular meetings, patients are part of steering committees, are involved in designing studies, provide feedback on study protocols, become ambassadors of projects, and help educate the general public alongside researchers and physicians. Additionally, there are regular meetings with patient organisations. In short, patients have really become full partners in our projects. There are several projects that we wish to point out in particular.

TRICALS

TRICALS is an international trial consortium, with partners from across Europe and Australia, with the aim to revolutionize the way trials are performed in ALS. At present approximately 4% of ALS patients are offered the possibility to enroll in a trial. While patient organisations and advocacy groups indicate that over 80% would like to participate in these studies. The aim of TRICALS is therefore to offer all ALS patients to possibility of enrolling in a trial by redefining eligibility criteria, simplifying outcome measures, initiating and performing investigator-initiated studies as well as partner with the pharmaceutical industry. Multiple patients have become ambassadors for this project and TRICALS is supported by both national and international patient organisations, such as EUPALS, ALS patients connected and the Motor Neurone Disease Association.



PHALS trial

In the spring of 2017 a case series was published in which it was reported that patients with ALS experienced spectacular improvement in response to treatment with penicillin G and hydrocortisone. Considering both drugs are freely available more and more patients were started on this regimen. Given that providing this treatment was not without controversy and the huge unmet need for effective drugs in ALS, we performed an investigator-initiated placebo-controlled trial with penicillin G and hydrocortisone in ALS. Patient organisations (ALS patients connected and Spierziekten Nederland) were involved in every aspect of this important study, from grant review to providing feedback on the treatment protocol as well as during the course of the trial.

Project MinE

This is an ambitious international project, led by the UMC Utrecht Brain Center, aiming to collect and whole genome sequence the DNA of at least 15,000 ALS patients and 7,500 controls, while adding data from external projects. Project MinE is a foundation where all crowd-funded donations are being processed in order to pay for the whole genome sequencing. The board of Project MinE includes 2 ALS patients and 1 relative of an ALS patient. They also contribute actively to the project based on their own professional expertise, for example by contributing to financial management of the foundation or the acquisition of new funding. All Project MinE data is FAIR (findable, accessible, interoperable and reusable) as we strongly believe that scientific data needs to be shared as soon as possible to the wider scientific community, while preserving privacy regulations.

Innovative ALS Care using e-health technology

In 2016, ALS Home monitoring and coaching was developed, in co-creation with patients and health care professionals, as a new care concept for personalized ALS-care. Key features of ALS Home-monitoring and Coaching are: 1) app-based self-monitoring of body functions and symptoms, 2) alerts, 3) follow-up by nurse practitioner and 4) on-demand support from the multidisciplinary ALS-team. The user-friendly ALS-app runs on a smartphone, tablet and personal computer. Currently ALS Home monitoring and Coaching is only available for patients from the ALS-team of UMC Utrecht but a nationwide implementation of this innovative e-health care within the Dutch ALS Care network (with 34 specialized ALS-care teams) is in preparation, which will make personalized ALS care available to all ALS patients in The Netherlands.

4.3 Key publications

1. [Kenna et al. NEK1 variants confer susceptibility to amyotrophic lateral sclerosis. *Nat Genet.* 2016 Sep;48\(9\):1037-42](#)
To identify genetic factors contributing to ALS, we conducted whole-exome analyses of 1,022 index familial ALS cases and 7,315 controls. Using novel gene-burden analyses, we identified loss-of-function variants in NEK1 as a risk gene for ALS. Independently, autozygosity mapping in a Dutch genetic isolate also identified NEK1. Replication analyses in sporadic ALS and independent controls confirmed the association (>10,000 samples analyzed). In total, NEK1 risk variants are observed in nearly 3% of ALS. NEK1 has been linked to cilia formation, DNA-damage response, microtubule stability, neuronal morphology and axonal polarity. Our results provide new insights into ALS etiopathogenesis and genetic etiology.
2. [van Rheenen et al. Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. *Nat Genet.* 2016 Sep;48\(9\):1043-8.](#)
To elucidate the genetic architecture of ALS and find associated loci, we assembled an imputation reference panel from whole-genome-sequenced patients and controls (n=1,861). Through association analysis in 12,577 cases and 23,475 controls, combined with 2,579 cases and 2,767 controls (replication cohort), we fine-mapped a new risk locus on Chr21 and identified C21orf2 as the associated gene. Additionally, we identified MOB1 and SCFD1 as new risk loci. We show that ALS is a complex genetic trait (SNP-based heritability: 8.5%) with polygenic architecture primarily due to low-frequency variants (frequency 1-10%). This study justifies focusing on whole-genome-sequencing to unravel the genetics of ALS. This publication is award for best neuromuscular publication of the year in 2017 by Spierziekten Nederland.



3. [Westeneng et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalized prediction model. *Lancet Neurol.* 2018 May;17\(5\):423-433.](#)

The prognosis of patients of ALS is highly variable, with some patients within months of onset to those who live >10 years. The variability leaves patients in a lot of insecurity about their future. We therefore aimed to generate a model that could reliably predict survival. In a large-scale international study (>10,000 cases) with partners from across Europe, we developed and validated such a model with excellent test characteristics using only clinical data that is available at the moment of diagnosis. This model provides patient an accurate prognosis, aids in planning clinical care and has broad utility in clinical research. This publication is award for best neuromuscular publication of the year in 2018 by Spierziekten Nederland.

4. [Harschnitz et al. Autoantibody pathogenicity in a multifocal motor neuropathy induced pluripotent stem cell-derived model. *Ann Neurol.* 2016 Jul;80\(1\):71-88.](#)

Using iPSC-derived Motor Neurons (MNs), we studied the binding of IgM to MNs, their complement-activating properties, and effects on structural integrity. IgM antibody binding to MNs was detected using sera from cases with and without detectable anti-GM1 IgM-antibody titers, but not with control-serum. Competition and depletion experiments showed that antibodies specifically bound to GM1 on iPSC-derived MNs. Binding disrupted calcium homeostasis by both complement-dependent and complement-independent pathways. MNs showed marked axonal damage after complement activation, and reduced antibody pathogenicity following treatment with immunoglobulin preparations. We demonstrate the pathogenicity of anti-GM1 IgM-antibodies in MMN.

5. [Goedee et al. Diagnostic value of sonography in treatment-naive chronic inflammatory neuropathies. *Neurology* 2017 Jan 10;88\(2\):143-151.](#)

The diagnosis of inflammatory neuropathy is based on extensive and complicated nerve condition studies that require experienced neurophysiologists. We therefore aimed to study whether this diagnosis could also be made with accuracy using simple and reproducible methods. This study provides Class II evidence that, in absence of clinical features that suggest a hereditary demyelinating neuropathy, sonographic enlargement of proximal median nerve segments and brachial plexus accurately identifies patients with chronic inflammatory neuropathies.

4.4 Most important contributions to society

Spinraza

In December 2016 Spinraza was approved for the treatment of SMA. Our group, dr. van der Pol in particular, played a huge role in providing Dutch patients access to this ground-breaking treatment. This involvement includes extensive discussion with our hospital board, regulators, and insurance companies. This highly effective treatment for this otherwise lethal neuromuscular disease that affects very young children is provided by our group. We are the national treatment center for SMA.

Although this development poses a major advance for patients with SMA, the costs associated with this treatment are very high (hundreds of thousands of euros per patient per year). This also raises the question of how we as a society deal with the raising costs of targeted, novel treatments. As a group, again dr. van der Pol in particular, played a large and important in the public debate on this topic.

Dextromethorphan and quinidine (DM/Q) treatment

In the summer was 2017, a study was published that showed that bulbar symptoms in ALS patients could be alleviated by treatment with Neudexta. This treatment was subsequently approved by the EMA and FDA. Despite obtaining marketing authorisation the pharmaceutical company that sells Neudexta opted to not sell the drug on the European market. Therefore, this highly relevant treatment option did not become available to our patients. Neudexta is however a combination of two existing drugs, namely dextromethorphan and quinidine (DM/Q). This means that a pharmacist can also prepare this formulation. We therefore sought out options to make this treatment available to patients in The Netherlands. After extensive discussion we now have a structural collaboration with the Transvaal apotheek in The Hague. This pharmacy makes capsules containing dextromethorphan and quinidine and ships to patients. As we are the national ALS center and see 90% of all patients in The Netherlands, we are able to guarantee a steady flow of prescriptions to the Transvaal apotheek, allowing them to drop the price as well as allocate staff to preparing DM/Q. This also ensures patients have rapid access to the drug. We are currently in process of getting the treatment reimbursed.



Both the Spinraza and the DM/Q story illustrate how the disease area Neuromuscular Disorders is dedicated to providing our patients with the best possible treatment. This is done by implementing results from research into clinical practice and by working with patient organisations, insurance companies and government agencies. We also achieve this goal by creative solutions as well as by discussion in the media and illustrating the relevance of these dilemmas in general.

E-Health services for patients with ALS

Since 2016, several e-Health services have been established to optimize care for patients with ALS. This includes ALS Home Monitoring and Coaching in which patients are monitored at home with respect to body functions and symptoms, and proactive, personalized care is provided at a lower burden for patients and their caregivers. Furthermore, the ALS Caregiver App was developed to support caregivers (www.als-centrum.nl/app-tips-en-info-naasten-als-patienten-gratis-downloaden/) as well as the website www.thuis-als-thuis.nl, which gives a virtual view of a family house with frequently used aids and adaptations, illustrated with embedded video and images and text documentation. This tool can support patients and their families in decisions about aids and adaptation

Table 3: Suggested research process indicators

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment	Mission Our mission is to provide excellent clinical care for patients with all forms of neuromuscular disease (in all age groups) and perform outstanding research (Top 5% in Europe) on motor neuron disease and neuropathy. Research questions The overall goal of all our research is to provide better treatment for patients with neuromuscular diseases, motor neuron diseases (ALS, SMA) and neuropathy in particular. We aim to do this by understanding the causes of these diseases through genetics and epidemiology. Unravelling the underlying mechanisms through molecular biology (IPSCs, organoids and animal models) and through clinical studies (imaging, cognition, biomarkers, etc.). We aim to translate these findings into clinical relevance (clinical trials, diagnostic and prognostic studies) and lastly, evaluate care, aim to improve care (e-health, symptomatic interventions) and study quality of life.
3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made	In collaboration with patient organisations as well as consortia, we have led or participated in the drafting of multiple research agendas, roadmaps as well as guidelines.
3.3. Stakeholders are involved in formulating the main research questions	Our strategic research program has monthly meetings with patient representatives from the diseases we study to discuss our research lines. For several grants we involved ALS patients connected, Spieren voor Spieren, the Motor Neurone Disease Association, EUPALS, and Spierziekten Nederland.
3.4. The research questions are feasible and are pursued using optimal and efficient design	As a research group we aim to perform ground-braking research (Top 5%). This means that we embark on ambitious projects and choices are not necessarily always for low-risk projects. By only conducting projects that are considered to be feasible, it seems unlikely that one will significantly advance the field. However, in order to perform high-quality competitive research on a broad range of topics considerable expertise needs to be in place. Within our group we therefore have database managers, numerous research assistants, epidemiologists, geneticists, molecular biologists and statisticians. The group consists over 50 individuals. Furthermore, we have extensive collaborations with multiple, (international) groups (imaging, IRAS, SurfSara, etc.).



3.5. What is 'the next step' if the project delivers positive results

Users of research findings

The disease area Neuromuscular Disorders has a clear vision on findings that should be advanced to the next phase. Our research is centered understanding the cause of the disease. This is done through large-scale genetics and epidemiological studies. Findings from these studies are advanced to functional studies. For instance, when a new ALS gene is discovered subsequently functional studies (cells, iPSCs, organoids, transgenic animal models) are performed at the department of Translational Neuroscience with the objective of identifying the underlying pathophysiological pathways. Similarly, epidemiological studies have pointed towards hypermetabolism, which can also be studied in disease models. These functional studies also inform clinical studies. For instance, if deficits at the neuromuscular junction are found in animal models, this would justify interrogating whether patients may share this feature (treatment target or as diagnostic tool). Genetics and epidemiology also allow subtyping of patients. In clinical studies we can further attempt to identify features of these subtypes (imaging, cognitive, other biomarkers). Once we have identified a subgroup with a potential treatment target (e.g. *unc13a* for lithium or *HERV-K* in ALS, NMJ in SMA) and we have sufficient natural history and biomarker data, we have the capacity to perform investigator-initiated trials (LITRA, valproic acid, creatinine, PHALS, SPACE, TRICALS). Data from clinical care is also used to optimize clinical care and here we also focus on e-health innovations. Essentially, there is a pipeline that starts at identifying the cause of the disease all the way through clinical trials and implementation in clinical practice.

At each step we involve relevant partners ranging from other research groups, to patient organisations and the pharmaceutical industry.

Support for innovation and valorisation

Within our unit there is a strong emphasis on implementation and valorisation. There are multiple private-public partnerships. For instance, with Accenture and with Julius Clinical. In particular, in the partnerships with Julius Clinical we work with their business developer in order to attract clinical trials to the UMC Utrecht Brain Center.

Funding

Our unit receives funding from multiple sources, such as public-private funds, governmental agencies (NWO), JPND, E-Rare, H2020, ERC, charities such as Stichting ALS Nederland, Prinses Beatrix Spierfonds, Spieren voor Spieren and the Thierry Latran foundation. We also initiated our own funding campaigns (e.g. Project MinE). Over the past years we have obtained more than 20 million euros in funding.

Memberships

Many members of our group are involved in guideline committees. For instance, prof. dr. Notermans and dr. Vrancken were involved in drafting the Dutch neuropathy guidelines, dr. van Es and prof. dr. van den Berg were involved in revising the Airlielhouse clinical trial guidelines for ALS, dr. van Es serves on the medical ethical review (METC) board of the UMC Utrecht and was an external consultant on the new 5-year strategy for the Dutch association of clinical genetics. Dr. Goedee drafted the national guidelines for neuro-imaging in neuromuscular disease. Prof. dr. Pasterkamp serves in a 'think tank' for translational research approaches from Prinses Beatrix Spierfonds. Multiple members serve or have served on scientific advisory boards (prof. dr. Pasterkamp, prof. dr. van den Berg, dr. van Es, dr. van der Pol, prof. dr. Veldink). We hold regular meetings with stakeholders (donors, patient organisations, pharma), have given many lectures for the general public (general interest, fundraisers) and work is covered extensively in the national and local media (prof. dr. van den Berg and dr. van der Pol in particular). We also have two designated communication officers in our team that put out online articles and videos on our work, communicate our work via twitter and are in contact with communication department of the hospital as well as the media. We have also interacted extensively with policy makers and insurance companies (Spinraza, Neudexta), ministry of Health and EMA about approval and reimbursement of treatments.



Table 4: Suggested output indicators

4.1 Research products for peers

1) Key publications per area

Amyotrophic lateral sclerosis (ALS)

- Koppers et al. C9orf72 ablation in mice does not cause motor neuron degeneration or motor deficits. *Ann Neurology* 2015 Sep;78(3):426-38.
- van Rheenen et al. Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. *Nat Genet.* 2016 Sep;48(9):1043-8.
- Kenna et al. NEK1 variants confer susceptibility to amyotrophic lateral sclerosis. *Nat Genet.* 2016 Sep;48(9):1037-42.
- van Eijk et al. Meta-analysis of pharmacogenetic interactions in amyotrophic lateral sclerosis clinical trials. *Neurology.* 2017 Oct 31;89(18):1915-1922.
- van Es et al. Amyotrophic lateral sclerosis. *Lancet.* 2017 Nov 4;390(10107):2084-2098.
- Westeneng et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. *Lancet Neurol.* 2018 May;17(5):423-433.

Spinal muscular atrophy (SMA)

- Bartels et al. Physical exercise training for type 3 spinal muscular atrophy. *Cochrane Database Syst Rev.* 2019 Mar 1;3:CD012120.
- Wadman et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. *Eur J Neurol.* 2018 Mar;25(3):512-518.
- Stam et al. A continuous repetitive task to detect fatigability in spinal muscular atrophy. *Orphanet J Rare Dis.* 2018 Sep 12;13(1):160.
- Stam et al. Protocol for a phase II, monocentre, double-blind, placebo-controlled, cross-over trial to assess efficacy of pyridostigmine in patients with spinal muscular atrophy types 2-4 (SPACE trial). *BMJ Open.* 2018 Jul 30;8(7):e019932.
- Wijngaarde et al. Cardiac pathology in spinal muscular atrophy: a systematic review. *Orphanet J Rare Dis.* 2017 Apr 11;12(1):67.

Neuropathy

- Harschnitz et al. Autoantibody pathogenicity in a multifocal motor neuropathy induced pluripotent stem cell-derived model. *Ann Neurol.* 2016 Jul;80(1):71-88.
- Goedee et al. Diagnostic value of sonography in treatment-naïve chronic inflammatory neuropathies. *Neurology.* 2017 Jan 10;88(2):143-151.
- Warendorf et al. Drug therapy for chronic idiopathic axonal polyneuropathy. *Cochrane Database Syst Rev.* 2017 Jun 20;6:CD003456.
- Telleman et al. Nerve ultrasound: A reproducible diagnostic tool in peripheral neuropathy. *Neurology.* 2018 Dec 28 (Epub).
- Warendorf et al. Statins do not increase risk of polyneuropathy: A case-control study and literature review. *Neurology.* 2019 Apr 30;92(18):e2136-e2144.

2) Registries, infrastructure, datasets & software tools

- The disease area Neuromuscular Disorders is the largest in the country and has detailed clinical registries, which for ALS, PMA, PLS, MMN and SMA are the largest in the world.
- The Dutch ALS center coordinates and participates in multiple, large-scale international projects. To this end, we have created research infrastructure for multiple projects. The largest of which are (1) the Progeny database that is used by >10 research groups from across Europe to store and exchange core clinical data and study results and (2) Surfsara, which is a supercomputer on which data is stored from Project MinE (largest genetic study on ALS ever performed with more research groups from than 20 countries participating worldwide) and is also used for data analysis.
- Multiple tools and resources have been developed including: (1) ENCALS survival prediction model. This online tool has the capability of accurately predicting survival in ALS based using clinical data and was developed using data from over 10,000 ALS patients from across Europe. (2) The Project MinE databrowser; this open access genetic database and data viewer that allows researchers to access the data from Project MinE (genetic data from over 10,000 individuals). (3) Expansion Hunter: this bioinformatics tool is able to reliably detect repeat expansions in whole-genome sequencing data as well as provide relevant size estimations.

3) 21 dissertations in the field of neuromuscular disease during the last 5 years

- ALS (16): Saris (2013), Groen (2014), Diekstra, Seelen, Huisman (2015), Koppers, Blokhuis, Pulit (2016), van Rheenen, Ticozzi, Groenestijn, van Doormaal, Walhout, Schmidt (2017), Dekker, Visser (2019).
- SMA (1): Wadman (2018).
- Neuropathy (4): Stork, Vlam (2015), Visser (2016), Goedee, Harschnitz (2017).



4.2 Research products for societal target groups

- 1) The availability of **Spinraza** for Dutch patients with SMA.
- 2) **Outreach activities & lectures for general audiences**
Neuromuscular researchers participate in fundraising activities and awareness campaigns such as the Amsterdam City Swim, Tour du ALS, lenteloop, Singelswim, etc. Research and developments within the field of ALS and in particular SMA have frequently attracted attention from the national media, which has led to multiple articles in national newspapers as well as TV-appearances by members of our group. Furthermore, members of our group have given lectures for the general public (Public lecture UMC Utrecht Brain Center): dr. M.A. van Es, prof. dr. L.H. van den Berg). Each year multiple members of our group give presentation at the annual, national patient symposium for neuromuscular disease (Spierziekten congres) and each we invite patients and their families to the UMC Utrecht, where we present our research and provide guided tours of our research facilities.
- 3) **Project MinE website** is also used by ALS charities from across the globe as an online platform for crowd funding and has raised over 10 million Euro to date.
- 4) Several **e-Health services** have been established to optimize the care for patients with ALS. This includes ALS Home Monitoring and Coaching (<https://www.als-centrum.nl/kennisplatform/project-innovatie-als-zorg-e-health/>), the ALS Caregiver App to support caregivers (www.als-centrum.nl/app-tips-en-info-naasten-als-patienten-gratis-downloaden/), and the website www.thuis-als-thuis.nl, an online tool that can support patients and their families in decisions about aids and adaptations.

4.3 Use of research products by peers

- 1) The **data infra-structure** that has been created for ALS research (Progeny, SurfSara) is actively used by groups from the US, UK, Australia, Belgium, Italy, Ireland, France, Switzerland and Spain.
- 2) Based on our research on nerve ultrasonography, we developed **national recommendations and guidelines** for performing nerve ultrasonography in the clinic. These have been accepted as the national guidelines are available online on the website of Nederlandse Vereniging voor Klinische Neurofysiologie (NVKNF).
- 3) Our paper: "de Vries BS, et al. Cognitive and behavioural changes in PLS and PMA: challenging the concept of restricted phenotypes. *J Neurol Neurosurg Psychiatry*. 2019" was the **Editor's pick** for February 2019 and was highlighted in an additional **podcast**.

4.4 Use of research products by societal groups

- 1) Our group has worked tirelessly to make the groundbreaking treatment with **Spinraza** for children suffering from SMA available in The Netherlands.
- 2) Treatment with **Neudexta** has been shown to be effective for bulbar symptoms in ALS. Despite that Neudexta has been approved by the EMA, it was not brought onto market in the EU. As Neudexta is a combination of two existing drugs (dextromethorphan and quinidine), the Dutch ALS center has made this combination product available to all ALS patients in The Netherlands through a collaboration with the Transvaal apotheek in The Hague.
- 3) The Dutch ALS center has bimonthly meetings/telephone conferences with **patient organisations** (ALS patients connected (APC)) and the ALS patient foundation (Stichting ALS Nederland). In these joint meetings, an advisory role for APC in all projects and therefore patients are actively involved in all our research projects (from grant proposal to presenting the final results).

4.5 Marks of recognition from peers

- 1) **Appointments as full professor** (3); prof. dr. J.H. Veldink (Neurogenetics), prof. dr. R.J. Pasterkamp (Translational Neuroscience) & prof. dr. N.C. Notermans (Neuromuscular disease).
- 2) **Science awards/scholarly prizes** (7): Paolo Gontijo international medicine award (2013; dr. M.A. van Es (ALS)), Forbes Norris Award (2013; prof. dr. L.H. van den Berg A (ALS)), Arthur K. Asbury Award (2014; dr. O. Härschnitz (neuropathy)), Dr. Jan Meerwaldt Prijs (2018; dr. R. Wadman (SMA)), Jaarprijs neuromusculaire ziekten (2016; dr. W. van Rheenen (ALS), 2019; drs. H.J. Westeneng (ALS)), membership Royal Netherlands Academy of Arts and Sciences (KNAW) (prof. dr. L.H. van den Berg).
- 3) **Research grants awarded to individuals:** Veni grants (2) from ZonMw to dr. M.A. van Es (2014), Sara Pulit (2017), Vidi grant to Kevin Kenna, ERC consolidator grant to prof. dr. J.H. Veldink (2017). NWO VICI grant to prof. dr. R.J. pasterkamp (2015). Prof. de. Leonard van den Berg was awarded the 'Winkler Medal' from The Netherlands Neurological Association for recognizing the most significant scientific contribution to neuroscience over 5 years (2000-2015).

4.6 Marks of recognition from societal groups

- 1) Fellowships from the Prinses Beatrix Spierfonds (3) (2016; dr. H.M. Blauw, 2017; dr. R. Wadman, 2019; dr. T.P.C. van Doormaal).
 - 2) Prof. dr. L.H. van den Berg was named as a member of the Royal Netherlands Academy of Arts and Sciences (KNAW lid).
 - 3) Dr. W.L. van der Pol played a vital role in ensuring that patients affected by SMA in The Netherlands have access to Spinraza. This work included advising and consulting with the ministry of Health and with insurance companies.
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5. UMC Utrecht Brain Center – Psychotic disorders

5.1 Mission, strategy, and organisation

Between 2014 and 2018 researchers from the departments of Psychiatry, Neurology, and Translational Neuroscience have worked together within the disease area Psychotic disorders. A group of over 25 researchers and clinicians together with many more junior researchers, postdocs, PhD and master students, have put all their efforts into making the mission of Psychotic Disorders a success. During that time Psychotic disorders has thrived as much as it has undergone changes. Prepared for the future, from 2019 on it will continue under the flag of Precision Psychiatry.

Mission

The mission of the disease area Psychotic Disorders was three-fold: 1) To understand the developmental trajectories of psychotic disorders, with a focus on brain and behavioural changes that occur during the first two decades of life – as these changes can be a target for early diagnosis and preventive intervention. 2) To investigate underlying mechanisms of stages and subtypes of psychotic disorders that offer an entry for personalized treatment, to augment and broaden current treatment options and improve functional outcome. 3) To investigate the efficacy of new interventions to prevent or treat (subtypes of) psychotic disorders, and investigate how we can optimize existing treatments to secure optimal functional and social outcome.

Strategy

For this purpose, we included several thousands of patients with schizophrenia, patients with bipolar disorder, their (twin) family members and unaffected individuals and these were often followed up longitudinally. Data on genetics, brain imaging, cognition, behaviour, medication, environment and outcome, and in smaller cohorts skin biopsies for neuronal stem cell research (iPSC), have been collected over the years and continue to provide a rich resource for our mission.

Organisation

We did not work in isolation, but we participated in and worked together with researchers within the areas Structure & Connections, Genetics, and Translational Neuroscience at UMC Utrecht Brain Center, and with the Utrecht University strategic theme 'Dynamics of Youth'. Additionally, we are engaged in multiple cohorts nationally (e.g., GROUP, CID, NEUROLABNL, BBMRINL) and internationally (e.g., EUGEI, PSYSCAN, OPTIMISE, ENIGMA). We also work closely with Anoiksis and Ypsilon, patient and family organisations, to respond to their priorities and needs. In the past five years, the disease area Psychotic Disorders has grown to be very strong and thriving with high level output and with local, national, and international visibility.

Transition

In 2017, the disease area underwent considerable changes. Prof. dr. Kahn, at the time chair of the Division Brain and head of research at the department of Psychiatry, left the UMC Utrecht to become head of the department of Psychiatry at Mount Sinai, New York, USA. Around the same time, prof. dr. Sommer, at the time head of the disease area Psychotic Disorders, left for a new position at UMC Groningen, and prof. dr. Joels, at the time chair of the UMC Utrecht Brain Center, became dean at UMC Groningen. While all three still hold assignments at UMC Utrecht Brain Center and continue some of their research on site, we entered a transition period: innovative strategies are now implemented to capitalize on the strengths of the disease area with the aim to let patients benefit from the gained scientific knowledge. The chair of the Division Brain was accepted by prof. dr. van Os, a psychiatrist with a track record in research in psychotic disorders and other mental health problems. He focuses on bridging the gap between the high prevalence of common mental disorder and the relative low capacity of any mental health service by developing e-communities and a better peer and citizen support and user-rated self-management tools. Prof. dr. Scheepers, head of the department of Psychiatry, provides with her focus on big data in psychiatry, network care, and the development of a story-bank, as well as through co-creations/scrums sessions with professionals and patients for innovation a transition towards clinical data use and citizen-participation in research. In the coming years we aim to focus more on mechanisms across disorders, on health and vulnerabilities, on individual variations, with treatments aimed at trans-syndromal symptom reduction. We will work closely together with patients, to benefit the individual better, earlier, and faster.



From Psychotic disorders to Precision psychiatry

There is an unresolved need for people with complex mental health difficulties to be cured and a growing body of knowledge indicates that mental illnesses are seldom cured. In the coming years, the new disease area Precision Psychiatry at the UMC Utrecht Brain Center will further transform into an area where research, education, care, and training are integrated. Prof. dr. Adan and dr. Bruining are shaping Precision Psychiatry and receive input from various researchers working in this disease area in the UMC Utrecht Brain Center (e.g. dr. Boks, prof. dr. Scheepers, prof. dr. Durston). The ambition in Precision Psychiatry is to optimize individual treatment decisions through integration of different elements of diagnostic and prognostic information, which have a solid scientific base. This integration will enable the development of treatment decision support systems that can be enhanced through a continuous iterative process of refinement and improvement and will inspire projects focusing on more long-term predictive elements. In order to reach more focused diagnosis and treatment we will need and use various sources of data, knowledge and research projects in recent years that are integrated in our newly developed care programs. This ambition can thrive on a wealth of available data and approaches present in our center that are ready to be implemented in the framework of Precision Psychiatry. These include experimental, model, and clinical data on neurobiological systems and mechanistic dimensions, including those from physiological recordings, brain imaging, 'omics' biomarkers, environmental exposures, and self-reported experience. The predictive value of these units for individual treatment decisions needs to be combined with improved clinical endpoint measurements including ecological dynamic assessments that track real-time changes in daily function. Linking data and analysing complex models at an aggregated level will lead to more sophisticated diagnostics, prediction models, and decision support systems that help professionals, patients, and their family in shared decision making. Precision psychiatry will be strengthened by YOUth (www.youthonderzoek.nl) as part of CID, a joined project between UMC Utrecht Brain Center and UU and by national science agenda (NWA) consortium NeuroLabNL (www.neurolab.nl). Recently, BBMRI-NL (www.bbmri.nl), EATRIS-NL, and DTL/ELIXIR-NL have jointly embarked on a common roadmap for a collective Personalized Health & Medicine Research Infrastructure in The Netherlands: Health-RI. Health RI focusses on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors (see e.g., movie at www.health-ri). Precision Psychiatry will be strengthened by and contribute to national biobanking infrastructure BBMRI-NL and from Health-RI. By participating in these national platforms, we bridge disorder-boundaries not only within psychiatry but also beyond, to develop personalized health identifiers and to optimize efforts for prevention and treatment of mental disorders. Within the disease area Precision Psychiatry we will focus our efforts in the coming years on connecting discovery, treatment, health services and user experience.

5.2 Research projects with patient involvement

Project PsyNet (Funded by ZonMw)

The PSYNET consortium, consisting of patients and different stakeholders in the region of Utrecht (general practitioners, psychiatric care, housing and social welfare), aims to demonstrate that the use of the PsyNet ICT platform can improve health care by facilitating a change in the way care processes are currently organised. PsyNet places the patient in the centre of a care network in which all connected parties can easily communicate and securely share relevant patient data. Expected impacts of PsyNet range from a decrease in the number of hospital admissions, caps in care plans, to facilitate access to the adequate services, and a consequent improvement of the quality of life and satisfaction about the care process. In addition, the PsyNet platform provides a single sign access to all shared data and a plug-in platform for other e-health applications that can be integrated. Patients were involved in the design of the project and are also participating in the implementation and analyses of data.

Project Psychosis Prognosis Predictor (Funded by ZonMw)

The patient and family organisations requested a better outcome predictor for those affected, which overlapped with our ultimate goal. For the ZonMw grant (500 kEuro), awarded to dr. H. Schnack and prof. dr. W. Cahn in 2018, local and national patient and family organisations (Anoiksis, VMDB, Ypsilon) were co-applicants. We aim to develop a prediction model for outcome for the individual patient that also indicates how changing certain factors can influence it in a favourable way. What is meant by 'favourable', is part of the project: patients and psychiatrists together will define outcome variables that are important to them. Machine-learning models will be trained and validated in existing and new patient data. Insight in how changing (lifestyle) factors may improve a patient's personalized outcome will increase the patient's opportunities for self-management, enable tailored interventions, reduce societal costs, and improve the lives of those affected by the illness.



5.3 Key publications

- 1) Bohlken et al. Structural Brain Connectivity as a Genetic Marker for Schizophrenia. *JAMA psychiatry*. 2016;73(1): 11-19.

Schizophrenia is accompanied by a loss of integrity of white matter connections that compose the structural brain network, which is believed to diminish the efficiency of information transfer among brain regions. However, it was unclear to what extent these abnormalities are influenced by the genetic liability for developing the disease. In twins discordant for schizophrenia and healthy twins (UTWINS) we find that global reductions in white matter integrity in schizophrenia are largely explained by the genetic risk of developing the disease. The reported reductions in white matter integrity likely represent a separate and novel genetic vulnerability marker for schizophrenia.

- 2) Schnack et al. Accelerated Brain Aging in Schizophrenia: A Longitudinal Pattern Recognition Study. *Am J Psychiatry*. 2016 Jun 1;173(6):607-16.

Despite the multitude of longitudinal neuroimaging studies that have been published, a basic question on the progressive brain loss in schizophrenia remains unaddressed: Does it reflect accelerated aging of the brain, or is it caused by a fundamentally different process? The authors used support vector regression to address this question. In schizophrenia patients, brain age was significantly greater than chronological age at baseline and progressively increased during follow-up. This appears to reflect two different processes: one relatively homogeneous, reflecting accelerated aging of the brain and related to various measures of outcome, and a more variable one, possibly reflecting individual variation and medication use. Differentiating between these two processes may not only elucidate the various factors influencing brain loss in schizophrenia, but also assist in individualizing treatment.

- 3) Houtepen et al. Genome-wide DNA methylation levels and altered cortisol stress reactivity following childhood trauma in humans. *Nat Commun*. 2016 Mar 21;7:10967.

DNA methylation likely plays a role in the regulation of human stress reactivity. Here we find that in a genome-wide analysis of blood DNA methylation showed the strongest association with cortisol stress reactivity. Replication was obtained in two independent samples using either blood or buccal cells. Our results extend preclinical evidence for epigenetic regulation of stress reactivity to humans and provide leads to enhance our understanding of the neurobiological pathways underlying stress vulnerability.

- 4) Kahn et al. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. *Lancet Psychiatry*. 2018 Oct;5(10):797-807.

No established treatment algorithm exists for patients with schizophrenia. Whether switching antipsychotics or early use of clozapine improves outcome in (first-episode) schizophrenia is unknown. This three-phase study was done in 27 centres, consisting of general hospitals and psychiatric specialty clinics, in 14 European countries and Israel. For most patients in the early stages of schizophrenia, symptomatic remission can be achieved using a simple treatment algorithm comprising the sequential administration of amisulpride and clozapine. Since switching to olanzapine did not improve outcome, clozapine should be used after patients fail a single antipsychotic trial-not until two antipsychotics have been tried, as is the current recommendation.

- 5) Guloksuz et al. Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EUGEI study. *World Psychiatry*. 2019 Jun;18(2):173-182.

Schizophrenia is a heritable complex phenotype associated with a background risk involving multiple common genetic variants of small effect and a multitude of environmental exposures. In this study evidence was found for additive interaction of molecular genetic risk state for schizophrenia with the presence of lifetime regular cannabis use and exposure to early-life adversities (sexual abuse, emotional abuse, emotional neglect, and bullying), but not with the presence of hearing impairment, season of birth (winter birth), and exposure to physical abuse or physical neglect in childhood. The results suggest that the etiopathogenesis of schizophrenia involves genetic underpinnings that act by making individuals more sensitive to the effects of some environmental exposures.



5.4 Most important contributions to society

Guidelines, GROUP and Psychosis Foundation

Wiepke Cahn was vice-president of the Dutch Psychiatric Association from 2012 until 2018 and in that capacity responsible for the development of the national care standards for mental health services (<https://akwaggz.nl>). In total 42 care standards and generic modules were developed (published in 2018). Various researchers from the UMC Utrecht Brain Center, together with other professionals and service users, were involved in the development of care standards regarding psychosis and its treatment. By using these guidelines, quality of care for people with a psychotic disorder (and their relatives) has improved significantly. In addition, various researchers from the the UMC Utrecht Brain Center have contributed to the schizophrenia spectrum disorder handbook (Cahn et al. 2019 – second edition), which is compulsory reading for psychiatrists in training. The most up-to-date knowledge on psychosis is therefore being implemented, guiding the future of mental health care and treatment.

Since the Genetic Risk and Outcome of Psychosis (GROUP) project, which was funded by the ZONMW Geestkracht program in 2003, there is a longstanding collaboration between four University Medical Centers (Utrecht, Groningen, Amsterdam, Maastricht) and 30 mental health institutes studying the etiology and course of psychotic illnesses. Patient and family organisations (Anoiksis/Ypsilon) were involved in the agenda setting for scientific research during the GROUP project. This collaboration was such a success, that all involved parties (i.e. researchers, service users, clinicians) decided to create the Psychosis Foundation. The Psychosis Foundation is initiated and chaired by the UMC Utrecht Brain Center and focuses on the prevention and complete recovery of psychosis. The foundation has 3 main goals: 1) The (financial) support of scientific research into psychotic disorders of the research institutes involved in the GROUP study; 2) Generating and allocating sponsor money for research questions on existing (GROUP) data, new GROUP cohort measurements and setting up and conducting new research into psychotic disorders; and 3) Everything serving the aforementioned goals. Patients, families, clinicians and researchers will jointly determine the focus of new research into psychosis. It is expected that this foundation, by the strong alliance between researchers and care users, will contribute greatly to the dissemination of scientific knowledge on psychosis within the scientific community and the public at large.

Learning health systems (LHS)

The method of building a learning health system by (re)using clinical data from the EPF (with applied data analytics) initiated by prof. dr. Scheepers is already adopted by four other mental health organisations in a compute visits data model. Other organisations are now going through a data readiness check, developed by the department of Psychiatry, to create an infrastructure that is flexible enough to participate in this growing network of LHS. In this way Dutch mental healthcare can share, replicate, validate, and adopt new algorithms in a fast and effective way. PsyNet (described above, www.psynet.nl) is a regional digital network structure to connect other organisations that are involved in mental health care in this development. This is also implemented in other regions in the Netherlands and in other patient domains (elderly). Prof dr. Scheepers is member of the Dutch quality counsel (sub-department of the care institute of the Netherlands appointed by the Ministry of Health) also adopting network care in their strategies.

Table 3: Suggested research process indicators

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment	<p>Mission We aim to understand the developmental trajectory of psychotic disorders -with a focus on brain and behavioural changes that occur during the first two decades of life- as these changes can be a target for early diagnosis and preventive intervention.</p> <p>Research questions We investigate underlying mechanisms of stages and subtypes of psychotic disorders that offer an entry for personalized treatment, to augment and broaden current treatment options and improve functional outcome.</p> <p>We investigate the efficacy of new interventions to prevent or treat (subtypes of) psychotic disorders. Moreover, we investigate how we can optimize existing treatments to secure optimal functional and social outcome.</p> <p>Patient organisations and the family organisation are often involved in the early stages of new research projects and discussions on new ideas are formulated jointly on our research lunches (for example). Patients are often involved to help design new studies, for example by choosing the outcome measure that they think is most relevant as the primary outcome.</p>
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3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

We participate in **multiple national and international research initiatives**:

- We participate in the Dutch National Research Agenda with NeuroLabNL to analyse optimal conditions for learning and safety of youth by studying the influence of genes and environment on the development of brain and behaviour in typically developing adolescents and in adolescents with antisocial behaviour (NWA 400.17.606; prof. dr. H. Hulshoff Pol WP3 leader).
- We participate in the Biobanking and BioMolecular resource Research Infrastructure for the National Roadmap of large-scale research facilities BBMRI-NL. The major goal of this project is to create an infrastructure for Dutch biobanks (>200 participating biobanks) and cohorts (NWO National Roadmap 184.033.111, prof. dr. H. Hulshoff Pol WP3 co-leader).
- We participate in the National NWO Gravity Grant Consortium Individual development 024.001.003 (prof. dr. C. Kemner PI; prof. dr. H. Hulshoff Pol WP1 Leader) which aims to understand individual differences in the development of social competence and behavioural control throughout development.
- We participate in the Dutch Brain Foundation grant (GH 2016-2-01) to study as consortium what the contribution of alcohol intake is on brain development across the Netherlands.

Our research questions relate to existing knowledge. Our research is transparently incorporated in over 30 reviews and meta-analyses, including as part of **international collaborations**, such as:

- 1) Van Erp et al. Cortical Brain abnormalities in 4474 Individuals with Schizophrenia and 5098 Control Subjects via the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) consortium. *Biol. Psychiatry* 2018. 1; 84: 644-654.
- 2) Brouwer et al. Genetic influences on individual differences in longitudinal changes in global and subcortical brain volumes: Results of the ENIGMA plasticity working group. *Hum Brain Mapp.* 2017 Sep;38(9):4444-4458.
- 3) Hibar et al. Common genetic variants influence human subcortical brain structures. *Nature* 2015 Apr 9; 520:224-229.
- 4) Filippi et al. Assessment of system dysfunction in the brain through MRI-based connectomics. *Lancet Neurol.* 2013 Dec;12(12):1189-99. Review.
- 5) Moran et al. A family affair: brain abnormalities in siblings of patients with schizophrenia. *Brain.* 2013 Nov;136(Pt 11):3215-26. doi:10.1093/brain/awt116. Epub 2013 May 22. Review.

3.3. Stakeholders are involved in formulating the main research questions

Our aims fully align with those of the Dutch Brain organisation (Hersenstichting) and with those of ZonMw, NWO and NWA.

Patient participation

- Patient organisations and family organisation request better outcome for those affected which is also our ultimate goal. For example, for the ZonMw grant (500 kEuro), awarded to dr. H. Schnack and prof. dr. W. Cahn in 2018 (Psychosis Prognosis Predictor), local and national patient and family organisations (Anoiksis, VMDB, Ypsilon) were co-applicants.
- Besides these main themes we have followed the patient organisations' wish to engage in discussions on a new name for schizophrenia. The stakeholders of this disease area are very divers. From the Dutch Brain Organisation, to regional professionals, family and patient associations like Ypsilon and Anoiksis to the Dutch government for legislation on drug use for psychiatric patients.
- Weekly presentations and discussions are organized where patient and Family members are present. Patients can give their input, which is used for new research projects and policy.
- Two times a year an open lecture is organized to inform patients, family members and participants of research projects about research results.
- Dr. M. Boks has close collaborations with the foundation for bipolar disorder patients (Plusminus) and a frequent presenter at their regular events.

Besides participation of patient organisations, **other stakeholders** are also involved in our projects:

- A consortium was formed with all regional stakeholders (general practitioners, social welfare, mental health organisations, home shelter, and addiction care) to connect research projects, work together, and collaborate on initiating innovation and new research projects. From 2019 on a yearly congress is organized with all researchers from this regional consortium.
- MIND (the umbrella organisation of mental illnesses) is involved in all Big Data and network projects to monitor the process and give input on an ongoing basis in order to determine the direction of the projects, name new research questions and be involved in implementation.
- Researchers are currently working on a study into the influence of alcohol on adolescent brain development, which was initiated by the Dutch Brain organisation (Hersenstichting) in collaboration with the Trimbos Institute.
- Dr. M. Boks is coordinator of the Dutch Bipolar Cohort study (N=2600) and has collaborations with stakeholders in bipolar disorder research such as the KenBis (www.kenniscentrumbipolairestoornissen.nl/) Amsterdam MC (location VU) and many national health care institutions (www.UMC Utrechtrecht.nl/nl/Ziekenhuis/Afdelingen/Hersencentrum/Meedoen-aan-wetenschappelijk-onderzoek/Resultaten-van-onderzoek-op-de-afdeling-psiichiatri/Bipolar-Genetics-de-resultaten).



3.4. The research questions are feasible and are pursued using optimal and efficient design

To make sure that our studies are performed in a methodologically and statistically correct manner, all our PhD students are supervised by a promotor, a co-promotor and supported by peers. Staff members dr. Brouwer (mathematician), dr. Mandl (computer scientist) and dr. Schnack (physicist) have extensive knowledge of and experience with imaging methodology, data analysis, and statistics, including using complex structural equation modelling, machine learning, and network analyses. Postdocs and staff members are expected to consult whenever necessary methodological and statistical experts. This way statistical and methodological expertise is involved in during all stages of our research from the early stages. Statistical analyses of large or complex studies can be performed together with the statisticians of the Julius Center and for cost-utility and/or prognostic modelling with Trimbos Institute. Outcomes, end terms, and analyses are determined on forehand and stated in websites such as clinicaltrials.gov and/or [eudraCT](https://eudraCT.europa.eu/).

3.5. What is 'the next step' if the project delivers positive results

Users of research findings

When studies provide a positive result, the researchers involved translate this into general practice. Some examples are:

- Our studies on focal stimulation for hallucinations, which are now discussed in the national and international guidelines for treating psychosis.
- Study on MRI deviations that showed that MRI need not be an asset of general diagnosis.
- Recent findings from the OPTIMISE study have shown positive results for amisulpride and we are now in discussion with the CVBG to see how we can give Dutch patients excess to this drug.
- Our research results (also the negative ones) are translated to guidelines for psychiatrists and general physicians, and we do whatever we can to make effective treatments available to (Dutch) patients.

Other important collaborations are Altrecht by means of prof. dr. W. Cahn and prof. dr. R. Adan, Broad Institute (Prof. dr. R. Kahn), UCLA (Prof. dr. R. Ophoff), Cambridge (Dr. L. de Witte), Copenhagen Capitol Psychiatry centrum (Dr. B. Oranje and Dr. R. Mandl) and Bergen (prof. dr. I. Sommer), Madrid and IoP London (Dr. H. Schnack).

We participate in BBMRI-NL and Health RI and with these national platforms bridge disorder-boundaries to develop personalized health identifiers. In this way we can optimize our efforts for prevention and treatment of disorders, including of psychotic disorders. BBMRI-NL (www.bbMRI.nl), EATRIS-NL, and DTL/ELIXIR-NL have jointly embarked on a common roadmap for a collective Personalized Health & Medicine Research Infrastructure in The Netherlands: Health-RI. Health RI focusses on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors (see movie at www.health-ri.nl).

Funding

Our projects have received funding from a broad range of national, international and public funds (e.g. ZonMW, NWO).

Memberships

- Prof. dr. H. Hulshoff Pol sets up a Youth Advisory Board with adolescents as part of the NeuroLabNL consortium with the aim to advise on scientific research focusing on adolescence.
- Prof. dr. H. Hulshoff Pol was chair of the scientific board of the Dutch Brain Organisation (Hersenstichting).
- Prof. dr. J. van Os was member of the scientific board of the Dutch Brain Organisation (Hersenstichting).
- Prof. dr. F. Scheepers is member of the Dutch Health counsel and member of the Quality counsel of Zorg Instituut Nederland.
- Prof. dr. W. Cahn was board member (vice president) of the Dutch Psychiatry Association (NVVP). She is also board member of the family association for psychosis (Ypsilon).
- Prof. dr. W. Cahn was member of the scientific board of Zorg Instituut Nederland.
- Prof. dr. W. Cahn is board member of National guidelines in psychiatry (Netwerk Kwaliteitsontwikkeling GGZ).
- Prof. dr. W. Cahn is chair of 'the genetic outcome of psychosis project (GROUP)' and of the Psychosis Foundation in formation. This is a collaboration between four academic hospitals in the Netherlands and 30 psychiatric hospitals as well as the patient and family organisation.
- Prof. dr. W. Cahn is chair of the taskforce of the Dutch Psychiatric association to further the integration on psychiatric and somatic disorders.
- Prof. dr. H. Hulshoff Pol together with Dr. N. van Haren and Dr. D. Brouwer play leading roles in the international data sharing initiative ENIGMA.
- Prof. dr. I. Sommer is a permanent member of the Netherlands Board on research Integrity (LOWI) and also from the permanent committee for large research facilities (NWO).
- Dr. M. Boks is an active member of the psychiatric genetic consortium (PGC) for Bipolar Disorder and the international cannabis consortium that also studies the role of cannabis in relation to psychosis risk.



Our work has been covered in general **media**:

- Prof. dr. F. Scheepers wrote different chapters of books about networkcare and big data and psychosis.
- Prof. dr. H. Hulshoff Pol edited a book on Neuroimaging of the Brain for psychiatrists and psychologists (Beeldvorming van het Brein, Uitgeverij de Tijdstroom 2015).
- Prof. dr. H. Hulshoff Pol wrote an invited chapter in “Women in Academic Psychiatry, A Mind to Succeed 2016 (Editor: Sophia Frangou), Springer Verlag, Switzerland (DOI 10.1007/978-3-319-32177-6).
- Prof. dr. R. Kahn wrote a popular scientific book on the harm of alcohol use.
- Prof. dr. I. Sommer published a popular scientific book together with the Hersenstichting that became a national bestseller (Haperende Hersenen).
- Prof. dr. W. Cahn published a popular scientific book on how to focus on family members in psychiatry.
- Different researchers presented their work on the yearly Dutch scientific meeting in MECC Maastricht.
- Dr. M. van der Heuvel, prof. dr. E. Hol and prof. dr. I. Sommer participated in the TV night from the Dutch Brain organisation as well as in the symposium for donations, which was hosted in the UMC Utrecht Brain Center.
- The hallucination researchers provided a demonstration of their research on the National Brain day.
- Prof. dr. W. Cahn is organizing an annual multidisciplinary meeting ‘let’s move’ on life-style interventions in psychiatry. Furthermore she organizes local schooling sessions on life-style.
- The hallucination researchers lead the national science project of 2016, together with “Weekend van de Wetenschap”. Additionally, they provided a demonstration of their research on the National Brain day.

Table 4: Suggested output indicators

4.1 Research products for peers	<p>1) Key publications</p> <ul style="list-style-type: none">• Guloksuzet al. (2019). Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EUGEI study. <i>World Psychiatry</i> 18, 173-182.• Bohlken et al. Structural Brain Connectivity as a Genetic Marker for Schizophrenia. <i>JAMA psychiatry</i>. 2016;73(1):11-19. oi:10.1001/jamapsychiatry.2015.1925.• Schnack et al. Accelerated Brain Aging in Schizophrenia: A Longitudinal Pattern Recognition Study. <i>Am J Psychiatry</i>. 2016 Jun 1;173(6):607-16.• Bohlken et al. Structural Brain Connectivity as a Genetic Marker for Schizophrenia. <i>JAMA Psychiatry</i>. 2016 Jan;73(1):11-9). <p>2) Development of the Psychosis Prognosis Predictor</p> <p>The psychosis prognosis predictor is developed to predict which changing (lifestyle) factors may improve a patient’s personalized outcome. This will increase the patient’s opportunities for self-management, enable tailored interventions, reduce societal costs, and improve the lives of those affected by the illness.</p> <p>3) Number of dissertations</p> <p>In total 29 dissertations were completed in the last five years: 2015 (7), 2016 (7), 2017 (5), 2018 (5), 2019 (5). A higher number of dissertations is expected for 2019.</p>
4.2 Research products for societal target groups	<p>1) Prof. dr. J. van Os was initiator of Psychosis public health action research: www.psychosenet.nl (150.000 visitors p. month).</p> <p>2) Prof. dr. I. Sommer wrote the popular scientific book ‘Haperende Hersenen’ and was interviewed on the Belgian television. This interview led the Belgian government to change their policy towards soccer training for youngsters (no heading anymore). The Dutch government is considering this, but so far decided not to change their policy. She also explained the etiology of hallucinations on television in a series of programs and a documentary.</p> <p>3) In April 2016 the program to reduce psychiatric suffering initiated by Sommer was agreed upon by the Minister of Health and now we have a 10 year program to improve recognition and treatment of psychiatric disorders (www.zonmw.nl/nl/programmas/programma-detail/onderzoeksprogramma-ggz/algemeen/).</p> <p>4) Prof. dr. H. Hulshoff Pol edited the “handbook beeldvorming in de psychiatrie” with contributions of many staff members.</p>
4.3 Use of research products by peers	<p>1) Genetic data from our cohorts are shared and have helped to achieve great discoveries, such as the one published by Sekar et al (see above).</p> <p>2) Our MRI data are re-used in many international collaborations (including consortia such as ENIGMA, PHENOM) and have helped to discover relevant biomarkers, for example see papers from the ENIGMA consortium (E.g., Hibar et al, Common genetic variants influence human subcortical brain structures. <i>Nature</i>. 2015 Apr 9;520(7546):224-9.)</p> <p>3) The neuronavigation tool developed by dr. B. Neggers is now used in many labs in Netherlands and all over the world.</p>



4.4 Use of research products by societal groups

- 1) The CVBG is now considering to approve amisulpride as an antipsychotic medication of first choice for the Dutch market, based on the optimize study. Its use is already recommended in the new guidelines.
- 2) Diagnosis and treatment of auto-immune encephalitis as a subtype of psychosis is now advocated in the general diagnosis of psychotic disorders.
- 3) Our hearing voices program is written down as a treatment protocol and implemented in several Dutch centers.

4.5 Marks of recognition from peers

- 1) Prof. dr. J. van Os was a 2016 Fellow, King's College London.
- 2) Prof. dr. W. Cahn is admitted to the board of the Dutch psychiatry association.
- 3) Prof. dr. I. Sommer is chair of the Dutch science board of psychiatry and member of the permanent committee for large scientific infrastructure.

4.6 Marks of recognition from societal groups

- 1) Dr. M. van der Heuvel was awarded the Brain Prize 2015.
 - 2) Prof. dr. J. van Os was a 2016 Fellow, King's College London.
 - 3) Prof. dr. R. Kahn was awarded the Pieter Baan lecture for life time work in 2016 by the Dutch psychiatric association.
 - 4) In 2018, prof. dr. R. Kahn received the Order of the Netherlands Lion, also referred to as the Order of the Lion of the Netherlands.
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6. UMC Utrecht Brain Center – Stroke

The disease area Stroke has large overlap with ‘Cerebral Ischemia’ of the strategic research program Circulatory Health and is therefore a good example of joined efforts of strategic research programs. The evaluation of this disease area is highly similar to the evaluation of Circulatory Health, but we elaborated on certain aspects that are specifically relevant for the UMC Utrecht Brain Center.

6.1 Mission, strategy, and organisation

Mission

The mission of our disease area is to improve the diagnosis, treatment, and prognosis of patients with cerebrovascular disease, including those with stroke, unruptured intracranial vascular malformations, or vascular cognitive impairment, and neonates with hypoxic-ischemic brain damage.

Strategy

To address this mission, we coordinate national and international mono- and multi-centre preclinical and clinical studies in the fields of ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, intracranial aneurysms, and vascular-cognitive impairment, with the aim to improve outcome after stroke. These clinical studies include intervention trials and etiologic, diagnostic, and prognostic studies, in patients from all ages including neonates. We develop innovative imaging methods to improve diagnosis, treatment, and prognostication in patients with cerebrovascular diseases, including vascular-cognitive impairment, and to support etiological research. Additionally, we integrate basic/translational research and translate preclinical results to patients. Results from our research, including the latest developments in neurosurgery, acute interventions and neurorehabilitation, and knowledge from translational research, are often directly implemented in the array of treatments we offer our patients.

Organisation

The disease area Stroke is characterized by a high regard for internal, external, and interdisciplinary collaboration, demonstrated by collaborative projects with the Departments of Internal Medicine, Translational Neuroscience (e.g. prof. dr. Hol), Clinical Epidemiology, Medical Imaging (e.g. prof. dr. Dijkhuizen), Neurology and Neurosurgery (e.g. prof. dr. van der Worp, prof. dr. Biessels, prof. dr. Rinkel), Radiology, Rehabilitation (e.g. prof. dr. Visser-Meilij), Intensive Care Medicine (e.g. prof. dr. Slooter), and Neonatology (e.g. prof. dr. de Vries), both within the UMC Utrecht Brain Center and with other national and international partners. Staff members have different responsibilities, for instance with regard to organising research meetings, organisation of teaching, etc. The clinicians associated to Stroke also perform clinical activities at a variable extent. All researchers participate in education of bachelor and master students (Biomedical Sciences, Medicine, and Neuroscience and cognition), doctors and/or nurses.

6.2 Research projects with patient involvement

The European stroke patient advocacy organisation Stroke Alliance For Europe (SAFE) has provided input to the randomised clinical trial PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke (PRECIOUS). The trial aims to assess whether the prevention of complications in the acute phase of stroke improves functional outcome. In total, 3800 patients will be recruited in 80 hospitals, including UMC Utrecht. SAFE is responsible for part of the dissemination of this project. In addition, SAFE is partner in the European acute stroke research project EuroHYP-1. EuroHY-1 is an European open randomised phase III clinical trial that will evaluate the benefit of therapeutic cooling in adult patients with acute ischaemic stroke.



6.3 Key publications

1. Greving et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol.* 2014; 13:59-66.

The PHASES score developed in our unit is an easily applicable aid for prediction of the risk of rupture of incidental intracranial aneurysms and is accessible via the internet in the form of an interactive tool.

2. Compter et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. *Lancet Neurol.* 2015;14:606-614.

This national randomized trial has demonstrated that stenting of symptomatic vertebral artery stenosis, a frequently performed clinical intervention, is associated with a major periprocedural vascular complication in about one in 20 patients. In the population studied, the risk of recurrent vertebrobasilar stroke under best medical treatment alone was low, questioning the need for and feasibility of a phase 3 trial.

3. van Asch et al. Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study. *BMJ.* 2015; 351:h5762.

This study demonstrates the diagnostic yield and accuracy of early computed tomography (CT) angiography followed by magnetic resonance imaging/angiography (MRI/MRA) and digital subtraction angiography (DSA) in patients with non-traumatic intracerebral hemorrhage.

6.4 Most important contributions to society

PHASES score

One of the most important contributions to society is the in house development of the PHASES score. This score is easily applicable aid for prediction of the risk of rupture of incidental intracranial aneurysms. The interactive tool is publically available and accessible via the internet. The PHASES score and tool is applied in many clinical centers worldwide in decision making on whether to treat an intracranial aneurysm or not.

Exercise guide and exercise app

In 2010, the exercise guide was developed and recently evaluated by stroke researchers of the UMC Utrecht and Rehabilitation Centre De Hoogstraat in collaboration with professionals of other hospitals, nursing homes, rehabilitation centers, and the Dutch Stroke patient organisation. It is a practical low-cost tool for patients to exercise from day one after an ischemic stroke to intensify their rehabilitation treatment. Nowadays, the exercise guide and exercise app have been accepted as required part of physical therapy by Dutch insurers.

Table 3: Suggested research process indicators

<p>3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment</p>	<p>Mission Through internationally recognized and societally well-embedded research the disease area Stroke adds to improvements in the diagnosis, treatment, and prognosis of patients with cerebrovascular disease, including those with stroke, unruptured intracranial vascular malformations, or vascular dementia, and neonates with hypoxic-ischemic brain damage.</p>
	<p>Research questions The focus of the research questions can be summarized as:</p> <ul style="list-style-type: none"> • Identification of genetic and other risk factors for the development and rupture of intracranial aneurysms; • Improvement of diagnostic tools for stroke, vascular cognitive impairment, and neonatal hypoxic-ischemic brain injury; • Development of new treatment strategies to improve outcomes after stroke and neonatal hypoxic-ischemic brain injury. • The disease burden for stroke and dementia in terms of economic costs and 'quality-adjusted life years' is high. In Europe, dementia ranks first for direct non-medical costs, and stroke second for direct healthcare costs.



3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made Together with the patient organisation Dutch Brain Aneurysm Patient Platform, we have developed a **research agenda** for the field of aneurysm research. We have brought our specific expertise to this agenda.

Our research in the field of stroke addresses key research questions in **Stroke Action Plan for Europe 2018 – 2030**, which has been developed by the European Stroke Organisation and the European stroke patient organisation SAFE. These questions include, but are not limited to: “which strategies will improve outcomes in ischaemic stroke patients who are not eligible for reperfusion therapies, or who do not recover after recanalisation?” and “Which treatment strategies will further improve outcome in patients with SAH by reducing brain injury?”

Our translational research follows **international recommendations and guidelines** for the optimisation of experimental and preclinical stroke research (e.g., the Stroke Treatment Academy Industry Roundtable and the Stroke Recovery and Rehabilitation Roundtable), in which imaging is put forward as a critical tool for translational studies.

Our investigators in the field of **neonatal brain injury** have an integrated program to recruit, care for, and study a uniquely fragile population across perinatal care with obstetricians, pediatric neurologists, surgeons, cardiologists, radiologists, imaging experts from the institute of sciences, and the Dutch connectome lab (combining methodology in acquisition and analysis). Additionally, we collaborate in (inter)national networks, consortiums and grants with other experts in Neonatal Neurology over the world. Together with the preclinical Department for Developmental Origins of Disease we develop bench-to-bedside perinatal (neuroprotective / neuroregenerative) research strategies.

Our research lines are **connected with the first 1001 days of a child’s life program** (research project of the Utrecht University strategic theme Dynamics of Youth) focusing from antenatal to their second birthday, the period critical to the development of their complex brains and the cognitive skills that depend on them. The aim of this program is to get broad support for initiation of scientific knowledge and expertise to enforce this critical first phase of these infants.

3.3. Stakeholders are involved in formulating the main research questions Investigators of different research lines meet at least annually with patient representatives from the diseases under study to discuss the strategic research program. Patient organisations we are closely in contact with are ‘Hersenletsel.nl’ and ‘Hersenaneurysma Patienten Platform’ at a national level. Clinical trials have been developed and are performed in close collaboration with the European stroke patient organisation SAFE. Other stakeholders include health funds (charities) such as the Netherlands Brain Foundation, Dutch Heart Foundation, and Alzheimer Nederland. Stakeholders are also other research groups involved in stroke research in the Netherlands and elsewhere.

3.4. The research questions are feasible and are pursued using optimal and efficient design Our studies are performed by or in close collaboration with clinical epidemiologists, statisticians, or methodologists. For studies of big data, omics, text mining, or machine learning expertise is sought in the UU and outside. For our preclinical studies, we follow the ‘Animal Research: Reporting of In Vivo Experiments’ (ARRIVE) guidelines.

3.5. What is ‘the next step’ if the project delivers positive results **Users of research findings** Multiple stakeholders are involved in most of our projects, including patient advocacy groups, industrial partners such as Nutricia-Danone and Philips, and other research groups.

Support for innovation and valorisation

We have a dedicated clinical trial developer who helps researchers make connections with industry.

Funding

We rely on a diversity of national and international funders. Funding in the last years was provided by for example the Dutch Heart Foundation, ZonMW, and NWO.

Memberships

Our researchers are or have been members of various international (guideline) committees. We present our work in professional literature and at professional society conferences. We emphasize the importance of dissemination of results to patients, care givers, patient organisations, funders, healthcare professionals. We have multiple newsletters per year and make use of social media.



Table 4: Suggested output indicators

<p>4.1 Research products for peers</p>	<p>1) Key publications</p> <ul style="list-style-type: none"> • Greving et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. <i>Lancet Neurol.</i> 2014;13:59-66. • Compter et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. <i>Lancet Neurol.</i> 2015;14:606-614. • van Asch et al. Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study. <i>BMJ</i> 2015;351:h5762. <p>2) development of publically available tool Our researchers developed and validated a fully automated and freely publicly available tool to segment hippocampal subfields at 7T MRI (https://www.nitrc.org/projects/ashs).</p> <p>3) Set-up of international platform The Vascular Cognitive Impairment group has set up an international platform to exchange brain lesion data and create vascular brain vulnerability maps for diagnostic purposes; DOI: 10.1016/j.dadm.2019.02.007</p> <p>4) Number of dissertations In total 24 dissertation were completed in the last five years: 2015 (6), 2016 (7), 2017 (5), 2018 (5), 2019 (1). The number of dissertations is expected to increase in 2019.</p>
<p>4.2 Research products for societal target groups</p>	<p>One of our researchers was last author of one of the articles in The Lancet 'Waste' series, with recommendations on how to increase value and reduce waste in biomedical research.</p> <p>PIs of the neonatal brain injury group have repeatedly appeared in national newspapers openly discussing the importance and safety issues of their in utero MRI study connected to Youth cohort, as a control group for infants with brain injury. This project is a collaboration between the antenatal and neonatal research lines. This media coverage paved the way between the general audience and several of our researchers, exemplifying to others how the public dialogue can help in gaining support for clinical research with the most fragile patients.</p> <p>Intracranial vessel wall MRI methods developed have been translated to clinical MRI scanners in close collaboration with Philips. These intracranial vessel wall MRI methods are now used on clinical MRI machines worldwide to better identify the cause of stroke in individual patients with cerebral ischemia including young stroke patients.</p>
<p>4.3 Use of research products by peers</p>	<p>1) One of our researchers has initiated an international consortium on the genetics of intracranial aneurysms within the international stroke genetics consortium (ISGC; https://strokegenetics.org/) currently comprising GWAS data of 10,000 well-phenotyped cases, making it the largest cohort worldwide. Different international researchers involved in the field of intracranial aneurysm genetics work with these data.</p> <p>2) The PHASES risk score (Greving 2014, see above) is applied in many clinical centers in decision making on whether to treat an intracranial aneurysm or not. So far the paper has been cited 241 times.</p> <p>3) Software tools for the analysis of neonatal brain injury developed in our unit are used by multiple research groups worldwide.</p>
<p>4.4 Use of research products by societal groups</p>	<p>Results of our trials HAMLET, VAST, and ESPRIT form an important basis of recommendations in international ischemic stroke guidelines; our studies on subarachnoid hemorrhage and unruptured intracranial aneurysms are used in international guidelines in this field.</p>
<p>4.5 Marks of recognition from peers</p>	<p>1) Research grant</p> <ul style="list-style-type: none"> • ERC StG grant, VIDI and Technical grants on intracranial vessel wall MRI to prof. dr. Hendrikse <p>2) Awards and fellowships</p> <ul style="list-style-type: none"> • Honorary award of the German speaking society of child neurology (GNP) to prof. dr. de Vries • Dekker fellowship to dr. Greving • 'klinisch fellowship' grant to dr. Ruigrok from the Netherlands Organisation for Scientific Research (NWO) <p>3) Scientific committee</p> <ul style="list-style-type: none"> • Prof. dr. de Borst is Chair of the Guideline Committee of the European Society for Vascular and Endovascular Surgery
<p>4.6 Marks of recognition from societal groups</p>	<p>1) Prof. dr. Hol is member of the KNAW committee for Alternatives for animal experiments in neuroscience.</p> <p>2) Dr. de Man-van Ginkel is co-author of Manifest for VWS ministry "Kwaliteit van zorg, nu en in de toekomst (24-04-18 discussed in the Dutch Parliament).</p> <p>3) 2bike4alzheimer award 2018 was dedicated to the research of dr. Geerlings' (2bike4alzheimer.inactievooralzheimer.nl/)</p>



Appendix: Organisational structure of the UMC Utrecht Brain Center from 2019 onwards

Management team

Jeroen Pasterkamp (division Neuroscience), chair
Manon Benders (division Woman and Baby), vice-chair
Leonard van den Berg (division Neuroscience)
Jeroen Hendrikse (division Cancer-Imaging)
Arjen Slooter (division Vital Functions)
Elly Hol (division Neuroscience)
Robert Stokroos (division Surgical Specialities)
Joanne Karssenbergh, communication
Marjolein Sneeboer, program manager

Advisory Board:

Stroke	Bart van der Worp	division Neuroscience
Precision Psychiatry (formerly Psychotic disorders)	Roger Adan and Higo Bruining	division Neuroscience
Epilepsy	Kees Braun	division Neuroscience
Neuromuscular disorders	Michael van Es	division Neuroscience
Developmental disorders	Jeroen Dudink and Freek Hoebeek	division Woman and Baby
Genetic Risks	Jan Veldink	division Neuroscience
Child Brain Center	Manon Benders	division Woman and Baby
Structure & Connections	Rick Dijkhuizen	division Cancer-Imaging
Translational Approaches	Elly Hol	division Neuroscience
Clinical Trials and Innovation (U-TRIAL)	Leonard van den Berg	division Neuroscience
Neuro-oncology (new)	Elly Hol and Tom Snijders	division Neuroscience



Appendix: program X-talks 2016-2017

Structure & Connections (September 9, 2016)

Beyond imaging-genetics

Organizers: Hilleke Hulshoff Pol & Martijn van den Heuvel

Genes are implicated in human brain structure and functions. This has been shown by heritability estimates in twin studies. Moreover, recently, using the genome-wide association study approach, several genes have indeed been associated with particular brain structures like the hippocampus, putamen and neocortex. These genes are identified thanks to unique collaborations among numerous labs around the world, in consortia that lead to shared, big data bases including MRI and DNA data from over 30.000 individuals. Many more genes are expected to be found in the near future using such approaches. However, this leads to the next question: what to do after a gene has been targeted as 'important'? The aim of this Structure & Connections meeting is to discuss what to do next, beyond the association, to maximize chances in finding solutions to treat brain diseases and improve healthy development and ageing.

Genetic Risk Factors (October 7, 2016)

Epigenome-Wide Association Analysis

Organizers: Jurjen Luykx &, Jan Veldink

Epigenome-wide association studies (EWAS) are revolutionizing the field of human genetics. The aim of such studies is to disentangle the contribution of the methylome and other genetic mechanisms at play in physiological and pathophysiological processes not 'readable' in our genetic code. This X-talks will cover recent and ongoing efforts to deepen our understanding of such mechanisms in brain disorders. Experts from outside and within UMC Utrecht will give presentations that are highly suited for a broad audience. We are proud that Bas Heijmans is amongst the speakers. To provide students and other researchers with the opportunity of learning the basics with regard to EWAS and epigenetics, we will start this X-talks with a general introduction by Bas Heijmans.

Environmental Risk Factors (November 11, 2016)

Preventive interventions and brain development

Organizers: Angela Sarabdjitsing & Christiaan Vinkers

Throughout life, the environment plays an important role in the susceptibility to disease and response to treatment. During this X-talk we will discuss both clinical and preclinical studies that target the environment from early life to advanced age. The importance of the early and later environment for brain development will be discussed, including the possibilities for preventive cognitive and biological interventions.

Translational Approaches (December 9, 2016)

Brain on a chip

Organizer: Elly Hol

Brain-on-a-chip and brain organoid technology enable the development of novel experimental models for studying the human brain and brain diseases. Building a realistic in vitro model of the human brain is a truly interdisciplinary effort of biomedical scientists, engineers, and biophysicists. Speakers from the UMC Utrecht and Utrecht University, and two guest speakers from technical universities will share their ideas about exciting novel human models for brain diseases.

From Research to Care (January 13, 2017)

Implementing research findings into clinical practice

Organizers: Arjen Slooter, Bas Neggers, Marjolijn Ketelaar & Tristan van Doormaal

Publishing research findings does not mean that these will be applied in routine, clinical practice, even when the journal has a high impact factor. How can one improve implementation? What determines inclusion of findings in a guideline? What guidelines find their way to clinical practice? Learn from the best examples and apply in the future!



Structure & Connections (February 10, 2017)

Trick or treat: brain MRI in intervention studies

Organizers: *Geert Jan Biessels & Rick Dijkhuizen*

At Brain Center Rudolf Magnus, brain imaging is extensively used in etiological and diagnostic studies. However, there is also great potential for imaging techniques in intervention studies. Images can be used to select the right subjects for intervention, to target the intervention on specific brain areas, or to assess the effect of treatment. This X-talk on Structure & Connections highlights opportunities, challenges and applications of brain imaging in intervention studies on brain disease in experimental animals and humans.

Genetic Risk Factors (March 10, 2017)

The latest on genome editing

Organizers: *Jurjen Luykx, Jan Veldink & Peter Burbach*

Genome editing is a fast evolving field at the crossroad of many branches of both medicine and genetics. We start this session by providing a brief introductory overview of genome editing. Recent advances in techniques as well as some of the first findings in genome editing, e.g. related to CRISPR/Cas9, will then be discussed. Finally, we hope to have lively discussions about some of the future applications of genome editing.

Environmental Risk Factors (April 7, 2017)

Medication during pregnancy and early infancy: impact on brain & behavior

Organizers: *Manon Benders/Jeroen Dudink & Heidi Lesscher*

The perinatal developmental period is extremely important for the wiring of a developing brain. Exogenous drugs at that time can have life-long consequences for brain and behavior. However, not treating is usually not an option. What have we learned from human and animal studies about perinatal drug treatment? Are there differences between males and females? Can early life treatment effects be reversed in later life? How do these insights impact on clinical practice?

Translational Approaches (May 12, 2017)

Complement and the nervous system

Organizer: *Mervyn Vergouwen*

The complement system is involved in infection and inflammation. Increasingly, the complement system is linked to the pathogenesis and outcome of diseases of the nervous system. In this X- talk, several investigators will discuss novel insights in the role of complement in the pathogenesis and outcome of diseases of the nervous system. The keynote lecture will be given by Piet Gros, who was awarded the NWO Spinoza Prize in 2010 for elucidating the three-dimensional structure of the C3 protein.

From Research to Care (June 9, 2017)

How to perform large-scale studies?

Organizer: *Arjen Slooter, Bas Neggers, Marjolijn Ketelaar & Tristan van Doormaal*

To be able to detect small effects, we need to include large numbers of patients. What should be characteristics of centers to approach when starting multicenter studies? How can we motivate other centers to raise inclusion, and how can we motivate patients to consent in participation?



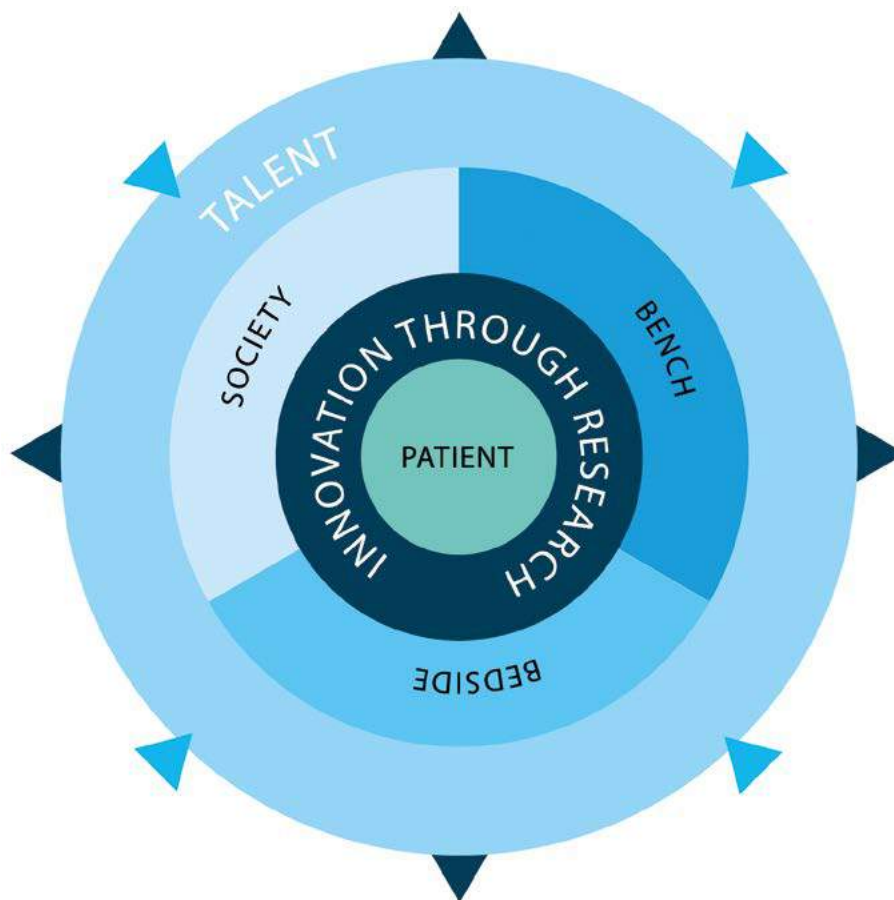
Self-evaluation report strategic research program **Cancer**





“Working to improve the outcome for cancer patients”

Multidisciplinary collaboration in cancer research is key to clinical innovation





List of abbreviations	85
1. Strategic research program Cancer	86
1.1 Mission	86
1.2 Strategy	86
1.3 Organisation	88
1.4 Crosslinks with other Strategic research programs	89
1.5 Composition and funding of the Strategic research program	90
1.6 SWOT analysis and strategy	91
1.7 Evaluation practices and/or policies	93
1.8 Talent management	93
1.9 Open Science activities	93
1.10 Involvement of patients in relevant phases of doing research	94
1.11 Participation and/or co-development in teaching	94
2. Theme: Fundamental	95
2.1 Mission, strategy and organisation of the theme	95
2.2 Urgency and relevance of the research questions	95
2.3 Relation to existing knowledge	96
2.4 Collaborations	96
2.5 Research Design	96
2.6 The next steps	96
2.7 Highlights of results	97
2.8 Most important scientific publications	99
2.9 Most important societal contributions	101
3. Theme: Translational	103
3.1 Mission, strategy and organisation of the theme	103
3.2 Urgency and/or relevance of the research questions	103
3.3 Relation to existing knowledge	104
3.4 Collaborations	105
3.5 Research Design	106
3.6 The next steps	107
3.7 Highlights of results	108
3.8 Research projects where patients are meaningfully involved	110
3.9 Most important scientific publications	111
3.10 Examples of research contributing to society	113



4. Theme: Clinical	114
4.1 Mission, strategy and organisation of the theme	114
4.2 Research questions and its urgency and/or relevance	114
4.3 Relation to existing knowledge	116
4.4 Collaborations	117
4.5 Research Design	117
4.6 The next steps	117
4.7 Highlights of results	119
4.8 Research projects where patients are meaningfully involved	126
4.9 Most important scientific publications	127
4.10 Most important societal contributions	129
5. Theme: Prevention and Survivorship	131
5.1 Mission, strategy and organisation of the theme	131
5.2 Urgency and/or relevance of the research questions	131
5.3 Relation to existing knowledge	131
5.4 Involvement of stakeholders	131
5.5 Optimal and efficient research design	132
5.6 The next steps	132
5.7 Highlights of results	133
5.8 Research projects where patients are meaningfully involved	136
5.9 Most important scientific publications	136
6. Appendices	140
Appendix 1: Research Leaders per Theme	140
Appendix 2: Tumor Working Groups	143
Appendix 3: UMC Utrecht observational cohorts/registries (status July 2019)	144
Appendix 4: Overview of teaching activities	146



List of abbreviations

Note: abbreviations of cohorts are described in Annex 3

ATMP	Advanced Therapy Medicinal Products
BBMRI	Biobanking and BioMolecular Resource Infrastructure
BMS	Biomedical Sciences
BOOG	Breast Cancer Research Group
BVN	Breast Cancer Society Netherlands
CAR	Chimere Antigen Receptor
cfDNA	cell free DNA
ctDNA	circulating tumor DNA
CIS	Clinical Image Sciences
CKI	Checkpoint inhibitor
CMM	Center for Molecular Medicine
CMV	Cytomegalovirus
CPCT	Center for Personalized Cancer Treatment
CRC	Colorectal-Cancer
CRU	Curriculum of Medicine
CS&D	Cancer, Stem Cells and Developmental Biology
CTMM	Center for Translational Molecular Medicine
CTO	Clinical and Translational oncology
dB&O	Division Imaging & Oncology
DCCG	Dutch Colorectal Cancer Group
DCE-MRI	Dynamic Contrast Enhanced – MRI
dH&L	Division Heart & Lungs
dHersen	Division Neurosciences
dHS	Division Surgical Specialties
dIG&D	Division Internal Medicine & Dermatology
dJC	Division Julius Centrum for Health Sciences & Primary Care
dLAB	Division Laboratories, Pharmacy & Biomedical Genetics
EBMT	European Society for Blood and Marrow transplantation
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EMBO	European Molecular Biology Organisation
ERC	European Research Council
ESN	Society for Inborn errors of Metabolism Netherlands
FLITS	Fluent In-House Trial Support
GAB	Grb2-Associated Binding
GI	Gastro-Intestinal
GSLS	Utrecht Graduate School of Life Sciences
HBO	University of Applied Sciences
HIFU	High Intensity Focused Ultrasound
HPB	Hepato-Pancreato-Biliary
HUB	Hubrecht Organoid Technology
I&I	Infection & Immunity
IKNL	Comprehensive Cancer Center the Netherlands

KIKA	Charity for childhood cancer
KNAW	The Royal Netherlands Academy of Arts and Sciences
KWF	Dutch Cancer Foundation
LTI	Laboratory for Translational Immunology
LTO	Laboratory for Translational Oncology
mCRC	metastatic colorectal cancer
MEN	Multiple Endocrine Neoplasia
MRI	Magnetic resonance imaging
NET	Neuro-Endocrine Tumors
NFK	Dutch Federation of Cancer Patient Organisations
NFU	Netherlands Federation of University Medical Centres
NWO	Dutch Research Council
PET	Positron Emission Tomography
PMC	Princes Máxima Center for pediatric oncology
PROMs	Patient-Reported Outcome Measures
PSB	Patient Sounding Board
PSMA	Prostate specific membrane antigen
PZNL	Cooperation Palliative Care Netherlands
RAKU	Regional Academic Cancer Center Utrecht
RCT	Randomised controlled trial
RIVM	National Institute for Public Health and the Environment
RMSC	Regenerative Medicine and Stem Cells
RNF43	Ring Finger Protein 43
SCT	Stem Cell Transplantation
SLIM	Study Logistics and Information Manager
SPECT	Single Photon Emission Computed Tomography
SUMMA	Selective Utrecht Medical Master
TEG	Genetically modified Immune cells
THINC	The Healthcare Innovation Center UMC Utrecht
Treg Cell	Immunosuppressive regulatory T Cell
TU/e	Technical University Eindhoven
TwICs	Trials within Cohorts
UNIEK	Utrecht Network Integral Expertise Cancer
UPORT	Utrecht Platform for Organoid Technology
UU	University Utrecht
Wnt	Wingless-related integration site
YIG	Young Investigator Grant
ZInNL	National Health Care Institute
ZonMW	Netherlands Organisation for Health Research and Development



1. Strategic research program Cancer

1.1 Mission

Cancer is the second leading cause of death globally. In 2018, it is anticipated that around 14 million people worldwide will be diagnosed with cancer, expected to reach over 22 million new cases of cancer a year in 2030. This is almost double the amount in 2012, according to the International Agency for Research on Cancer, mainly due to the growth and aging of people. When looking at death as a result of cancer, cancer is the second leading cause of death globally. This year close to nine million people will die of the disease, which equals an approximately 24,000 cancer deaths each day, numbers that are expected to have increased by 50% in 2030.

In The Netherlands, a similar steady rise in incidence and death rate is observed where cancer has become the major cause of death having surpassed those by cardiovascular diseases in 2008. Innovative approaches in cancer prevention, diagnostics and treatments are urgently needed to curtail these ever increasing numbers.

Next to the obvious physical and psychological anguish of patients and their families, the global financial burden of cancer is substantial and is anticipated to increase dramatically as the number of patients increase, and cancer diagnostics and treatments become more expensive. Therefore, aside from the patient perspective, the associated economic burden also forces the scientific community to put every effort in reducing the number of patients suffering from (the sequelae of) cancer.

The strategic research program Cancer of the UMC Utrecht is responsible for the strategic framework of the cancer research and the coordination of its implementation. The mission of the program is defined as: “working to improve the outcome of cancer patients”. To achieve this, we focus on innovative research overarching fundamental, translational and clinical science. Multidisciplinary collaborations and fostering talent are in our view fundamental to achieve our mission.

1.2 Strategy

Cancer researchers increasingly report on diagnostic and therapeutic breakthroughs based on molecular and cellular features of the tumor tissue and its environment, independent of organ type. To do justice to these scientific developments, the strategic research program Cancer decided to redefine the focus and steer away from the previously defined organ-specific focus areas, i.e. breast and gastrointestinal cancer.

The current focus is on four themes within a so-called ‘innovation loop’ (figure 1A). The four themes consist of

1. Fundamental research: unravel the biology of cancer.
2. Translational research: translation of knowledge into innovative approaches and using clinical data to define basic research questions.
3. Clinical research: evaluation of new diagnostics, prognostics and treatments.
4. Prevention and Survivorship: improve healthy living and quality of life.

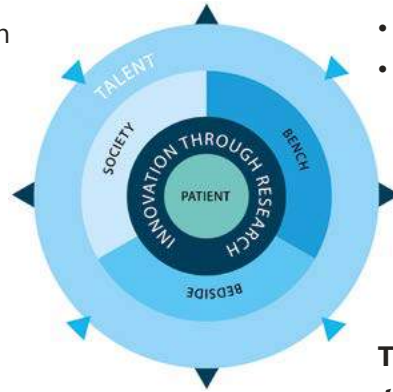
Scientific data obtained as a result of this innovation loop support our mission on improving the outcome and quality of life of our patients. In the clinic this enforces our research areas that have already been internationally recognized for their excellence, such as, molecular – and cellular-based systemic therapies, image-guided therapies and minimal invasive loco-regional interventions (see 4.7 Highlights of results and 4.9 and 4.10).

Structural cross-links between the scientific foci within the innovation loop and the care-path of our patients are in that regard crucial. Eleven multi-disciplinary tumor working groups have been installed, covering all major tumor-types (figure 1B). Associated professionals include clinical- and translational scientists, securing the delivery of the most innovative care to our patients. Close interactions with fundamental scientists result in the creation of bi-directional research questions adding to the further unravelling of cancer biology and thereby revealing potential new avenues of prevention, diagnostics and treatments.



Prevention & survivorship
improve healthy living and quality of life

- causes and prevention
- (early) diagnosis
- survivorship care
- palliative care



Fundamental research
unravel the biology of cancer

- genomics
- molecular and cell biology
- immunological landscape

Clinical research
Evaluate diagnostics, prognostics and treatments

- molecular - and cellular based systemic therapy
- image-guided therapy
- minimally invasive surgery

Translational research
translate knowledge into

- biomarkers
- therapeutic leads
- image-guided therapies

Figure 1A: Innovation loop of the Strategic research program Cancer

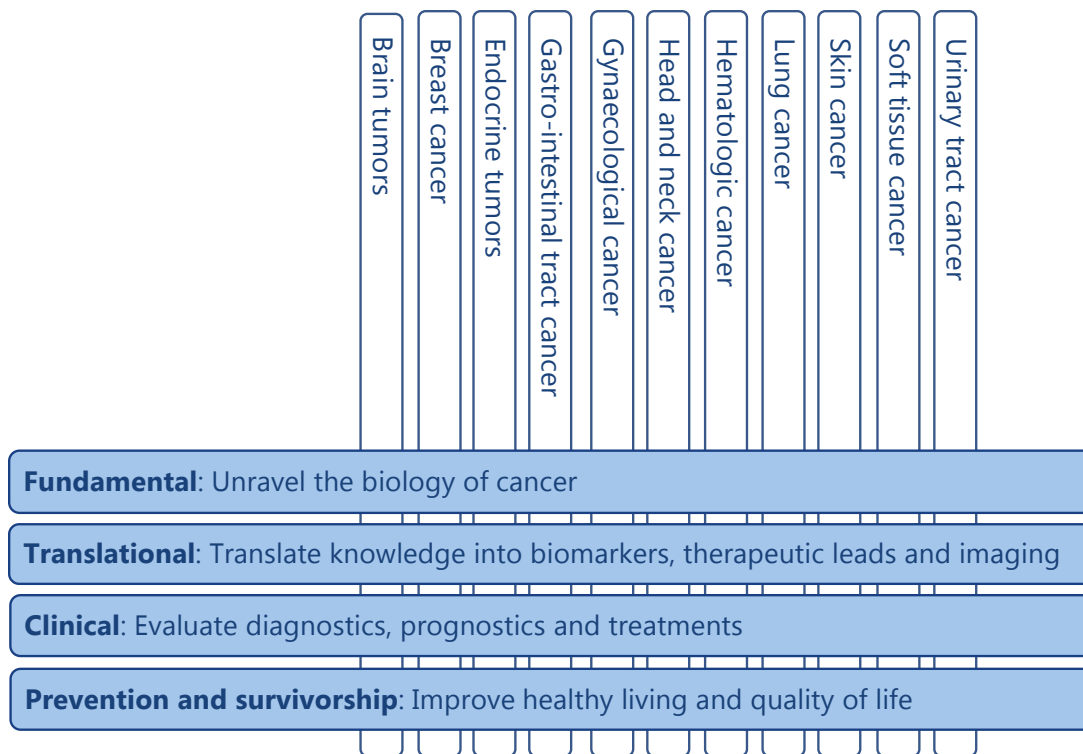


Figure 1B: Matrix of the Tumor Working Groups and the innovation loop

Thus, the matrix between science and care clearly enables us to rapidly implement innovative approaches to further advance patient outcome. Of note, this matrix is a rather unique approach, at least in the national field of cancer research, but is in our view fundamental to achieve the clinical progress that is so urgently needed.



Unique topics in Clinical Translation

Molecular - and cellular based systemic therapy (non-immuno- and immunotherapy)

- Molecular markers for risk and early detection.
- Molecular targeted and organoid -guided(-combinations), incl. Phase I/II trials.
- Immunotherapy: toxicity and development of new check-point inhibitors, cell therapy, innate immune system.

Image guided therapy

- MRI guided radiotherapy.
- MRI guided High Intensity Focused Ultrasound (HIFU).
- Peptide Receptor Radionuclide Therapy.
- Radio-embolisation.
- Digital pathology.
- Response prediction and monitoring, incl. Artificial Intelligence.

Minimally invasive surgery

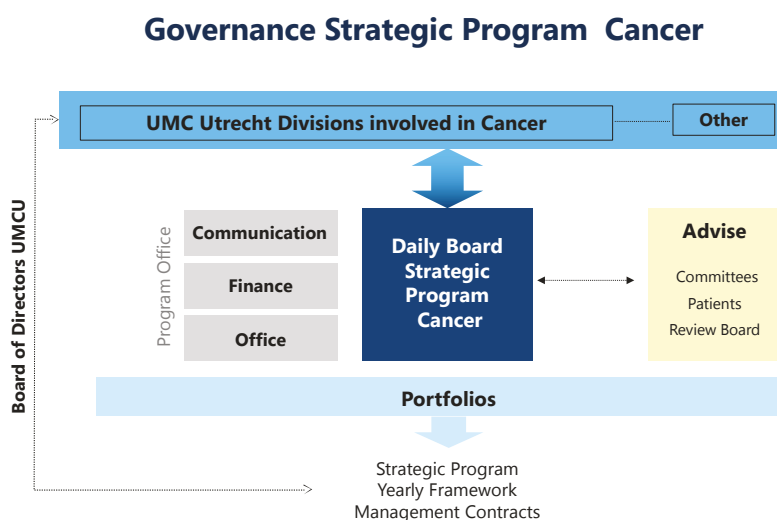
- Upper Gastro-Intestinal (GI): robotic-assisted surgery for treatment of esophageal cancer.
- Endocrine: robot-assisted trans-axillary approach for thyroid nodules.
- Urology: robotic cystectomy and prostatectomy.
- Other robotic programs: in Hepato-Pancreato-Biliary (HPB)-, rectal and breast cancer robotic programs are emerging, while other minimally invasive programs are rapidly expanding.

1.3 Organisation

Cancer researchers from seven UMC Utrecht Divisions contribute to the Strategic research program Cancer. A general board, consisting of researchers of these divisions and a communication- and a program manager, is responsible for the overall execution of the Program (see chart below). In addition, each board member has responsibility for one or two of five portfolio's dealing with overarching issues. Interaction between the Program and the divisions is secured by having installed two advisory boards that meet on a regular basis. The first advisory board assembles the scientific - and overall management professionals of the contributing Divisions whereas the second advisory board includes all involved department heads.

In addition, various platforms have been installed in order to stimulate multi- and cross-disciplinary research and collaboration. These consist, amongst others, of the above-mentioned tumor boards, dedicated research meetings, and scientific symposia for all researchers involved in the program.

Organisation of the Strategic research program Cancer



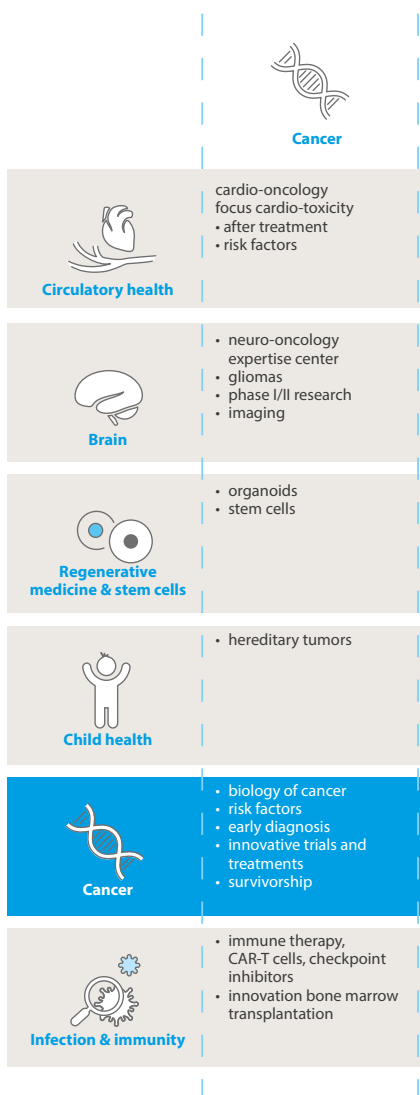
Divisions UMC Utrecht:

- Imaging & Oncology (dB&O)
- Laboratories, Pharmacy & Biomedical Genetics (dLAB)
- Julius Center for Health Sciences & Primary Care (dJC)
- Internal Medicine & Dermatology (dIG&D)
- Neurosciences (dHersen)
- Surgical Specialties (dHS)
- Heart & Lungs (dH&L)



Representative Daily Board	Function	Portfolio(s)
Elsken van der Wall	MD Medical Oncology	Chair
Boudewijn Burgering	Molecular Biologist	Fundamental & Translational Research
Susanne Lens	Molecular Biologist	Talent Management & Education
Onno Kranenburg	Translational Biologist	Fundamental & Translational Research, Facilities
Nico van den Berg	Imaging Physics	Talent Management & Education, Facilities
Gerlof Valk	MD Endocrinology, Epidemiologist	Clinical Science & Care
Carla van Gils	Epidemiologist	Clinical Science & Care
Jurgen Kuball	MD Hematology	Facilities
Inge Noordijk	Communication Manager	All
Erna Erdtsieck-Ernste	Program Manager	All

1.4 Crosslinks with other Strategic research programs



The Strategic research program Cancer clearly benefits from the expertise found in other Strategic research programs, as is depicted in Fig. 3.

Especially worth mentioning is the tight collaboration with the Strategic research program Infection & Immunity, where expertise on immunology and tumor biology are brought together to address the explosive data on the relevance of immune- and cellular therapies in solid- and hematological malignancies.

Figure 3. Crosslinks between the Strategic research program Cancer with the other Strategic research programs.



1.5 Composition and funding of the Strategic research program

During the years 2013-2018 the care for patients with cancer was assembled in one division, named Cancer Center, and simultaneously part of the cancer research was reallocated between divisions. Currently, several divisions involved in cancer care and research are in the process of merging. The present allocation of our researchers with a total of 255 fulltime-equivalent (FTE) is indicated in Table 1. As illustrated cancer research is now mainly clustered in the divisions B&O, LAB and JC. The number of PhDs, that finished their thesis in the period 2013-2018, was 218. Annually, this number ranged from 26-45 per year. (note: a complete list of graduated PhDs will be available during the site visit)

Table 1: Composition of cancer research FTEs in the Strategic research program

Divisions#	Percentage cancer research (%)	Amount of cancer research (FTE)	Relative contribution of research from each division to the Strategic research program Cancer
Imaging & Oncology (dB&O)	55%	110	
Laboratories, Pharmacy & Biomedical Genetics (dLAB)	49%	107	
Julius Centrum for Health Sciences & Primary Care (dJC)	18%	22	
Internal Medicine & Dermatology (dIG&D)	5%	7	
Surgical Specialties (dHS)	5%	5	
Neurosciences (dHersen)	2,4%	4	
Heart & Lungs (dH&L)	<1%	1	

Division Woman & Baby has less than 1 FTE and is therefore not included in this table.

The average external (research grants, contract research, other) funding of cancer research as depicted in Fig 4A was approx. 27.8 Meuro per year and relatively stable over the past 6 years. Part of the external funding (approx. 24%, i.e. 6.5 Meuro per year) is shared with other Strategic research programs on the scientific intersections as indicated in Fig. 3, especially with Strategic research programs Infection & Immunity (tumor immunology) and Regenerative Medicine & Stem Cells (cycle processes). (note: part of the funding of projects shared with neuro-oncology and pediatric oncology is not included in this table. This results in total corrected funding amounts as indicated in Table 2.)

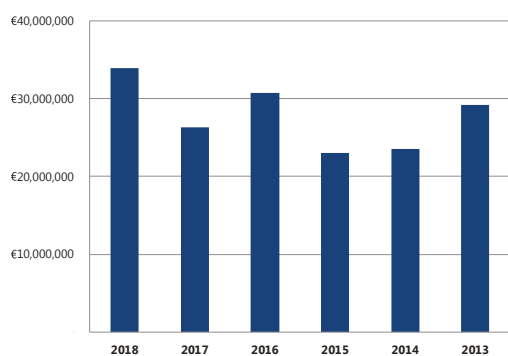


Figure 4A: Amount of total external funding for Cancer Research not corrected for shared research topics.

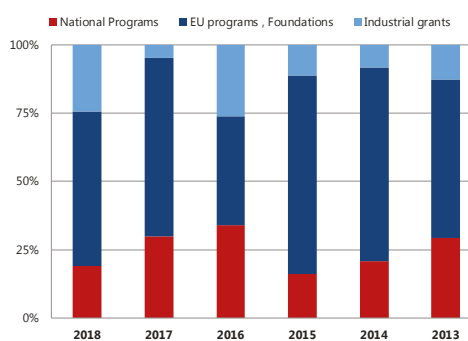


Figure 4B: The relative contribution of each of the funding types.

Fig. 4B shows that foundations/EU programs are the main contributors of the external funding with a mean of 61% of the total amount of External funding. In the period 2013-2018 93 projects have been financed by the KWF with a total amount of funding of 34 Meuro.

Industry makes up to an average of 15% annually. However, not included in either the table or the figures is external funding provided by means of research infrastructure. Especially in the field of Imaging the Strategic research program Cancer has several large co-creation projects with industry for which imaging equipment is made available.



Growth in 2018 is mainly due to a large contribution from Oncode institute (8,25 Meuro) for the fundamental scientists of the Center for Molecular Medicine (CMM) as well as the participation in the NWO-roadmap for large infrastructures (NWO 2,5 Meuro).

Table 2: Research funding (corrected for shared research topics with other Programs¹)

	2018	2017	2016	2015	2014	2013
National Grants²	€ 5,648,771	€ 6,724,746	€ 9,572,216	€ 3,372,687	€ 4,455,670	€ 6,727,638
External Grants³	€ 17,575,440	€ 14,711,525	€ 10,874,190	€ 14,460,948	€ 13,049,222	€ 14,998,057
Contract Research⁴	€ 7,537,376	€ 1,110,919	€ 7,041,861	€ 2,150,060	€ 1,942,630	€ 2,984,618
Total Funding	€ 30,761,588	€ 22,547,190	€ 27,488,267	€ 19,983,694	€ 19,447,522	€ 24,710,313

Note 1: Part of project funding shared with neuro-oncology and pediatric oncology is not included in this table.

Note 2: Competitive grants from Dutch national research funders (e.g. NWO, ZonMw, KNAW)

Note 3: Grants from external, not-for-profit parties (e.g. European Commission and health charities)

Note 4: Grants from industry.

1.6 SWOT analysis and strategy

Strengths

1. Leading international position on image guided cancer therapies as result of own technical innovation and co-development with large industrial partners.
2. Longstanding (inter-)national reputation in molecular-based science of cancer biology, including broad involvement in the national Oncode Institute.
3. Leading international position in organoid-based research, incl HUB and UPORT facilities.
4. Frontrunner in innovative immune-and cellular therapies.
5. Broad clinical implementation of minimal invasive techniques.
6. Strong entrepreneurship in molecular, cellular and imaging sciences with co-development, spin-offs and noteworthy public-private partnerships.
7. Innovation cycle – technology development and translation towards clinic – with a strong fundamental and technical scientific core (both molecular and medical physics).
8. Availability of large patient (and population-based) cohorts linked to biobanked patient materials with involvement of cancer epidemiologists and statisticians with expertise in innovative designs and state-of-the art methodological techniques.
9. Unique partners at Utrecht Science Park and strategic regional alliances (UNIEK, RAKU) strengthen fundamental, translational and clinical science and care.
10. Official integrated patient participation by a patient sounding board (PSB).
11. High quality education at all levels.

Weaknesses

1. Centralized organisation for clinical trial support and - execution not yet optimized.
2. Cross-connection between researchers from various disciplines and themes is not equally utilized.
3. Unclear role and responsibilities between the Strategic research program and Divisions.
4. Limited dedicated research and teaching time, especially for clinicians.
5. Unclear career perspective for senior postdocs and assistant professors.
6. No structural plan to implement data science expertise and infrastructure, many fragmented initiatives in the different divisions.
7. Weak visibility of our expertise on rare diseases because participation in the European Expertise Centers and Reference network is lagging behind.



Opportunities

1. Translational laboratories (Oncology, Immunology and Imaging) to stimulate crosslinks between fundamental and clinical research.
2. Start of U-Trial, a centralized trial team, accelerates leading experimental research of new treatments.
3. National health directive to focus on prevention and extra-mural health care fits within the focus areas of our Program.
4. Stronger interaction of research and clinic on use of artificial intelligence for Imaging, Pathology and treatment management.
5. Further strengthen valorisation by cross-institutional Oncode collaborations and CAR-T stakeholder platform.
6. Further clinical development of image guided/minimally invasive therapies (e.g. MR-Linac network) together with external public and private partners.
7. Relocation en strengthening of key Good Manufacturing Practice facilities (Tracers, Advanced Therapy Medicinal Products) to facilitate first in men studies.
8. Positioned to expand networks with general and academic hospitals.
9. New research collaborations with the Princes Máxima Center for pediatric oncology (PMC) now cover research on the entire lifespan.

Threats

1. Persistent cost-reduction in national health care threatens investments in research.
2. Lack of dedicated time for research of (pre-)clinical scientists threatens development and implementation of innovation and may weaken our competitive status by driving our talented (clinician) scientists to other institutions.
3. Potential decline in degree of autonomy and flexibility of fundamental scientists, forced amongst others by increasing (external and internal) focus on health/patient care, poses a risk of losing competitive advantage by not providing a nurturing environment to researchers.
4. Lack of means of the UMC Utrecht to meet increasing demands on financial matching of grants.
5. Insufficient financial support for teaching / education may diminish the high-quality standards of our unique master (e.g. SUMMA) and PhD programs.
6. Lack of structural support of the Cell Therapy Facility and Good Manufacturing Practice of compounds as key facilities for clinical trials.
7. Increasing demand and complexity of regulatory aspects, e.g. EU-directory on clinical research.

Strategy

We envision that we can counteract some topics addressed under weaknesses and threats. We anticipate that the redesign of our Program with focus on 4 domains and the strong multi-disciplinary interaction between fundamental, translational and clinical scientists will further enhance our strong position in molecular, cellular and imaging science. This also aligns with a strong trial portfolio and the unique patient cohorts including biobank data, and expertise in building and utilizing these data for research. Illustrative in this regard is our contribution in the development of and participation in the recently founded national COIN project (Circulating tumor DNA On the road to Implementation in the Netherlands). Our redesign will not only create a stimulating unique multi-disciplinary environment but also will increase the likelihood of obtaining external funding that provide current scientists with dedicated research time and will likewise result in influx of talented professionals. To name a few initiatives: regular meetings between Oncode researchers from the campus and translational and clinical scientists from UMC Utrecht are being organized addressing bi-directional research questions. An "Oncotalent program" has been installed that addresses, amongst others career paths, mentorships and grant-writing support. Tumor working groups have been asked to establish National Expertise Centers that subsequently can apply to the European Network. Overall communication and 'branding' of our Program is essential and various initiatives have been taken by the newly appointed communication manager that stimulate visibility and the creation of internal and external collaborative networks. Other weaknesses and threats demand close tuning with the management teams of the Divisions and the UMC Utrecht Board of Directors.



1.7 Evaluation practices and/or policies

Crucial to the success of the Strategic research program Cancer are the research leaders (approx. 100) of the UMC Utrecht. We have identified those research leaders based on the following definition:

A fundamental, translational or clinical cancer researcher who

- has his/her own research group (including one or more PhDs),
- has his/her own research line,
- has acquired (independent) one or more research grants,
- has (inter)national recognition for his/her expertise evidenced by invitation for lectures, reviews etc.

For clinical researchers, who, besides their research, also perform minimally 40% patient care, 3 of the above-mentioned criteria are applicable.

1.8 Talent management

To foster our talents the Strategic research program Cancer has started activities at various levels of career track. For post-doctoral students and assistant professors an “Oncotalent” program was launched. Together with post-doctoral students and assistant professors events (e.g. mentoring program, speed dating sessions, masterclasses) will be organized and offered to help these young researchers in their (academic) career development and facilitate them to build a cross disciplinary network within UMC Utrecht. Besides, from 2019 onwards the Strategic research program Cancer will be responsible (in collaboration with their divisions) for the yearly Associate and Full Professor strategy.

1.9 Open Science activities

Open Science is the ongoing transition in how research is performed and how knowledge is shared. It represents a new approach to the scientific process based on cooperative work and new ways of knowledge distribution using digital technologies and new collaborative tools. The Program operationalizes Open Science in three domains: openness of the research agenda & stakeholder involvement, openness of data and protocols and open access publications according to the policy of the UMC Utrecht.

A. Openness of the research agenda & stakeholder involvement

Yearly, the UMC Utrecht has established 12 Open Lectures for the lay public, to be organized twice by each Program. In addition, cancer researchers organize various Open Lectures that address topics on a specific cancer type or on new technical or ethical developments. Four times a year, volunteers of the Dutch Cancer Foundation are invited for a lecture by 2 of their awardees and a guided lab tour. At a regular base, the research strategy is discussed with representatives of the Patient Sounding Board as well as with various Patient Advocacy Groups. Bachelor- and master students are yearly updated on the progress of the Program. And finally, various professionals are involved in public activities such as (social-) media, articles in lay- magazines, visits to primary schools etc.

Obviously, scientific progress is discussed at regular intervals with our collaborators from the campus, regional teaching hospitals, other universities and UMC's including the Netherlands Cancer Institute, and partners such as the Comprehensive Cancer Center the Netherlands (IKNL) as well as medical technology companies and pharma.

Examples are indicated in the boxes with “research products” as described for each theme.

B. Openness of data and protocols

It is our vision that a high-quality data infrastructure is indispensable for research and innovation. This must be structurally embedded and independent from ‘local’ initiatives of individual researchers. Researchers must be supported (access and user support) to generate standardized and harmonized data to secure quality and reproducibility, in order to increase future societal impact. Therefore, we stimulate:

- Science conform FAIR principles (Findable, Accessible, Interoperable, Re-usable).
- Our departments have specialists for omics data management and analysis.
- Execution, storage and sharing of human samples according to the Biobank protocol.
- Good Clinical Practice (GCP)-compliant phase I/II research by a dedicated professional team.
- Implementation of trial offices and U-Trial for execution of clinical research (advise, quality control, teaching, monitoring, registration of studies in public database etc).



C. Open Access publications

As part of Open Science, we stimulate publication of research findings in Open Access journals and on preprint servers to make publicly funded research indeed publicly available. UMC Utrecht researchers can apply for financial support at the Utrecht University Open Access fund that partly reimburses article processing charges. Currently 53% of our papers (period 2016-2018) is either a “gold”, “green” or “hybrid” publication.

1.10 Involvement of patients in relevant phases of doing research

The strategic research program Cancer greatly values partnership with patients. In 2007 we founded the patient sounding board (PSB) of the Cancer Center composed of patient advocates, nursing staff and medical personnel. They convene every 2-3 months and are asked for requested and unsolicited advice on topics varying from patientcare, health care strategy to research. The redesign of the Program also has been discussed expressing our aim to further shape the role of patients in the developments of specific research projects. In addition, at the starting phase of Center for Personalized Cancer Treatment (CPCT) some members of the PSB were joined with newly appointed patient advocates with expertise in research to form the CPCT PSB where they were asked to advice on the content and the strategy of CPCT. Several examples of patient involvement and participation are described in the 4 themes of our strategic research program.

1.11 Participation and/or co-development in teaching

It is our ambition to be an internationally recognized top institute that trains the next generation of clinicians and nurses, MD/PhD and cancer researchers. In line with the recently published position paper of the KNAW^{annex 4}, emphasizing the importance of intertwining of research and education for high quality academic training of future (health) professionals, we want to retain and recruit teachers that are active investigators and clinicians. Together with the continuous development of new thematic courses, updating of the existing ones, and the recent Bachelor Research Hub, this ensures coverage of the latest developments and approaches in cancer care, diagnosis and disease biology in the various curricula. Our 7 divisions are asked to participate in this innovation of education.

The Program Cancer contributes significantly to education ranging from bachelor student to medical specialist (detailed information is available in annex 4).

- Bachelor: various courses for (bio)-medical students and a Hub for small research projects.
- Master phase: various (inter-disciplinary) master programs and research internships.
- PhD programs: Cancer, Stem Cells and Developmental Biology (CS&D), Clinical and Translational Oncology (CTO), Medical Imaging (ImagO) and Epidemiology offer courses, symposia and masterclasses.
- Medical specialists: rotations within the subspecialty oncology are offered.
- Imaging specialists: annual courses on MRI in radiotherapy and Deep Learning for radiotherapy.
- Nurses: training as an oncology nurse. For talents (master)courses (with NFU), post-HBO courses (University of Applied Sciences) on palliative care, and a HBO-summer course Oncology are offered.
- Post-Docs/assistant Professors: “Oncotalent” program for career development.
- Other: various International Summer Schools.



2. Theme: Fundamental

2.1 Mission, strategy and organisation of the theme

A major goal of all fundamental research within the Program is to make discoveries that have impact on patients and society. A recent opinion paper stated that “Today’s most transformative medicines exist because of fundamental discoveries that were made without regard to practical outcome and with their relevance to therapeutics only appearing decades later.” (Spector et al., *Sci. Transl. Med.* 10, eaaq1787 (2018)). As such, fundamental science is a crucial domain in our “innovation-loop”.

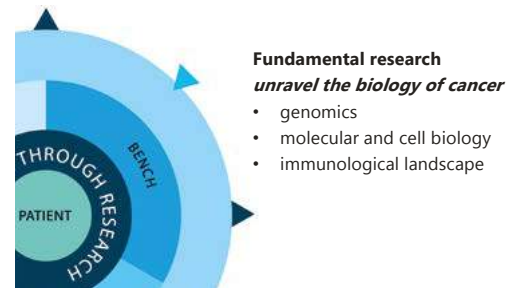


Fig. 1 Topics of the theme

Current developments in precision medicine predict that tailored patient treatment and/or patient stratification for therapy will increasingly rely on improved insights in disease-causing mechanisms. As an example, the discovery of the Maurice lab that RNF43/ZNRF3 (Ring Finger Protein 43/E3 ubiquitin ligase zinc and ring finger 3) mutations drive Wnt (Wingless-related integration site) hypersensitivity in cancer (Koo et al, *Nature* 2012, cited 450 times) has provided basic knowledge that have led to the initiation of current Phase I clinical trials in which cancer patients carrying RNF43 mutations are treated with Wnt secretion inhibitors (Novartis) and Wnt receptor blocking antibodies (Boehringer). Insights into the role of the tumor microenvironment have more recently been fueled by fundamental understanding of the immune system and its response to different cancer types (see also Theme Translational, Clinical and Strategic research program Infection and Immunity). In line with this, the Peperzak group developed a novel technology to improve the killing machinery of engineered T cells for use in cancer immunotherapy. This approach is applicable to all types of engineered T cells and has the potential to improve immunotherapy worldwide.

Fundamental cancer research in the UMC Utrecht is performed by research groups in the Center for Molecular Medicine (abbreviated as CMM, and harboring the departments of Molecular Cancer Research, Cell Biology, Stem Cells, and Genetics) and in the departments of Hematology and Immunology. The majority of the fundamental scientists are gathered at the CMM working floors where regular scientific working discussions are held. The aim of the Strategic research program is to further improve on natural interactions between fundamental, translational and clinical scientists to pose the crucial questions to be solved by sharing each expertise.

2.2 Urgency and relevance of the research questions

The mission of the fundamental cancer research unit is to unravel basic molecular and cellular mechanisms that underlie carcinogenesis and induce a tumor promoting environment. These are addressed in the three main topics, genomics, molecular and cell biology and immunological landscape, and involve many research lines that are also potentially underlying other diseases. For example, signal transduction, the molecular mechanisms of cellular communication, is essential for normal cell and organismal function, but defects in signal transduction are known not only to induce cancer but also cause many other human diseases. Thus, whilst our research groups study numerous aspects of cancer biology, the results potentially add to the understanding of a variety of other diseases. The reverse pertains to the unravelling of many immunological phenomena related to failures in our infection defense mechanisms or aberrant immune-responses in autoimmune diseases which are now known to be hugely relevant in cancer development and treatment. The relevance of fundamental research is the premise that in order to effectively treat the disease, knowledge of the underlying molecular and cellular mechanisms is essential. This is supported by the fact that, over the last years, most of the progress seen in cancer outcome has been achieved by systemic treatment with targeted agents including immunotherapy, the target being the specific mutation discovered by molecular science. However, with still an only 60% 5 years general overall survival including cancer types barely reaching 15%, there is still a significant knowledge gap to be solved.



As mentioned earlier, our main three topics focus on:

Genomics

- Identification and molecular characterisation of novel disease driving mechanisms. Genomics and bioinformatics approaches are used to understand the genetic basis of cancer.

Molecular and Cell Biology

- Understanding of the molecular mechanisms underlying (stem) cell fate decisions and cancer biology, including aberrant signal transduction, cell division, chromatin and gene regulation, cellular disorganisation, cell-cell communication and senescence.

Immunological Landscape

- Development of advanced therapeutic dendritic cell vaccines and adoptive (engineered) immunotargets, discovery of new targeted antibodies and insight into cellular cytotoxicity and tumor immune evasion processes.

2.3 Relation to existing knowledge

In view of the above, the primary goal of the fundamental cancer research unit is to generate new knowledge in cancer biology and the tumor microenvironment that will eventually benefit the patient. This is done in close collaboration with national and international counterparts in order to share ideas and join forces. As an example, eight of our researchers are part of the Onco Institute that provide collaboration on the highest expertise level within The Netherlands and internationally.

2.4 Collaborations

Research leaders of the fundamental cancer research unit collaborate with fundamental, translational and clinical researchers at all levels both locally, nationally and internationally (see also above). The research questions are mainly determined by the individual research leaders. Discussion with and choice of collaborators shapes how the research question is addressed. In individual cases, interactions with patient representatives have been established, including when formulating grant applications.

Four times a year volunteers of the Dutch Cancer Society (KWF), many of them being cancer patients themselves, are invited to a guided lab tour where research-topics are being addressed and discussed.

2.5 Research Design

The research leaders of the fundamental cancer research unit are acknowledged experts in their respective fields as illustrated by the considerable number of high-profile papers, citations and invitations to speak at international conferences and research institutes. As a result of their broad visibility, collaboration with colleagues extends to knowing the researchers that can provide expertise on adjoining fields, such as statisticians and methodologists, and of those who are (inter)national experts on the development and implementation of new technologies. This too add to their shared vision of always thriving to answer the research questions in the best possible way making use of all expertise available, national and international.

2.6 The next steps

Obviously, results of our fundamental science will to a large extent form the basis of new grant applications. Through participation in the Onco Institute, valorisation of our research products is clearly emphasized and is structurally addressed in joined research meetings. Moreover, it is our strongly felt responsibility to share the progress of our research with society and as such data are frequently covered by the general media (see description of results) or presented at various patient organisations.



2.7 Highlights of results

Research products for peers

Datasets, biobanks

- CPCT-2 Dataset (see also annex 3) (**Cuppen**).

Infrastructure

- Feasibility of organoids as a pre-clinical model to screen drug compounds and assistance in personalized therapy design (**Snippert, Maurice, Kranenburg**).
- Bioinformatics platform: tools and methods to deal with novel genomics technology, in particular 3rd generation (nanopore) sequencing (**de Ridder**).

Instruments, compounds, software tools

- Novel machine learning methodology (**de Ridder**).
 - Metabolomics method - Direct Infusion Mass-Spectrometry (**Verhoeven-Duif**).
-

Research products for societal target groups

Policy documents

- Initiation of ONCODE Institute with ministries of VWS (Health, Welfare and Sport), OCW (Education, Culture and Science) and EZ (Economic Affairs and Climate Policy) and with KWF: Uniting fundamental cancer researchers in The Netherlands to bring their research discoveries into the clinic faster (**Bos, Clevers**). Current UMC Utrecht Oncode investigators are: **Bos, Burgering, Cuppen, Lens, Maurice, Meyaard, de Ridder, Snippert**.

Publications accessible for a large audience

- 2015 Interview about the possibilities of growing stem cells for treatment of patients on National broadcast. <http://dewerelddraaitdoor.vara.nl/media/332678> (**Clevers, Bos**).
- 2016: Interview about the launch of Oncode, trans-university collaboration on cancer research <https://dewerelddraaitdoor.bnnvara.nl/media/355825> (**Bos**).

"Products" designed for public use

- 2018: A movie with the MouseAge consortium, <https://vimeo.com/255209277> to ask for awareness of aging as a major health problem in the future and how we should tackle it.

Outreach activities

- 2015 Professors on stage: Debate on (fundamental) cancer research for a layman audience (**Lens**).
 - Summer school for primary school students: Together with cancer-genomics.nl we developed a 2 hour practical on DNA for the Summer School Junior of Utrecht University. Our practical was taught to about 180 pupils in the 4 highest classes of primary school. The children isolated their own DNA and created a 'candy DNA-strand' based on their own hair color. A TV item was made by RTV Utrecht with a short interview of the DNA-lab coordinator, Ragna Senf.
 - Workshop for high school teachers: In collaboration with U-talent we developed a teacher-workshop on molecular insights into cancer and the personalized treatment of cancer. So far the workshop has been organized successfully twice.
 - Four times yearly: guided lab-tours for volunteers of the Dutch Cancer Foundation.
-



Use of research products by peers

Use of biobanks and data collections

- Hartwig Foundation uses data from CPCT (**Cuppen**).

Use of research facilities/infrastructure

- Use of the organoid platform is described in the theme “Translational” (**Maurice**).
- Funding from NWO to setup a novel laboratory course in which students Biomedical Sciences and Medicine work together in a lab to address an actual patient problem or a patient with unknown diagnosis/disease. Patients are also involved and will benefit (**Bovenschen**)

Use of software tools, instruments

- CHORD: a tool which allows for the pan-cancer detection of homologous recombination deficiency, which is relevant for platinum- or parp inhibitor-based anti-cancer therapy. This tool is already taken up in the whole genome sequencing-based patient report from Hartwig Medical Foundation and used for stratifying patients towards experimental (off-label) therapy (**Cuppen**).
-

Use of research products by societal groups

Consortia, public-private partnerships

- 2016 H2020 consortium MECHANO CONTROL (**de Rooij, Derksen**) - Mechanical control of biological function.
- The discovery that RNF43/ZNRF3 mutations drive Wnt hypersensitivity in cancer (Koo et al, Nature 2012, cited 450 times) has provided a foundation for ongoing Phase I clinical trials in which cancer patients carrying RNF43 mutations are treated with Wnt secretion inhibitors (trial designed by Novartis) (**Maurice**).
- 2019 Consortium Netherlands Organisation for Health Research and Development (ZonMW) /Health Holland (**de Keizer**) on healthy aging (8 M EUR).
- Partnership with SkylineDX for valorisation of the novel machine learning methodology (**de Ridder**).

Implementation in guidelines, reimbursement

- Feedback on policy reports regarding Chimere Antigen Receptor (CAR) T cells to the National Health Care Institute (ZInNL) (**Minnema, Jak**).

Patent (applications), spin-offs

- 2015 Hartwig (**Cuppen**) Next Generation Sequencing (NGS) and bioinformatics approaches developed within CMM have been at the basis for these developments. HMF is currently world leading in whole genome sequencing-based cancer diagnostics.
 - 2015 spin-off: Gadeta BV - valorisation of a first set of gamma-delta T-Cell Receptors ($\gamma\delta$ -TCRs). The spin-off company was named as one of the top 10 spin-offs of 2016 worldwide by Nature Biotechnology. In 2018 the company started a strategic partnership for the clinical exploration of main leads with KITE and GILEAD (**Kuball**).
 - 2018 spin-off: Cleara Biotech BV (**de Keizer**) - an approach to specifically eradicate senescent cells.
 - 2018 spin-off: Cyclomics BV (**de Ridder**) - a protocol to use third generation (nanopore) sequencing for improved detection of cell-free tumor DNA which enables better cancer diagnostic using liquid biopsies.
 - 2018: Patent application on a novel technology in cancer immunotherapy (**not to be disclosed**).
-

Marks of recognition from peers

Awards, individual research grants: Veni, Vidi, Vici, ERC, Marie-Curie, KWF-Young Investigator grant (KWF-YIG)

- 2013: KWF-YIG (**Snippert**), Vici (**Cuppen**), Marie Curie ITN (**Maurice**).
- 2014: KWF YIG (Dansen).
- 2015: Vici (**Maurice**).
- 2016: Vidi (**de Ridder**).
- 2017: Vidi (**Gloerich**), Veni (de Henau), KWF YIG (**Rodriguez-Colman**),
- 2018: ERC Starting Grant (**Snippert**).



Elected memberships of scientific committees

- European Molecular Biology Organisation (EMBO) Member (**Bos, Burgering**).
- reviewing board ERC (**Burgering, Lens**).
- Worldwide Cancer Research (**Burgering, Coffe**).
- European Strategy Forum on Research Infrastructures- EuroBioImaging. 2010-2014: Steering Committee (**Klumperman**).
- NL-BioImaging-AM. Dutch Roadmap initiative for Research Infrastructure for Advanced Microscopy (**Klumperman**).

Editorial boards

- Molecular and Cellular Biology (**Bos**), PLoS ONE, Front. Cell. Dev. Biol. (**Bovenschen**), Journal Biological Chemistry (**Burgering**), Glia (**Hol**), Scientific reports (**Kalkhoven**), various immunology/cancer journals (**Leusen**)
-

Marks of recognition from societal groups

Public prizes

- 2013: Martinus van Marum Prijs, Koninklijke Hollandsche Maatschappij der Wetenschappen (**Snippert**).
- 2014: Josephine Nefkens price for cancer research (**Bos**).
- 2018: Teacher of the Year 2018' of the Faculty of Medicine and as 'Teacher of the year 2018-2019' of the whole Utrecht University (**Bovenschen**).

Membership of civil society advisory bodies

- Scientific council KIKa (charity for childhood cancer) (**Bos, Kuball**).
- Scientific board of Pediatric Brain Cancer Foundation Koppie-AU (**Bovenschen**).
- Scientific Committee KWF (**Burgering, Kuball, Maurice**).
- Reviewing Board Dutch Rheumatology Foundation (**Coffe**).
- Chair Netherlands Organisation for Scientific Research (NWO) Veni review board (**van Mil**).
- Board Member of European Society for Blood and Marrow transplantation (EBMT) from 2015-2019 and chair of the Legal and Regulatory Affairs Committee from 2020 (**Kuball**).
- Member of the KNAW Comenius Network that directly advises the minister and ministry of OCW (**Bovenschen**).

Consultancies for public or private sector

- Scientific advisor Cleara Biotech BV (**Burgering**).
 - Study section member for the Swedish Research Council (**Coffe**).
 - Dutch Technology Centre : Member of the Core group (**Klumperman**).
 - recurring panel member of nation-wide policy platforms (Fakton Forum, Providence Capital forum), retirement funds (ABP, NETSPAR), the Dutch ministry of Health, Welfare and Sport (VWS) (Medtech Forum), to Dutch political parties (CDA think tank), and the EU parliament (**de Keizer**).
 - Member of the Young Academy of Europe (**Maurice**).
-

2.8 Most important scientific publications

Interplay between metabolic identities in the intestinal crypt supports stem cell function.

Rodríguez-Colman MJ, Schewe M, Meerlo M, Stigter E, Gerrits J, Pras-Raves M, Sacchetti A, Hornsveld M, Oost KC, Snippert HJ, Verhoeven-Duif N, Fodde R, Burgering BM. Nature. 2017 Mar 16;543(7645):424-427.

It is very well known how ligands such as WNT or Notch determine stem cell fate and function in the small intestine model. This paper described for the first time how differential metabolism helps in determining stem cell function. An intricate interplay between the metabolism of the stem cell and the metabolism of the Paneth cell is unraveled and shows that in contrast to common belief stem cells are high in mitochondrial metabolism whereas Paneth cells are high in glycolytic metabolism in order to provide stem cells with lactate to sustain their mitochondrial metabolism. This metabolic interplay is essential for proper stem cell function and differentiation.



Specific Labeling of Stem Cell Activity in Human Colorectal Organoids Using an ASCL2-Responsive Minigene.

Oost KC, van Voorthuisen L, Fumagalli A, Lindeboom RGH, Sprangers J, Omerzu M, Rodriguez-Colman MJ, Heinz MC, Verlaan-Klink I, Maurice MM, Burgering BMT, van Rheeën J, Vermeulen M, Snippert HJG. *Cell Rep.* 2018 Feb 6;22(6):1600-1614.

This paper demonstrates our ability to develop a novel genetic tool that is now widely used by many groups within CMM but also outside CMM to study stem cell function. The tool allows rapid and easy labeling of stem cells of epithelial origin in any living biological sample, including but not limited to organoid cultures.

Tissue-specific mutation accumulation in human adult stem cells during life.

Blokzijl F, de Ligt J, Jager M, Sasselli V, Roerink S, Sasaki N, Huch M, Boymans S, Kuijk E, Prins P, Nijman IJ, Martincorena I, Mokry M, Wiegerinck CL, Middendorp S, Sato T, Schwank G, Nieuwenhuis EE, Verstegen MM, van der Laan LJ, de Jonge J, IJzermans JN, Vries RG, van de Wetering M, Stratton MR, Clevers H, Cuppen E, van Boxtel R. *Nature.* 2016 Oct 13;538(7624):260-264.

This paper demonstrates how organoids can be used to determine mutation rates and if they depend on lifespan. Surprisingly, adult stem cells remain equally genetically stable over time. We combined various strengths of the Utrecht Life Sciences community: clinical material from various departments, organoid technology from Hubrecht Institute and HUB, next-gen sequencing facility supported by UMC Utrecht, UU, Hubrecht Institute and genetics, and genomics and bioinformatics expertise within CMM. The paper has been cited almost 150 times since its publication in October 2016.

Enhancer hubs and loop collisions identified from single-allele topologies.

Allahyar A, Vermeulen C, Bouwman BAM, Krijger PHL, Verstegen MJAM, Geeven G, van Kranenburg M, Pieterse M, Straver R, Haarhuis JHI, Jalink K, Teunissen H, Renkens IJ, Kloosterman WP, Rowland BD, de Wit E, de Ridder J, de Laat W. *Nat Genet.* 2018 Aug;50(8):1151-1160.

This work demonstrates our ability to create the bioinformatics tools and methods to deal with novel genomics technology, in particular 3rd generation (nanopore) sequencing. In this successful collaboration with the de Laat lab, we have shown that with the right data analytics profound conclusions with regard to genome organisation can be drawn. It is my intention to continue this work to study the multi-way 3D organisation in cancer cells and make predictive models for how non-coding mutations can deregulate target genes.

Stabilisation of the transcription factor Foxp3 by the deubiquitinase USP7 increases Treg-cell-suppressive capacity.

van Loosdregt J¹, Fleskens V, Fu J, Brenkman AB, Bekker CP, Pals CE, Meerding J, Berkens CR, Barbi J, Gröne A, Sijts AJ, Maurice MM, Kalkhoven E, Prakken BJ, Ovaa H, Pan F, Zaiss DM, Coffey PJ. *Immunity.* 2013 Aug 22;39(2):259-71.

Immunosuppressive regulatory T (Treg) cells are critical for maintaining tolerance and preventing autoimmunity and have been shown to be usurped by tumors to prevent immune clearance. The transcription factor FOXP3 is the master regulator of both Treg cell development and function. This paper (together with accompanying N&V) was the first to demonstrate that the transcription factor Foxp3 can be tightly regulated by cycles of ubiquitination. This 'dogma' is now widely appreciated in the field of immunology and provides opportunities for novel therapeutic strategies for treatment of both autoimmunity and cancer.

RhoB Mediates Phosphoantigen Recognition by Vγ9Vδ2 T Cell Receptor.

Sebestyén Z, Scheper W, Vyborova A, Gu S, Rychnavska Z, Schiffler M, Clevén A, Chéneau C, van Noorden M, Peigné CM, Olive D, Lebbink RJ, Oostvogels R, Mutis T, Schuurhuis GJ, Adams EJ, Scotet E, Kuball J. *Cell Rep.* 2016 May 31;15(9):1973-85.

This paper elucidates the crucial role of a small GTPase in the inside out recognition mechanism of a tumor cell by a γ9δ2 T cell receptor and has been critical to implement toxicity and safety studies for TEG001 and allow entering the phase I clinical trial.

Axin cancer mutants form nanoaggregates to rewire the Wnt signaling network.

Anvarian Z¹, Nojima H², van Kappel EC¹, Madl T^{3,4,5,6}, Spit M¹, Viertler M⁴, Jordens I¹, Low TY^{7,8}, van Scherpenzeel RC¹, Kuper I¹, Richter K⁹, Heck AJ^{7,8}, Boelens R³, Vincent JP², Rüdiger SG¹⁰, Maurice MM¹. *Nat Struct Mol Biol.* 2016 Apr;23(4):324-32.



In this study, we uncovered that patient-derived cancer point mutations in the tumour suppressor protein Axin1 promote tumour growth in vivo through formation of small-scale, soluble aggregates that rewire the signalling interactome. We show that the tumorigenic phenotype can be reverted by inhibiting the aggregational behaviour of these cancer mutants, thus offering potential for therapeutic strategies. The work is highly interdisciplinary and involved collaborations with structural biologists and mass spectrometry experts at the Bijvoet Center (UU), Utrecht and fly geneticists at Crick Institute, London.

Rif1 Is Required for Resolution of Ultrafine DNA Bridges in Anaphase to Ensure Genomic Stability.

Hengeveld RC, de Boer HR, Schoonen PM, de Vries EG, Lens SM*, van Vugt MA*. Dev Cell. 2015 Aug 24;34(4):466-74. (*equal contribution)

In a collaborative effort with the group of Marcel van Vugt (UMCG) we revealed a thus far unrecognized function of the DNA repair protein Rif1: the resolution of ultrafine DNA bridges in anaphase. Ultrafine DNA bridges are DNA entanglements that are a normal consequence of DNA replication in S phase. However, these entanglements need to be resolved in early anaphase to prevent DNA damage. We identified Rif1 as an essential player in this resolution process.

2.9 Most important societal contributions

Anti-LRP5/6 VHHs promote differentiation of Wnt-hypersensitive intestinal stem cells

The majority of healthy adult tissues contain a reservoir of stem cells that regulate the supply of new cells to compensate for cell loss due to aging or injury. The production of new cells occurs via cell division and is tightly regulated by the growth signal Wnt. When newly produced cells no longer receive Wnt signals, they will stop dividing and adopt a specialized task within the tissue they reside. Cancer cells often acquire mutations that lead to the inappropriate activation of Wnt signaling which drives excessive cell division without restrictions. The lab of Prof dr Madelon Maurice investigates the molecular basis by which Wnt signaling controls adult stem cell activities and how mutations impact on this system to drive uncontrolled growth. Previously, the Maurice lab discovered a subset of cancers that acquire a strongly increased number of receptors at the cell surface, which drives a state of Wnt hypersensitivity (Koo et al, Nature 2012). Due to these alterations, these cancer cells acquire stem cell-like properties and keep producing new cells to fuel cancer growth. These findings implied that Wnt receptor inhibition holds potential to inhibit the growth of these tumours.

Madelon Maurice and her team worked with the UK-based company Isogenica to develop single chain antibodies that bind and strongly inhibit the activity of the Wnt receptor LRP6. In collaboration with Prof. dr. Piet Gros (University Utrecht), the three-dimensional crystal structure of the antibody-receptor complexes was elucidated. The most potent inhibitory antibodies were shown to occupy the receptor at a position that strongly overlaps with a natural Wnt antagonist, thus revealing their activity as competitors for Wnt binding. Maurice and coworkers additionally showed that antibody treatment of Wnt-hypersensitive intestinal tumor organoids impaired their growth and promoted collective terminal cellular differentiation. As a consequence, the population of cancer stem cells was gradually depleted. The results of this study show that antibody-mediated targeting of Wnt receptors provides a strategy for treatment of Wnt-hypersensitive tumors. The work has been published (Fenderico et al. Nature Communications, Vol 10, Article number: 365, 2019). Importantly, collective specialisation of tumor stem cells was heralded recently as a promising strategy for the eradication of metastatic human cancer.

CyclomicsSeq – ultra sensitive sequencing of cell free DNA in the blood

Recurrent disease after initial remission is responsible for most cancer deaths. Detection of cancer recurrence as early as possible is therefore key to improving patient outcome and quality of life. To achieve this, frequent assessment of tumor burden is required necessitating non-invasive biopsies of cancer patients. For this purpose, 'liquid biopsies', in particular those leveraging cell free DNA (cfDNA) are an emerging diagnostic approach, which has shown promise as a generic biomarker for cancer diagnostics. However, it is difficult to reach accurate and sensitive detection of cancer mutations in liquid biopsies, as the absolute and relative amounts of tumor cfDNA among the total pool of cfDNA molecules in blood plasma is very low.

To address this urgent clinical need the Kloosterman and de Ridder labs have developed CyclomicsSeq, an innovative (patent filed) 'one-stop' diagnostic technology. CyclomicsSeq is aimed at reliably detecting mutations in extremely small amounts of cell-free tumor DNA obtained from blood-based liquid biopsies. Moreover, the technology offers a comprehensive test as it can detect mutations in complete genes and gene panels. CyclomicsSeq is based on third-generation real-time sequencing technology enabling flexible testing and fast turn-around times. These features provide a major competitive advantage over other liquid biopsy technologies that are fundamentally limited in sensitivity or scope.



After reaching proof of concept on head and neck cancer (HNC) patient samples, Kloosterman, Marozzi and de Ridder founded a UMC Utrecht spinoff company Cyclomics. The company is well positioned to be the first to deliver a liquid biopsy assay based on third generation sequencing.

It is expected that application of CyclomicsSeq method will enable optimized detection of recurrent disease by fast, sensitive and cost-efficient sequencing of tumor mutations in a targeted or genome-wide manner. In the longer term, successful development and application of the circulating tumor DNA (ctDNA) sequencing invention will enable blood-based tumor monitoring at unprecedented sensitivity and specificity, thereby improving clinical decision making for a wide range of cancers. Successful implementation of the technology will thus improve clinical care for - possibly a wide range of - cancer patients and reduce mortality.

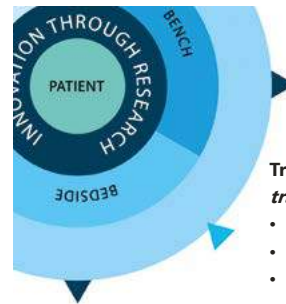


3. Theme: Translational

3.1 Mission, strategy and organisation of the theme

The translational research section aims to create clinical impact by translating the knowledge gained from fundamental research into clinically useful tools in the broadest sense. These can be new diagnostic tools or treatments, but also new technological advances or imaging modalities. Vice versa, clinical data are used to design new fundamental research questions, and patient-derived tissues are used to build better cancer models.

Essential for successful translation of discovery science to clinical practice is a close and two-way collaboration between biomedical scientists and the clinicians who diagnose and treat cancer patients. First, clinically-driven problems and questions have to be formulated in a bi-lateral manner so that discovery science can effectively support the development of clinical solutions.



**Translational research
translate knowledge into**

- biomarkers
- therapeutic leads
- image-guided therapies

Fig. 1 Topics of the theme

Closer and more effective interaction between clinicians and basic scientists should enable a platform where 'translation' is a format that supports probing translational questions in every stage; from laboratory findings to clinical usage. The UMC Utrecht has a formidable pool of outstanding scientific and clinical experts who -through an effective combined application of medical and biological knowledge- should be able to bridge the current gaps in translational oncology.

Research within the theme "Translational" in the UMC Utrecht is primarily performed by cancer researchers from the Laboratory for Translational Oncology (LTO), Laboratory for Translational Immunology (LTI) and Center for Image Sciences (CIS). Multidisciplinary collaboration and interactions between these departments as well as with the other three themes are key to facilitate translation.

Note: therapeutic lead discovery of tumor immunology is shared with the Strategic research program Infection & Immunity (I&I).

The text parts provided in Italic are the same as described in I&I.

3.2 Urgency and/or relevance of the research questions

By acquiring fundamental knowledge on cancer progression and response/resistance to treatment specific targets for personalized therapeutic intervention and diagnosis will be identified. Ultimately, this may lead to patient stratification for treatment based on the specific features of the disease. This is both 'Personalized Medicine' and 'Healthcare Research'. Furthermore, by coupling existing medicines to specific patient categories (i.e. 'drug repositioning') we will contribute to a more sustainable form of personalized cancer therapy. In general, we are striving to maximize treatment effects while minimizing burden, leading to increased cure and a better quality of life for patients with cancer.

Biomarkers

Organoid Technology is increasingly being used as a novel biomarker platform for predicting drug response. The available data suggest that drug responses observed in cancer patients are faithfully reproduced in patient-derived organoids. A clinical study prospectively evaluating the value of organoids as a response prediction platform in colorectal cancer is currently ongoing at the UMC Utrecht (OPTIC).

In addition, small versatile tracers that bind specific targets in tumor subgroups are increasingly being used to develop 'theranostics' approaches. Typically, the tracers are labeled with radioactive isotopes first allowing tumor subtype detection by Positron Emission Tomography (PET) (e.g. Gallium), and – in case tumors are positive – the same tracers are used but now coupled to a radiotherapeutic isotope (e.g. yttrium).



RNA-based tumor classification is developed as a more common tool to classify tumors into 'molecular subtypes'. This offers new opportunities for advancing subtype-targeted therapies. Novel biomarkers are being developed and validated in multiple cancer types including colorectal and breast cancer subtypes, and these are used in clinical studies to select subgroups of patients for subtype-targeted therapy.

In all these projects the dJC (the UMC Utrecht division for clinical epidemiology) cooperates as a center of expertise addressing and analyzing all relevant aspects of biomarker development.

Therapeutic Leads

Organoid technology holds promise as a platform for personalized therapy but is also increasingly being used as a platform for drug repurposing. Groups of tumor organoids representing specific tumor subtypes are used to search for (existing) anti-cancer drugs in unbiased screens, or in rational combinations, for instance steered by common genetic features.

Fundamental research on aggressive breast cancer has led to the design of preclinical intervention strategies involving various novel targets.

Tumor immunology aims to provide next generation (personalized) immune therapies to patients with (hematological) malignancies by finding novel targets for cancer immune therapies (e.g. extend the scope of Chimere Antigen Receptor (CAR) T therapies, TEG concept = T cells engineered to express a defined $\gamma\delta T$ cell receptor) and developing intelligent combinations with targeted therapies by finding novel targets for cancer immune therapies (e.g. extend the scope of CAR T therapies, TEG concept), develop personalized transplantation care and next generation immune checkpoint inhibitors (ICI) (assess predictors and analyze underlying mechanisms of toxicity, resistance, role with microbiome).

Image-guided therapies

A key focus of the UMC Utrecht has been the development of non-invasive image-guided cancer therapies aiming for less hospitalisation and less side effects with similar or better therapeutic outcome. Image-guided therapies have the potential to meet important societal needs such as the more active and physical life styles of cancer patients and the financial sustainability of the health care system.

The combination of an MRI scanner and a precision radiation system (MRI-Linac) is an example of such an image-guided therapy that revolutionizes current radiation therapy (see also the narrative of this Theme). The UMC Utrecht has played a pioneering, pivotal role in the development of this so called MRI-guided Radiotherapy. Other examples of image-guided cancer therapies within the UMC Utrecht are High Intensity Focused Ultrasound (HIFU) treatment of breast cancer and bone metastases, intravenous and intra-arterial Peptide Receptor Radionuclide Therapy (lutetium-177-dota-tate; lutetium-177-PSMA) for prostate cancer and Holmium-166-Radio-embolisation for treatment of liver metastases (this latter is discussed in the Clinical theme). In addition to therapies, research lines towards the use of high precision imaging (e.g. metabolic imaging using high field x-nuclei imaging, so called META-scanner project) for response assessment and personalisation of treatment are on-going.

In 2016 the UMC Utrecht, in collaboration with the Sectra company, was the first Dutch hospital to build and implement digital pathology in routine clinical diagnostics, paving the way for artificial intelligence. An integration with the radiology Sectra PACS has recently been realized. First steps for integration of an artificial intelligence algorithm to detect mitoses in the digital workflow have been taken.

3.3 Relation to existing knowledge

Research in this theme fits well within the Dutch Knowledge and Innovation Agenda, in particular the routes 'Health-care research, sickness prevention and treatment' and 'Personalized medicine: the individual at the Centre'.

The UMC Utrecht and the Hubrecht Institute have developed organoid technology for many different cancers. Efforts to professionalize and standardize patient-derived organoid biobanking include the formation of the HUB foundation (generating Organoid Biobanks and performing screens) and The Utrecht Platform for Organoid Technology (UPOINT; standardizing all logistical issues surrounding patient-derived tissue collection, including for instance informed consent procedures, anonymisation and practical issues.)

In addition, in vitro and in vivo live cell imaging technologies, state-of-the-art single cell analysis technologies and platforms for (phospho)proteomics and metabolomics are all available at the UMC Utrecht or on the Utrecht university campus either as facilities, as fee-for-services, or hosted in spin-off companies. Many of the Research Leaders hosting such technologies are affiliated with UPOINT, allowing direct access of the technologies for the analysis of novel organoid models.



The Utrecht sequencing facility (USEQ) and the Utrecht Bioinformatics Expertise core (UBEC) allow easy access to the generation and analysis of many types of DNA and RNA sequencing data. Furthermore, the Utrecht Patient Oriented Data (UPOD) is a facility allowing clinical data mining and is now being coupled to organoid-based data, thus establishing a link between patient-centered clinical and experimental data.

Within the last 5 years cancer immune therapy became a game changer in cancer therapies, and today three major drug pipelines entered clinical practice: cancer specific antibodies, checkpoint inhibitors and living drugs (e.g. CAR T cells). Within the theme hematology and tumor immunology, we have been involved during the last decade in developing these three branches.

We have a strong and long-standing pipeline in developing IgA as potential backbone for cancer immune therapy (Group Leusen), which has the power to complement IgG-based immune therapies in collaboration with commercial partners. In addition, we have discovered novel checkpoint inhibitors and generated clinical cohorts to test efficacy and toxicity parameters connected to checkpoint inhibitor treatments (Groups Meyaard & Suijkerbuik). We also developed different so-called advanced therapy medicinal products (ATMPs), such as mesenchymal stromal cells that entered clinical practice for the treatment of graft versus host disease after stem cell transplantation and next generations of CAR T (see example of development: TEGs, metabolic cancer targeting Groups Kuball & Sebestyen). In addition, we also explored whether for the most successful cellular therapy to date, namely the allogeneic stem cell transplantation, further harmonisation is possible as progress is mainly hampered by historical approaches that have been grown over decades in stem cell transplantation centers world-wide. We have also connected and harmonized the allogeneic stem cell transplantation programs between the UMC Utrecht and PMC through a comprehensive biobank (Groups Nierkens, Lindemans, Kuball) and on young adult cohorts with harmonized treatment schedules as fundament for innovative drugs generated (Groups Vormoor, Kuball). Thereby, we created a unique position of the UMC Utrecht for future development of novel therapies in Europe. Finally, exploring the combination of novel small molecules with immune therapy based concept, particularly in B cell malignancies, is a new development and will be used to cross-fertilize the Strategic Theme Cancer and I&I (Group Peperzack & Minnema) and allow developing overarching themes for the next wave of drugs and a more structured patient journeys from the age of 0 to 100 (see also <http://www.tumor-immunology-utrecht.nl>).

The department of Radiotherapy of the dB&O of the UMC Utrecht has been the pioneer of MRI-guided radiotherapy and has developed a clinical system in close collaboration with industrial partners Elekta and Philips Healthcare. With other international academic partners, the so-called Atlantic consortium has been founded that aims to exchange knowledge/expertise and data to develop new clinical MRI-guided radiotherapy treatments and evaluate the efficacy and quality of life.

The HIFU research group within dB&O is in close collaboration with clinicians constantly striving towards broad clinical translation of the HIFU treatment for breast cancer. Furthermore, in collaboration with the Princess Maxima Center for pediatric oncology (PMC), research has been initiated towards thermo-acoustic modulation of the permeability of the blood-brain-barrier for delivery of chemo therapeutic agents.

The research line of high precision imaging using high field MRI is being pursued with industrial partners Philips and Tesla Engineering LTD where the proto-typing of a new small footprint 7 Tesla MR system aimed at metabolic imaging is ongoing at the UMC Utrecht. This system should enable personalized medicine for treatment of various cancers (e.g. early response prediction in neo-adjuvant chemotherapy for breast cancer patients).

3.4 Collaborations

The researchers in this theme closely collaborate within a multidisciplinary setting with various stakeholders and participate in relevant professional organisations, amongst others:

- Through monthly meetings within the Tumor Working Groups (see Annex 2), researchers regularly meet with all relevant clinical specialists. This provides a platform for joint design of grant proposals and study design. These can be new intervention studies, but also translational research programs accompanying new clinical trials.
- The clinical translation concerning MRI-guided Radiotherapy is locally organized through clinical working groups within the department of Radiotherapy consisting of radiation-oncologists, medical physicists and technologists.
- Organoid technology represents a strong platform for many collaborations both in the fundamental and clinical science domains. Utrecht Life Sciences has acknowledged this by financially supporting the Utrecht Platform for Organoid Technology as one of its 'hubs', in order to stimulate the application of organoid technology on the Utrecht campus and its strategic partners.



- The division Julius Center provides all essential expertise on biomarker development and, as such, is involved in many different projects.
- Patient advocates are involved early during study design for input.
- Regular meetings of UMC Utrecht clinicians and translational researchers with PIs from the Oncode institute have recently been started to maximize the translational/clinical impact of research at Oncode and shape a stable bond between fundamental, translational and clinical research.
- Collaborations also exist with industry and not-for-profit organisations. In particular, active collaborative research programs are in place with Genmab, Gadeta and Nutricia on the Utrecht campus. Furthermore, Philips and Elekta are important partners in co-development of image guided treatments. The participation of these industrial partners in our research is key to facilitate the transfer of fundamental and technological innovations to clinical implementation.
- Technology optimisation concerning MRI guided radiotherapy occurs through collaborations within the Atlantic MR Linca consortium founded by 7 major academic institutes and two industrial partners (Elekta, Phillips) and recently joined by 10 others <https://www.elekta.com/meta/press-all.html?id=8C22F1E959DD584A>.
- The Utrecht Applied Data Science platform facilitates groups within the Utrecht University and interested external parties to share knowledge and facilitate interdisciplinary collaboration on data science and AI. Within this platform the division Imaging& Oncology has initiated a special interest group concerning deep learning for imaging to stimulate research in this theme within the university and attract external parties.
- The digital pathology platform has been and will be further developed in collaboration with Sectra (<https://www.sectra.com/pathology>) and PALGA.
- European Invasive Breast Cancer Consortium (ELBCC). Initiated by the department of Pathology, the ELBCC has been founded, bringing together all experts on research and treatment of invasive lobular breast cancer. Within this consortium, fundamental questions are addressed in collaboration, nationwide databanks are shared and cross-country collaborative trials are set up.

3.5 Research Design

- In many cases, research groups collaborate closely with researchers from the dJC aiming to design innovative clinical studies, achieve optimal data analysis and address all relevant aspects of biomarker development.
- Furthermore, the Utrecht Bioinformatics Expertise Core (UBEC) provides help and advice on analysis of '(multi-)omics' datasets.
- ATMP development: ATMP facility of the UMC Utrecht provides support during designing studies dealing with cellular therapies.
- Active collaborations between translational research groups and basic research groups at the CMM, the Hubrecht institute and the UU ensure optimal application of innovative technologies in ongoing translational research projects. These include (but are not limited to) organoid (co-culturing) methods, single cell technologies, organ-on-a-chip models, various 'omics' technologies ((phospho-)proteomics, transcriptomics, lipidomics, and metabolomics), high-end imaging applications and novel mouse models for studying spontaneous metastasis.
- All research groups within the dB&O have regular research exchange and coordination by means of joint meeting and research presentations. These meetings take place on junior and senior staff levels.
- Translation of new imaging and image processing methodologies from basic imaging research groups, towards testing in clinical studies and further clinical deployment in the departments of radiology and radiotherapy is occurring regularly by means of partnering of clinical and basic researchers. Basic research groups include the Image Sciences Institute, high field research group, HIFU group, computational imaging group and nuclear imaging group that are directly embedded into the radiology & radiotherapy departments. Current active topics of translation consist of deep learning applications and imaging hardware & reconstruction methods.
- Within the radiotherapy department, all expert groups (e.g. MRI physicists, computer scientists, medical physicists, technologists, clinicians, epidemiologists) are involved through direct participation in (clinical) research to drive the MRI-guided radiotherapy development. Furthermore, the department of radiotherapy has a strong educational program on the use of MRI in Radiotherapy within the UMC Utrecht where more than international 200 participants participate yearly. Recently, a research line including educational dissemination on the use of Deep learning for MRI guided Radiotherapy has started.



- The clinical translation on Image-guided cancer therapies occurs through a mix of clinical studies and direct clinical implementation. Unique in the clinical development of MRI guided radiotherapy treatments is the Momentum study within the Atlantic consortium that is coordinated and facilitated by the trial office of the UMC Utrecht. All data of all MRI-guided Radiotherapy treatments within the Atlantic consortium is stored in the Momentum database and available for researchers from the consortium. By joining forces in this way and creating an open data infrastructure and collaborative atmosphere, the learning curve towards defining optimal treatments should be as short as possible.

3.6 The next steps

Biomarkers en therapeutic leads

Organoid Technology will continue to be explored as a novel platform for personalizing treatment. Moreover, identifying and validating tracers with potential 'theranostics' value will remain to be a major effort, typically involving fundamental research groups (providing the biological rationale for using specific tracers), the dJC (biomarker development), companies or research groups developing novel tracers, and the department of radiology (clinical testing). The researchers of these two topics collaborate in many different projects with companies, either as supporters of research-initiated clinical trials (e.g. Bristol Meyers and Squib, Gadeta), or as collaborators in externally funded projects (e.g. Nutricia Research, BiOrion), or as project funders themselves (e.g. Genmab). Regular contact with the Valorisation Office of the UMC Utrecht facilitates innovation and valorisation. All new grant proposals are sent to the relevant patient organisations for input.

Tumor-immunology: we initiated a startup company which will further utilize IgA as backbone for novel therapies. Checkpoint development: LAIR-1 (Leukocyte-associated immunoglobulin-like receptor 1) based anti-cancer therapy is developed with an US based biotech company, with the ambition of investigational new drug filing by the in 2010. This would bring a receptor discovered by Meyaard in 1997 and studied ever since, into clinical application. We also invested in clinical cohorts and a novel computational pipeline to identify potential checkpoint receptors encoded in our genome, of which still hundreds are available. We will now select lead candidates for further characterisation and will generate antibodies in our in-house facility that can serve as blockers. This effort is embedded in Oncode and with the aim to explore this concept with commercial partners or also spin out the platform given its high potential.

Next generation of CAR T, the TEG pipeline: The patient organisation is involved in academic clinical trial designs and next steps during the dose escalation study. For further valorisation key stakeholders (Gadeta, KITE, Gilead) are involved in the project. For the TEG pipeline we expect that the startup company will perform a next series of clinical trials while we will focus within academia on novel targets as well as bispecific projects and aim to potentially open a second company on the GAB (Grb2-Associated Binding) concept.

Image-guided therapies

The UMC Utrecht will continue to invest in fundamental research as well as in clinical translation of image guided therapies and high precision imaging. Important lines of fundamental research include experimental radiotherapy, MRI technology, image reconstructions and (AI based) image processing, including digital pathology, and data science. For successful translation and dissemination of these techniques, the formation of consortia that include industrial as well as academic partners is believed to be key. For example, the further development and dissemination of MRI-guided Radiotherapy is driven by the close collaboration with our industrial and academic partners within the Atlantic consortium and other academic partners that all have installed 1.5 T MRI-Linacs. This is facilitated by means of regular meetings, exchange of researchers and co-publications. Another example includes the consortium around the high field metabolic imaging.



3.7 Highlights of results

Research products for peers

Datasets, biobanks (for cohorts see also Annex 3)

- Organoid biobanks for more than 14 different types of (cancer) tissue, including for instance ovarian, neuroendocrine, bladder, breast, colon and head and neck cancers, and corresponding normal tissues. In many cases genetic information (RNA/DNA sequencing) is available, allowing the study of selected subsets of cancers (**Kranenburg**).
- Momentum database: this is a worldwide cohort where (clinical) data of MRI-Linac patients from various international institutes of the Elekta MR-Linac consortium are collected (**Verkooijen**).
- EMBRACE dataset from the EMBRACE international study on MRI guided brachytherapy of cervical cancer (**Schulz**).

Infrastructure

- CPCT: DNA screening center (**Cuppen**).
- UPORT: Utrecht Platform for Organoid Technology (**Kranenbrug, Maurice**).
- Digital pathology infrastructure (**van Diest**).
- The data infrastructure of the international MR-Linac Momentum study is facilitated by the trial office of the Imaging/Oncology division (**Verkooijen**).
- AI4UU initiative. This recent initiative offers centralized Graphic Processing Unit computing resources for training Artificial Intelligence (AI) applications. This initiative is initiated by Imaging/Oncology division and the High Performance computing cluster from BioInformatics (UBS) and various groups from the Utrecht University (**Veldhuis**). This also connects to the Utrecht Applied Datascience initiative.
- ELBCC – infrastructure for research and treatment of invasive lobular breast cancer (**Derksen**).

Compounds, instruments, software tools

- 2013-2018: Organoid patent portfolio (HUB foundation).
 - 2013: Dipole antennas for high field body magnetic resonance imaging (**van den Berg**).
 - 2015: Time-Domain MRI for quantitative MRI for treatment monitoring and time reduction of MRI examinations (**van den Berg**).
 - 2014: MRI-guided high intensity focused ultrasound (HIFU) for tumor ablation and medicine deposition (**Bos, Moonen**).
 - 2015: Device and method for simultaneous X-ray and gamma photon imaging with a stacked detector (**de Jong**).
 - 2016/2017: CD20 antibodies and anti-DG2 antibodies (neuroblastoma) (Leusen).
 - 2018: development of the MRI Linac system for real time and on-line MRI guidance of external beam radiotherapy (**Lagendijk, Raaijmakers**).
 - 2016: Software tool (VQuest) for educational testing with volumetric (3D) images (**Vincken**).
-

Research products for societal target groups

Publications accessible for a large audience

- 2014: News item application of HIFU in breast cancer treatment. <https://www.telegraaf.nl/nieuws/1018168/vetbolletjes-met-chemo-naar-gezwel> (**Moonen**).
- 2015: News item about implementation of digital pathology. <https://www.rtvutrecht.nl/nieuws/1339567/eerste-digitale-afdeling-pathologie-in-umc-utrecht.html> (**van Diest**).
- 2018: News item MR-Linac <https://www.telegraaf.nl/nieuws/2474320/slimme-jannen-oefenden-bestraling-op-een-karbonaadje> (**Lagendijk**).
- 2018 News item about Lutetium-177-PSMA therapy in TV broadcast TVMAX. <https://www.maxvandaag.nl/sessies/themas/gezondheid-sport/nieuwe-behandeling-uitgezaaide-prostaatanker/> (**Lam**).
- 2018 Dutch language chapter for general public in Biomedical sciences and society: “Checkpointblokkers: Doorbraak in kankertherapie” in “Ons Afweersysteem” Biocahier Biowetenschappen en Maatschappij, nr 3, 2018. (**Meyaard, Suijkerbuijk**).



Outreach activities

- 2013-2017: International Summerschool "Clinical Translational Oncology" for advanced bachelors / beginning masters.
 - Semi-annual meetings (informative & discussion) with the patient working group Intestinal Cancer.
-

Use of research products by peers

Use of biobanks and data collections

- Use of organoids: tens of academic research groups in Europe and USA use our organoids. Pharmaceutical and other industrial partners uses in general organoids produced by Hubrecht Organoid Technology (HUB), > 10 companies have licenses and > 40 make use of the services.

Use of research facilities/infrastructure

- UPORT organoid infrastructure: 13 active projects and > 1000 included patients.

Use of compounds, instruments, software tools

- 2009- now The Image Sciences Institute (ISI = is part of CIS) provides various open source image processing software. Examples include the Elastix deformable registration tool box which was developed at ISI. Support and further extension is now done in collaboration with the Rotterdam Erasmus Medical Centre and Leiden University Medical Centre. <http://elastix.isi.uu.nl/> (**Bartels**).
-

Use of research products by societal groups

Consortia, public-private partnerships

- 2010-2017 CTMM consortium - Volta/Voltavalo HIFU (**Moonen**).
- 2016 H2020 MECHANO CONTROL Mechanical control of biological function (also described in theme Fundamental) (**de Rooij, Derksen**)
- 2018 H2020 EXPERT – Expanding, Platforms for Efficacious mRNA Therapeutics (**Schiffelers**).
- 2018-2021 H2020 ITEA, STARLIT, Developing real guided MRI guided radiotherapy (**Raaymakers**).
- 2013-2018 FP7 – iPaCT, Image Guided Pancreatic Cancer Therapy (**Moonen**).
- 2018-2021 EuroNanMed NSC4DIPG, NanoSonoChemotherapy for Diffuse Intrinsic Pontine Glioma (**Moonen**).
- European Lobular Breast Cancer Consortium (www.elbcc.org) (**Derksen**).
- Atlantic consortium for MRI-guided Radiotherapy (**Lagendijk, Raaymakers**).
- META scanner for high field metabolic imaging (**Klomp**).

Implementation in guidelines, reimbursement

- CE+ FDA approval for the use of the MR-LINAC in clinical care (**Lagendijk**).
- Prognostic value of FDG-PET/CT in triple negative tumors after neoadjuvant treatment – Oncoline guidelines (**Gilhuijs**).

Patent (applications), spin-offs

- 2013-2018 : 10 patent applications (**van den Berg, Bos, de Jong, Gilhuijs** (stopped in 2017), **Leusen**, not disclosed).
 - 2014-2018 spin-offs: i.o. (Leusen), QuantibU (**Veldhuis, Leiner, Isgum**), Vquest (**Vincken**).
 - Organoid technology patents portfolio (**various**).
-



Marks of recognition from peers

Awards, individual research grants (Veni, Vidi, Vici, ERC, Marie-Curie)

- 2013: Vici (**Cuppen**), VENI (**Wijnen**), ERC (**Zwanenburg**), Samuel P Asper Award (**Offerhaus**).
- 2014: Vidi (**Berg**), Vici (**Meyaard**), ERC (**de Jong**), Marie Curie (**Schiffelers**) 2015 ERC Advanced Grant (**Moonen**).
- 2016: KWF-YIG (**Plantinga**).
- 2017: VENI (Sbrizzi, Bakker), KWF-YIG (**Bakker**).
- 2018: Frieda den Hartog Jagerprijs (**Offerhaus**).
- 2019: The William and Francis Fry Award - International Society for Therapeutic Ultrasound (**Moonen**).

Elected memberships of scientific committees

- Panel member for Cancer Research UK New Investigators (**Derksen**).
- director of the MSc programme Medical Imaging offered at UU and Technical University Eindhoven (TU/e) (**Bartels**).
- Member National grant evaluation committee cost-effectiveness research (ZON MW Doelmatigheid) (**de Jong**).
- Secretary general of the Dutch Society of Immunology (**Meyaard**).
- 2016 President of European Society of Molecular Imaging (**Moonen**).
- Chair Translational working group of the DCCG (**Kranenburg**).
- Board member ZonMW Off-Road committee (**van den Berg**).

Editorial boards

- 7 translational Cancer scientist are appointed in editorial boards (**Derksen, van Diest, Leusen, Meyaard, Offerhaus, Schiffelers, Raaymakers**).

Marks of recognition from societal groups

Public prizes

- Knight's Cross of the Order of Merit from Poland (**Offerhaus**).

Membership of civil society advisory bodies

- Board member of The nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) (**Willems**).

Consultancies for public or private sector

- 2013-2018 Board of directors public-private CTMM (**Luijten**).
 - Member of the Digital Pathology advisory board of Philips and Sectra (**van Diest**).
 - Directeur Stichting Hartwig Medical Foundation, Scientific Advisory Board InteRNA Technologies BV (**Cuppen**).
-

3.8 Research projects where patients are meaningfully involved

Patient participation UPORT

Technology is one of the 'hubs' of Utrecht Life Sciences, aiming to bring excellent researchers from different disciplines together to work on societal relevant issues and scientific breakthroughs. Two patient advocates are part of the UPORT steering group. In addition, patient advocates are consulted in all organoid-related grant proposals and regular meetings are held in Utrecht (UMC Utrecht) or at the relevant organisations. UPORT aims to maximize the benefits of organoid technology for patients, clinicians and researchers. This is achieved in multiple ways. UPORT provides a standardized infrastructure for acquisition and processing of patient-derived tissues. In addition, UPORT stimulates the application of existing organoid model systems in research & clinical trials as well as the development & analysis of new organoid model systems. By establishing an 'organoid' community involving patient advocates, and a research and education network, UPORT ensures the continued relevance and sustainability of its activities.

Clinical introduction online and real-time MRI guided prostate cancer radiotherapy

This study is part of two major research lines at the UMC Utrecht; (i) the development and clinical introduction of the MRI-linac and (ii) the development of MRI-guided prostate cancer treatments. This project has started in 2018 and will run for 3 years. The overall aim of the project is to achieve evidence-based implementation of MRI-linac radiotherapy for patients with prostate cancer, with the aim to (i) reduce the risk of acute toxicity and late complications, (ii) improve



local tumor control, (iii) provide extreme hypofractionation treatment in an outpatient setting (iv) reduce costs. This will be done by building a multicenter multi-trial facility for evaluation of new interventions for treatment of non-metastasis prostate cancer patients at UMC Utrecht and St. Antonius hospital. Secondly, by developing a non-invasive, hypo-fractionated, low toxicity, outpatient prostate cancer treatment using the MRI-linac. A major aspect of the study investigation is to design an efficient, patient friendly treatment. Patients will receive the complete treatment in a single center with major expertise, patient throughput and patient friendliness. The prostate cancer patient society will participate in the development and evaluation of the business case and in the investigation of the Quality of Life evaluation.

3.9 Most important scientific publications

3.9.1 Biomarkers

A Novel Diagnostic Tool for Selecting Patients With Mesenchymal-Type Colon Cancer Reveals Intratumor Subtype Heterogeneity.

1. Ubink I, Elias SG, Moelans CB, Laclé MM, van Grevenstein WMU, van Diest PJ, Borel Rinkes IHM, Kranenburg O. *J Natl Cancer Inst.* 2017 Aug 1;109(8).

In this paper a novel clinically applicable diagnostic test was developed to identify the most aggressive molecular subtype of CRC (consensus molecular subtype 4 classification). The test is used in a follow-up clinical study to select patients for subtype-targeted therapy. This is an example of how fundamental research into subtype-specific signaling pathways that drive metastasis and therapy resistance, can be used to develop diagnostic tools and targeted therapy in a concerted fashion.

Ongoing chromosomal instability and karyotype evolution in human colorectal cancer organoids.

Bolhaqueiro ACF, Ponsioen B, Bakker B, Klaasen SJ, Kucukkose E, van Jaarsveld RH, Vivié J, Verlaan-Klink I, Hami N, Spierings DCJ, Sasaki N, Dutta D, Boj SF, Vries RGJ, Lansdorp PM, van de Wetering M, van Oudenaarden A, Clevers H, Kranenburg O, Foijer F, Snippert HJG, Kops GJPL. *Nat Genet.* 2019 May;51(5):824-834.

In this paper it is demonstrated that ongoing chromosomal instability is a continuous source of the generation of intra-tumor heterogeneity. This may have profound impact on how tumor evolution impacts metastasis and therapy resistance.

Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer.

Ehteshami Bejnordi B1, Veta M2, Johannes van Diest P, van Ginneken B, Karssemeijer N, Litjens G, van der Laak JAWM; the CAMELYON Consortium, Hermesen M, Manson QF, Balkenhol M, Geessink O, Stathonikos N, van Dijk MC, Bult P, Beca F, Beck AH, Wang D, Khosla A, Gargeya R, Irshad H, Zhong A, Dou Q, Li Q, Chen H, Lin HJ, Heng PA, Haß C, Bruni E, Wong Q, Halici U, Öner MÜ, Cetin-Atalay R, Berseth M, Khvatkov V, Vylegzhanin A, Kraus O, Shaban M, Rajpoot N, Awan R, Sirinukunwattana K, Qaiser T, Tsang YW, Tellez D, Annuscheit J, Hufnagl P, Valkonen M, Kartasalo K, Latonen L, Ruusu-vuori P, Liimatainen K, Albarqouni S, Mungal B, George A, Demirci S, Navab N, Watanabe S, Seno S, Takenaka Y, Matsuda H, Ahmady Phoulady H, Kovalev V, Kalinovsky A, Liauchuk V, Bueno G, Fernandez-Carrobles MM, Serrano I, Deniz O, Racoceanu D, Venâncio R. *JAMA.* 2017;318(22):2199-2210.

This paper shows that in the setting of a challenge competition, some deep learning algorithms achieved better diagnostic performance than a panel of 11 pathologists participating in a simulation exercise designed to mimic routine pathology workflow; algorithm performance was comparable with an expert pathologist interpreting whole-slide images without time constraints. Whether this approach has clinical utility will require evaluation in a clinical setting.

3.9.2 Therapeutic leads

An organoid platform for ovarian cancer captures intra- and interpatient heterogeneity.

Kopper O, de Witte CJ, Löhmußaar K, Valle-Inclan JE, Hami N, Kester L, Balgobind AV, Korving J, Proost N, Begthel H, van Wijk LM, Revilla SA, Theeuwssen R, van de Ven M, van Roosmalen MJ, Ponsioen B, Ho VWH, Neel BG, Bosse T, Gaarenstroom KN, Vrieling H, Vreeswijk MPG, van Diest PJ, Witteveen PO, Jonges T, Bos JL, van Oudenaarden A, Zweemer RP, Snippert HJG, Kloosterman WP, Clevers H. *Nat Med.* 2019 May;25(5):838-849.

In this paper an organoid biobank was created for ovarian cancer, representing an unparalleled platform for studying the disease in all its heterogeneity, and for testing novel therapies.



$\gamma\delta$ T cells elicited by CMV reactivation after allo-SCT cross-recognize CMV and leukemia.

Scheper W, van Dorp S, Kersting S, Pietersma F, Lindemans C, Hol S, Heijhuurs S, Sebestyen Z, Gründer C, Marcu-Malina V, Marchant A, Donner C, Plachter B, Vermijlen D, van Baarle D, Kuball J. *Leukemia*. 2013 Jun;27(6):1328-38.

We elucidated the crucial role of $\gamma\delta$ T cells and $\gamma\delta$ T cell receptors in controlling leukemia relapse after allogeneic stem cell transplantation. This paper exemplifies the concept of TEGs, which opens the avenue towards many novel targets through a myriad of $\gamma\delta$ TCR active against tumors. This paper has been among others key for the establishment of the UMC Utrecht spin-off company GADETA.

Translating $\gamma\delta$ T cells and their receptors into cancer immune therapies.

Sebestyen Z, Prinz I, Déchanet-Merville J, Silva-Santos B, Kuball J. *Nature Reviews Drug Discovery* 2019 in print IF 57.000

"Do's and don'ts" for developers how to translate $\gamma\delta$ T cells and their receptors into therapeutic concepts.

α E-catenin is a candidate tumor suppressor for the development of E-cadherin-expressing lobular-type breast cancer.

de Groot JS, Ratze MA, van Amersfoort M, Eisemann T, Vlug EJ, Niklaas MT, Chin SF, Caldas C, van Diest PJ, Jonkers J, de Rooij J, Derksen PW. *J Pathol*. 2018 Aug;245(4):456-467.

This paper identifies a novel tumor suppressor gene in a subset of breast cancers.

3.9.3 Image-guided therapies

In vivo T2-based MR thermometry in adipose tissue layers for high-intensity focused ultrasound near-field monitoring.

Paul Baron Mario Ries Roel Deckers Martijn de Greef Jukka Tanttu Max Köhler Max A. Viergever Chrit T. W. Moonen Lambertus W. Bartels
Magn Reson Med. 2014 Oct;72(4):1057-64.

This paper describes a method to monitor temperature during high intensity focused ultrasound treatment by means of MRI in fatty tissue. This is important as standard MRI thermometry fails in fatty tissue. In this way, temperature can be monitored for instance in the whole breast in case of HIFU treatment of breast cancer.

First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment.

Raaymakers BW, Jürgenliemk-Schulz IM, Bol GH, Glitzner M, Kotte ANTJ, van Asselen B, de Boer JCJ, Bluemink JJ, Hackett SL, Moerland MA, Woodings SJ, Wolthaus JWH, van Zijp HM, Philippens MEP, Tijssen R, Kok JGM, de Groot-van Breugel EN, Kiekebosch I, Meijers LTC, Nomden CN, Sikkens GG, Doornaert PAH, Eppinga WSC, Kasperts N, Kerkmeijer LGW, Tersteeg JHA, Brown KJ, Pais B, Woodhead P, Lagendijk JJW. *Phys Med Biol*. 2017 Nov 14;62(2).

This paper describes the proof-of-principle of a MRI-guided radiotherapy treatment on a 1.5 MRI-Linac prototype system. The paper describes the designed workflow and the overall achieved accuracy and clinical experience in a clinical study setting.

Amide chemical exchange saturation transfer at 7 T: a possible biomarker for detecting early response to neoadjuvant chemotherapy in breast cancer patients.

Krikken E, Khlebnikov V, Zaiss M, Jibodh RA, van Diest PJ, Luijten PR, Klomp DWJ, van Laarhoven HWM, Wijnen JP. *Breast Cancer Res*. 2018 Jun 14;20(1):51.

This paper demonstrates the potential of using 7T MRI for response prediction of neoadjuvant chemotherapy in patients with breast cancer.



3.10 Examples of research contributing to society

Organoids as bridge between fundamental research and clinical implementation

Organoids, a recent scientific discovery by the Clevers lab (Hubrecht Institute) have been shown to reflect the tumor of origin both genetically and phenotypically. In the UMC Utrecht we aim to translate the use of organoids to the clinic by evaluating the use of organoids as predictive biomarker for response to therapy and by using organoids to understand drug response and to find new effective drug combinations. This may lead to drug repositioning and novel combinations for specific subgroups of patients which will lead to improved survival.

For the last 35 years the Bos lab has focused their research on Ras and Ras-related proteins. Ras is mutated, among others, in 50% of colorectal cancers (mCRC). These cancers have a poor prognosis and currently no treatment is available that target mutant Ras. Using patient-derived organoids we aim to find drug combinations that are effective for mCRC and found a triple combination which we are now translating into the clinic. Earlier work at the Dutch Cancer Institute suggested benefit of the combination of an inhibitor of EGFR/ERBB2 with a MEK1/2 inhibitor in patients with RAS mutated colorectal cancer which however was not confirmed in the clinic. Meanwhile, using tumor organoids from colorectal cancer patients with mCRC, we found the same combination to be cytostatic rather than cytotoxic (Verissimo et al., 2016). We therefore performed a synthetic lethality screen of 414 drugs currently approved or tested in clinical trials, that in combination with the clinical recommended phase II dose (RP2D) of a MEK inhibitor + pan EGFR inhibitor results in cytotoxicity. The hits strongly favored microtubule targeting drugs, that were validated in >20 different RAS mutant colorectal cancer organoids where we found a consistent and very strong anti-tumor effect of the doublet combination (EGFR/MEKi) with vinorelbine. These promising effects were confirmed in patient-derived organoid bearing mouse models. Together these data provide a strong rationale to evaluate the triplet combination of trametinib and lapatinib with vinorelbine in patients with mutant RAS mCRC that have poor clinical outcome after failure of standard chemotherapeutic regimens. We have therefore designed a phase I/II clinical trial for RAS-mutated metastatic colorectal cancer that is expected to start Q4 2019, making it a clear example of how thorough fundamental and translational research lead by clinical questions, with a crucial role of new technologies, e.g. organoid models, results in the design of promising clinical studies.

MR-linac self-evaluation

Progress in radiotherapy is accelerating by incorporating advanced MR imaging in all aspects of the radiotherapy process; in treatment preparation, treatment delivery and response assessment. The UMC Utrecht is internationally leading this process. The radiotherapy process moves from the situation with a single fixed treatment plan at the beginning of a treatment series, while using that plan for six to seven weeks and, disregarding all anatomy variations, towards an online and real-time MR image guided intervention.

The MRI linac system has been invented and developed at the UMC Utrecht (Lagendijk and Raaymakers). The high field MRI gives a clear view of the exact tumor position at the actual moment of treatment. The radiotherapy is thus being delivered while the patient is lying inside the MRI. As such, dose distributions can be optimized; normal tissue dose can be minimized and tumor dose can be increased, lowering toxicity and improving tumor control. By the reduced normal tissue dose the need for fractionation also diminishes such that the patient can be treated in fewer fractions.

The first-in-men study has been realized, showing an amazing 0.3 mm stereotactic targeting accuracy. A major international consortium has been created to organize the clinical studies all within the R-Ideal/Momentum framework. Because accurate dose painting with the MR-linac becomes available, optimal information about the exact tumor position and tumor characteristics becomes mandatory. Advanced imaging will be the main focus of each radiotherapy department requiring the whole spectrum of imaging modalities to characterize the tumor and its response to treatment. Developments like AI and deep learning are almost mandatory to realize the image processing and decision making for these real-time processes.

The UMC Utrecht is internationally driving this development on all of the above aspects; the MR-linac has been invented and developed at the UMC Utrecht. In close collaboration with Elekta and Philips this system had been commercialized and is now fast becoming the next generation international standard for radiotherapy. At the end of 2020 three MR-linacs will be installed at Radiotherapy UMC Utrecht, combined with 1.5 and 3T simulators, a newly developed MRI/PET and an 1.5 T MRI brachytherapy system. Presently these research lines are being translated to the Princess Máxima Center for pediatric oncology (PMC). They will be completed with the 7T metascanner development and the MRI guided HIFU research line. Those developments indicate the huge UMC Utrecht power and concentration on MRI guided therapy, expertise that will benefit cancer patients all over the world.



4. Theme: Clinical

4.1 Mission, strategy and organisation of the theme

In our mission to improve the outcome for cancer patients we are faced with a high frequency of over- and under treatment in both early and late stage disease. More adequate prognostic and predictive biomarkers, and innovative diagnostic and treatment tools are urgently needed to optimize cancer treatment for each individual affected. The mission of the theme 'clinical' is to learn from patient data to be able to transform clinical challenges to new fundamental questions, and to translate new fundamental findings into daily practice. Our ambition requires access to real world data through comprehensive clinical cohorts as well as unique therapeutic facilities and techniques to facilitate first in men to phase III studies to allow gaining new insights from cohorts as well as implementation of novel concepts into the clinic.

For facilitating clinical research real world patient cohorts are essential to provide us with those issues that patients in routine daily clinical practice are faced with (see Annex 3). By designing the cohorts in such a way that they can function as multi trial facilities (following the Trials within Cohorts, TwiCs, design), we provide an infrastructure for efficient evaluation of innovation.

Well characterized, unselected real world patient cohorts as well as an elaborate Phase 1-3 clinical trial portfolio will support our mission by the availability of clinical data, images, tissues, liquids and PROMs of patients treated in daily clinical practice. Besides, additional data and materials of specific patient groups are obtained through specific study designs and phase 1/2 and phase 3 clinical studies, aiming at answering more specific hypotheses.

As such, the real world cohorts as well as unique clinical techniques are used for:

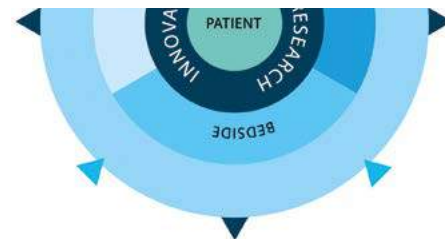
- I. Prognostic and predictive research.
- II. Biological and (epi)genetic research.
- III. Development of new personalized therapies for different subgroups.
- IV. Health care policies and cost-effectiveness studies.

Conditional for such a strategy is an excellent clinical research infrastructure with a strong clinical trial office, competitive facilities (i.e. imaging facility, robotic surgery facility and ATMP facility, that allows minimal manipulation of cellular products as well as complex genetic manipulations), cancer epidemiologists, statisticians, and experts in artificial intelligence with expertise in innovative designs and state-of-the art methodological techniques.

Research within the theme "Clinical" in the UMC Utrecht is performed by cancer researchers from all 7 divisions. Multi-disciplinary collaboration and interactions with the other three themes (including the three translational labs) are key to address the crucial clinical questions.

4.2 Research questions and its urgency and/or relevance

A substantial number of tumors are still not controlled through current cancer therapies. As such, in the Netherlands over 40,000 patients die of cancer every year, and an even larger number has to live with long term treatment related adverse effects. In order to counteract these data, we urgently need 1) better discrimination between patients who need intensive treatment and those who could benefit from treatment de-escalation or even from no treatment at all, and 2) development of high precision, targeted treatments, i.e. those interventions that exclusively destroy cancer cells.



Clinical research
Evaluate diagnostics, prognostics and treatments

- molecular - and cellular based systemic therapy
non-immunotherapy
immunotherapy
- image-guided therapy
- minimally invasive surgery

Fig. 1 Topics of the theme



With that in mind, in the topics of the theme Clinical (see Fig 1.) the following overarching goals are addressed:

- Molecular and cellular guided systemic treatments where biomarkers will predict those patients that benefit from selected targeted agents.
- Providing next generation immune- and cellular therapies and define innovative combined treatment approaches (e.g. in combination with other targeted agents or radiotherapy).
- Innovative image guided therapies to improve tumor control while sparing surrounding healthy tissues.
- Minimal invasive surgical procedures to minimize harm and enable surgical resections in complex situations.

Feasibility, safety and (early) effectiveness of these innovations are evaluated in dedicated cohorts of unselected patients that are specifically designed for fast and efficient evaluation of innovation.

In more detail, the research questions for each of the topics are:

Molecular- and cellular based systemic therapy, non-immunotherapy

Division B&O in the UMC Utrecht has a long history of a dedicated, well-organized, strong early phase clinical trial unit, in which annually >20 phase I/I-II trials (Medical oncology, Hematology) are carried out, both sponsored and investigator driven trials.

With a close collaboration of fundamental researchers (Hubrecht Institute, CMM, Oncode), translational researchers (LTO, LTI) and clinical researchers there is strong multidisciplinary backbone that together addresses the research questions from bench to bedside and back.

Research is focused on personalized treatment, improving quality of life and prevention of over- and under treatment, illustrated by:

- Molecular guided therapy in specific phase 1 trials (e.g. investigator driven phase I/II trial evaluating a novel organoids based triple combination for RAS mutant tumors).
- Organoids as a tool to predict response to treatment (OPTIC) in collaboration with HUB and LTI.
- ctDNA as a predictive marker in adjuvant and metastatic treatment.
- Large cohort studies including biobanking of tissue, blood, PROM's and the possibility of TwiCs.
- Nutritional supplements to improve tolerance of chemotherapy.

Molecular- and cellular based systemic therapy, immunotherapy

Within the UMC Utrecht, extensive expertise is build over more than a decade on the advanced therapy medicinal products (ATMP) development as well as unique expertise in the discovery on novel checkpoint inhibitors (CKI). The focus of immune therapy within the dB&O and LTI of the UMC Utrecht is to:

- Develop the next generation of allogeneic stem cell transplantation platform.
- Develop the next generation of immune modulating agents (focus: novel checkpoint CKI) – and cellular therapies (focus: innate immune system, TEG, CAR T, MSC) for patients with hematological malignancies and solid tumors and implementation in first in human studies.
- Model treatment response in 3 D bioprints (Focus B cell malignancies and leukemia).
- Introduce intelligent combinations of immune therapies with HIFU and targeted therapies.
- Unravel causes of immune CKI resistance and toxicities and the impact of the microbiome in tumor control and effectiveness of CKI.
- Implementing AI in predicting treatment response for different types of immune interventions.

Image-guided therapy

The strong focus of the Imaging Division on advanced (MRI) imaging, image data science and image-guided therapy makes the UMC Utrecht internationally leading in this area. The Imaging Division has brought forward a strong and successful development of high quality diagnostic imaging, tumor characterisation and strategies for response assessment and prediction using MRI and PET. It has also resulted in a strong and successful focus on MRI-guided cancer treatment, such as

- MRI guided radiotherapy.
- MRI-driven brachytherapy.
- Holmium-166 radioembolisation interventions.
- MRI guided High Intensity Focused Ultrasound (HIFU).
- Intravenous and intra-arterial Peptide Receptor Radionuclide Therapy (lutetium-177 dotatate, lutetium-177-PSMA).



With researchers from the Image Sciences Institute, quantitative imaging, deep learning and artificial intelligence are applied to develop solutions to allow efficient patient care and optimize tumor characterisation. This is done in close collaboration with the department of pathology with their focus on digital pathology (see also translational research).

Minimally invasive surgery

The UMC Utrecht has been one of the first centers of the Netherlands to widely implement minimally invasive robotic surgery in cancer treatment. An integral robotic program has paved the way for combined innovative technological procedures, such as integration of pre-operative imaging and bio-optical imaging during robotic interventions. Unique examples are.

- Upper GI: world leading robotic-assisted surgery for treatment of esophageal cancer attracting international surgeons to visit the UMC Utrecht to learn this technique through courses, proctoring programs and case observations. The UMC Utrecht conducted the only RCT on this topic showing the superiority of this technique and is regional coordinator for the centralized research and treatment of gastro-esophageal cancer: clinical studies, genetic profiling, MRI imaging and radiotherapy planning, reducing pulmonary complications by vagus nerve sparing, preconditioning and fast track rehabilitation after esophageal resection as well as minimally invasive gastrectomy in cardia carcinoma.
- Endocrine: unique robot-assisted trans-axillary and trans oral approach for thyroid nodules, which attracts patients from the entire country.
- Urology: complex robotic cystectomy to become one of the referral centers for this procedure in the Netherlands.
- HPB: the first robotic HPB unit in the Netherlands which, together with the regional partners, is leading in Europe and the main proctoring center attracting many international surgeons.
- Other robotic programs: The rectal cancer robotic program and minimally invasive breast surgery (see narrative) are emerging, while the gynecological robotic procedures are expanding.

4.3 Relation to existing knowledge

The topics of the current theme perfectly fit into the recently published strategy by the Dutch Research Council, the so-called Dutch National Research Agenda (NWA) Theme "Personalized Medicine". As stated before, lack of sufficient tumor control and unwanted, often long term, side effects demand focus on a personalized approach in cancer care.

Within the topic Molecular- and cellular based systemic therapy - non-immunotherapy we foresee the importance of (unselected) real life patient cohorts in which care and research are integrated, as they are perfectly suited to determine the most optimal personalized approach for each and every patient. This is clearly illustrated by the main theme of the 2019 ASCO conference: "Care for every patient and learn from every patient".

Within the topic Molecular- and cellular based systemic therapy - immunotherapy we build on the extensive expertise on the ATMP development as well as the unique expertise in the discovery on novel checkpoint inhibitors. In addition, the harmonized allogeneic stem cell transplantation programs between the UMC Utrecht and PMC generate a unique position for the future development of novel therapies in Europe and the generation of young adult cohorts with harmonized treatment schedules as fundament for innovative drugs.

Within the topic of Image Guided Therapies we build on existing knowledge. An exciting example is the MRI-guided Linear Accelerator, which was conceptualized by Prof Jan Lagendijk at the UMC Utrecht in the late 1990s. Together with industry partners Elekta and Philips, this concept was developed into a CE and FDA approved machine, with which patients are currently being treated with 0.3 mm precision. Another UMC Utrecht invention is the new generation holmium-166 microspheres for personalized radioembolisation, as is the intra-arterial instead of intravenous use of lutetium-177-dotate in neuro-endocrine tumor patients. Finding, in public-private collaboration, new treatment modalities, new treatment techniques and new indications has been the scope of our research for years.

Within the topic Minimally Invasive Surgery, research contains all aspects of optimizing the surgical treatment for patients with patients with various types of malignancies. This includes MRI imaging and radiotherapy planning, genetic profiling to predict response to chemoradiotherapy, staging and restaging, preconditioning of surgical candidates, minimally invasive robotic surgery, developing vagal nerve sparing operating techniques.



4.4 Collaborations

The research groups in this theme closely cooperate with various stakeholders and participate in relevant professional organisations, amongst others :

- Patient organisations: several tumor working groups have regular meetings with the associated patient advocacy groups (e.g. HEMATON) which allows input from patients in both new research proposals and ongoing trials.
- Regional hospitals for tuning of research and care in tumor boards (e.g. UNIEK/ RAKU).
- National tumor boards (e.g. HOVON working parties, BOOG, DCCG).
- Health Foundations (e.g. Dutch Cancer Foundation, KIKA).
- Netherlands Comprehensive Cancer Organisation for National cancer registrations (IKNL).
- PALGA: an worldwide unique nationwide network and registry of histo -and cytopathology data.
- European Reference networks, e.g. EuroBloodNet, EndoERN and EuraCAN.
- Joint research meetings with ONCODE to bridge fundamental and clinical science.
- Hubrecht Organoid Technology (HUB) for all organoid trials and organoid biobanking.
- Covering life span research by collaborations with Princes Máxima Center for pediatric oncology (PMC).
- Corporate trial groups (e.g. HOVON, DORP) and medical societies (e.g. EBMT).
- Research consortia consisting of public and private stakeholders, and include patient organisations (e.g. International consortium for MRI-guided radiotherapy with institutions from Europe and North America and private partners such as Philips and Elekta).
- National research infrastructures (e.g. Health-RI, BBMRI-NL, Parelnoer).

4.5 Research Design

In the design of our research portfolio we have the availability of the following experts:

- Setup of clinical cohorts and following innovative trial designs, including early health technology assessments (dJC, THINC), involving: structural collaboration with statisticians and methodologists from the UMC Utrecht, dJC, and from other UMC's. New scientific proposals: evaluation of research questions on their relevance, uniqueness, and feasibility by external partners (e.g. IKNL).
- Statistical design: expertise statistics via dJC, LTI and HOVON.
- ATMP development: ATMP facility of the UMC Utrecht provides support during designing studies dealing with cellular therapies.
- Biobanking: the UMC Utrecht biobank facility is the backbone for all biobanks to allow standardized collection of material collected during clinical trials or general biobanking initiatives.
- Deep learning and artificial intelligence: Image Sciences Institute (part of CIS), pathology department and TU/e.

4.6 The next steps

Within the four topics of the theme clinical there are several ways to implement our research data into the clinic.

Molecular- and cellular based systemic therapy, non-immunotherapy

The need for real life data of a broad spectrum of patients, in combination with a biobank and quality of life data in order to achieve personalized treatment, is clearly recognized worldwide. The Netherlands has the perfect infrastructure to implement the integration of research and care and as such is world leading.

A good example is the concept, design and operation of the Prospective Dutch CRC cohort (PLCRC, <https://plcrc.nl/for-international-visitors>), which is initiated and led within the UMC Utrecht.

- The design of PLCRC also generated the interest of European study groups, now exploring possibilities to implement this design in their countries.
- We expect that in 5 years from now > 25.000 Colorectal cancer patients are being included in > 70 hospitals in the Netherlands, with > 50 substudies with an ICT suited for the registration in several substudies and analysis of big data.
- Possible users of research findings are demonstrably involved in the project, e.g. other (clinical) research groups, general practitioners, nurses, small and medium enterprises, pharmaceutical and medtech companies, etc.



- Results of substudies are shared with the national and international CRC community.
- Data of PLCRC are translated to clinical practice and taken into account in the updates of guidelines to optimize CRC care regionally, national and international.

The framework of PLCRC can be used for cohorts in other Tumor boards.

Molecular- and cellular based systemic therapy, immunotherapy

After answering the research questions in the topic "Immunotherapy" the following steps will be:

- For the TEG pipeline we expect that the startup company will perform a next series of clinical trials while we will focus within academia on novel targets as well as bispecific projects and aim to potentially open a second company on the GAB concept.
- Transplantation platform: Implementation of the concept across different centers in Europe (extend current guidelines) and the further development of post transplantation platform with academic partners.
- Developing smart combinations between targeted therapies (e.g. HIFU, small molecules) and immune therapies are discussed with different companies exploring proprietary compounds.
- Detecting and exploring novel checkpoint opportunities will be discussed with different valorisation partners.

Image-guided therapy

Public-private collaboration safeguards valorisation, implementation and dissemination. Holmium-166 microspheres were developed in the UMC Utrecht. After CE-mark as a medical device a start-up company (Quirem Medical BV) was initiated and the treatment was further valorized (QuiremSpheres® and QuiremScout®). In further collaboration between UMC Utrecht, Quirem and investing company Terumo, a global phase III RCT is being constructed.

For evidence-based implementation of MRI guided radiotherapy using the MR Linac (na UMC Utrecht invention), an Academic Industrial Partnership, coordinated by the UMC Utrecht, and involving large international cancer centers (including MD Anderson, Sunnybrook and Royal Marsden Hospital) and industry partner Elekta, has been set up. In this so called MOMENTUM study, prospective clinical and technical data are collected to allow technical optimisation of the machine as well as providing clinical evidence of effectiveness.

The UMC Utrecht also leads the H2020 Further Consortium, which aims to determine the (cost)effectiveness and position of MRI-guided High Intensity Focused Ultrasound for pain relief in patients with bone metastases within Europe.

Minimally invasive therapy

As the UMC Utrecht is a world leading expert center for robotic minimally invasive surgery, new innovations such as image guided surgery, artificial intelligence and new robotic systems projects will be implemented. Collaborations with industrial partners are being established given the clinical robotic expertise available in the UMC Utrecht. Robotic systems enable placing a computer between a patient and the surgeon, therefore enabling the use of artificial intelligence, but also augmented and virtual reality as well as smart, computerized tools to be used in surgery.

The teaching and proctoring programs on minimally invasive surgery are worldwide recognized and attract surgeons from all over the world. The programs will be further developed and refined. Also, programs for teaching surgical residents are developed in collaboration with the Dutch nationwide robotic working group chaired by the UMC Utrecht.



4.7 Highlights of results

4.7.1 Molecular- and cellular based systemic therapy, non-immunotherapy

Research products for peers

Datasets, biobanks: see overview in Annex 3.

Infrastructure

- Infrastructures: for prospective cohorts of patients (e.g. UMBRELLA, PLCRC, PRESENT), in which clinical and imaging data are prospectively collected, together with regular long term patient reported outcome measures. The cohorts follow an innovative trial design (Trials within Cohort design), which allows fast and simultaneous randomized evaluation of multiple interventions within these cohorts (**Verkooijen, Koopman, Vink, May, van Gils**).
- The national MEN database was set up to build the scientific basis for the clinical practice guidelines (see also “MEN guidelines” in section “Research projects where patients are meaningfully involved” (**Valk, Vriens**).
- Professional phase 1/2 research unit with an experienced team of medical doctors en research nurses headed by Dr. Eelco Gort (**Witteveen**).

Instruments, compounds, software tools

- With the support of PLCRC the ICT tool “Study Logistics and Information Manager (SLIM)” was developed further (dJC, UMC Utrecht), to be able to support cohorts like PLCRC (**Vink**).
 - Models for therapy response prediction: colorectal cancer (**Kranenburg, Roodhart, Koopman, Vink**).
-

Research products for societal target groups

Publications accessible for a large audience

- 2014: News item about breast cancer risk in MEN-1.
<https://www.pinkribbon.nl/nieuws/2014/08/07/onderzoekers-umc-utrecht-ontdekken-nieuw-borstkankergen/> (**Valk**).
- 2018: Interview in Elsevier “personalized treatment for colorectal cancer patients”(in Dutch). (**Koopman**).
- 2018: TV Show with interview about screening of breast cancer (Breast cancer month Pink Ribbon Campaign)
https://www.koffietijd.nl/Maandag_1_oktober_2018 and a TV show organized by the Dutch Cancer Foundation “Vraag vandaag” with topic : new approaches in breast cancer treatment (**van der Wall**).
- 2018: Interview in nationwide magazine for specialists in internal medicine: “onderzoek en management”. (**van der Wall**).

“Products” designed for public use

- 2016: “Keuzehulp” tool for patients, www.ddk.keuzehulp.nl (**Koopman**).
- In collaboration with PROFILES digital feedback on the PROM scores was developed for every patient participating in PLCRC and completing the Quality of Life questionnaires digitally (**Vink**).
- 2017: Carepath MEN 1, information for patients [link PDF](#) (**Valk, Vriens**).

Outreach activities

- 2013: chair editorial board of www.hersentumor.nl (**Snijder**).
 - 2013-2018 (4 times/year): Lectures and lab tour for KWF volunteers (**van der Wall**).
 - Lay presentations of to participants attending/participating to different KWF and Alpe d’HuZes events and the ‘Healthcare 2025’ meeting held by the Amsterdam Economic Board and Chamber of Commerce for healthcare innovation (**Roodhart**).
 - 2016-2017: World congress ‘WorldMEN 2016’ on rare endocrine tumour syndromes including parallel sessions for patients and a [presentation](#) on the yearly meeting of patient advocacy group NET (**Valk, Vriens**).
 - 2018: Webinar colon cancer (**Kranenburg, Koopman**).
-



Use of research products by peers

Use of biobanks and data collections

- PLCRC cohort is used by > 20 sub studies, e.g. MEDOCC, OPTIC (**Koopman, Vink**).
- Large organoid biobank with clinical data for all tumor types and tissues in collaboration with Hubrecht Organoid Technology (HUB) used by researchers and pharmaceutical companies worldwide (**Kranenburg, Roodhart**) – see further description in theme “Translational”.
- MEN-database & Biobank infrastructure is adopted and implemented by MD Anderson, TX and NIH, MD, USA and is used by Dana Farber Cancer Institute Boston, MA, USA. (**Valk, Vriens**).

Use of research facilities/infrastructure

- The infrastructure of PLCRC is increasingly becoming used by researchers from the UMC Utrecht and other institutes. The first years were used to develop the infrastructure. Now the logistics are in place, more than 2/3 of Dutch hospitals are open for inclusion, and almost 6000 patients are included, providing a resource for data and tissue. This results in multiple grant and study proposals, and collaborations to facilitate scientific research. These proposals are both from the UMC Utrecht and from other hospitals and organisations.
- European Expertise Center: Neuro-endocrine tumors (NET, together with AVL), MEN 1-syndroom MEN 2-syndrome (including sporadic medullary thyroid carcinoma), and the Von Hippel Lindau syndrome (VHL), and thyroid tumors (**Valk**).

Use of software tools, compounds, instruments

- SLIM is being used by several other cohorts e.g. YOUTH cohort (UU, UMC Utrecht), PACAP and POCOP cohorts (University medical Center Amsterdam, location AMC).
-

Use of research products by societal groups

Consortia, public-private partnerships

- One of the substudies of PLCRC resulted in a public-private partnership, which was also supported by Health Holland. Also various others resulted in large public-private consortia, mainly in the field of ctDNA.

Policy documents, implementation in guidelines, reimbursement

- member of Dutch guideline group: Fertility preservation for women with cancer (2015-2016), Dutch Alliance of Gender and Health care (>2012), Modelreglement Embryowet (NVOG and KLEM) Advisory board August 2018 Member of the working group for development of fertility preservation guidelines in female cancer patients (0-18 years) as part of the IGHG project/PancareLife European project (>2016-2018) (**Bos**).
 - Results of the CAIRO3 study in guidelines (see also key publication Simkens et al) (**Koopman**).
-

Marks of recognition from peers

Awards, individual research grants (Veni, Vidi, Vici, ERC, Marie-Curie)

- 2014: Huizinga penning of the Dutch Association of Hospital Pharmacists (**Huitema**).
- 2017 Boerhaaveprijs van Stichting J.M. Fentener van Vlissingen Fonds (**Seute**).
- 2017 PhD Supervisor of the Year (**Koopman**).
- Associated Professor at the Sidney Kimmel Cancer Center at Johns Hopkins Medical Institutions (**van der Wall, van Diest**).

Elected memberships of scientific committees

- 2013-2015 Member Guideline committee ‘Intracranial meningeoma’ (**Snijder**).
- 2014 Member Dutch Advisory group Cancer in pregnancy (**Witteveen**).
- Board member DCCG (chair from 2019 onwards) (**Koopman**).
- Chair breast cancer research group (BOOG) (**van der Wall**).
- 2017 onwards: Clinical Advisory Board ONCODE (**Koopman**).



Editorial boards

- NTvO, i.e Dutch Journal on Oncology (**Witteveen**).
-

Marks of recognition from societal groups

Public Prizes

- 2015: Galenus research prize (**Huitema**).

Membership of civil society advisory bodies

- Chair visitatiecommissie kwaliteit NVMDL (**Vleggaar**).
- Donation 80,000 euro - personal action "Stop hersenkanker nu" (**Snijder**).
- Advisory committee ZonMW "Goed Gebruik Geneesmiddelen" and ZInNL (**Koopman**).
- Member of the Fentener van Vlissingen Foundation Board (**van der Wall**).

Consultancies for public or private sector

- Scientific advisory board of several pharmaceutical companies (**Koopman**).
-

4.7.2 Molecular- and cellular based systemic therapy, immunotherapy

Research products for peers

Datasets, biobanks: see overview in Annex 3

- Biobanks for supporting all research activities: SCT Biobank UMC Utrecht & Checkpoint inhibitor biobank UMC Utrecht (UNICIT cohort) & LML Biobank.

Infrastructure

- Changing the landscape how to treat patients suffering from multiple myeloma: A breakthrough publication in New England Journal of Medicine in 2015 that describes targeting of CD38 using the monoclonal antibody Daratumumab for multiple myeloma was co-authored by Monique Minnema and cited 370 times.

Instruments, compounds, software tools, knowledge

- See patent (applications), spin-offs.
-

Research products for societal target groups

Publications accessible for a large audience

- 2016: Article about Leukemia with reaction of Kuball. <https://www.volkskrant.nl/wetenschap/supercel-deelt-leukemie-tik-uit~b5361961/> (**Kuball**).
- 2017: News article on the website of Children's Hospital about stem cell transplantation. <https://www.hetwkz.nl/nl/Ziekenhuis/Professionals/Nieuws-voor-professionals/2017/Slimmer-doseren-van-medicatie-redt-levens-na-stamc> (**Kuball**).
- 2018: Jürgen Kuball, EBMT Treasurer discusses European institutions working towards the accelerated development of cellular therapies to tackle cancer and other debilitating disorders of the hematopoietic system and the work of the EBMT Registry. <https://www.youtube.com/watch?v=uScUjZsIVyI> (**Kuball**).

Outreach activities

- Lay presentations of to participants attending/participating to different KWF and Alpe d'HuZes events (**Minnema, Raymakers, Kuball, Koopman**).
 - Lay presentations and publications (Elsevier, public cahier, info day patient society, Utrecht Science Park etc) (**Suijkerbuijk**).
-



Use of research products by peers

Use of research facilities/infrastructure/knowledge

- European Expertise Center: malignant hematology.
- First symposium “innovation in cellular therapy” CART cells and beyond, (**Minnema**).
- Invited Review based on expertise: Translating $\gamma\delta$ T cells and their receptors into cancer immune therapies. Sebestyen Z, Prinz I, Déchanet-Merville J, Silva-Santos B, Kuball J. Nature Reviews Drug Discovery 2019 in print IF 57.000 “Do’s and don’ts” for developers how to translate $\gamma\delta$ T cells and their receptors into therapeutic concepts.
- Spreading unique expertise and creating clinical consortia for orphan diseases: Efficacy of retreatment with immunomodulatory drugs and proteasome inhibitors following daratumumab monotherapy in relapsed and refractory multiple myeloma patients. Oostvogels R, Jak M, Raymakers R, Mous R, Minnema MC. Br J Haematol. 2018 Oct;183(1):60-67. IF 5.67. First and only paper thus far describing efficacy of treatment in multiple myeloma patients after they have relapsed after daratumumab treatment and providing options in real life settings.

Use of biobanks and data collections

- Bortezomib based induction followed by stem cell transplantation in light chain amyloidosis: results of the multi-center HOVON 104 trial. Minnema MC, Nasserinejad K, Hazenberg B, Hegenbart U, Vlummens P, Ypma PF, Kröger N, Wu KL, Kersten MJ, Schaafsma MR, Croockewit S, de Waal E, Zweegman S, Tick L, Broijl A, Koene H, Bos G, Sonneveld P, Schönland S. Haematologica. 2019 Mar 28. IF 9.09.
The HOVON trial group organizes and supports trials in hem onc at both national as international level. This trial is the effort of 15 participating sites in the Netherlands, Belgium and Germany and investigates prospectively the use of bortezomib in a rare disease outside the standardly reported retrospective expert center provided data.

Use of software tools, compounds, instruments

- Multiple Patents have been licensed to the UMC Utrecht startup company GADETA and the cellular therapy company Miltenyi Biotech with Kuball as inventor. E.g. 2013: WO 2013 /147606 A1 Combinatorial gamma 9 delta 2 T cell receptor chain exchange, (C. Grunder, J. Kuball), licensed to Gadeta & 2017.
-

Use of research products by societal groups

Consortia, public-private partnerships

- Raymakers and Minnema performed contract research with Philips Research BV between 2017-2019 with the aim to create a diagnostic tool based on cell signaling activity that predicts drug efficacy in patients suffering from hematological malignancies.

Policy documents, implementation in guidelines, reimbursement

- Achieving a qualified opinion of the EBMT Registry. Kuball is a co-founder of the legal and regulatory affairs committee of EBMT and the liaison between EMA and EBMT since 2017. This allowed to implement the EBMT registry as public registry for all post marketing surveillance studies for CART cells. This project resulted in a qualified opinion of EMA on the Cellular Therapy Registry of EBMT. In order to allow transparent access to the cellular therapy registry, we created a stakeholder group linking pharmaceutical companies, with health technology assessment (HTA) bodies, health care professionals as well as patient organisations (**Kuball**).
- Providing articles presentations at patient organisation Hematon and supplied feedback on policy reports regarding CART cells to the Zorginstituut Nederland (ZiNl) as well as to EUnetHTA and EMA.
- Use of CD38-specific antibody Daratumumab for Multiple Myeloma in the Dutch national clinical guidelines (**Minnema**).
- Use of anti CD19 CART cells in relapsed and refractory diffuse large B cell lymphoma in Dutch National clinical guidelines (Minnema).
- European (EBMT) and Dutch guidelines for stem cell transplantation (**Kuball**).
- abT cell depletion in guidelines of EBMT as well as guidelines of HOVON. This resulted in the reimbursement of the procedure by the Dutch insurances from 01/2020 (**Kuball**).



Patent (applications), spin-offs

- Multiple Patents have been licensed to the UMC Utrecht startup company GADETA and the cellular therapy company Miltenyi Biotech with Kuball as inventor. E.g. 2013: WO 2013 /147606 A1
 - GADETA established in 2015: Valorisation of a first set of gdTCRs (gamma-delta T-cell Receptor, see selection of patents). Kuball is scientific co-founder of the company.
-

Marks of recognition from peers

Awards, individual research grants (Veni, Vidi, Vici, ERC, Marie-Curie)

- Marie-Curie to Dennis Beringer group Kuball.

Elected memberships of scientific committees

- Chair Legal Regulatory Affairs Committee of EBMT (**Kuball**).

Editorial boards

- Frontiers Immunology (Special Section gdT cell biology) (**Kuball**).
-

Marks of recognition from societal groups

Membership of civil society advisory bodies

- Scientific Board member of KWF and KIKA (**Kuball**).
 - Member of the international Waldenström patient organisation IWMP, patient advisor especially for the rare Bing Neel syndrome (**Minnema**).
 - Advisory board member for the Dutch Melanoma Patient Society (**Suijkerbuijk**).
-

4.7.3 Image guided therapy

Research products for peers

Datasets, biobanks: see overview in Annex 3

Infrastructure

- Top 3 internationally recognized expert center on radioembolisation, illustrated by the number of publication on this topic in peer reviewed journals and in the public domain (**Lam**).

Instruments, compounds, software tools

- Simplicit^{90y}™ software for radioembolisation treatment planning, developed in collaboration with BTG and Mirada (**Lam**).
 - UMCS (Monte Carlo simulation tool for SPECT imaging reconstruction) (**de Jong**).
-

Research products for societal target groups

Publications accessible for a large audience

- 2015: news item on website <https://www.ziekten.nl/therapie-met-radioactieve-bolletjes-nu-ook-ingezet-tegen-hoofd-en-halstumoren/> (**Lam**).
- 2018: Article in a large nationwide newspaper based on the inaugural speech about new trial designs <https://www.nrc.nl/nieuws/2018/05/28/van-iedere-patient-kun-je-iets-leren-a1604434> (**Verkooijen**).



Outreach activities

- International proctorships on radioembolisation (**Lam**).
 - Workshops on image-guided treatment (**Lam**).
 - UMBRELLA patient day 2017 and 2018: lay presentations, workshops and meet-the-research sessions for breast cancer patients participating in the regional breast cancer cohort (**Verkooijen**).
-

Use of research products by peers

Use of biobanks and data collections

- MOMENTUM registry for patients treated on MR Linac is used by international researchers and industry (ELEKTA).
- UMBRELLA breast cancer cohort is used by RIVM, LUMC, researchers from other divisions.

Use of software tools, compounds, instruments

- Simplicit^{90y}™ software for radioembolisation treatment planning, developed in collaboration with BTG and Mirada (**Lam**).
-

Use of research products by societal groups

Consortia, public-private partnerships

- 2017 H2020 consortium LIMA (**Gilhuijs**) - Liquid biopsies and Imaging for improved cancer care.
- 2018 H2020 consortium FURTHER (**Verkooijen**); 2018-2023; Focused Ultrasound and RadioTherapy for Noninvasive Pain Treatment in Bone Metastases.

Policy documents, implementation in guidelines, reimbursement

- Dutch Guidelines on Radioembolisation (**Lam**).
- Member of the International Dosimetry Steering Committee on Radioembolisation, publishing consensus recommendations (**Lam**).
- Member of the working group on The Dutch Guideline for (Screening on) Breast Cancer (**Pijnappel, van den Bongard, Verkooijen**).

Patent (applications), spin-offs

- Quirem Medical BV (QuiremSpheres® and QuiremScout®).
-

Marks of recognition from peers

Awards, individual research grants (Veni, Vidi, Vici, ERC, Marie-Curie)

- 2014 CIRSE Award of Excellence and Innovation in Interventional Radiology (**Lam**).

Elected memberships of scientific committees

- Board Member of the National Education Committee on Nuclear Medicine (**Lam**).
- president of the Dutch College of Breast Imaging (201-2015). Treasurer and board member of the European Society of Breast Cancer Imaging (EUSOBI), Member of the multidisciplinary audit team of the EUSOMA (**Pijnappel**).
- Member of the Scientific Advisory Board of the Dutch Expert Center for Screening (**Verkooijen**).

Editorial boards

- Series editor Computational Imaging and Vision, Springer, guest editor of nine journal issues, (co)author/editor of 18 books (**Viergever**).
 - PET Clinics (**Lam**).
-



Marks of recognition from societal groups

Public prizes

- Nominee PhD Supervisor of the Year 2018 (**Lam**).

Membership of civil society advisory bodies

- Foundation Image-guided treatment of Cancer (SBBVK), Dutch Federation of Cancer patient organisations (NFK), Prostate Cancer foundation, NET Foundation (**Lam**).
- Vice-Chairman of the Board of the CHECK (Cohort Hip & Cohort Knee Research) Foundation, related to the Dutch Arthritis Foundation (**Viergever**).
- Scientific Advisory Board Pink Ribbon (**vdBongard**).
- Scientific advisory board Dutch Cancer foundation (**Gilhuijs**).

Consultancies for public or private sector

- Consultant for BTG and Terumo (**Lam**).
 - CEO of the LRCB (Dutch Expert Centre for Screening) (**Pijnappel**).
-

4.7.4 Minimally invasive surgery

Research products for peers

Datasets, biobanks: see overview in annex 3

Infrastructure

- HPB: performed the first robotic distal pancreatectomy, first robotic whipple surgery, and first robotic minor and major hepatectomies in the Netherlands. Instrumental in the set up robotic hepatectomy in 4 other Dutch university and top-clinical hospitals Are currently gaining international interest as one the few proctors for robotic liver and pancreas surgery in Europe.
 - Upper GI: world leaders in robotic and minimally invasive surgery. Board memberships of EDS, Society for gastro-intestinal surgery, chair robotic working group. Proctoring for multiple international robotic programs. Leaders of international minimally invasive surgery courses.
-

Research products for societal target groups

Publications accessible for a large audience

- 2017: news item about adapted care around esophagus surgery <https://utrecht.nieuws.nl/stadsnieuws/62858/umc-utrecht-bereikt-minder-voorzorg-betere-resultaten-slokdarmkanker/> (**Hillegersberg**).
- 2017: News item about donation for research (rare type of ovarium cancer) <https://www.rtlnieuws.nl/gezondheid/artikel/69556/familie-patiente-geeft-tonnen-voor-kankeronderzoek-we-willen-vrouwen-hoop> (**Zweemer**).
- 2017: Movie report about Pancreas surgery (neuro-endocrine) and robot surgery during the NET symposium. (**Vriens**).

“Products” designed for public use

- 2019: Video folder for urological cancers (**Meijer**).

Outreach activities

- Lay presentations on robotic liver- and pancreas surgery (RAKU patientendag, Nederlandse Lever patientenvereniging) (**Molenaar, Hagendoorn**).
-



Use of research products by peers

Use of research facilities/infrastructure

- European Expertise Centers: Head and Neck tumors (**de Bree**).
- European Expertise Centers: Glial tumors (**Robe**).
- European Expertise Center: rare pediatric soft tissue tumors (together with PMC) (**Witkamp**).

Use of research products by societal groups

Consortia, public-private partnerships

- RAKU - largest regional HPB unit in the Netherlands (**Hillegersberg, Borel Rinkes, Molenaar, Hagendoorn**).

Policy documents, implementation in guidelines, reimbursement

- Ductoscopy from 2019 onwards implemented in guidelines (see narrative) (**Witkamp**).
-

Marks of recognition from peers

Awards, individual research grants (Veni, Vidi, Vici, ERC, Marie-Curie)

- 2013 Catharijne Award for outstanding translational research & surgical oncology patient care (**Borel Rinkes**).

Elected memberships of scientific committees

- Member of the Cochrane Ear, Nose & Throat Disorders Group (**de Bree**).
- Member of the guideline committee Dutch Working group Head and Neck Cancer (**de Bree**).
- President of the European Digestive Surgery (**Hillegersberg**).

Editorial boards

- Journal of Gastroenterology and Hepatology Research, Digestive Surgery, Diseases Esophagus (**Hillegersberg**).
 - Board member Dutch Pancreatic Cancer Group (**Molenaar**).
-

Marks of recognition from societal groups

Membership of civil society advisory bodies

- member of the permanent Scientific committee OESO World Organisation for Specialised studies on diseases of the esophagus (**Hillegersberg**).
- Board member Michaël van Vloten Fonds and Fentener van Vlissingen Fonds (**Borel Rinkes**).
- Board Member "Hoofd-Hals patients group" for head and neck cancer patients (**de Bree**).
- Scientific Board Hersenstichting (**Robe**).

Consultancies for public or private sector

- Medical Advisor "Best Doctors" Inc, Europe (**Borel Rinkes**).
-

4.8 Research projects where patients are meaningfully involved

HOVON-associated TARGET study NTR 7136

By introducing abT cell depletion we have chosen in the past years for a transplantation platform which maintains innate immune subsets early after transplantation. To date, we retrospectively analyzed a large cohort of patients (n=105) which received an abT cell depleted allograft. In line with previous reports we observed rapid IR of NK and gdT cells. With our homogenous cohorts linked to prospective biobanking, we aim to overcome previous hurdles of heterogeneity in subsets of IR to better address how cytomegalovirus (CMV) reactivation contributes to the graft-versus-leukemia potential of an allograft. In this prospective study we will test whether avoiding substantial fluctuation of fludarabine levels in patients improves innate IR and clinical outcome after allo-SCT. This project has also power to explore whether targeted fludarabine is a useful intervention even outside the context of allo-SCT such as CAR T cell therapies.



Together with the Dutch Cancer Registry and with input from the patient organisation SAN we have developed the first national cancer registry of acute leukemia Amyloidosis. This registry will provide us with unique and precious information on the incidence, prevalence, diagnosis, treatment and survival of this rare and complex disease and will provide tools to improve care and access to trials for patients.

Prospective Dutch CRC cohort (PLCRC)

The Prospective Dutch CRC cohort provides an infrastructure for scientific research into colorectal cancer. After informed consent, clinical data are collected, and tissue and blood are stored. Patients are also asked to complete (quality of life) questionnaires for determining PROMs. Since the summer of 2018, patients can gain insight into the scores achieved. If desired, they receive a feedback with part of the scores as they can be calculated from the completed questionnaires. This feedback, the choice of items and the graphic representation has been developed with input from and in consultation with a delegation from the colorectal cancer working group, the patient platform for patients with colorectal cancer.

MEN Guidelines

The national MEN database was set up to build the scientific basis for the clinical practice guidelines which are up to now based on expert opinion and meagre scientific evidence. The patient advocacy group was consulted already in a very early stage, as to what clinical questions they deemed important to study. The patient advocacy group considered quality of life as an important topic to study. More specifically, they considered questions regarding frequency and content of follow-up visits, effects and complications of surgery (and the impact of neuro-endocrine tumors as important topics since these affect quality of life. In a process of informed shared decision-making, research questions and study aims were formulated. Thereafter, within the UMC Utrecht, a retrospective MEN1 database was carefully designed based on the clinical dilemmas of MEN1 patients and their treating physicians encountered in daily practice. In an unique nationwide collaboration, known as the Dutch MEN Study Group (DMSG), with active participation of the patients, more than 90% of the total Dutch MEN1 population is included in the database. Together with the patients themselves, important lessons were learned about the quality of life of patients and the impact of screening and interventions. Based on this unique collaboration, during 10 years of research multiple clinical dilemmas have already influenced the care for patients with MEN1 worldwide. In close collaboration with the patients, ongoing prospective clinical data collection and the collection of biobank materials has commenced in 2016 for the MEN 1 syndrome. This will further increase the quality of the data and enables clinical epidemiological and translational research in the near future. The MEN 1 database is currently also extended to MD Anderson Cancer Center to enable mutual research projects. In 2019 a subsequent database is started for the MEN 2 syndrome.

4.9 Most important scientific publications

4.9.1 Molecular- and cellular based systemic therapy, non-immunotherapy

Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group

Simkens LH, van Tinteren H, May A, ten Tije AJ, Creemers GJ, Loosveld OJ, de Jongh FE, Erdkamp FL, Erjavec Z, van der Torren AM, Tol J, Braun HJ, Nieboer P, van der Hoeven JJ, Haasjes JG, Jansen RL, Wals J, Cats A, Derleyn VA, Honkoop AH, Mol L, Punt CJ, Koopman M. *Lancet*. 2015 May 9;385(9980):1843-52.

This study reported that maintenance treatment with capecitabine plus bevacizumab after six cycles of CAPOX-B in patients with metastatic colorectal cancer is effective and does not compromise quality of life. This paper has had direct consequences for the treatment of colorectal cancer.

Histologic Factors Associated With Need for Surgery in Patients With Pedunculated T1 Colorectal Carcinomas.

Backes Y, Elias SG, Groen JN, Schwartz MP, Wolfhagen FHJ, Geesing JMJ, Ter Borg F, van Bergeijk J, Spanier BWM, de Vos Tot Nederveen Cappel WH, Kessels K, Seldenrijk CA, Raicu MG, Drillenburg P, Milne AN, Kerkhof M, Seerden TCJ, Siersema PD, Vleggaar FP, Offerhaus GJA, Lacle MM, Moons LMG; Dutch T1 CRC Working Group. *Gastroenterology*. 2018 May;154(6):1647-1659.

In a cohort-nested matched case-control study of 708 patients with pedunculated T1 colorectal carcinomas, we developed a model based on histologic features of tumors that identifies patients who require surgery (due to high risk of metastasis) with greater accuracy than previous models. Our model might be used to identify patients most likely to benefit from adjuvant surgery. The study is the result of a Dutch nation-wide network initiated from the UMC Utrecht.



Genomic and transcriptomic plasticity in treatment-naive ovarian cancer

Hoogstraat M1, de Pagter MS, Cirkel GA, van Roosmalen MJ, Harkins TT, Duran K, Kreeftmeijer J, Renkens I, Witteveen PO, Lee CC, Nijman IJ, Guy T, van 't Slot R, Jonges TN, Lolkema MP, Koudijs MJ, Zweemer RP, Voest EE, Cuppen E, Kloosterman WP. *Genome Res.* 2014 Feb;24(2):200-11.

The study highlights the plasticity of ovarian cancer genomes, which may contribute to their strong capacity to adapt to changing environmental conditions and give rise to the high rate of recurrent disease following standard treatment regimes. This paper further clearly shows the collaboration between clinic and pre-clinic and resulted in research grants of 2.5M€.

Prognostic relevance of epilepsy at presentation in glioblastoma patients.

Berendsen S, Varkila M, Kroonen J, Seute T, Snijders TJ, Kauw F, Spliet WG, Willems M, Poulet C, Broekman ML, Bours V, Robe PA. *Neuro Oncol.* 2016 May;18(5):700-6.

This multidisciplinary work demonstrates unequivocally and on the largest cohort analyzed thus far that epilepsy at presentation is associated with prolonged survival of glioblastoma patients independent of age, sex, performance status, type of surgery, postsurgical treatment, tumor volume and location. This prognostic effect cannot be solely explained by early diagnosis, or by anti-epileptic treatment, pointing to a probable distinct tumor biology. This finding is since used as a determinant of the prognostic of patients at presentation.

MOLECULAR- AND CELLULAR BASED SYSTEMIC THERAPY, IMMUNOTHERAPY

RhoB Mediates Phosphoantigen Recognition by V γ 9V δ 2 T Cell Receptor.

Sebestyen Z, Scheper W, Vyborova A, Gu S, Rychnavska Z, Schiffler M, Cleven A, Chéneau C, van Noorden M, Peigné CM, Olive D, Lebbink RJ, Oostvogels R, Mutis T, Schuurhuis GJ, Adams EJ, Scotet E, Kuball J. *Cell Rep.* 2016 May 31;15(9):1973-85.

This paper elucidates the crucial role of a small GTPase in the inside out recognition mechanism of a tumor cell by a g9d2T cell receptor and basis for the patent application 2017/62508807.

Possibilities and limitations of an in vitro 3D bone marrow model for the prediction of clinical responses in patients with relapsed multiple myeloma.

Braham MVJ, Alblas J, Dhert WJA, Öner FC, Minnema MC. *Haematologica.* 2019 Apr 19.

This paper describes the use of a 3D in vitro bone marrow model in which we succeeded to sustain and proliferate primary myeloma cells for >4 weeks outside the body. We used the 3D model to evaluate concordance of the in vivo responses to cancer drugs in patients and the effects of these drugs in the model. We demonstrated that for certain drugs there is high concordance in response and therefore this model is the basis for large scale testing in patients. The model resulted in several successful research grants.

Untouched GMP-Ready Purified Engineered Immune Cells to Treat Cancer.

Straetemans T, Gründer C, Heijhuurs S, Hol S, Slaper-Cortenbach I, Bönig H, Sebestyen Z, Kuball J. *Clin Cancer Res.* 2015 Sep 1;21(17):3957-68.

We developed a novel GMP-grade isolation technique utilized for engineered immune cells. This resulted in patent application 20170319674.

4.9.2 Image guided therapy

Efficacy of Radioembolisation with 166Ho-Microspheres in Salvage Patients with Liver Metastases: A Phase 2 Study.

Prince JF, van den Bosch MAAJ, Nijsen JFW, Smits MLJ, van den Hoven AF, Nikolakopoulos S, Wessels FJ, Bruijnen RCG, Braat MNGJA, Zonnenberg BA, Lam MGEH. *J Nucl Med.* 2018 Apr;59(4):582-588.

The results of this clinical phase II study confirmed the safety and efficacy of radioembolisation using 166Ho-microspheres, a new treatment modality against hepatic malignancies, developed in the UMC Utrecht. It may be regarded as a milestone in the development of 166Ho-microspheres and were used as a basis for CE-mark and the design of phase III studies.

Feasibility of stereotactic radiotherapy using a 1.5 T MR-Linac: Multi-fraction treatment of pelvic lymph node oligometastases.

Werensteijn-Honingh AM, Kroon PS, Winkel D, Allbers EM, van Asselen B, Bol GH, Brown KJ, Eppinga WSC, van Es CA, Glitzner M, de Groot-van Breugel EN, Hackett SL, Intven M, Kok JGM, Kontaxis C, Kotte AN, Lagendijk JJW, Philippens MEP, Tijssen RHN, Wolthaus JWH, Woodings SJ, Raaymakers BW, Jurgenliemk-Schultz IM. *Radiother Oncol* 2019; 134:50-54.

This study confirms feasibility of MR-Linac treatment of oligometastases with extremely high precision.



Modality-specific target definition for laryngeal and hypopharyngeal cancer on FDG-PET, CT and MRI.

Ligtenberg H, Jager EA, Caldas-Magelhaes J, Schakel T, Pameijer F, Kasperts N, Willems S, Terhaard CHJ, Raaijmakers CPJ, Philippens MEP. *Radiother Oncol*, 123, 63-70, 2017.

The paper answers one of the key questions in radiotherapy for laryngeal tumors: "What is the exact target visualized on MR-CT-PET imaging?" in a true multidisciplinary effort between the departments of pathology, radiology, head-and-neck surgical oncology and radiotherapy. The results directly translate in "Treatment with maximal impact and minimal damage".

4.9.3 Minimally invasive therapy

Robot-assisted minimally Invasive thoracoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer: A randomized controlled trial.

van der Sluis PC, van der Horst S, May AM, Schippers C, Brosens LAA, Joore HCA, Kroese CC, Mohammad NH, Mook S, Vleggaar FP, Borel Rinkes IHM, Ruurda JP, van Hillegersberg R. *Ann Surg*. 2019 Apr;269(4):621-630.

This is the first randomised trial to investigate the value of robotic-assisted minimally invasive techniques for esophagectomy. We showed that in the robot group patients suffered fewer cardiopulmonary complications, less pain, reduced ICU length of stay and reported improved quality of life. Oncological outcomes were equivalent. This study is the first trial to investigate this important question and cements UMC Utrecht as world leaders in minimally invasive and robotic esophagogastric surgery. The study has been cited over 30 times since its publication 2 months ago.

Management of Severe Pancreatic Fistula After Pancreatoduodenectomy.

Smits FJ, van Santvoort HC, Besselink MG, Batenburg MCT, Slooff RAE, Boerma D, Busch OR, Coene PPLO, van Dam RM, van Dijk DPJ, van Eijck CHJ, Festen S, van der Harst E, de Hingh IHJT, de Jong KP, Tol JAMG, Borel Rinkes IHM, Molenaar IQ; Dutch Pancreatic Cancer Group. *JAMA Surg*. 2017 Jun 1;152(6):540-548.

In this propensity-matched cohort, catheter drainage as first intervention for severe pancreatic fistula after pancreatoduodenectomy was associated with a better clinical outcome, including lower mortality, compared with primary relaparotomy. This study forms the basis for the PORSCHE trial, which is a nationwide stepped-wedge Cluster randomized trial to implement this best practice in all Pancreatic Centers in the Netherlands and therefore has significant impact.

Robotic versus open minor liver resections of the posterosuperior segments: a multi-national, propensity score matched study.

Nota CL, Woo Y, Raoof M, Boerner Th, Molenaar IQ, Choi GH, Kingham TP, Latorre K, Borel Rinkes IH, Hagendoorn J, Fong Y. *Ann Surg Oncol*. 2018;26:583-90.

First international (UMC Utrecht, Memorial Sloan-Kettering New York, City of Hope Los Angeles, Yonsei Seoul) propensity-score matched patient cohort undergoing robotic hepatectomy for tumors located in difficult-to-reach parts of the liver. This study shows that robotic assistance allows minimal invasive liver resections in cases that are currently performed via an open approach (laparotomy) by most hospitals, resulting in a 50% decrease in hospital length of stay for these patients.

4.10 Most important societal contributions

Targeting cancer as metabolic disease

In order to partially overcome tolerance of natural $\gamma\delta$ T cells and to gain additional insights in cancer targeting, we have invested many years in successfully capturing the molecular needs of defined $\gamma\delta$ T cells and their receptors to protect us from cancer. These insights represented the start of a paradigm shift where I have shown that cancer can be targeted therapeutically as a metabolic disease, and disease control does not depend on the mutational load of cancers. We turned these insights into a clinical concept that combines the knowledge of cancer targeting through individual receptors expressed on $\gamma\delta$ T cells with the high proliferation and memory capacity of conventional $\alpha\beta$ T cells, and thereby bypasses the tolerogenic nature of $\gamma\delta$ T cells in advanced cancer patients. This concept of next generation of CAR T, namely "TEGs" (T cells Engineered with defined Gamma delta TCRs), and its commercialisation with a first lead structure has been acknowledged as a major breakthrough in the field. Along with multiple patents written within my group this resulted in the establishment of the UMC Utrecht spin-off company GADETA. The spin-off company was named as one of the top 10 spin-offs of 2016 worldwide by Nature Biotechnology. In 2018 the company started a strategic partnership for the clinical exploration of main leads with KITE and GILEAD. In the meanwhile we have shown that TEGs as the next generation of personalized cancer care are able to target the leukemic stem cell, as well as to eliminate primary multiple myeloma in a 3D bone marrow niche, and we are currently recruiting patients for an academically driven first in man trial. Additional studies are planned as company sponsored trials.



Holmium-166 radioembolisation: new generation microspheres for individualized treatment.

Radioembolisation has emerged as a safe and effective treatment modality in patients with liver malignancies. In these patients, dosimetry-based treatment planning, balancing efficacy against toxicity, is of the utmost importance, since compromised functional reserve often precludes therapy. While older generation yttrium-90 (⁹⁰Y) microspheres have limitations for dosimetry-based individualized treatment planning, holmium-166 (¹⁶⁶Ho) microspheres were specifically designed for this purpose. More accurate individualized treatment planning is expected to lead to improved outcome, both for efficacy and toxicity.

These new generation ¹⁶⁶Ho microspheres were invented and developed in the department of Radiology and Nuclear Imaging of the UMC Utrecht. Imaging of ¹⁶⁶Ho microspheres before (i.e. scout dose) and after treatment may be used to create an individualized, effective, and safe treatment plan. This is possible due to the unique ¹⁶⁶Ho isotope characteristics (¹⁶⁶Ho: T1/2 of 27 hours, gamma-radiation 81 keV, beta-radiation 1.8 MeV, paramagnetic), which make ¹⁶⁶Ho microspheres suitable for quantitative imaging, using SPECT and MRI, already at low quantities, such as used during a scout procedure.

¹⁶⁶Ho microspheres (QuiremSpheres®, Quirem Medical, Deventer, The Netherlands) have been tested for safety and efficacy in respectively a clinical phase I and phase II study and are now CE marked. Recently, also a scout dose of ¹⁶⁶Ho microspheres (QuiremScout®) was CE marked. This led to reimbursement in the Netherlands (colorectal cancer liver metastases) and in many other European countries. Several clinical phase II studies in patients with hepatocellular carcinoma and colorectal cancer liver metastases are recruiting.

A phase II study showing the additive value of ¹⁶⁶Ho radioembolisation in patients with neuroendocrine tumor liver metastases observed a more than doubled response rate compared to treatment with lutetium-177 (¹⁷⁷Lu) dotatate (PRRT) alone.

Currently, preparations for a multicenter RCT in patients with colorectal cancer liver metastasis are underway, as well as an RCT in patients with neuroendocrine tumor liver metastases. All in close collaboration with start-up company Quirem Medical and Japanese multinational Terumo, ultimately providing us the evidence for full-scale implementation in international guidelines.

Ductoscopy in the detection and treatment of intraductal breast lesions in women suffering bloody nipple discharge

Approximately 5% of all referrals to breast clinics are because of bloody nipple discharge. For the Netherlands this means 3500–4500 women/year. In women suffering persistent bloody nipple discharge, classic surgical procedures such as microdochectomy are still golden standard to rule out malignancy. These are procedures under general anesthesia with all negative side effects as result.

Ductoscopy is a minimally invasive micro-endoscopic technique, allowing direct visualisation of the milk ducts through their natural orifices in the nipple. It has shown to be a very sensitive tool in visualizing intraductal lesions causing bloody nipple discharge. It can be performed under local anesthesia at the outpatient clinic and has proofed to be safe. However, the role of ductoscopy remained uncertain, due to the lack of microbiopsy tools needed for pathologic diagnosis and treatment of found lesions.

After fine tuning the ductoscopy technique and testing the addition of different diagnostic and treatment techniques (such as autofluorescence and laser ablation) on mastectomy specimens in laboratory setting, we found that the use of a simple basket shaped wire in combination with ductoscopy was able to detect, diagnose and treat intraductal lesions in women suffering bloody nipple discharge.

Thereafter we performed a prospective cohort study in 250 women suffering bloody nipple discharge by adding interventional ductoscopy to the diagnostic work-up. We found that in 70% of them, a classic surgical procedure could be omitted.

This finding had the following consequence's;

- Interventional ductoscopy is now recognized as standard of care in bloody nipple discharge by the Dutch breast cancer patient advocacy and professional organisations
- Interventional Ductoscopy will be added to the national guideline in the Netherlands in 2019
- Zorg Instituut Nederland is evaluating ductoscopy for full reimbursement

Classic surgery has scarring, sensitivity loss of the nipple and impairment of breastfeeding as a consequence. Also, there is a risk of surgical complications, that can delay recovery. Omitting surgery therefor improves quality of live and it also saves healthcare costs, since the costs of interventional ductoscopy are half of that of classic surgery.

Together with the TU Delft our team is now developing a ductoscopy tool box, in order to enhance the effectiveness of ductoscopy even more.



5. Theme: Prevention and Survivorship

5.1 Mission, strategy and organisation of the theme

As the number of cancer patients continues to rise and survival improves, more patients are living with the long-term consequences of cancer. At the same time still 40% of all patients die from this disease. These observations necessitate research into the possibilities for prevention and early diagnosis on the one hand, and on improvement of treatments, quality of life and palliative care, on the other hand. To this end, large patient -and population-related cohort studies and clinical trials are performed, in close collaboration between clinicians, translational researchers and epidemiologists.

Research within the theme “Prevention and Survivorship” in the UMC Utrecht is primarily performed by cancer researchers from the divisions Julius Center and Imaging & Oncology, and of the department of Pathology. Professionals within this theme collaborate closely with the fundamental, translational and clinical scientists to address the crucial questions to be solved in prevention and survivorship issues.



Fig. 1 Topics of the theme

5.2 Urgency and/or relevance of the research questions

Causes, prevention and (early diagnosis)

To find leads for prevention we identify risk factors by integrating epidemiology, high quality exposure assessment, and molecular biology into multidisciplinary investigations in large population-based cohorts. We use this knowledge to develop and evaluate ways of preventing cancer in randomized controlled trials. As the outcome of cancer clearly relates to an early diagnosis, we evaluate new personalized methods for detection of cancer at its earliest stages, including determination of biomarkers in DNA, blood, nipple fluid (for breast cancer) and imaging. We investigate existence of delay of cancer diagnosis in primary and secondary care, and ways to improve here upon. Benefits are carefully weighed against potential harm and costs.

Survivorship and palliative care

For patients with cancer, we investigate how lifestyle (interventions) can reduce side effects of treatment and improve prognosis, self-empowerment and quality of life. Together with regional partners in primary and secondary care, we develop new models of collaborative cancer care during treatment and follow-up, aiming to optimize quality of life and shared decision making. For patients with cancer who are in the last phase of life we map the symptomatology and investigate the required interventions and the optimal professional involvement in palliative care.

5.3 Relation to existing knowledge

The research questions addressed fit into the Dutch Knowledge and Innovation Agenda (Prevention Knowledge Agenda and Personalised Medicine Knowledge Agenda, theme Oncology) and also into the agenda of the Taskforce ‘Juiste zorg op de juiste plek’, the advice of the Dutch Health Council ‘Onderzoek waarvan je beter wordt’ (‘Research that makes you better’), and the National Palliative Care Programme.

5.4 Involvement of stakeholders

Patient advocates and patient organisations are involved in all of our research topics and participate actively in the different project teams. The palliative care group works with a specialized board of patients and their family and friends.



5.5 Optimal and efficient research design

Cancer epidemiologists and statisticians of the division Julius Center for Health Sciences & Primary Care (dJC) are strongly involved in this theme. At the dJC there is extensive knowledge and expertise with the development and evaluation of new methodological techniques and trial designs. All clinical trials initiated in the dJC are evaluated by a multidisciplinary team of experts (Fluent In-House Trial Support, FLITS) before sending off grant applications or protocols to funding organisations. FLITS checks and provides advice on all key aspects of the design and execution of a trial to ensure optimal and efficient trial design.

An efficient design that is being used in the Cancer program is the so-called Trials within CohortS design (TwiCs), also known as the cohort multiple randomized controlled trial (cmRCT) design. The use of this design and its further evaluation and development is an initiative of the Radiotherapy department in collaboration with the dJC. It is now being applied to construct and study several cohorts of cancer patients in the UMC Utrecht. It allows simultaneous evaluation of multiple interventions and it minimizes contamination between study arms. In the UMC Utrecht we developed a two-staged patient-centered informed consent procedure resulting in higher, more representative recruitment than in classic RCTs.

5.6 The next steps

Causes, prevention and (early) diagnosis

Research in our population-based cohorts, such as the European Prospective Investigation on Nutrition and Cancer (EPIC), for which we run the Dutch cohort (EPIC-NL), has been authoritative in the field of dietary and lifestyle advice to prevent cancer. Because of its large size of over 500,000 participants and its ongoing follow-up since the beginning of the nineties (over 96,000 incident cancer cases), it has the power to provide hard evidence for a number of risk factors that now have found their way to preventive guidelines for cancer by, for example, the American Cancer Society, the World Cancer Research Fund, and the 'Wereld Kanker Onderzoeksfonds' (which were in turn adopted by the Dutch Voedingsbureau).

Within our research agenda on prevention, physical exercise is an important theme. We have developed exercise training programs that we investigated for (biomarkers of) cancer prevention and that are extended to cancer survivors (see under Survivorship).

In secondary prevention we aim to develop a personalized screening for higher risk groups. A nationwide study on a screening intervention in women with extremely dense breasts has been initiated and chaired by our group and executed together with, a.o., the Center for Population Screening of the National Institute for Public Health and the Environment (CvB, RIVM), the screening organisations and the Dutch Expert Centre for Screening. In collaboration with these partners and other policy makers (Dutch Health Council (Gezondheidsraad) and Ministry of Health, Welfare and Sport (VWS) it is currently discussed how to proceed towards implementation into daily practice.

At the department of Pathology, a unique cohort of nearly 600 women bearing a high risk of developing breast cancer is being build where annual imaging data, blood and nipple fluid are sampled in order to find a molecular biomarker predicting the development of breast cancer at its earliest stages, paving the way for intraductal preventive approaches.

Another example of research that is likely going to have impact in the coming years is the CEDAR study that showed that in primary care, a diagnostic strategy with routine clinical data and a point-of-care fecal immunochemical test (FIT) may safely rule out colorectal cancer and other significant colorectal disease and prevent unnecessary endoscopy referral. An implementation trajectory is currently being developed.

With the focus of identifying individuals at increased risk to develop cancer, the genetics department developed and implemented methods of rapid genetic counseling and testing of newly diagnosed breast cancer patients. This procedure has now been integrated into usual breast cancer care on a national scale. The group has conducted a large intervention study among breast cancer surgeons and specialized nurses to increase the referrals of patients with low health literacy and/or a migrant background who are now underrepresented in the outpatient clinic. This intervention is currently implemented on a national scale.



Survivorship care

We develop and evaluate physical activity programs to lower cancer risk in the population and also to decrease fatigue and other serious side-effects of treatment in cancer survivors. The results of our randomized controlled trials in this field are included in national and international guidelines and have laid the foundation for a UMC Utrecht led EU Horizon 2020 consortium called PREFERABLE investigating the role of exercise in metastatic breast cancer. We are also establishing a national foundation ('OncoFITness') to implement the results of our trials into clinical practice. The goal is to establish a nationwide network of fitness centers providing specialized exercise programs enabling cancer patients to train with evidence-based programs close to home.

Together with regional partners in primary and secondary care, we develop new models of collaborative cancer care during treatment and follow-up, aiming to optimize quality of life and shared decision making. An example of this is the GRIP-project, studying the role of a structured follow-up after a cancer diagnosis by a primary care team, including a general practitioner (GP) and a home care oncology nurse (HON) who support the patient in shared decision making. This health care path is currently being implemented in several regions in strong collaboration with other regional health care providers and the Dutch Federation of Cancer Patient Organisations (NFK).

Palliative care

The UMC Utrecht harbors one of the academic Centers of Expertise of Palliative Care. In close collaboration with regional (including Hospice Demeter) and national partners in palliative care, various research projects focus on areas extending from the palliative to the terminal stages of the disease. These include issues related to shared decision making, how to guide patients in dealing with toxicities of treatments, and determining the optimal care path in end stage disease. The principal investigators are strongly involved in the professional organisations where research results are implemented in routine care. This topic is otherwise unique in that several PhDs have been obtained by associated nursing professionals.

5.7 Highlights of results

Research products for peers

Datasets, biobanks

- 2013-2018: continuous update European Prospective cohort on Cancer and Nutrition (EPIC) (**Peeters, van Gils**) The total cohort comprises ca. 500,000 persons of whom 67000 had developed cancer during follow-up (last update 2016). The Dutch EPIC-NL cohort comprises ca 40,000 persons of whom >4,500 developed cancer Availability of medical, lifestyle and dietary questionnaires, blood/DNA samples at recruitment (before cancer diagnosis).
- 2018: DENSE-on biobank: Medical and lifestyle questionnaire data, imaging (mammography and MRI (~10,000 exams) and blood and nipple fluid samples of 4,800 women with extremely dense breasts and a control group of 1,000 women with very fatty breasts (**van Gils**).
- The UMBRELLA (**Verkooijen, van Gils**) and PLCRC cohorts (**Koopman, Vink, May**) are open for use and are a rich resource for research questions in the field of survivorship and in the future also palliative care of breast and colorectal cancer patients. The cohorts are further described in theme Clinical as well as in annex 3.
- 2007 -ongoing: biobank on nipple fluid and blood with annual collection of data in women at high risk of developing breast cancer, including genetic carriers, aiming to predict carcinogenesis at its earliest stages (**van Diest, van der Wall**).

Infrastructure

- Infrastructure for prospective cohorts of patients, in which clinical and imaging data are prospectively collected, together with regular long term patient reported outcome measures. The cohorts follow an innovative trial design, i.e. Trials within Cohorts design (TwICs), which allows fast and simultaneous randomized evaluation of multiple interventions within these cohorts (**Verkooijen**).
- Researchers from this theme were involved in the organisation of Julius Support for Research & Trials, which is a joint effort of the Julius Center for Health Sciences and Primary Care, Julius Clinical and Cochrane Netherlands. It has been set up to assist researchers with the design, conduct, data management, analysis and reporting of medical research. <https://www.juliussupport.nl/>



- Researchers from this theme were advisors for THINC (The Healthcare Innovation Center). THINC is part of the UMC Utrecht Julius Center and contributes to the continuous development of scientific knowledge at the service of healthcare innovation. It aims at a broad range of healthcare innovations including medical technology, devices, mHealth, eHealth and care pathways.
- Conductor and Chair of the annual nationwide course in Palliative Care.

Instruments, compound, software tools

- 2017 Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer. JAMA. 2017;318(22):2199-2210. doi:10.1001/jama.2017.14585 (**van Diest**).
- 2018 Computer Aided Diagnosis tool for increasing specificity of DCE-MRI screening in women with dense breasts (**Gilhuijs, van Gils, Veldhuis**).
- Monitoring instrument for palliative care: Utrecht Symptoom Dagboek (Utrecht Symptom Diary), chosen as 'good example' by ZonMW verbeterprogramma Palliatieve zorg (**Teunissen**).

Research products for societal target groups

Publications accessible for a large audience

- 2018: Nationwide broadcast BNR <https://www.bnr.nl/podcast/beter/10345384/de-patholoog-als-innovatie-strategie> (**van Diest**).
- 2018: Table discussion "genetic counselling in low-educated citizen with breast cancer". <https://denieuwemaan.ntr.nl/de-nieuwe-maan-26-oktober/> (**Ausems, Witkamp**).

"Products" designed for public use

- 2017 App MyBodyMyData, <https://www.UMC Utrechtrecht.nl/nl/Nieuws/App-myBody-myData-geeft-patient-regie> (**Veldhuis**).

Outreach activities

- 2013-ongoing Public lectures on cancer genetic counseling, 2-4 times/year (**Ausems**).
- 2014 Patientensymposium BVN/BOOG/PRP Personalized medicine: pathologie diagnostiek (**van Diest**).
- UMC Utrecht health course on cancer (Fall 2014) – 5 clinicians and researchers in cancer together with 10 medical students, provided a 5-evening course on cancer for 80 participants from the general public (**Willems, van Gils, Raymakers**).
- Studium Generale UU lectures: lectures on cancer-related topics with a societal impact, open for the general public (**Luijten, Clevers, Verkooijen, Cuppen, van Gils, van der Wall**).
- Publiekslezing Tivoli Vredenburg "Doodsangst en mogelijkheden om die tegen te gaan", Utrecht 2018 (**Teunissen**).

Use of research products by peers

Use of biobanks and data collections

- 2013-ongoing: continuous update EPIC This data/biobank collection is frequently used by various research groups throughout the world as indicated by large amount of publications in PubMed. (**Peeters, van Gils**).
- PLCRC is further described in theme "Clinical".

Use of research facilities/infrastructure

- Julius Research Support is used by various research groups within the UMC Utrecht.
- THINC is currently promoted within the UMC Utrecht and recently presented as one of the 6 key platforms in the valorisation and implementation process (Pontes Symposium UMC Utrecht 25 June 2019).

Use of software tools, compounds, instruments

- Monitoring instrument for palliative care: Utrecht Symptoom Dagboek (Utrecht Symptom Diary), chosen as 'good example' by ZonMW verbeterprogramma Palliatieve zorg. The instrument has been included in the national guidelines for palliative care (IKNL 2015; 2018) and the IKNL/PZNL report 'Meetinstrumenten palliatieve zorg' (IKNL jan 2019) which allows free use for all. The USD is widely used, especially in the 7 UMC expertise centers for Palliative Care and in high care hospices. (**Teunissen**).



Use of research products by societal groups

Large consortia, public-private partnerships

- H2020 consortium: 2018 PREFERABLE (**May**) - Project on Exercise for Fatigue Eradication in Advanced Breast cancer to improve quality of life.
- H2020 consortium: 2018 FURTHER (**Verkooijen**) - Focused Ultrasound and RadioTHERapy for Noninvasive Palliative Pain Treatment in Patients with Bone Metastasis.

Implementation in guidelines, reimbursement

- Outcome GRIP-study (**de Wit, van der Wall**) implemented in Regional Care Paths.
- Implementation of outcomes in the Physical activity Guideline (Health Council)
<https://www.gezondheidsraad.nl/documenten/adviezen/2017/08/22/beweegrichtlijnen-2017> (**May**).
- OncoFITness – network of fitness centers specialized in oncological fitness (**May**).

Patent (applications), spin-offs

- 2013 Patent (granted 2016) - DDX3 as Biomarker for Cancer (**van Diest**).
-

Marks of recognition from peers

Awards, individual research grants (Veni, Vidi, Vici, ERC, Marie-Curie)

- 2014 Veni (**May**).
- 2014 Corry Hermann Award – Dutch Female Medical Professionals Association (**van der Wall**).
- 2017 Supervisor of the Year Graduate School of Life Sciences Utrecht (**Koopman**).
- Associated Professor at Sidney Kimmel Cancer Institute at Johns Hopkins Medical Centers, Baltimore, USA (**van Diest, van der Wall**).

Elected memberships of scientific committees

- Chair/Member board of the Dutch Organisation for Clinical Breast Cancer research (**van der Wall, Pijnappel**).
- Expert member Dutch Association for Hospice care (**Teunissen**).
- Member of the European Working Group for Breast Screening Pathology (**van Diest**).
- Chairman Society for Inborn errors of Metabolism Netherlands (ESN) (**Verhoeven-Duif**).
- Scientific director of the Dutch Biobank institution Parelsoer Institute (**Valk**).
- Member of the Committee on Palliative Care of the Dutch Society of Medical Oncology (de Graeff).

Editorial boards

- 17 editorial boards (**van Diest**).
 - Framingham on Gastrointestinal Cancers, Netherlands Journal of Oncology (**Koopman**).
 - Editor: “Psychosociale zorg in de oncologie. Een praktijkboek voor dokters”. En tevens redacteur van het boek: “Probleem-georiënteerd denken in de palliatieve zorg” (de Graeff).
-

Marks of recognition from societal groups

Public prizes

- Knighted by former HRM Queen Beatrix of the Netherlands, for her contribution to increase breast cancer awareness (**van der Wall**).

Membership of civil society advisory bodies

- Member of Population Screening Act (WBO) committee of the Health Council of the Netherlands (**van Gils**).
- Member Health Council committee “Physical activity Guideline” (**May**).
- Member Medicine board Gezondheidsraad (**van der Wall**).
- Member of the working group on “The Dutch Guideline for Screening on Breast Cancer” (**Pijnappel, Verkooijen**).
- Scientific advisory board Dutch Cancer Society (**Gilhuijs, van Gils**).
- Vice chair Scientific Committee of KiKa (**May**).



- Scientific advisory board Borstkanker Vereniging Nederland (**Pijnappel**).
- Member of the Advisory Board of the Netherlands Comprehensive Cancer Organisation (IKNL) (**van der Wall**).
- Member of the General Advisory Board of the Dutch Cancer Foundation (**van der Wall**).

Consultancies for public or private sector

- Member of Program Committee Breast cancer Screening, Center for Population Screening of National Institute for Public Health and the Environment (RIVM) (**Pijnappel**).
- Member of the Digital Pathology advisory board of Philips and Sectra (**van Diest**).
- Methodology Advisory Board: international collaboration between clinicians and researchers of the UMC, MD Anderson, the Christies, NKI, Royal Marsden, Sunnybrook, University of Wisconsin and Elekta (**Verkooijen**).

5.8 Research projects where patients are meaningfully involved

[The Utrecht Cohort for Multiple BREast cancer intervention studies and Long-term evaluation \(UMBRELLA\)](#)

The ambition of UMBRELLA is to learn from every patient with breast cancer that sets foot in the UMC Utrecht. We started with all breast cancer patients that come to the UMC Utrecht for radio therapeutic treatment and at the 'innovation clinic' of the UMC Utrecht, a researcher/research assistant asks all new patients with breast cancer consent for 1) use of routine clinical data for research, 2) capturing Patient Reported Outcomes, 3) collection of biomaterial and 4) broad randomisation to future (experimental) interventions. 90% of patients agrees to participation in UMBRELLA, and 85% provide broad consent for randomisation. UMBRELLA serves as a trial infrastructure, and one exercise RCT has been completed. A second trial will start in September 2019. Several imaging studies, a pilot dance intervention, and cohort studies have been completed. UMBRELLA now includes >2700 patients and every year, 150 of them are invited to visit the UMBRELLA day at the UMC Utrecht.

Here, scientific lectures and workshops are given, and UMC Utrecht researchers present their (ongoing) breast cancer research projects for UMBRELLA participants to give feedback on. The patients are asked to write down their idea for research topics for UMBRELLA in the coming years. We use these topics to set our research agenda.

[Utrecht Symptom Diary, a PROM in the continuum of cancer care](#)

The Utrecht Symptom Diary (USD) is a PROM with an applicability in research, education and patient-prioritized care. The USD was developed (2005) as a clinical tool to measure prevalence, severity and priorities of physical and psychological symptoms daily to support quality of life oriented care. To facilitate patients at home and in hospice specifically, a web-based USD app was created (2014) for maintenance of patient autonomy as long as possible. Patients, relatives, general practitioners and nurses share identical insights into symptom burden to monitor the effectiveness of interventions and to simplify communication about priorities of the patient. In 2016 the USD was expanded with social and existential outcomes in collaboration with the 'Utrecht patient palliative care board'. Although validation is not completed yet, the USD is recommended in national symptom guidelines and applied in collaborative research projects.

5.9 Most important scientific publications

Receptor Conversion in Distant Breast Cancer Metastases: A Systematic Review and Meta-analysis.

Moelans CB, van Diest PJ. *J Natl Cancer Inst* 2018;110:568-580.

This meta-analysis, which is founded by multiple studies of our own research group on the topic, highlights through a systematic review of the literature that receptor conversion in distant breast cancer metastases is a common phenomenon for the estrogen - and progesterone receptors and to a lesser extent for the (Human Epidermal Growth Factor Receptor2 (HER2 receptor). This receptor conversion also has prognostic value. Consequently, distant metastases need to be biopsied for reassessment of receptor status, which is now part of most international guidelines on breast cancer.



MR imaging as an additional screening modality for the detection of breast cancer in women aged 50-75 years with extremely dense breasts: the DENSE trial study design.

Emaus MJ, Bakker MF, Peeters PH, Loo CE, Mann RM, de Jong MD, Bisschops RH, Veltman J, Duvivier KM, Lobbes MB, Pijnappel RM, Karssemeijer N, de Koning HJ, van den Bosch MA, Monninkhof EM, Mali WP, Veldhuis WB, van Gils CH. *Radiology*. 2015 Nov;277(2):527-37.

Description of a randomized controlled trial on the effect of adding MRI to mammography screening in women with extremely dense breasts. The study is initiated and coordinated by the department of Epidemiology from the Julius Center and the Radiology department. 4,700 women were randomized to the MRI arm and a 4-fold number to the usual care arm. Collaboration with 7 other large Dutch hospitals. 3.5Meuro research grants. High anticipated impact on practice of breast cancer screening.

Impact of different palliative systemic treatments on skeletal muscle mass in metastatic colorectal cancer patients.

Kurk SA, Peeters PHM, Dorresteijn B, de Jong PA, Jourdan M, Kuijf HJ, Punt CJA, Koopman M, May AM. *J Cachexia Sarcopenia Muscle*. 2018 Oct;9(5):909-919.

In this study we show that - during consecutive palliative systemic treatment regimens using repeated abdominal computed tomography scans of metastatic colorectal cancer (mCRC) patients - that loss of skeletal muscle mass is reversible. Since skeletal muscle mass loss is associated poor clinical outcome this study is relevant for patients, since it may be a clue for new therapies. This study is an example of our clinical interest to conduct studies relevant for patients and our drive to cooperate with relevant parties.

Patient-reported symptoms and stepwise symptom management in patients on epidermal growth factor inhibitors: A retrospective, descriptive cohort study.

Koldenhof JJ, Langenberg MHG, Witteveen PO, Teunissen SCCM. *Eur J Cancer Care (Engl)*. 2018 Mar;27(2).

This paper shows the relevance of USD data for research. It indicates that in patients application of PROMs together with a stepwise symptom management plan enhances early recognition of symptom burden, pro-active symptom management and effect evaluation of interventions performed whereby well-being recovers.

Breast-cancer predisposition in multiple endocrine neoplasia type 1.

Dreijerink KM1, Goudet P, Burgess JR, Valk GD; International Breast Cancer in MEN1 Study Group: Elfi B. Conemans, Chantal Cornelissen, Marja T. van Blokland, Michael Mannstadt, Carla R.C. Pieterman, Christine Binquet, Olaf M. Dekkers, Madeleine L. Drent, Anouk N.A. van der Horst-Schrivers, Wouter W. de Herder, Bas Havekes, Eric Fliers, Ad R. Hermus, Menno R. Vriens, H.Th. Marc Timmers, Elsken van der Wall, Myles Brown, Rob B. van der Luijt, Paul J. van Diest. *N Engl J Med* 2014;371:583-584.

Paper with high societal impact as it indicates that patients with MEN should be screened more regularly for breast cancer.

Explicit prognostic information and reassurance about nonabandonment when entering palliative breast cancer care: findings from a scripted video-vignette study.

van Vliet LM, van der Wall E, Plum NM, Bensing JM. *J Clin Oncol*. 2013 Sep 10;31(26):3242-9.

When discussing the transition to palliative care for patients with breast cancer, to find a balance between giving explicit information while not overwhelming patients and being realistic while remaining hopeful. The effect of explicit prognostic information and reassurance about nonabandonment at the transition to palliative care showing that explicit prognostic information may lead to better outcomes than general information. In addition, reassurance about nonabandonment might provide realistic hope but should be lived up to.

Direct-infusion based metabolomics unveils biochemical profiles of inborn errors of metabolism in cerebrospinal fluid.

Haijes HA, van der Ham M, Gerrits J, van Hasselt PM, Prinsen HCMT, de Sain-van der Velden MGM, Verhoeven-Duif NM, Jans JJM. *Mol Genet Metab*. 2019 Mar 15. pii: S1096-7192(19)30035-6.

A new metabolomics method (Direct Infusion Mass-Spectrometry) that we developed and published has been validated for patient care and is in use to diagnose undiagnosed patients. Direct-infusion based metabolomics unveils biochemical profiles of inborn errors of metabolism in cerebrospinal fluid.



Impact of rapid genetic counselling and testing on the decision to undergo immediate or delayed prophylactic mastectomy in newly diagnosed breast cancer patients: findings from a randomised controlled trial.

Wevers, M. R., Aaronson, N. K., Verhoef, S., Bleiker, E. M., Hahn, D. E., Kuenen, M. A., van der Sanden-Melis, J., Brouwer, T., Hogervorst, F. B., van der Luijt, R. B., Valdimarsdottir, H. B., van Dalen, T., Theunissen, E. B., van Ooijen, B., de Roos, M. A., Borgstein, P. J., Vrouwenraets, B. C., Vriens, E., Bouma, W. H., Rijna, H., Vente, J. P., Witkamp, A. J., Rutgers, E. J., and Ausems, M. G. Br J Cancer. 2014; 110: 1081-1087.

In this large multicenter study the medical and psychosocial impact of rapid breast cancer genetic counseling, before surgical treatment, was assessed in a randomized controlled trial. The study showed that patients who received their DNA-test result before surgery opted more often for direct bilateral mastectomy, and that the procedure did not have any measurable adverse psychosocial effects. The study contributed to setting up a rapid genetic testing procedure as usual care.

Staged-informed consent in the cohort multiple randomized controlled trial design.

Young-Afat DA, Verkooijen HM, van Gils CH, van der Velden JM, Burbach JP, Elias SG, van Delden JJ, Relton C, van Vulpen M, van der Graaf R. Epidemiology 2016;27:389-92.

This study describes a novel approach for maximizing enrolment of patients in RCTs. In the first stage, all potential participants are asked informed consent to participate in a cohort study and broad consent to be either randomly selected to be approached for experimental interventions or to serve as control without further notice during participation in the cohort. In a second stage, at the initiation of an RCT within the cohort, informed consent to receive the intervention is then only sought in those randomly selected for the intervention arm. This approach was implemented in 2013 at the UMC Utrecht and >6000 cancer patients have now been enrolled in cohorts, three RCTs have been completed, and three are ongoing.

DNA promoter hypermethylation in nipple fluid: a potential tool for early breast cancer detection.

de Groot JS, Moelans CB, Elias SG2, Jo Fackler M, van Domselaar R, Suijkerbuijk KP, Witkamp AJ, Sukumar S, van Diest PJ, van der Wall E. Oncotarget. 2016 Apr 26;7(17):24778-91

Nipple fluid aspiration (NAF) provides direct non-invasive sampling of fluid from the mammary ductal system where the majority of breast cancers originate. DNA promoter hypermethylation occurs early and at a high frequency in breast carcinogenesis. Methylation levels of 13 genes were analyzed by QM-MSP in NAF from health women and women with breast cancer. Methylation patterns could discriminate between healthy and cancerous tissue but not between the affected and the non-affected breast of women with breast cancer.

Time to diagnosis and treatment for cancer patients in the Netherlands: Room for improvement?

Helsper CCW, van Erp NNF, Peeters PPHM, de Wit NNJ. Eur J Cancer. 2017 Dec;87:113-121.

In this paper the time intervals between first presentation in general practice and start of treatment for different types of cancer were assessed, based on analysis of nationwide primary care registration data linked to the National Cancer Registry. Median diagnostic, referral and treatment interval in days was reported for breast, colon, prostate, lung cancer and melanoma. This papers benchmarks the length of diagnostic intervals in the Netherlands, facilitates international comparison and pictures potential improvement in early diagnosis in primary care.

5.10 Most important societal contributions

The importance of biobanks with solid phenotypic data in care of rare tumors.

In collaboration with all University Medical Centers (UMC's) the UMC Utrecht Multiple Endocrine Neoplasia (MEN) research team built a national database including clinical data and biobank materials. Based on the clinical observation that breast cancer occurs often in young female MEN 1 patients the hypothesis that MEN 1 is associated with a higher chance for breast cancer was tested in the clinical database. Female MEN 1 patients appeared to have an almost 3 times higher chance for breast cancer at a fifteen years earlier age compared with the normal Dutch population. This finding was confirmed in three independent clinical databases in France, the USA and Tasmania. In addition, nuclear localisation of menin (the gene product of the MEN 1 gene) was reduced by more than 50% in 80% of breast cancer samples. Subsequent analysis on DNA sequencing or multiplex ligation-dependent probe amplification showed loss of heterozygosity at the MEN1 locus in tumors. (Dreijerink et al. NEJM, 2014) This finding was further substantiated with an epidemiologic study showing that the elevated risk was not related to other known breast cancer risk factors or familial cancer history. (van Leeuwen et al., DJCEM 2017) Subsequent studies confirmed the oncogenic actions of the tumor suppressor menin in breast cancer cells. (Dreijerink et al. Cell Reports 2017).



As a consequence of this observation the MEN 1 syndrome this syndrome is changed from an endocrine tumor syndrome to a cancer syndrome. What's more, female MEN 1 patients should be screened from the age of 40 years to be able to early diagnose breast cancer and prevent morbidity and premature death. This has been implemented in the Dutch national screening guidelines whereas at an international level it is now discussed whether clinical practice guidelines should be adapted accordingly. As such, a clinical observation based on solid biobank data, changed clinical day to day practice at an (inter-) national level.

Providing solid evidence for personalized breast cancer screening

Women with high mammographic breast density have a higher breast cancer risk, and high breast density severely hinders the detection of tumors with mammography. Laws in 37 USA States indicate that all women should be informed of breast density after mammography. In the Netherlands, parliamentary questions have been asked as to why women do not know about their breast density and whether screening policy should be adapted. With a fully-automated volumetric density measurement method we showed that the sensitivity of the nation-wide digital mammography-based screening program is only 61% for those with extremely dense breasts, compared to 86% in women with fatty breasts (Wanders et al. *Breast Cancer Res Treat* 2017, *Breast Cancer Res* 2017). The international guideline committees do not recommend supplemental screening for these women, however, because there is no evidence that this will decrease morbidity or mortality and/or increase quality of life due to less invasive treatments. To solve this, RCTs are needed with multiple screening rounds that do not just focus on increased detection but report important outcomes, such as interval cancer rates, breast cancer stage at diagnosis, and (predictions of effects on) breast cancer mortality. Researchers from the Julius Center and the Imaging Division therefore initiated and conducted the DENSE trial, the first and until now only RCT on supplemental screening with MRI for women with dense breasts (Emaus et al. *Radiology* 2015). The multicenter-trial started in 2012 and comprises 3 biennial MRI screening rounds. It runs in 8 academic and large regional hospitals. We randomized in a 1:4 ratio: MRI-arm: n=8,061, usual mammography screening: n=32,312. The third round is near completion. The results of the first MRI screening round show that supplemental MRI screening in women with extremely dense breasts results in earlier stage cancers and fewer interval cancers than screening with mammography alone. (European Congress of Radiology (March 2019) and manuscript under revision for publication in a high-impact clinical journal). The data from incident screening rounds and longer follow-up are now being analyzed in combination with simulation studies to assess the reduction in the rate of advanced cancers and eventually mortality. In the meantime we collaborate with the National Institute for Public Health and the Environment (RIVM, Center for Population-based screening), and the Ministry of Health, Welfare and Sports for dissemination of the results to the public, patient organisations and health care providers and to examine the possibilities for implementation.



6. Appendices

Appendix 1: Research Leaders per Theme

THEME: FUNDAMENTAL

Name		Division and Department	
Prof. Hans	Bos	dLAB	CMM
Dr. Niels	Bovenschen	dLAB	Pathology, LTI
Prof. Boudewijn	Burgering	dLAB	CMM
Prof. Paul	Coffer	dLAB	LTI, LTO, RMSC
Prof. Edwin	Cuppen	dLAB	CMM
Dr. Tobias	Dansen	dLAB	CMM
Dr. Martijn	Gloerich	dLAB	CMM
Dr. Gijs	Haaften	dLAB	CMM
Prof. Elly	Hol	dHersenen	Neuroscience
Dr. Aniek	Janssen	dLAB	CMM
Dr. Eric	Kalkhoven	dLAB	CMM
Dr. Peter	De Keizer	dLAB	CMM
Prof. Judith	Klumperman	dLAB	CMM
Dr. Bobby	Koeleman	dLAB	CMM
Prof. Susanne	Lens	dLAB	CMM
Dr. Jeanette	Leusen	dLAB	LTI
Prof. Madelon	Maurice	dLAB	CMM
Dr. Saskia	Van Mil	dLAB	CMM
Dr. Jeroen	De Ridder	dLAB	CMM
Dr. Maria	Rodriguez-Colman	dLAB	CMM
Dr. Johan	De Rooij	dLAB	CMM
Dr. Hugo	Snippert	dLAB	CMM
Dr. Yvonne	Vercoulen	dLAB	CMM
Dr. Fried	Zwartkruis	dLAB	CMM



THEME: TRANSLATIONAL

Name			Division and Department	
Dr.Ir.	Wilbert	Bartels	dB&O	CIS
Dr.	Nico	Van den Berg	dB&O	CIS
Dr.	Clemens	Bos	dB&O	CIS
Prof.	Edwin	Cuppen	dLAB	CMM
Dr.	Patrick	Derksen	dLAB	Pathology, LTO
Prof.	Paul	Van Diest	dLAB	Pathology
Dr.	Sjoerd	Elias	dJC	Epidemiology
Dr.	Kenneth	Gilhuijs	dB&O	CIS
Dr.	Hans	Hoogduin	dB&O	CIS
Dr.	Ivana	Isgum	dB&O	CIS
Prof.	Pim	De Jong	dB&O	CIS
Prof.	Hugo	De Jong	dB&O	CIS
Dr.	Dennis	Klomp	dB&O	CIS
Prof.	Onno	Kranenburg	dB&O	LTO
Prof.	Jurgen	Kuball	dB&O	Hematology, LTI
Prof.	Jan	Lagendijk	dB&O	CIS
Dr.	Alexander	Leemans	dB&O	CIS
Dr.	Jeanette	Leusen	dLAB	LTI
Prof.	Peter	Luijten	dB&O	CIS
Dr.	Gert	Meijer	dB&O	CIS
Prof.	Linde	Meygaard	dLAB	LTI
Prof.	Chrit	Moonen	dB&O	CIS
Prof.	Johan	Offerhaus	dLAB	Pathology
Dr.	Niels	Raaijmakers	dB&O	Radiotherapy
Prof.	Bas	Raaymakers	dB&O	CIS
Dr.	Jeanine	Roodhart	dB&O	Med. Oncology, LTO
Prof.	Raymond	Schiffelers	dLAB	Clin. Chem. Lab
Dr.	Hugo	Snippert	dLAB	CMM
Dr.	Peter	Van Tintelen	dLAB	Genetics
Dr.	Koen	Vincken	dB&O	CIS
Dr.	Stefan	Willems	dLAB	Pathology
Dr.	Jaco	Zwanenburg	dB&O	CIS



THEME: CLINICAL

Name			Division and Department	
Dr.	Desiree	Van den Bongard	dB&O	Radiotherapy/CIS
Prof.	Inne	Borel Rinke	dB&O	Surgery
Dr.	Annelies	Bos	dV&B	Gynaecology
Prof.	Remco	De Bree	dB&O	Surgery
Dr.	Lodewijk	Brosens	dLAB	Pathology
Dr.	Kenneth	Gilhuijs	dB&O	CIS
Dr.	Jeroen	Hagendoorn	dB&O	Surgery
Prof.	Richard	Van Hillegersberg	dB&O	Surgery
Prof.	Alwin	Huitema	dLAB	Pharmacy
Prof.	Miriam	Koopman	dB&O	Medical oncology
Prof.	Jurgen	Kuball	dB&O	Hematology
Prof.	Marnix	Lam	dB&O	Radiology/CIS
Dr.	Richard	Meijer	dB&O	Surgery
Prof.	Monique	Minnema	dB&O	Hematology
Prof.	Quintus	Molenaar	dB&O	Surgery
Dr.	Leon	Moons	dIG&D	Internal Medicine
Prof.	Ruud	Pijnappel	dB&O	Radiology/CIS
Dr.	R.A.P,	Raijmakers	dB&O	Hematology
Prof.	Pierre	Robe	dHersenen	Neuro-surgery
Dr.	Jeanine	Roodhart	dB&O	Med. Oncology, LTO
Dr.	Jelle	Ruurda	dB&O	Surgery
Dr.	Henk	Schreuder	dV&B	Gynaecology
Dr.	Tatjana	Seute	dHersenen	Neuro-oncology
Dr.	Tom	Snijders	dHersenen	Neuro-oncology
Dr.	Karijn	Suijkerbuijk	dB&O	Medical oncology
Prof.	Chris	Terhaard	dB&O	Radiotherapy/CIS
Prof.	Gerlof	Valk	dB&O	Endocrine oncology
Prof.	Lenny	Verkooijen	dB&O	Trial Office Epidemiology
Prof.	Max	Viergever	dB&O	CIS
Prof.	Frank	Vleggaar	dIG&D	Internal Medicine
Prof.	Menno	Vriens	dB&O	Surgery
Prof.	Elsken	Van der Wall	dB&O	Medical oncology
Dr.	Arjen	Witkamp	dB&O	Surgery
Prof.	Els	Witteveen	dB&O	Medical oncology
Prof.	Ronald	Zweemer	dB&O	Gynaecology



THEME: PREVENTION & SURVIVORSHIP

Name			Division and Department	
Dr.	Margreet	Ausems	dLAB	Genetics
Prof.	Paul	Van Diest	dLAB	Pathology
Prof.	Carla	Van Gils	dJC	Epidemiology
Dr.	Geert	Janssens	dB&O	Radiotherapy
Prof.	Miriam	Koopman	dB&O	Medical oncology
Dr.	Anne	May	dJC	Epidemiology
Dr.	Charlotte	Onland-Moret	dJC	Epidemiology
Prof.	Petra	Peeters	dJC	Epidemiology
Prof.	Ruud	Pijnappel	dB&O	Radiology
Prof.	Hans Kristian	Ploos van Amstel	dLAB	Genetics
Prof.	Saskia	Teunissen	dJC	Palliative Care
Prof.	Gerlof	Valk	dB&O	Endocrine oncology
Dr.	Wouter	Veldhuis	dB&O	Radiology
Prof.	Nanda	Verhoeven-Duif	dLAB	Genetics
Prof.	Lenny	Verkooijen	dB&O	Trial Office Epidemiology
Prof.	Menno	Vriens	dB&O	Surgery
Prof.	Elsken	Van der Wall	dB&O	Medical Oncology
Prof.	Niek	De Wit	dJC	General Practice

Note: 12% of the Research Leaders is part of two themes.

Appendix 2: Tumor Working Groups

Tumor Working Groups	Chair
Brain tumors	Dr. Tatjana Seute
Breast cancer	Dr. Celine Vreuls
Endocrine tumors	Prof. Menno Vriens
Gastro-intestinal tract cancer	Prof. Miriam Koopman
Gynaecologic cancer	Prof. Ronald Zweemer
Head and neck cancer	Prof. Remco de Bree
Hematologic cancer	Prof. Monique Minnema
Lung cancer	Drs. Anne van Lindert
Skin cancer	Dr. Karijn Suijkerbuijk
Soft tissue cancer	Dr. Arjen Witkamp
Urinary tract cancer	Dr. Richard Meijer



Appendix 3: UMC Utrecht observational cohorts/registries (status July 2019)

Note: During the site visit a list of running trials will be available

Name	Description Website	Year	Primary coordinator	Coordinator UMC Utrecht	Inclusion	No. of Centers#
COIMBRA	Brain Metastasis No website available yet	2019	UMC Utrecht	Verhoeff	8	1 regional
CPCT-2	Platform for next-generation DNA sequencing from patients with advanced (incurable) or metastatic cancer https://www.cpct.nl/cpct-02/	2012	UMC Utrecht	Cuppen	>6000	>40
DENSE-on biobank	MRI Population screening in women women with dense breast tissue Dense website	2012	UMC Utrecht	V Gils	5800	8
DBTR	Dutch Brain Tumor Registry DBTR information	2014	LWNO IKNL	Seute De Vos	>4700	8
Dickens	Routine primary care data (free text and coded) available for over 20,000 cancer patients (all cancer types). Cohort information	1996-2019	UMC Utrecht	Helsper	>20.000	64 GP practises
DMTR	Dutch Melanoma Treatment Registry DMTR information	2013	All centers	Suijkerbuijk	6294	14
EPIC-NL	European Prospective Investigation Into Cancer and nutrition-The Netherlands www.epicnl.eu	1993-1997	UMC Utrecht	Vermeulen, Onland-Moret, vd Schouw v Gils	> 40,000 >4,500 cancer	4
HEBON	Hereditary Breast and Ovarian Cancer Research The Netherlands https://www.hebon.nl/	1997	NKI-AVL	Ausems	> 25.000 all centers	9
LEMA	Lung cancer early molecular assessment trial LEMA information	2017	NKI-AVL	v Lindert	938 98 (UMC Utrecht-part)	10
Surgical Liver database	Surgical Liver database	2008	UMC Utrecht	Borel Rinkes	>400	1
LML	Leukemia, myeloma and lymphoma clinical database and biobank. Parelsnoer Institute-LML	2009	UMC Utrecht LUMC	Minnema	2019	2
MEN	Nationwide longitudinal Multiple Endocrine Neoplasia clinical database and biobank Parelsnoer Institute-MEN	2014	UMC Utrecht	Valk Vriens	>400	8
MOMENTUM	The Multiple Outcome Evaluation of Radiotherapy Using the MR-linac Momentum information	2019	UMC Utrecht	Verkooijen	100	7
NET	Longitudinal neuro-endocrine tumors clinical database and biobank No website available yet	2018	UMC Utrecht NKI-AVL	Valk Vriens	>600	2
NET-QUIBIC	NETherlands QUALity of life and BIomedical Cohort studies in Head and Neck Cancer www.kubusproject.nl	2013	VuMC	Terhaard	>160	5
Name	Description Website	Year	Primary coordinator	Coordinator UMC Utrecht	Inclusion	No. of Centers#



NIPLE FLUID STUDY	Prevention of Hereditary Breast Cancer by Monitoring MicroRNA expression in Nipple Aspirate Fluid (including Ornament and High risk study) Nipple Fluid study information	2008	UMC Utrecht	vd Wall v Diest	159+535	1
OLYMPOS	Observational cohort of patients treated with stereotactic radiotherapy for Oligo LYMPH nOde and other soft tissue metastasiS; the OLYMPOS cohort	2017	UMC Utrecht	Jürgen-liemk-Schulz	126	1 (regional)
OMT	Oesophageal and gastric cancer Parelsoer Institute-OMT	2014	UMC Utrecht	Ruurda	385	5
PAN	Pearl Pancreatic cancer and pancreatitis Parelsoer Institute-PAN	2014	AMC UMC Utrecht	Molenaar	1400	8
PLCRC	Prospective Dutch Colorectal Cancer cohort www.plcrc.nl	2012	UMC Utrecht	Koopman	5542	52
PRESENT	PRospective Evaluation of interventional StudiEs on boNe metastases		UMC Utrecht	Verkooijen	>1700	1 (regional)
PROFILE	preoperative multiparameteric MRI at high field strength No website available	2013-2016	UMC Utrecht	Gilhuijs	46	2
SELECT	Dynamic contrast-nhanced MRI of ER+/HER2- unilateral breast cancer No website available yet	2005-2010 (retrospective)	UMC Utrecht	Gilhuijs	400	>6
SEND	Sentinel node biopsy in early oral cancer	2017	UMC Utrecht	De Bree	>500	8
STC biobank	Stem cell transplantation (SCT) biobanking from the EBMT registry STC information	1974	EBMT members	Kuball	>500.000	All
STC biobank Utrecht	Stem cell transplantation (SCT) biobanking of the UMC Utrecht linked to the clinical information available within the EBMT registry	2006 biobank	UMC Utrecht, PMC	Kuball	>300	2
T1 CRC	Dutch T1 Colorectal Cancer cohort www.t1crc.com	2000-2017	UMC Utrecht	Moons Lacle	3500	45
TARGET-HCC	Multicenter international registry studies on yttrium-90 glass radioembolisation in HCC patients (NCT02954094) TARGET-HCC information	2016	Target Pharma Solutions, Inc.	Lam	300	10
UMBRELLA	Utrecht cohort for Multiple BReast cancer intErvention studies and Long-term evaluation www.UMC Utrechtrecht.nl/umbrella	2013	UMC Utrecht	Verkooijen v Gils	>2700	2#
UNICIT	UNraveling Immune Checkpoint Inhibitor induced Toxicity UNICIT information	2018	UMC Utrecht	Suijkerbuijk	100	2
UPC	Utrecht Prostate Cohort: Evaluation outcome local therapy (surgery versus radiotherapy and active surveillance) No website available yet	2019	UMC Utrecht	vd Voort van Zyp	To be started	2
WES-Kidts	Children with kidney cancer	2015	UMC Utrecht, PMC	Jongmans	120	1

inclusion in Monro Breast Center and UMC Utrecht from 5 different hospitals
"Regional" means inclusion from regional hospitals within the UMC Utrecht.



Cohorts to be started in 2019

Name	Description Website	Year	Primary coordinator	Coordinator UMC Utrecht	Inclusion	No. of Centers#
LIMA	multiparametric MRI and liquid biopsies No website available yet	2019	UMC Utrecht	Gilhuijs	To be started	>3
ProBCI	Prospective Bladder Cancer Infrastructure: T1, invasive or metastasized bladder cancer. No website available yet	2019	UMC Utrecht	Meijer	To be started	4
Tbt	Thyroid Gland tumors No website available yet	2019	UMC Utrecht	Valk Vriens	To be started	>5
Tbt	Children with (recurrent) cancer No website available yet	2019	UMC Utrecht/ PMC	Jongmans	To be started Q3 2019	1

Appendix 4: Overview of teaching activities

Bachelor phase	<p><i>Curriculum of Medicine (CRU)</i>: Currently cancer is presented in three bachelors courses and in the elective courses: Image-Guided Radiotherapy, and Precision Medicine.</p> <p><i>Biomedical Sciences (BMS)</i>: The general basics of cancer and more specific and clinical aspects of cancer are taught throughout the 3 years bachelor. Courses include: "Molecular Pathology", "Gene therapy", "Cancer and Aids", "Clinical Oncology". Third year courses include: "Doceren via het DNA lab" on science education, and Molecular Mechanisms of Cancer that includes working on a short research project in the lab. Finally, The Bachelor Research Hub is a dedicated laboratory space, where bachelor students (Biomedical Sciences and Medicine) meet researchers and clinician(scientists) and have the opportunity to do biomedical and clinical research thereby stimulating interdisciplinary learning.</p>
Masters phase	<p><i>CRU</i>: Oncology research internships. A preparation course Int Medicine and Surgery.</p> <p>Selective Utrecht Medical Master (SUMMA): General basics of oncology/hematology (Yr1) and oncology research internships (Yr 3,4). In 2021 an interdisciplinary course will start where SUMMA, BMS and students from TU Eindhoven together will address a clinical issue.</p> <p><i>BMS</i>: The master/PhD program "Cancer, Stem Cells and Developmental Biology (CS&D)" organizes various theoretical master courses on the mechanistic aspects of cancer biology. In addition, major (9 months) and minor (6 months) cancer research projects are offered by research groups in the UMC Utrecht, Hubrecht Institute and PMC.</p> <p>Master's programme Medical Imaging" is offered by the Image Sciences Institute of the Imaging/Oncology division, in collaboration with the Department of Biomedical Engineering at Eindhoven University of Technology (TU/e). The master's program, which has tight links to the PhD programme Medical Imaging (see below), has a unique multi-disciplinary technological focus combining knowledge from physics, mathematics, computer science, medicine and biology. Courses are offered in the UMC Utrecht and at the TU/e. The students are trained in, e.g. image modalities, image acquisitions & processing, programming, quantitative image analysis and on use of artificial intelligence for medical imaging. Exposure to the research within the Imaging/Oncology is interweaved as lecturers are drafted from researchers within radiology and radiotherapy. See website: http://mix.isi.uu.nl/</p> <p>Master Epidemiology: the aim of this master's program is: 1) to provide students with extensive knowledge and practical skills in patient-oriented research design, implementation, quantitative analysis and its application to clinical medicine and public health. 2) to form a solid basis for health research and disease control programs, including application in low and lower-middle income countries.</p>
PhD programs	<p>The PhD programs Cancer, Stem Cells and Developmental Biology (CS&D) and Clinical and Translational oncology (CTO) offer courses, symposia and masterclasses in a multidisciplinary setting allowing interaction between PhD students with a fundamental, translational or clinical research project. Courses on cutting-edge topics are continuously developed, e.g. a new course on immuno-oncology, a collaborative initiative of 3 PhD programs: CTO, CS&D and I&I (infection & immunity).</p> <p>The Graduate Program Medical Imaging (ImagO) is one of the PhD programs of the Utrecht Graduate School of Life Sciences (GSLs), that is not only joined by PhD students of Radiology and Radiotherapy but also from other (non-cancer) specialties.</p> <p>The PhD program Epidemiology is also part of the GSLs. It is joined by many of the UMC Utrecht PhD students working on cancer (and non-cancer) related topics.</p>
Medical specialists	<p>In the training of medical specialists, rotations within the subspecialty oncology are offered. In addition, a new education strategy is currently being established that aims to develop and organize oncology education at a multidisciplinary level, reflecting the care-paths of our patients.</p>

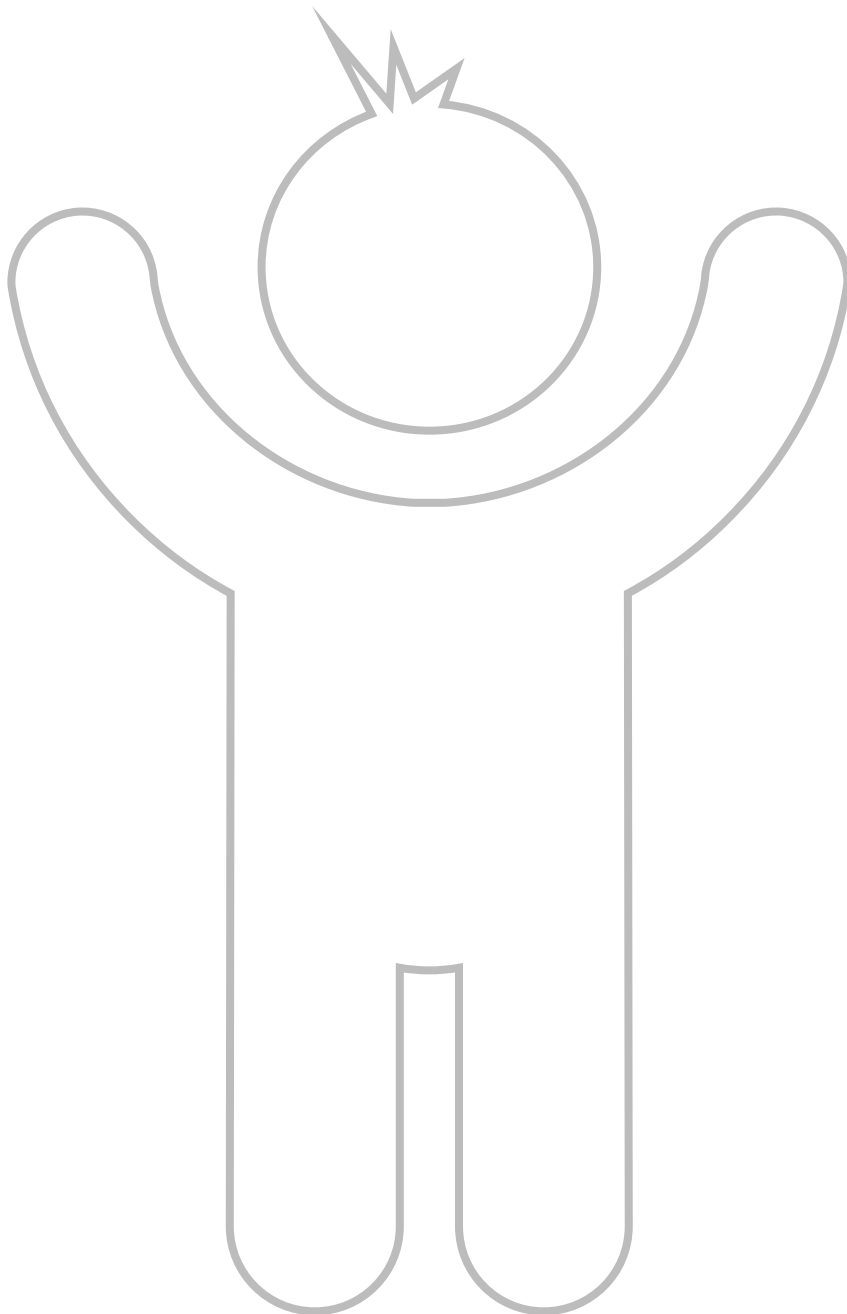


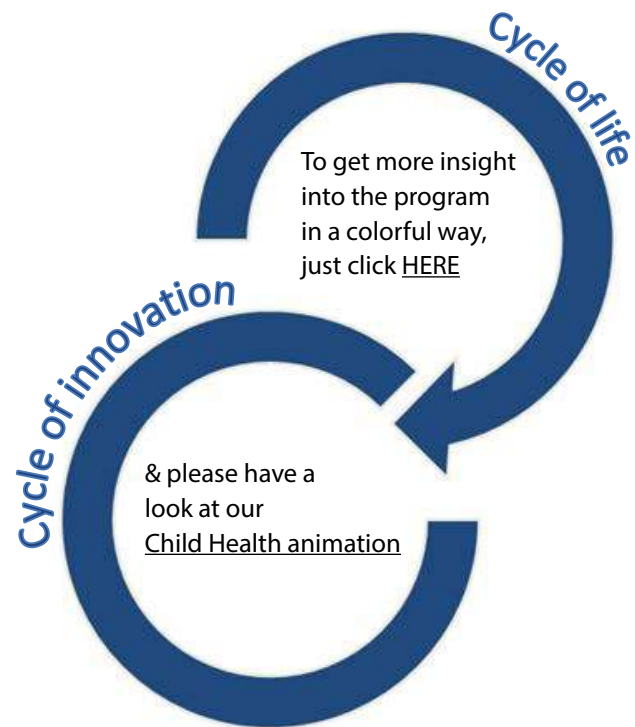
Imaging specialists	Since 2009 annual courses on <i>MRI in radiotherapy</i> are given, consisting of a 3 days general course, recently expanded with a fourth day addressing dedicated topics on MRI guided Radiotherapy. Each course, consisting of theoretical lectures mixed with practical instructional sessions, is attended by an ever increasing number of (inter-) national clinicians, physicists and technologists. In addition, an advanced course for medical physicist on MRI in Radiotherapy is organized. Finally, a dedicated course for Dutch radiographers/technologists is given with a focus on hands-on sessions for sequence optimisation and console training. The department of radiotherapy provides a single day course on the use of <i>Deep Learning for radiotherapy</i> , geared towards clinical physicists and clinicians which, as of 2019 will expand to several days aiming at physicists, clinicians and reps from industry.
Nurses	We meet the nationwide 'SONCOS' standard of 50% of nurses working in an oncology department being trained as an oncology nurse ; in certain subspecialties we even reach 90%. Given the nurse shortage we focus on talent attraction and retention by developing and offering (master)courses (with NFU), post-HBO courses (HBO = University of Applied Sciences) on palliative care, and a HBO-summer course Oncology. Moreover, PhD research on patient care is conducted and stimulated. Three full professors have been appointed on this topic.
Post-doctoral	"OncoTalent" program
Other	International Summer School Translational Oncology for national and international bachelor, master and PhD students. Co-organizer of the EACR/FEBS Summer School on molecular mechanisms in signal transduction and cancer.

*KNAW: Spagaat of Duet? Verwevenheid van onderwijs en onderzoek aan Nederlandse Universiteiten. December 2018.



Self-evaluation report strategic research program **Child Health**







1. The Child Health program	152
1.1 Mission, strategy & organisation	152
1.2 Description of the composition and funding of the Child Health program	157
1.3 SWOT analysis of the Child Health Program	159
1.4 Description of evaluation practices and/or policies in the Child Health Program	159
1.5 Description of Open Science activities	160
1.6 Description of the overall efforts of the strategic research program to involve patients in relevant phases of doing research	161
1.7 Description of the overall participation and/or co-development of the Child Health	162
2. Child Health research areas	164
2.1 Congenital and hereditary disorders	164
Kidney	164
Heart	166
Metabolism/Liver/GI	169
2.2 Severe inflammatory disorders	172
Auto immunity	173
Cystic Fibrosis	177
Recurrent Respiratory Infections	179
2.3 Ante and perinatal damage	183
Pre- and periconception	183
Obstetrics	186
Neonatology	189
Appendices	192
Appendix A: Description of the core team members	193
Appendix B: Kidney	194
Appendix C: Heart	197
Appendix D: Metabolism/Liver/GI	200
Appendix E: Auto immunity	203
Appendix F: Cystic Fibrosis	205
Appendix G: Recurrent Respiratory Infections	207
Appendix H: Pre/periconception	209
Appendix I: Obstetrics	211
Appendix J: Neonatal damage	213



1. The Child Health program

1.1 Mission, strategy & organisation

The Child Health Program

Mission

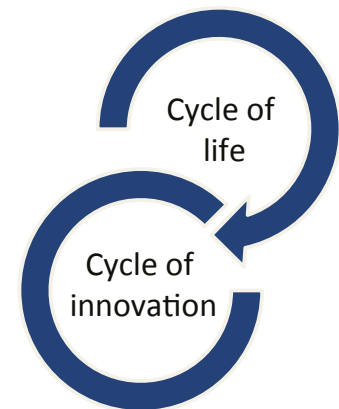
The Child Health Program of the UMC Utrecht is an integrated framework for child-centered interdisciplinary research, aligning patients, clinicians, investigators and resources, so that we can lead by filling significant gaps to improve the lives of children during childhood and thereafter.

Since 2014 major changes have been induced with regard to the Child Health Program. These changes were made to 1) increase the societal impact and revenues of the program for patients and 2) to align the program to the Connecting U strategy of the UMC Utrecht.

A new chairman and a new steering committee were appointed in 2015 and a rearrangement process of the Child Health program was started. The renewal process was quite unique compared to the other programs of UMC Utrecht and Child programs of other academic centers in- and outside The Netherlands. The rearrangement process was organized bottom-up instead of top-down, and originated from input of many principal investigators, patients and societal stakeholders. During multiple interdisciplinary and highly interactive sessions the former strategy was re-evaluated, new developments and opportunities were analyzed. It was acknowledged that care for children has dramatically changed over the last few decades, with a huge increase of survival rates. At the same time these developments resulted in an increase of long-term complications with new challenges for caregivers, parents and patients. It was felt that in the new Child Health strategy long term research and life cycle approach should be in the center of the program. This has led to a broadly shared new mission statement, vision and ambition.

Vision

Child Health is one of six hospital-wide strategic research themes. All diseases in focus of the Child Health program are characterized by their influence on the individuals' entire lifespan. These disorders often start at the beginning of life, or even before birth, and can have consequences far into adulthood. Within the Child Health program the 'Cycle of Life' approach is strongly intertwined with the so called 'Cycle of Innovation'. Within this 'Cycle of Innovation' ambitious interdisciplinary teams of patients, clinicians and investigators – from bench to bedside to society - strive to develop and implement novel approaches for treatment, (early) diagnosis, prognosis and monitoring of children with chronic diseases to fulfill unmet medical and psychosocial needs, to improve the lives of these children and their relatives. Both cycles interact at any moment in our hospital.



Cycle of life

Human life starts at conception, but even pre-conceptionally: health of the parents to be is important for the future of their children. Childhood is characterized by a continuous physical and psychosocial development. Diseases and medical interventions in early life as well as the genetic background, epigenetic imprinting and medical interventions (such as infertility treatment) have an important impact on individual, mental and social functioning during (late) childhood and adulthood.

Congenital malformations, premature birth, low birth weight, perinatal asphyxia, severe diseases in early life (like juvenile idiopathic arthritis, cystic fibrosis, childhood cancer and related interventions can have lifelong effects. This may even affect the health of the next generation. Therefore, focus on innovations in the (early) diagnosis, prognosis, monitoring and treatment of sick children and the development of longitudinal cohorts to acquire information on their long-term outcomes is crucial to improve the lives of children, and their relatives, during childhood and thereafter.



Cycle of Innovation

Introducing the Cycle of Innovation in the Child Health program means that the program aims to create a scientific infrastructure integrating various fields of biomedical and health research connected to groups of children with chronic diseases and their parents/relatives. Advancing research for the benefit of these children requires an interdisciplinary approach including basic, translational and applied (medical) research. Patient problems, new technologies or societal developments continuously raise new research questions. With a coherent (interdisciplinary) research strategy answering these research questions ultimately will lead to meaningful outcomes for patients, their families and society. Therefore, all committed scientists and professionals involved somehow in the care of our sick children, closely collaborate in their ambition to unravel the pathogenic mechanisms of diseases, to study new diagnostic and prognostic tests and markers and to develop, evaluate and implement innovative multidisciplinary therapies on a longitudinal basis in an ethically, legally and socially sound way. Answers and solutions will be created and communicated with patients, relatives and the public. The value of research for patients, medical care and even for society at large, in all its phases should be clear, evaluated and will most probably lead to new research questions.

Goals

We focus on healthy development of a child, from pre-conception to adulthood. We have established an interdisciplinary child-centered research community that aligns with the European Commission's philosophy of Responsible Research and Innovation (RRI) and aims to:

- Improve pediatric disease outcomes within a lifespan context.
- Cure congenital and hereditary diseases by unravelling pathogenesis; by developing diagnostic and prognostic markers and tools; and by developing and implementing novel therapeutics and lifestyle interventions.
- Improve resilience and quality of life for children and their relatives during childhood and thereafter.

Angela Saini in *Cell Stem Cell* wrote: '*... the significance of their results is hard to overstate.*'
(related to the CF-organoid work in Child Health)

Research Areas & Strategic Themes

The patient groups in focus of the Child Health program, formulated in 2014, are similar to the former program. The new strategic plan both preserves the strong parts of the old program and changes focus towards long term impact for patients and society. The Child Health program links top referent care for pediatric patient groups to interdisciplinary research from fundamental to translational to longitudinal applied medical research. All chronic diseases in focus of the Child Health program share that they start in early beginning of life and can have consequences far into adulthood. The research areas are:

Congenital and hereditary disorders (see page 164 & appendices B, C and D)

Many disorders of genetic origin are extremely rare and require academic specialist care. The Child Health Program especially focuses on congenital diseases of the heart, liver and kidney and plays a key role in the respective European Reference Networks.

Severe inflammatory disorders (see page 172 & appendices E, F and G)

The Child Health Program hosts several Centers of Excellence for children with sustained severe inflammatory disorders, like Juvenile Idiopathic Arthritis, Cystic Fibrosis, and Recurrent Respiratory Tract Infections. Since last SEP evaluation in 2013 the research line Inflammatory Bowel Diseases has not been able to continue successfully and was stopped after internal evaluation.

Ante- and perinatal damage (see page 183 & appendix H, I and J)

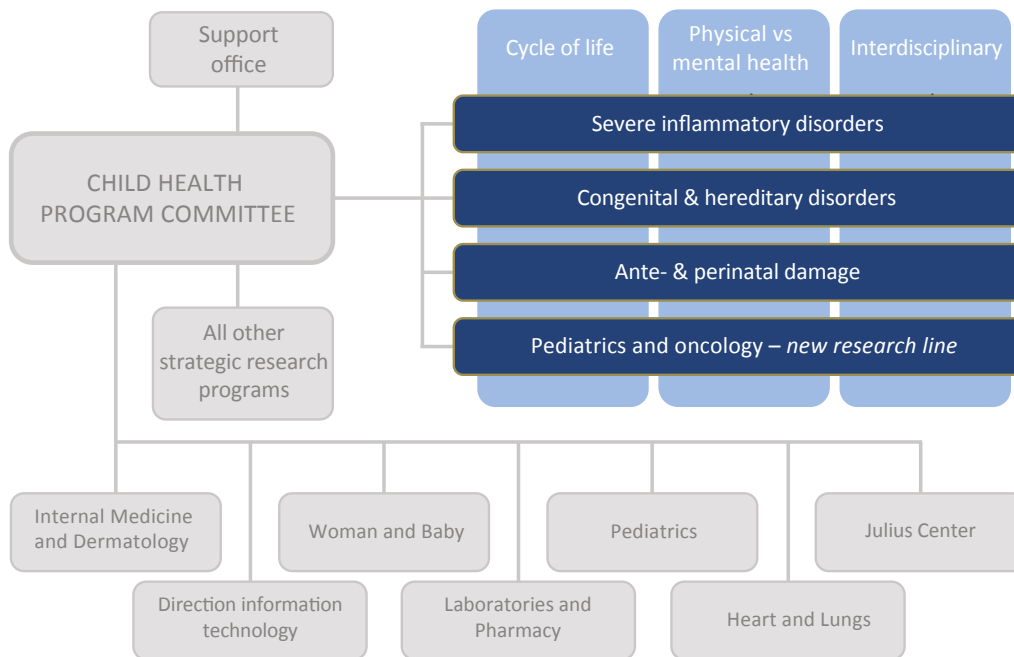
This research area has a life-cycle character, hosting several national and European Centers of Excellence. It includes care and research through periconceptional, antenatal and perinatal phases up to Neonatal Intensive care and research, aiming for the best long-term outcome of maternal and child health. Pregnant women, babies and their families are the center of service while striving for excellence and innovation.



Pediatrics and oncology

Since 2018, pediatric oncology care in The Netherlands is concentrated in the Princess Maxima Center, Utrecht, next to the Wilhelmina Children's Hospital. The pediatric care for these children and the care for late survivors is given in close collaboration with the Wilhelmina Children's Hospital. Research collaboration is being developed to improve outcome of children with cancer regarding physical as well as psychosocial outcomes, enabling these survivors to develop and participate in daily life similar to their peers. The outcome of this strategic research program will therefore have large impact on societal outcome. This research line is new in Child Health, but due to its developmental state this research is not evaluated yet in this SEP.

The research areas within the Child Health Program are cross-linked by three Strategic Themes that are represented in all research areas as shown figure below.



Life-cycle research

Prognosis of pediatric diseases have improved dramatically over the past few decades. For example, the life expectancy of children with cystic fibrosis has increased from about 10 years in the 1950s to almost 50 years in current times. The first heart surgery in children was performed in at the end of the 1940s, when the lifespan was very short. Today, heart surgery is routine and most children with congenital heart disease are operated on and therefore have a normal life expectancy. The viability border for newborns came down to 24 weeks of gestation, with consequences for their health later in life. Advances in cancer research and care are also providing a better and longer quality of life for children with cancer.

Interestingly, the advancements in survival rates and success of combating acute complications have, in turn, changed care requirements of pediatric patients. New long-term complications of diseases are emerging, for example, cardiac arrhythmias can develop in adults after pediatric heart surgery and 40% of children with cystic fibrosis develop diabetes in adulthood. In addition, the effects of drug treatment in children with, for example, juvenile rheumatoid arthritis on the function of the liver, kidneys and lungs in adulthood are unknown. Research in chronically ill children demands parallel focus on long-term health for adults.

Interdisciplinary innovation loops

Our Child Health Program has created a scientific infrastructure that integrates various fields of biomedical research connected to groups of children with chronic diseases and their parents/relatives. Advancing research for the benefit of these children requires an interdisciplinary approach including basic, translational and applied medical research, but also from the humanities (ethics) and social sciences. Patient involvement is key in all aspects of research in the Program.

Patient problems, new technologies and societal developments continuously raise new research questions. Our coherent, interdisciplinary research strategy enables us to answer these research questions and discover meaningful outcomes for patients, their families and society. Therefore, all of our scientists and professionals who are involved in



the care of our sick children, collaborate closely and share the same ambition to find the best solutions for our young patients. In addition, we're dedicated to communicating our findings to our patients, relatives and the public; there is clear value in collecting feedback and properly evaluating our research as these will inevitably lead to new research questions. It is through this innovation loop that societal issues are considered when defining research directions, and where we can accelerate scientific results quickly from bench to bedside.

Physical – mental interaction

Evidently, physical restrictions in childhood can have profound influence on the psychosocial development and identity formation in adulthood. Pain and discomfort in early life can affect basic trust in children. Deprivation from parents, families and friends during early life might influence social adaptations. Absence from school and inability to participate in sports might have a negative impact on the development of resilience in adolescence. It's not enough to only pay attention to the physical health of children.

On the other hand, psychological problems during childhood can have major adverse effects on medical treatment and the course of a disease. For example, denial of symptoms and poor adherence to therapy can highly influence outcome of chronic diseases. Therefore, we pay particular attention to the development of children with chronic diseases and study determinants of, for example, pain and fatigue at both the basic science and clinical care levels. This can help to develop and evaluate intervention programs. Our ultimate goal in this strategic theme is to empower and to engage children and their relatives to be fit for their future.

Child Health organisation

Chair

Since 2015 the Child Health Program is chaired by Prof Dr Kors van der Ent (1962). He is an experienced pediatric pulmonologist with leading clinical activities in patients with Cystic Fibrosis and specialist lung diseases. He is successful in leading his own research group and adheres to an holistic approach in clinical care. The Board of UMC Utrecht financially guarantees his availability for the program for two days a week. The chair is responsible for the overall strategy of the program, for representation of the program and acts as the ambassador and linking pin to all stakeholders of the program. The chair has monthly work meetings with the Dean of UMC Utrecht, to discuss the relevant and actual issues regarding the scientific strategy of the UMC Utrecht and Utrecht University. The chair is supported by a Program manager, drs Anneke van de Brug, who is available for four days a week.

Core Team

The Program has a steering committee, the so-called core team, consisting of senior scientists who are active in the program. In 2015 a new core team was installed, consisting mainly of the medical heads of the participating Divisions within the UMC Utrecht. While the Child Health Program focused on bottom-up capacity building, there was a growing distance between several of the core team members in their directive roles and the bottom-up energy from many of the young upcoming scientists.

Following the changes in the UMC Utrecht leadership structure of the divisions and the disconnection of dual positions in 2018 a partially new Child Health core team was installed. All new core team members adopt the UMC Utrecht Connecting U strategy and represent both basic and clinical science, methodology and ethics. They all are highly respected researchers in their research fields and work close together with the (Principal) Investigators of these various research areas. The core team members are spread over the different patient groups who are in focus of the Program, to guarantee a balanced approach of the different groups.

The core team has a 2 hourly meeting every 6 weeks, discussing strategic issues regarding the program and monitoring developments and outcomes of different research groups. The support office prepares all these meetings using an annual calendar with important topics over the year.

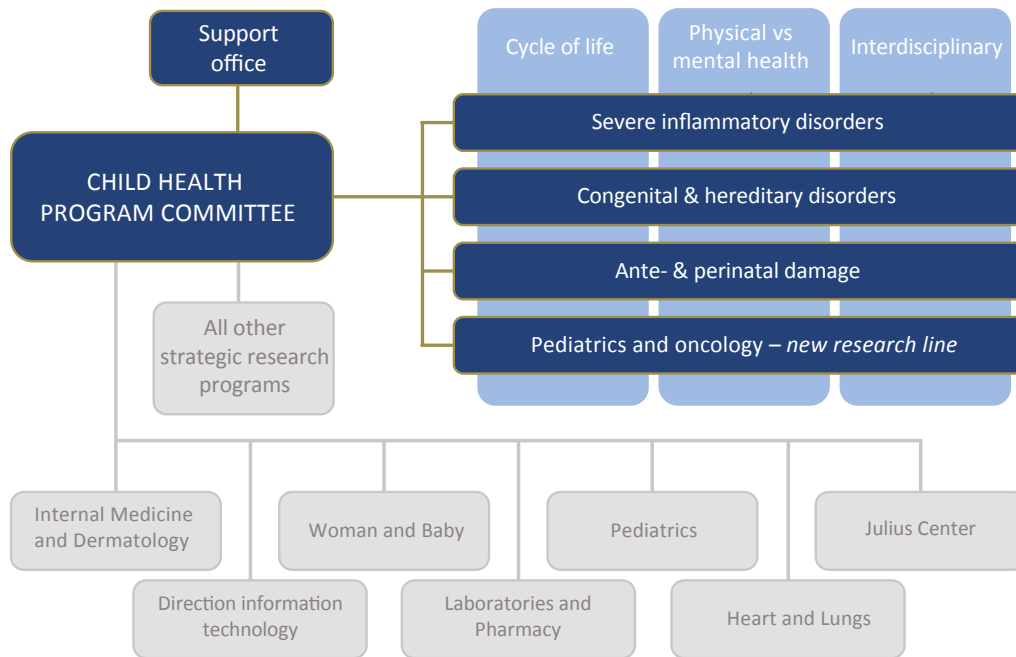
Core Team Composition



An detailed description of the various core team members and support staff can be found in appendix A.



This figure is a schematic overview of the embedding of the Child Health Program.



PI meetings

Principal Investigators in the Child Health Program are those researchers who have a distinct own research profile within one of the four research themes, lead at least 3-4 others (technicians, PhD-students) and who are willing to make an active contribution to the program. Currently, the Child Health Program has about 23 Principal Investigators (PI's) who aren't professor, 19 PI's who are professor and 33 Investigators (I's). They cover both the basic and clinical science fields as well as psychology, physiotherapy, ethics, and nursing.

The PI's & I's have regular half-day PI meetings (outside the hospital), scheduled and organized by themselves about overarching themes like patient participation, fund raising, career management, public relations etc.

Besides stimulation of personal development, the PI meetings act as a mix-and-match platform for young scientists who do not meet naturally. External experts can be invited and often patients or other stakeholders give their input to discussions. Core team member can, but not necessarily have to join the meetings. The Program chair and manager are involved in programming and support of the meetings.

Patient participation

Involvement of patients in prioritizing, set-up, evaluation and implementation of research is highly stimulated in the new Child Health Program. Several patient groups within the Program have their own patient advisory groups (E.g. Rheumatism, Respiratory Infection, Cystic Fibrosis) who are actively involved in all stages of research. Currently, a more overall patient advisory board is installed, consisting of representatives from each of the specific patient groups. Last years, there was increasing interaction between Child Health research and patients, ranging from joint grant applications and joint scientific publications to joint advocacy and fund raising and the parent of a patient got a part-time appointment at UMC Utrecht to build on professional and institutionalized patient participation in Child Health Research. Patients are routinely engaged in the ethics program.

Internal communication

Internal communication is realized by intranet and biweekly newsletters by mail. The communications advisor is the cross point for Child Health related news issues like scientific achievements and research and funding opportunities. Besides these communications within the Child Health Network the broader hospital society is involved in the Child Health activities every year. Each year there is a 2-3 days event within the Wilhelmina Children's Hospital, to reach out to all medical doctors, nursing staff, other caregivers and hospital personnel and patients and parents. During these events Investigators within Child Health can demonstrate and explain their work to the non-scientific part of the hospital. These events are supported by issuing an annual Child Health glossy, which is available throughout the year for all hospital visitors. Each glossy covers one of the 3 strategic themes of the Program (2017 Interdisciplinary; 2018 Physical Mental Interaction; 2019 Life Cycle Approach).



External communication

External communications is realized by internet, but the program also actively stimulates organisation of patient and other stakeholder meetings. These external communications primarily led by the different PIs of the Program and supported by the communication adviser of the Program. These meetings are often disease specific, but also overarching meetings (medical and scientific congresses and meetings as well as Publikslezingen).

In 2019 we presented the Child Health Program in the [Child Health research magazine](#) that can be used by all Investigators of the Program to present themselves to their international networks and we issued an [animation](#) to explain the Child Health organisation in an accessible way.

Divisions

The UMC Utrecht is organized in functional patient related units with their own targets and budgets. The strategic research programs of the UMC lack an own budget, but are thematically steering the research efforts of the Divisions. This matrix-construction asks for seamless interactions between Divisions and the overriding strategic research programs. The Child Health Program predominantly covers the Divisions of Pediatrics, Division of Woman and Baby and the Division Laboratory. The crosslinking is guaranteed by the members in the core team and the annual program action plan. This plan is part of the annual management contracts of the Divisions with the UMC Utrecht Board. Because the focus of the strategic research program is in the Division of Pediatrics, the chair of the Program once a month is invited in the management team to discuss ongoing issues. To ensure the connection of the strategic research programs to all Divisions of the UMC Utrecht, two-monthly strategic all chairs of the Programs meet with all chairs of the Divisions and the Board of UMC Utrecht in the UMC-meeting (“strategisch-overleg”).

1.2 Description of the composition and funding of the Child Health program

Composition (research FTE in UMC)

This table shows the number of FTE research capacity within the University Medical Center Utrecht, The Child Health program is the smallest program with regard to FTE (6.5%). These FTE's are located within 9 different divisions of the UMC, illustrating the cross-border characteristic of the Program.

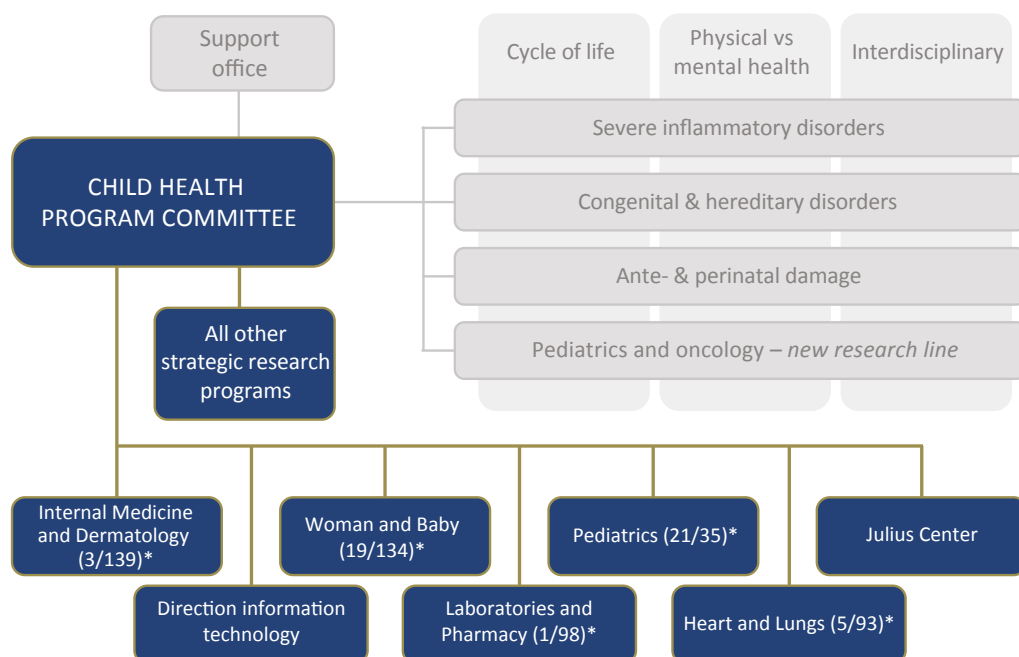
Research FTE and composition UMC Utrecht

	2018		2017		2016		2015		2014		2013	
	#	FTE	#	FTE	#	FTE	#	FTE	#	FTE	#	FTE
Scientific staff (1)	882	302	757	321	833	280	833	282	856	245	859	228
Post-docs (2)	340	163	331	198	525	279	562	283	391	133	417	138
PhD students (3)	962	552	662	410	403	256	463	275	855	384	870	375
Total research staff	2183	1017	1750	929	1761	815	1858	840	2102	761	2146	740
Other tenured staff	190	91	262	151	NA	NA	NA	NA	261	118	270	125
Total Staff	2374	1108	2012	1081	1761	815	1858	840	2363	879	2416	866

Note 1: Comparable with WOPI categories HGL, UHD and UD; tenured and non-tenured staff

Note 2: Comparable with WOPI category Onderzoeker

Note 3: Standard PhD (employed) and Contract PhDs (externally or internally funded but not employed)



* number of fte for Child Health in relation to the total research fte per division

Table 2: Research funding

This table shows the financial research capacity within the University Medical Center Utrecht. Mean income during last 6 years was M€ 148, of which M€ 105 originated from the 2nd, 3rd and 4th geldstroom.

UMC Utrecht research funding by source

UMC Utrecht

	2018	2017	2016	2015	2014	2013
Direct Funding (1)	€ 51,400,000	€ 52,100,000	€ 56,300,000	€ 53,900,000	€ 53,900,000	€ 47,100,000
National grants (2)	€ 15,341,707	€ 28,393,113	€ 23,877,213	€ 17,062,423	€ 18,503,039	€ 21,491,913
External grants (3)	€ 66,227,511	€ 58,307,101	€ 47,150,283	€ 58,853,910	€ 56,101,803	€ 53,266,936
Contract research (4)	€ 20,421,442	€ 24,210,959	€ 19,834,387	€ 17,885,006	€ 13,427,912	€ 13,670,862
Total Funding	€ 153,390,660	€ 163,011,173	€ 147,161,883	€ 147,701,339	€ 141,932,754	€ 135,529,711

- Direct Funding (1) Block funding from government
- National grants (2) Competitive grants from Dutch national research funders (e.g. NWO, ZonMw, KNAW)
- External grants (3) Grants from external, not-for-profit parties (e.g. European Commission and health charities)
- Contract research (4) Grants from industry

Mean competitive income of the Child Health program over 2nd, 3rd and 4th geldstroom was clearly increasing in this period and was up to 8-10% of the UMC income.

Child health

	2018	2017	2016	2015	2014	2013
National grants (2)	1,894,871	€ 3,529,020	2,168,355	€ 1,579,184	€ 1,031,585	€ 1,144,430
External grants (3)	4,599,053	€ 5,711,599	7,337,379	€ 2,268,385	€ 3,287,500	€ 3,808,356
Contract research (4)	1,627,640	€ 2,207,749	1,243,258	€ 969,618	€ 1,891,163	€ 624,306
Total Funding	€ 8,121,564	€ 11,448,368	€ 10,748,992	€ 4,817,187	€ 6,210,248	€ 5,577,092



1.3 SWOT analysis of the Child Health Program

In the table below a SWOT analysis of the Child Health Program is provided. It includes developments during (2013-2018) as well as expected developments.

Internal	Strengths	Weaknesses
	<ul style="list-style-type: none"> • Highly motivated investigators • Specific long term patient cohorts • Well organized patient involvement • Societal impact • National vs international networks (eg ERN's) • Embedding basic science (eg stem cells, genetics) • Interdisciplinary/ ethics / social sciences • Strong branding as a hospital (mother/child) • Life cycle approach • Gender balance 	<ul style="list-style-type: none"> • Poor availability of bibliometric information as provided by the UMC Utrecht • Data management/ big data science • Weak performance in personal grants & H2020 • Shortage of patent, grants & legal support • High turnover support staff • Underperformance of some research lines (like IBD)
External	Opportunities	Threats
	<ul style="list-style-type: none"> • Realizing more clinical trials via U-trial • Collaboration Healty urban living/DoY • Collaboration with Wageningen/Eindhoven • Collaboration with Nutricia, PMC, RIVM • Linkage research and care (eg genetics) • Outreach via summaprogram & summerschools • Global health 	<ul style="list-style-type: none"> • Reduction imbursement / national 'academic component' • Lack of dedicated research time • Shortage in specialized (non)medical staff (eg nurses) • Uncontrolled bureaucracy & increased costs

To address the mean weaknesses of the program we have asked the divisions to support the program in 2020 and onwards with regard to these issues.

- Strategic research program related laboratory capacity
- Protected research time for PI's
- Enforcement of support infrastructure (data management, grant support, legal support)
- Underperforming research-line IBD was stopped

1.4 Description of evaluation practices and/or policies in the Child Health Program

After renewal of the mission and vision of the Child Health Program in 2015 more and more people have indicated that they want to be PI within Child Health, their numbers growing from around 25 to more than 80. Although this illustrated the attractiveness of the Program and showed how the Child Health activities were appreciated by the researcher, it also had a dilution effect. The growth has not always improved the sense of ownership and responsibility towards the Child Health program (for example, evident in participation in PI meetings).

The core team is convinced that the success of the Program depends on the quality of individual researches and aims to increase the power of the Program by investments in personal leadership and communication skills of individual scientists. Furthermore, clear paths for career-development within the Program and personal coaching are thought to be crucial for scientific success.

That is why in 2018 the core team has once again looked into the definition and determination of Investigators and Principle Investigators (PI's) within Child Health. This so-called 'Fleet Survey' (Vlootschouw) with pre-set criteria resulted in identification of 17 professor and 18 non-professor PI's and of 30 Investigators within the Program.

This 'Fleet Survey' is repeated annually at a core-team meeting, to create opportunities for Investigators to become PI.

Criteria for Investigator

An Investigator within the Child Health Spearhead is a researcher (m / f) who has taken great strides in his / her research career. The research falls within the research themes of Child Health and an Investigator supervises at least 2 PhDs. Investigators feel and take responsibility with regard to the Child Health program and are committed to the further development of good Child Health research. They regularly visit the PI days, actively participate in Child Health activities and their organisation.



The Investigators ensure that their teams are aware of Child Health developments and encourage them to cooperate / participate in related activities. Investigators ensure their news is included in the Child Health newsletter and inform the communication adviser about developments in order to make these developments visible to the outside world. About once a year, each Investigator has a development meeting with two members of the core team. In this interview, the necessary steps will, among other things, be discussed to grow into the position of Principal Investigator.

Criteria for Principal Investigator (PI)

The PIs are the engines of the Child Health program. They serve as an example for all those involved in Child Health and are the representatives of Child Health. A PI has at least the level of associate professor or is expected to do so in the short term (i.e. its own research identity, at least 3-4 of its own PhD students finalized and creates his own research funding).

PIs are expected to be actively deployed within Child Health. He / she actively promotes the Child Health principles (life course research, interdisciplinary and physical & mental interaction) and is the contact person for the SEP and the Child Health website. The PIs are named as Child Health researchers in the Cooperation Agreements (in Dutch: SWO's) between the divisions and the Child Health program. In addition, Child Health resources such as a new magazine, presentations at Child Health events and the awarding of boost grants are prioritized to PIs.

A PI is present at least half of the PI meetings and prepares, together with others, at least 1 meeting per year. PIs play an active role in the content organisation of the Child Health activities such as a conference, Child Health event and magazine. The PIs ensure that their news appears in the Child Health newsletter and inform the communication adviser about developments in order to make these developments visible to the outside world. Approximately once a year, each PI has a development meeting with 2 core team members and the PI board is evaluated within the core team every two years.

1.5 Description of Open Science activities

Openness of research agenda & stakeholder involvement

At the UMC Utrecht we stimulate stakeholder involvement in priority setting in research, especially patient organisations, to make research responsive to societal challenges. The strategic research program 'Patient participation' accelerates and professionalizes this long-standing practice.

Child Health has many stakeholders, such as other UMCs, regional hospitals, patient organisations and companies. Within a couple of the research lines the research agenda is being set together with patient delegations.

A few examples of Child Health stakeholders are

- NCFS
- Reumafonds
- Prinses Maxima Center for pediatric oncology
- RIVM (National Institute for Public Health and the Environment)
- Municipality of Utrecht
- GGD Utrecht
- Trimbos Institute
- Jantje Beton
- Stichting Hartekind
- Dutch Kidney foundation
- University of Utrecht – Dynamics of Youth & department of veterinary medicine
- Nutricia
- Philips

With most of these stakeholders we have documented products of collaboration. Some illustrations of active stakeholder involvement in both basic and clinical science within Child Health was described in peer reviewed literature:

- Noordhoek JJ et al. Aligning patients' needs and research priorities towards a comprehensive CF research program. *J Cyst Fibros.* 2019 May;18(3):382-384.
- Schoemaker CG et al. Dutch juvenile idiopathic arthritis patients, carers and clinicians create a research agenda together following the James Lind Alliance method: a study protocol. *Pediatr Rheumatol Online J.* 2018 Sep 15;16(1):57.



- Noordhoek J et al. Intestinal organoids and personalized medicine in cystic fibrosis: a successful patient-oriented research collaboration. *Curr Opin Pulm Med.* 2016 Nov;22(6):610-6.

Openness of data and protocols

We facilitate data sharing practices, with the aim of making research data FAIR available to other researchers, to speed up the process of scientific discovery. The governance for research data, including technical infrastructure and dedicated personnel, is expanding rapidly.

The researchers of the Child Health are following the guidelines and policy of the UMC Utrecht on data management. This means that for all research involving patients a data management plan is generated and discussed with data managers of the division the researcher is employed at. From September 2019 onwards, this will also hold true for all research without patient involvement.

Investigators of Child Health are actively participating in the set-up and implementation of the Digital Research Environment (DRE) in close collaboration with the RadboudUMC and ErasmusMC. This system will enable data storage according to FAIR principles. Recently Child Health participated in a 750k€ Stimuleringsgrant Infrastructure of the University Utrecht to further enable safe data-acquisition, data-storage and data-sharing. A Child Health data-catalogue will be part of this system in the future.

We stimulate the registration of protocols for clinical trials (clinicaltrials.gov, trialregister.nl, clinicaltrialsregister.eu). Awareness of this kind of registration is heightened in collaboration with the quality officers of the participating divisions. Results of clinical trials will always (if possible) be published in journals. To be able to publish the results a trial needs to be registered

Open access publications

Finally, we stimulate publication of research findings in Open Access journals and on preprint servers to make publicly funded research indeed publicly available. UMC Utrecht researchers can apply for financial support at the Utrecht University Open Access fund that partly reimburses article processing charges. We actively stimulate to include budgets for Open Access publication of study-results in grant-applications. During last 5 years the core team members of Child Health had an Open Access publication rate of about 50%, stimulating others within the program. Some examples are:

- Berkers G, et al. Rectal Organoids Enable Personalized Treatment of Cystic Fibrosis. *Cell Rep.* 2019 Feb 12;26(7):1701-1708.
- Taylor-Cousar JL, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *N Engl J Med.* 2017 Nov 23;377(21):2013-2023.
- Prevaes SM, et al. Concordance between upper and lower airway microbiota in infants with cystic fibrosis. *Eur Respir J.* 2017 Mar 29;49(3).
- Sachs N, et al. Long-term expanding human airway organoids for disease modeling. *EMBO J.* 2019 Feb 15;38(4).
- van Houten CB, et al. Observational multi-centre, prospective study to characterize novel pathogen-and host-related factors in hospitalized patients with lower respiratory tract infections and/or sepsis - the "TAILORED-Treatment" study. *BMC Infect Dis.* 2018 Aug 7;18(1):377.
- Shenoj S, et al. The burden of systemic juvenile idiopathic arthritis for patients and caregivers: an international survey and retrospective chart review. *Clin Exp Rheumatol.* 2018 Sep-Oct;36(5):920-928.
- Swart J, et al. Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more than 15,000 patients from Pharmachild and national registries. *Arthritis Res Ther.* 2018 Dec 27;20(1):285.

1.6 Description of the overall efforts of the strategic research program to involve patients in relevant phases of doing research

Involvement of patients in prioritizing, set-up, evaluation and implementation of research is highly stimulated in the new Child Health Program. Several patient groups within the Program have their own patient advisory groups (E.g. Rheumatism, Respiratory Infection, Cystic Fibrosis) who are actively involved in all stages of research.

Currently, a more overall patient advisory board is installed, consisting of representatives from each of the specific patient groups. The Wilhelmina Children's Hospital has its own young patient board (Kinderraad), which is involved in discussions in agenda setting and trial performance. Patients are routinely engaged in the ethics program.



Last years, there was increasing interaction between Child Health research and patients, ranging from joint grant applications and joint scientific publications to joint advocacy and fund raising and the parent of a patient got a part-time appointment at UMC Utrecht to build on professional and institutionalized patient participation in Child Health Research.

Currently one PhD within Child Health focuses entirely on the role of patients in all stages of scientific research, resulting in several peer reviewed papers and expected thesis defense in 2020. Several papers were written by patients themselves as a first author.

- Noordhoek JJ et al. Aligning patients' needs and research priorities towards a comprehensive CF research program. *J Cyst Fibros*. 2019 May;18(3):382-384.
- Schoemaker CG et al. Dutch juvenile idiopathic arthritis patients, carers and clinicians create a research agenda together following the James Lind Alliance method: a study protocol. *Pediatr Rheumatol Online J*. 2018 Sep 15;16(1):57.
- Noordhoek J et al. Intestinal organoids and personalized medicine in cystic fibrosis: a successful patient-oriented research collaboration. *Curr Opin Pulm Med*. 2016 Nov;22(6):610-6.

1.7 Description of the overall participation and/or co-development of the Child Health program in teaching, specifically at the master and PhD level

Child Health has a strong focus on education, and for a very good reason: Education holds the key to our future. Our education program is aimed at different audiences ranging from patients to health professionals and scientists. Almost all PhD students participate in one or two graduate programs (extensively described elsewhere)

- The Graduate School of Life Sciences organizes all Utrecht University Master's and PhD programs focused on micro-organisms, plants, animals, humans, the molecules of life, and health & disease. It combines training and education for Master's students and PhD candidates, thus incorporating theory and practice at both levels and allowing overall quality control and consistency.
(www.uu.nl/organisatie/faculteit-geneeskunde/onderwijs/graduate-school-of-life-sciences)

- MSc in Epidemiology Postgraduate <https://www.uu.nl/masters/en/epidemiology-postgraduate>

Besides these two graduate programs, the Child Health Program specifically supports targeted programs for talent management that help young researchers focus their efforts towards real and sustainable societal impact.

TULIPS program

New researchers within the Child Health program are actively stimulated to participate in the national TULIPS program (Training Upcoming Leaders in Pediatric Science), an initiative of the Dutch Society for Childcare. The vision of TULIPS is that high-quality research is required to improve child health. TULIPS has the mission to empower young clinician scientists to become international competitive researchers. Therefore, TULIPS provides distinct, selective 2-year curricula for PhD students and Postdoctoral fellows.

Both curricula provide interactive training sessions and weekend educational retreats to create opportunities for collaboration and to enhance competences required to become successful in Pediatric Science.

EUREKA Institute

The Eureka Institute of Translational Medicine is the result of a close collaboration between the UMC Utrecht, various other top universities (Stanford University, Duke/NUS Medical School, University of Arizona, University of Miami, University College London and the University of Toronto), research institutions (TIP, Center for Translational Molecular Medicine), foundations (Dutch Arthritis Foundation) and industry (Nutricia Research). Nature Medicine and Nature Biotechnology have supported the program, in addition to providing learning materials. The Eureka Institute was initiated to develop an international community of translational medicine professionals equipped to catalyze the application of discoveries for the benefit of human health. The Institute offers a unique translational medicine course, the International Certificate Program and within this framework we've developed a special program for researchers appointed within Child Health. This program stimulates new researchers in crucial areas, such as teambuilding and collaboration; critical thinking and problem solving; translational medicine and valorisation. In collaboration with the Eureka Institute, we also organize masterclasses with internationally renowned facilitators for young talent in Child Health.



Summer Schools

The Child Health program hosts several Summer Schools during the summer. These educational activities introduce global child health to young doctors and master's students and stimulate working together in an international environment. The Summer School on translational medicine is organized together with students from the international Apollo Society (<https://www.apollosociety.eu/>) and hosts an impressive international faculty. By organizing joint events between summer schools, we are building a lasting network of young researchers.

About 100 students from all over the world participated in the Child Health Summerschools of 2019 and are now ambassadors of improving health in children now and in the future.



Boost Grants

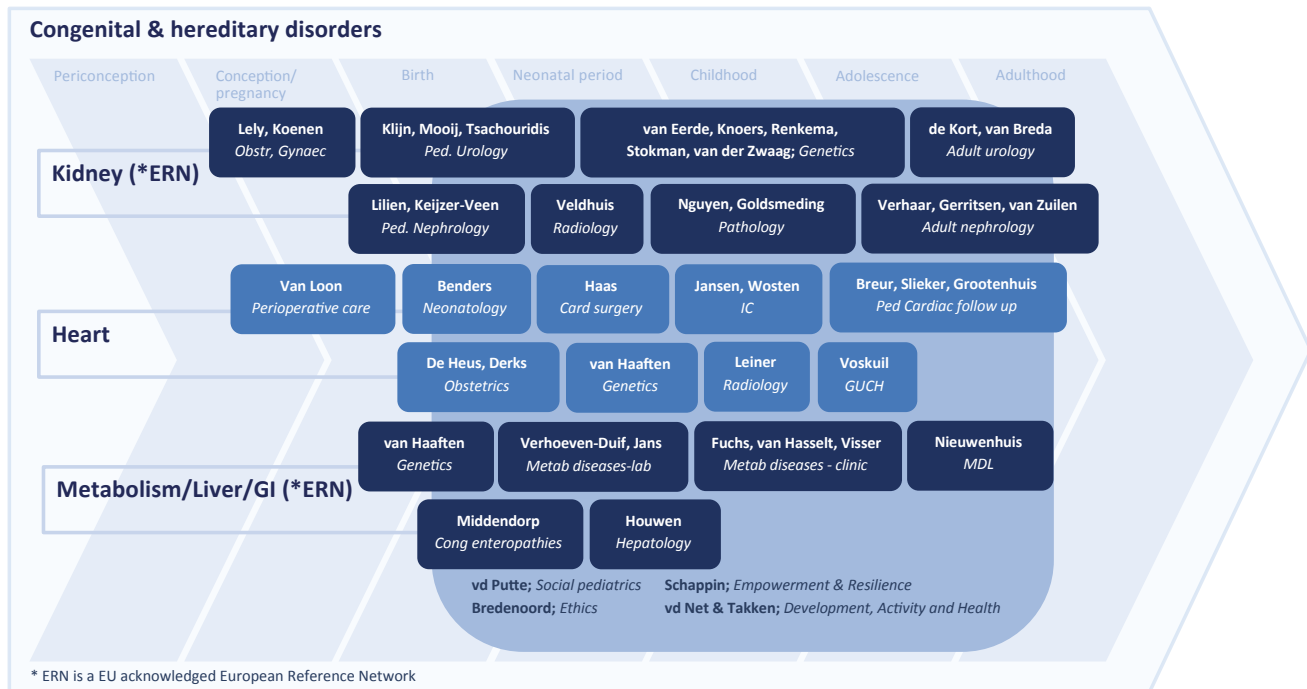
One of the main strategic themes of the Child Health program is interdisciplinary research. To stimulate young investigators to share their research experiences with colleagues outside their own professional expertise, we have launched annual Boost Grants. Young investigators within the program are asked to submit research proposals in collaboration with one or more investigators in the program with whom they have never worked before. Each year, this produces 15-20 new research ideas that are presented and discussed during general Child Health meetings. The three best ideas are rewarded with an amount of 15,000 Euros to start the project and generate pilot data for future larger grant applications.



2. Child Health research areas

2.1 Congenital and hereditary disorders

Many of these disorders of known and (yet) unknown genetic origin are extremely rare and require academic specialist care. The Child Health Program especially focuses on congenital disease of the heart, liver and kidney and plays a key role in the European Reference Networks for these respective areas.



Kidney

Organisation, strategy & mission

The Expert Centre Hereditary and Congenital Nephrologic and Urologic disorders is a national accredited expert center and member of ERKNET (the kidney European Reference Network). In this international framework we take pride in multidisciplinary care and state of the art diagnostics for patients with hereditary renal disease and urologic malformations. Nephrogenetics oriented research is a one of the central themes. Our multidisciplinary network enables swift transition from bedside to bench and back directly supporting improvement in care for vulnerable patients. One example is a case of severe syndromal congenital nephrotic syndrome diagnosed by Pediatric Nephrology. Regular diagnostics by Clinical Genetics did not reveal a known cause. Successive experimental work by Biomedical Genetics led to identification of mutations in a candidate gene hitherto not known to be associated with human disease. Functional analysis of renal tissue by Pathology corroborated the finding. Further proof was found by in-vitro knock-down experiments. Testing of the discovered gene (autosomal recessive) was then applied in prenatal diagnostics, allowing the family to have healthy offspring. (1) The Expert Center is uniquely embedded in the "Kidney Research Utrecht" environment in which all kidney oriented researchers (like the Masereeuw group (UU), the Verhaar group (nephrology), the Van De Heuvel group (Princess Maxima Center)) interact and create synergy for collaborative projects. Another example is a family with children previously diagnosed with nephropathic cystinosis. Expert knowledge from Pediatric Nephrology and Clinical Genetics led to confirmation of an alternative diagnosis, not at all associated with nephropathic cystinosis. This spared the patients from lifelong and demanding treatment. By interaction with the Masereeuw group, an experimental model showed why the phenotype in this family was alike to nephropathic cystinosis. This in turn will lead to improvement of therapy for nephropathic cystinosis.



Both talent management and line responsibilities are ruled by the divisions, not by the research theme. As the Kidney unit consists of researchers from several divisions projects embarked upon are the result of concerted efforts, creating cooperations between different relevant parties within the local network. Van Eerde is coordinator for the Expert Center.



* ERN is an EU acknowledged European Reference Network

Lifecycle

Both for (pediatric) urology patients and for (pediatric) nephrology patients we have well established programs for transition of adolescent patients. Also, we have 3 multidisciplinary outpatient clinics: pediatric nephrology (Dr. M. Lilien / Dr. M.G. Keijzer-Veen) & clinical genetics (A.M. van Eerde) adult nephrology (Dr. M. Rookmaaker) & clinical genetics (A.M. van Eerde) adult nephrology (drs. F.E. van Reekum) & obstetrics (Dr. A.T. Lely).

We ensure optimal care for families with renal disease and/or urologic malformations from childhood to adulthood, including preconception and prenatal care. Our research is aimed towards optimizing personalized care in all stages .

Interdisciplinary

The Center encompasses (pediatric) nephrology, (pediatric) urology, clinical and laboratory genetics, obstetrics, nephropathology, radiology, and research. In our meetings we discuss complex cases to see in which cases research could improve patient care. All Utrecht kidney research key players participate in "Kidney Research Utrecht". We have many national and international collaborations.

Physical & mental development

KLIK and ProFEEL are large pediatric quality of life research cohorts that the Kidney Unit has started to participate in.

Patient Participation

The Center is well-connected with patient organisations, foremost the Dutch Kidney Patient Association. We involve patients in the set-up of our studies and grant applications. We enthusiastically participate in opportunities for educating patients and laypersons, for instance during World Kidney Day.

Goals next 3 to 6 years

Please explain what the research theme aims to achieve in the next 3 to 6 years and how success of the research theme is demonstrated for these goals.

In the next 3-6 years we want to considerably extend and further develop the systematic collection of data to extensively phenotype and genotype patient groups of interest. It concerns both clinical (follow-up) data and genetic data, biobanking of urine, DNA, medical data. We want to integrate clinical, biological and genetic data. In order to find novel avenues for intervention (and evaluate present interventions) and improve our diagnostic and care pathways.

An ongoing or finished research project where patients are meaningfully involved

Recognition of the NFU expert center for TSC was strongly supported by the Dutch TSC association. They are also involved in the setting up of the national TSC registry. The recent Dutch Kidney Foundation senior postdoc grant awarded to Van Eerde (375K), entails a project for a Genetic Kidney Disease registry, the Dutch Kidney Patient Association will help set-up of the consent (for use of past data, but also newly generated data, return of results, incidental findings etc.



Important scientific publications

These papers represent not necessarily the absolute overall top from our research focus, but top papers also showcasing our diversity.

Schutgens et al.

Tubuloids derived from human adult kidney and urine for personalized disease modeling. (2)

The first paper describing renal (tubular) organoids. One of the key examples of the excellent Utrecht embedding of the unit, with lines also to the Hubrecht Institute.

Snoek et al.

NPHP1 (Nephrocystin-1) Gene Deletions Cause Adult-Onset ESRD.(7)

Paper showing that this ciliopathy, a monogenic renal disease classically thought of as pediatric, causes 0,5 % of all adult onset end stage renal disease. With many of these patients over 30 years at first renal replacement therapy. This has bearing on risk for familymembers, related donation practice etc

Paauw et al.

Sildenafil During Pregnancy: A Preclinical Meta-Analysis on Fetal Growth and Maternal Blood Pressure. (8)

Paper in which a method is presented for cross-species meta-analysis.

Hennus et al.

Long-term effect of conservative treatment versus low threshold endoscopic desobstruction on urine incontinence and urgency in boys with persistent overactive bladder symptoms: A cohort study. (6)

This paper has led to more urodynamic studies and less valve resections in boys with persistent overactive bladder symptoms.

An important societal contribution

The interconnected structure of the Kidney unit, containing researchers from different clinical and basic science backgrounds, enables detection of unusual patterns of rare disease. These patterns fuel hypotheses on alternative explanations and mechanisms of disease. Short lines of communication between the relevant parties in the unit guarantee fast design of experiments. The structure of the unit provides access to state of the art experimental conditions (renal organoids, zebra fish models, ao) to test these hypotheses. Knowledge gained from these experiments is brought back to the clinical setting and provides direct improvement of care for patients and their families. This strategy has had a demonstrable effect in the care of families affected by rare renal diseases, as mentioned in the examples above.

The clinicians involved, through the accredited expertise function, get referrals from a large area in the Netherlands. Moreover, patient organisations (ao for ciliopathies, tuberous sclerosis) are advising their members to turn to the UMC Utrecht for specialized care.

The experience gained from concentration of care for patients with rare renal diseases leads to better care for these patients, to improvement in the identification of the specific needs of these patients and families, and to early recognition of aberrant patterns of disease. Genetic and basic research in patients with these aberrant patterns leads to gain of knowledge on pathways involved. Implementation of this knowledge in regular genetic diagnostics (gene-panels, whole exome sequencing) then improves patient care and provides novel opportunities for family counseling.

For more detailed information on process and output indicators see Appendix B

Heart

Organisation, strategy & mission

During the past decades, the care for patients with congenital heart disease (CHD) has improved dramatically. Where only a minority of patients survived fifty years ago, currently more than 90% of patients live into adulthood. Therefore both research and clinical care need to shift from improving mortality to reducing morbidity. To accomplish this we developed the Congenital Heart Disease life span project. A lifecycle project that focusses on improvement of diagnostics and long term cardiovascular and neurodevelopmental outcome in patients with severe congenital heart disease.



Lifecycle

The UMC Utrecht is one of the four national expertise centers for treatment of congenital heart disease. Yearly around 5000 children and adults visit the outpatient clinic of the center for congenital heart disease. Furthermore around 400 cardiac surgeries and 300 cardiac catheterisations are performed yearly in patients with congenital heart disease. Our surgical mortality rates in complex neonatal cardiac surgery are among the lowest in Europe (eg Document Samen Beter (2016) or EACTS database). With our focus shifting from decreasing mortality to reducing morbidity we have developed the Congenital Heart Disease Life Span Program: a unique life cycle approach with an extensive research program fully integrated in clinical follow-up from as early of 20 weeks gestation up to late adulthood. Cardiac- as well as neurocognitive follow-up is protocolized for all major congenital heart defects and includes sequential MRI scanning of the fetal as well as pre- and postoperative heart and brain. Follow-up is fully aligned with the other patient focus groups of the Child Health and Circulatory Health programs of the UMC Utrecht. There is one outpatient clinic for both children and adults with congenital heart disease located in the Wilhelmina Children's Hospital. One team of dedicated congenital heart disease echo technicians performs all echocardiography's. There are weekly multidisciplinary meetings where children and adults with congenital heart disease are discussed with pediatric cardiologists, GUCH (Grown-Up Congenital Heart disease) cardiologists, congenital heart surgeons, cardiac anesthetists and pediatric intensivists. One team of surgeons and interventional cardiologists perform all surgeries and catheterisations in children and adults. Furthermore, there are special outpatient family clinics for genetic arrhythmia's/cardiomyopathies where entire families are jointly treated by the pediatric and adult cardiologist.



Logo of the CHD life span project

Interdisciplinary

Within the multidisciplinary clinical research team close collaboration exists with several research groups. Neurodevelopmental outcome is assessed in close collaboration with the group of Prof dr Manon Benders (neonatology) and Renske Schappin (psychology). Furthermore, close collaboration on cardiac imaging exists with the group of prof Tim Leiner (radiology). In collaboration with the groups of van Dr Gijs van Haaften (genetics) and Prof dr ir Jeroen Bakkers (Hubrecht) the genetic origin of congenital heart disease is being unraveled. Finally, the UMC Utrecht plays a prominent role in several international consortia on neurodevelopmental outcome in congenital heart disease; e.g. the EU-ABC consortium and CNOC consortium.

Physical and mental development

Both physical and mental development deserve our full attention since problems often occur with a 20% need for special education in children with severe congenital heart disease. We have developed a special cardiac developmental outpatient clinic (Hart op Weg) lead by a physiotherapist (Drs Maaike Sprong) and a neonatologist (Dr Mona Toet). In recent years follow-up has been intensified in close collaboration with the departments of neonatology (Prof dr Manon Benders), psychology (Dr Renske Schappin), social pediatricians (Prof dr Elise van der Putte, Dr Sanne Nijhof) and physiotherapy (Dr Tim Takken, Dr Janjaap van der Net) resulting in the Congenital Heart Disease Life Span project which incorporates both intensive life-long neuro-cardiac imaging as well as therapeutic interventions to improve neurocognitive outcome in patients with severe congenital heart disease. We strongly believe that the incidence of severe brain injury in congenital heart disease can be reduced by 20% with the use of preventive medication during the crucial neonatal and perioperative period and by executive function training programs in the first years of life.



Patient participation

In the UMC Utrecht we strongly believe that our patients are experts in the field of their disease and that setting research priorities should be a joint effort. Therefore close collaboration with all patient organisations exists (Stichting Hartekind, PAH, Hartstichting, Hart4Onderzoek). Together we set research priorities, evaluate research projects and provide feedback to our patients.

Goals next 3 to 6 years

Within 3 to 6 years the UMC Utrecht will have a leading role in performing national and European trials in the fetal and neonatal period on improvement of cardiac and neurodevelopmental outcome in severe congenital heart disease. National and European grants will be obtained with the UMC Utrecht as main applicant.

The leading role in cardiac and neurodevelopmental outcome will facilitate other groups to expand the current research pipeline. In 3 to 6 years fetal MRI scanning of the heart, brain and placenta will be established and has led to the first trial to improve prenatal brain maturation by improvement of cerebral perfusion and/or oxygenation depending on the specific type or cardiac defect. Also, in 3 – 6 years large steps will be made in postnatal imaging. Computational Fluid Dynamics will enable us to simulate interventions and analyze the result using a pulsatile MRI compatible model with 3D prints.

An ongoing or finished research project where patients are meaningfully involved

The Crucial trial is the result of a meaningful cooperation between all national stakeholders (cardiac centers, patient organisations). Patient organisations were involved in many ways. We had meetings where patients were able to give their opinion on study design and outcome. Furthermore patient representatives helped us to write patient information documents. Also patient representatives currently work closely with us to optimize inclusion and to communicate results of the study. Patient organisations are leading in the way we distribute our results, write newsletters etc..

Important scientific publications

Algra SO, Jansen NJ, van der Tweel I, Schouten AN, Groenendaal F, Toet M, van Oeveren W, van Haastert IC, Schoof PH, de Vries LS, Haas F. Neurological injury after neonatal cardiac surgery: a randomized, controlled trial of 2 perfusion techniques. Circulation. 2014;129:224-33.

This publication shows that our unit is able to perform a high end clinical trial comparing different bypass techniques in a critical population with severe congenital heart disease. This trial is the birth of our congenital heart disease life span program and established neuroimaging in patients with severe congenital heart disease.

Stegeman R, Lamur KD, van den Hoogen A, Breur JMPJ, Groenendaal F, Jansen NJG, Benders MJNL. Neuroprotective Drugs in Infants with Severe Congenital Heart Disease: A Systematic Review. Front Neurol. 2018;9:521. doi: 10.3389/fneur.2018.00521

In this invited systematic review we describe potential neuroprotective drugs in patients with congenital heart disease. The invitation to write this review shows that we are considered experts in this field. Furthermore performing the review convinced us that allopurinol had the highest neuro- and cardio protective potential of the available drugs. This has ultimately led to the successful grant application of the Crucial trial (ZonMw €1,5M).

Harakalova M, van Harssel JJ, Terhal PA, van Lieshout S, Duran K, Renkens I, Amor DJ, Wilson LC, Kirk EP, Turner CL, Shears D, Garcia-Minaur S, Lees MM, Ross A, Venselaar H, Vriend G, Takanari H, Rook MB, van der Heyden MA, Asselbergs FW, Breur HM, Swinkels ME, Scurr IJ, Smithson SF, Knoers NV, van der Smagt JJ, Nijman IJ, Kloosterman WP, van Haelst MM, van Haften G, Cuppen E. Dominant missense mutations in ABCC9 cause Cantú syndrome. Nat Genet. 2012;44:793-6.

This publication shows that the heart program can successfully collaborate with many other stakeholders resulting in a high impact publication. This multidisciplinary work has led to an ongoing unique cooperation with yearly Cantu meetings where patients from all over Europe visit the WKZ to learn from our research but also to undergo several diagnostic tests (e.g. echocardiography) to expand our knowledge and form a world leading consortium with our American counterpart.

Stelt van der F, Siegerink SN, Krings GJ, Molenschot MC, Breur JMPJ. Three-Dimensional Rotational Angiography in Pediatric Patients with Congenital Heart Disease – A Literature Review. Pediatr Cardiol. 2019;40:257-264

This review shows that we are world leading in the application of 3 dimensional rotational angiography in congenital heart disease, that we are a unit that critically evaluates its results and that uses new techniques to bring patient care and research forward.



An important societal contribution

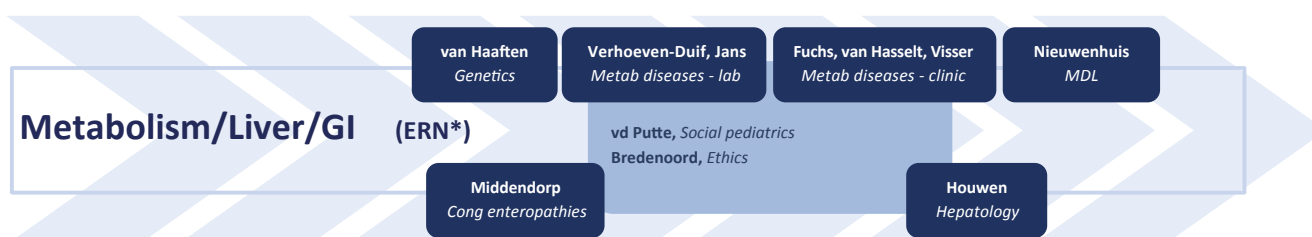
In spite of the fact that neurodevelopmental problems frequently occur and are a major burden in severe congenital heart disease, research concerning the origin and treatment of brain damage has not been performed so far in the Netherlands and only scarcely worldwide. With the congenital heart disease life span program we developed a unique clinical infrastructure with extensive perinatal en perioperative cardiac and brain imaging. The program has generated unique data and has led to the first prospective national trial in pediatric cardiology (Crucial trial). This trial will ensure that the unique CHD life span infrastructure will be implemented in all congenital heart centers in the Netherlands. This will result in a world leading neuro-cardiac consortium. Together with our European partners we will be able to make a difference in neurodevelopmental outcome in patients with severe congenital heart disease.

For more detailed information on process and output indicators see Appendix C.

Metabolism/Liver/GI

Description of the organisation, strategy & mission

Metabolic disorders, as well as congenital liver and intestinal disease, although individually rare, together represent an important cause of morbidity and mortality in childhood. The pathophysiology of these type of diseases is often not well understood, especially when the basic defect is not known yet. Our research group - combining clinical and laboratory metabolic, hepatic, gastroenterologic, genetic and organoid specialists in the UMC Utrecht and RMCU in the Hubrecht Institute - has been essential in identifying genes causing a number of these diseases: metabolic diseases (MCT1, TRAPPC2L deficiencies; glutamine metabolism: GLS hyperactivity and GLS deficiency; and disorders in protein transcription and translation: ARS deficiencies and POLR2A disease), cholestatic liver diseases (PFIC), congenital diarrhea or enteropathies (MVID, STX3, ANKZF1, DGAT1 deficiencies, CHAPLE syndrome) and others (NSMCE3, UNC13A, HIST1H4C). Some of these disease groups are progressively recognized as a relatively common cause of multi-organ disease (ARS deficiencies) and understanding disease mechanisms has led to novel clinically applied treatment strategies (PFIC, Cantu, ARS deficiencies). This was made possible through multidisciplinary & deep phenotyping approaches combined with innovative disease models (liver and intestinal organoids, CRISPR/Cas gene edited cells, zebrafish models). Therapies applied or under investigation in our department include small molecules (currently tested in a personalized in vitro organoids for PFIC), dietary interventions (e.g. targeted amino acid supplementation in Malate Aspartate Shuttle defects and ARS deficiencies), hematopoietic stem cell treatments (clinically applied with standardized follow-up for MPS1 and other lysosomal storage diseases) and liver stem cell transplantations (currently being optimized in animal models prior to the first in human trial).



* ERN is a EU acknowledged European Reference Network

Lifecycle & physical and mental development

Regular follow-up and evaluation of patients is being performed within the Sylvia Toth Center, a unique facility in which patients have a one day multidisciplinary and holistic work-up, not only including medical care (consultation by all required medical specialists) but also physical and mental evaluation (by a physical therapist and child psychologist) and sampling of biological materials. This is targeted towards symptoms (developmental delay, muscle weakness), disease (CLN3, VLCAD) or treatment follow up (Haematopoietic stem cell transplantation for Lysosomal storage disorders). For Cantu syndrome we organize international annual Clinics; during these days the patients are seen by several specialist and receive an update on research. These long-term follow-up programs are needed to gain insight in the long-term consequences of rare diseases and provide a solid framework to evaluate novel treatment strategies.



Patient participation

Both patient care and research for patients with these diseases is being supported by the VKS (Vereniging voor Kinderen met Stofwisselingsziekten, Hanka Meutgeert), Stichting Metakids (various projects), the MLDS (Maag Lever Darm Stichting), Stofwisselkracht, as well as several private foundations aiming at improved survival and quality of life of patients. Together they stimulate research for patients with metabolic diseases and congenital liver and intestinal diseases and safeguard patient interests through regular meetings, focus group discussions (for example for liver stem cell transplantations) and contacts during study participation.

Interdisciplinary

The research teams of the department of pediatric gastroenterology (Prof. Dr. R.H.J. Houwen, Dr. W.L. van der Woerd) and the department of Metabolic Diseases (Dr. S.A. Fuchs and Dr. P.M. van Hasselt) are closely intertwined. They collaborate with the Laboratory of Metabolic diseases (Dr. J.J.M. Jans, Prof. Dr. N.M. Verhoeven-Duif) and the department of genetics (Dr. G van Haaften) to better understand the metabolic consequences of the diseases studied. Studying the pathophysiology and developing novel treatment strategies (small molecule based therapies, stem cell based therapies, RNA based therapies) are mainly done using patient derived organoids in the RMCU at the Hubrecht Institute (Dr. S.A. Fuchs, Dr. S. Middendorp, Prof. Dr. E.E.A. Nieuwenhuis). To develop new cell based therapies (e.g. liver cell transplantation) a close collaboration with the Hubrecht Institute (Prof. Dr. H. Clevers) and the Faculty of Veterinary Medicine (Dr. B. Spee) exists. In preparation for these clinical applications ethical aspects are being investigated in collaboration with Prof. Dr. A. Bredenoord. For modeling of human developmental syndromes we collaborate with the group of Prof. Dr. Jeroen Bakkers at the Hubrecht Institute. Additional collaborations exist for MPS (Dr. J.J. Boelens, Dr. C. Lindemans, Dr. Sakkers, Dr. Nierkens), delineating residual disease despite HSCT and approaches to improve this; NCL (Prof. Dr. M.M. van Genderen and C. van Alfen, Bartimeus; Dr. S. Nierkens), delineating the disease course and investigating clinical and cellular biomarkers; Fatty acid oxidation (FAO) defects (Prof. R. Wanders and Prof. R. Houtkooper, Amsterdam UMC), delineating the disease course before and after introduction in the newborn screening program and evaluating novel treatment strategies. For both patient care and research there is recognition as an expertise center within the Netherlands, as well as internationally as a member of the relevant European Reference Networks.

Goals next 3 to 6 years

Improve *diagnosis* of diseases in metabolism / liver / GI

- Implement untargeted metabolomics and multi-omics in diagnostic care.
- Develop and implement FACS- and Imagestream-based diagnostic platforms for inborn errors.
Success: *Discover* and describe 5 new inborn errors (of metabolism), using a combination of techniques (metabolomics, proteomics, RNAseq, functional cellular imaging) as well as state of the art genetic approaches, including population genetics.

Improve *treatment* for patients with diseases in metabolism / liver / GI by combining deep phenotyping with innovative cellular assays and treatment strategies.

- Prepare all aspects of the first in human (FIH) liver stem cell transplantation trial, including optimisation of cell cultures, GMP compliance, upscaling, final safety and efficacy tests and risk/benefit estimation, regulatory aspects, clean room facilities, clinical aspects.
Success: perform the FIH liver organoid cell transplantation.
- Develop a robust in vitro assay for 5 genetic/metabolic diseases for drug testing and evaluation in a personalized manner.
Success: treat the first patients after prior personalized effect estimation in their organoids.

An ongoing or finished research project where patients are meaningfully involved

In preparation for the “first in human” liver organoid transplantation trial, which we hope we can start during the coming years, we organized focus group discussions with representatives of the patient organisations, and the ethicist involved (AB) as well as with different patients groups, their parents or “normal members of society” to discuss several aspects of a “first in human” organoid transplantation trial (for example patient selection: oncology model? Children?). These discussions were very useful, will help in designing the optimal trial and were described in a thesis (Sarah Boers, Utrecht University, May 2019).



Important scientific publications

Long-term culture of genome-stable bipotent stem cells from adult human liver.

Huch M, Gehart H, van Boxtel R, Hamer K, Blokzijl F, Verstegen MM, Ellis E, van Wenum M, **Fuchs SA**, de Ligt J, van de Wetering M, Sasaki N, Boers SJ, Kemperman H, de Jonge J, Ijzermans JN, **Nieuwenhuis EE**, Hoekstra R, Strom S, Vries RR, van der Laan LJ, Cuppen E, Clevers H. *Cell* 2015;160(1-2):299-312. (IF 31.4) (more than 100 citations per year)

With this paper and the recently published articles on metabolomics (Haijes ea. MGM 2019; Haijes ea. *Metabolites* 2019) we aim to illustrate our investments in technological innovations to facilitate in vitro modeling (first publication of liver organoid technology) and functional read outs (first description of the use of metabolomics in cerebrospinal fluid for clinical diagnostics and pathophysiological elucidation).

Aminoacyl-tRNA synthetase deficiencies in search of common themes.

Fuchs SA, Schene IF, Kok G, Jansen JM, Nikkels PGJ, van Gassen KLI, Terheggen-Lagro SWJ, van der Crabben SN, Hoeks SE, Niers LEM, Wolf NI, de Vries MC, Koolen DA, **Houwen RHJ**, Mulder MF, **van Hasselt PM**. *Genet Med.* 2018 Jun 6. doi: 10.1038/s41436-018-0048-y. (IF 9.8)

This paper is an example of our broader efforts to better understand rare diseases by grouping them and using existing (published) data by performing a structured review followed by a meta-analysis. This paper illustrates the added value of deep phenotyping for rare diseases for better recognition, clinical care (awareness of potential symptoms), insight in disease mechanisms and treatment. Following publication, the first IARS patient has been treated with isoleucine with beneficial outcomes.

Intestinal failure and aberrant lipid metabolism in patients with DGAT1 deficiency.

Van Rijn JM, Ardy RC, Kuloğlu Z, Härter B, van Haaften – Visser DY, van der Doef HPJ, van Hoesel M, Kansu A, van Vugt AHM, Thian M, Kokke FTM, Krolo A, Keçeli Başaran M, Gurcan Kaya N, Ünüsoy Aksu A, Dalgıç B, Ozcay F, Baris Z, Kain R, Stigter ECA, Lichtenbelt KD, Massink MPG, Duran KJ, Verheij JBG, Lugtenberg D, Nikkels PJG, Brouwer HGF, Verkade HJ, Scheenstra R, Spee B, **Nieuwenhuis EES**, Coffey PJ, Janecke AR, **van Haaften G**, **Houwen RHJ**, Müller T, Middendorp S, Boztug K. *Gastroenterology* 2018;155:130-143. (IF 20.877)

This paper expands the phenotype of a rare form of congenital diarrhea and describes the use of small molecules to enhance the expression of the protein deficient in this disease, which is likely to be an approach that will be widely used in the future for many genetic diseases.

Identification of human D lactate dehydrogenase deficiency.

Monroe GR, **van Eerde AM**, Tessadori F, Duran KJ, Savelberg SMC, van Alfen JC, Terhal PA, van der Crabben SN, Lichtenbelt KD, **Fuchs SA**, Gerrits J, van Roosmalen MJ, van Gassen KL, van Aalderen M, Koot BG, Oostendorp M, Duran M, Visser G, de Koning TJ, Cali F, Bosco P, Geleijns K, de Sain-van der Velden MGM, Knoers NV, Bakkers J, **Verhoeven-Duif NM**, **van Haaften G**, **Jans JJ**. *Nat Commun.* 2019 Apr 1;10(1):1477 (IF 12.353)

This paper is an example of our disease discovery ambition. This paper is important as it not only describes a new inborn error of metabolism but also the discovery of a new enzyme in human metabolism with broader impact for other acquired disorders. Furthermore, this paper illustrates the success of our multidisciplinary approach including genetics, metabolomics, zebrafish biology and clinic, that is also visible in our other disease discovery papers.

Identification of a Loss-of-Function Mutation in the Context of Glutaminase Deficiency and Neonatal Epileptic Encephalopathy.

Rumping L, Büttner B, Maier O, Rehmann H, Lequin M, Schlump JU, Schmitt B, Schiebergen-Bronkhorst B, Prinsen HCMT, Losa M, Fingerhut R, Lemke JR, Zwartkuis FJT, **Houwen RHJ**, **Jans JJM**, **Verhoeven-Duif NM**, Jamra R, **van Hasselt PM**. *JAMA Neurol.* 2018 (IF 11.46)

In this paper and a related paper on GLS hyperactivity (Rumping ea *Hum Mol Genet.* 2019) we were in the unique position to describe the consequences of both a loss of GLS activity and GLS hyperactivity. We used innovative techniques to delineate pathogenicity: For loss of GLS activity we performed Retrospective Guthrie card analysis of affected and unaffected siblings and 10 age-matched controls per sibling to undo storing effects. For GLS hyperactivity we aligned more than ~12000 GLS protein sequences from >1000 genera to unveil the extreme conservation of the mutated Ser482 residue – similar only to catalytic residues.



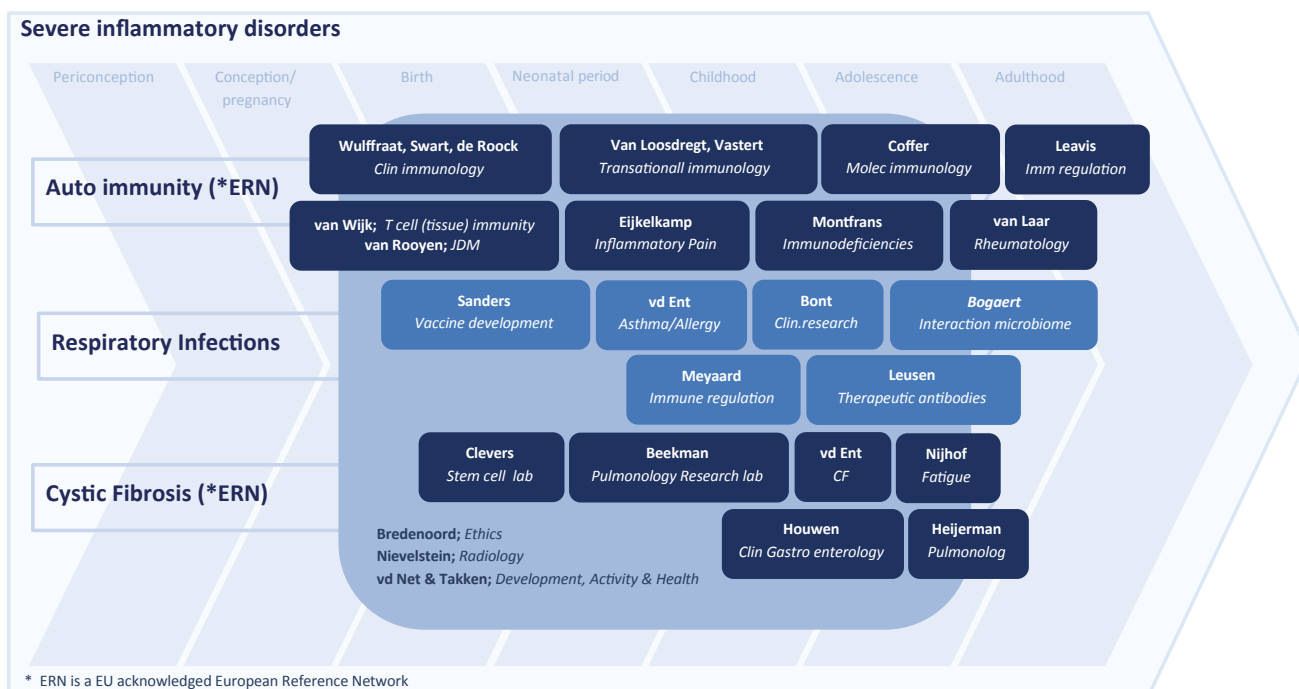
An important societal contribution

During the last five years we advanced the fields of metabolic disease and rare genetic liver/intestinal disease in a close collaboration between clinicians, researchers and laboratory specialists, both by improving diagnostics and therapies. Patients with a range of rare genetic diseases, e.g. PFIC, ARS deficiency, GLS deficiency, CHAPLE syndrome and many more, have benefited, either because a diagnosis can now be made for the first time, as the disease had not been described before (eg GLS deficiency), or the diagnostic trajectory could be shortened considerably through the implementation of new diagnostic modalities, such as metabolomics and exome sequencing and combinations thereof. The resulting insight into the pathophysiology resulted in successful treatment for several of these diseases, for which no therapy was available before (eg ARS deficiency, CHAPLE syndrome; papers in preparation). Overall in the period that covers this review (2015-2019) we have published over 100 papers, of which ~20 had an impact of more than 10, including a NEJM paper. We foresee that during the next five years we will achieve a similar progress, both in the field of diagnostics and therapeutics. In this respect the newly founded Dutch initiative “United for Metabolics”, uniting all six university medical centers in the Netherlands, and in which several group members have an important role, will be essential. In addition the emerging therapeutic role of small molecules (eg proteasome inhibitors), which can be tested in patient derived organoids, as was showed by our UMC Utrecht collaborators (Cell Rep 2019), will foreseeable add to the therapeutic arsenal. Liver cell transplantation for rare metabolic diseases, using hepatocytes derived from organoid culture, will be implemented during these five years, and will have an important impact for patients worldwide.

For more detailed information on process and output indicators see Appendix D.

2.2 Severe inflammatory disorders

The Child Health Program has a strong interest in inflammatory disorders of the airways, joints and the gut. Both genetic and environmental factors play a role in the development of uncontrolled chronic inflammation with subsequently serious disability and loss of quality of life. Our efforts are to increase our understanding of how environmental factors interact with genetically determined immune- and metabolic responses. This knowledge can help to develop novel preventive and therapeutic interventions and ultimately decrease the burden of disease in children and their families.

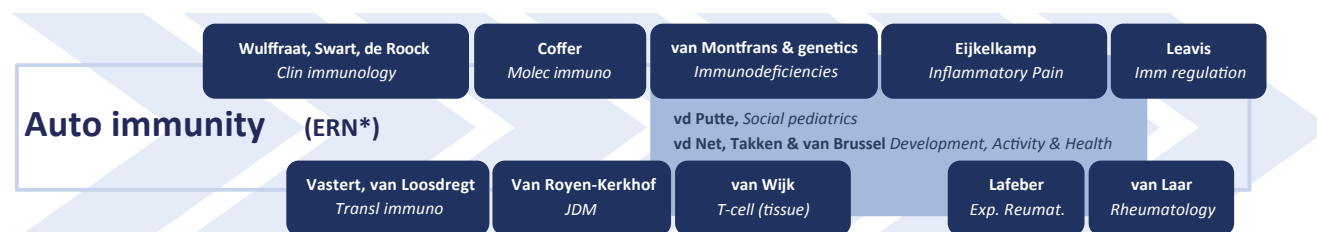




Auto immunity

Organisation, strategy & mission

Our research group is a product of both the clinical department of pediatric rheumatology and the translational research groups from the Laboratory for Translational Immunology (LTI). The first one is the largest academic center for juvenile arthritis and other pediatric rheumatic diseases in the Netherlands. Since 2016, we are listed as EULAR Center of Excellence as only the 2nd pediatric rheumatology department worldwide. In 2018, the Dutch Arthritis Foundation appointed our department as Research Center of Excellence. Our translational research group combines both fundamental and clinically orientated projects and conducts several investigator initiated clinical trials.



* ERN is a EU acknowledged European Reference Network

Lifecycle

Juvenile Idiopathic arthritis (JIA) is a chronic inflammatory disease that affects approximately 1/1000 children and can lead to restricted mobility, disability and severe loss of quality of life.

JIA can affect children from the age of as early as 1 year, making it a true chronic pediatric inflammatory disease, facing all the aspects and challenges of the developing child. JIA is an umbrella term, the disease is classified into several subtypes. It also is a quite heterogeneous disease, with on the one side oligo-articular JIA, with in general a milder disease course with respect to the joints at least. Chronic uveitis can however be prominent and a real disease burden, affecting almost ¼ of the children with this subset of JIA. Poly articular JIA generally has a chronic disease course, lasting into adulthood. Systemic JIA is more an acquired auto-inflammatory disease, characterized by severe systemic inflammation besides arthritis, and with a variable prognosis.

We diagnose around 40 patients / year and follow around 600 patients in our clinic. Around the age of 16 we start the process of transition to the rheumatology department in the UMC Utrecht (headed by prof. van Laar). This process can take several years and there is a tendency, supported by both patients and physicians, to be more flexible in the transition timewise. We are currently implementing our longitudinal studies into the transition process, ensuring that patients (if they consent) continue to contribute to research projects reflecting true life cycle science.

Interdisciplinary

Collaboration is essential for rare diseases like JIA and therefore we have set up collaborations where possible to achieve our goals. We work together with as many stakeholders as possible, including patients and parents as mentioned before. On a national level, we collaborate in the Werkgroep Academische Kinderreumatologie (WAKR), connecting all 6 academic pediatric rheumatology departments. Internationally, we are involved in many networks, societies and platforms. We have coordinated multiple international research projects including EUTRAIN (2012-2015, on translational research in juvenile arthritis), SHARE (2012-2015, developing international best practices on diagnosis and treatment for rare pediatric rheumatic diseases). Currently we are 1 of the 2 leading centers in UCAN-CANDU, a Dutch Canadian Collaborative research project aiming to develop personalized treatment regimes in JIA. Importantly, we also manage the UCAN-U platform, developing novel research techniques, standardisations and operation procedures allowing for international collaborative efforts in pediatric rheumatology. With these collaborations we aim to translate mechanistic studies into improved clinical care for patients with childhood arthritis by: 1) Sharing materials, protocols, and expertise. 2) Providing an infrastructure that facilitates exchange between researchers. 3) Providing training and education of professionals. 4) Organizing international meetings for clinicians, researchers, patients to evaluate current research and set goals for the future.

Physical & mental development

Current therapy allows most children with JIA to live a 'normal' life, including sports, school and a career, but at the expense of chronic immunosuppressive treatment with potential side effects, less understood disease manifestations or complaints like fatigue and concentration problems and the uncertainty whether the disease will flare or not.



We aim to be very aware of the problems that our patients face and are constantly exploring ways to improve their quality of life. This requires collaborations, not only between hard core laboratory sciences and clinicians (pediatric rheumatologists), but also with general pediatricians, exercise and physiology scientists, physiotherapists, social pediatricians and pain specialists/scientists.

Patient participation

Our department has formally appointed Dr. C Schoemaker in 2016 as patient representative for our department. Besides being a senior scientist himself at the Dutch National Center for Public Health and Environment (RIVM), Dr. Schoemaker is also the father of a JIA patient and is a specialist in patient participation. He helps us to facilitate patient participation by training researchers and (parents of) patients on patient involvement in research projects in dedicated courses together with prof Maarten de Wit. Currently (2018-2019), we are creating a research agenda based on needs and focus of patients according to the James Lind Alliance methodology. Anouk Verwoerd, one of our PhD students, will be executing this process together with all stakeholders, under supervision of dr. Schoemaker and the James Lind Alliance.

In addition, our department collaborates with the jeugdremavereniging and KAISZ (patient organisation for rare auto-immune and auto-inflammatory disease) on several different projects and occasions to both inform (parents of) patients on uptodate information on their diseases and therapy, to inform patients on current research projects and to boost awareness on pediatric rheumatic disease in society. Finally, we have long lasting relations with international patient organisations like ENCA, the systemic JIA foundation and the auto-inflammatory alliance.

Goals next 3 to 6 years

Our research theme aim works towards:

- **Excellent science.** We strive towards innovative research that increases our understanding of immune responses in health and autoimmunity. Our goal is to increase our scientific output even more compared to the last period. Besides publications in disease-specific journals such as Arthritis & Rheumatology we anticipate to also publish in broader immunology journals with high impact factors. Another goal is to acquire competitive (personal) grants, and funding in larger scientific consortia settings, similar to UCAN-CANDU. We are currently setting up several state-of-the-art techniques in our laboratories (partially in collaboration) to help us reach these goals and push our scientific understanding forwards including nanopore sequencing, single-cell RNA-seq combined with TCR-seq, single-cell ATAC-seq, and metabolomics.
- **Excellent impact for patients.** We aim to perform research that truly benefits patients with (auto)immune-related diseases. We aim to reach this goal by 1) the generation of eHealth applications. As further explained before, the eHealth applications that we are currently developing will help us to provide better care, monitor our clinical trials at a detailed level, and generate further knowledge about the disease. 2) Performing clinical trials that are based on our research. One of our strengths is the combination of both clinical and fundamental research. We want to exploit this even more efficiently and push the development of clinical trials based on our research 3) Development/involvement in making official (international) guidelines for the treatment of (auto)immune-related diseases. Our clinical scientists are already involved as members of different guideline committees for the treatment of numerous (rare) childhood diseases (including JIA, JDM, immunodeficiencies) and will keep promoting and leading evidence based care. 4) We are presently generating of a national JIA research agenda, this will help to involve patients in our research and perform scientific projects generated by patients.
- **Increased interdisciplinary.** Although we already have strong collaborations between researcher/MD/patient, we envision a more prominent role for diagnostics and monitoring. A stronger collaboration with the diagnostic department will benefit our search for biomarkers and clinical trials. We believe that this will directly benefit both our research and patient care.

An ongoing or finished research project where patients are meaningfully involved

One of our projects is the generation of a national JIA research agenda our patient representative Casper Schoemaker together with our PhD student Anouk Verwoerd will lead the Priority Setting Partnership that will set a research agenda for Juvenile Idiopathic Arthritis. This partnership consists of patients, parents of patients, and medical personnel (pediatricians and nurses). Also an ethicist is included to govern similar input of all parties. This project is carried out in close collaboration with the juvenile arthritis patient association (Jeugdremavereniging) and the Dutch Society for Pediatric Rheumatology (NVKR). The first important steps in this methodology have been taken and we have already collected more than 600 questions via an online platform, of which the vast majority was came from patients.



Next steps will be to combine, check and prioritize these questions in organized meetings with the priority setting partnership. This agenda, aimed to be completed first quarter of 2020, will result in better research with more impact, not only nationally, but also internationally.

Important scientific publications

Identification of FAM173B as a protein methyltransferase promoting chronic pain.

Willemsen HLD, Kavelaars A, Prado J, Maas M, Versteeg S, Nellissen LJJ, Tromp J, Gonzalez Cano R, Zhou W, Jakobsson ME, Maleski J, Posthuma G, Habib AM, Heijnen CJ, Falnes PØ, **Eijkelkamp N**. *PLoS Biol.* 2018 Feb 14;16(2):e2003452.

Pain is an evolutionarily conserved physiological phenomenon necessary for survival, yet it can become pathological when it becomes independent of e.g. inflammation. The molecular mechanisms are poorly understood, limiting the development of highly needed novel analgesics. This manuscript is important because genetic variations in the genomic region encoding FAM173B have been linked to chronic pain in humans. In this study, we identify the role and function of the hitherto unknown FAM173B in the development of pathological inflammatory pain. Therefore, this manuscript provides an important conceptual framework to explain why persistent inflammatory pain can develop in humans and it opens the possibility for new ways to treat chronic pain.

PD-1+CD8+ T cells are clonally expanding effectors in human chronic inflammation.

Petrelli A, Mijnheer G, Hoytema van Konijnenburg DP, van der Wal MM, Giovannone B, Mocholi E, Vazirpanah N, Broen JC, Hijnen D, Oldenburg B, Coffey PJ, **Vastert SJ, Prakken BJ, Spierings E, Pandit A, Mokry M, van Wijk F**.

J Clin Invest. 2018 Oct 1;128(10):4669-4681.

By demonstrating that in chronic autoimmune inflammation PD1 expressing cells are clonally expanding effector and not exhausted cells we introduce a novel view on PD1 expression and T-cell exhaustion. The probable pathogenic role of these CD8 effector cells makes them interesting potential targets in chronic inflammation. Furthermore, our data imply that in a cancer setting, anti-PD1 therapy may not only rescue exhausted CD8 T cells but may further unleash very effective effectors leading to both tumour and tissue destruction. Our paper was highlighted in: Bernard NJ. Some PD-1+ CD8+ T-cells are not exhausted. *Nat Rev Rheumatology* 2018 Sep 26.

Nemo-like Kinase Drives Foxp3 Stability and Is Critical for Maintenance of Immune Tolerance by Regulatory T Cells.

Fleskens V, Minutti CM, Wu X, Wei P, Pals CEGM, McCrae J, Hemmers S, Groenewold V, Vos HJ, Rudensky A, Pan F, Li H, Zaiss DM, Coffey PJ. *Cell Rep.* 2019 Mar 26;26(13):3600-3612.e6

Immunosuppressive regulatory T (Treg) cells are critical for maintaining tolerance and preventing autoimmunity and have been shown to be usurped by tumors to prevent immune clearance. The transcription factor FOXP3 is the master regulator of both Treg cell development and function. We have made a series of novel observations that demonstrate that FOXP3 function can be critically controlled by post-translational modification. The current 'translatable' study demonstrates that pharmacologically or genetically modulating Foxp3 phosphorylation can either activate or inhibit Treg cell function, providing novel therapeutic strategies for autoimmunity and cancer respectively.

Inhibition of Super-Enhancer Activity in Autoinflammatory Site-Derived T Cells Reduces Disease-Associated Gene Expression.

Peeters JG, Vervoort SJ, Tan SC, Mijnheer G, **de Roock S, Vastert SJ, Nieuwenhuis EE, van Wijk F, Prakken BJ, Creighton MP, Coffey PJ, Mokry M, van Loosdregt J**. *Cell Rep.* 2015 Sep 29;12(12):1986-96.

This is the first study that demonstrates that the (super)enhancer landscape is altered in primary immune cells of patients with an autoimmune disease. It also shows that inhibition of (super-)enhancer activity preferentially reduces the expression of "disease-specific" genes. This study provides a better understanding of disease pathogenesis, and proposes a novel therapeutic strategy for the treatment of autoimmune diseases. We are currently following-up on this study by assessing other cell-types and exploring the therapeutic potential of enhancer-activity modulation.

Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more than 15,000 patients from Pharmachild and national registries.

Swart J, Giancane G, Horneff G, Magnusson B, Hofer M, Alexeeva E, Panaviene V, Bader-Meunier B, Anton J, Nielsen S, De Benedetti F, Kamphuis S, Staņevića V, Tracahana M, Ailioaie LM, Tsitsami E, Klein A, Minden K, Foeldvari I, Haas JP, Klotsche J, Horne AC, Consolaro A, Bovis F, Bagnasco F, Pistorio A, Martini A, Wulffraat N, Ruperto N. *Arthritis Res Ther.* 2018 Dec 27;20(1):285.

This paper describes the first results of Pharmachild, an European Pharmacovigilance register on side effects and treatment responses on synthetic and biological drugs, used in JIA for maintenance therapy. Pharmachild was set up as an FP4 European grant funded project in 2011 by prof. N. Wulffraat and dr. J. Swart, in collaboration with the Pediatric Rheumatology European Trial Organisation (PRINTO).



This register serves as a critical and valuable tool for collaborative research on the effect and potential side effects of treatments in pediatric rheumatology worldwide.

Treat-to-target using first-line recombinant interleukin-1 receptor antagonist monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five year follow-up study.

Ter Haar NM, van Dijkhuizen EHP, Swart JF, van Royen-Kerkhof A, El Idrissi A, Leek AP, de Jager W, de Groot MCH, Haitjema S, Holzinger D, Foell D, van Loosdregt J, Wulffraat NM, de Roock S, Vastert SJ.

Arthritis Rheumatol. 2019 Mar 8.

This study describes the 5 year results from our prospectively followed cohort in systemic JIA, using rIL-1RA (an IL-1 blocking biological) as 1st line treatment in these patients. This treat to target study, aiming for clinical inactive disease within 3 months, presents really a paradigm shift in the treatment of sJIA patients in multiple ways. First, by using rIL-1RA as 1st line treatment, we show that corticosteroids can be effectively avoided as treatment in ~70% of patients while in the remainder, its use is necessary in significantly shorter time and in lower doses, minimizing its (long term) side effects. Secondly, we aimed for tapering and stop of rIL-1RA therapy when patients achieved clinical inactive disease at time point T =3 months. By doing so, we were able to stop maintenance therapy in > 50% of children within the 1st year of disease, while inactive disease states were maintained throughout the follow-up of the study. Finally, we described for the first time a cohort of sJIA patients (n=12) without overt arthritis at time of diagnosis, comparing them to sJIA patients with over arthritis (fulfilling the clinical ILAR criteria), effectively showing that based upon clinical features, laboratory characteristics and response to biological therapy, these cohorts did not differ. As such, we provide scientific data for the concept that arthritis is not a required criterium for the diagnosis of sJIA, which now increasingly is being recognized in the field.

An important societal contribution

In 2017, our department was granted funding (5,4 million €) by ZonMW, CIHR (their Canadian equivalent) and the Dutch Arthritis Foundation for UCAN CAN DU, a Dutch-Canadian collaborative grant that links all 6 Dutch and all 18 Canadian academic pediatric rheumatology departments in a translational research project. Our department is the Dutch principal research center and Prof. Wulffraat is the Dutch PI (with prof. R. Yeung from Toronto as Canadian PI and Toronto as Canadian research center). In this project also dr. J. Swart (as clinical research PI) and dr. B. Vastert (as assigned young researcher, responsible for the translational research setting together with dr. S. de Roock are involved with critical responsibilities in the overall . execution and management of this major collaborative research project (108 researchers involved). UCAN CAN DU aims to develop a biologically based/informed classification of JIA, and to predict response to both start of biological therapy in JIA as well as successful taper and stop of therapy in JIA patients. Over the project duration (2017-2022), we will develop the necessary (research) infrastructure in order to be able to transform the current step-up treatment strategies in JIA into stratified/personalised treatments. This encompasses novel IT solutions, cutting edge translational science and development of eHealth tools in compliance with European Union (GDPR) and Canadian Regulations. Upon request of involved patient partners, we are feeding back real time derived research and clinical data to the patients, in accordance with ethical committee approval, and accompanied by clear explanations on the clinical meaning of these data to the treating physician and the patients.

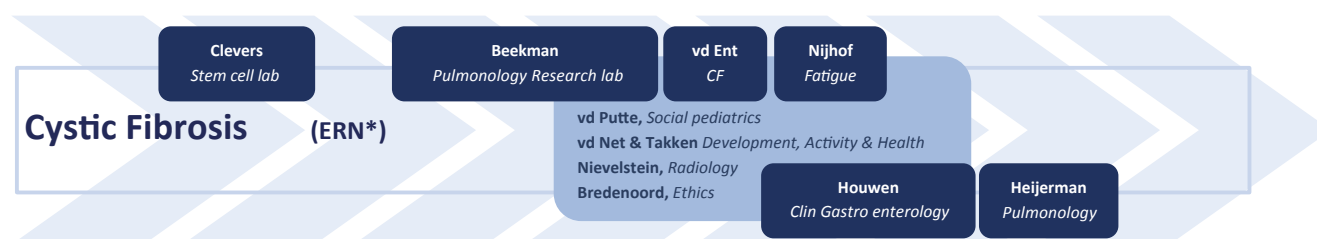
For more detailed information on process and output indicators see Appendix E.



Cystic Fibrosis

Description of the organisation, strategy & mission

About one third of all Dutch patients with CF are treated by the UMC Utrecht. The UMC Utrecht is a key partner of the Dutch Cystic Fibrosis Foundation, chairs the CF-core network of the European Reference Network for rare lung diseases (ERN-LUNG) and coordinates a large H2020 initiative to realize CFTR-modulating therapies for patients with orphan mutations that might benefit from existing drug development efforts on other mutations in 15 countries of the EU. The research group of the CF-Center Utrecht developed stem cell based assay technology to model human pulmonary disease, which raised huge international interest to predict and understand the individual impact of new CFTR modulating drugs.



Lifecycle

About one third of all patients with Cystic Fibrosis (CF) in the Netherlands is treated in the University Medical Center Utrecht. Both care and research are typically organized according to a life cycle perspective. All diagnostic and treatment modalities are offered to our patients, starting with early diagnosis in the neonatal heel prick screening program to continuous positive airway pressure ventilation and a lung transplant program for those with end stage disease. The clinical teams of the pediatric department (headed by Prof C.K. van der Ent) and the adult department (headed by Prof H.G.M Heijerman) started a combined life cycle outpatient department in 2018. In this approach not age is the major determinant of care-giving, but care is provided by the physician most familiar with the specific problems of the patient. The pediatric and adult teams share a long-term follow-up database in which early determinants can be connected to late outcomes of disease. Both teams also share one clinical research team which is responsible for all clinical trials in both children and adults.

Interdisciplinary

Within the multidisciplinary clinical research team the pulmonologists collaborate with researchers covering respiratory tract infections (Prof L.J. Bont), liver disease (Prof R. Houwen) and imaging (Dr R. Nievelein). During last decade the clinical research mainly focused the diagnosis and treatment of (Pseudomonas-related) respiratory tract infections. Since 2012 revolutionary breakthroughs with regard to possibilities to modify the CFTR protein became available. Dr Beekman, heading the pediatric pulmonology research lab –in collaboration with the Hubrecht Lab- developed an intestinal stemcell based model to measure CFTR function in individual patients. This model has enormously boosted personalized medicine in the international field of CF, and was successfully applied in the clinic within four years after the initial development. Since then, the CF-Center Utrecht has a leading role in organoid-based research within the Clinical Trial Network of the European Cystic Fibrosis Society and the CF-core network of the European Reference Network for lung diseases (ERN-LUNG).

Physical & mental development

CF is a highly multifaceted multi-organ disease, not only affecting physical, but also developmental aspects of life. Physical exercise is an important cornerstone of CF-treatment and in Utrecht the exercise physiology department (headed by Dr J.J. van der Net and Dr T. Takken) is highly involved in CF-research. Many patients suffer from severe fatigue, which is an area of research for both clinicians within the team, exercise physiologists in close collaboration with specialized social pediatricians (Prof E. van der Putte and Dr S Nijhof). The research field of physical and mental development in CF is an important part of the Healthy Play, Better Coping program, which cross-links the physical aspects in pediatrics with societal aspects in the Strategic research program Dynamics of Youth of the Utrecht University. The entrepreneur role of the Utrecht CF-team in the development and application of intestinal organoid-guided therapies also asks for many ethical considerations. Using both qualitative and quantitative approaches Prof A.L. Bredenoord pioneers the ethical topics in CF-research, particularly in the creation, storage and use of organoids.



Patient participation

Being a life-long disease, CF has major impact on the lives of patients and their families. Many of the investigator initiated CF-studies in our unit have their own patient advisory board, which enables them to give feedback on study-design and results. In the Netherlands the Dutch Cystic Fibrosis Foundation (NCFS) plays a leading role in prioritizing patient-oriented research topics, study protocol review and funding. In 2016 a formal Memory of Understanding between the NCFS and UMC Utrecht was signed, confirming a preferred partnership between both parties to stimulate patient-oriented research and mutual relationships.

Together with the NCFS the CF-Center Utrecht is elaborating an innovative Patients oriented Outcome Measure (PROM), based on a 360 degrees approach. Being the coordinator of a large European Project (HIT-CF Europe) the department closely collaborates with CF-Europe, as the umbrella organisation of national organisations of patients with CF.

Goals next 3 to 6 years

- Develop a path for drug access for people with rare, orphan CFTR mutations using patient-derived stem cell cultures
- Develop proof-of-concept for treatments of people with CF who do not have access to CFTR modulating therapies
- Develop and expand a biobank of patient tissues and patient data for use in research and individualized care
- Develop individualized diagnostics and proof-of-concept treatments using individual stem cell cultures for CF-like diseases.
- Expand an dedicated Ethics Program for innovative CF/organoid research

An ongoing or finished research project where patients are meaningfully involved

H2020 HIT-CF project:

This project aims to generate access to therapies for people with CF who carry ultrarare mutations. These people do not currently benefit from new drugs on the market or from drugs in development due to economic realities of drug development for ultrarare conditions. Patient-derived intestinal organoids will be used to stratify patients for one of three drug products that are currently in development for common mutations. The project aims to select positive drug responders from 500 patients across Europe and validate drug efficacy in clinical trials. Continuous interactions with regulators and payers aim to implement the organoid test into clinical practice in the context of drug selection for patients with rare mutations, whereas a European governance structure will be developed for the ethical usage of data and patient-materials.

Important scientific publications, including an explanation of why the publications are important

Stratifying infants with cystic fibrosis for disease severity using intestinal organoid swelling as a biomarker of CFTR function.

de Winter-de Groot KM, Janssens HM, ..., van der Ent CK, Beekman JM.

Eur Respir J. 2018 Sep 17;52(3). 4 citations (web of science)

First proof-of-concept that intestinal organoids can be used to stratify patients for disease severity, as exemplified for infants with CF. Suggests that organoids may finetune categorizing patients on CFTR function and anticipated disease severity, and suggests added clinical value for patients with unclear diagnosis.

Characterizing responses to CFTR-modulating drugs using rectal organoids derived from subjects with cystic fibrosis.

JF Dekkers, G Berkers, ..., CK van der Ent and JM Beekman.

Sci Transl Med 2016, Jun 22;8(344):344ra84. 120 citations (web of science)

First demonstration that organoid data associates with clinical efficacy of treatment and first examples that in vitro drug response by organoids can successfully select patients for treatment.

A functional CFTR assay using primary cystic fibrosis intestinal organoids J.F. Dekkers, C.L. Wiegerinck, H.R. de Jonge,

I. Bronsveld, H.M. Janssens, **K.M de Winter- de Groot**, A.M. Brandsma, N.W.M. de Jong, M.J.C. Bijvelds, B.J. Scholte,

E.E.S Nieuwenhuis, S. van den Brink, H. Clevers, **C.K. van der Ent**, **S. Middendorp**, **J.M. Beekman**. *Nature Medicine* 2013

Jul;19(7):939-45. 319 citations (web of science)

This paper describes the first functional assay in intestinal organoids, a CFTR dependent swelling assay, with suggested impact for scientific studies, drug development and personalized medicine of CF.

Functional Repair of CFTR by CRISPR/Cas9 in Intestinal Stem Cell Organoids of Cystic Fibrosis Patients.

Schwank G, Koo BK, ..., Beekman JM, Clevers H.

Cell Stem Cell. 2013 Dec 5;13(6):653-8. 512 citations (web of science)

First time that genetic disease in human stem cells was gene corrected by Crispr-Cas9. It demonstrates the value of collaborating across fields.



Mechanism-based corrector combination synergistically restores $\Delta F508$ -CFTR folding and function in cystic fibrosis Tsukasa Okiyonedo, Guido Veit, ..., **Jeffrey M. Beekman**, Gergely L. Lukacs.
Nat Chem Biol. 2013 Jul;9(7):444-54. 199 citations (web of science)

This paper suggested that highly effective CFTR modulator therapy could be developed by synergizing compound combinations, as became a reality in the current triple combination therapies that are highly effective in clinical trials.

Important societal contribution

The research unit aims to provide optimal, individual care by developing new diagnostic and therapeutic approaches for unmet medical needs in CF. In 2010, the CF center added a PI on basic research to its team, with a mission to develop tools that improve individual typing of disease so that individual clinical decision making could be better supported in the context of progressive disease. The UMC Utrecht team developed an innovative assay that measures individual CFTR function in patient-derived stem cell cultures; IP was also obtained and access to the technology in a commercial setting was licensed to foundation HUB.

The impact of this assay derives from its complementary value to the largest transformation in CF care and drug development since the description of the gene 30 years ago. Since 2012, CF can be treated by therapeutics (CFTR modulators) that repair the basis of disease. These drugs were initially available for only a handful of patients (~5%) with known 'gating' mutations. Who else could benefit, how do these drugs work, can more effective drugs be made and can we improve the selection of preclinical drugs in development, what is a reasonable pricing for such drugs, how do patients experience such new technologies? In all these field, the UMC Utrecht CF center played a leading role in the regional, national and international space.

Who else could benefit has been our most clear societal contribution to date. By using patient-derived organoids, we created the first example that personalized medicine was actually achievable based on drug efficacy screening in living cells. Currently approximately 12 people in the Netherlands with rare mutations have got access to treatment based on the preclinical organoid test, and we are validating this test at the EU level so that we can integrate it in care systems. With payers, we are also validating whether we can identify non-responders to improve cost-efficacy of treatment. Our work illustrates that future care systems may include living, patient-annotated biorepositories that can be used to match patients to drugs without additional clinical tests and discomfort.

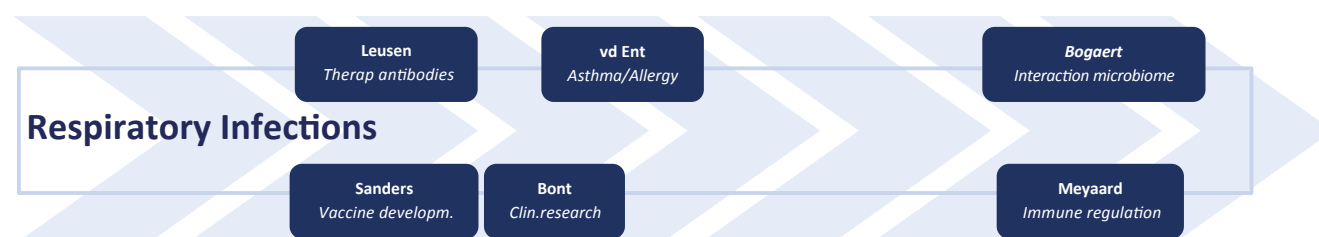
Apart from a direct effect on patients, we should also acknowledge the broader importance of this first example of personalized medicine using adult stem cells. In 2012, personalized medicine applications for CF based on organoids were being valued as very unlikely to have impact by 2 out of 3 reviewers of a grant. In 2018, it is normal to think of organoids as tool for personalized medicine. We think that our work has significantly contributed to this shift in paradigm, which will help to push the way forward for personalized medicine applications in many other diseases as well.

For more detailed information on process and output indicators see Appendix F.

Recurrent Respiratory Infections

Description of the organisation, strategy & mission

Pneumonia accounts for 16% of all deaths of children under 5 years old (Pneumonia fact sheet, World Health Organisation 2016). Pneumonia can be caused by viruses, bacteria or fungi. Respiratory syncytial virus (RSV) is major causes of childhood mortality and morbidity. RSV infection is the second most frequent cause of death during infancy following malaria. Next to RSV, bacterial infections with *S. pneumoniae* still cause up to 380.000 childhood deaths as in 2015. Most children with RSV bronchiolitis were previously healthy until infected (Mazur, Lancet Infect Dis 2018). Virtually all children dying from RSV infection live in developing countries. RSV-related morbidity is substantial in all parts of the world. Although all children are infected with RSV during the first two years of life, about 1% of all children in the world will be hospitalized for RSV infection in the first year of life.





Lifecycle

RSV infection is an important cause of severe RI at both ends of the age spectrum. RSV infection is associated with long-term airway disease. About half of the children with a history of RSV infection will have asthma-like symptoms. There is evidence that infant RSV infection increases the risk of chronic obstructive pulmonary disease (COPD) (Vorap-hani, AJRCCM 2014; Martinez, N Engl J Med 2016). RSV infection is also more severe in older adults, in particular those with severe other diseases (Falsey, N Engl J Med 2005). In those people, the burden is similar to what is seen with influenza infection. The RSV Research Group has performed epidemiological RSV incidence studies in adults together with collaborators at the department of Internal Medicine and the General Practice department. Alongside RSV, the group has a long term research track record on bacterial RTI, in particular *S. pneumoniae* and prevention by vaccination. Furthermore, our respiratory microbiome research has shown that the bacterial profile, with *S. pneumoniae* and non-typable *Haemophilus influenzae* presence, predisposes to a more severe course of clinical RSV infection.

Interdisciplinary

An interdisciplinary approach is needed to understand and treat children infected with RSV infection. In the Utrecht RSV Research Group various disciplines are positioned around the patient and their parents. There is an active RSV patient advisory board with two professional employees (Nicole Derksen and Inge Oliemans). Various medical specialists are involved in these teams, including obstetricians, neonatologists, pulmonologists, intensive care specialists, radiologists and infectious diseases specialists. Nurses play a major role in treating children with RSV infection as they are most often at the bedside and are closest to the parents. Research nurses have always been the corner stone of our clinical research. Basic scientists with different background are involved in our research. There is a strong connection to basic immunology with embedding in the laboratory of translational immunology (LRT, prof Linde Meyaard). We try to understand whether children get sick directly from airway damage cause by the virus or the immune response to infection (“fire vs fire controle damage”). We develop novel therapeutic antibodies against RSV infection (dr. Jeanette Leusen, I&I, UMC Utrecht). We validated a blood diagnostic to distinguish viral from bacterial RI (Van Houten, Lancet Infect Dis, 2017). Other translational research focuses on the airway microbiome (prof Debby Bogaert and Prof Elisabeth Sanders, Child Health, UMC Utrecht) and host genetics (prof Gerard Koppelman, UMCG) within clinical trials and in relation to clinical respiratory disease. We study the global molecular epidemiology of RSV in detail hoping to understand how the virus infects baby’s and tries to escape the immune system, but also to understand how a treatment or vaccine may be developed (dr Robert Jan Lebbink, I&I, UMC Utrecht). Epidemiologists and more basic modeling specialist play a key role in all parts of the research work. The research group has a strong interest in Global Child Health with relevant collaborations with the World Health Organisation (WHO), the Bill and Melinda Gates Foundation (BMGF), the European Center of Disease Control (ECDC), the National Institute of Health (NIH) of the United States and various pharmaceutical companies. Debby Bogaert has research activity at global health research units in Asia (NIHR global health research unit RESPIRE, led by University of Edinburgh) and Africa (NIHR global health research unit MPRU, led by UCL) and collaborates within the Wellcome Trust funded MARVELS project (Malawi pneumococcal challenge model).

Physical & mental development

Children with a history of RSV infection appear to develop normal although recurrent episodes of wheeze is associated with decreased health of life in specific domains. Mental development is normal. Families of RSV patients may be negatively affected by the unexpected severe disease of their child which is only a few weeks old. We found evidence that this is a major stressor for their families. Together with the RSV patient advisory board we try to develop systems to inform and support these families.

Patient participation

There is strong involvement of patients in the RSV Research Group. Nicole Derksen is employed by the UMC Utrecht as the chairperson of the Dutch Patient Advisory Board (PAB) and the EU PAB for RSV infection. She is supported by Inge Oliemans, who was recently appointed by UMC Utrecht as a communication expert of the PAB. The RSV PAB is involved in all parts of the research, including prioritizing research questions, drafting grant applications, writing patient information and communicating with various stakeholders. An international RSV PAB has been set up by Nicole Derksen and is currently functioning.

Goals next 3 to 6 years

We aim to continue our translational research with impact for patient and society. We will intensify our UMC Utrecht collaborations with research theme I&I, both with the Laboratory of Translational Immunology (LTI) and the Microbiology Department. We aim to leverage our broad networks and collaborations. We aim to further invest in and expand our global health activities by expanding research in poor resource settings.



We will optimize our external communication to society by employing communication experts and patient representatives.

An ongoing or finished research project where patients are meaningfully involved

RESCEU - The IMI-funded RESCEU consortium aims to investigate the burden of disease of RSV. Four prospective clinical cohort studies are currently being performed in healthy term born infants (10,000), RSV infected children (550), healthy older adults (1000) and adult patients with COPD (500). These large cohort studies aim to provide a better understanding of the incidence of RSV in these populations but also aim to perform biomarker research to see which patients are more vulnerable of getting infected with RSV or who becomes more severely ill. In RESCEU, we had the opportunity to expand our existent Dutch patient advisory board to a professional EU PAB for RSV bronchiolitis. Nicole Derksen, was hired to be the first employed chairperson of the RSV PAB. Following its initial success, the consortium decided to use the contingency budget of the consortium to further expand the PAB activities after which a communication expert was hired by Mrs. Derksen.

Important scientific publications

Louis Bont (RSV research): *Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial.* Scheltema et al. *Lancet Respir Med.* 2018.

This RCT is done to determine how RSV infection is causally related to asthma development. It shows in detail that there are consequences of early RSV infection on mild asthmatic symptoms, but not on severe asthma or lung function at age 6. These results received attention by RSV vaccine developers, FDA/EMA, the WHO and the Gates foundation because they inform the potential added value of upcoming RSV vaccines.

Lieke Sanders (vaccine research): *1: Barug et al. Maternal pertussis vaccination and its effect on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomized controlled trial.* *Lancet Infect Dis.* 2019.

This randomized trial showed that timely maternal Tdap immunisation- maternal antibodies dampen the response to the primary series of pertussis vaccinations even when the first dose is delayed until 3 months of age. This research has directly contributed to the advice of the National Health Council to change the primary series of vaccinations in the National Immunisation Programme for all term born infants from a 3+1 schedule at age 2, 3, 4 and 11 months to reduced 2+1 schedule at ages 3, 5 and 11 months in case of timely maternal Tdap vaccination.

Debby Bogaert (microbiome research): *Bacterial and viral respiratory tract microbiota and host characteristics in children with lower respiratory tract infections: a matched case-control study.* Man WH et al. *Lancet Respir Med.* 2019

We studied in over 150 children under the age of six hospitalized with LRTI, and 300 healthy children, whether information on the microbial composition of the respiratory tract helped to understand pathogenesis of these infections. We found that the microbiome in the back of the nose and throat was related to that seen in the lungs, making it easier to understand and diagnose infections. These findings could impact on a decision of whether or not to use antibiotics more accurately than based on symptoms and current diagnostics.

Lilly Verhagen (mucosal immunology research): *LM Verhagen et al. Introduction of the 13-valent pneumococcal conjugate vaccine in an isolated pneumococcal vaccine-naïve indigenous population.* *Eur Respir J* 2016

This study was the first to evaluate the impact of both infant and catch up pneumococcal conjugate vaccination in vaccine-naïve children at high risk for pneumococcal disease. As a consequence, the vaccine was implemented free of charge in the national immunisation program for vulnerable native Amerindian populations in Venezuela. In this work and a related study (Verhagen et al. *Vaccine* 2016) we showed that antibody levels could be reliably measured in mucosal samples (saliva), which paved the way for follow-up studies focusing on the role of salivary antibodies in respiratory tract infection transmission and disease.

Important societal contribution

The Respiratory Infections theme is formed by investigators with complementary expertise, including 3 full professors. Within UMC Utrecht, the investigators are not only active in the Child Health theme, but also in the I&I theme. In addition, they are deeply embedded in other organisations allowing their research results to find their way to users. The ability to perform research of respiratory microbiome at the highest scientific level is a critical asset of the research theme. The work by Prof Debby Bogaert is highly respected by her (inter)national peers and she has lined up all tools (sampling, storage, DNA isolation, metagenomics sequencing, bioinformatics) to move the field further. Her work is published in highly ranked journals and is well cited.



The RI theme aims to have public and global health impact, while working with industry at the same time. We are active in IMI-funded projects on pertussis (PERISCOPE, Sanders) and RSV infection (RESCEU, Bont, Sanders) showing a unique interaction between the three parties (academia, public health and industry) which is rarely paralleled in other EU countries. RI investigators actively collaborate with the public health institute of the Netherlands (RIVM), where prof Elisabeth Sanders is Chief Science Officer Host Response.. Investigators (Bont, Sanders) are regular advisors of the World Health Organisation and the European Center of Disease Control to advise on surveillance programs, vaccine development and harmonisation of assays. The RI have the aim to advance the development of preventive and treatment interventions, including vaccines.

Louis Bont continuously works public health and global health institutes (WHO, BMGF, ECDC, CDC). He works with Pfizer, Novavax, Janssen, AstraZeneca and Sanofi on RSV vaccine development as external advisor, but also leading part of the research programs, such as the AstraZeneca-funded INFORM study on the molecular epidemiology of RSV infection looking for escape mutants of the novel antibody nirsevimab. Interaction with industry is further strengthened by his role in U-TRIAL, collaboration with Julius Clinical and the ReSViNET Foundation. Together with Nutricia Danone at campus the PRIMA study is another example of public-private partnership in which beneficial breast milk factors are identified eventually aiming to improve formula feeding. Research is done in collaboration with an independent patient advisory board (PAB) with 2 professional employees which have set an example to other researchers. Finally, investigators have used ethical principles in their work. They have used publication (Mazur, Lancet Infect Dis 2015 & Mazur Lancet Respir Med 2019) to provide an ethical guide for maternal vaccine development. Narsyn trial aims to develop a preventive intervention for RSV infection that will be affordable for developing countries. Louis Bont is the chairman of the UMC Utrecht IRB.

Elisabeth Sanders has served in various capacities as a member of the national Health Council, in particular with respect to the introduction of new vaccines in the national vaccination program. She has been board member of the National Pediatric Society on immunology and infectious diseases (NVK), the National Interuniversity Working Group of Immunodeficiency Disease and the Dutch Society of Immunology NVVI . She is member of the WHO SAGE working group on pneumococcal conjugate vaccinations and participates in various expert panels on pneumococcal conjugate vaccinations. She has been chair of the scientific panel of 'Het TerMeulenfonds' of the Netherlands Organisation for Scientific Research for children (NWO) and member of the scientific advisory board of the Royal Netherlands Academy of Arts and Sciences. The research by professor Sanders has led to changes in international guidelines for prevention of recurrent otitis media by pneumococcal vaccines. Based on her work, pneumococcal conjugate vaccine is no longer advised in (inter)national guidelines for older children who already had had previous otitis episodes. Her research on vaccination schedules has directly led to changes in the national vaccination programme of the Netherlands with reduced-dose schedules and longer intervals between doses.

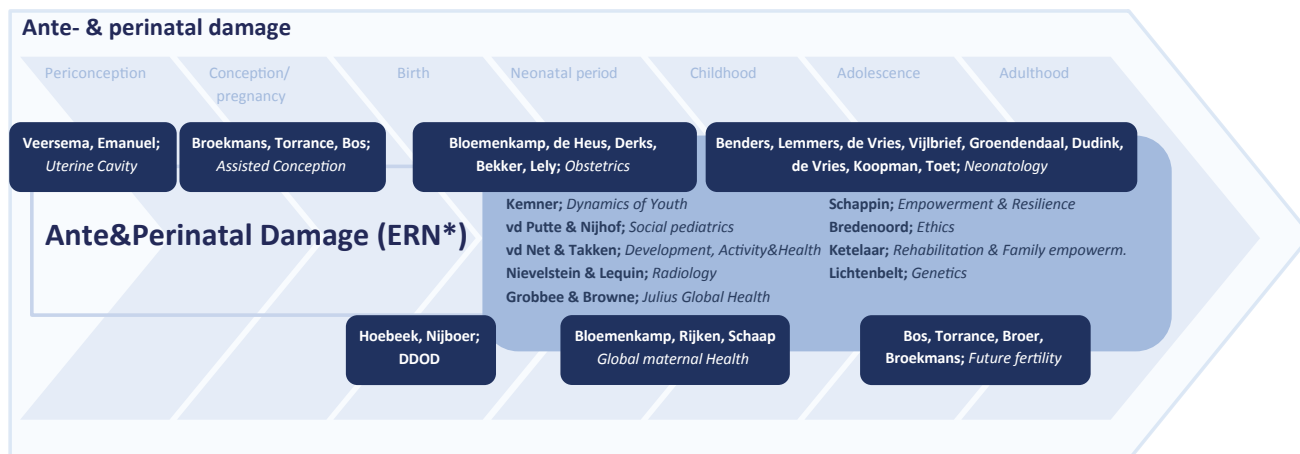
Debby Bogaert has worked within public-private partnerships with Danone and TNO and Friesland Campina (TKI) on understanding how infant nutrition can affect infant health through affecting the natural flora of gut, respiratory tract and skin. Bogaert has advocated publicly for rapid translation of new technology into diagnostics through publications, blogs and information provided for policy makers. Her group shares actively their scientific output (presentations at conferences, publications, news releases and interviews) through social media (Twitter and LinkedIn).

For more detailed information on process and output indicators see Appendix G.



2.3 Ante and perinatal damage

The research line ante- & perinatal damage has a life-cycle character hosting several Centers of Excellence. It provides high quality care in connection with research through the periconceptional, antenatal and perinatal phases up to neonatal intensive care, aiming for the best long-term outcome of child health (treating disease, preventing damage). Women, babies and their families are the center of our service. We strive for excellence and innovation.



Pre- and periconception

Organisation, strategy & mission

The research line pre-and periconception has a life-cycle character providing high quality care in connection with clinical and translational research to patients with fertility problems, patients with hereditary diseases to prevent disease transmission, as well as young and old patients undergoing gonadotoxic treatments.

The “reproductive origin of health and disease” hypothesis stresses the significance of the pre-and peri-conceptional events for the future health of the child. Our efforts are aimed at increasing knowledge, thereby aiming to develop new preventative and therapeutic interventions that ultimately will decrease or eliminate the burden of disease for the future parents and future children.

The Center for Reproductive Medicine and Gynecology has both care and research aimed at optimizing the chance of a healthy conception and thereby the chance of a healthy child. Our clinical research into assisted conception interventions and gynecological surgery of the uterus treating congenital and acquired abnormalities in general and Asherman Syndrome in particular, as well as our fundamental and translational research on endometrium, intrauterine growth restriction and genetic trait transmission (preimplantation genetic diagnosis (PGD)) are all driven by patient care and conducted by our internationally leading experts. Thereby our work focusses on the Human Lifecycle, which fits well within the Child Health strategic theme, as many formerly lethal childhood diseases (e.g. extreme preterm birth) are now considered severe early life events with high-risk of developmental or chronic consequences. When children with a chronic disease reach adulthood, they may be confronted with reduced fertility for which assisted reproduction counseling and preservation strategies can be offered. Many will also have questions on whether their disease may be passed on to their future offspring. For these individuals, PGD can be offered to prevent transmission of their genetic trait to the next generation.





Lifecycle

Both Reproductive Medicine research and care have a unique lifecycle perspective starting preconceptionally with pre-implantation genetic diagnosis (PGD) and fertility interventions, to the birth of a healthy child. Furthermore, for the long-term effect of childhood disease on later fertility, our department provides care and performs research aimed at fertility counselling and fertility preservation. Ovarian tissue cryopreservation (OTC) in girls with cancer is covered in the PAREL study ('Preserving ovARian function through cryoprEservation and informing giRLs with cancer on infertility due to gonadotoxic treatment'). The counseling and preservation options after cancer treatment are integrated in well-organized follow-up consultations for late effects of childhood cancer survivors in the late-effects outpatient department (LATER-poli) in the Princess Maxima Center/UMC Utrecht (Gynecologists dr. A.M.E. Bos, dr. S. L. Broer and Paediatric Oncologist prof. dr. M.M. van den Heuvel-Eibrink) and will be implemented in the WKZ/UMC Utrecht in 2019 (dr. H. Torrance, prof. dr. F. Broekmans, dr. M. Bartels) for girls with benign hematological disorders or cystic fibrosis (prof. dr. K. van der Ent).. These teams will share a long-term follow-up database in which early determinants can be connected to late fertility outcome.

Interdisciplinary

The Reproductive Medicine research team collaborates with UMC Utrecht researchers from the fields of Obstetrics (dr. T. Lely, dr. M.N. Bekker, prof. dr. Bloemenkamp), Benign Hematological Disorders (dr. M. Bartels), Childhood Oncology (prof. dr. M.M van den Heuvel-Eibrink), Clinical Genetics (dr. M. Ausems, dr. K. Lichtenbelt), Microbiology (prof van de Wijgert) and Pathology (prof. Goldschmeding and dr. Nikkels). For early determinants of late fertility outcomes in girls with several other childhood diseases, collaboration is being established with dr. H. van Santen/dr. H van der Kamp (Endocrinology) and prof. dr. K. van der Ent (Cystic Fibrosis).

Nationally, the RM team is one of the strongest partners in the NVOG consortium 2.0 (the research consortium of the Dutch Society for Obstetrics and Gynecology), 'PGD Nederland' (the Dutch consortium for PGD) and the OMEGA collaboration. The Reproductive Medicine part of the NVOG consortium 2.0 is a highly effective research network including all Dutch fertility clinics, making it very powerful to perform high quality, relevant studies within restricted time periods. In 'PGD Nederland' the researchers perform long-term follow-up of pregnancies and children born after PGD. Research into potential long-term health effects of IVF/ICSI on children, adolescents and young adults born conceived via these techniques is performed in the large OMEGA cohort. Internationally, the researchers have leading roles in the European Society for Human Reproduction and Embryology (ESHRE), the ESHRE PGD consortium, the Cochrane Society and COMMIT. In the field of onco-fertility, collaboration has been set up with the Prinses Maxima Center for care as well as research by starting a Fertility Working Group. Nationally, the re-imburement of (still) experimental fertility preservation options as ovarian tissue cryopreservation (OTC) is not covered by the insurance companies. In collaboration with all the Dutch Fertility Centers and the Prinses Maxima Center a joint trajectory of application for conditional admission to the 2020 basic package has been started in May 2018 (ZonMW submission for a national prospective follow up cohort study of women undergoing ovarian tissue cryopreservation (OTC) followed by auto-transplantation or without auto transplantation of the cryopreserved ovarian tissue).

Patient Participation

The RM research team has regular consultations with Freya, the Dutch society for people facing infertility, which stimulates patient-oriented research and mutual relationships. Since 2017 we are part of COMMIT (a Cochrane initiative) which aims to develop a core outcome measure set for assisted conception research. In this process we closely collaborate with Freya and Fertility Europe, the European umbrella organisation representing patient associations in the field of (in)fertility in more than 20 European countries. In 2018 the "Setting Future Priorities for Infertility Research" was launched by the COMMIT group in which Freya, Fertility Europe and researchers from the UMC Utrecht are again partners. Patients are also actively involved in setting the national research agenda of the NVOG in conjunction with ZonMW, a process which has been led by Frank Broekmans as chair of the special interest group Assisted Reproduction. Couples with fertility problems are actively involved in setting up research agendas. In the field of onco-fertility, patients are actively involved in research initiatives, locally in collaboration with the Fertility working group in the Princess Maxima Center and nationally with the special interest group Fertility Preservation.

Our (inter) national strategic research program in numbers

Annual average: 1-2 PhD graduations, 2 Master and Bachelor students from various UMC Utrecht (bio-) medical curricula, €400,000 external funding ('2nd+3rd geldstroom'), 20 peer-reviewed research papers, 1 (inter-)national clinical protocols, hosting 1-2 international workshops/symposia/conferences. 15 times exposure in (social) media. In total we have 1.2 fte scientists on 1st'geldstroom' (and 12 clinical staff) and 1.6 fte scientists on project-based (2nd+3rd'geldstroom') contracts.



Goals next 3 to 6 years

- Future fertility:
 - Implement research into future fertility of girls and young females with chronic childhood disease (including benign hematologic disorders and cystic fibrosis) in longitudinal cohorts. Success can be measured in the longer term (>5 years) as we plan to perform longitudinal screening for ovarian reserve status and observed fertility. Success will consist of (publication of) high quality data showing whether these females are at increased risk of subfertility (by reporting on actual fertility), reduced ovarian reserve (by reporting on ovarian reserve status) and on the longer-term early menopause (which carries several health risks). Study points can be combined with preconceptional counselling (covering maternal risks, fetal risks and risk of transmission of disease to offspring) if young females develop an active wish to conceive during follow-up.
 - Continue and expand the collaboration with the princess Maxima center for Pediatric Oncology concerning fertility preservation in children with cancer and follow-up of ovarian reserve status in the girls. Next to the existing opportunities for fertility preservation in adults (semen, oocytes, embryo's) preservation of ovarian and testicular tissue are currently being implemented. Success can be measured by reporting the number of children in the cohort, describing the first data on ovarian reserve status, reporting on actual fertility and on actual use of preserved fertility cells and tissues.
- Implantation research:
 - Both clinical and translational (SCRaTCH trials, ENORM biobank). Aim is to unravel the role of the endometrium in infertility and pregnancy complications. Success can be measured by completion of the clinical studies within the timeframe and budget and (de-) implementation of study results in clinical practice.
 - Evaluation Placenta Implantation of Pregnant women with Asherman's disease in their medical history (EPIPA study). Aim is to estimate the percentage of abnormal placental implantation (ultrasound) in woman after uterine surgery for M. Asherman, obstetrical outcome and post-partum recurrence.
 - Recent clinical observations in the UMC Utrecht have led to the hypothesis that "Endometrial Arrest occurs in woman with M. Asherman due to presence of trophoblast and/or different microbiota in the uterine cavity. In collaboration with Medical Microbiology and Pathology new research projects will be started.
- Assisted Conception research, including participation in Reproductive Medicine research consortium trials that focus on improvement of IVF stimulation (OPTIMIST study), embryo culture (MEDIUM, selectimo studies) and embryo handling (Selectimo study) conditions, with potential effect on immediate (single embryo transfer) and long term (cardio-metabolic health) safety for the offspring. Aim: improvement of efficacy and safety for mother and child. Success can be measured by completion of the studies within the timeframe and budget and final (de-) implementation of study results in clinical practice

Important scientific publications

Kasius A, Smit JG, **Torrance HL, Eijkemans MJ**, Mol BW, Opmeer BC, **Broekmans FJ**.

Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. Hum Reprod Update. 2014 Jul-Aug;20(4):530-41.

The thickness of the endometrium is often seen as a proxy for endometrial receptivity. This review shows that endometrial thickness has a limited capacity to identify women who have a low chance to conceive after IVF. Endometrial tissue from women with thin endometrium is included in our epithelial organoid and stromal cell research line.

Hanstede MF, van der Meij E, Goedemans L, **Emanuel MH**.

Results of centralized Asherman surgery, 2003 – 2013. Fert & Steril 2015 Dec: 104(6): 1561-1568.

Because Asherman Syndrome is a rare disease and adhesiolysis is a difficult hysteroscopic procedure centralisation is important. Centralisation is not only essential because of the volume-outcome relation but also of improving support of women with AS, education, awareness and advocacy.

Heijligers M, Peeters A, **Broekmans F**, van der Hoeven M, Arens Y, de Die-Smulders C.

Growth, health, and motor development of 5-year-old children born after preimplantation genetic diagnosis. Fertil Steril. 2019 Jun;111(6):1151-1158.

Five-year-old children born after PGD show normal growth, health, and motor development when compared with children born after IVF/ICSI and NC children from families with a genetic disorder.



Smit JG, Kasius JC, **Eijkemans MJ**, Mol BW, **Broekmans FJ**, **Torrance HL**.

Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial. Lancet. 2016 Jun 25;387(10038):2622-9.

Before the inSIGHT, many physicians were offering hysteroscopy to asymptomatic women pre-IVF in order to increase pregnancy rates. The study showed that hysteroscopy does not increase the live birth rate in subsequent IVF treatment. The Lancet published these results with a strong message to specialists worldwide to stop offering hysteroscopy pre-IVF in asymptomatic women.

Important societal contribution

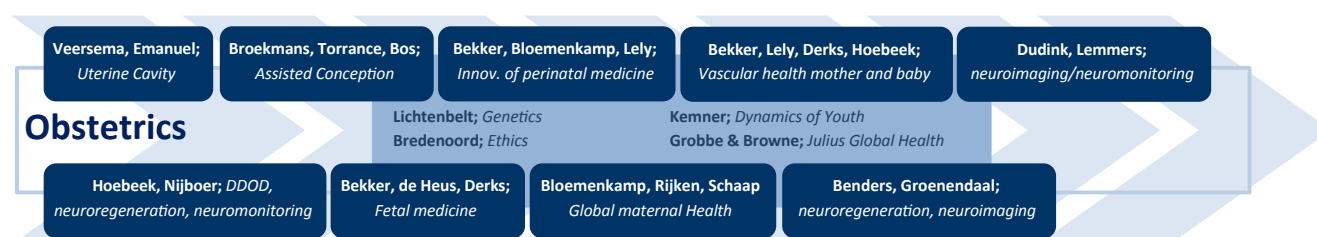
SCRaTCH-IVF study. In the assignment of endometrial scratching as tool for research into implantation processes, patient organisations such as the NPCF and Freya were involved in the context of the ‘Kennisagenda’ of the NVOG. Subsequently, in the Grant application for the studies, patient-based information and opinion on the study goals and feasibility was included (through online questionnaires hosted on the Freya website but also structured interviews among UMC Utrecht patients). The questionnaire included questions on: i) whether the research question and chosen outcomes met the patient’s needs; ii) what the patient felt was the minimal clinically relevant difference the intervention should achieve (related to sample size); and iii) whether they would be willing to take part in this type of research (feasibility). Freya organised an online-poll on the willingness to participate in the SCRaTCHing studies. The study was executed very well within the time frame set out for ZONMW. The team of investigators and Freya are currently discussing the involvement of patients in disseminating the results to the public/target groups. The main target is that the findings have a maximum effect on the implementation into daily practice.

For more detailed information on process and output indicators see Appendix H.

Obstetrics

Organisation, strategy & mission

The research line antenatal damage has a life-cycle character hosting several Centers of Excellence. It provides high quality care in connection with research and teaching. The “reproductive and developmental origins of health and disease” hypothesis stresses the significance of the periconceptual and perinatal environment and potential harmful events for the future health of the child. Our efforts are aimed at increasing knowledge, thereby aiming to develop new preventative and therapeutic interventions that ultimately will decrease or eliminate the burden of disease for the (prospective) mothers, families and future children.



Life-cycle

Obstetrics is in care and research the heart of life-cycle science cycle and therefore collaborates closely with fertility, gynecology, neonatology and the Department of Developmental Origins of Disease (DDOD). Approximately 10% of pregnancies are complicated by placenta insufficiency, which present as maternal hypertensive disorders (including preeclampsia) and fetal growth restriction (FGR). No therapy apart from termination of pregnancy is available. Dr. Lely leads the translational research line focuses on causes, consequences and development of cures for the placenta and long-term effects for mother and child (in-vitro models). FGR and congenital anomalies are common causes of perinatal death and morbidity therefore our research focusses on normal and abnormal fetal development and the long-term fetal outcome. Dr. Bekker and Dr. De Heus lead an innovation-driven strategic research program on fetal imaging by ultrasound and MRI with focus on growth restriction, cardiac anomalies and the fetal brain. Within the department of obstetrics, quality of care improvement developing new strategies in the obstetric care, by new innovative digital technologies and medical solutions and evaluation of these interventions are an important research subject, including autonomy and empowerment of patients and health careworkers. Dr. Bekker focusses on eHealth technologies such as telemedicine and big data analysis.



Prof Bloemenkamp focusses on Global Maternal and Child health, since quality of care continues to be a prominent public health issues in low, middle and even in high-income countries. Her research line includes, (inter)national maternal mortality and morbidity registration and audit, complications of Caesarean sections, prevention and management of postpartum hemorrhage, induction of labor, innovations in healthcare delivery).

Interdisciplinary

Patient centered family care is facilitated in collaboration with medical specialists from the UMC Utrecht (cardiology, nephrology, rheumatology/immunology), epidemiologist, psychologists, ethicists and WKZ (neonatology, cardiology, nephrology, urology, neurology) in other to provide care, science, teaching and innovate for high-risk pregnancies. The translational FGR researchline collaborates intensely with Prof. Hoebeek DDOD. The department collaborates with the NVOG consortium 2.0 (Dutch Consortium for Healthcare Evaluation in Obstetrics and Gynaecology)) in several multicenter studies, a highly effective research network including all Dutch hospitals, making it very powerful to perform high quality, relevant clinical studies within restricted time periods. Examples of studies from our department within this consortium are the SUGARDIP and PROBAAT 1 and 2 (induction of labour) studies. We also work together with the NIPT (non-invasive prenatal genetic test) consortium for genetic testing and the Julius Center for our global health program (Dr. Rijken). Also, we are involved in the international network INOSS (the International Network of Obstetric Survey Systems).

Physical & mental development

Women with complications during pregnancy (including hypertension) are at increased risk physical and mental problems later in life (i.e post-partum depression) and need intensive monitoring during their pregnancy and afterwards. Within the eHealth and healthcare evaluation programs (see below ICHOM) both physical and mental health evaluation as well as improvement by patient empowerment is made.

Patient Participation

Within all research lines close cooperation with patient advisory boards is a major point of interest. Patient advisory boards are involved in the grant writing team but also in the performance and analysis of the studies. Within NVOG 2.0 consortium patients are heavily involved in setting the national research knowledge agenda. The perspective of the pregnant women regarding the obstetric care is an important theme within our research. Together with the Health Care institute (Zorginstituut of the Netherlands, ZIN) patient reported outcomes measures (PROM) of the International ICHOM set for maternity care are being implemented in the obstetric care. A clinical decision aid has been developed together with our neonatologists but also with the patient advisory board of premature delivery and parents. Dr. Lely and Prof Bloemenkamp have close collaboration with HELLP foundation (hypertensive disorders in pregnancy), NVN (Kidney patient Organisation), Harteraad (thrombosis), NVLE (Lupus patient organisation) and clotting diseases (NZVS) for women with high-risk pregnancies.

Goals next 3 to 6 years

- To develop (novel) therapies and strategies for improvement of placenta and maternal vascular health for both fetal growth restriction and preeclampsia.
- To predict and diagnose early placental dysfunction and consequently fetal growth restriction by novel strategies such as placental MRI techniques and cell free fetal DNA/methylation analysis in maternal blood.
- To assess normal and abnormal brain development in fetuses with and without congenital anomalies by prenatal ultrasound and MRI crosslinking to translational animal studies.
- To implement registries, audit and start strategies and health innovations from the “lessons learned” in order to decrease maternal morbidity and mortality in low-, middle- and high-income countries. This will be done step by step; from high, middle towards low -income countries (and vice versa), who can serve as examples for other countries. Link global maternal health to global child health, by investigating the outcome of children born of mothers with severe maternal morbidity of maternal mortality.
- Explore possibilities to design and conduct maternal vaccination trials in order to prevent infection for mother and child, especially in the areas where there is already expertise within our hospital (for example CMV (Utrial) and RS virus Prof L. Bont).
- Innovation of perinatal medicine (digital health, value-based health care, induction of labour at home Probaat-3): use novel technologies to improve obstetric outcomes, to empower patients and to reduce costs.



An ongoing or finished research project where patients are meaningfully involved

PALM study: randomized clinical trial on anti-hypertensive drugs in women after hypertensive disorders of pregnancy. Women from the HELLP foundation were asked during an online questionnaire on the willingness to participate in an intensive drug cross-over study. Moreover, a selection of patients was involved in designing and refinement of the trial. The final analysis of the trial is soon finished and will be presented at the patient meeting and discussed with obstetric professionals to be implemented in the guidelines on hypertensive disease in pregnancy.

Important scientific publications

Measuring client experiences in maternity care under change: development of a questionnaire based on the WHO Responsiveness model.

*Scheerhagen M, van Stel HF, Birnie E, **Franx A**, Bonsel GJ. PLoS One. 2015 Feb 11;10(2):e0117031. Atherosclerosis 2015 Jul;241(1):211-8.*

Involving the patients reported experiences and patient reported outcomes have become in health care. This questionnaire has been developed for measuring these outcomes in maternity care.

*Paauw ND, Terstappen F, Ganzevoort W, Joles JA, Gremmels H, **Lely AT**. Sildenafil During Pregnancy: A Preclinical Meta-Analysis on fetal Growth and Maternal Blood Pressure. Hypertension. 2017 Nov;70(5):998-1006.*

Fetal growth restriction is a major cause of perinatal death and morbidity. Until now no therapy is available other than delivery. This meta-analysis addresses the potential role of Sildenafil during pregnancy.

*Clinical utility of non-invasive prenatal testing in pregnancies with ultrasound anomalies. Beulen L, Faas BHW, Feenstra I, van Vugt JMG, **Bekker MN**. Ultrasound Obstet Gynecol. 2017 Jun;49(6):721-728.*

Non-invasive prenatal testing is usually offered in a screening setting for aneuploidy. In this study we value of offering this test instead invasive prenatal diagnostic testing.

*Classification of maternal deaths: where does the chain of events start? Lancet. 2017 Sep 2;390(10098):922-923.. van den Akker T, **Bloemenkamp KWM**, van Roosmalen J, Knight M; Netherlands Audit Committee Maternal Mortality and Morbidity; UK Confidential Enquiry into Maternal Deaths.*

An important societal contribution

Safe@Home

In pregnancies at risk for hypertensive complications, frequent hospital visits are executed to monitor maternal well-being. These visits, either planned or unplanned, can be burdensome for the pregnant patient, her support system but also to antenatal care resources. We developed a home telemonitoring platform for prenatal care with an app to 1) inform patients about hypertension in pregnancy 2) perform daily measurements of symptom scoring 3) home monitoring of blood pressure with Bluetooth connection. This platform was tested as a 'proof of concept' in the UMC Utrecht. The results were promising: the alert system was accurate, pregnant women were satisfied and perceived more autonomy, we found a reduction of hospital visits and hospital admission days and we are currently analyzing the costs. Currently, we are developing the system for use on a national level in combination with an integrated care pathway. We will test it in 6-8 other hospitals. This study is needed to scale up the strategy and to contribute to a future-proof introduction into prenatal care in The Netherlands. Patients were strongly involved in the development and analysis of the system. This video shows a patient exploring how her experience is with the system. Also, one of the large Dutch insurance companies has endorsed this project and supports the further development.

Watch "2019 - Gestational hypertension study SAFE@HOME at UMC Utrecht using Luscii" on Vimeo:

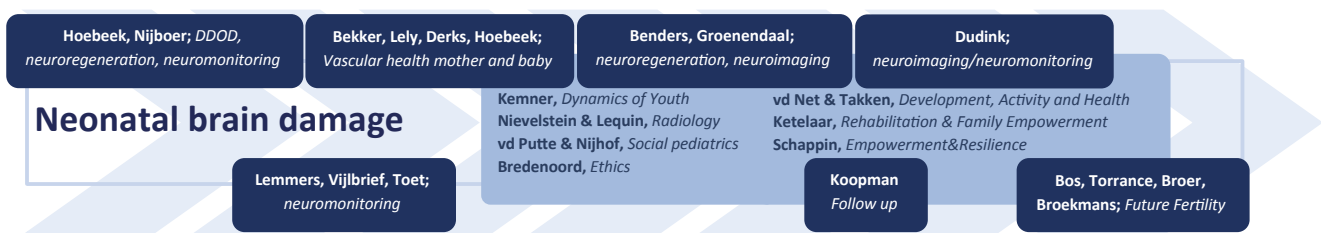
<https://vimeo.com/312898541?ref=em-share>

For more detailed information on process and output indicators see Appendix I.



Organisation, strategy & mission

Our mission is to “build better brains” and to optimize outcome for a better future in vulnerable infants being critically ill after birth. The aim of our research group is to use our routine clinical neuroimaging, neuromonitoring and routine neurodevelopmental follow up until the age of 8-10 yrs, to understand the effects of major early perinatal life events on brain development. To reach this aim several early neuroprotective and neuro-regenerative intervention trials are initiated after preterm birth, congenital (heart) defects, hypoxic-ischemic encephalopathy and perinatal stroke. The research line ante- & perinatal damage has a life-cycle character since its life-long consequences of early life events.. Neonatal Neurology is a recognized (Dutch Academic Hospitals: NFU) expertise center. In close collaboration with the Department for Developmental Origins of Disease (former NIDOD laboratory), the neonatal neurology has a bench-to-bedside perinatal research approach, in order to develop translational perinatal brain injury models, and effective therapies reducing and repairing the incidence and severity of brain injury caused by perinatal problems. This research line is connecting two research themes of the UMC Utrecht: Child health and Brain, in the subthemes: developmental disorders, perinatal stroke, and epilepsy.



Lifecycle

Our research starts before birth in close collaboration with the obstetric department. Our clinical care and antenatal and neonatal clinical observational and neuroprotective/-regenerative intervention trials with long-term follow-up with a family-centered approach continues until the age of 8-10 years. We are participating in the congenital heart Disease Life Span: preventing collateral damage, based on the neonatal neurology expertise. A strong part of our observational clinical research is that we have several fetal and neonatal cohorts, with cerebral MRI's and neuromonitoring combined with long-term neurodevelopmental outcome until the age of 8-10 years. Our clinical cohorts are compared with other large neonatal neurology centers over the world (London, Zurich, Toronto), where we study differences in long-term outcome and clinical risk factors. Additionally, a normal cohort is recruited in the Utrecht YOUth cohort (<https://www.uu.nl/en/research/youth-cohort-study>); fetal and neonatal MRI are collected, this provides a comprehensive examination of the developing brain in more detail and it enables to link normal perinatal brain development to long-term neurocognitive and behavioral outcome until young adulthood. This is useful as a reference group for our clinical cohorts and running clinical intervention trials.

Interdisciplinary

We have an integrated care program to recruit, and study a uniquely fragile population across perinatal care with obstetricians, pediatric neurologists, surgeons, cardiologists, radiologists, imaging experts from the Image of Sciences Institute and the Dutch connectome lab. We also work in close partnership with the pediatric rehabilitation, pediatric psychiatry and physiotherapists and psychologists. This interdisciplinary approach creates better clinical care and is successful for funding neuroprotective intervention trial (1.8 mlj Crucial) in the congenital heart Disease Life Span: preventing collateral damage We collaborate extensively in international networks with other experts in Neonatal Neurology over the world (King's college London, Sick Kids Toronto, Edinburgh), several of these networks were funded by grants of the European Society Pediatric Research (130€) initiated by us. Collaboration is expressed by several shared peer-reviewed papers. Our research lines relates to “the first 1001 days” of a child’s life program focusing from conception to their second birthday, the period critical to the development, a research theme from the Dynamics of youth the UU, related ot the UMC Utrecht research theme BRAIN. Together with our industrial partners (e.g. Nutricia Research) we are running 2 clinical intervention trials within this research theme. Additionally, with (pediatric) psychiatric and psychological expertise in stress we are building our national interdisciplinary research line NEOSTRESS, around birth and later, in an integrative family approach ('Hippo' trial with all clinical centers in the NL, sponsored by the Vriendenloterij, two running observational studies: 'Resprout' and 'Bios', and an interventional music study to stimulate brain development in preterm babies, sponsored by 'Sylvia Toth').



Physical & mental development

Our clinical observational trials are focusing on predicting long-term neurological and developmental deficits, in close collaboration with rehabilitation specialists, physiotherapists and psychologists (shown by several papers: van Kooij (Dev Med Child Neurol 2012), Kersbergen (J Pediatr 2016), Keunen (Dev Med Child Neurol 2017), Tataranno (Pediatr Res 2018)). There is a continuum of care and research by close collaboration with child psychiatry and child neurology. The research field of physical and cognitive development of neonatology is part of “Healthy play and better coping” program, which cross links the physical aspects of pediatrics with social and societal aspects in the strategic research program DOY of the Utrecht University. Next to neuroimaging and neuromonitoring research, digital health, such as Applied Data Analytics in Medicine (ADAM), is used in predicting adverse physical and cognitive outcome in preterm babies.

Patient Participation

Parents of our babies are our experts. Therefore, we ask parents to participate in improving and optimizing our research (agenda). In the past years, we have set up a program to empower parents, called ‘The VOICE’ program. In the VOICE program, parents are (1) educated, (2) trained in ‘shared care’ and (3) shared decision making. Parents are being structurally interviewed to get feedback on our care and research and a neonatal ‘parent board’ has been created. One of the tasks of this board is to provide input on new studies (e.g. formulate research questions and goals, express impact on proposed studies on parents and infants). Additionally we have weekly meetings with parents of babies on the NICU to evaluate care and research.

Collaboration with the European Foundation for the Care of Newborn Infants (EFCNI), a network representing the interests of preterm and newborn infants and their families within Europe is shown by our involvement in European protocols. Following discharge all our parents are invited to exchange experiences in empathic questionnaires.

Goals next 3 to 6 years

- To further improve our research organisation for an optimal integrated approach to expand knowledge on the long-term effects of adverse early life events:
 - We will collaborate on shared research grant applications; e.g. the TKI-Health Holland calls together with Obstetrics and the Department for Developmental Origins of Disease.
 - We will expand the involvement of relevant research partners in our weekly and monthly research meetings to crystallize our aims, to optimize planning and (cross-disciplinary) collaborations.
 - We will collaborate to generate translational in vivo and ex vivo models for adverse early life events, such as chorioamnionitis and intra-uterine growth restriction (IUGR) to study the consequences and ultimately optimize the cures.
 - We will share our biobank of neuro-imaging and -monitoring (fair data policy, open science) and follow up programs databases; Share expertise of statisticians, data managers, research office staff members, trial manager, research nurses and clinical epidemiologists:
- To further expand involvement of patient organisations in defining our research questions:
 - We will have patient organisations involved in >80% of all new prospective studies;
 - We will optimize our outreach (e.g. communications of >80% of all our research findings with patient organisations); we will organize annual public talks.
- Innovation of neonatal medicine (pharmaceutical industry, digital health and value-based health care):
 - We will intensify collaborations with private partners from the pharmaceutical industry (Chiesi pharmaceuticals, Nutricia) to develop neuro-protective and regenerative therapies with shared IP.
 - We will invest in advanced hospital and home neuromonitoring of infants: hardware and software development (in collaboration with ANT-Neuro, Artinis, Philips, TU Eindhoven and Delft);
 - We will perform big data analysis projects (applied data analytics In Medicine: ADAM projects: BIG data for Small Babies and PREDICT).

An ongoing or finished research project where patients are meaningfully involved

The NEOSTRESS program: preterm and term born infants admitted to the neonatal intensive care unit spend a critical period for brain development in a vulnerable environment rather than in the womb or at home. During this period, babies are exposed to many stressful stimuli, which result in significant neurobiological changes. We are now conducting several studies, we have set up a program to empower parents (‘the VOICE’ program). We are understanding better how stress and stress relievers (e.g. skin-to-skin care, sleep) influence brain connectivity by collaborating with the national (Hippo-trial: Amsterdam Medical Center, Erasmus MC, Leiden University MC) and international research partners (University of Edingbrough, University of Leuven, Kings College London, University of Munich).



Important scientific publications

We finished in the last 5 years 3 European funded projects in neonatal neurology (Neobrain, Nemo, Answer), which led to several publications.

*Wagenaar N, Martinez-Biarge M, van der Aa NE, van Haastert IC, **Groenendaal F, Benders MJNL**, Cowan FM, de Vries LS.* Neurodevelopment After Perinatal Arterial Ischemic Stroke. *Pediatrics*. 2018 Sep;142(3) An important paper answering some of the most important questions clinicians and parents of affected children will want to know when a newborn is diagnosed with a perinatal arterial ischemic stroke. This shows a successful collaboration with another group in the UK.

Claessens et al 2019 submitted:

Brain injury in infants with critical congenital heart disease: insights from two clinical cohorts with different practice approaches. Collaboration and comparison of two different practice approaches in babies with congenital heart disease, with Sick Kids Toronto, and University Medical Center Utrecht. Part of the Congenital Heart Disease life span: preventing collateral damage a multidisciplinary research group around infants with congenital heart diseases.

*Tusor N, **Benders MJ**, Counsell SJ, Nongena P, Ederies MA, Falconer S, Chew A, Gonzalez-Cinca N, Hajnal JV, Gangadharan S, Chatzi V, Kersbergen KJ, Kennea N, Azzopardi DV, Edwards AD.*

Punctate White Matter Lesions Associated With Altered Brain Development And Adverse Motor Outcome In Preterm Infants. *Sci Rep*. 2017 Oct 16;7(1):13250 Punctate white matter injury is commonly seen in infants born preterm. However, they are different in size and shape and neuroimaging findings. With this international collaboration a classification has been made which can predict neurodevelopmental outcome. This study shows a longstanding solid collaboration with King's College London, with exchange of PhD students.

An important societal contribution

Our research has a high societal contribution shown by the media interest. The past few years there were several performances in newspapers and popular TV talk shows, and public lectures. Building better brain is expressed in different societal programs, meet the professor, meet the expert, and invited talks in more than 25 international conferences.

Additionally, we participate in a knowledge exchange program for physicians and biomedical scientists, Trialect company from Boston. And we teach young doctors (Erasmus program) in neonatal neurology and they bring their knowledge back home to their patients (more than 5-6 applicants yearly), for building a better brain internationally.

For more detailed information on process and output indicators see Appendix J



Appendices

Appendix A: Description of the core team members	193
Appendix B: Kidney	194
Appendix C: Heart	197
Appendix D: Metabolics/Liver/GI	200
Appendix E: Auto immunity	203
Appendix F: Cystic Fibrosis	205
Appendix G: Recurrent Respiratory Infections	207
Appendix H: Pre/periconception	209
Appendix I: Obstetrics	211
Appendix J: Neonatal damage	213



Appendix A: Description of the core team members

Prof. Dr *Kors van der Ent*, MD, PhD is chair of the Child Health Program. He is an experienced pediatric pulmonologist with special interest for chronic diseases, like cystic fibrosis. Besides top-notch science he is mainly focused on what really matters for patients and their families.

Prof. dr. *Louis Bont* MD, PhD has an interest in understanding, preventing and treating respiratory syncytial virus (RSV) bronchiolitis. He was one of the founders of the TULIPS program, which furthers the career of multidisciplinary early stage researchers in the field of child health.

Prof. dr. *Nico Wulffraat* MD, PhD is a pediatric immunologist and rheumatologist who works on JIA and stem cell transplantation. He leads studies on autologous stem cell transplant in JIA, vaccination development and drug treatment trials.

Prof. dr. *Manon Benders*, MD, PhD focuses on neonatal imaging of brain development and predicting outcome. She also investigates neuroprotective and neuro-regenerative strategies to reduce brain injury.

Prof. dr. *Kitty Bloemenkamp* MD, PhD is and has been a PI of several randomized controlled trials, observational studies and experimental studies in the field of maternal health. She is the Chairman of Nethoss (Netherlands Obstetric Survey Study), National Enquiry of Maternal Death Review, Netherlands and of INOSS (International Network of Obstetric Survey Systems).

Prof. dr. *Annelien Bredenoord*, PhD is a professor of Ethics of Biomedical Innovation. Her research group seeks to identify, evaluate and promote policies and practices that ensure that the emerging biosciences (e.g. DNA sequencing, organoids and stem cells, big data / AI) develop in an ethically and socially responsible matter.

Dr. *Gijs van Haaften* PhD focuses on understanding the genetics and biology of monogenic disorders, with a focus on metabolic, craniofacial and cardiac disorders. He leads a multidisciplinary research group linking clinical genetics with functional studies, for example using CRISPR/Cas9 editing in zebrafish to model genetic diseases and develop treatments.

Prof. dr. *Berent Prakken* MD, PhD, is pediatric immunologist, Vice Dean UMC Utrecht & Education Director biomedical education center.

Support office

Anneke van de Brug MSc is the Child Health Program manager. She is a versatile manager with broad experience in various roles within childcare and research. She enjoys stimulating (clinical) researchers working together in multidisciplinary research and is eager to continuously think up opportunities to promote excellent scientific results.

Celine Uit de Weerd-Bakker is the Child Health communications advisor.

In 2015-2017 Prof Dr *Norm Rosenblum* from Sick Kids, Toronto, acted as an external advisor. Prof Rosenblum is a highly recognized scientist in Child Health research and has a major interest in the education and career development of clinician scientists at an individual and program level. He visits Utrecht twice a year and has been involved in several meetings with principle investigator of the Child Health Program.



Appendix B: Kidney

Table 3 – Process indicators Kidney

1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment

We aim to deliver lifelong patient-centered high-quality, innovative and effective care, in a unique multidisciplinary environment for patients with nephrological and urological conditions, and their families and carers.

Our research is directed towards improvement of this care on all levels: We want to gain fundamental insights in etiology and thereby design potential interventions, and to evaluate the long term outcome of our current interventions, in these patient cohorts that specifically need lifelong care, both in health and quality of life.

The Kidney unit does not entail one single group with one single focus. Illustrative examples of research questions that are pursued are:

- What causes congenital anomalies of the kidney and urinary tract
- What are the monogenic causes for end stage renal disease in adulthood
- What are causes of nephronophthisis
- What are risk factors for progression of renal disease (mainly focusing on):
 - Nephronophthisis
 - renal damage after oncological treatment
 - nephrological complications of TSC
 - CAKUT
- How can we improve timely diagnostics
 - Can we identify early biomarkers of hereditary or other progressive renal disease?
 - Can we improve genetic diagnostics, by discovering new causes, pathways
- Can renal stem cells be used as a target for renal regeneration and/or a building block for bioengineered devices to provide renal replacement therapy

- What are the results of our current treatment modalities
- What are new treatment modalities
- Which factors predict the long term outcomes of our patients

- Renal disease and pregnancy:
 - What are the outcomes of pregnancy in women with chronic kidney disease and after renal transplantation
 - Can we prevent (the development of hypertension due to) fetal growth restriction by in-utero interventions

2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

The Dutch Kidney Foundation and the Kidney Patient Association have developed a research agenda, “Nierziekten de baas”, based on current gaps in knowledge and patient needs. Our research is very much in line with this agenda. From a wider perspective, we align our projects with the “Nationale Wetenschapsagenda”.

We interact with patient organisations (Kidney Patient Association; Joubert association, Bardet Biedl Association, TSC Foundation), funders (Dutch Kidney Foundation), to bring our specific multidisciplinary expertise to this agenda.

The research teams are frequently asked to contribute to review articles in leading journals in the field (such as Nature Reviews Nephrology).

3. Stakeholders are involved in formulating the main research questions

Our unit regularly meets with patient representatives from the diseases we study to discuss our research lines (see 3.2). Our most important funding body (Dutch Kidney foundation) involves patients in scoring of funding applications.

4. The research questions are feasible and are pursued using optimal and efficient design

We collaborate on a structural or ad hoc basis with bioinformaticians and statisticians of the UMC Utrecht dept. Clinical Genetics and [UMCG dept of Genetics](#), Bioinformatics Expertise Core (UBEC) (www.UBEC.nl), and Oncoproteomics laboratory VUmc. We collaborate with epidemiologists of the Julius Center. We are currently forming an infrastructure to build a national cohort of children with severe congenital abnormalities of the kidneys and urinary tract in cooperation with the UMC Amsterdam, Radboud UMC and Erasmus MC.

5. What is ‘the next step’ if the project delivers positive results

- a. We disseminate the findings of our projects in professional literature (please also see table in addendum) and through scientific meetings. We are connected to the relevant patient organisations, where we divulge the knowledge gained and in our clinic we translate it back to practical consequences.
- b. We do not foresee a marketable product as an outcome of our projects in the near future. Currently, several of the projects running in the unit are directed at repurposing of existing drugs to treat genetic renal disease. However in the Kidney Research Utrecht embedding, public private partnerships exist.
- c. We receive funding for our projects from national charities (Nierstichting, Stofwisselkracht) and international funding (Eurenomics)
- d. Members of the unit are involved in national (Rookmaaker, Liliën: Nederlandse federatie voor Nefrologie, Lely and Van Eerde: SKMS guideline Renal disease and pregnancy) and international guideline committees (van Eerde, Liliën: ERKNet). Attention to our work is drawn through local and national media coverage, in close collaboration with the Public Affairs department of the UMC Utrecht.



Table 4 – Output indicators Kidney

1. Research products for peers

With our multidisciplinary perspective, we contribute to research that covers a broad field. Key examples of research connected to the unit are:

- Schutgens et al 2019. (2) The first paper describing renal (tubular) organoids. One of the key examples of the excellent Utrecht embedding of the unit, with lines also to the Hubrecht Institute.
 - Stokman et al 2018. (3) As just one example of databases we lead : Kouncil renal ciliopathy database, funded with a Consortium Grant from the Dutch Kidney Foundation.
 - We offer a broad set of regularly updated genepanels for diagnostic genetic testing. With the design of these panels our results can be implemented in patient care right away. Link (ctrl F “nierziekten”)
 - co-organisation of a European CME (With both the ERA EDTA and ERKNET): “ How to become your local nephrogeneticist” Belgrade 2018. Broad practical dissemination of our and other leaders’ in the field clinical and research experience.
-

2. Research products for societal target groups

- In 2016 we organized daytime activities for World Kidney Day, but also an evening layperson symposium (“publiekslezing”) featuring our research, including demonstrations. This was a big success that was well received. In 2017/2018 and 2019 we have organized World Kidney day daytime activities. In 2019 we invited the school class of one of our renal disease patients, and gave them a big tour and all kinds of kidney related activities.
 - We actively participate in/give lectures for symposia organized by patient organisations:
 - “Nierpatientendag” Lely/ Van Eerde
 - Stokman: Joubert Vereniging, VHL vereniging
 - We feature in informational movies aimed at informing patients. (Dutch Kidney Patient Association: Lilien: nephronophthisis movie Van Eerde, hereditary renal disease movie. WKZ Child Health movie Pushing Boundaries through Scientific Knowledge. (Lilien, Van Eerde)
 - We feature in: <https://www.UMC Utrechtrecht.nl/en/Research/Strategic-themes/Child-Health-science-for-life/Congenital-and-hereditary-disorders/Kidney>.
-

3. Use of research products by peers

- Ajzenberg et al.(4) A practical example of a protocol for non-invasively obtaining human cells for functional studies from deciduous teeth.
 - Paauw et al.(5) PREVEND dataset with pregnancy outcomes are shared with other researchgroups.
 - Hennis et al. (6) Led to more urodynamic studies and less valves resections in boys with persistent overactive bladder symptoms.
-

4. Use of research products by societal groups

- Development of the Guideline for Dutch Nephrology Association: genetics for nephrologists (2018) (Van Eerde, Rookmaaker, Lilien. Inspired amongst others by our paradigm changing paper where we show that a monogenic renal disease classically thought of as pediatric, causes 0,5 % of all adult onset end stage renal disease. With many of these patients over 30 years at first renal replacement therapy.(7) This has bearing on risk for familymembers, related donation practice etc.
 - Set-up of ciliopathy outpatient clinic at the request of patient organisations (Lilien, Stokman, Van Eerde)
 - The outpatient clinic for renal disease and pregnancy is a great success (Lely and V Reekum)
-

5. Marks of recognition from peers

- 2017 ERA-EDTA Stanley Shaldon Award for young investigators (Van Eerde). Dutch Kidney Foundation Kolff senior stipend (Renkema, Van Eerde)
 - Lely: Invited lecture on pregnancy and renal transplantation - ISSHP 2019 Prague
 - Nguyen: New established member of Scientific Board of Dutch Kidney Foundation. Before: Goldschmeding. (qualifies both as peer and as societal recognition)
-

6. Marks of recognition from societal groups

- Awarded grants from the Dutch Kidney Foundation are also scored by representatives of the Kidney Patient Association.
 - Recognition to be accredited NFU Expert Center and ERKNET member was also based on patient representative evaluation.
 - Nguyen: New established member of Scientific Board of Dutch Kidney Foundation. Before: Goldschmeding. (qualifies both as peer and as societal recognition)
-

Also, we have roughly queried the Scopus database for relevant publications by the Kidney Unit members from 2014-2019, the result amounts up to 134 papers (analyzed through Scopus for funding sponsors).



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Appendix C: Heart

Table 3 – Process indicators Heart

1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment: Urgency and/or relevance of the research questions

Congenital heart disease (CHD) is a major burden of disease. When expressed in years lost to disability, CHD can be compared to stroke or rheumatic disease. Major long-term morbidity is mainly caused by arrhythmias, heart failure and neurocognitive impairment. Especially children with severe (duct dependent) CHD are at risk for these long-term complications leading to impaired quality of life and disabilities. The mission of our unit is to investigate the origin of heart failure and neurocognitive impairment and to significantly reduce it. We focus on excellent surgical, percutaneous and medical interventions and follow-up in children with severe CHD. Furthermore, we are the first to have developed a neurodevelopmental follow-up program with MRI including fetal, pre-operative and post-operative MRI scans of the brain. Furthermore, the program uses state of the art invasive and non-invasive imaging to enhance early detection and treatment of cardiac failure. This program is extensively supported by patient organisations and other stakeholders.

2. Relation to existing knowledge and stakeholder involvement

It is unknown when neurocognitive impairment develops in children with CHD. This may be during fetal life due to an abnormal circulation, during labor due to decreased capacity to deal with asphyxia or during cardiac surgery. We do know that neurocognitive impairment is a major burden of disease later in life in children with severe CHD with > 20% needing special education. This problem is well recognized by patient organisations who have reduction of neurocognitive impairment in CHD high on their research agenda. This agenda was developed together with experts in the field and the patient organisations. The program we have developed will answer this question and will focus on interventions to reduce neurocognitive impairment. Interventions include surgical, interventional techniques, intensive care treatment, new imaging techniques, developmental training programs and medication. Examples of new treatment options are novel percutaneous treatment options in congenital heart disease (PMID 30834894 PMID 30041787 PMID 29550016) or initiation of neuroprotective drugs in congenital heart disease (PMID 30018590).

During the last years we have established a strong and meaningful collaboration with patient organisations. This has resulted in several joint performances on national radio and television where attention was raised for research priorities (e.g. long term neurodevelopmental morbidity in severe congenital heart disease). Furthermore this has resulted in active patient participation in study design and communication of study results as well as in joint informative meetings for patients and parents of children with congenital heart disease.

3. Stakeholders are involved in formulating the main research questions

This question has been combined with question 2.

4. The research questions are feasible and are pursued using optimal and efficient design

The Heart program is fortunate to have several PIs who also are epidemiologists (van Loon, cardiac anesthesiologist-epidemiologist, Slieker, pediatric cardiologist- epidemiologist, Schappin psychologist- epidemiologist, Groenendaal, neonatologist- epidemiologist). There are structural meetings where new research initiatives are presented. PI-epidemiologists are always present at these meetings to discuss study design and outcome at the most early stage. In the larger trials we cooperate with Julius Clinical, a commercial spin-off of the department of biostatistics of the Medical faculty of the Utrecht University, on a regular base. Furthermore, in our research meetings we discuss feasibility of application of animal intervention (e.g. medication or intrauterine interventions) in our (unborn) patients. This has resulted in changes in study protocols, for example in the crucial trial where we intended to also treat the mothers of a child with a severe congenital heart disease with allopurinol based on animal studies. Since human evidence was lacking we decided to only perform extra uterine administration of the drug.

5. What is 'the next step' if the project delivers positive results

A wide network of leaders in the field is involved in our project. At the UMC Utrecht we have experts in the field of neurocognitive and motor development. Furthermore we are in close contact to all 3 other cardiac centers in the Netherlands and several experienced centers in Europe and North America. Recently all Dutch centers for congenital heart disease, the Hubrecht laboratory, the anatomical labs of Leiden and Amsterdam universities applied for a large Dutch Heart Foundation grant (CVON) to establish a national translational consortium for congenital heart disease. We are part of CNOG (cardiac and neurodevelopmental outcome collaborative) and lead the formation of a European Neuro-Cardiac consortium (European consolidator grant). For development of new treatments we are in close contact to the imaging and medical device industry (Siemens, Medtronic, Edwards, Stentit(TU Eindhoven)). We are also in close contact with the pharmaceutical industry (Jansen-Cilag, ACE pharmaceuticals). We are involved in a European consortium developing microtablets for children (LENA project; European Union; 7th Framework Programme n° 602295). Funding for our project is received mainly from non-profit organisations, charities, companies and national and EU grants.

In 2019 we will start conducting the Crucial trial; a national randomized double blind placebo controlled trial to test the cardiac and neuroprotective properties of allopurinol (grants by ZonMW €1,5M, Hartekind & Vrienden WKZ €260K). In this trial we closely collaborate with the producer of allopurinol (ACE pharmaceuticals). Extensive agreements have been made to ensure successful valorisation of this study e.g. agreements on the price of the product if the indication for use will be extended and how this will be accomplished. These agreements have been made in close contact with a valorisation officer of the UMC Utrecht.

Several of our group members have important roles in scientific communities and have given lectures for international societies concerning these topics (Jansen, Benders, Krings, Breur, Grotenhuis). Furthermore we appeared on national television and in national newspapers several times with our 3DRA program and congenital heart disease life span project.



Table 4 – Output indicators Heart

1. Research products for peers

The most important research product of our unit the unique infrastructure we have realized the last years. All patients with severe CHD enroll in a unique follow-up project “the CHD life span project, preventing collateral damage”. This project focusses on improvement of neurodevelopmental and cardiac outcome in children with severe CHD. When detected antenatally patients enroll in this cohort and antenatal MRI scans of brain and heart are performed. Postnatally they undergo extensive neuromonitoring during their transition phase and peri-operatively. Furthermore, MRI scans of the heart and brain are repeated pre- and post-operatively. At fixed time points cardiac and neurocognitive tests are performed all in line with the Child Health program and large follow-up cohorts of the Utrecht University (YOUth cohort). In this way our patients can be compared to peers. This pipeline is unique in the world. Other large centers have developmental follow-up programs, however this pipeline is unique in combining fetal and postnatal data as well as that we manage to include the most severe cases like hypoplastic left heart syndrome (HLHS) with the help of a dedicated team facilitating transport to the MRI scanner. Other centers do not succeed in performing post-operative scans in these patients due to hemodynamic instability. With this pipeline we will be able to investigate the origin of neurological damage in CHD and we will be able to perform well executed prevention studies. Since 2016 around 200 patients have enrolled in this project. This cohort is the largest cohort worldwide undergoing such extensive prenatal as well as postnatal imaging and consequent neurocognitive follow-up.

Furthermore our 3D cath lab is world leading. We have hosted or co-hosted all international congresses on 3DRA in CHD all over the world. We have written the chapter on 3DRA in the upcoming new standard work in catheterisation: Cardiac Catheterisation in Congenital Heart Disease. From fetus to adult by Gianfranco Butera et.al.

Several recent publications show how our multidisciplinary team succeeds in answering complex research questions:

- Claessens NHP, Khalili N, Isgum I, Ter Heide H, Steenhuis TJ, Turk E, Jansen NJG, de Vries LS, Breur JMPJ, de Heus R, Benders MJNL. Brain and CSF Volumes in Fetuses and Neonates with Antenatal Diagnosis of Critical Congenital Heart Disease: A Longitudinal MRI Study. *AJNR Am J Neuroradiol.* 2019;40:885-891
- Claessens NHP, Algra SO, Ouweland TL, Jansen NJG, Schappin R, Haas F, Eijssers MJC, de Vries LS, Benders MJNL; CHD Lifespan Study Group Utrecht. Perioperative neonatal brain injury is associated with worse school-age neurodevelopment in children with critical congenital heart disease. *Dev Med Child Neurol.* 2018;60:1052-58
- Algra SO, Jansen NJ, van der Tweel I, Schouten AN, Groenendaal F, Toet M, van Oeveren W, van Haastert IC, Schoof PH, de Vries LS, Haas F. Neurological injury after neonatal cardiac surgery: a randomized, controlled trial of 2 perfusion techniques. *Circulation.* 2014;129:224-33.

2. Research products for societal target groups

- Hans Breur was invited on national television (NPO 1, EO) to explain 3DRA in a medical informative program.
- Hans Breur was invited together with stichting Hartekind to explain research priorities in pediatric cardiology, why these priorities are so important and to explain the burden of CHD. (BNR nieuwsradio). <https://www.bnr.nl/radio/bnr-gezond/10021965/uitzending-18-februari-wat-als-zoet-niet-meer-smaakt>.
- Hans Breur and Manon Benders have appeared on national television and in national newspapers explaining the congenital heart disease life span project.
- In June 2019 Heynric Grotenhuis explained the use of fetal cardiac MRI on the national news bulletin (NPO 1)

3. Use of research products by peers

Currently we are chairing a European consortium on neurodevelopmental outcome in severe congenital heart disease (ABC consortium) funded by a European Consolidator grant. With this consortium we will shortly provide new international guidelines to uniformly score brain injury in this patient group so that different cohorts can be compared. We are currently finalizing the results of > 200 brain MRI's in children with severe congenital heart defects that were scored using our proposed methodology and the relation of the scored lesions with neurodevelopmental outcome. We strongly believe that our congenital heart disease life span program is the beginning of strong national and international alliances that will influence future management of children with severe congenital heart disease.

4. Use of research products by societal groups

We were the first in the Netherlands to start using 3DRA in children. Worldwide large centers have adopted our protocols to perform 3DRA. G. Krings has performed on site teaching of this technique in several world renowned centers. Furthermore due to our efforts 3DRA has become a “verrichtingen code” during catheterisation adapted by health insurance. Furthermore we are co-chair/faculty in all important international meetings on catheterisation in congenital heart disease (e.g. IPC Milan (co-chair), CSI Frankfurt (faculty), SCAI (USA) (faculty), PICS (USA) (faculty), 3Di3 Ohio (USA) (co-chair)).

We host a 3 day international symposium on congenital heart disease (www.utrechtsessions.nl) which will be held for the 8th time in 2020. Since 2018 we dedicate the first day of our international symposium to patients, parents and involved stakeholders. This first day is in Dutch and is organized together with stichting Hartekind and the PAH for patients and parents.



5. Marks of recognition from peers

- One of our PhD students (Stegeman) just won the young investigator award during the joint meeting of the European Academy of Pediatrics Societies with his research “percutaneous treatment of aortic coarctation in very low birth weight infants”
- Another of our PhD students (N Claessens) has won the young investigator award of the Dutch society of pediatrics (june 2019) and the Young Investigator Exchange Program Award Society of Pediatric Research (may 2018).
- The Crucial trial, initiated by the CHD life span group, was awarded €1,5M by ZonMw.
- Hans Breur was awarded a research grant of €200k for the CHD life span project by stichting Hartekind and a research grant of €200k for his research project Next generation sequencing in congenital heart disease by the “Vrienden van het WKZ”.
- Gregor Krings has become a faculty member of several world leading conferences on cardiac catheterisation in congenital heart disease (IPC Milan, CSI Frankfurt) and was appointed to the medical advisory boards of Siemens and appointed as consultant for Medtronic and Edwards. The latter appointment has led to the development of a new covered stent enabling percutaneous pulmonary valve replacement in patients not suited for this therapy earlier.
- Heynric Grotenhuis was awarded with a research grant of stichting Hartekind for the Velocity study (€200k)
- Kim van Loon was awarded a research grant to study perioperative neuroprotection (€150K)

6. Marks of recognition from societal groups

- Hans Breur was appointed as a member of the scientific advisory board of Stichting Hartekind.
- Gabriëlle van Iperen was appointed as a member of the committee of recommendation of stichting Hartekind

Final remark

This SEP analyses has focused on Heart. However some of the core members have more important roles in different units. For example Manon Benders is a prominent member of the steering committee of the CHD life span project and is a leading researcher of neonatal brain research.



Appendix D: Metabolics/Liver/GI

Table 3 – Process indicators Metabolics/Liver/GI

1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment

a. Our mission is to provide 'better care for the rare'. Through internationally recognized and nationally embedded research (United for Metabolic Disease initiative (UMD)), our research unit adds to improve the whole spectrum of care for patients with metabolic/liver/GI disease by focusing on improved diagnostics (new born screening, untargeted diagnostic assays), improved understanding of the disease phenotype (deep phenotyping, in vitro modeling) and novel treatment strategies (personalized medicine, novel (stem cell, small molecule based) treatment strategies).

b. Care for patients with rare genetic/metabolic/liver/GI diseases can be further improved by implementing new diagnostic and therapeutic strategies, as outlined above. We have done this and will continue to do this in a unique setting, including a multidisciplinary long-term follow up facility (Sylvia Toth Centre e.g. for CLN3, FAO defects, MPS1 patients receiving HSCT), state of the art technological methods (genomics, metabolomics, transcriptomics, imagestream analyses, organoid technology), embedded in the Utrecht Science park (RMCU, Hubrecht Institute), with strong national and international collaborations in relevant fields.

2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

Our research focusses on improving diagnostics and therapies in (ultra) rare genetically determined metabolic, GI and liver diseases. For GI and liver diseases a road map was recently set out (Houwen RH, JPGN 2018;Goulet O, JPGN 2018), which suggests to combine new genetic and molecular techniques to improve understanding of the disease mechanisms and use this knowledge to develop therapies. For metabolic diseases, a new national road map has been made, which resulted in the UMD consortium. With all metabolic pediatricians, internists, lab scientists, patient representatives and fundraisers, we collaboratively determined the areas of research that need to be addressed to improve care for our patients.

3. Stakeholders are involved in formulating the main research questions

We have involved all stakeholders in setting the research agenda. For specific patient groups or research projects, patient days or patient focus groups are organized. In most of our grants, a patient representative is part of the project committee. Moreover, our strategic research program annually meets with patient representatives from the diseases we study to discuss our research lines.

4. The research questions are feasible and are pursued using optimal and efficient design

The ultra-rare nature of most of the (rare) diseases studied makes them ill-suited for RCTs and other methods commonly used in more frequent disorders. To best capture information from existing knowledge we perform a meta-analysis of cases retrieved using a structured review. Deep phenotyping of patient cohorts is used to counteract the smaller sample size. Tailored to research trajectories, staff and PhD students are trained to perform state-of-the-art statistical analyses, including mixed model analyses. For additional support, we collaborate with numerous other experts in the area required, including bio-informaticians. Altogether, we perform a wide range of activities and have a variety of facilities at our disposal (including the genetic, metabolic and organoid laboratories and collaborating Hubrecht-groups).

5. What is 'the next step' if the project delivers positive results

a. For the liver stem cell transplantations, we collaborate with the Clevers group and are in the process to finish preclinical culture/GMP/ effect/safety experiments and to pave the clinical pathway. In addition, we collaborate with the ethical department (Bredenoord) for parallel ethical research into the eligibility of these trials by ethical committees .

To finally launch the first-in-human trial, additional stakeholders will be attracted (we had already started a consortium with European hepatocyte transplantation centers for a EU grant, and will reactivate this network when the FIH is feasible).

For novel (eg small molecule) treatment strategies, we collaborate with the vdEnt/Beekman groups. They have been successful in the field of CF, and it is likely that similar strategies will work for other genetic diseases as well.

b. We make use of the Transfer Technology office regularly

Together with Stefan Nierkens (U-Dair) we are looking into patent options (and other forms of commercialisation) with regards CLN3 biomarkers we developed.

c. We have received several grants (NWO, Metakids, MLDS) for the studies evaluating novel treatment strategies. However, If liver stem cell transplantations is to become a reality, more finances will be needed to which prof. Nieuwenhuis and prof. Clevers have committed themselves.

d. Membership of the board of the UMD, several guideline committees (eg Wilson disease guidelines, SSIEM trainin and education committees), as well as the metabolomics Quality Assurance and quality Control Consortium (mQACC) initiated by the NIH.



Table 4 – Output Indicators Metabolics/Liver/GI

1. Research products for peers

Infrastructure

- Deep phenotyping and standardized follow up resulted in several publications (PMIDs:29875423, 28848061, 31182507, 29392585.)
- We set up a laboratory in the RMCU with now 5 PhD students and positions available for 3 more PhD students, a technician and good collaborations for liver/intestinal organoid research; including a facility to pick up liver / intestinal tissue (inter)nationally for biobanking purposes.
- We expanded the diagnostics and research metabolic diseases laboratory, now 35 fte and developed a new method for untargeted metabolomics, including a bioinformatics pipeline, to be used by peers both inside and outside the Netherlands. (See PMIDs:30641898 and 30926434).
- We have developed biomarkers to assess severity of CLN3 disease and other lysosomal storage disorders associated with lymphocyte vacuolation as well as an assay in saliva in MPS1 patients after HSCT, unveiling a weakspot of this treatment: proper transport across cells.

PhD dissertations: N=8

Caroline Wiegerinck 6-2015 (Middendorp, Nieuwenhuis)

Wendy van de Woerd 11-2015 (Houwen)

Desiree van Haften 11-2017 (Houwen)

Feilong Sun, 6-2018 (van Hasselt)

Jorik van Rijn 5-2019 (Middendorp, Nieuwenhuis)

Sarah Boers 5-2019 (Bredenoord)

Lynne Rumping, 5-2019 van Hasselt, Jans, Verhoeven)

Rúben Ramos 10-2019 (Jans, Verhoeven)

Chapters:

Inborn Metabolic Diseases: Diagnosis and Treatment. 6th edition (Ed. Jean-Marie Saudubray, Matthias Baumgartner, John Walter). Chapter 36. Disorders in the Transport of Copper, Iron, Magnesium, Manganese, Selenium and Zinc. Peter M. van Hasselt, Peter Clayton, Roderick H.J. Houwen – ‘This work is recognised as the standard textbook for professionals involved in the diagnosis and management of inborn errors of metabolism (IEM) and an essential resource in this multidisciplinary field.’

2. Research products for societal target groups

Our biobank with liver and intestinal organoids is also available for other researchers.

SF was invited in several national television shows as an expert in the field.

All members of our group had good visibility in the patients' organisation such as VKS and the charity Metakids

Television (SF):

- 2019 (march 13th): live presence in Tijd voor Max (Omroep Max) as a Metabolic Pediatrician.
- 2018 (sept 25th): live presence in “5 uur live” as Metabolic Pediatrician:
- 2018: nomination for “Klokhuis wetenschapsprijs 2018.
- 2017: live presence in “RTL-live” as Metabolic Pediatrician and researcher: <https://www.metakids.nl/page/1356/rtl-live/>

National newspapers:

- 2018 (October 30th) (PvH): call for longer storing of neonatal Guthrie cards: <https://www.volkskrant.nl/wetenschap/kinderarts-bewaar-hielprikbloed-langer-het-kan-zeldzame-ziektes-helpen-ontrafelen~b48fb1ab/>
- 2017: <https://www.telegraaf.nl/nieuws/53710/eindelijk-aandacht-voor-dodelijke-ziekte>

Other societal publicity

- 2018: contribution about organoids in the Cahier “de hielprik / erfelijke metabole ziekten”, for the foundation for biomedical science and society (www.biomaatschappij.nl), founded in 1969 by Prince Claus and Princess Beatrix to promote biomedical science: https://issuu.com/biomaatschappij/docs/de_hielprik (pages 58-59)
- 2018: development of the “metabolic escape bus” to raise public awareness of metabolic diseases and research (illustrating my “miniliver” research)
- press release 2017: <https://www.metakids.nl/media/inline/2017/2/2/persberichtbijlagen-54251065.pdf>
- different layman journals 2017 and 2018: <https://www.oudersvannu.nl/nieuws/metabole-ziekten-in-top-3-doodsoorzaken-kinderen-in-nederland/>
<https://www.jan-magazine.nl/psyche/vertrouwelijk/artikel/onbekende-ziekte-in-top-3-doodsoorzaken-bij-kinderen-in-nederland>
http://marjonwaller.nl/wp-content/uploads/2018/06/1408004-Happy-Child-magazine_def_lowres.pdf
- Interview by Tom van 't Hek at the Metakids lunch 2016 (cited and picture in national journal “de Telegraaf”)
- <https://www.UMC Utrechtrecht.nl/nl/Nieuws/Landelijk-stofwisselingsziekten-sneller-opsporen>
- <https://www.UMC Utrechtrecht.nl/nl/Nieuws/Actie-tegen-stofwisselingsziekten>
- Meet the professor 2018, a visit to schools

Patient publicity

- various contributions to patient journals and patient organisation websites: “Stofwisselkracht”, Nederlandse Maag, Darm Lever Stichting (NLVisie 2, 2016 (<http://www.leverpatientenvereniging.nl/archief-navisie>; 2016 Nummer 2, pg 12-13); Nieuwsbrief MLDS nr 2 2016: “Onderzoeker aan het woord”; sales/corporate leaflet MLDS over onderzoek PFIC in lever organoids (2016); <https://www.mlids.nl/onze-onderzoeken/fuchs-pfic/>; <https://www.metakids.nl/toekenningen2018>; presentation for PFIC patients (Rijssen, 2018)



3. Use of research products by peers

Our best publications from the period now reviewed have at least 10 citations/year (eg Huch et al, Cell 2015, Ozen et al, NEJM 2018)

We are regularly contacted for advice on specific disease groups on national, and international basis by researchers and patient alike (eg ARS-deficiencies, NCLs, PFIC, Wilson disease)

The untargeted metabolomics method we developed is now used for other patient groups, and by other research groups (nationally and internationally).

4. Use of research products by societal groups

- Patient registration and retrieval:

The DDRMD we chair (Dutch Diagnosis Registry for Metabolic Diseases) is being used widely when describing national cohorts of various inborn errors. This registry was also recently used for decisions on which diseases to include in the expanded neonatal screening.

- WES as a diagnostic tool:

The evidence for an economic basis and effectiveness of using a WES to diagnose genetic diseases as described by our group has significantly impacted the ease and frequency to apply WES in diagnostics

- Novel treatments for patients with inborn errors:

Our group has provided a firm basis to apply hematopoietic stem cell treatments for inborn errors of metabolism in a safe and efficacious manner, which are now considered standard of care for MPS and other lysosomal storage disease. (PMID: 25708213). Other types of novel treatments include amino acid supplementation (serine for serine deficiencies, amino acids for patients with corresponding ARS deficiencies).

5. Marks of recognition from peers

Clinically

We are regularly contacted for advice on specific disease groups on national and international basis (ARS-deficiencies, CLNs, hematopoietic stem cell transplantations). Patients are regularly transferred to our center for multidisciplinary deep phenotyping at the Sylvia Toth Center.

Facilities

Our untargeted metabolomics method is now used for other patient groups, and by other research groups (nationally and internationally).

Our organoid facility is increasingly approached for use of the technology for in vitro modeling of inborn errors.

Grants, awards and other signs of peer recognition

- During the evaluation period (2014-2018) more than 4,000,000 euros from grants was obtained.
 - members of this group received several awards, including the Elisabeth von Freyburg Penning, and were part of talent programs (Steyn Parve program, Leading Ladies Program, Eureka Certificate Course).
 - members of this group participated (chair or otherwise) in several international committees and boards, eg evaluation committee of the European joint program on rare diseases, SSIEM, ESPGHAN as well as national committees, eg Horizon scan, Neonatal screening boards and Vereniging Erfelijke Stofwisselingsziekten Nederland.
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6. Marks of recognition from societal groups

Several research projects were paid for by patient organisations, e.g. Beat Batten, PFIC patient support group.

[The 'Paving the way project' was funded by the Beat Batten foundation, a societal group who aims to combat CLN3 disease.

A PhD student was funded by the PFIC patient organisation

A project funded by the parents of an ARS-deficient patient]

Advisory positions to the Dutch Health Council and the CBG (Dutch branch of EMA)



Appendix E: Auto immunity

Table 3 – Process indicators Auto immunity

1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment

- By combining both fundamental and clinical research, and through international collaboration our unit advances understanding of mechanisms of disease and therapy resulting in improved care for children with chronic immune mediated inflammatory diseases.
- We aim to understand immune regulation and how this is disturbed in chronic inflammation with the aim to improve care. We use both bench-to-bedside approaches, but also bedside-to-bench approaches for which we utilize our established biobanks containing primary patient cells and serum (JIA, Juvenile Dermatomyositis, auto-inflammatory diseases, Primary Immune Deficiency-patients).

2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

We intensively collaborate with patient organisations such as the jeugdremavereniging. Also, we appointed a dedicated patient representative (Casper Schoemaker). In addition, we have a strong collaboration with the Dutch Arthritis Society which appointed us as research center of excellence (2019-2024). Our research does adhere to multiple topics/ questions from the national research agenda. We are currently developing a national research agenda for juvenile arthritis for which we use the James Lind alliance methodology.

3. Stakeholders are involved in formulating the main research questions

We regularly organize patient meetings to update them about our findings and discuss our future directions. Furthermore we appointed a dedicated patient representative. Almost all of our researched (also non-MD) periodically attend patient clinic ours, to allow for direct contact with patients and ask questions. We have a close collaboration with both the juvenile arthritis patient organisation, and the Dutch Arthritis Foundation (DAF). As described below in more detail, together with all stakeholders, we are developing a (inter-) national JIA research agenda.

4. The research questions are feasible and are pursued using optimal and efficient design

Our group employs dedicated biostatisticians (collaboration with the group of M. Mokry) that are directly involved in our research projects and also in the design of new projects. In addition, we collaborate with the Julius Center for Clinical Research regarding novel clinical trial design.

5. What is 'the next step' if the project delivers positive results

- Our investigator initiated clinical trials aim to transform care for children with immune mediated inflammatory diseases. Currently, we are leading a biomarker based taper and stop clinical trial in systemic JIA, with participation of all 6 academic pediatric rheumatology departments in the Netherlands. Moreover, we are currently performing a project in preparation of a phase III randomized controlled clinical trial exploring the potential of Nicotinamide in tapering and stop strategies for non-systemic JIA. Thirdly, through our leading position in UCAN CANDU, we are in the process of transforming the current step-up therapy strategy for new-onset JIA to stratified / personalized therapy regimens. These trials are intended to directly improve care for JIA patients throughout the world.
- We have regular contacts and follow-up meetings with UMC Holding Company, a UMC spin-off providing expert advise and help in protecting intellectual property issues and commercialisation opportunities.
- We aim to involve all stakeholders in our research, exemplified that since 2016, we have received significant funding of charities (Vrienden WKZ/UMC), pharma (Sobi, involving public-private funding opportunities and patient information projects, Novartis, Abbvie) and patient organisations (the Jeugdremavereniging is a partner (also funding) on the James Lind Alliance Research Agenda). In 2016, we organized with our UCAN partner in Aachen (prof. K. Tenbrock) a fundraising and awareness creating charity bike tour from Utrecht to Genua, connecting 8 pediatric rheumatology centers in the Netherlands, Germany, Switzerland and Italy, boosting international collaboration (www.ucanr4a.eu).
- Our department was the principal investigator center for SHARE, an EAH European Union Research Grant (850k€) developing international best practices on the diagnosis and treatment for rare pediatric rheumatic diseases (prof. N. Wulffraat, dr. S. Vastert). This initiative resulted in > 15 key note, highly cited research papers from 2015-now, and provided the first developed international guidelines for amongst others macrophage activation syndrome, Juvenile Dermatomyositis, scleroderma, rare primary vasculitides and auto-inflammatory diseases. This project also supported the election of prof. Wulffraat as chair of the current European Research Center on pediatric auto-immune, auto-inflammatory and immune deficiency disorders (ERN-RITA).



Table 4 – Output indicators Auto immunity

1. Research products for peers

Key publications of the past five years and their impact have been described below.

We have established various biobanks containing primary patient materials, and are presently collecting the samples for the UCAN-CANDU biobank which collects blood samples of all JIA patients in Canada and The Netherlands. These samples can also be used for scientific purposes by all members of UCAN-CANDU.

We actively train numerous (PhD)students which leads to 4-5 dissertations per year.

2. Research products for societal target groups

- S. Vastert was member of the NVKR committee that developed the first national treatment guideline on JIA (published through the Dutch Society of Pediatrics in 2019).
 - Klokhuis, an educational tv program broadcasted on the Dutch national television, with weekly outreach in most elementary schools in the Netherlands as well, and directed for children aged 8 years and older (and their parents) developed in 2018 in collaboration with dr. S. Vastert and 1 of his patients, a dedicated broadcasting (20 minutes) on how it is to deal with Juvenile Idiopathic Arthritis, a disease that is constantly present but not always recognized/appreciated by their surroundings.
 - By being granted funding (5,4 million €) for UCAN CAN DU, our department (Prof. Wulffraat, dr. Swart, dr. Vastert and dr. de Roock) is currently developing the necessary (research) infrastructure in order to be able to transform the current step-up treatment strategies in JIA into stratified/personalised treatments. This encompasses novel IT solutions, cutting edge translational science and development of eHealth tools in compliance with European Union (GDPR) and Canadian Regulations. Upon request of involved patient partners, we are feeding back real time derived research and clinical data to the patients, in accordance with ethical committee approval, and accompanied by clear explanations on the clinical meaning of these data to the treating physician and the patients. This newly developed infrastructure really enables direct translation of this research project into clinical practice within the term of the grant (2017-2022).
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3. Use of research products by peers

Together the PI's in the autoimmune section have generated 311 publications (2015-2019) which have been cited more than 2000 times.

These articles included publications in the following journals as last author:

2x Blood (IF 15), 4x Arthritis Rheum (IF 8), 3x J Clin Invest (IF 13), Autophagy (IF 11), 4x Ann Rheum Dis (IF 12), Lancet (IF 53), 2x Cell Rep (IF 8), eLife (IF 8), Nat Rev Rheum (IF 15), Nat Rev Gastroenterol Hepatol (IF 17), 2x Nat Rev Immunol (IF 42).

4. Use of research products by societal groups

- the development and publication of the SHARE guidelines on JIA/JDM/SLE/Vasculitis/Scleroderma/Periodic fevers
 - Anakinra as 1st line treatment in sJIA
 - Acceptance of recommendations for vaccinations in JIA/under immunosuppressive treatment
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5. Marks of recognition from peers

- We were appointed as EULAR Center of Excellence, from 2016-2012. We are the 2nd Paediatric Hospital worldwide with this acknowledgement for pediatric rheumatology/immunology.
 - We were recently appointed Dutch Arthritis Society Center of Excellence 2018-2013
 - Together the PI's in this autoimmune section have acquired 40 grants (2015-2019) totaling €17.2M
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6. Marks of recognition from societal groups

- Prof. Wulffraat is recently (2018) appointed/chosen as chair of the current European Research Center on pediatric auto-immune, auto-inflammatory and immune deficiency disorders (ERN-RITA).
 - dr. Annet v Royen and dr. Femke van Wijk were granted in 2018 a specific research grant from the American Patient Organisation on Myositis (100k \$) to develop their biomarker guided therapy strategy into clinics.
 - Both in 2016 (dr. J. Swart on pharmacovigilance of biological therapy in JIA) and 2018 (dr. L. Nijhuis on development of a stop strategy for biologicals and DMARDS making use of maintenance therapy with vitamin B3/Nicotinamide), researchers from our department were awarded (bronze medals) by the French Patient Organisation Kourir for the most relevant research from a patient perspective on the congress of the European Pediatric Research European Society (PREs).
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Appendix F: Cystic Fibrosis

Table 3 – Process indicators Cystic Fibrosis

1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment

A lifelong, healthy living for people with CF inspires us. We aim to provide optimal, individual care by developing new diagnostic and therapeutic approaches for unmet medical needs in CF. This requires a multidisciplinary research infrastructure that aligns stakeholders so that new innovations can be efficiently assessed in the context of short and long term health.

2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

Care for CF is changing from symptomatic to 'curative' using CFTR modulators that repair the basic disease defect. Additional therapies remain needed, as well as personalized applications of treatments and solutions for those that still do not benefit. We design 5 years strategic research programs with the Dutch CF patient foundation (www.ncfs.nl/onderzoek/lopend) to ensure optimal alignment with patient expectations and needs. The current HIT-CF2 program aims to develop, validate and implement ethically sound personalized care based on innovations from our research center.

3. Stakeholders are involved in formulating the main research questions

Patients: We design 5 years strategic research programs with the Dutch CF patient foundation (www.ncfs.nl/research) to ensure optimal alignment with patient expectations, needs, and dissemination of results. For many projects, patients are part of advisory boards already during the design phase.

Industry: we have performed many public private partnerships where industry partners and UMC Utrecht jointly form projects.

Payers and regulators (EMA) have been involved from the initiation phase of an EU H2020 initiative to develop a living biomarker for patients with rare forms of CF.

4. The research questions are feasible and are pursued using optimal and efficient design

We have structural collaborations with statisticians that are specialized in rare diseases and small clinical trial designs (Prof Dr K Roes and team). Additionally, we collaborate with the IT specialists and datamanagers from Julius Clinical to develop appropriate data infrastructures according to FAIR principles.

5. What is 'the next step' if the project delivers positive results

We have a wide range of projects, spanning basic science to clinical studies. As such, we have many end-users that can benefit integrated, and we reach out to them via various communication channels (e.g. interviews by Associated press, Al Jazeera, Nature Medicine, Cell stem cell, Science, etc). Our strongest integration is with patients through the Dutch patient foundation and other fundraisers (e.g. Muco and friends). Additionally, we have a unique H2020 project where three competing industries joined to create breakthroughs for patients, that also connects strongly to payers and EMA. We are also strongly assisting preclinical drug development of industry in collaborative or contract research and by building high quality biorepositories. Valorisation of knowhow and IP is via continued interactions with the Utrecht Holding (e.g. organoid swelling, or antimicrobial peptides), and outlicensed IP can then be valorized by other parties such as foundation Hubrecht Organoid Technology. Academic users are fostered through involvements at European (CF society (ECFS)) level: CF coordinating center of the European Research Network Lung; part of the ECFS clinical trial network, and board member of the ECFS basic science working group.

Table 4 – Output indicators Cystic Fibrosis

1. Research products for peers

From 2012 – 2018: the UMC Utrecht CF center contributed to approximately 165 articles in peer reviewed journals. Key publications included a series of articles that described the first application of personalized care using adult stem cell organoid cultures (Dekkers et al, Nat Med 2013, Dekkers et al, Sci Transl Med 2016, de Winter et al, ERJ 2018); in addition we contributed to field-defining preclinical studies (mode of action of CFTR modulators, Okinoyeda et al Nat Chem Biol 2013, Dekkers et al, ERJ 2016) or the first genetic repair of human stem cells by crispr cas9 (Schwank et al., 2013 Cell stem cell), and the development of key CFTR modulators (Taylor-Cousar et al, NEJM, 2017), as well as the ethics of organoids for CF (Bredenoord et al, Science 2017; Boers & Bredenoord, Nat Cell Biol 2018; Boers et al, J Cyst Fibr 2018). Number of dissertations: 11.

- UMC Utrecht with HUB build an intestinal stem cell biorepository that provides the largest sustainable CF patient collection in the world (www.hub4organoids.eu).
- UMC Utrecht develop intellectual property and knowhow on in vitro disease models and antimicrobial peptides.

2. Research products for societal target groups

EXAMPLES

- Reporting of scientific advancements in (inter)national lay media: Volkskrant, De wereld draait door, RLT4 nieuws, Associated press, New York Times, The atlantic, BBC podcast the naked scientists, etc.
- Interviews by scientific media: Nature Medicine, Cell Stem Cell, SciBX (Science business exchange by Nature group).
- Regulatory bodies: report of EMA on potential of our work (EMA/26775/2016) and reference to our work in ZIN document on advice for ivacaftor market entry that facilitated access to patients with rare mutations.



3. Use of research products by peers

EXAMPLES

- Citations of published work:
 - Schwank et al, Cell stem Cell 2013, google scholar: 797 citations
 - Dekkers et al, Nature Medicine, 2013 google scholar 405 citations
 - Dekkers et al, Science Transl Med, 2016 google scholar 150 citations
 - High quality research publications leads to recruitment of co-funding and private public partnerships
 - Use of biobanked materials and outlicensing knowhow for academic and commercial research
-

4. Use of research products by societal groups

EXAMPLES

- Provisionary reimbursement by ZIN or Vertex pharmaceuticals of CFTR modulators beyond the CFTR mutations on the label.
 - Diagnostic classification of difficult to diagnose patients
-

5. Marks of recognition from peers

- UMC Utrecht coordinates a 8.5M H2020 EU grant
 - Prizes: ECFS award 2017 (person of the year), ERS excellence award for research in cystic fibrosis (2017), Gerd Doring prize 2015, NRS Best thesis award, Maarten Kappellen prijs 2012, NRS best translational research 2012-2014, many poster and presentation prizes at international conferences.
 - PI Beekman and van der Ent are frequently invited for lectures on (inter)national conferences, including keynote lectures (ECFS basic science meeting 2019, German patient meeting 2017), act at international review boards for clinical studies (van der Ent) or research grants (Beekman).
-

6. Marks of recognition from societal groups

EXAMPLES

- Quotation of the Dutch minister of health in a Cell stem cell interview on personalized medicine application of organoids
 - Willy van Heumen prize 2017 for alternatives on animal experimentation
 - Memory of understanding with the Dutch CF foundation recognizing UMC Utrecht as preferred research partner
-



Appendix G: Recurrent Respiratory Infections

Table 3 – Process indicators Recurrent respiratory infections

1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment

We believe that key research questions can only be answered through multidisciplinary and networking approaches. We have the mission to do high quality research, to improve knowledge of respiratory infections, and to develop safe and effective therapeutic and preventive interventions. We work with global experts to decrease the global burden of respiratory infections during childhood.

2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

We actively work with patients and translate their needs into research. We acknowledge their specific expertise and input on the research agenda. Similarly, we continuously interact with public health (RIVM) (IMI-funded RESCEU, PERISCOPE), global health (p.e. WHO) (BMGF-funded GOLD) and private institutions (AstraZeneca-funded INFORM) to serve all stakeholders of childhood respiratory infections.

3. Stakeholders are involved in formulating the main research questions

We obtained research funds from the EU specifically to involve patients in the research of RSV infection. We have founded the ReSViNET foundation which is an active academic network with annual meetings (for example this year in Ghana), and publications (p.e Mazur, Lancet Respir Med 2015)

4. The research questions are feasible and are pursued using optimal and efficient design

We always have appropriate budget for data management, only use professional database systems (pe Castor, Research Online) and continuously work with the Julius Center, where expertise in research methods is available. A senior researcher (Christiana Naaktgeboren) of the Julius Center has been employed by the RSV research group. She is co-supervisor of young researchers and a liaison to all expertise within the Julius Center.

5. What is 'the next step' if the project delivers positive results

- In our networks (ReSViNET, GEN, GOLD, IMPRINT, PERFORM, EUCLIDS, I-Move) we have collaborations with multiple stakeholders
- In our unit there is a dedicated business developer (Leyla Kragten, Julius Clinical) that helps researchers make connections with industry. Louis Bont is part of the U-TRIAL management team.
- In our unit we rely on a diversity of funders, in cases we combine public-private funds to strengthen our valorisation efforts.
- In our unit we emphasize the importance of dissemination to a broad range of possible users, for each project there is a combination of strategies. We publish recent results in professional literature and give lectures for a professional society. We regularly present our work in the public media (BBC news, NOS news, NRC).
- We support talent development. All researchers at any stage of their career are continuously supported to develop themselves while provided freedom to do so.

Table 4 – Output indicator Recurrent respiratory infections

1. Research products for peers

Recent original publications with senior authorship of the RI team.

- Bacterial and viral respiratory tract microbiota and host characteristics in children with lower respiratory tract infections: a matched case-control study. Man et al. *Lancet Respir Med*. 2019
 - Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. Scheltema et al *Lancet Respir Med*. 2018
 - Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. Scheltema et al *Lancet Glob Health*. 2017
 - A host-protein based assay to differentiate between bacterial and viral infections in preschool children (OPPORTUNITY): a double-blind, multicentre, validation study. Van Houten et al *Lancet Infect Dis*. 2017
- Number of **dissertations**: about 5 per year for the Respiratory Infections group.

2. Research products for societal target groups

Elisabeth Sanders works at RIVM and UMC Utrecht and her goal is to translate research into prevention of respiratory infections and public health strategies. Recent reviews with senior authorship of the RI team.

- The microbiota of the respiratory tract: gatekeeper to respiratory health. Man et al. *Nat Rev Microbiol*. 2017
- The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. Mazur et al (by ReSViNET foundation). *Lancet Infect Dis* 2018.
- Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. Mazur et al (by ReSViNET foundation). *Lancet Respir Med* 2015.

We initiated a maternal vaccination working group with obstetricians, neonatologists and the RIVM that impacted on the ZonMW Research Agenda for “Mother and Child health”

An *ethical framework* for post-trial access for maternal vaccines was developed: Mazur et al, Lancet Respir Med 2019.



3. *Use of research products by peers*

H-index (last 5 years) by Google Scholar
D Bogaert 31 (18)
L Bont 35 (17)
EA Sanders 46 (17)

Microbiota data are made in public repositories upon publication, allowing peers to replicate the data and use them for teaching purposes or meta- or new analyses.

Protocol of our metagenomic pipelines have been shared upon request as well as knowledge is actively shared through societal guidelines (ERS monograph 2019), or invited method paper (ERJ 2019). Moreover, we actively provide workshops and lectures at societal meetings to share knowledge regarding study design, laboratory pipelines and data analyses tools (ATS, ERS, ECCMID).

4. *Use of research products by societal groups*

L Bont wrote a UMC Utrecht blog about the negative consequences of requiring a minimum of 4 first author original publications on the quality of PhD-led research (www.UMC Utrechtrecht.nl/nl/Nieuws/Minimaal-vier-artikelen-in-je-proefschrift) which was picked up internally and externally (www.dub.uu.nl/nl/blog/minimaal-vier-artikelen-je-proefschrift-helemaal-niet-nodig).

5. *Marks of recognition from peers*

D Bogaert VIDI (ZonMw); Senior Scottish Clinical Fellowship award (NRS) (2016)
L Bont International Congress of Pediatric Pulmunology (CIPP) Award for Contribution to Understanding Childhood Respiratory Disease and Global Medical Education.
Elisabeth Sanders UMCG JONXIS medal for Pediatric Research translated into Clinical Practice (June 2019)

6. *Marks of recognition from societal groups*

Researchers of the RI team are regular advisors of national and international public health institutes (RIVM, CDC, ECDC) and global health bodies (WHO), international regulators (EMA, FDA), funders (ZonMw, Wellcome Trust, EU, NIH, BMGF) and decision makers (gezondheidsraad).

Microbiome work received recognition from international press, including BBC news, BBW world, the Guardian.



Appendix H: Pre/periconception

Table 3 – process indicators pre/periconception

1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment

- Through internationally recognized and societally well-embedded clinical and translational research our program adds to the improvement of health and wellbeing of: individuals/prospective parents confronted with (future) fertility or genetic problems and their future offspring.
- Our research will improve the diagnosis and prognosis of: the disease burden of infertility reduced ovarian reserve/early menopause and implantation failure.

2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

Our main research questions are formulated together with patient organisations, funders and (inter-) national research agendas.

- Examples: In 2018 the “Setting Future Priorities for Infertility Research” (PSP) was launched by the international COMMIT group (subdivision of Cochrane) in which Freya, Fertility Europe, the WHO and researchers (Helen Torrance) from the UMC Utrecht are partners and which aims to define international research questions which should have priority for funding in the field of infertility. Patients are also actively involved in setting the national research agenda of the NVOG in conjunction with ZonMW, a process which has been led by Frank Broekmans as chair of the special interest group Assisted Reproduction and pillar Reproductive Medicine of the NVOG.
- In 2018 we received ZonMW funding together with the Rehabilitation experts from the Hoogstraat to work together with BOSK (an organisation for parents of children with cerebral Palsy) to study which items should be added to our outpatient follow up program (e.g. sleep problems, eating disorders, physical activity).

3. Stakeholders are involved in formulating the main research questions

Our strategic research program annually meets with patient representatives from the diseases we study to discuss our research lines. For several grants we involved organisations such as Freya,

Example: The research team has regular consultations with Freya, the Dutch society for people facing infertility, which stimulates patient-oriented research questions and mutual relationships. Since 2017 our team has been part of COMMIT (a Cochrane initiative) which aims to develop a core (patient orientated) outcome measure set for infertility research. In this process we closely collaborate with Freya and Fertility Europe, the European umbrella organisation representing patient associations in the field of (in)fertility in more than 20 European countries. As mentioned above our team is also part of PSP in which Freya and Fertility Europe are also actively involved.

4. The research questions are feasible and are pursued using optimal and efficient design

Two team members are qualified Clinical Epidemiologists, consulted for statistical and methodological support. Our Department employed a professor from Julius Center, for many years and who provides extensive, top of the range bio-statistical support with our researchers.

Together with our research office team members, and our data managers, we ensure that research is done to the highest scientific standards. This includes according to European Privacy Laws.

5. What is ‘the next step’ if the project delivers positive results

- We are funded by the Dutch governmental institutions, including NWO, and ZonMW.
- We are members of a number of guideline committees and working groups.
- We are involved in clinical (inter)national guidelines and benchmarking, such as NVOG and Reproductive Medicine research consortium.

Table 4 – output indicators pre-/periconception

1. Research products for societal target groups

The researchers provided a wealth of research products for target groups outside of academia. In all research lines the importance of e-health and big data became apparent, which was also acted upon. Large datasets from the peri- and preconception (Broekmans/Torrance created 3 IPD datasets), as well as the antenatal and neonatal research lines have been deposited or are pending for public use.

Together the investigators participated in several local and national outreach activities, ranging from workshops on neuroanatomy for children to patient-participation gatherings focusing on fertility problems.

Several of the PIs have been lecturing for general audience and appeared in national written and broadcasted media. One example is the media coverage of the *in utero* MRI study, a collaboration between the antenatal and neonatal research lines: Prof. Benders and Dr. Bekker repeatedly appeared in national newspapers openly discussing the importance and safety issues of these studies. This media coverage paved the way between the general audience and several of our researchers, exemplifying to others how the public dialogue can help in gaining support for clinical research with the most fragile patients.

Our research products are directly translated into educational programs, several of which are organized as international summerschools (Reproductive & Maternal Health: A Global Perspective; Global Childhealth; MRI of preterm brain). Inhouse generated software packages are distributed to participants, (e.g. software programs called Signalbase and Bedbase).



2. *Use of research products by peers*

A citation analysis published in the literature demonstrated that the UMC Utrecht is among the most cited center in Clinical Reproduction worldwide ([Trends in clinical reproductive medicine research: 10 years of growth](#)). Aleixandre-Benavent R, Simon C, Fauser BC. *Fertil Steril*. 2015 Jul;104(1):131-7.e5).

Use of datasets: OPTIMIST dataset was used to validate the McLernon prediction models

Software tools: IMPORT and EXPORT database on ovarian response prediction used for design of the Optimist trial

Research facilities: Isala Hospital, Antonius Hospital and Spaarne Hospital used the Research Facility for their local PhD candidates: Anouk Rutten, Mirjam Hanstede, Julienne Janse

3. *Use of research products by societal groups*

The professional society is going to change IVF treatment guideline nationally and internationally based on research by our unit (OPTIMIST RCTs). Prof. Broekmans chaired the Guideline Development group of the European Society for Human Reproduction and Embryology ESHRE on this topic. An implementation study will be performed alongside this changed policy.

The INSIGHT trial results are part of the updated COCHRANE library

4. *Marks of recognition from peers*

Several PhD students from Reproductive Medicine received prizes from various scientific societies including ASRM, VFS and de Snoo – van 't Hoogerhuys foundation

Dr. Torrance was asked to be part of COMMIT/PSP: a subdivision of Cochrane which is aiming to set core outcome measure sets and future priorities for fertility research

Prof. dr. F. Broekmans: Chairman of Special Interest group Reproductive Endocrinology ESHRE, Chairman Pillar Reproductive Medicine of NVOG, Chairman SIG Assisted Reproduction Pillar RM of the NVOG. Associate Editor for Human Reproduction, Chairman Guideline Development group Ovarian Stimulation.

Dr. M.H. Emanuel was awarded as Dutch inventor of the year for the development of hysteroscopic morcellation and tissue removal and won several awards from the society of Reproductive Surgeons and The American Association of Gynecological Laparoscopists.

Several PhD students supervised by dr. S. Veersema received prizes from the European Society Gynecological Endoscopy.

5. *Marks of recognition from societal groups*

Prof. Broekmans advises the Minister of Health about reproductive medicine health care policy

Prof. Broekmans is the chair of the 'pijler Voortplantingsgeneeskunde' of the Dutch society for Gynaecology and Obstetrics (NVOG)

Prof. Broekmans is Coordinator of the SIG Reproductive Endocrinology of the ESHRE



Appendix I: Obstetrics

Table 3 – process indicators Obstetrics

1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment

- Through internationally recognized and societally well-embedded clinical and translational research our program adds to the improvement of health and wellbeing of:
 - Pregnant women, specifically with maternal disease, complications of pregnancy such as hypertensive disease, abnormal placentation, postpartum hemorrhage.
 - high-risk newborns: preterm infants, infants with congenital abnormalities or growth restriction and infants with perinatal hypoxic-ischemic brain injury.
- Our research will improve the diagnosis and prognosis of:
 - Maternal high-risk pregnancy outcomes and Abnormal brain development and injury, in high risk infants as stated above.

2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

Our main research questions are formulated together with patient organisations, funders and (inter-) national research agendas.

Examples: The Dutch Society of Obstetrics and Gynaecology (NVOG) has a national knowledge (gap) agenda, which was determined with patient organisations, funders (i.e. ZonMW, leading the change), researchers of the obstetric field and stakeholders. Most of the research projects of the department obstetrics are embedded within this agenda (maternal and vascular health, maternal mortality and morbidity, fetal growth restriction, congenital anomalies, Probaat-3, Sugardip). Within the inter(national) obstetric surveillance systems (INOSS, Nethoss) research questions are formulated and researched with using same definitions and outcome datasets of severe maternal mortality and morbidity. The ICHOM data set was developed internationally together with patients and stakeholders with input from researchers from our group (Prof Franx, Dr Groenendaal, Prof Bonsel). Dr Bekker is member of the board of the Dutch TRIDENT consortium performing the nationwide implementations studies of the non-invasive prenatal test (NIPT).

3. Stakeholders are involved in formulating the main research questions

Patient advisory boards are involved in the grant writing team but also in the performance and analysis of the studies. Within the Dutch Society of Obstetrics and Gynaecology, (NVOG) patients are heavenly involved in setting the national research knowledge agenda. We also include pregnant women themselves in the development and analysis of all research. For example the home-telemonitoring system (safe@home) has been developed with and for pregnant women. The perspective of the pregnant women regarding the obstetric care is an important theme within our research. Together with the Health Care institute (Zorginstituut of the Netherlands) (ZIN) patient reported outcomes measures (PROM) of the International ICHOM set for maternity care are being implemented in the obstetric care. Tools to improve shared decision making are being developed, such as decision aids regarding the counseling of imminent extreme preterm labor and the decision between comfort care or active care. This decision aid has been developed together with our neonatologists but also with the patient advisory board of premature delivery and parents.

4. The research questions are feasible and are pursued using optimal and efficient design

Three team members are qualified Clinical Epidemiologists, consulted for statistical and methodological support. Our Department employed a professor from Julius Center, for many years and who provides extensive, top of the range bio-statistical support with our researchers. Together with our research office team members, and our data managers, we ensure that research is done to the highest scientific standards. Within the NVOG-2 consortium trial-, data-management and statistical analysis is guaranteed. This according to European Privacy Laws. All research in collaboration with the other departments such as Prinses Maxima Center for Oncology, and the Department of Developmental Origins of Disease (DDOD) is supported by the Trial and Data Center from the Division.

5. What is 'the next step' if the project delivers positive results

- Nutricia-Danone (preventive studies placenta insufficiency), Roche, Phillips (ehealth, big data for small babies), Luscci, Ferring, NWO TOP, VIDJ, EU, Gates, Leardal call on global health and eHealth.
- For our business development, we collaborate with dedicated partners within the UMC Utrecht, such as the THINK initiative at the Julius Centre. In addition we are supported by the startup incubator UtrechtInc. Also, the UMC Utrecht has a valorisation officer supporting researchers via centralized clinical trials (U-trials.) And we have an officer/representative for clinical trials via our research theme child health.
- We are funded by the Dutch governmental institutions, including NWO, and ZonMW, the European Union, charities such as the Nierstichting (Kidney Foundation) and research contracts with private partners (companies like Nutricia/Danone).
- We are members of a number of national guideline committees and working groups including Otterlo and ARCH workgroup We underscore the importance of dissemination to a broad range of possible users, for each project there is a combination of strategies including as mentioned above.

We are involved in clinical (inter)national guidelines and benchmarking, such as NVOG, regularly invited for discussions with Dutch policy-makers, EU panel discussions with EU research officers and WHO. We have coverage of about 10 times a year in the general media or grey literature, such as newspapers (volkskrant, NRC), talk programs on television or radio (see next paragraph).



Table 4 – output indicators Obstetrics

1. Research products for peers

Antenatal (22 PhD dissertations completed, 18 ongoing PhDs)

- Franx/Bekker lead a program for measuring Patient reported outcomes en experiences (PROMs & PREMS) together with Zorginstituut Netherlands. Franx developed a Standardized outcome measures for pregnancy and childbirth, an ICHOM proposal together with an interdisciplinary and international Working Group (Scheerhagen et al 2015, Nijagal et al 2018). Dr Bekker will lead a program to implement PROMs/PREMS in obstetric health care and will develop learning tools to support the implementation (granted by ZonMw 2019).
 - Van Rijn/Franx have developed a biobank (as part of the UMC Utrecht Biobank) of placental bed biopsies of women with a history of placental bed disorders, including preeclampsia and intrauterine growth restriction and controls. This gives us the opportunity to study preeclampsia and intrauterine growth restriction and long-term risk cardiovascular disease. (Veerbeek et al 2016). This is a METc approved biobank stored at the department. Governance is with the PI: Franx
 - Clinical expertise on IUGR has expanded and provided several new clinical and translational research initiatives (Pauw et al., 2017, Hypertension) linking maternal cardiovascular health to child health. This will be continued now by linking the research initiatives to the unique resources for translational research of the Department for Developmental origins of Diseases (Lely/Hoebeek) and imaging research (Bekker/deHeus/Benders).
-

2. Research products for societal target groups

The researchers provided a wealth of research products for target groups outside of academia. In all research lines the importance of e-health and big data became apparent, which was also acted upon. Several of the PIs have been lecturing for general audience and appeared in national written and broadcasted media. This media coverage paved the way between the general audience and several of our researchers, exemplifying to others how the public dialogue can help in gaining support for clinical research with the most fragile patients. Our research products are directly translated into educational programs, several of which are organized as international summerschools (Reproductive & Maternal Health: A Global Perspective; Global Childhealth; MRI of preterm brain).

3. Use of research products by peers

Meta-analysis across species technique which is frequently used in discussion of failure on drug investigation in pregnancy. PREVENT and PREVFEM (kidney disease after pregnancy) datasets are integrated into international datasets. Nethoss and maternal mortality data are used within INOSS network: Vandenberghe G, Bloemenkamp K, Berlage S, Colmorn L, Deneux-Tharaux C, Gissler M, Knight M, Langhoff-Roos J, Lindqvist PG, Oberaigner W, Van Roosmalen J, Zwart J, Roelens K; INOSS (the International Network of Obstetric Survey Systems). The International Network of Obstetric Survey Systems study of uterine rupture: a descriptive multi-country population-based study. BJOG. 2019 Feb;126(3):370-381. oi: 10.1111/1471-0528.15271. Epub 2018 Jun 12. PubMed PMID: 29727918.

Probaat 1 and 2 data are incorporated in systematic reviews and meta-analysis. Ten Eikelder ML, Mast K, van der Velden A, Bloemenkamp KW, Mol BW. Induction of Labor Using a Foley Catheter or Misoprostol: A Systematic Review and Meta-analysis. Obstet Gynecol Surv. 2016 Oct;71(10):620-630.

4. Use of research products by societal groups

National Obstetric congress in Paramaribo, Suriname (2016 and 2019), in which data from registries and audit of maternal mortality and morbidity are discussed, new guidelines are implemented and reviewed. 180 obstetric caregivers are trained in acute obstetrics situations which needed attention according to outcome of the studies.

Outcome of induction of labor trails (Probaat) are incorporated in national Dutch guideline induction of labor.

5. Marks of recognition from peers

Dr .Bekker is member of the board of the dutch TRIDENT group, responsible for the nationwide TRIDENT studies implementing cell free fetal DNA testing in the Netherlands. She has given several invited lectures and workshops (national/international). Prof. Lely received a klinisch fellowship from ZonMw.

Prof. Bloemenkamp is chair of Dutch audit committee maternal mortality and morbidity (AMS/Nethoss) and of International Obstetric Surveillance systems (INOSS). Prof. Bloemenkamp is member of expertteam of women with clotting diseases (Nederlands Zorgnetwerk voor vrouwen met een stollingsstoornis) and of women with autoimmunedisease such as SLE, APS (NVLE).

Prof. Bloemenkamp, Dr Lely and Dr Bekker are asked to serve as opponent in several international PhD thesis defense ceremonies.

6. Marks of recognition from societal groups

Prof. Lely of the obstetric staff are program member of ZonMw.

Dr. Bekker (obstetrics) is program member of the Citrien fund of ZonMw.

Prof. Bloemenkamp is invited as expert/ consultant for obstetric care in Suriname (PAHO) and WHO (sepsis, postpartum hemorrhage, maternal mortality).



Appendix J: Neonatal damage

Table 3 – process indicators Neonatal damage

1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment

- Through internationally recognized and societally well-embedded clinical and translational research our program adds to the improvement of health and wellbeing of high-risk newborns: preterm infants, infants with congenital abnormalities and infants with perinatal hypoxic-ischemic brain injury.
- Our research will improve the diagnosis and prognosis of abnormal brain development and injury, in high risk infants (e.g. infants born preterm).

2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

Our main research questions are formulated together with patient organisations, funders and (inter-) national research agendas.

In 2018 we received ZonMW funding together with the Rehabilitation experts from the Hoogstraat to work together with BOSK (an organisation for parents of children with cerebral Palsy) to study which items should be added to our outpatient follow up program (e.g. sleep problems, eating disorders, physical activity).

Examples of the perinatal Neuroprotection and Neuroregeneration with neuroimaging research agenda in close collaboration of obstetrics, neonatology and department of Developmental Origins of Disease (former NIDOD) generated over the last 5yrs over 30 reviews papers, such as Vaes et al., 2019 Front. Physiol and Annink et al., 2017, Curr Pharm Des:

Neuroprotection with allopurinol in longstanding perinatal program rewarded in funding from the:

- European Union's Horizon 2020 research (6 million, perinatal asphyxia, No 667224, 13 countries, over 100 hospitals – UMC Utrecht scientific PI) and
- Dutch Science foundation (1.8 million, reducing perinatal brain injury in babies with congenital heart defects, ZONMW project 80-84800-98-42022, Dutch multicenter). Neuroregeneration with stem cells: Preclinical (rodent/baboon) studies by NIDOD and subsequent clinical study in neonatology funded strategic research program until 2020 by The Netherlands Organisation for Scientific Research (NWO). 'Adult mesenchymal stem cells (MSC) to regenerate the neonatal brain: from bench-to-bedside' (€1.7m).
- 'Nutribrain'-study in collaboration with Nutricia research, Albino: H2020 RCT with allopurinol in Hypoxic-Ischemic Events, Crucial trial: RCT with allopurinol in CHD babies (ZonMw), Dinosaur for stroke regeneration, Passion (ZONMW) stroke regeneration with stem cells).

3. Stakeholders are involved in formulating the main research questions

Our strategic research program annually meets with patient representatives from the diseases we study to discuss our research lines. For several grants we involved organisations such as: VOC, BOSK, Stichting hartekind. Additionally, we have several industrial partners in health technology, nutrition companies, and pharmacy. With whom we formulate research and perform several (pre)clinical trials.

4. The research questions are feasible and are pursued using optimal and efficient design

Three team members are qualified Clinical Epidemiologists, consulted for statistical and methodological support. Our Department employed a professor from Julius Center, for many years and who provides extensive, top of the range bio-statistical support with our researchers. Together with our research office team members, and our data managers, we ensure that research is done to the highest scientific standards. This includes according to European Privacy Laws. All research collaborations are supported by the Trial and Data Center.



5. What is 'the next step' if the project delivers positive results

Nutricia-Danone (neuroprotective nutritional interventions), ANT-Neuro, Eemagine, Artinis, Chiesi (stem cells), Roche, Phillips (ehealth, big data for small babies), Luscci, Rythmm, Ferring and Merck Serono, ACE pharmaceuticals (allopurinol studies)

For our business development, we collaborate with dedicated partners within the UMC Utrecht, such as the THINK initiative at the Julius Centre. In addition we are supported by the startup incubator UtrechtInc. Also, the UMC Utrecht has a valorisation officer supporting researchers via centralized clinical trials (U-trials.) Examples are studies such as Nutribrain, dolphin, ALBINO, crucial. And we have an officer/representative for clinical trials via our research theme child health.

We are funded by the Dutch governmental institutions, including NWO, and ZonMW, the European Union (in FP7 and H2020 calls) ,charities such as the Brain Foundation (Hersenstichting) and research contracts with private partners (companies like Chiesi, Nutricia/Danone).

We are members of a number of guideline committees and working groups, including the Dutch working group on postmortem examination, the Dutch working group on extremely preterm birth, the Dutch working group on post term birth, and the working group on benchmarking of Neonatology.

We underscore the importance of dissemination to a broad range of possible users, for each project there is a combination of strategies including as mentioned above.

We are involved in clinical (inter)-national guidelines and benchmarking, such as NVK, NVOG, N3 and Reproductive Medicine research consortium, and regularly invited for discussions with Dutch policymakers and EU panel discussions with EU research officers.

We have coverage of about 50 times a year in the general media or grey literature, such as newspapers (Volkskrant, NRC), talk programs on television or radio (see next paragraph).

We will expand our international visiting traineeships, e.g. by collaborating with the Trialect-company for knowledge/cultural exchange among physicians and biomedical scientists. We will also initiate an exchange program for your fellows to visit other Neonatal-Neurology expertise centers.

Table 4 – output indicators Neonatal damage

1. Research products for peers

(12 PhD dissertations completed, 10 ongoing PhDs)

- Preclinical techniques have been developed to improve selection infants for therapeutic hypothermia after perinatal asphyxia (Neonatology. 2017;112(1):24-2). Novel MRI techniques were developed to serve as biomarkers for long-term neurodevelopmental outcome following perinatal asphyxia (Arch Dis Child Fetal Neonatal Ed. 2017 Mar;102(2):F147-F152; J Pediatr. 2018 Jan;192:33-40.e2).
 - Key publication of model for preterm brain injury: Impaired oligodendrocyte maturation in preterm infants: Potential therapeutic targets. van Tilborg E, Heijnen CJ, Benders MJ, van Bel F, Fleiss B, Gressens P, Nijboer CH. Prog Neurobiol. 2016
 - Combined fetal inflammation and postnatal hypoxia causes myelin deficits and autism-like behavior in a rat model of diffuse white matter injury. Van Tilborg E, Achterberg EJM, van Kammen CM, van der Toorn A, Groenendaal F, Dijkhuizen RM, Heijnen CJ, Vanderschuren LJM, Benders MNJL, Nijboer CHA. Glia. 2018
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2. Research products for societal target groups

The researchers provided a wealth of research products for target groups outside of academia. In all research lines the importance of e-health and big data became apparent, which was also acted upon. For antenatal and neonatal research lines IP's have been deposited or are pending for public use.

Together the investigators participated in several local and national outreach activities, ranging from workshops on neuroanatomy for children to patient-participation gatherings focusing on normal neurodevelopment and neurodevelopmental disorders.

Several of the PIs have been lecturing for general audience and appeared in national written and broadcasted media. One example is the media coverage of the in utero MRI study, a collaboration between the antenatal and neonatal research lines: Prof. Benders and Dr. Bekker repeatedly appeared in national newspapers openly discussing the importance and safety issues of these studies. This media coverage paved the way between the general audience and several of our researchers, exemplifying to others how the public dialogue can help in gaining support for clinical research with the most fragile patients.

Our research products are directly translated into educational programs, several of which are organized as international summerschools (Reproductive & Maternal Health: A Global Perspective; Global Childhealth; MRI of preterm brain). Inhouse generated software packages are distributed to participants, (e.g. software programs called Signalbase and Bedbase).

Explanation of research as expert about fetal and neonatal MRI: p20-25NewScientist 2019:

https://issuu.com/vbku/docs/umc_utrecht_brain_center_2019_speci?e=5493772/67869484

Talkshow television/general newspapers:

- <https://dewerelddraaitdoor.bnnvara.nl/media/684222>
- <https://www.volkskrant.nl/nieuws-achtergrond/bij-ieder-onderzoek-met-patienten-zijn-zorgvuldigheid-en-veiligheid-leidend-en-dus-ook-bij-mri-scans-bij-baby-s~bf3263d8/>
- <https://www.nrc.nl/nieuws/2017/02/10/wat-heet-te-vroeg-bij-een-vroeg-geboren-baby-6630424-a1545435>
- <https://www.volkskrant.nl/wetenschap/zwangere-vrouwen-ondergaan-eindelijk-mri-scan-en-zorgen-zo-voor-belangrijke-informatie-bij-vroeggeboorte~b2d4c9c6/>

Big data for small babies, public speaker and journal ICT health:

- <https://www.finaps.nl/casestudies/data-analytics-umc-utrecht/>
- <https://www.finaps.nl/news/interview-manon-benders-umc-utrecht-en-tim-pijl-finaps-in-ict-health/>
- <https://www.cio.co.nz/article/656413/how-big-data-saving-small-babies/>

3. Use of research products by peers

Use of research facilities: PhD from Italy, Portugal, Croatia, are visiting on a regular exchange the neonatology to gain knowledge in the research we do in neonatal Neurology, and with a main aim in research in neonatal Neurology. They make use of the development of signal base and MRI post-processing imaging.

Used software tools as mentioned above by: University Hospital Leuven (L. Thewissen), AZ St Jan Brugge (A Casaer), University Hospital Tartu, Estland (T Meshvat), UZ Milaan (S Pisoni, M. Fumagali).

Development of benchmarking procedures to compare NICUs in the Netherlands and abroad.

Development of (inter-)national guidelines for treatment of Perinatal Asphyxia, Posthaemorrhagic Ventricular Dilatation, Cerebral Sinovenous Thrombosis and Neonatal Seizures.

Development European neonatal neuroimaging and neuromonitoring guidelines (European Standards of Care for Newborn Health).

4. Use of research products by societal groups

One of our team members in Neonatology is responsible in the Netherlands to implement neonatology treatment protocols, including new treatments, Utrecht provided hypothermia protocol and teaching as standard care for the entire country.

Symposia and protocol on hypothermia was provided nationally

International courses on MRI of the newborn brain and Hands-on cerebral ultrasound courses were given.

Several workshops on neonatal neuro-monitoring were given all over the world.

5. Marks of recognition from peers

Prof. de Vries: honorary award of the German speaking society of child neurology (GNP)

Prof. de Vries: Harwood Nash Lecture, Toronto

Several PhDs of neonatology won several prizes during the European society for pediatric research and the world congress pediatric associated societies

3 Staff members are member of the prestigious European Neonatal Brain Club (ENBC) and one staff member of the prestigious international collegium of Perinatology (ICP)

International collaborative efforts have led to multidisciplinary H2020-research initiatives including both public and private partners.

Several staff members are asked to serve as opponent in several international PhD thesis defense ceremonies.



Self-evaluation report strategic research program **Circulatory Health**





1. Self-evaluation Circulatory Health	219
1.1 Reflection on previous SEP recommendations	219
1.2 Reflection on previous objectives	220
1.3 Governance and organisation of the program	224
1.4 Collaborations with UMC Utrecht divisions	226
1.5 SWOT analysis	229
1.6 Evaluation practices and/or policies	229
1.7 Patient involvement	229
2. Research themes	231
2.1 Heart failure	231
2.2 Cerebral ischemia	232
2.3 Aneurysms	233
2.4 High risk (hypertension, diabetes and atherosclerosis)	234
3. Expertise areas	236
3.1 Genetics	236
3.2 Imaging	236
3.3 Cardiovascular Clinical Epidemiology	236
3.4 Global Cardiovascular Health (A) and Diversity (B)	237
4. Future prospects 2020-2025	239
Appendices	242
Appendix A: Composition of supportive Circulatory Health bodies	243
Appendix B: Circulatory Health principal investigators	244
Appendix C: Research theme Heart Failure	246
Appendix D: Research theme Cerebral Ischemia	255
Appendix E: Research theme Aneurysms	258
Appendix F: Research theme High Risk - Diabetes, Hypertension and Atherosclerosis	262
Appendix G: Expertise area Genetics	272
Appendix H: Expertise area Imaging	276
Appendix I: Expertise area Cardiovascular Clinical Epidemiology	279
Appendix J: Expertise area Global Cardiovascular Health (A) and Diversity (B)	284
Appendix K: Expertise area Global CV Health (A) and Diversity (B)	288



1. Self-evaluation Circulatory Health

In January 2019, the strategic theme Circulatory Health was officially launched as one of the six focus programs of the UMC Utrecht. This strategic theme was based on the existing portfolio of cardiovascular research in the UMC Utrecht and on the existing infrastructure of the research departments involved. The main objectives set out for the program were to:

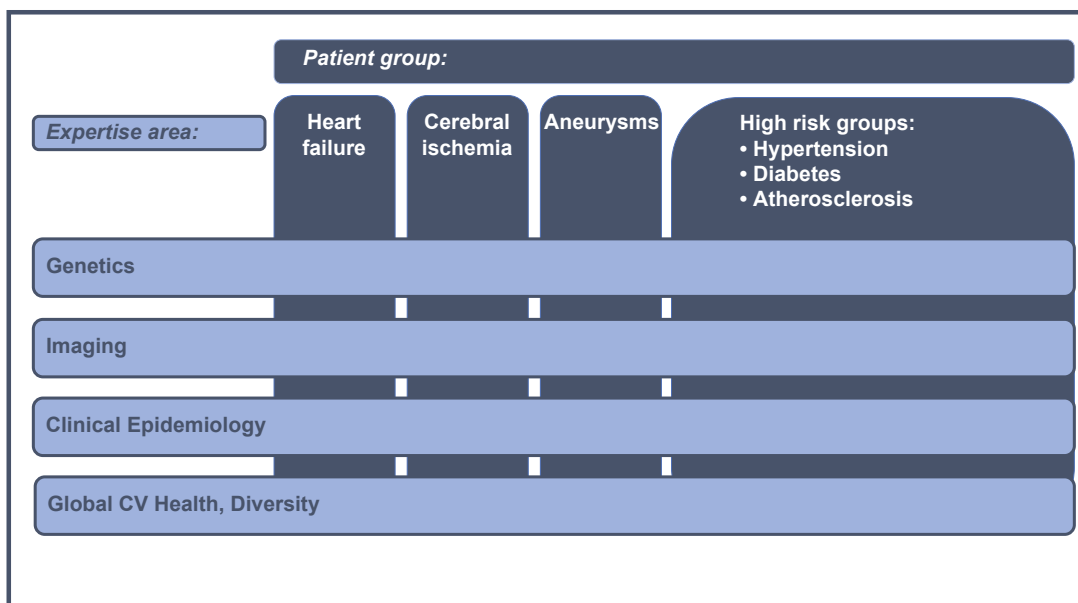
- Structure cardiovascular research more clearly within the UMC Utrecht.
- Introduce a clear focus in this research.
- Stimulate collaboration between departments and divisions, active in this field.
- Strengthen and extend cardiovascular research as to become an internationally recognized cardiovascular center.
- Provide state-of-the-art patient care and excellent cardiovascular education.

All these objectives relate back to one **mission**: to (inter)nationally reduce the burden of cardiovascular disease. To establish that, our **strategy** over the years focused on improving the prediction, prognosis, prevention and treatment of cardiovascular disease. This strategy has been extensively described in previous documents, e.g. the internal 2016 midterm SEP and in the business case Circulatory Health for 2015-2019. At present, the program provides a highly integrated environment for state-of-the-art patient care (the Center for Circulatory Health, "Hart- en vaatcentrum"), a stimulating environment for performing internationally competitive (translational) research and a clearly structured line of cardiovascular education.

This self-assessment covers the period 2013-2018 and represents a follow-up on the external 2010-2012 SEP (June 2014) and the internal 2013-2016 midterm evaluation (October 2016). In this assessment we reflect on the recommendations and objectives described in these evaluations and the results obtained.

1.1 Reflection on previous SEP recommendations

The first recommendation of the previous (midterm) SEPs was to focus research on the potentially most successful and competitive clusters. Therefore, the program now carries a clear focus in its research on four patient groups/research themes: heart failure, cerebral ischemia, aneurysms and patients at higher risk for cardiovascular disease. Expertise areas defined for studying these patient groups include genetics, imaging, clinical epidemiology and global cardiovascular (CV) health/diversity (see figure).



These strategic research focuses are evaluated constantly and determined by multiple factors that could change over time (e.g. positioning of key principal investigators (PIs), patient numbers, clinical relevance, (inter)national developments, funding opportunities). Therefore the chosen patient groups/themes are evaluated periodically for relevance and feasibility.



The added value of Circulatory Health lies in the cross-fertilisation that has been created between scientists from the different participating research groups and departments, as well as merging of research infrastructures (patient cohorts, databases, laboratories) that share a common research focus. The selected themes and expertise areas have been prioritized in all strategic and investment decisions, leading to significant focus in the research portfolio over time.

The second recommendation was to reduce the number of program coordinators and PIs to increase effective operation. There are currently 88 registered PIs in the program (see Appendix B), which is 17 PIs less than were registered at the time of the SEP 2010-2012. The introduction of the new strategic focus allowed us to appoint a limited number of research coordinators who represent the selected research themes (see table below). These research coordinators chair so-called research tables, in which PIs interactively discuss research focus, staffing, infrastructure, funding opportunities, etc. for that particular research theme. The research tables advise the program manager research (prof. dr. F. Asselbergs) on the implementation of research policy (investments, appointments and other decisions to be made).

Research theme	Coordinator
Heart Failure	• Prof. dr. A. Hoes, prof. dr. F. Asselbergs till 2018
	• Prof. dr. F. Rutten, dr. L. van Laake from 2018 onwards
Cerebral ischemia	Dr. B. van der Worp
Aneurysms	• Dr. J. van Herwaarden till 2018
	• Prof. dr. D. de Kleijn from 2018 onwards
High risk	Prof. dr. F. Visseren

It was also noticed that the program's emphasis was on translational research with relatively little basic research. A third recommendation, therefore, was to direct more attention to basic research. In the review period several efforts have been made to improve the position of basic research:

- Several full professors with a basic research focus were appointed: prof. dr. J. Bakkers (Genetic metabolic diagnostics, 2015), prof. dr. E. van Rooij (Molecular cardiology, 2015) and prof. dr. J. Sluijter (Cardiovascular regenerative medicine, 2018).
- The cardiovascular research activities in regenerative medicine from the departments of nephrology and cardiology were relocated to the Hubrecht Institute building to stimulate collaboration between basic scientists working in the field of regenerative medicine.
- In 2018 plans were developed and executed to create the Laboratory for Circulatory Health (CHL) in which all basic, preclinical and clinical researchers will work together at one physical location to enhance communication and cooperation between them and to decrease lab costs by sharing facilities.

1.2 Reflection on previous objectives

In the business case Circulatory Health 2015-2019 and in the midterm SEP (2016) the strategy and main *objectives* were laid down. Below the objectives are described and reflected on.

Research (preclinical and clinical):

a. To strengthen basic cardiovascular research by supporting and stimulating collaborations with other UMC Utrecht strategic research programs and other research institutes on analogous topics.

A strong connection has been built with the Hubrecht Institute (groups of prof. dr. E. van Rooij and prof. dr. J. Bakkers) on cardiovascular topics such as disease mechanisms and regenerative medicine. Also the collaboration between UMC Utrecht strategic themes (Brain, Child Health, Regenerative Medicine, Cancer, Infection & Immunity) on overlapping topics has been efficiently improved since 2018 (e.g. on topics like high blood pressure in pregnant women, stem cell research, congenital heart defects, stroke, cardio-oncology).

b. To sustain a large animal facility, specialized in cardiovascular research and device development.

Circulatory Health (in particular the groups of prof. dr. J. Sluijter, prof. dr. D. de Kleijn, prof. dr. G.J. de Borst, prof. dr. M. Vos) participates in and makes use of The Common Animal Laboratory ([GDL](#), site in Dutch), which is a Utrecht University institute that facilitates research and education for which laboratory animals are necessary.



Within the GDL, animal experiments are conducted by researchers who mainly come from the UMC Utrecht, the faculties of Science and Veterinary Medicine, and to a limited extent by researchers from outside the university.

c. To stimulate public-private partnerships (valorisation) with regard to device, drug and biomarker development.

Examples of public-private partnerships presently active within Circulatory Health:

- The collaboration between Philips and dr. J. van Herwaarden/prof. dr. G.J. de Borst, which led to the world's first application of the Fiber Optic RealShape (FORS) technology for minimal invasive vessel surgery. Formerly, guiding wires and catheters were visualized during minimal invasive vessel surgery in 2D-fashion with X-rays. With FORS these medical auxiliary tools are 3D visualized with light that comes from optical fibers in the guiding wires, which improves the clarity and contrasts of imaging considerably. Since guiding wires and catheters are now better visible the expectation is that this type of surgery takes less time and facilitates the operation procedure. Moreover, both patients and medical professionals will benefit since they will be less exposed to X-rays.
- In collaboration with AMT (EU grant EUROSTARS and "Kansen voor West"; Prof. dr. P. Doevendans) smart vessel connectors are being developed.
- The ACDC project: Together with Abott a new electroporation modality is being developed for ablation of arrhythmogenic cardiac substrate. After very successful safety studies the project is progressing towards a large Randomized Clinical Trial (RCT) in the Netherlands.
- The cardiovascular moonshot REGMED collaboration with various companies and universities with the goal to refurbish human hearts for autologous reimplantation.
- The collaboration between 24care and heart failure researchers to develop EMPOWER, a telemedicine platform for heart failure patients to improve self-management (<https://www.24care.nu/empower>).

d. To stimulate divisions to execute plans for the improvement of research volume, quality, valorisation and talent management focused on the aforementioned four disease entities and key methodologies of the program.

Circulatory Health emphasizes in its discussions with participating divisions the importance of clinical research and the need to give clinicians time to fulfill their academic tasks and be part of our 'research matrix' to connect with research. In theory all clinical PIs of Circulatory Health are 'clinical scientist' but their resources are limited and for some disproportionately much time is on patient care.

e. To encourage genetic and Big Data studies on cardiovascular clinical research.

PIs of Circulatory Health have founded and contributed to multiple global genetic consortia. The appointment of prof. dr. F. Asselbergs and recently prof. dr. P. van Tintelen has catalyzed the cardiogenetics program within Circulatory Health. Sophisticated genetic techniques such as genome-wide association studies (GWAS), next generation DNA sequencing, Chip-seq, single-cell RNA sequencing, 4C, and also clinical data are applied to newly discover cardiovascular disease-related genes. For example, genes that contribute to heart failure and cardiomyopathy, atherosclerosis, aneurysms, and cardiovascular risk factors such as hypercholesterolemia, diabetes and hypertension. A nice example is the focused research on the PLN^{R14Del} cardiomyopathy for which 9 M€ is available through a Leducq grant with a partner in Cincinnati and the PLN foundation (PI: prof. dr. P. Doevendans).

f. To utilize the resources that will be delivered by the Utrecht Cardiovascular Cohort (UCC).

The UCC is operational and represents a biobanking cohort with the purpose of generating a similar and exchangeable dataset and biomaterials from all cardiovascular patients treated in the UMC Utrecht. For further information on UCC, see paragraph 1.3.

g. To identify key research competences that are lacking in our research pipelines from bench to the bed and subsequently stimulate initiating professorships at these positions.

In 2018 we started the initiative to set up the Laboratory for Circulatory Health (CHL); the virtual implementation is expected in the fourth quarter of 2019. This will be the programmatic and physical integration of UMC Utrecht departments that are currently fragmented across various laboratory rooms, departments and divisions in the hospital. It includes all PIs of research groups conducting cardiovascular laboratory tests, their staff, and infrastructure. The laboratory is viewed as the engine of the innovative power of Circulatory Health. The CHL brings together basic, preclinical and clinical researchers from different expertise areas, thus providing a central platform for direct communication and cooperation between the right stakeholders, which in our view is a prerequisite for performing efficient and distinguishing translational research. We aim to create a scientific, multidisciplinary environment with a driven, creative, innovative, and entrepreneurial character where team spirit, innovation and focus on solutions are important characteristics.



Clinical care:

- a. To create, together with the leadership of the involved divisions, an integrated Center for Circulatory Health (“Hart- en vaatcentrum”), in which clinical- and patient-reported outcomes are monitored continuously as a measure for quality control and performance.**

The Center for Circulatory Health (“Hart- en vaatcentrum”) opened officially on November 30th, 2018. Specialists who provide patient-centered care are: cardiologist, vascular internist, vascular surgeon, neurologist and a cardiovascular nurse specialist to organize patient-centered care, ascertaining that patients experience one coherent health care process, even when multiple disciplines are involved. In 2018, 200 patients have been seen following a multi-disciplinary care path. The Center for Circulatory Health very recently received, as first Center in the Netherlands, the EAPC Center Accreditation from the European Association of Preventive Cardiology (EAPC) for the period June 2019-2022.

- b. To integrate care with research.**

Priority for inclusion in UCC will be given to patients that fit the research focus areas. Moreover, integrated care involving multiple disciplines is centered around the specific research domains to ensure that academic clinical care clearly links with our research agenda. Furthermore, to ensure that decisions within clinical departments and divisions fit our research agenda we established a Circulatory Health program committee that includes not only the executive committee of Circulatory Health but also four members of management teams from the largest divisions involved in cardiovascular care.

The Netherlands Federation of University Medical Centers (Nederlandse Federatie van Universitair Medische Centra, NFU) recognizes expertise centers for rare diseases. UMC Utrecht has 21 centers of expertise for rare disorders where patients and healthcare providers can go for expert and integrated care. In collaboration with regional treatment centers, the expertise centers bundle and develop knowledge and expertise in the field of rare disorders, develop protocols and guidelines, coordinate research and ensure adequate referral of patients within and outside the Netherlands. Three out of the 21 centers are connected to Circulatory Health:

- Center for Congenital Vascular Abnormalities Utrecht.
- Center for Hereditary Cardiovascular Diseases.
- WKZ Children’s Heart Center (in collaboration with Child Health).

- c. To increase the impact and visibility of clinical research.**

Circulatory Health also invests in nursing sciences. Prof. dr.T. Jaarsma has been appointed in 2018 and is an expert in the field of self-care and self-management in people with chronic (cardiovascular) disorders.

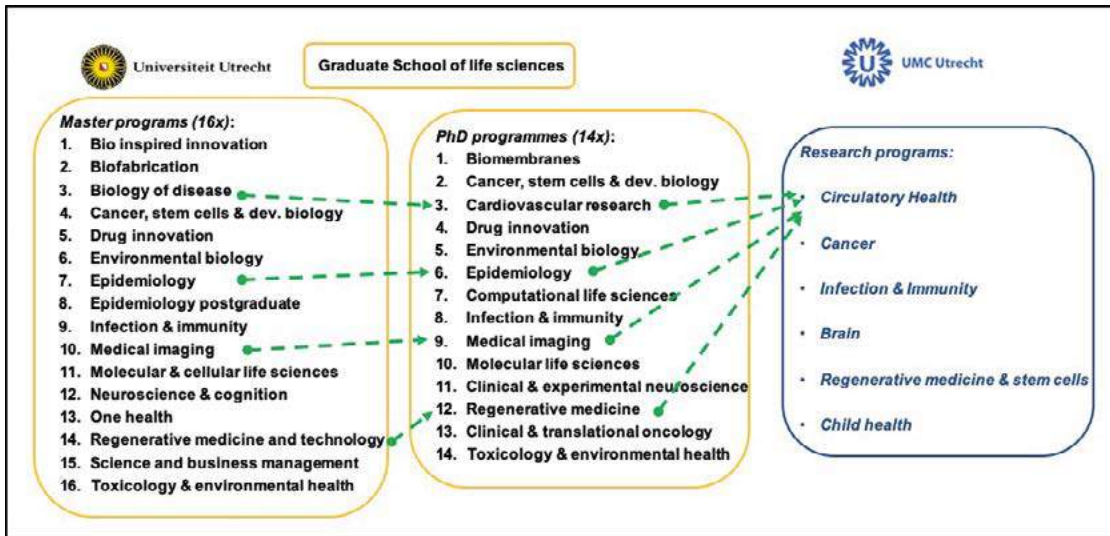
Education:

- a. To develop the UMC Utrecht into an internationally acknowledged cardiovascular education center, not only focusing on education and training of cardiovascular (bio)medical talents and specialists but also on connecting education to patients.**
- b. To operate a talent-scouting program in collaboration with the (bio)medical curricula and UMC Utrecht divisions.**
- c. To facilitate international opportunities for cardiovascular electives in top cardiovascular institutes, and bind talents to our own PhD and medical training programs.**

Circulatory Health has invested considerably in education for the general public, (bio)medical bachelor and master students, as well as for PhD candidates. Since early 2014 the executive management team has assigned the portfolio Education to one of its members; moreover, the program office is supported by an educational coordinator. Initially, the two main objectives were to visualize and, wherever appropriate, strengthen cardiovascular education on Circulatory Health-related topics within the three UU (bio)medical educational directions (i.e. Biomedical Sciences, Medicine and the Selective Utrecht Medical Master [SUMMA]). The first objective has led to the publication of an educational brochure for students to visualize potential cardiovascular tracks within these UU educational directions (3rd edition published in 2018). For the second objective, new elective courses were developed or existing courses were re-designed for both bachelor students Biomedical Sciences and Medicine. Within these bachelor studies the following courses are presently earmarked as ‘Circulatory Health-related’, characterized by a strong involvement of principal investigators and lecturers active within Circulatory Health: 1. *Biomedical Sciences*: Vascular Biology; Cardiac Pathology; 2. *Medicine*: The role of bloodstream and vessel wall; Cardiac disease: from cause to treatment. In this regard it is important to realize that these bachelor studies contain largely fixed curriculae with standard courses, where only the elective parts are accessible for further deepening.



At the master and PhD level, UU offers different educational programmes, which for the Life Sciences are organized by the Graduate School of Life Sciences (GS-LS). The present interrelationships between UU master/PhD programs and the UMC Utrecht strategic research programs is shown in the figure below; with green dashed lines cardiovascular-related educational lines are indicated.



Our overall objective is to create a visible cardiovascular educational line from the UU master programs, via the UU PhD programs, all the way to the UMC Utrecht strategic research program Circulatory Health. However, such obvious line requires the consent of the UU board of directors that, at present, has not been obtained. Nevertheless, in 2017-2018 the master program Biology of Disease officially introduced a cardiovascular track and Circulatory Health principal investigators/lecturers are strongly involved in the organisation and execution of education at both master and PhD levels, through e.g.:

- Directorships of the master programs Biology of Disease (including the cardiovascular track) and Epidemiology.
- Directorships of the PhD programs Cardiovascular Research and Epidemiology.
- Participation in and coordination of several master (e.g. Cardiovascular Epidemiology, Biomolecular and Cellular Cardiology) and PhD courses (Innovations in Clinical Cardiovascular Medicine, Sophisticated Laboratory Techniques in Cardiovascular Research).
- Advisory roles during master (bio)medical interships and PhD projects.

Obviously, the intention for the coming years is to continue our involvement in bachelor, master and PhD (bio)medical education to guarantee a solid and visible basis for cardiovascular education. To illustrate Circulatory Health's commitment to PhD candidate training and supervision the number of completed PhD studies for the review period, supervised by PIs related to Circulatory Health, are summarized in the table below (source: Research Office, UMC Utrecht):

Table - Number of dissertations period 2013-2018

	2013	2014	2015	2016	2017	2018
Number of dissertations	79	91	77	70	66	65

Presently, we are shifting our attention to the development and organisation of education for a general audience and for medical professionals (such as general practitioners [GPs], nursing specialists and assistants learning for medical specialist). For several years now PIs of Circulatory Health are participating in the 'Public Lecture' series of the UMC Utrecht and in workshops to explain complex scientific topics, related to our research themes, to a laymen audience. From 2019 onwards, four times a year grand rounds are organized, in which clinical cases from the Center for Circulatory Health ("Hart- en vaatcentrum") are interactively discussed with our post-academic medical professionals. Noteworthy in this context is also the symposium which was organized around the opening of the Center for Circulatory Health on November 30, 2018, which focused on the impact of preventive and innovative patient care. For both target groups we are currently developing, in collaboration with Elevate, a Massive Open Online Course (MOOC) to familiarize medical professionals as well as the general public with the ins and outs of the cardiovascular diseases treated within the UMC Utrecht. Besides a MOOC, E-zines for each research theme are being generated to inform a broad audience of interesting and exciting developments within our strategic research program.



Talent management and marketing activities:

- a. To provide talented (young) professionals with an education and training program for further career development. The Jacob Jongbloed Talent Society (JJTS; named after a famous Utrecht cardiovascular scientist) was founded in 2012 by the program aiming to strengthen the academic carrier of the most talented cardiovascular researchers. This education and training program had editions in 2014 and 2016. In 2018 new candidates were selected for the JJTS 3rd generation, which started at the beginning of 2019 and is still ongoing.
- b. To provide travel grants to stimulate research and scientific exchange within the four chosen research themes of the program.
In the period 2013-2018 Circulatory Health provided 104 travel grants to PhD candidates and/or starting postdoctoral fellows for a total amount of € 158.610,- to visit (inter)national scientific meetings related to their field of research.
- c. To start marketing campaigns to inform (future) patients, researchers, and students on the state-of-the-art Center for Circulatory Health.
In 2016 a "Public meets Private" symposium was arranged by the members of the 2nd generation JJTS. The first Circulatory Health magazine was released in 2018 and the Center for Circulatory Health ("Hart- en vaatcentrum") opened officially on November 30, 2018 including the symposium 'Impact of prevention and innovative care' with prof. dr. S. Yusuf (McMaster University, Ontario, Canada) as keynote speaker. At the end of 2018 a start was made with the development of an online learning environment (in collaboration with Elevate). To connect with cardiovascular patients and to create awareness for the effect of lifestyle factors on cardiovascular health, Circulatory Health organizes so-called Cardiovascular Days, the last edition being on June 22, 2019 (<https://www.UMC Utrechtrecht.nl/Ziekenhuis/Afdelingen/Hart-en-vaatcentrum/Agenda/Hart-en-vaatdag-22-juni>).

1.3 Governance and organisation of the program

Circulatory Health is anchored in the UMC Utrecht 'Connecting U' strategy (2015-2020). The program 'effective management' has led to an organisational re-orientation at the UMC Utrecht. In 2018 the position of the strategic research programs has been strengthened within the UMC Utrecht, with as primary responsibility the research strategy and the implementation/monitoring of that strategy. From April 1, 2018, the new UMC Utrecht management structure (U-Team, rolling start) is operational with a more prominent position for the chairman of Circulatory Health. The chairman is accountable to the executive board of the UMC Utrecht.

The Circulatory Health program adapted to this new situation and is led by the program committee as of January 1st, 2019. This program committee consists of four members of the management teams from the divisions with the largest scope in cardiovascular care. Four professors with a track record within the field of Circulatory Health and an executive secretary complete the program committee, which meets four to six times a year. The program committee is responsible for the development of the program's policy, ambitions, focus and achievements with regard to clinical care, research, education and marketing & communications. As the program committee has a broad range of responsibilities, portfolio management has been assigned for clinical care (prof. dr. P. Doevendans, period 2013-2019), research (prof. G. Pasterkamp, period 2013-2017; prof. dr. F. Asselbergs, period 2017-2019) and education (prof. dr. H. van Rijen, period 2013-2017; prof. dr. F. Visseren, period 2017-2019). For urgent and daily matters the program committee is represented by its executive committee, which meets once every two weeks.

The program and executive* committees consist of:

Prof.dr. F. Asselbergs (chairman from 1 August 2019)*

*Prof.dr. P. Doevendans**

Prof.dr. D. Grobbee (chairman, period 2013-2019)*

*Prof.dr. F. Visseren**

M. Houterman, MSc (executive secretary)*

Prof.dr. C. Gaillard

J. de Graaf, medical doctor M&G

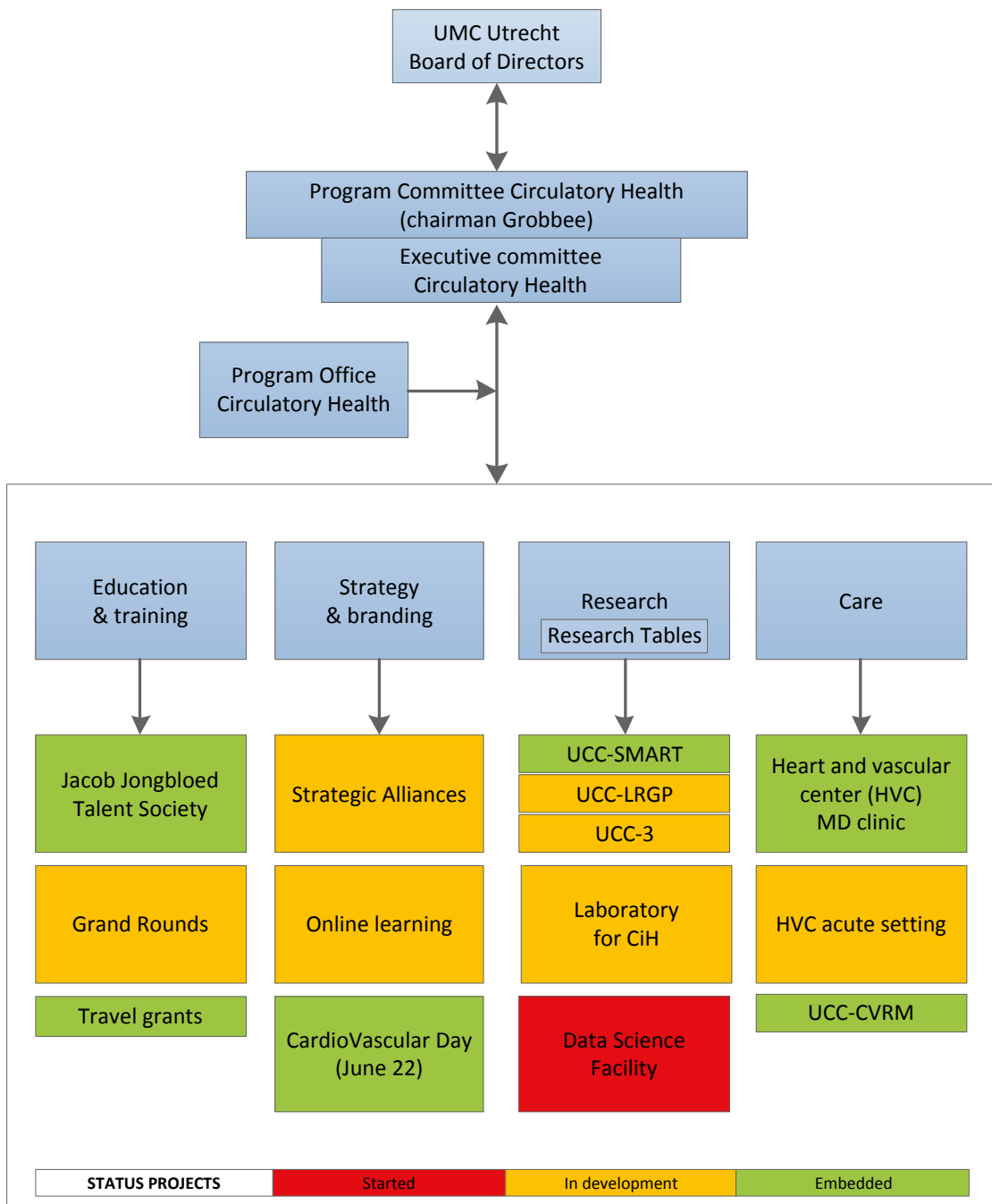
Drs. R. van Lunteren

Prof.dr. W. Suyker

To assist the program committee and executive committee in the development and execution of its policy and projects a program office is operational. This office consists of a program manager and several project officers with varying backgrounds and expertise (nursing, marketing & communication, business administration, research/education). For its composition see Appendix A.



The organisation of Circulatory Health and the status of current projects are schematically summarized in the following figure:



To elaborate on the indicated status of projects, two of them are highlighted:

Utrecht Cardiovascular Cohort (UCC)

To optimize the integration of research and clinical care the UCC was introduced in 2013. The UCC represents a biobanking cohort with the purpose of generating a similar and exchangeable dataset and biomaterials from all cardiovascular patients treated in the UMC Utrecht. Since beginning 2013, the steering committee UCC (composition see Appendix A) has worked on establishing the appropriate conditions and inclusion pathways for establishing this cohort. This steering committee meets once every month and is supported by the support office program manager and a specifically appointed project coordinator. In Spring 2015 the first inclusions were started. The UCC has three components, namely UCC-CVRM, UCC-SMART and UCC-LRGP.



The *UCC-CVRM* component aims to provide care to all new cardiovascular patients in accordance with the Dutch Cardiovascular Risk Management (CVRM) guideline. At the end of 2018 4,140 patients participated in the cohort. Sixty percent of the participating patients in UCC have given permission for participation in scientific research and for extra blood collection for the biobank. From 90% of this group information is received via questionnaires and measurements. All the required data for almost 80% is present (complete CVRM lab). Obviously there is a commitment to complete the data in the database. The UCC-CVRM database is in 2018 enriched with routine care data of general practitioners and the Pharmaceutical Key Figures Foundation (medication prescriptions).

In the *UCC-SMART* section, additional measurements are offered to 800 very high-risk patients from the UCC-CVRM group with the aim to improve the care of patients with cardiovascular disease in the future. Since 2018 UCC-SMART is a combination of UCC with the SMART cohort that has been running for 22 years, with data from 13,300 patients of which 10,096 are still actively participating in the annual follow-up.

UCC-LRGP (LRGP = “Leidsche Rijn GezondheidsProject”): UCC-Utrecht Health Project is an initiative that will start in 2019 involving a phenotypic enrichment of age and sex specific sample of 1000 recent participants of the Utrecht Health Project. The enrichment closely follows what is measured in UCC-SMART so that we expand the distribution of cardiovascular risk and phenotyping across the whole population, from general population to symptomatic patients referred to a tertiary hospital. The enrichment includes imaging of the heart, the abdomen, the carotid arteries, and additional questionnaire on cognition, dietary intake, physical activity, medication, and several blood measurements. The areas we cover are heart failure, abdominal aneurysms, carotid stenosis, and atrial fibrillation.

Laboratory for Circulatory Health (CHL): work in progress

The CHL is the programmatic and physical integration of UMC Utrecht departments that are currently fragmented across various laboratory rooms, departments and divisions in the hospital. It includes all PIs of research groups conducting cardiovascular laboratory tests, their staff, and infrastructure. A laboratory is a crucial component to achieve impact for patients with cardiovascular disease. The laboratory is the connection between basic, translational and clinical research, all with a view to improve prevention, prediction, prognosis and treatment of cardiovascular disease. To maximize innovation and connection between the laboratory and clinical research, it is essential to design and position the CHL close to the clinical need.

The business case for the CHL was designed in 2018 and governance will be agreed on in 2019 with the relevant divisions, followed by a virtual opening. Housing in a new location is part of the Strategic Housing Development Vision (SOH) of the UMC Utrecht.

1.4 Collaborations with UMC Utrecht divisions

Circulatory Health collaborates with all ten divisions of the UMC Utrecht (see table below). With regard to research, the collaboration is organized by:

- Representation in one of the program’s management bodies, such as the program committee, the committee’s executive management team and the research boards of the strategic teams.
- Meetings between management teams (once or twice a year) of the program and division, and formalisation of decisions in a signed agreement.
- Representation in the Steering Committee for the clinical Center for Circulatory Health, which consists of the medical and economic managers of four divisions. This committee meets every month and steers both on the further implementation of the clinical Center for Circulatory Health and the UCC.
- Frequent meeting of the division’s and program’s managers research.



UMC Utrecht Division	Program management			Program-division collaboration				
	Repr. in program committee	Repr. in executive management team	Repr. in research boards of strategic themes	Formal agreement 2012-2013	Formal agreement 2014-2016	Formal agreement 2016-2018	Formal agreement 2019-2020	Annual meeting managers division - program
Heart and Lungs (DH&L)	X	X	X	X	X	X		X
Surgical Specialties (DHS)	X		X	X		X	X	X
Internal Medicine and Dermatology (DIGD)	X	X	X	X	X	X	X	X
Neurosciences	X		X	X	X	X		X
Julius Center for Health Sciences and Primary Care (Julius Center)	X	X	X	X	X	X	X	X
Imaging-Cancer (Imaging)			X	X	X	X		X
Woman and Baby (DV&B)			X	X	X	X	X	X
Laboratories, Pharmacy and Biomedical Genetics (DLAB)			X	X				X
Vital functions (DVF)				X	X	X		X
Pediatrics								X

Principal Investigators (PI)

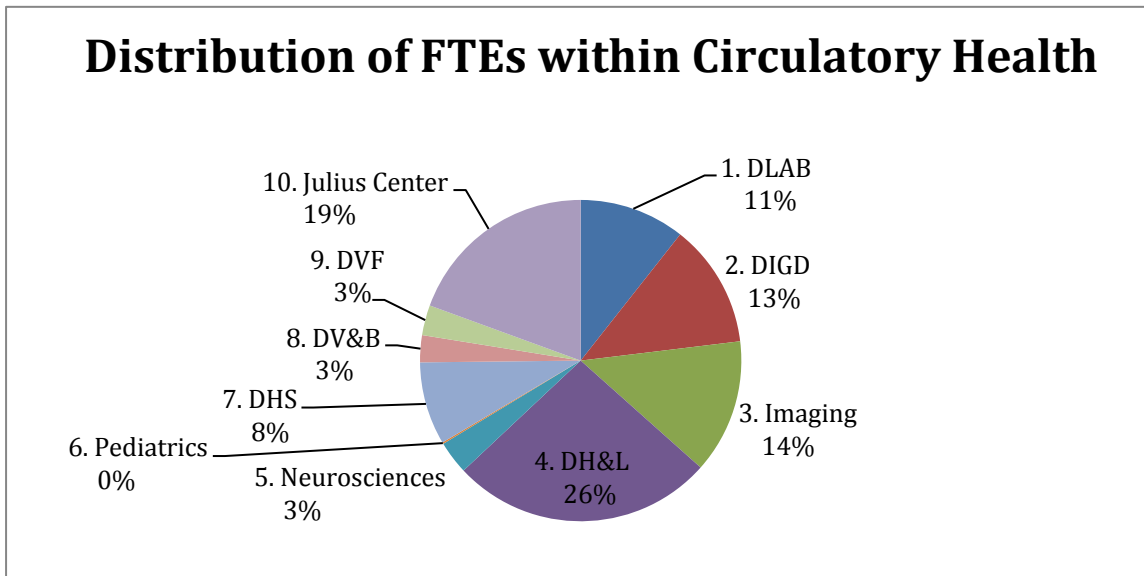
There are currently 88 registered PIs in the program (see Appendix B), which is 17 PIs less than were registered at the time of the SEP 2010-2012. This reduction was a reaction on the recommendation of the review panel to simplify the organisation and to implement further selection (reduced number of program coordinators and PIs). PIs have been identified using the following criteria (either/or):

- Top research within their own research area.
- Strong clinical position.
- Strong research funding acquisition capabilities.
- Research topic or discipline essential to strengthen the research activities of other groups participating in Circulatory Health.
- PI and the group are aligned and show commitment to the Circulatory Health program.



Distribution of fulltime equivalents (FTEs) over the divisions

A schematic distribution of FTEs, participating in Circulatory Health, over the different divisions is shown in the diagram below (source: Research Office, UMC Utrecht):



* For abbreviations of the divisions, see the tabel above.

Research funding

Research funding obtained by Circulatory Health PIs in the period 2013-2018 (source: Research Office, UMC Utrecht):

	2018	2017	2016	2015	2014	2013
Research grants (1)	2,275,897	4,168,455	2,920,090	1,120,351	1,743,250	841,440
Contract research (2)	4,762,502	8,529,722	8,380,920	3,953,706	4,240,854	6,281,845
Other (3)	2,997,926	3,154,502	3,302,322	3,407,703	3,476,394	2,408,799
Total (in €)	10,036,325	15,852,679	14,603,332	8,481,760	9,460,498	9,532,083

Note 1: Research grants obtained in national scientific competition (e.g. grants from NWO and the Royal Academy).

Note 2: Research contracts for specific research projects obtained from external organisations, such as industry, government ministries, European organisations and charitable organisations.

Note 3: Funds that do not fit into the other categories.



1.5 SWOT analysis

In the table below a SWOT analysis of the strategic research program Circulatory Health is provided, including relevant trends and developments during 2013-2018 and a forecast for the coming years; CV = cardiovascular.

SWOT – Circulatory Health		
	Strengths	Weaknesses
Internal	<ul style="list-style-type: none"> World class research in end stage heart failure treatment, carotid surgery and secondary CV prevention Strong connections with general practitioners active in CV research, and (inter)national links CV imaging (for example FORS technology, 4 profs.) CV cohort (UCC) & biobank Connection between care, research and education Multidisciplinary collaboration between CV disciplines Training options in academic setting Expertise centers with regional/national referral patterns (tertiary care profile) Innovative climate Public-private partnerships Talent policy (Jacob Jongbloed Talent Society) 	<ul style="list-style-type: none"> Organisational structure and budget stream does not align with Circulatory Health focus area Number of involved divisions and departments in cardiovascular care and research decrease efficiency and power Low commitment to the program (distance to the workplace) Capacity issue Lack of time for clinical scientist to do research Lack of diversity Housing of cardiovascular involved scientists and clinicians throughout institute, no centralized center for Circulatory Health Dependency on UMC Utrecht housing strategy
	Opportunities	Threats
External	<ul style="list-style-type: none"> Synergy with (top) clinical hospitals in the region Investment in clinical trials through U-Trial From chain care to network care Relocation of care (replacement of care, e-Health) Data Science and Open Science Central role in strategic alliances within Utrecht region Centralisation of congenital heart defects Theme prevention and 'region academy' 	<ul style="list-style-type: none"> Financing of academic healthcare Lack of dedicated budget focus area Need for internationalisation strategy for funding opportunities Priorities set by external bodies Mismatch research focus and academic care

1.6 Evaluation practices and/or policies

In 2013 and 2016, Circulatory Health has carried out a bibliometric analysis by Thomson Reuters – Evidence (documents are available upon request). A new bibliometric analysis is planned for the end of 2019. As mentioned before, PIs have been identified and evaluated using the following criteria (either/or):

- Top research within their own research area.
- Strong clinical position.
- Strong research funding acquisition capabilities.
- Research topic or discipline essential to strengthen the research activities of other groups participating in Circulatory Health.
- PI and the group are aligned and show commitment to the Circulatory Health program.

Further evaluation of researchers is being conducted by division management through 'Performance & Goals', because hierarchically their position is within the division.

1.7 Patient involvement

Description of (research) projects where Circulatory Health involves patients meaningfully:

1. Cooperation with "Harteraad"

"Harteraad" is the patient association for cardiovascular patients and their loved ones. "Harteraad", formerly known as the "Hart&Vaar Groep" (Cardiovascular Group), has been involved in various projects of Circulatory Health for several years and is embedded in the Dutch Heart Association. "Harteraad" participates in many Circulatory Health projects, such as events, lectures, "Hart & Vaar" café and the Center for Circulatory Health ("Hart- en vaarcentrum").



2. *UCC patient panel*

On June 12, 2018, the first UCC patient meeting was held. Together with patients the objectives and characteristics of UCC were discussed. Moreover, it was discussed what patients themselves can do about their cardiovascular risk, what the future plans are and how the best cooperation can take place between patients and healthcare providers. From this patient meeting, 67 patients indicated that they wanted to act as a sounding board within the UCC patient panel.

3. *Relationship building with various patient associations*

Presently, a relationship is actively being built with the following patient organisations:

1. Heart patients Netherlands (<https://www.hartpatienten.nl/>).
2. Pulmonary Arterial Hypertension Foundation (PHA Foundation).
3. Diabetes Association Netherlands (www.dvn.nl).
4. Kidney Patients Association Netherlands (NVN).
5. Contact group Marfan Netherlands (<https://www.marfansyndroom.nl/>).
6. Patient association Hersenletsel.nl.
7. Brain Aneurysm Patients Platform (<http://www.hersenaneurysma.nl/index.php>).
8. Phospholamban (PLN) Foundation.



2. Research themes

2.1 Heart failure

The main research interest of the research theme Heart Failure covers (1) early detection of new onset or worsening heart failure and its complications (such as arrhythmias) in primary, secondary and tertiary care; (2) the importance of co-morbidity in the development, recognition, prognosis and treatment of heart failure; and (3) innovative ways to improve prognosis in all four stages of heart failure such as through e-health, devices, advanced imaging techniques and gene and cell therapy. Basic research focuses on the elucidation of underlying pathways in heart failure, with special emphasis on genetic susceptibility to develop heart failure, the discovery of novel biomarkers and electrical-mechanical remodelling, with the aim to improve prevention of new onset or worsening heart failure and to develop novel therapeutic (and monitoring) targets which will be validated in population-based studies and primary and secondary care patients.

Research objectives:

- Development of a drug discovery pipeline for heart failure using induced pluripotent stem cells (ipsc); creation of an animal model for diastolic heart failure, and models for genetic cardiomyopathies (zebrafish, pigs).
- The use of (epi-)genetic analyses to unravel the mechanisms responsible for complex heart failure and cardiomyopathies.
- To apply the unique expertise in our large animal facility where device and drug testing is executed, meeting high quality standards including electrophysiological studies; the development of models to understand right heart failure during LVAD therapy; and the examination of strategies for biventricular longterm support.
- Expansion of research lines aiming to understand microvascular dysfunction as the underlying cause of diastolic dysfunction using imaging technologies and by studying epigenetic mechanisms in circulating endothelial cells.
- Exploration of mechanisms involved in electromechanical remodelling and arrhythmogenesis using large and small animal models, zebrafish and stem cell-derived cardiomyocytes.

Below specifics and short descriptions are provided of the scientific publications, considered most important, by investigators from the research theme heart failure over the period 2013-present:

1. Uijl A, Koudstaal S, Direk K, et al. Risk factors for incident heart failure in age- and sex-specific strata: a population-based cohort using linked electronic health records. *Eur J Heart Fail.* 2019; doi:10.1002/ejhf.1350.
This paper shows how routine care dataset linkage of primary care and hospital data result in precise estimates of risk for incident heart failure in different age- and sex-specific strata.
2. Madonna R, Van Laake LW, Davidson SM, et al. Position paper of the European Society of Cardiology working group Cellular Biology of the Heart: cell-based therapies for myocardial repair and regeneration in ischemic heart disease and heart failure. *Eur Heart J.* 2016; 37(23):1789-98.
This paper exemplifies our status as internationally renowned experts in the field of stem cell research and therapy for heart failure, as well as our collaborative capacity in bringing together an international, multidisciplinary group of prominent scientists.
3. Kievit RF, Gohar A, Hoes AW, et al. Queen of Hearts and RECONNECT consortium. Efficient selective screening for heart failure in elderly men and women from the community: A diagnostic individual participant data meta-analysis. *Eur J Prev Cardiol.* 2018;25(4):437-446.
This individual participant data meta-analysis on screening for heart failure of community-based cohorts provided a useful screening tool for general practitioners. In addition it is a good example of cooperation within the UMC Utrecht and specialists from other academic centers within the CVON consortia Queen of Hearts and RECONNECT.
4. Mast TP, James CA, Calkins H, et al. Evaluation of structural progression in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *JAMA Cardiol.* 2017;2(3):293-302.
This paper exemplifies our status as internationally renowned experts on cardiac imaging, as well as our collaboration with the top in ARVC/ACM research.
5. Kranias EG, Doevendans PA, Glijnis PC, Hajjar RJ. PLN Foundation. *Cir Res.* 2018;123(12):1276-1278.
In this paper the collaboration is being highlighted between a patient-initiated foundation and academic research.



Below the most important societal contributions by investigators from heart failure over the period 2013-present are provided:

1. The creation, maintenance, and translation in Dutch of the European Society of Cardiology/Heart Failure Association (ESC/HFA) website for patients and carers: www.heartfailurematters.org (hartfalendoetertoe).
2. Participation in the ESC Guidelines on acute and chronic heart failure (2012, 2016).
3. Participation in the ESC Guidelines on hypertrophic cardiomyopathy (2014).
4. Development of patient decision tool on symptoms, together with the Dutch Heart Society (2019-).
5. Awareness of gender differences in cardiovascular disease (2018).
6. Development of ACM risk calculator app to inform patients with arrhythmogenic cardiomyopathy about prognosis (2019).

For more detailed information about process, output and open science indicators of Heart Failure see Appendix C.

2.2 Cerebral ischemia

The main research interest of the research theme Cerebral Ischemia concerns the diagnosis, treatment, and prognosis of patients with acute ischemic stroke, carotid artery disease, intracranial vasculopathy, genetics of stroke, and TIA. The focus lies on (1) intervention and imaging in ischemic stroke; (2) secondary prevention focusing on carotid occlusion and stenosis and vertebral artery stenosis, both with respect to clinical epidemiology and medical treatment; (3) vascular cognitive impairment and neuropsychology, in which the association with other types of dementia and with diabetes is investigated with respect to genetics and imaging techniques; and (4) the association of ischemic stroke and intracerebral vasculopathy and rare neurovascular diseases such as Moya-Moya.

Research objectives:

- Development of models that predict outcome based on multiparametric imaging data.
- Development of non-invasive brain stimulation to improve functional recovery after stroke.
- Identification and investigation of novel genes that play a role in the aetiology of ischemic stroke.
- Development of novel CT and MR imaging techniques for intracranial vessels, brain perfusion and parenchymal damage.

Below specifics and descriptions are provided of the scientific publications, considered most important, by investigators from the research theme Cerebral Ischemia over the period 2013-present:

1. Compter A, Van der Worp HB, Schonewille WJ, et al, for the VAST Investigators. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. *Lancet Neurol.* 2015;14(6):606-614.
This national randomized trial has demonstrated that stenting of symptomatic vertebral artery stenosis, a frequently performed clinical intervention, is associated with a major periprocedural vascular complication in about one in 20 patients. In the population studied, the risk of recurrent vertebrobasilar stroke under best medical treatment alone was low, questioning the need for and feasibility of a phase 3 trial.
2. Van Asch CJJ, Velthuis BK, Rinkel GJE, et al, on behalf of the DIAGRAM investigators. Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study. *BMJ.* 2015;351:h5762. doi: 10.1136/bmj.h5762
This study demonstrates the diagnostic yield and accuracy of early computed tomography (CT) angiography followed by magnetic resonance imaging/angiography (MRI/MRA) and digital subtraction angiography (DSA) in patients with non-traumatic intracerebral hemorrhage.
3. Van Seeters T, Biessels GJ, Kappelle LJ, et al, The prognostic value of CT angiography and CT perfusion in acute ischemic stroke. *Cerebrovasc Dis.* 2015;40(5-6):258-269.
This study showed that CT angiography and CT perfusion can help predict outcome of ischemic stroke. Currently CT angiography and CT perfusion are standard clinical practice and play an important role in decision making in acute ischemic stroke.



Below the most important societal contributions by investigators from Cerebral Ischemia over the period 2013-present are provided:

1. Dutch Heart Association: "Dutch people do not sufficiently recognize the signs of a stroke".
2. Dutch Heart Foundation campaign 'Stroke Alarm' (2016):
 - <https://www.hartstichting.nl/hart-en-vaatziekten/beroerte/herken-de-signalen-van-een-beroerte>;
 - <https://www.UMC Utrechtrecht.nl/nl/Ziekenhuis/Afdelingen/Hart-en-vaatcentrum/Nieuws/Nederlanders-herkennen-de-signalen-van-een-beroert>

For more detailed information about process, output and open science indicators of Cerebral Ischemia see Appendix D.

2.3 Aneurysms

The main research interest of the research theme Aneurysms focuses on abdominal, thoracic, extracranial, and cerebral vessel dilatations/ruptures. Research focuses on (1) development and improvement of innovative (minimal-invasive) endovascular treatment; (2) development of new 3D visualisation techniques that facilitate endovascular interventions with extremely reduced X-ray doses, in close collaboration with a commercial company; (3) discovery of risk factors for aneurysm rupture; and (4) stentgraft behaviour and improvement for repair of thoracic aortic diseases (aneurysms and dissections)(performed in close collaboration with other international centres of excellence in Italy (Milano, Pavia) and the USA (Boston, Michigan)).

Research objectives:

- Examination of non-invasive strategies for AAA treatment, which includes the development of an innovative vessel navigation system that supports endovascular procedures almost without X-ray need.
- Expansion of aneurysm biobank activities, including (epi)genetic analyses on tissue and circulating cell levels.

Below specifics and descriptions are provided of the scientific publications, considered most important, by investigators from the research theme Aneurysms over the period 2013-present:

1. Greving JP, Wermer MJH, Brown RD, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol.* 2014; 13(1): 59-66.
The PHASES score developed in our unit is an easily applicable aid for prediction of the risk of rupture of incidental intracranial aneurysms and is accessible via the internet in the form of an interactive tool.
2. Laarman MD, Vermunt MW, Kleinloog R, et al. Intracranial aneurysm-associated single-nucleotide polymorphisms alter regulatory DNA in the human circle of Willis. *Stroke.* 2018;49(2):447-453.
This study demonstrates that genetic variants linked to intracranial aneurysms are located in regulatory regions of the DNA, where they likely affect the expression of genes involved in cell adhesion and extracellular matrix formation.
3. Cremers CH, van der Bilt IA, van der Schaaf IC, et al. Relationship between cardiac dysfunction and cerebral perfusion in patients with aneurysmal subarachnoid hemorrhage. *Neurocrit Care.* 2016;24(2):202-206.
This study shows that patients suffering from a ruptured cerebral aneurysm, often also suffer from temporary cardiac dysfunction. Those with temporary cardiac dysfunction have a poorer outcome.
- 4A. Backes D, Rinkel GJE, Greving JP, et al. ELAPSS score for prediction of risk of growth of unruptured intracranial aneurysms. *Neurology.* 2017;88(17):1600-1606.
- 4B. Backes D, Vergouwen MD, Tiel Groenestege AT, et al. PHASES Score for Prediction of Intracranial Aneurysm Growth. *Stroke.* 2015;46(5):1221-1226.

These studies show that scores are important to predict growth and thereby risk of rupture of intracranial aneurysms. They can help physicians decide on optimal timing of follow-up imaging in patients with unruptured intracranial aneurysms.

Below the most important societal contributions by investigators from Aneurysms over the period 2013-present are provided:

1. The PHASES score developed in our unit is an easily applicable aid for prediction of the risk of rupture of incidental intracranial aneurysms and is accessible via the internet in the form of an interactive tool. The score is applied in many clinical centers worldwide in decision making on whether to treat an intracranial aneurysm or not.



2. One of our researchers has initiated an international consortium on the genetics of intracranial aneurysms within the international stroke genetics consortium (ISGC; <https://strokegenetics.org/>) currently comprising GWAS data of 10,000 well-phenotyped cases, making it the largest cohort worldwide. Different international researchers involved in the field of intracranial aneurysm genetics work with these data.
3. In collaboration with Philips one of our researchers applied, as a world's first, the Fiber Optic RealShape (FORS) technology for minimal invasive vessel surgery. Formerly, guiding wires and catheters were visualized during minimal invasive vessel surgery in 2D-fashion with X-rays. With FORS these medical auxiliary tools are 3D visualized with light that comes from optical fibers in the guiding wires, which improves the clarity and contrasts of imaging considerably. Since guiding wires and catheters are now better visible the expectation is that this type of surgery takes less time and facilitates the operation procedure. Moreover, both patients and medical professionals will benefit since they will be less exposed to X-rays.

For more detailed information about process, output and open science indicators of Aneurysms see Appendix E.

2.4 High risk (hypertension, diabetes and atherosclerosis)

"High risk" denotes research in patients that are at a particularly high risk for developing a first clinical or subsequent cardiovascular event. Many patients in the focus areas of the program have such elevated risk (in particular patients with hypertension, diabetes, atherosclerosis), and require optimal selection of primary or secondary preventive interventions. They are subject of targeted research.

Certain groups stand out with regard to identifiable risk factors and are at particular interest for the strategic research program. The patient groups hypertension, type 2 diabetes and patients with female-specific risk factors cover an area of closely related risk factors and diseases leading to increased cardiovascular risk. The main group hypertension has a specific focus on complicated hypertension. Diabetes has a specific focus on type 2 diabetes and cardiovascular diseases. The group of patients with female-specific risk factors has a focus on HELLP, gestational diabetes, PCOS and POF. For etiologic, diagnostic, prognostic and therapeutic research regarding the relations between hypertension/diabetes mellitus/female-specific risk factors and vascular disease, three cross-connections can be identified: insulin resistance (obesity, metabolic syndrome, PCOS, HIV), sympathetic activity (new interventions, chronic kidney disease) and vascular stiffness/media calcification (vascular imaging, vascular ageing, pseudoxanthoma elasticum). These cross-links between hypertension and diabetes mellitus work synergistically and create a unique and integrated translational research network with a strong focus on patient outcomes and novel therapies.

Specific interest and expertise is developed over the last few years in prediction of cardiovascular risk in various high-risk groups, including patients with diabetes, patients with clinical manifest vascular disease, apparently healthy people and elderly subjects/patients. To further personalize cardiovascular prevention it is important to know an individual's cardiovascular risk. The SMART cohort (>13,000 patients) is an important infrastructure for this type of research, conducted in close collaboration with (inter)national partners, such as Harvard Medical School, Boston (Prof. dr. P. Ridker), Imperial College London (Prof. dr. N. Poulter), University of Sydney (Prof. dr. M. Woodward, Prof. dr. J. Chalmers), University of Gotheborg, Sweden (Prof. dr. S. Gudbjörnsdottir) by pooling data from various cohorts and clinical trials. This has resulted in a research track on 'Prediction of lifetime cardiovascular risk and prediction of individual treatment effects'.

Research objectives:

- Becoming a leading center in clinical research in blood pressure-lowering therapy with devices (renal denervation, barostenting, barostimulation).
- Strengthening clinical research in the field of diabetes and vascular disease.
- Strengthening position in the chronic kidney disease, blood pressure and preeclampsia & developmental plasticity field; in collaboration with Obstetrics.
- Establishing a leading role in pre-clinical research understanding mechanisms of cardiovascular disease in the female sex.
- Strengthening position as a leading center in research on the cardiorenal syndrome (CRS) field. Development of new metabolic models of CRS with HFpEF.



Below specifics and descriptions are provided of the *scientific* publications, considered most important, by investigators from the research theme High Risk over the period 2013-present:

1. Celeng C, Maurovich-Horvat P, Ghoshhajra BB, et al. Prognostic value of coronary computed tomography angiography in patients with diabetes: a meta-analysis. *Diabetes Care*. 2016;39(7):1274-1280.
This study showed that CTA in patients with diabetes allows for safely ruling out future events, and the detection of CAD could allow for the identification of high-risk patients in whom aggressive risk factor modification, medical surveillance, or elective revascularisation could potentially improve survival.
2. Aengevaeren VL, Mosterd A, Braber TL, et al. Relationship between lifelong exercise volume and coronary atherosclerosis in athletes. *Circulation*. 2017;136(2):138-148.
This study showed that athletes with a high lifelong exercise volume are more likely to develop more atherosclerotic plaque, especially more coronary artery calcification, than athletes with less intense exercise volume.
3. Zoet GA, Benschop L, Boersma E, et al.; CREW Consortium. Prevalence of subclinical coronary artery disease assessed by coronary computed tomography angiography in 45- to 55-year-old women with a history of preeclampsia. *Circulation*. 2018;137(8):877-879.
This study showed that women aged 40-55 with a history of previous preeclampsia have a higher risk of developing coronary atherosclerosis with a higher level of a coronary artery calcification.
4. Kaasenbrood L, Boekholdt SM, Van der Graaf Y, et al. Distribution of estimated 10-year risk of recurrent vascular events and residual risk in a secondary prevention population. *Circulation* 2016;134(19):1419-1429.
In this study the SMART risk score was externally validated in >18,000 patients with cardiovascular diseases. Currently the most used risk score to predict the risk of subsequent cardiovascular events and available at <https://www.u-prevent.com>.
5. Dorresteijn JA, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. *BMJ*. 2016;352:i1548.
In this paper a novel methodology is described to predict lifetime risk and to predict individual treatment effects.

Below the most important societal contributions by investigators from High Risk over the period 2013-present are provided:

1. Contribution to various cardiovascular guidelines including ESC/ESH Hypertension guideline 2018 (dr. W. Spiering), Dutch Cardiovascular Guideline (Prof. dr. A. Hoes, Prof. dr. F. Visseren).
2. <https://www.u-prevent.com>: Interactive website with various lifetime cardiovascular risk calculators for patients with diabetes, patients with clinical manifest vascular disease, apparently healthy people and elderly subjects/patients. The website was released August 2018 and is now mentioned in the Dutch CardioVascular Risk Management (CVRM) guidelines.

For more detailed information about process, output and open science indicators of High Risk see Appendix F.



3. Expertise areas

3.1 Genetics

The cardiovascular genetics area has a broad range of expertises and is involved throughout Circulatory Health across different research themes. Using genome-wide association studies (GWAS), next generation DNA sequencing, Chip-seq, single-cell RNA sequencing, 4C, and clinical data, new genes have been discovered that contribute to heart failure and cardiomyopathy (enlarged and thickened heart muscle), atherosclerosis (stroke, coronary heart disease), aneurysms, and cardiovascular risk factors such as hypercholesterolemia, diabetes and hypertension. Most genetic work is done in collaboration with other international research groups. Pls of Circulatory Health founded several global consortia and contribute to many others.

In this expertise area, we aim to understand underlying biological mechanisms to detect novel drug targets and better ways to select those patients who will truly benefit most from cardiovascular therapies. Every patient responds slightly differently to a disease and treatment, calling for a shift in care towards precision medicine. Our focus is on disease modifiers that explain phenotypic heterogeneity such as exposure effects (for example, environment, sports, medication, occupation) and genetic modifiers (genes or mutations that can alter the expression of another gene, allelic imbalance) in order to study how and why a disease presents differently in patients. It is our expectation that these deep genetic interrogations, once thought of as futuristic, may one day become standard care, not only for patients, but also for healthy individuals.

For more detailed information about process, output and open science indicators of Genetics see Appendix G.

3.2 Imaging

The Imaging area strives to deliver the best possible imaging services for patients with cardiovascular diseases. To achieve this, guideline-recommended current state-of-the-art methods are incorporated and new imaging techniques and methods are developed for clinical use. The questions being pursued concern both common and uncommon cardiovascular diseases for which UMC Utrecht is a tertiary referral center. These include but are not limited to ischemic and non-ischemic hereditary and acquired cardiomyopathies, congenital heart disease, heart failure, aorta, complex peripheral arterial disease, brain aneurysms, hemorrhagic stroke, ischemic stroke, multisystem aspects of cardiovascular disease such as heart-brain and bone-cardiovascular interactions. In addition, specific groups with elevated cardiovascular risk are studied, such as women with reproductive disorders. Finally, cardiovascular risk in healthy athletes is studied. In all of these areas there is a need for fast, reliable and comprehensive imaging. As such, there is a strong focus on development of new cardiac and vascular CT and MR imaging techniques and post-processing methods and bringing these to the clinic.

For more detailed information about process, output and open science indicators of Imaging see Appendix H.

3.3 Cardiovascular Clinical Epidemiology

Cardiovascular clinical epidemiology conducts scientific research into solutions for the early recognition, prevention and treatment of various cardiovascular conditions among which heart failure, stroke, heart attack, aneurysms, peripheral arterial disease and venous thrombotic conditions. The goal is to delay the vascular aging process during the course of life and thereby reduce the burden of disease due to cardiovascular disease.

Our research follows the DEPT_H approach: i.e., research into Diagnosis, Etiology (causes), Prognosis and Therapy. Methods are applied from the total range of statistical and epidemiological study designs, ranging from multi-center randomized controlled studies into the effects of preventive and therapeutic interventions to large and small cohorts, case control and cross-sectional studies into determinants and prognosis of vascular conditions. In our research we closely and intensely collaborate with various disciplines of the Julius Center (e.g., methodology group) and with researchers and clinicians in the UMC Utrecht within Circulatory Health.



Cardiovascular clinical epidemiology research is structured in three themes:

1. The theme *Brain* focuses on research into determinants and functional consequences of vascular and neurodegenerative changes in the brain that occur with aging and that have a major impact on patients, healthcare and society. The emphasis is on normal and accelerated brain aging and on both macro- and microvascular changes. For our etiologic research we use advanced innovative imaging techniques to study neurobiological mechanisms that underlie vascular brain aging. We also use state-of-the-art modeling techniques for prediction to develop diagnostic and prognostic prediction rules for brain abnormalities. We study these aspects in all clinical settings; from the general population to third-line care and in different (patient) populations and make efficient use of existing infrastructure and existing cohorts in the general population, in primary care and in the hospital.
2. The theme *Heart* focuses on subclinical and clinical heart conditions that have important consequences for patients, health care and society. Clinical topics include heart failure, atrial fibrillation, ischemic heart disease and acute coronary syndrome. Emphasis is on normal and accelerated heart aging and on both macro- and microvascular changes. The strategic research program focuses on improvement of early detection of new disease and progression of disease. Furthermore, focus is on the importance of co-morbidity in the development, recognition, prognosis and treatment of heart diseases and on innovative ways to improve prognosis, such as eHealth and Big Data analysis techniques. In addition, we aim to clarify underlying mechanisms, including genetic susceptibility.
3. The theme *Vasculature and Precursor Conditions* focuses on increasing knowledge on (potentially) modifiable causes, consequences and treatment options of accelerated development of precursor conditions and abnormalities in vascular structure and function. Among precursor conditions are overweight, hypertension, dyslipidemia, renal dysfunction, and (type 2) diabetes. Among vascular abnormalities are plaques and thickened wall thickness of the carotid artery, thickened muscles in the heart, and the presence of calcium in the arteries in the body. Among the causes that we address are genetic factors, environmental exposures, biomarkers, nutritional factors, factors in and around pregnancy and reproduction, lifestyle factors and early in life exposures.

For more detailed information about process, output and open science indicators of Clinical Epidemiology see Appendix I.

3.4 Global Cardiovascular Health (A) and Diversity (B)

Global cardiovascular health

Global Cardiovascular Health focuses on the improvement of health around the world and reduction of health disparities between countries and populations. The mission of our unit is (1) to promote cardiovascular health, equality in health and well-being worldwide by generating the best evidence in order to guide health decision-making; (2) to bridge epidemiology and public health; and (3) to build high impact global cardiovascular health research capacity. Through internationally recognized and societally well-embedded research our unit contributes to the prevention and management of cardiovascular diseases globally. Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. The contribution of low- and middle-income countries to the global burden of cardiovascular disease is estimated at 80%. This is characterized by higher mortality rates and high burden of morbidity due to sub-optimal care, partially related to health system challenges. Our work therefore aims to: (1) study cardiovascular risk factors and disease outcomes internationally; (2) to develop, implement and scale-up cost-efficient approaches; and (3) to support clinical decision making for primary and secondary prevention of cardiovascular diseases globally.

Diversity

Through internationally recognized and societally well-embedded research the Circulatory Health strategic research program adds to the improvement of the health of patients with cardiovascular diseases, with an important focus on women. The Dutch Cardiovascular Alliance has the ambition to reduce cardiovascular disease by 25% in 2030, and there is much to gain in cardiovascular health in women specifically. As mentioned by the Netherlands Science Agenda (NWA) route of healthcare, prevention and treatment, it is predicted that there will be 7 million people with chronic conditions in 2030 (which is 40% of our society). This will increase pressure on our healthcare system and research to revise, adapt and improve diagnostic tracks are crucial, as cardiovascular disease is the second field of medicine with the most healthcare costs. The NWA route specifically addresses attention to differences between people and researching current healthcare pathways to directly implement in clinical practice. The knowledge routes prevention and personalized medicine refer to innovations in e-Health, biomarkers, and improving diagnoses as areas of investments.



Our strategy is in line with these ambitions and dedicated to improve knowledge on heart disease in women that often have a chronic nature. By investigating current paths of healthcare, by identifying women who have remained underdiagnosed, or that have a poor prognosis, and by understanding diversity, we aim to improve quality of care in women.

For more detailed information about process, output and open science indicators of Global Cardiovascular Health and Diversity see Appendix J.



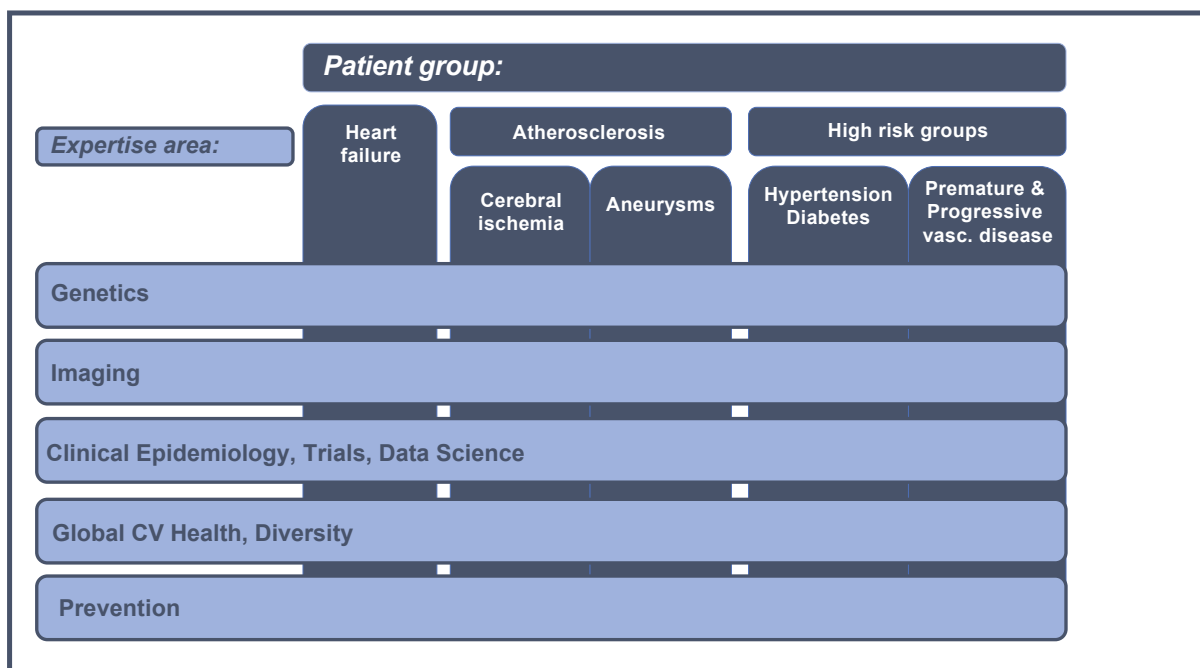
4. Future prospects 2020-2025

Center for Circulatory Health of the future

In our Center for Circulatory Health (“Hart- en vaatcentrum”) the clinical disciplines cardiology, vascular medicine, vascular surgery and neurology (supported by a cardiovascular nursing specialist) collaborate at one particular location to provide patients as efficiently as possible with the multidisciplinary care they need. Our aim for the upcoming years is to organize cardiovascular care in a regional network. The UMC Utrecht is willing to take the initiative to set up this strategic alliance and realize synergy through collaboration with the hospitals in the region Utrecht. In addition, we focus internally on optimizing the acute setting (emergency care) for cardiovascular patients.

Strategic Research focus

As mentioned before, our strategic research focus is considered a moving target and determined by factors that could shift over time (e.g. positioning of key PIs, patient numbers, clinical relevance, etc). Therefore the chosen themes are critically evaluated periodically. We selected four research themes and four methodological approaches that are applied in all disease research themes (see paragraph 1.1). The selected themes and approaches are prioritized in all strategic and investment decisions, leading to significant focus in the currently broad research portfolio over time. An inventory of planned investments aiming to intensify/improve research within the chosen themes/approaches was made in the business case Circulatory Health 2015 – 2019. With the organisational experience gained in the past six years and feedback received from our PIs, we discussed and re-valuated our research diagram. Considering the achievements within certain of our research areas and also emerging developments in the cardiovascular field, it is our intention to further improve collaboration between the professionals within Circulatory Health. To accommodate that, our research diagram will be adjusted for the upcoming strategic period 2020-2025 (see below).



The expertise area ‘prevention’ will be more visible in the new diagram. Within high risk groups secondary prevention is one of our strengths (hypertension, diabetes, lipids), but our society demands more and more attention to prevention (both primary and secondary). The UMC Utrecht has the ability to add value to the impact of disease prevention through its scientific strength. In addition, the professionals working on cerebral ischemia and aneurysms are more closely connected and with often the same underlying condition, namely atherosclerosis. Therefore we intend to integrate the research focus for those patients group. The review period 2013-2018 also learned that within the high risk groups the topic ‘premature and progressive vascular disease’ is of high impact due to the expertise in the UMC Utrecht and in our new diagram we will acknowledge that. Clinical epidemiology will be expanded with trials and data science (see UMC Utrecht wide themes on the next page).



Increasing societal impact: development of valorisation and implementation tracks

Scientists within our strategic theme are highly motivated to develop their research products into practical applications, with the ultimate goal to improve cardiovascular care for patients. However, valorisation and implementation tracks of research products are not always obvious and also dependent on multiple stakeholders with different interests. Implementation always implies a degree of innovation and infers that theories of change and diffusion of innovation should be taken into account. It also implies that larger degrees of change might encounter more resistance. To support researchers in their valorisation and implementation goals and to improve the route to societal impact, Circulatory Health intends to develop valorisation and implementation tracks in line with the program's research themes. Implementation readiness criteria will be defined for the research themes, which should identify topics ready for the next phase. Upon identification, an implementation plan for these topics will be developed by performing stakeholder mappings, constructing expert panels to identify communication nodes and structural constraints, and aiding in the search for implementation funding. Similar routes will be taken for the valorisation tracks in which Technology Transfer Offices (TTO) will be consulted for valorisation readiness criteria. The TTO will be asked for support in drawing up contracts, negotiating with companies, development of a business plan or finding possible partners.

Consolidation & sustainability

Prof. dr. D. Grobbee will step down as chairman of Circulatory Health after 10 years of presidency and Prof. dr. F. Asselbergs will be appointed as his successor from 1 August 2019 onwards.

A request for long-term financing (2020-2025) in the new strategic period is submitted to the board of directors of UMC Utrecht; a decision is expected in summer 2019. This request is similar to the current contribution, adjusted for inflation and the new collective labor agreement. The financial dependence of the strategic themes on participating divisions remains an important point of attention. Circulatory Health cannot achieve sufficient impact only with a contribution from the board of directors.

UMC Utrecht wide themes

A. U-Trial

The UMC Utrecht stimulates the conduction of clinical trials in order to translate experimental research into patient therapies more efficiently without compromising on quality and patient safety. To support that the Utrecht Trial Innovation Alliance (U-TRIAL) was created. The board of directors and the Julius Center invest in U-TRIAL to increase the number of trials and the quality and impact in daily practice of clinical studies. In this way, innovations reach patients in the Netherlands and abroad more quickly, certainly if the design and implementation of the studies is innovative. At present, The UMC Utrecht generates relatively few innovative, high-impact trials for a leading academic hospital, according to the standard analysis that the UMCs perform every six years. The UMC Utrecht opts for an incentive in this area from the clinical-scientific content. Every strategic theme will receive a clinical trial specialist with scientific experience in the field of impact-rich trials and with a suitable network. These clinical trial generators will also keep an eye on what is going on within Circulatory Health and identify opportunities. If there are ideas for research, they can estimate the potential, search for partners (for financial support) with the U-TRIAL management team and stimulate international cooperation. For this purpose, dr. M. Alings will be appointed in 2019 as clinical trial specialist for Circulatory Health.

B. Data Science/U-Data

Data Science is going to have a huge impact on tomorrow's healthcare. This science uses techniques, theories and models derived from different disciplines within the broad field of mathematics, statistics, information science and computer sciences. Machine learning, classification, cluster analysis, data and text mining, databases and visualisation are of particular interest. The overall aim of Data Science is to extract scientific knowledge and insights from (both structured and unstructured) data and to apply this knowledge with impact in healthcare.

With U-Data our goal is to establish a vision and set up a collaboration in the field of data science that several UMC Utrecht groups are already working on in a fragmented way. The "Data Science Facility for Circulatory Health" works together with other initiatives, including the Applied Data Analytics in Medicine (ADAM) program at UMC Utrecht, and the focus area Applied Datascience of Utrecht University. This "Data Science Facility" is the programmatic integration of all data science activities (advanced data analytics, mapping and curating data sets and registries) and includes all staff and their infrastructure active in the field of cardiovascular disease.



C. Prevention

In the new UMC Utrecht strategy 2020-2025 prevention will be a prominent topic and the Dutch academic hospitals are expected to play a directing role on this theme within their own region. In this context, every UMC is the academic catalyst to investigate the impact of prevention on society and to translate this into a national policy with the aim to create a healthier environment. Our goals are (1) to establish a vision on prevention and reduction of cardiovascular diseases, both regionally and (inter)nationally; (2) to determine an impactful research agenda; and (3) to define the UMC Utrecht's management role therein.



Appendices

Appendix A: Composition of supportive Circulatory Health bodies	243
Appendix B: Circulatory Health principal investigators	244
Appendix C: Research theme Heart Failure	246
Appendix D: Research theme Cerebral Ischemia	255
Appendix E: Research theme Aneurysms	258
Appendix F: Research theme High Risk - Diabetes, Hypertension and Atherosclerosis	262
Appendix G: Expertise area Genetics	272
Appendix H: Expertise area Imaging	276
Appendix I: Expertise area Cardiovascular Clinical Epidemiology	279
Appendix J: Expertise area Global Cardiovascular Health (A) and Diversity (B)	284
Appendix K: Expertise area Global CV Health (A) and Diversity (B)	288



Appendix A: Composition of supportive Circulatory Health bodies

Composition program office:

M. Houterman, MSc (program manager)
H. Romeijn (advisor marketing & communication)
W. Gouw-Ellenbroek (advisor/coordinator center for Circulatory Health)
B. van Dinther (project coordinator UCC)
Dr. M. Bierhuizen (coordinator education/research)

Composition of the steering committee UCC:

Prof. dr. M. Bots (epidemiology; chairman)
Prof. dr. F. Asselbergs (cardiology)
Prof. dr. G. de Borst (vascular surgery)
B. van Dinther (project coordinator UCC)
Prof. dr. M. Emmelot-Vonk (geriatrics)
Dr. Imo Hoefer (laboratory)
M. Hollander, (general practice)
M. Houterman, MSc (program manager Circulatory Health)
Prof. dr. P. de Jong (radiology)
Dr. N. van der Kaaij (cardiothorax surgery)
Dr. T. Lely (gynecology)
Dr. Y. Ruigrok (neurology)
Prof. dr. M. Verhaar (nephrology)
Prof. dr. F. Visseren (vascular medicine)



Appendix B: Circulatory Health principal investigators

Division-PI	Department	Patient group / Expertise area
Division Neurosciences		
Prof. dr. G.J. (Geert Jan) Biessels	Neurology	Cerebral ischemia
Prof. dr. L.J. (Jaap) Kappelle	Neurology	Cerebral ischemia
Prof. Dr. G.J.E. (Gabriel) Rinkel	Neurology	Aneurysms
Prof. Dr. A. (Bart) van der Zwan	Neurosurgery	Cerebral ischemia (chairman Research Table) & Aneurysms
Dr. Y.M. (Ynte) Ruigrok	Neurology	Aneurysms
Dr. M.D.I. (Mervyn) Vergouwen	Neurology	Aneurysms
Dr. H.B. (Bart) van der Worp	Neurology	Cerebral ischemia
Division Heart & Lungs		
Prof.dr. F.W. (Folkert) Asselbergs	Cardiology	Heart failure & Genetics & Management Circulatory Health
Prof. dr. S.A.J. (Steven) Chamuleau	Cardiology	Heart failure
Prof. dr. P.A.F.M. (Pieter) Doevendans	Cardiology	Heart failure
Prof. dr. J.P.G. (Joost) Sluijter	Experimental cardiology	Heart failure & Laboratory for Circulatory Health
Prof. dr. W.J.L. (Willem) Suyker	Management	Heart failure & Management Circulatory Health
Prof. dr. M.A. (Marc) Vos	Medical physiology	Heart failure
Dr. M. (Marco) Alings	Cardiology	Heart failure & U-TRIAL
Dr. M.P. (Marc) Buijsrogge	Cardiothoracic surgery	Heart failure
Dr. M.J.M. (Maarten-Jan) Cramer	Cardiology	Heart failure
Dr. P.F. (Paul) Gründeman	Experimental cardiology	Heart failure
Dr. M.A.G. (Marcel) van der Heyden	Medical physiology	Heart failure
Dr. N. (Niels) van der Kaaij	Cardiothoracic surgery	Heart failure
Dr. J.H. (Hans) Kirkels	Cardiology	Heart failure
Dr. L.W. (Linda) van Laake	Cardiology	Heart failure (chairman Research Table)
Dr. P. (Peter) Loh	Cardiology	Heart failure
Dr. M. (Mathias) Meine	Cardiology	Heart failure
Dr. H.M. (Hendrik) Nathoe	Cardiology	Heart failure & operational team Center for Circulatory Health
Dr. P. (Pieter) Stella	Cardiology	Heart failure
Dr. H. (Hester) den Ruijter	Experimental cardiology	Heart failure & High risk
Dr. G.Tj. (Gertjan) Sieswerda	Cardiology	Heart failure
Dr. A.A.B. (Toon) van Veen	Medical physiology	Heart failure
Dr. M. (Michiel) Voskuil	Cardiology	Heart failure
Dr. A.O. (Adriaan) Kraaijeveld	Cardiology	Heart failure
Prof. dr. J. (Jeroen) Bakkers	Molecular cardiogenetics	Heart failure (Hubrecht Institute)
Prof. dr. E. (Eva) van Rooij	Molecular cardiology	Heart failure (Hubrecht Institute)
Division Julius Center		
Prof. dr. D.E. (Rick) Grobbee	Clinical epidemiology	Chairman Circulatory Health
Prof. dr. M.L. (Michiel) Bots	Epidemiology	Heart failure & Aneurysms & Chairman Utrecht Cardiovascular Cohort
Prof. dr. ir. M.J.C. (René) Eijkemans	Biostatistics	Data Science
Prof. dr. A.W. (Arno) Hoes	Management	Heart failure (from June 1 2019, board of directors UMCU)
Prof. dr. F.H. (Frans) Rutten	General practice medicine	Heart failure (chairman Research Table)
Prof. dr. Y.T. (Yvonne) van der Schouw	Epidemiology	High risk
Prof. dr. Tiny Jaarsma	Nursing science	Heart failure
Prof. dr. H.A. (Jet) Smit	Public health/epidemiologie	Prevention
Prof. Dr. Monique Verschuren	Public Health	Prevention
Dr. M.I. (Mirjam) Geerlings	Epidemiology	Cerebral ischemia & Aneurysms
Dr. K. (Kerstin) Klipstein-Grobusch	Epidemiology	Global CV Health, diversity
Dr. J.B. (Hans) Reitsma	Epidemiology	Clinical Epidemiology
Dr. C.S.P.M. (Cuno) Uiterwaal	Epidemiology	Clinical Epidemiology
Dr. G.A. (Ardine) de Wit	Epidemiology	Clinical Epidemiology
Dr. S.A.E. (Sanne) Peters	Epidemiology	Global CV Health, diversity & Heart failure



Dr. G.J. (Geert-Jan) Geersing	General practice medicine	Clinical Epidemiology
Division-PI	Department	Patient group / Expertise area
Division Laboratories, Pharmacy and Biomedical Genetics (DLAB)		
Prof. Dr. R. (Ray) Schiffelers	Clinical chemistry / hematology	Laboratory for Circulatory Health
Dr. J.P. (Peter) van Tintelen	Clinical genetics	Genetics
Dr. D. (Dennis) Dooijes	Clinical genetics	Genetics
Dr. I. (Imo) Höfer	Lab. klinische chemie/haematologie	Utrecht Cardiovascular Cohort
Dr. C. (Coen) Maas	Clinical chemistry / hematology	Genetics
Dr. R. (Roel) de Weger	Pathology	Genetics
Dr. H.A. (Richard) van Wijk	Clinical chemistry / hematology	Genetics
Division Internal Medicine and Dermatology		
Prof. dr. M.H. (Mariëlle) Emmelot-Vonk	Geriatry	Utrecht Cardiovascular Cohort
Prof. dr. C.A.J.M. (Carlo) Gaillard	Management	Management SP
Prof. dr. H.A.H. (Karin) Kaasjager	Vascular medicine & nephrology	High risk
Prof. dr. M.C. (Marianne) Verhaar	Nephrology	Heart failure
Prof. dr. F.L.J. (Frank) Visseren	Vascular medicine	High risk (chairman Research Table)
Dr. P.J. (Peter) Blankestijn	Nephrology	High risk
Dr. R. (Rachel) Giles	Nephrology	
Dr. T.W. (Timon) van Haeften	Internal medicine & infections diseases	
Dr. C. (Caroline) Cheng	Nephrology	
Dr. W. (Wilko) Spiering	Vascular medicine	High risk
Dr. J. (Jan) Westerink	Vascular medicine	High risk & operational team Center for Circulatory Health
Division Surgical Specialisms		
Prof.dr. G.J. (Gert Jan) de Borst	Vascular surgery	Cerebral ischemia & Aneurysms
Prof. dr. D.P.V. (Dominique) de Kleijn	Vascular research	Aneurysms (chairman Research Table) & Atherosclerosis
Dr. J.A. (Joost) van Herwaarden	Vascular surgery	Aneurysms
Dr. C.E.V.B. (Stijn) Hazenberg	Vascular surgery	Aneurysms & operational team Center for Circulatory Health
Division Woman & Baby		
Prof. dr. M.J.N. (Manon) Benders	Neonatology	Cerebral ischemia
Dr. M.N. (Mireille) Bekker	Gynaecology	High risk
Dr. A.T. (Titia) Lely	Gynaecology	High risk
Division Vital Functions		
Prof. dr. D. (Diederik) Van Dijk	Intensive care center	
Prof. dr. W.A. (Wilton) van Klei	Anesthesiology	
Division Imaging - Oncology		
Prof. dr. R.M. (Rick) Dijkhuizen	Imaging	Cerebral ischemia & Aneurysms
Prof. dr. J. (Jeroen) Hendrikse	Radiology	Cerebral ischemia & Aneurysms
Prof. dr. P.A. (Pim) de Jong	Radiology	Heart failure & Utrecht cardiovascular cohort
Prof. dr. T. (Tim) Leiner	Radiology	Heart failure & Aneurysms
Prof. dr. P.R. (Peter) Luijten	Management	
Prof. dr. B.K. (Brigitta) Velthuis	Radiology	Heart failure & Cerebral ischemia & Aneurysms
Dr. I. (Ivana) Isgum	Imaging	
Dr. I.C. (Irene) van der Schaaf	Radiology	Cerebral ischemia & Aneurysms
Division Child		
Prof. Dr. F. (Frans) Haas	Pediatric cardiology	
Dr. J.M.P.J. (Hans) Breur	Pediatric cardiology	Heart failure
Dr. G.J. (Gregor) Krings	Pediatric cardiology	Heart failure
Dr. M. (Michal) Mokry	Cardiovasculair Genetics	Aneurysms



Appendix C: Research theme Heart Failure

Table 3 – Process indicators Heart Failure

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment	<p>a. The mission of our research unit is to improve the survival and quality of life of patients with heart failure by prevention, risk stratification, early diagnosis, and development of novel treatments aimed at providing optimal personalized, evidence-based patient management.</p> <p>b. Heart failure creates a large healthcare problem, with ~200 000 patients living with heart failure in the Netherlands. Objectives:</p> <ul style="list-style-type: none">• <i>Combat underdiagnosis:</i> By applying classical diagnostic research and machine learning applications improve diagnosis, notably in primary care.• <i>Better understanding heart failure:</i><ul style="list-style-type: none">• Unraveling the cellular and molecular mechanisms that underlie the pathogenesis of different forms of heart failure.• Applying in vitro and in vivo human heart failure models.• Translational research, e.g. (i) circadian clock application; (ii) discovery of novel biomarkers (diagnostic and disease pathway related); (iii) tissue engineering of myocardial tissue; (iv) advanced operation theaters for small and large animal (micro)surgeries for cardiac intervention studies; (v) state-of-the-art molecular and histopathological analyses of human myocardial tissue of advanced heart failure; (vi) cardiogenetics with special focus on cardiomyopathies (e.g. dilating and arrhythmogenic cardiomyopathy).• <i>All aimed at paving the way to development of novel treatment opportunities.</i>• <i>Improve prognosis and tailored care:</i><ul style="list-style-type: none">• By classical epidemiological research and machine learning application optimize the individual care pathway of patients diagnosed with heart failure.• Smart ICD technology and non-invasive eHealth applications.• Improve personalized self-care of patients with heart failure, e.g. sophisticated serious gaming and home-centered non-invasive eHealth applications.• Advanced heart failure and structural heart disease management (e.g. GUCH) with a focus on mechanical circulatory support and innovative (catheter-based) interventions.
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<p>3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made</p>	<p>Our research roadmap is based on:</p> <ul style="list-style-type: none">• Strategic focus within the UMC Utrecht strategic theme Circulatory health.• Strategic agenda of the Netherlands Heart Foundation based on patient plus researchers priorities; gender, early detection of cardiovascular disease, better treatment and management of heart failure and atrial fibrillation, healthy ageing.• Knowledge agenda of the Dutch Cardiology Society; heart failure and cardiomyopathy, arrhythmias, valvular disease, congenital heart disease (e.g GUCH).• Mission statement of the Dutch Cardiovascular Alliance; early recognition of cardiovascular disease.• Netherlands Organisation for Scientific Research (NWO); Vascular Medicine second phase. <p>We are well-known for our research in optimizing early diagnosis of heart failure, in the general population, but also high-risk groups, e.g. type 2 diabetes, COPD, frail elderly, and those who visit the general practitioner (GP) for shortness of breath. However this is in relatively small samples of the general population. A next step could be achieved by applying machine learning techniques to real world practice data linking primary care with secondary and tertiary care. The research question how 'Big Data' can be used for heart failure research advances the field by exploring how these data can be used, as we have recently reviewed (<i>Hemingway H, Asselbergs FW, Danesh J, et al. Big data from electronic health records for early and late translational cardiovascular research: challenges and potential. Eur Heart J. 2018;39(16):1481-1495</i>).</p> <p>Our focus on multi-morbidity and considering multiple outcomes becomes clear with the CVON project RED-CVD; aimed at early detection of the 'big three in the cardiovascular continuum'; atrial fibrillation and coronary artery disease, this in participants of primary care disease management programs for type 2 diabetes or COPD. We pay special attention to sex differences and renal functioning in the development of LV diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) within the consortia Queen of hearts, RECONNECT, and CHANCE.</p> <p>There is a collaboration with Somalogic USA for the development of proteome algorithm for HFpEF. Our team has published a national position paper on cardio-oncology.</p> <p>We have developed a national cardio-oncology registry (ONCOR), which is adopted by all other Dutch university centers.</p> <p>A bench-to-bedside approach and understanding (the disease development) of arrhythmogenic cardiomyopathy (ACM) with dog models and genetic research.</p> <p>A bench-to-beside approach of cardiac repair and protection, including extracellular vesicle approach with intracardiac communication, and tissue bio-printing.</p> <p>We led the publication of the national mechanical circulatory support consensus document and co-authored European guidelines on end-stage heart failure (<i>Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(11):1505-1535</i>), in which gaps in knowledge are identified. Based on this, our research in advanced heart failure focuses on improving outcomes for Mechanical Circulatory Support (MCS) patients and creating a better understanding of the disease through combining biomarker, histo-pathological, genetic and imaging research studies. Internationally, GUCH care is predominantly based on expert consensus due to the heterogeneous patient group, which is why we focus on applied research on state-of-the-art minimally invasive interventions, supported by thorough imaging studies of mechanics and hemodynamics.</p>
<p>3.3. Stakeholders are involved in formulating the main research questions</p>	<p>The research agenda is developed with input from major stakeholders: patient representatives, pharmaceutical companies, legal and ethics experts, (inter)national funding organisations such as applied and engineering sciences (TTW), and the European Society of Cardiology (ESC). See as an example also https://www.bigdata-heart.eu/. Consequently, several stakeholders, notably patients are actively involved in our research including the start with formulation of the research questions and objectives.</p> <p>Within an Innovative Medicines Initiative (IMI) consortium, our research unit collaborates in a pan-European consortium in which the patient representative European Heart Network (EHN), pharmaceutical companies, and the European Society of Cardiology (ESC) all ensure that research questions are relevant and topical. Furthermore, dissemination via the ESC greatly helps incorporating novel findings of our research unit in contemporary guidelines on heart failure.</p> <p>The Utrecht Cardiovascular Cohort (UCC) steering committee, which coordinates the data linkage of patients visiting the UMC Utrecht for any cardiovascular issue, meets monthly to discuss progress and extension of projects, including heart failure.</p> <p>The Circulatory Health research theme Heart Failure meets 3-4 times a year and involves all physicians and researchers active in the field of heart failure. During these meetings plans are made for cooperative research projects nationally (CVON, NWO, ZonMw) and internationally (H2020, ERA-CVD).</p> <p>We interact closely with patient organisations such as the Phospholamban (PLN) foundation, "Harteraad", "Stichting Hartekind".</p>



<p>3.4. The research questions are feasible and are pursued using optimal and efficient design</p>	<p>In our studies we make use of classical epidemiological approaches, both predictive (diagnostic and prognostic) and etiological (causal relations and Randomized Controlled Trials (RCTs)), as well as Big Data/machine learning, omics and text mining research. To guarantee optimal and efficient design we collaborate in a consortium with clinicians, data scientists, clinical epidemiologists, industry partners, and (bio)statisticians. We use state-of-the-art technology in the experimental labs at UMC Utrecht, Medical Physiology, and RMC Utrecht/Hubrecht Institute. In the GDL (animal labs) we apply advanced operation techniques for small and large animal (micro) surgeries for cardiac intervention studies in specialized operation theatres.</p>
<p>3.5. What is 'the next step' if the project delivers positive results</p>	<p>a. For projects related to heart failure epidemiology, we collaborate with academic partners from UK, Spain, and Sweden. Large pharmaceutical companies are also involved in projects related to external validity of randomized trials in the field of heart failure (Servier, Bayer, Vifor, Novartis). One important next step for our unit is advancing the field of Big Data research into heart failure research and impact regulators and pharmaceutical companies on novel ways of coming to evidence and how future studies should be designed. Moreover, we are involved in (inter)national projects building registries of patients with heart failure, facilitating future registry-based trials that are more feasible to execute, are cheaper, and come faster to a conclusion than classic RCTs. Further, we collaborate closely with device companies (e.g. Medtronic, Abbott) on improvement and incorporation of technology use and we are well positioned in collaborative networks within the ESC and the Heart Failure Association (HFA).</p> <p>b. For innovation and valorisation our research unit is facilitated by the UMC Utrecht. In 2018 a valorisation grant (TOP-EV Netherlands Heart Foundation) was received.</p> <p>c. In the period 2013-2018 researchers in our unit have received funding from a variety of sources (companies, patient organisations, (inter)national research funding organisations, etc). Some selected examples of funding entities:</p> <ul style="list-style-type: none">• Pharmaceutical and device companies such as Abbott, Medtronic, Novartis, Sopachem, Roche, Nanion, Amgen, MiRagen. Philips Healthcare, Bayer, Sanofi.• National funding entities:<ul style="list-style-type: none">- <i>Netherlands Heart Foundation</i>: CVON Hustcare (2012), CVON Queen of Hearts (2014), CVON CONCORgenes (2014), CVON RECONNECT (2015), CVON CHANCE (2016), CVON REMAIN (2016), NHS COBRA3 (2016), CVON RED-CVD (2017), CVON ARGUS (2017), ERA-CVD CARDIO-PRO (2017), CVON eDETECT (2017), CVON PRIME (2018), CVON AI 2018, NHS Private-Public (2018), CVON-PREDICT1+2 (2014, 2019).- <i>NWO</i>: Gravitation Materials Driven Regeneration (MDR) (2017), NWO-TOP (2017), ZonMw PRIDE (2017), Veni (P. Nguyen, Hubrecht Institute, 2018).• European funding: ERA-CVD network grant (2016), ERA-CVD CARDIO-PRO (2017), ERC consolidator (2014+2016), ESC Research Grant 2016, Marie Skłodowska-Curie (2016), Cost Action CardioRNA, ESC First contact initiative grant, EU-CResPace (2016), EU-Cert-ICD (2013).• Other: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) foundation (2014), Dalijn foundation (2014), Foundation Leducq network grant (2014), Phospholamban (PLN) foundation (2018), "Meer Kennis met Minder Dieren" (MKMD), "Proefdiervrij". <p>d. Members of our research unit are closely involved in development of (inter)national heart failure guidelines and are part of working groups. Selected examples:</p> <ol style="list-style-type: none">1. L. van Laake (2012-2018): member of the Working group on Takotsubo cardiomyopathy of the HFA, the research Network 'Cardiolinc', www.cardiolinc.org, the working group on myocardial function of the ESC, the translational committee of the HFA, and the working group on cellular biology of the heart of the ESC.2. F.H. Rutten (2012- 2018): 2012 and 2016 ESC guideline on acute and chronic heart failure, working group on patient care of the HFA, and working group on HFpEF, and member of the core group for www.heartfailuremat-ters.org.3. A.J. Teske (2019-2021): member of the working group on Cardiac imaging of the HFA, the national working group of cardio-oncology.4. N. De Jonge (2016-2020): Member of the Study group on Mechanical Circulatory Support of the Committee on Advanced Heart Failure of the HFA of the ESC.



Table 4 – Output indicators Heart Failure

4.1 Research products for peers

Key publications:

1. Uijl A, Koudstaal S, Direk K, et al. Risk factors for incident heart failure in age- and sex-specific strata: a population-based cohort using linked electronic health records. *Eur J Heart Fail.* 2019. doi: 10.1002/ehf.1350.
2. Madonna R, Van Laake LW, Davidson SM, et al. Position paper of the European Society of Cardiology working group cellular biology of the heart: cell-based therapies for myocardial repair and regeneration in ischaemic heart disease and heart failure. *Eur Heart J.* 2016; 37(23):1789-1798.
3. Kievit RF, Gohar A, Hoes AW, et al; Queen of Hearts and RECONNECT consortium. Efficient selective screening for heart failure in elderly men and women from the community: a diagnostic individual participant data meta-analysis. *Eur J Prev Cardiol.* 2018;25(4):437-446.
4. Mast TP, James CA, Calkins A, et al. Evaluation of structural progression in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *JAMA Cardiol.* 2017;2(3):293-302.
5. Kranias EG, Doevendans PA, Glijnis PC, Hajjar RJ. PLN Foundation. *Cir Res.* 2018;123(12):1276-1278.
6. Hemingway H, Asselbergs FW, Danesh J, et al; Big Data at Heart Consortium. Big data from electronic health records for early and late translational cardiovascular research: challenges and potential. *Eur Heart J.* 2018;39(16):1481–1495.
7. Gladka MM, Molenaar B, de Ruitter H, et al. Single-cell sequencing of the healthy and diseased heart reveals cytoskeleton-associated protein 4 as a new modulator of fibroblasts activation. *Circulation.* 2018;138(2):166-180.
8. Mast TP, Teske AJ, Walmsley J, et al. Right ventricular imaging and computer simulation for electromechanical substrate characterisation in arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol.* 2016;68(20):2185-2197.

Our research unit works on infrastructure to analyse several datasets in different locations in an identical fashion using a common data model OMOP; see <https://thehyve.nl/solutions/ohdsi>. Currently, UK and Swedish data are mapped and work is underway to include Spain and the Netherlands as well. Using this approach, meta-data standardized toolkits allow researchers to answer research questions quickly and at lower cost than harmonizing all datasets every time to answer a single or several research questions.

In 2014 co-founder of CART-Tech (a UMC Utrecht spin-off company); www.Cart-Tech.com 'Technical solutions to improve cardiac regenerative therapy' (S. Chamuleau).

In 2017 initiation of Preclinicaltrials.eu - Creator of an International register of preclinical trial protocols. The goal is to provide a comprehensive listing of preclinical animal study protocols.



4.2 Research products for societal target groups

Selected examples of lectures given by unit researchers to general audiences:

- T. Jaarsma (2019): UMC Utrecht Public Lecture, "Hartfalen: zelfmanagement en e-Health".
- H. den Ruijter (2016): UMC Utrecht Public Lecture, "Hart- en vaatziekten: voor man en vrouw verschillend".
- S. Peters (2018): UMC Utrecht Public Lecture, "Man-vrouw verschillen in risicofactoren voor hart- en vaatziekten".
- L. van Laake (2018): lecture for "Harteraad", Novel developments in the treatment of heart failure.
- S. Chamuleau (2016): UMC Utrecht Public Lecture, "Stamcellen".
- F. Asselbergs (2017,2018): Public Lectures for patients with congenital heart disease and hypertrophic cardiomyopathy.
- P. van Tintelen (2018): Public Lecture for patients with arrhythmogenic cardiomyopathy.

Selected examples of media & outreach activities by unit researchers:

- H. den Ruijter (2018): Volkskrant, "Vrouwen overlijden vaker na hartaanval".
- H. den Ruijter (2018): Television "Eva Jinek" and "RTL4 Koffietijd", Sex differences in cardiovascular disease.
- F. Rutten (2018): VIDA (patient journal "Harteraad"), Heart failure in COPD.
- J. Sluijter(2015): Telegraaf, Organ printing.
- J. Sluijter (2015): Television "Tijd voor Max" and scientific radio program 'De kennis van nu'.
- F. Asselbergs (2016, 2017): NOS news item "Fikse daling ziekenhuisopnames door minisensor in slagader"; RTL Live television "Cardioloog Folkert Asselbergs legt alles uit over een hartinfarct".

Other research products for societal target groups:

- Involvement in generation of guidelines on heart failure:
 - Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail. 2016;18(8):891-975.
 - McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-1847.
 - Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-2779.
 - Arrhythmogenic Cardiomyopathy (ACM) risk calculator: Eur Heart J; 2019, in press; made publicly available via <https://arvcrisk.com/>.
 - ACM registry patient cohort set up, design, and database format available for other researchers. Open access data catalogue with real-time information on available data.
 - UNRAVEL Research Data Platform and Biobank to improve care for cardiomyopathies (www.unravelrdp.nl). Data being used in different CVON consortia (CVON DOSIS, ERA-CVD).
 - A text-mining tool for diagnosis (Medic Miner) has been developed and is currently implemented in our electronic health record system (Chipsoft) for Hospital IT departments to be used.
 - Organisation of a national ACM patient day in 2019.
 - Heartfailurematters.org. A website for heart failure patients and their carers in 10 languages, including Dutch.
 - SPECKLEPEDIA.com. A website dedicated to technicians and cardiologists to implement advanced imaging in heart failure patients and for early disease detection.
 - Chair (F. Asselbergs) of national policy document on telemonitoring of heart failure patients together with patient organisation, GP, nurses and cardiologists: https://www.nationalezorggids.nl/sections/zorgverzekering/articles/31698-samenwerkingsafspraken-over-telebegeleiding-bij-hartfalen?related_news_list_page=4
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4.3 Use of research products by peers

Selected examples of publications with the total number of citations (Google Scholar, June 5 2019):

- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37(27):2129-2200. (cited 5985 times)
- Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(39):2733-2779. (cited 1518 times)
- Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. *ESC Heart Fail*. 2014;1(1):4-25. (cites 331 times)
- Wahquist C, Jeong D, Rojas-Munoz A, et al. Inhibition of miR-25 improves cardiac contractility in the failing heart. *Nature* 2014;508(7497):531-535. (cited 278 times).
- Dicinson BA, Semus HM, Montgomery RL, et al. Plasma microRNAs serve as biomarkers of therapeutic efficacy and disease progression in hypertension-induced heart failure. *Eur J Heart Fail* 2013;15(6):650-659. (cited 143 times)
- Van Riet EE, Hoes AW, Wagenaar KP, et al. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* .2016;18(3):242-252. (cited 186 times)
- Van Riet EE, Hoes AW, Limburg A, et al. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. *Eur J Heart Fail*. 2014;16(7):772-777. (cited 124 times)
- Tiburcy M, Hudson JE, Balfanz P, et al. Defined engineered human myocardium with advanced maturation for applications in heart failure modeling and repair. *Circulation* 2017;135(19):1832-1847. (cited 118 times)
- Cowie MR, Anker SD, Cleland KGF, et al. Improving care for patients with acute heart failure: before, during and after hospitalisation. *ESC Heart Fail*. 2014;1(2):110-145. (cited 134 times)
- Crespo-Leiro MG, Metra M, Lund LA, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20(11):1505-1535 (cites 31 times)
- Bhonsale A, Groeneweg JA, James CA, et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur Heart J*. 2015;36(14):847-855. (cited 163 times)
- Groeneweg JA, Bhonsale A, James CA, et al. Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. *Circulation Cardiovasc Genet* 2015;8(3):437-446 (cited 162 times)

Our research products are disseminated by participation in and organisation of scientific meetings and by sharing datasets/facilities. Examples:

- At major conferences (HFA ESC and ESC conferences) special sessions are devoted to update peers on the advances of our Bigdata@heart consortium.
- Using the common data model OMOP (<https://thehyve.nl/solutions/ohdsi/>) we stimulate to use our data sets and harmonize them with datasets across countries.
- 2017-2019 Annual HFA Winter meeting of translational research, Les Diablerets, Switzerland.
- 2013-2018 Joint meetings ESC Working groups on myocardial function and cellular biology of the heart, Varenna, Italy.
- The Utrecht Cardiovascular Cohort (UCC) as a starting point for optimisation of patient care, quality control and research (Asselbergs FW, Visseren FL, Bots ML, et al. *Uniform data collection in routine clinical practice in cardiovascular patients for optimal care, quality control and research. The Utrecht Cardiovascular Cohort. Eur J Prev Cardiol*. 2017;24(8):840-847).
- Use of Biofab, IPS facility and small and large animal facility (J. Sluijter).
- Optimizing the use of routine care EHR data – which is generated regardless of potential scientific purposes- and convey it into meaningful insights in current gaps in evidence.

4.4 Use of research products by societal groups

Selected examples of the use of our research products by societal groups:

1. Jaarsma T, Hoes AW, Rutten FH. Heartfailurematters.org. A website of the ESC/HFA for patients and carers in 10 languages, including Dutch.
 2. Rutten FH (2019). Development of patient decision tool on symptoms. Together with Dutch Heart Society.
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4.5 Marks of recognition from peers

Selected examples of recognitions marks from peers:

- T. Jaarsma (2018-): board member of the HFA.
- F. Rutten: co-coordinator and co-developer of the HFA “teach the teacher” program for cardiologists, GPs and heart failure nurses; member of the HFA patient care committee (2014-2016); involved in the update of the Dutch GP guideline on heart failure (2018-); Carl Bakx award (2016) for transition of cardiovascular care between secondary and primary care.
- H. den Ruijter (2017-2022): member of the young academy of the Royal Netherlands Academy of Sciences (KNAW).
- J. Sluijter: vice-chair (2014-2016) and chair (2016-2018) of the ESC working group on cellular biology of the heart.
- A. te Riele (2018-): member of the writing committee on diagnostic criteria for ACM and of the international expert panel on research priorities in ACM.
- T. Leiner: chair of the publications committee of the Society for Cardiovascular Magnetic Resonance (SCMR) (2017-2019); first author of 2019 “Indications for CMR” document; executive committee, International Society for Magnetic Resonance in Medicine (ISMRM) (2018-2021); president of ISMRM (2020-2021).
- N. de Jonge (2016-): Member of the working group on mechanical circulatory support of the Netherlands Society of Cardiology (NVVC) and Netherlands Society of Thoracic Surgeons (NVT) with consensus paper on left ventricular assist device (LVAD) therapy (2019).

Selected examples of personal grants received:

J. Groeneweg (2013), F. Asselbergs (2014), A. te Riele (2014), A. Baas (2016), M. Gladka (2016) and J. Hjortnaes (2017): Dutch Heart Foundation Dekker fellowships.

Selected examples of invited lectures:

- F.H. Rutten: HFA congresses (2013-2018); ESC congresses (2012-2014, 2016, 2018, 2019); North America Primary Care Research Group (NAPCRG) congress (2017).
- A. Vink: European Congress of Pathology (2013, 2017, 2018); Association of European Cardiovascular Pathology (2018).
- L.W. van Laake: Keynote speaker at Young DZHK (2018); Heart Failure Congress of the ESC (2018); Chairperson of multiple scientific sessions at the Heart Failure Congress of the ESC and the ESC Congress (2017).
- J. P. Sluijter: Shanghai University China (2016, 2018); Cardiology Basic Research Program at Beth Israel Deaconess Medical Center, Harvard Medical School, USA (2014); ESC Frontiers in Cardiovascular Biology (2014).
- A.J. Teske: EuroEcho (EAVCI) (2010-2014).
- F. Asselbergs: HFA congress (2019), ESC congress (2018, 2019), ESC Digital health (2019).
- T. Leiner: European Society of Radiology (ESR) (2014-2019); International Society for Magnetic Resonance in Medicine (ISMRM) 2014-2019; European Society of Magnetic Resonance in Medicine and Biology (ESMRMB) (2017-2018).
- B. Velthuis: European Society of Radiology (ESR) 2014-2019, ECR 2017-2018, ESC 2014, EuroPrevent 2014, EuroCMR 2019.
- M.J. Cramer : National and international invited lectures such as for the Indonesian Heart Association, North American Symposium on Knowledge Organisation (ASKO) on cardiac imaging.
- M.C. Verhaar: Kidney: the epicenter of microvascular disease and HFpEF, American Heart Association (2017).
- T. van Veen: Gordon Research Conference of cardiac arrhythmias (2013); Heart Rhythm Society (2014, 2015); American Heart Association (2015); European Cardiac Arrhythmia Society (2017).



Invited editorials:

- Rutten FH, Hoes AW. Natriuretic peptide tests in suspected acute heart failure. *BMJ*. 2015;350:h1164.
- Rutten FH, Clark AL, Hoes AW. How big a problem is heart failure with a normal ejection fraction? *BMJ*. 2016;353:i1706.
- Groenewegen A, Rutten FH. Near-home heart failure care. *Eur J Heart Fail*. 2019;21(1):110-111.
- Rutten FH, Broekhuizen BDL. Misclassification of both chronic obstructive pulmonary disease and heart failure. *JAMA Network Open*. 2018;1(8): e185486.
- Van Laake LW, Lüscher TF, Young ME. The circadian clock in cardiovascular regulation and disease: Lessons from the Nobel Prize in Physiology or Medicine 2017. *Eur Heart J* 2018; 39(24):2326-2329.
- Teske AJ, Mast TP. Moving from multimodality diagnostic tests toward multimodality risk stratification in ARVC. *JACC Cardiovasc Imaging*. 2017;10(5):514-517.
- Teske AJ, Verjans JW. Takotsubo cardiomyopathy - stunning views on the broken heart. *Neth Heart J*. 2016;24(9):508-510.
- Crnko S, Ernens I, Van Laake LW. New dimensions in circadian clock function: the role of biological sex. *Cardiovasc Res*. 2018; 114(2):203-204.
- Westenbrink BD, Van Laake LW, Brugts JJ. Cardiopulse: the postgraduate course in heart failure. *Eur Heart J* 2016; 37(5):428-429.
- Dierickx P, Van Laake LW. Muscle-on-chip: an in vitro model for donor-host cardiomyocyte coupling. *J Cell Biol* 2016; 212(4):371-373.
- Ahmad T, Freeman JV, Asselbergs FW. Can advanced analytics fix modern medicine's problem of uncertainty, imprecision, and inaccuracy? *Eur J Heart Fail*. 2019;21(1):86-89.
- Asselbergs FW, Meijboom FJ. Big data analytics in adult congenital heart disease: why coding matters. *Eur Heart J*. 2019;40(13):1078-1080.

Scientific committees and editorial boards:

- F. Rutten: Board member of Research Advisory Committee of the Dutch Heart Foundation (2016-); board member of the steering committee and supervisor of the GP "kaderopleiding hart- en vaatziekten" (2007-); co-coordinator and co-developer of the HFA "teach the teacher" programme for cardiologists, GPs and heart failure nurses (2014-2016); editorial board of *Family Practice* (2012-2018); chair Grant evaluation Committee Netherlands Heart Foundation Dekker program for clinical scientist and postdoc (2019-).
- A. Vink: Committee member of the update of the guidelines for autopsy investigation of sudden cardiac death of the Association for Cardiovascular Pathology (2016-2017).
- J. Sluijter: Associate editor *J Cardiovasc Translational Research* (2016-).
- A. Teske: HFA study group on cardiac imaging (2019-2021); National cardio-oncology working group (2017-).
- L. van Laake: Scientific Board member of the Netherlands Heart Institute (2019-); board member Young@Heart, Netherlands Heart Institute (2017-2019); board member grant evaluation Committee Netherlands Heart Foundation Dekker program (2019-); associate editor of *Netherlands Heart Journal*; editorial board member of *J Geriatric Cardiol*.
- T. Leiner: Member of Scientific committees of European Society of Radiology, Netherlands Heart Days, International Society of Magnetic Resonance in Medicine (ISMRM); Chairman, 2017 Scientific Program Committee of European Society of Magnetic Resonance in Medicine and Biology; board of trustees member of the Society for Cardiovascular Magnetic Resonance (2016-2019); associate editor / editorial board member *J Magn Res Imaging (JMRI)*, *J Cardiovasc Magn Res (JCMR)*, *Radiology Cardiothoracic*; *Netherlands Journal of Medicine (NTvG)*.
- B. Velthuis: Board Member Dutch section of Cardiovascular Radiology and European Society of Cardiovascular Radiology; scientific program committee Netherlands heart days.
- M. Cramer: Board member of the Dutch Vascular Forum; project leader CONNECT Acute Coronary Syndrome of the Netherlands Society of Cardiology; editorial Board of *Netherlands Heart Journal*.
- M. Verhaar: Member of the Scientific Board of the Kidney Foundation; scientific advisory board European Renal Association-European Dialysis and Transplant Association (ERA-EDTA).
- F. Asselbergs: Chairman Data infrastructure Dutch CardioVascular Alliance; CSO Durrer Center for Cardiovascular Disease; international member use & access committee DZHK.

4.6 Marks of recognition from societal groups

Selected examples of recognition marks of societal groups:

- F. Rutten: member of the research advisory board of the Dutch Heart Society; Dr. Carel Bakx award (2016).
 - M. Bots: participant of Meet the Professor (outreach to primary schools).
 - J. Sluijter: participant of Meet the Professor (outreach to primary schools); 'Pleisters voor het hart', Biologencongres (2013) Burgers Zoo Arnhem; *Herstel van hartspierdefecten, wat brengt de toekomst ons? Landelijke dag Erfelijke Hartaandoeningen*, (2018).
 - M. Cramer: Yearly CVOI-Cramer lecture at Tour de horizon Dutch Heart Association, Cardiovascular Education Institute; chief medical advisor "Harteraad" Province Utrecht; Eindhoven honorary medal Netherlands Heart Foundation; honorary fellow Indonesian Heart Association.
 - L. van Laake: Member of the scientific board of the Netherlands Heart Institute (NHI); board member of Young@Heart, NHI; committee member of "Samen voor de Patient" (UMC Utrecht); founding member "Jonge Gezondheidsraad", an advisory board for the government and parliament on the current level of knowledge regarding public health issues and research.
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Table 5 – Open Science indicators Heart Failure

5.1 Openness of the research agenda & stakeholder involvement	<p>Stakeholders:</p> <ul style="list-style-type: none">• Patient organisations: “Harteraad”, PLN Foundation, European Heart Network (EHN), Nierpatienten Vereniging Nederland.• Pharmaceutical and device companies: Abott, Medtronic, Novartis, Sopachem, Roche, Nanion, Amgen, MiRagen.• Funding agencies: e.g. Dutch Heart Foundation, NWO, ZonMW, H2020, ERA, NIH.• European Society of Cardiology (ESC).• Heart Failure Organisation (HFA).
5.2 Openness of data and protocols	<p>Projects in our unit have a data management plan in line with policies of the UMC Utrecht and Utrecht University; data are stored accordingly at the Durrer Center (NHI) or at servers in the UMC Utrecht.</p> <p>Presently, we are creating a research platform (https://www.unravelrdp.nl/) for sharing and harmonisation with other research centers, e.g. within Detecting-HF (ERA-CVD consortium) and IMI Bigdata@Heart (https://www.bigdata-heart.eu/).</p> <p>Our unit stimulates the registration of protocols for clinical trials, and ensures registrations of trial and publishing of results of clinical trials (clinicaltrials.gov, trialregister.nl, clinicaltrialsregister.eu), such as for (diagnostic) trials TREE, EVITA-HF, STRETCH, Tophu, UHFO-DM, UHFO-DD, UHFO-COPD.</p>
5.3 Open Access publications (1)	<p>Our general approach is to publish as much as possible in online, open access journals for wider dissemination.</p> <p>The UMC Utrecht stimulates open dissemination of scholarly publications (e.g. doctoral theses) via the platform NARCIS (https://www.narcis.nl/).</p> <p>Below some examples of open access publications of our unit:</p> <ol style="list-style-type: none">1. Van Setten J, Warmerdam EG, Groot OQ, et al. Non-HLA Genetic Factors and Their Influence on Heart Transplant Outcomes: A Systematic Review. <i>Transplant Direct</i>. 2019;5(2):e422.2. Bracco Gartner TCL, Deddens JC, Mol EA, et al. Anti-fibrotic effects of cardiac progenitor cells in a 3D-model of human cardiac fibrosis. <i>Front Cardiovasc Med</i> 2019;6:52.3. Van Riet EE, Hoes AW, Limburg A, et al. Extended prediction rule to optimise early detection of heart failure in older persons with non-acute shortness of breath: a cross-sectional study. <i>BMJ Open</i>. 2016;6(2):e008225.4. Van Everdingen WM, Maass AH, Vernooij K, et al. Comparison of strain parameters in dyssynchronous heart failure between speckle tracking echocardiography vendor systems. <i>Cardiovasc Ultrasound</i>. 2017;15(1):25.



Appendix D: Research theme Cerebral Ischemia

Table 3 – Process indicators Cerebral Ischemia

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment	<p>a. Through internationally recognized and societally well-embedded research our unit adds to improvements in the diagnosis, treatment, and prognosis of patients with cerebrovascular disease, including those with ischaemic stroke or vascular cognitive impairment, and neonates with hypoxic-ischemic brain damage.</p> <p>b. The focus of the research questions can be summarized as:</p> <ul style="list-style-type: none"> • Improvement of diagnostic tools for stroke, vascular cognitive impairment, and neonatal hypoxic-ischemic brain injury. • Development of new treatment strategies to improve outcomes after stroke and neonatal hypoxic-ischemic brain injury. <p>The disease burden for cerebrovascular disease in terms of economic costs and 'quality-adjusted life years' is high. In Europe, dementia (including vascular dementia) ranks first for direct non-medical costs, and stroke second for direct healthcare costs.</p>
3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made	<p>Together with the patient organisation Dutch Brain Aneurysm Patient Platform, we have developed a research agenda for the field of aneurysm research. Our unit has brought its specific expertise to this agenda.</p> <p>Our research in the field of stroke addresses key research questions in the Stroke Action Plan for Europe 2018 – 2030, which has been developed by the European Stroke Organisation and the European stroke patients advocacy organisation Stroke Alliance For Europe (SAFE). These questions include but are not limited to: "Which strategies will improve outcomes in ischaemic stroke patients who are not eligible for reperfusion therapies, or who do not recover after recanalisation?" and "Which treatment strategies will further improve outcome in patients with Subarachnoid Hemorrhage (SAH) by reducing brain injury?"</p> <p>Our preclinical research follows international recommendations and guidelines for the optimisation of experimental and preclinical stroke research (e.g., the Stroke Treatment Academy Industry Roundtable and the Stroke Recovery and Rehabilitation Roundtable), in which imaging is put forward as a critical tool for translational studies.</p> <p>Our investigators in the field of neonatal brain injury have an integrated program to recruit, care for and study a uniquely fragile population across perinatal care with obstetricians, pediatric neurologists, surgeons, cardiologists, radiologists, imaging experts from the Institute of Sciences and the Dutch Connectome Lab (combining methodology in acquisition and analysis) and collaborate in (inter)national networks, consortiums and grants with other experts in Neonatal Neurology over the world. Together with the preclinical Department for Developmental Origins of Disease we develop bench-to-bedside perinatal (neuroprotective/neuroregenerative) research strategies.</p> <p>Our research lines are connected with the first 1001 days of a child's life program (research theme of Dynamics of Youth, University Utrecht) focusing from antenatal to their second birthday, the period critical to the development of their complex brains and the cognitive skills that depend on them. The aim of this program is to get broad support for initiation of scientific knowledge and expertise to enforce this critical first phase of these infants.</p>
3.3. Stakeholders are involved in formulating the main research questions	<p>Investigators of different research lines meet at least annually with patient representatives from the diseases under study to discuss the strategic research program. The European stroke patients advocacy organisation Stroke Alliance For Europe (SAFE) has provided input to the randomised clinical trial PRECIOUS, which aims to assess whether the prevention of complications in the acute phase of stroke improves functional outcome. In addition, SAFE is responsible for part of the dissemination of this project.</p>
3.4. The research questions are feasible and are pursued using optimal and efficient design	<p>Our studies are performed by or in close collaboration with clinical epidemiologists, statisticians, or methodologists. For studies of Big Data, omics, text mining, or machine learning expertise is sought in the University Utrecht and outside. For our preclinical studies, we follow the 'Animal Research: Reporting of In Vivo Experiments' (ARRIVE) guidelines (NC3Rs).</p>
3.5. What is 'the next step' if the project delivers positive results	<p>a. Multiple stakeholders are involved in most of our projects, including patient advocacy groups such as SAFE, industrial partners such as Nutricia-Danone and Philips, and other research groups across Europe and elsewhere.</p> <p>b. We have a dedicated clinical trial developer (U-Trial) who helps researchers make connections with industry.</p> <p>c. In our unit we rely on a diversity of national and international funders (most notably the Dutch Heart Foundation and the European Union), including companies.</p> <p>d. In our unit researchers have been members of various international (guideline) committees (Dutch Stroke Guideline; European Stroke Guideline; Vascular Surgery Guideline). We present our work in professional literature and at professional society conferences. We emphasize the importance of dissemination of results to patients, care givers, patient organisations, funders and healthcare professionals. We have multiple newsletters per year and make use of social media.</p>



Table 4 – Output indicators Cerebral Ischemia

4.1 Research products for peers	<p>Selected peer-reviewed publications:</p> <ol style="list-style-type: none">1. Compter A, Van der Worp HB, Schonewille WJ, et al; for the VAST Investigators. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. <i>Lancet Neurol.</i> 2015;14(6):606-614.2. Van Asch CJJ, Velthuis BK, Rinkel GJE, et al; on behalf of the DIAGRAM investigators. Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study. <i>BMJ.</i> 2015;351:h5762.3. Van Seeters T, Biessels GJ, Kappelle LJ, et al, The prognostic value of CT angiography and CT perfusion in acute ischemic stroke. <i>Cerebrovasc Dis.</i> 2015;40(5-6):258-269.4. Hilkens NA, Algra A, Diener HC, et al; Cerebrovascular Antiplatelet Trialists' Collaborative Group. Predicting major bleeding in patients with noncardioembolic stroke on antiplatelets: S2TOP-BLEED. <i>Neurology.</i> 2017; 89(9): 936-943. <p>Other products for peers:</p> <ul style="list-style-type: none">• Researchers in our unit developed and validated a fully automated and freely publically available tool to segment hippocampal subfields at 7T MRI (https://www.nitrc.org/projects/ashs).• The Vascular Cognitive Impairment group has set up an international platform to exchange brain lesion data and create vascular brain vulnerability maps for diagnostic purposes; http://www.dadm.alzdem.com/article/S2352872919300211/pdf
4.2 Research products for societal target groups	<p>Selected research products for societal target groups:</p> <ul style="list-style-type: none">• H.B. van der Worp was last author of one of the articles in The Lancet 'Waste' series, with recommendations on how to increase value and reduce waste in biomedical research (<i>Chan AW, Song F, Vickers A, et al. Increasing value and reducing waste: addressing inaccessible research. Lancet. 2014;383(9913):257-266.</i>• An exercise guide and exercise app ("Oefen App Beroerte", available in Google Playstore) have been accepted as required part of physical therapy by Dutch insurers. The guide was developed and recently evaluated by UMC stroke researchers.• Intracranial vessel wall MRI methods developed have been translated to clinical MRI scanners in close collaboration with Philips. These intracranial vessel wall MRI methods are now used on clinical MRI machines worldwide to better identify the cause of stroke in individual patients with cerebral ischemia including young stroke patients.• Dutch Heart Association: campaign 'Stroke Alarm' (https://www.hartstichting.nl/hart-en-vaatziekten/beroerte/herken-de-signalen-van-een-beroerte)
4.3 Use of research products by peers	<p>Selected examples of research products used by peers:</p> <ul style="list-style-type: none">• Software tools for the analysis of neonatal brain injury developed in our unit are used by multiple research groups worldwide.• The brain artery anastomosing devices ELANA, SELANA, and MICRO SELANA that have been developed in collaboration with our unit are used by neurosurgeons worldwide.• The SMART-MR cohort has been used in a genetic association replication study (Chauhan G, Adams HHH, Satizabal CL, et al. Genetic and lifestyle risk factors for MRI-defined brain infarcts in a population-based setting. <i>Neurology.</i> 2019; doi:10.1212/WNL.0000000000006851; PREDICT-SMART-PSD).
4.4 Use of research products by societal groups	<p>Results of our trials HAMLET, VAST, and ESPRIT form an important basis of recommendations in international ischemic stroke guidelines.</p>
4.5 Marks of recognition from peers	<p>Selected examples of recognitions marks from peers:</p> <ul style="list-style-type: none">• L. de Vries: Harwood Nash memorial lecture (2012); honorary award of the German speaking society of Child Neurology (2015).• J. Greving (2013): Senior Postdoc Dekker fellowship (Dutch Heart Foundation).• H. van der Worp (2018): President of the European Stroke Organisation.• J. Hendrikse: ERC StG grant (2015-2020), Vidi (2013-2018) and Technical grants (STW-Dutch Heart Foundation; 2017-2021) on intracranial vessel wall MRI.• G. de Borst (2017-current): Chair of the Guideline Committee of the European Society for Vascular and Endovascular Surgery.
4.6 Marks of recognition from societal groups	<p>Selected examples of recognitions marks from societal groups:</p> <ul style="list-style-type: none">• E. Hol: member of the KNAW committee for writing a report on alternatives for animal experiments in neuroscience.• J. de Man-Ginkel: co-author of Manifest for Dutch VWS ministry "Kwaliteit van zorg, nu en in de toekomst" (24-April-18 discussed in the Dutch Parliament).• Geerlings (2018): 2bike4alzheimer award 2018 (https://2bike4alzheimer.inactievooralzheimer.nl/).



Table 5 – Open Science indicators Cerebral Ischemia

5.1 Openness of the research agenda & stakeholder involvement	Stakeholders involved: <ul style="list-style-type: none">• Patient organisation Dutch Brain Aneurysm Patient Platform.• The European stroke patients advocacy organisation Stroke Alliance For Europe (SAFE).• Industrial partners, such as Nutricia-Danone and Philips.
5.2 Openness of data and protocols	To promote the independent re-use of data of our H2020-funded randomized clinical trial PRECIOUS (PREvention of Complications to Improve OUTcome in elderly patients with acute Stroke) and to save the costs of unnecessarily compiling new datasets, access to a clean, anonymous, and well-annotated dataset will be made publicly available via the PRECIOUS website and in a public data repository within 18 months of the final follow-up of the last patient. Anonymous data will also be included in the Virtual International Stroke Trials Archive (VISTA; http://www.vista.gla.ac.uk/). This sharing of participant-level data will provide others the opportunity to examine new research questions and will therefore increase the impact of PRECIOUS.
5.3 Open Access publications (1)	The UMC Utrecht stimulates open dissemination of scholarly publications (e.g. doctoral theses) via the partially open platform NARCIS (https://www.narcis.nl/). Example of an open access publication of our unit: <ul style="list-style-type: none">• Weaver NA, Zhao L, Biesbroek JM, et al. The meta VCI map consortium for meta-analyses on strategic lesion locations for vascular cognitive impairment using lesion symptom mapping: design and multi-center pilot study. <i>Alzheimers Dement (Amst)</i>. 2019;11:310-326.



Appendix E: Research theme Aneurysms

Table 3 – Process indicators Aneurysms

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment	<p>a. Arterial aneurysms are a focal dilation of 50% of the normal arterial diameter with abdominal aortic aneurysm (AAA) as the most common type increasing with age, while extracranial carotid artery aneurysms (ECAA) are rare but can happen at a young age. Rapid growth and large diameter are associated with aneurysms at risk for rupture. There is, however, always the question if the risk coming with an (endovascular) operation is lower than the risk of rupture and death.</p> <p>In general, the mission of the aneurysm research theme is to perform internationally recognized and societally well-embedded research, clinical care and highly complex care with the aim to improve the health of patients with aneurysms.</p> <p>b. Recently an extensive list of research questions and research aims were defined for our theme. These research aims are diverse and distinctive and incorporate fundamental, applied and translational research and could result in promising technology (e.g. X-ray reducing surgery techniques), new treatments and improved personalized care (e.g. prediction rules). For instance, it is our aim to:</p> <ul style="list-style-type: none">• improve (endovascular) treatment of aortic aneurysms with reduced radiation.• determine natural history of carotid aneurysms to determine who to operate or not.• understand aneurysm development and pathology via the largest aneurysm tissue biobank in the world.• identify genetic determinants and biomarkers in the development and rupturing of aneurysms.• further develop Big Data applications in aneurysm research and patient care.• further develop X-ray reducing surgery techniques.• improve prediction of the rupturing chance of unruptured aneurysms.
3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made	<p>Our research roadmap is based on:</p> <ul style="list-style-type: none">• Strategic focus within the UMC Utrecht strategic theme Circulatory health.• Strategic agenda of (inter)national funding organisations which are based on patient plus researchers priorities.• clinically relevant questions. <p>These questions are addressed in clinical trials, by extensive biobanking of aneurysm tissue and blood, in large animal models and in the research laboratory which gives our research a multidisciplinary character with clinical relevance.</p>
3.3. Stakeholders are involved in formulating the main research questions	<p>Stakeholders are vascular surgeons, scientists, patient (“Harteraad”), funding organisations ((Dutch Heart Foundation, NWO, EU H2020) and companies (Philips), which are all involved in determining research topics and projects. Within the Utrecht Cardiovascular Cohort (UCC), the strategic research program closely collaborates with all UMC Utrecht divisions that are involved in care of patient at risk or with vascular disease. The UCC steering committee meets monthly to discuss progress, also involving the topic of aneurysms.</p> <p>In some of our projects patient representatives from the diseases under study are invited to discuss our research lines. For several grants, we involved clinicians, epidemiologists and basic scientists (UMC Utrecht), and patient organisations (e.g. “Harteraad”, “Hersenaneurysma patiënten platform”).</p> <p>The individual members of the aneurysm program discuss individually with other stakeholders, for grant proposals within the Netherlands (CVON, NWO, ZonMw) and within Europe (H2020, ERA-CVD).</p>
3.4. The research questions are feasible and are pursued using optimal and efficient design	<p>Unit researchers structurally collaborate with experts (statisticians and/or methodologists) in clinical epidemiology (available at the Julius Center, UMC Utrecht), which are involved in all projects based on knowledge of the content and methodology. PhD candidates are encouraged to follow epidemiology and statistical courses (including Master of Epidemiology) during their PhD study. In addition, for Big Data, omics, text mining and machine learning expertise is sought.</p>



3.5. What is 'the next step' if the project delivers positive results

In the projects we have collaborations with multiple stakeholders: within EU and USA we collaborate with several clinical research groups on both AAA and ECAA. Philips is for both clinical as preclinical research an established partner. We also collaborate with patient organisations (<https://www.hartstichting.nl/>), interest groups and knowledge centers.

In our unit we rely on a diversity of funders, such as ZonMw, Dutch Heart Foundation, EU H2020 and funding by industry to strengthen our valorisation efforts.

Staff members are involved in a variety of organisations, e.g. fellowships of the European Society of Cardiology (ESC) and the European Society of Vascular Surgery, and membership of national and European guidelines committees regarding aneurysm treatment. For instance, I. Vaartjes is a member of Dutch Health Council commission on screening AAA.

Selected examples of general media coverage:

- **Television:**
 - J. van Herwaarden:
 - 2010: TV-channel "Nederland 1", Program about complex aneurysm repair with recorded endovascular procedure (first operator), "Afslag UMC".
 - 2019: NOS-Journaal, Public announcement of first clinical use of new Fiber Optic RealShape Technology (FORS).
- **Radio:**
 - J. van Herwaarden:
 - 2019: NOS Radio1-journaal, Public announcement of first clinical use of new Fiber Optic RealShape Technology.
 - 2019: BNR Nieuwsradio, Public announcement of first clinical use of new Fiber Optic RealShape Technology.
- **Written media:**
 - www.AD.nl (2019): [Glasvezel maakt röntgenstraling bij vaatoperaties in UMC bijna overbodig.](#)
 - www.nu.nl (2019): [UMC Utrecht eerste met 3D-beelden tijdens vaatoperaties.](#)
 - www.hartpatienten.nl (2019): [Wereldprimeur: UMC Utrecht werkt met unieke 3D technologie.](#)

Table 4 – Output indicators Aneurysms

4.1 Research products for peers	<p>Key publications:</p> <ol style="list-style-type: none"> 1. Greving JP, Wermer MJH, Brown RD, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. <i>Lancet Neurol.</i> 2014; 13(1): 59-66. 2. Laarman MD, Vermunt MW, Kleinloog R, et al. Intracranial aneurysm-associated single-nucleotide polymorphisms alter regulatory DNA in the human circle of Willis. <i>Stroke.</i> 2018;49(2):447-453. 3. Cremers CH, van der Bilt IA, van der Schaaf IC, et al. Relationship between cardiac dysfunction and cerebral perfusion in patients with aneurysmal subarachnoid hemorrhage. <i>Neurocrit Care.</i> 2016;24(2):202-206. 4. Backes D, Rinkel GJE, Greving JP, et al. The ELAPSS score for prediction of risk of growth of unruptured intracranial aneurysms. <i>Neurology.</i> 2017;88(17):1600-1606. 5. Backes D, Vergouwen MD, Tiel Groenestege AT, et al. PHASES Score for Prediction of Intracranial Aneurysm Growth. <i>Stroke.</i> 2015;46(5):1221-1226. 6. De Ruiter QMB, Jansen MM, Moll FL, et al. Procedure and step-based analysis of the occupational radiation dose during endovascular aneurysm repair in the hybrid operating room. <i>J Vasc Surg.</i> 2018;67(6):1881-1890. 7. Buck DB, Van Herwaarden JA, Schermerhorn ML, Moll FL. Endovascular treatment of abdominal aortic aneurysms. <i>Nat Rev Cardiol.</i> 2014;11(2):112-23. 8. Agyemang C, Van Oeffelen AA, Norredam M, et al. Ethnic disparities in ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage incidence in the Netherlands. <i>Stroke.</i> 2014;45(11):3236-3242. 9. Nieuwkamp DJ, Vaartjes I, Algra A, et al. Risk of cardiovascular events and death in the life after aneurysmal subarachnoid haemorrhage: a nationwide study. <i>Int J Stroke.</i> 2014;9(8):1090-1096. <p>Selected examples of dissertations:</p> <ul style="list-style-type: none"> • Dominique Buck (2015): Innovations in abdominal aneurysm repair. • Arnoud Kamman (2017): Clinical studies in risk stratification & therapy of thoracic aortic disease. • Vanessa Pourier (2018): Clinical approaches in the treatment of extracranial carotid artery aneurysms. <p>Researchers from our group set up several cohorts (2013-2018):</p> <ul style="list-style-type: none"> • Utrecht Cardiovascular Cohort (UCC; ongoing, > 5000 inclusions). • NHF facts and figures database of all Dutch inhabitants (I. Vaartjes).
4.2 Research products for societal target groups	<p>Selected examples of unit researcher involvement in product generation for societal target groups:</p> <ul style="list-style-type: none"> • Fiber Optic Real Shape technology (FORS). • Chimney graft technique for EVAR. • Endovascular repair of the aortic arch. • Utrecht Cardiovascular Cohort (UCC).



4.3 Use of research products by peers	The FORS catheter program with Philips has been developed from a technological finding at Philips via large animal studies into a first in men at UMC Utrecht and is now being tested in a clinical multi-center trial.
	Selected examples of publications with the total number of citations (Google Scholar, June 28 2019): <ul style="list-style-type: none">• Greving JP et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms. <i>Lancet Neurol</i> 2014. PMID:24290159. (471 citations).• Buck DB, Van Herwaarden JA, Schermerhorn ML, Moll FL. Endovascular treatment of abdominal aortic aneurysms. <i>Nat Rev Cardiol</i>. 2014;11(2):112-23. (33 citations)
	Colleagues from a foreign research institute used our assays or our datasets, as is evident e.g. in the following references: <ul style="list-style-type: none">• Wood AM, Kaptoge S, Butterworth AS, et al. Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. <i>Lancet</i>. 2018;391(10129):1513-1523.• Harrison SC, Holmes MV, Burgess S, et al. Genetic Association of Lipids and Lipid Drug Targets With Abdominal Aortic Aneurysm: A Meta-analysis. <i>JAMA Cardiol</i>. 2018;3(1):26-33.• Powell JT, Sweeting MJ, Ulug P, et al; EVAR-1, DREAM, OVER and ACE Trialists. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. <i>Br J Surg</i>. 2017;104(3):166-178.
4.4 Use of research products by societal groups	Example of participation in guideline generation: Wanhainen A, Verzini F, Van Herzele I, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms. <i>Eur J Vasc Endovasc Surg</i> . 2019;57(1):8-93.
4.5 Marks of recognition from peers	Selected examples of recognitions marks from peers: <ul style="list-style-type: none"><i>a. Grants/fellowships:</i><ul style="list-style-type: none">• J. Greving (2013): Dekker fellowship from the Dutch Heart Foundation.• J. Greving (2013): Rudolf Magnus Young Talent Fellowship.• J. Greving (2017): CVON Young Talent fellowship.• I. Vaartjes (2018): Dutch Heart Foundation grant for the project "Eerder herkennen".<i>b. Membership of committees:</i> I. Vaartjes (2019): Dutch Health Council, commission screening.<i>c. Invited lectures:</i><ul style="list-style-type: none">• A. Algra (2016, Barcelona): European Stroke Organisation Conference: Teaching course on management of asymptomatic intracranial aneurysms.• D. de Kleijn: ESC meeting in 2012, 2015, 2016, 2017, 2018; EAS 2019; keynote lectures Selectbio meetings 2015, 2016, 2017, 2018, 2019.<i>d. Visiting professor:</i> D. de Kleijn: NUS Singapore 2016-2017.



Table 5 – Open Science indicators Aneurysms

5.1 Openness of the research agenda & stakeholder involvement	Listing of stakeholders involved: <ul style="list-style-type: none">• Vascular surgeons and scientists (national and international).• Patient organisation (“Harteraad”) and funding organisations (Dutch Heart Foundation, NWO and EU).• Companies (Philips)
5.2 Openness of data and protocols	a. All material is stored on central drives of the UMC Utrecht following a standard format. b. Data are shared generally through contacting the steeringcommittee of the specific study through websites (e.g. UCC): https://www.UMC Utrechtrecht.nl/en/Research/Strategic-themes/Circulatory-Health/Facilities/UCC . Data and scripts from the Dutch Heart Foundation facts and figures database of all Dutch inhabitants are stalled in the secured environment of Statistics Netherlands and all analysis are performed according to the Dutch privacy legislation. Studies can be replicated after obtaining permission from data owners (Statistics Netherlands, Dutch Hospital Data, cohort owners). c. Our unit stimulates the registration of protocols for clinical trials and also for preclinical research. Examples: <ul style="list-style-type: none">• Welleweerd JC, Bots ML, Kappelle LJ, et al. Rationale and design of the extracranial Carotid artery Aneurysm Registry (CAR). <i>J Cardiovasc Surg (Torino)</i>. 2018;59(5):692-698.• Vergouwen MD, Rinkel GJ, Algra A, et al. Prospective randomized open-label trial to evaluate risk factor management in patients with unruptured intracranial aneurysms: Study protocol. <i>Int J Stroke</i>. 2018;13(9):992-998.• Gathier CS, van den Bergh WM, Slioter AJ; HIMALAIA-Study Group. HIMALAIA (Hypertension Induction in the Management of Aneurysmal subArachnoid haemorrhage with secondary IschaemiA): a randomized single-blind controlled trial of induced hypertension vs. no induced hypertension in the treatment of delayed cerebral ischemia after subarachnoid hemorrhage. <i>Int J Stroke</i>. 2014;9(3):375-80.• Clinical trial registration of: Rationale Treovance Registry (2015-2016); Treo Registry (2017); Anchor trial (Aneurysm Treatment using the Aptus™ Heli-FX™ EndoAnchor System Global Registry) (2012-2018); First in Human study for Fiber Optic RealShape (FORS) (2018).
5.3 Open Access publications (1)	The UMC Utrecht stimulates open dissemination of scholarly publications (e.g. doctoral theses) via the platform NARCIS (https://www.narcis.nl/). Selected examples of open access publications: <ol style="list-style-type: none">1. De Vries EE, Van Laarhoven CJHCM, Kuijff HJ, et al. Volumetric assessment of extracranial carotid artery aneurysms. <i>Sci Rep</i>. 2019;9(1):8108.2. Belvroy VM, de Beaufort HWL, van Herwaarden JA, et al. Tortuosity of the descending thoracic aorta: Normal values by age. <i>PLoS One</i>. 2019;14(4):e0215549.3. Van Bakel TM, Romarowski RM, Morganti S, et al. Blood flow after endovascular repair in the aortic arch: a computational analysis. <i>Aorta (Stamford)</i>. 2018;6(3):81-87.



Appendix F: Research theme High Risk - Diabetes, Hypertension and Atherosclerosis

Table 3 – Process indicators High Risk - Diabetes, Hypertension and Atherosclerosis

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment

Diabetes

Our efforts are aimed at improving the life and reducing complications in patients with diabetes, with a specific focus on (but not limited to) advanced technology, pregnancy, CF/lung transplant, and micro- and cardiovascular (surrogate) outcomes. With a broader view of the subject, to improve the life and times of patients with diabetes through national and international collaborative efforts in (inter)national guidelines, consensus and expert opinion papers, as well as the development and implementation of patient-centered treatment goals.

Hypertension

- To improve the care for patients with difficult to treat hypertension.
- To further strengthen our position as an (inter)national hypertension referral center in care, education and research. Research is focused on unmet needs identified by (inter)national guidelines, consensus and expert opinion papers.
- To further improve multi-disciplinary high risk care for women with risk pregnancy (diabetes, renal disease including hypertension).

Atherosclerosis

Atherosclerosis is the underlying cause of cardiovascular events including myocardial infarction, angina, stroke, claudication with a strong influence of risk factors and genetic components. Our research groups have been world-wide leading in atherosclerosis research.

Through investments in biobanking and strong collaboration between lab and clinic, unique patient material (vascular lesions) and technologies to dissect the phenotype of atherosclerotic plaques on gene and cellular level, we provide novel insights in mechanisms of atherosclerotic disease. This knowledge is highly innovative and facilitates the search for risk stratified drug targets and for validation of outcomes in experimental (non human) models.

The translation from bench to clinical application is accelerated when validation in human plaque samples is executed. Next to this, clinical trials (eg ACST-2, Omizumab, LoDoCo) and large animal models are present and initiated.

With the worlds largest human plaque biobank (AtheroExpress; including genetic characterisation), excellent wet lab facilities and a state-of-the-art pig facility including a hybrid cath lab using genetically modified LDLr KO atherosclerotic pig models, makes this a truly translational research group.

Prediction and prevention of vascular disease

Prediction of vascular risk in various groups of patients is the corner stone of personalized cardiovascular preventive care in high risk patient groups, including patients with hypertension, diabetes and atherosclerotic vascular disease. This theme can be viewed as overarching the patient groups in high risk groups and other research themes in the Circulatory Health scientific portfolio.

At the UMC Utrecht there is specific expertise in methodology of prevention research (Julius Center) and various large cohorts such as SMART (>13,500 patients), AtheroExpress, EPIC-NL and the recently started Utrecht Cardiovascular Cohort (UCC) initiative. The mission of this relatively 'young' research theme within the Circulatory Health program is to integrate prediction and prevention to enable prediction of individual treatment effects. This enables patient participation ('shared decision making') in deciding on lifelong preventive treatments and opens doors to more precise, more effective and more efficient delivery of preventive care.



3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made

3.3. Stakeholders are involved in formulating the main research questions-

Diabetes

- Emphasis is placed on patient-centered care through shared decision making. To enhance this process research is focused on individualized prediction of treatment effects and prioritisation of different treatment goals.
- Research is providing quantitative estimates of consequences (adverse events) of diabetes mellitus and its determinants.
- Sensible and target-based intervention and assessment of advanced technology in type 1 diabetes and type 2 diabetes (including but not limited to insulin pump therapy, continuous glucose monitoring and the hybrid closed loop with the ultimate goal of clinical introduction of the closed loop).
- Improving diagnosis and treatment of various forms of diabetes in pregnancy (type 1 diabetes, type 2 diabetes, GDM, MODY) with emphasis on diagnosis (GDM) and treatment (GDM, type 1 diabetes, type 2 diabetes, MODY) with maternal and neonatal outcome analysis. In collaboration with the UMC Utrecht department of Woman & Baby.
- Improving diagnosis and treatment of patients with CF, RD and/or pulmonary transplant. Outcome analysis regarding diabetes, lipids and blood pressure and analysis of putative increased risk of vascular disease.
- Clinical trials in type 1 and type 2 diabetes regarding the above mentioned topics.
- Pearl string initiative.

National/international:

- We strive to improve out-patient and in-patient care by multi-disciplinary discussion and strict outcome assessment of our treatments. The latter is part of the DPARD/DICA national register of which we are a stakeholder and founding party.
- We are involved in a number of international collaborations, one of which is the COS-panel that is currently involved in a number of core outcome sets in pregnancy, which have been published.
- On a national level, we are involved in the directorate of the diabetes section of the Dutch Internist Society (NIV) and stakeholder of the Diabetes Round Table of the reimbursement authorities ("Zorginstituut Nederland", ZIN).

Hypertension

- We focus our research on apparent resistant hypertension which is a clearly identified and big unmet need.
- Presently we focus research on mechanisms and outcome of different device-based therapies, especially in patients with resistant hypertension and with specific kidney diseases/conditions. In addition, we focus our research on the working hypothesis that renal hypoxia is often driven by hypertension.
- Research aims are developed and defined in cooperation with patient organisations and regulatory agencies (ZIN, ZonMW) and are also recognized by peers, as is evidenced by consensus papers, etc.
- Focus for the future will also include "medication adherence". Poor adherence is increasingly recognized as a major problem in the hypertension field.
- Hypertensive disorders after hypertension in pregnancy is a focus of the collaboration between the UMC Utrecht Obstetrics and Vascular/Epidemiology Departments (with the large CREW consortium project as a current example).

Example of a systematic review:

- Sanders MF, Reitsma JB, Morpey M, et al. Renal safety of catheter-based renal denervation: systematic review and meta-analysis. *Nephrol Dial Transplant.* 2017;32(9):1440-1447.

Atherosclerosis

Research agenda's (national/EU) point to the utilisation of "Big Data". Our research group is contributing to the generation and exploration of data on (epi)genetic, transcriptomic and proteomic levels in large quantities in unique tissue samples. We often take part in international consortia where data are merged (genetics) which leads to the detection of new genes that are involved in disease development.

Most grants in our groups are embedded in national and international consortia such as CVON, H2020, ERA and LeDucq. These consortia encompass a diversity of medical specialties and in the Netherlands patient organisations are asked to co-evaluate the proposals. We also are often involved in private-public collaborations, visit Bio-Events (pitch talks with companies) to discuss our research approach and how it matches with the expectations of the community. Within large animal work, we collaborate with academic but also private partners, among which the Philips FORS project.

Prediction and prevention

Stakeholders such as patient groups ("Harteraad"), healthcare payers (ZilverenKruis, Achmea), hospitals, primary care physicians and medical specialists as well as specialized nurses are involved in developing the prediction and prevention research theme and in setting specific goals. The infrastructure consists of (inter)national collaboration with Steering Committees of large randomized trials and cohorts and researchers from North-America (USA and Canada), Europe, Australia. In recent years we have managed to bring data together of >700,000 patients in dozens of cohorts and trials. The prediction and prevention research theme is headed by Prof.F. Visseren. Public-private initiatives are recently developed with the ICT company ORTEC.



3.4. The research questions are feasible and are pursued using optimal and efficient design

Diabetes/Hypertension

- There is a long-standing close cooperation in both development of new research questions and designing new trials with the Julius Center (in particular Y. van der Graaf, Y. van der Schouw and M. Bots). PhD students of the Department of Vascular Medicine have almost all earned a separate Master Epidemiology. Ample resources are thus available for advanced epidemiology and statistical know-how. In diabetes research, the investigator-initiated trials are supported by staff and the conduct is in the hands of the principal investigator, trial manager and close collaborators. For advanced statistics, support is guaranteed. PhD students are closely supervised by the (co-) promotor.
- PhD students acting as study doctors in industry-sponsored trials are closely (weekly and more often if necessary) supervised in their duties. All PhD students have at least weekly meetings with supervisors. No research is started before a sound plan of approach has been laid down including stringent research questions, methodology and delineation of the primary outcome. At the outset the possible outcome of the research is discussed in terms of potential impact in patient care.
- During the JCI tracer in 2016 the research unit of the Department of Vascular Medicine was chosen as an example for the whole hospital and passed with flying colors.
- If needed methodological and statistical analysis support is sought from the usual UMC Utrecht sources if necessary in design, conduct and analysis.

Atherosclerosis

Our research proposals are always discussed with epidemiologists and in the field of genetics and transcriptomics, we communicate with experts to optimally execute the necessary quality checks. PhD students are stimulated to follow statistics and epidemiology courses including the Master of Epidemiology.

3.5. What is 'the next step' if the project delivers positive results

Diabetes

- We are an established referral center for advanced technology leading to new trials (both investigator- and industry-initiated), participation in national policy panels and the reimbursement authorities (ZIN). A number of physicians are involved in the national diabetes section of the NIV and involved in generating and evaluation of guidelines and as well as generating and evaluation of care and policy statements by the Dutch Diabetes Federation.
- The same is true for the subjects of pregnancy and CF/lungtransplant as well as evaluation of novel therapies in type 2 diabetes.
- There is active participation in the generation of international core outcome sets in pregnancy-related diabetes.

Hypertension

- There is a periodic evaluation of study progress and future steps with patient organisations, pharmaceutical and device companies and regulatory authorities.
- Contacts with medical industries are mainly based on personal contact. There is currently no specific business developer for innovation and valorisation.
- Our current research is funded by ZonMw, Dutch Kidney Foundation, Nuts-OHRA, device companies (Medtronic, St.Jude/Abbott, RECOR, Ablative solutions, Vascular Dynamics, pharmaceutical companies [among others Novo-Nordisk, Astra-Zeneca, Sanofi, etc.]) and through internal funding of high potential young researchers.
- Over the past years, renal denervation research was funded by ZonMw and the Dutch Kidney Foundation ("Nierstichting"), device industries whereas the treatment was reimbursed by the "voorwaardelijke financiering door de zorgverzekeraar". This unique mixture of funding sources makes it possible to evaluate the role and possible place of a new treatment option. The ultimate goal is to find out whether a new treatment should be approved as part of the basic health care insurance or not. The government decided that starting 2017 device-related therapies were not part of basic health care any more and therefore not reimbursed by the system.
- Results of our research are not only published in specialized scientific journals and discussed at (inter)national congresses but also made available to the general public and our patients. We use different techniques including meetings to discuss the outcome of specific trials (for example Sympathy trial), multiple Public Lectures, etc, all focused on the general population and specifically on our patients.



Selected examples of 'the next step' (consensus statements defining future research paths, memberships, etc):

- as member of several guideline and expert committees in the field of hypertension and cardiovascular high risk populations P. Blankestijn contributed to several consensus statements, which are already stated in table 4.1.
- W. Spiering was Task Force member of the 2018 ESC/ESH Guidelines on arterial hypertension; moreover, he is the current president of the Dutch Hypertension Society and is member of the Working Group of Hypertension of the Dutch Society of Vascular Internists, that is often consulted for hypertension-related issues for guidelines or governmental directives.
- Other examples of e.g. KDIGO (Kidney Disease Improving Global Outcome) consensus meetings:
 - Chan CT, Blankestijn PJ, et al; Conference participants. Dialysis initiation, modality choice, access, and prescription: conclusions from a Kidney Disease: Improving Global Outcomes(KDIGO) Controversies Conference. *Kidney Int.* 2019. pii:S0085-2538(19)30138-3.
 - Wanner C, Herzog CA, Turakhia MP; Conference Steering Committee. Chronic kidney disease and arrhythmias: highlights from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2018;94(2):231-234.
 - Turakhia MP, Blankestijn PJ, Carrero JJ, et al; Conference Participants. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J.* 2018;39(24):2314-2325.

Atherosclerosis

- In a Health Holland project we develop and test a novel imaging approach to image dysfunctional endothelium and clinically silent thrombus. If animal tests are positive we will then assess safety perspectives to start a clinical MRI study. The radiologists are informed about the progress of this project. This is a private-public partnership and we are also establishing contacts with global operating imaging and pharmaceutical industry who are in need of imaging technologies to assess "silent thrombus".
- In an ERA consortium we are in search for mechanisms that drive plaque erosion. Targets are searched for in endothelial cells. The outcomes of these studies are related to contacts with industry.
- In the LeDucq consortium we will assess and explore cell specific mechanisms that play a role in cell plasticity in the lesion. Intraplaque cell differentiation has major effects on plaque characteristics and thrombus formation. We are currently preparing a proposal with 2 other LeDucq consortia how to translate future observations towards clinical application. This is an ongoing discussion where also a large pharmaceutical industry will be involved.
- With Philips the FORS project is funded in pre-clinic and clinic with the Department of Vascular Surgery in the lead.
- In a private-public CVON project (CIRCA) we are in search for a gene-based signature in platelets that can diagnose cardiac ischemia in which we collaborate with a bioinformatics company. When outcomes are positive this company will develop a PCR-based test that could be applied in primary healthcare.
- In another private-public CVON program on plasma vesicle biomarkers for coronary atherosclerosis (Stable (SA) and Unstable Angina (UA)), we are now establishing with NLC a start-up to develop a clinical test for SA.
- We get requests from large pharmaceutical companies to share outcomes on associations of gene and protein expression with plaque characteristics as well as pre-clinical large animal models. These associations provide information on beneficial and potential adverse effects of potential drug targets. (Patient informed consent includes permission to collaborate with companies (anonymized data) or therapeutic interventions (medication, devices) in animal models)
- G. Pasterkamp is involved in meetings with public and private stakeholders where strategies (research domains and drug targets) are discussed. Consultancy fees are donated to the lab

Prediction and Prevention

- The next step is to develop lifetime prediction algorithms for other groups of patients (heart failure, atrial fibrillation, chronic kidney disease).
- To implement algorithms in the interactive U-Prevent.com website to make the algorithms available for clinical practice and to further develop functionality together with the ICT company ORTEC, such as automatic filling of algorithms from the electronic health record of a patient, saving patient data on specific accounts. The website also needs CE certification and various safety and privacy updates to keep the website up to quality standards and specific (inter)national rules and regulations.
- Research grants for public-private collaboration have been submitted, including the "IMDI-DCVA: Hart voor duurzame zorg" grant submission 'Implementing device-based personalized cardiovascular disease prevention in clinical practice: putting big data to work'.



Table 4 – Output indicators High Risk - Diabetes, Hypertension and Atherosclerosis

4.1 Research products for peers

Diabetes

Key publications:

1. Celeng C, Maurovich-Horvat P, Ghoshhajra BB, et al. Prognostic value of coronary computed tomography angiography in patients with diabetes: a meta-analysis. *Diabetes Care*. 2016;39(7):1274-1280.
2. Seferović PM, Petrie MC, Fillipatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20(5):853-872.
3. Franssens BT, Van der graaf Y, Kappelle LJ, et al. Body weight, metabolic dysfunction, and risk of type 2 diabetes in patients at high risk for cardiovascular events or with manifest cardiovascular disease: a cohort study. *Diabetes Care* 2015;38(10):1945-1951.
4. Koopal C, Visseren FLJ, Westerink J, et al. Predicting the effect of fenofibrate on cardiovascular risk for individual patients with type 2 diabetes. *Diabetes Care*. 2018;41(6):1244-1250.
5. Bosi E, Choudhary P, De Valk HW, et al. Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;7(6): 462-472.
6. Sharif S, Van der Graaf Y, Nathoe HM, et al. HDL cholesterol as a residual risk factor for vascular events and all-cause mortality in patients with type 2 diabetes. *Diabetes Care* 2016;39(8):1424-1430.

E-Health:

- An app has been developed which makes it possible to calculate the risk for (new) cardiovascular morbidity and mortality in all high risk patients, including patients with diabetes. Included risk score are the Dutch CVRM SCORE, ADVANCE risk score (for type 2 diabetes) and the newly developed and externally validated SMART risk score for patients with known cardiovascular disease (including patients with diabetes). The app is freely available for download in the Android and Apple store.
- A large e-Health project with finance of Achmea has been set-up to evaluate the safety and cost-effectiveness of home monitoring in high-risk pregnancies including hypertension and preeclampsia (HOTEL study).

Hypertension

Key publications:

1. De Jager RL, Van Maarseveen EM, Bots ML, Blankestijn PJ; SYMPATHY investigators. Medication adherence in patients with apparent resistant hypertension: findings from the SYMPATHY trial. *Br J Clin Pharmacol*. 2018;84(1):18-24.
2. De Jager RL, De Beus E, Beeftink MM, et al; SYMPATHY Investigators. Impact of medication adherence on the effect of renal denervation: The SYMPATHY Trial. *Hypertension*. 2017;69(4):678-684.
3. Spiering W, Williams B, Van der Heyden J, et al; CALM-FIM_EUR investigators. Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study. *Lancet*. 2017;390(10113):2655-2661.

Further we contribute to a global network on chronic kidney disease and cardiovascular risk. This network has produced a series of papers in high ranking journals. Examples are:

- Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* 2015;3(7):514-525.
- Chang AR, Grams ME, Ballew SH, et al; CKD Prognosis Consortium (CKD-PC). Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. *BMJ*. 2019;364:k5301.
- Coresh J, Heerspink HJL, Sang Y, et al; Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. *Lancet Diabetes Endocrinol*. 2019;7(2):115-127.
- Heerspink HJL, Greene T, Tighiouart H, et al; Chronic Kidney Disease Epidemiology Collaboration. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. *Lancet Diabetes Endocrinol*. 2019;7(2):128-139.



Selected examples of consensus statements defining future research paths within a field:

- Verloop WL, Agema WR, Allaart CP, et al. Renal denervation for the treatment of hypertension: the Dutch consensus. *Neth J Med.* 2014;72(9):449-454.
- Schlaich MP, Schmieder ME, Bakris G, et al. International expert position statement: percutaneous transluminal renal denervation for the treatment of resistant hypertension. On behalf of the Global Medical Education Committee on Renal Denervation. *J Am Col Card* 2013;62(22):2031-2045.
- Mahfoud F, Böhm M, Azizi M, et al. Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design. *Eur Heart J.* 2015;36(33):2219-2227.
- Mahfoud F, Schmieder ME, Azizi M, et al. Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: state of the art and considerations for the future. *Eur Heart J.* 2017;38(44):3272-3281.
- Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 2016;37(29):2315-2381.
- Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39(33):3021-3104.

Hypertension and/or renal denervation related PhD projects:

- W. Verloop (2015): The dreams of renal denervation: a translational approach.
- E. de Beus (2017): Resistant hypertension: consequences and treatment options.
- M. Beeftink (2017): Challenges in the management of hypertension and heart failure.

Atherosclerosis

Selected research products for peers:

1. Aengevaeren VL, Mosterd A, Braber TL, et al. Relationship between lifelong exercise volume and coronary atherosclerosis in athletes. *Circulation.* 2017;136(2):138-148.
2. Zoet GA, Benschop L, Boersma E, et al.; CREW Consortium. Prevalence of subclinical coronary artery disease assessed by coronary computed tomography angiography in 45- to 55-year-old women with a history of preeclampsia. *Circulation.* 2018;137(8):877-879.
3. Pasterkamp G, Hoefer I, Prakken B. Lost in the citation valley. *Nat Biotechnol.* 2016;34(10):1016-1018.
4. Major expansion of data resources in the Athero-Express study including plaque epigenetic data, whole plaque RNA seq data and successful single cell RNA seq data.
5. Initiation of LDLr KO atherosclerotic pig model.
6. First in man FORS catheter.
7. Patent vesicle biomarkers for diagnosis SA and UA.

Prediction and prevention:

Selected research products for peers:

1. Kaasenbrood L, Boekholdt SM, Van der Graaf Y, et al. Distribution of estimated 10-year risk of recurrent vascular events and residual risk in a secondary prevention population. *Circulation* 2016;134(19):1419-1429.
 2. Dorresteijn JA, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. *BMJ.* 2016;352:i1548.
 3. Koopal C, Visseren FLJ, Westerink J, et al. Predicting the effect of fenofibrate on cardiovascular risk for individual patients with type 2 diabetes. *Diabetes Care.* 2018;41(6):1244-1250.
 4. Kaasenbrood L, Poulter NR, Severs, PS, et al. Development and Validation of a Model to Predict Absolute Vascular Risk Reduction by Moderate-Intensity Statin Therapy in Individual Patients With Type 2 Diabetes Mellitus: The Anglo Scandinavian Cardiac Outcomes Trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Collaborative Atorvastatin Diabetes Study. *Circ Cardiovasc Qual Outcomes* 2016;9(3):213-221.
 5. Berkelmans GFN, Gudbjörnsdottir S, Visseren FLJ, et al. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with type 2 diabetes mellitus. *Eur Heart J* 2019; doi: 10.1093/eurheartj/ehy839
 6. Dissertations:
 - J.A.N. Dorresteijn (2013): Personalized Vascular Medicine. Tailoring cardiovascular disease management to the individual patient.
 - J. van der Leeuw (2014): Individualized cardiovascular disease prevention: prediction of risk and treatment effect.
 - L. Kaasenbrood (2016): Individualized vascular disease prevention in high-risk patients.
 - G Berkelmans (2018): Lifetime predictions for individualized vascular disease prevention. Whom and when to treat?
-



4.2 Research products for societal target groups

Diabetes

Selected examples of unit researcher involvement in product generation for societal target groups:

- On individualized prediction:
 - Dr. J. Dorresteijn, prof. F. Visseren (2016): 'Van trial naar individu' (Medisch Contact) (<https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/van-trial-naar-individu.htm>).
- The "Vaatrisico app" and the SMART risk score for patients with diabetes and vascular disease gained a lot of attention in the media, among which Nu.nl and NOS.nl:
 - Prof. F. Visseren (2013): 'Nieuw voorspelmodel hart- en vaatziekten' (NOS.nl) (<http://nos.nl/video/502685-nieuw-voorspelmodel-hart-en-vaatziekten.html>).
 - Prof. F. Visseren (2013): 'Nieuw model voorspelt hart- en vaatziekten bij vaatpatiënten' (NU.nl) (<http://www.nu.nl/gezondheid/3412793/nieuw-model-voorspelt-hart--en-vaatziekten-bij-vaatpatienten.html>)
- U-prevent:
 - Prof. F. Visseren (2018): NOS journaal, 'Digitale doorbraak in de gezondheidszorg'.
 - Dr.J. Dorresteijn (2018): 'U-Prevent: Jannick Dorresteijn in gesprek met Kysia Hekster' (Radio 1).
 - Prof. F.L.J. Visseren (2018): NPO Radio5, 'U-Prevent'; <https://www.nporadio5.nl/openhuis/gemist/audio/346359/frank-visseren-maakte-website-die-werking-medicijn-voorspelt>

Hypertension

- P.J. Blankestijn: wrote a policy report for "Zorginstituut Nederland (ZIN)" on renal denervation, contributed to various meetings on the Ministry of Health and of the combined health insurance companies. He is also an expert for Dekra Certification (notified body for CE certification).
- W. Spiering has developed the EmmaHBPM app for guideline-based telemonitoring of blood pressure (EmmaHBPM; <https://www.medicinemen.eu/nl/emmbloeddruk-2/>).
- Other examples of news items:
 - New treatment for high blood pressure? (NierNieuws; 2014) (<http://www.niernieuws.nl/?titel=nn-tv-eeen-nieuwe-behandeling-van-hoge-bloeddruk&artid=7177&cat=10&all=&maand=>).
 - High blood pressure in chronic kidney disease patients often insufficiently treated (Hartpatiënten Nederland; 2015) (<http://www.hartpatienten.nl/nieuws/hoge-bloeddruk-bij-patiënten-met-chronische-nierziekte-vaak-onvoldoende-behandeld>).
 - Dialysis easy to improve (AD; 2012) (<http://www.ad.nl/binnenland/dialyse-makkelijk-te-verbeteren-afade7ee/>).
- A.T. Lely: presentation on kidney disease and pregnancy, for contributors of the "Nierpatiënten Vereniging Nederland (NVN)".

Lectures by staff members to general audience of patient organisations:

- 2016: World Diabetes Day Meeting UMC Utrecht 'What do trials tell you, and what don't'.
- 2017: Public Lecture UMC Utrecht on Diabetes.
- 2015: Public Lecture UMC Utrecht on Hypertension.

Atherosclerosis

Selected examples of products for societal target groups:

- G. Pasterkamp has initiated the valorisation track for associate professors. In 2016 he presented this initiative to members of the 2^e kamer. This resulted in a citation in the Science vision document of the Ministry of OCV as best practice: Initiator for installation of valorisation Ass. Profs in UMC Utrecht.
- G. Pasterkamp (2016): First author on paper about the sense of citations and "bean counting" in science. (Pasterkamp G, Hoefler I, Prakken B. Lost in the citation valley. *Nat Biotechnol.* 2016;34:1016-1018).

Selected examples of general media coverage:

- **Television:**
 - J. van Herwaarden (2019): NOS-Journaal, Public announcement of first clinical use of new Fiber Optic RealShape Technology (FORS).
 - J. van Herwaarden (2019): RTV Utrecht, "U-Vandaag": Public announcement of first clinical use of new Fiber Optic RealShape Technology (FORS).
- **Radio:**
 - J. van Herwaarden (2019): NOS Radio1-journaal, Public announcement of first clinical use of new Fiber Optic RealShape Technology.
 - J. van Herwaarden (2019): BNR Nieuwsradio, Public announcement of first clinical use of new Fiber Optic RealShape Technology.
- **Written media:**
 - G. Pasterkamp (2014): Front page Telegraaf newspaper with observation that plaque characteristics have changed over the last decade in the presence of atherosclerotic disease.
 - www.AD.nl, www.nu.nl, www.hartpatienten.nl (2019): FORS technology.



4.3 Use of research products by peers

Diabetes

Selected examples of publications frequently used by peers:

- Kranenburg G, Van der Graaf Y, Van der Leeuw J, et al. The relation between HbA1c and cardiovascular events in patients with type 2 diabetes with and without vascular disease. *Diabetes Care* 2015;38(10):1930-1936.
- Van der Leeuw J, Visseren FL, Woodward M, et al. Estimation of individual beneficial and adverse effects of intensive glucose control for patients with type 2 diabetes. *Diabetologia* 2016;59(12):2603-2612.

Hypertension

Selected examples of publications frequently used by peers:

- De Beus E, Bots ML, Van Zullen AD, et al. Prevalence of apparent therapy-resistant hypertension and its effect on outcome in patients with chronic kidney disease. *Hypertension* 2015;66(5):998-1005.
- De Jager RL, Sanders ME, Bots ML, et al. Renal denervation in hypertensive patients not on blood pressure lowering drugs. *Clin Res Cardiol* 2016;105(9):755-762.
- Tangri N, Grams ME, Levey AS, et al. Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. *JAMA*. 2016;315(2):164-174.
- Van der Leeuw J, Visseren FL, Woodward M, et al. Predicting the effects of blood pressure-lowering treatment on major cardiovascular events for individual patients with type 2 diabetes mellitus: results from Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation. *Hypertension* 2015;65(1):115-121.

Several of the datasets of the UMC Utrecht groups using individuals with diabetes, and /or elevated blood pressure, have been used in consortia over the world. Datasets include SMART, Utrecht Health Project, EPIC-NL, UMPIRE-UMC Utrecht part (PMID:28436727) , USE-IMT (PMID:28323823).

Atherosclerosis

- Many international researchers ask for collaborations with our group because of the valuable data resources in the Athero-Express biobank. These data are used for validation of experimental research from (for example) Cambridge, Bristol, Virginia, Oxford, Kings College, Paris and many other universities.
- For the same reason we are often asked to participate in and coordinate international consortia such as LeDucq (coordinator G. Pasterkamp, granted 2018), Horizon 2020 (Taxonimisis 2017 and 2 projects recently submitted) and ERA (coordinator G. Pasterkamp)
- As indicator: In the last 5 years papers with authorships of G. Pasterkamp were cited 2930 times. Papers with D. de Kleijn (H-index 71) were cited 21887 times in the last 5 years.

4.4 Use of research products by societal groups

Diabetes/hypertension

Results obtained with our SMART cohort, published during the reporting period, were used to develop and validate a prediction model for recurrent vascular events: the SMART Risk score. This score is now part of the Vascular Risk app, that is freely available for download to the public (both Android and Apple store). The app makes it possible to calculate the risk for (new) cardiovascular morbidity and mortality in all high risk patients, including patients with diabetes.

Other selected examples:

- U-prevent (<https://www.u-prevent.com>) in the guidelines and app.
- Renal denervation in guidelines.
- Use of datasets for the annual report of “Facts and figures on cardiovascular disease in the Netherlands” for the Netherlands Heart Foundation.

Atherosclerosis

We get requests from large pharmaceutical companies to share outcomes on associations of gene and protein expression with plaque characteristics. These associations provide information on beneficial and potential adverse effects of potential drug targets. (Patient informed consent includes permission to collaborate with companies (anonymized data)).

Prediction and prevention

The European Society of Cardiology requested input from U-Prevent in an ESC cardiovascular risk prediction app.



4.5 Marks of recognition from peers

Selected examples for **Diabetes/Hypertension:**

- P.J. Blankestijn has been and is a member, also including chairmanship, of various boards and committees including the Council (highest body) within the European Renal Association - European Dialysis Transplant Association (ERA-EDTA), the main European Nephrology Society. He has delivered in the period 2013- 2018 multiple invited lectures on hypertension and related subjects during major international and also national and regional (inter)national meetings in the cardiovascular and kidney field all over the globe. Examples of major meetings include the annual meetings of European Society of Hypertension, American Society of Hypertension, European Society of Cardiology, American Society of Nephrology and ERA-EDTA, Chinese Society of Nephrology, Japanese Society of Nephrology, etc.
P.J. Blankestijn authored invited Editorial Comments in multiple journals on various hypertension-related subjects, including the Lancet and more focused subject journals.
- Both P.J. Blankestijn and W. Spiering are registered as European Society of Clinical Hypertension specialists. The UMC Utrecht is recognized as a European Society of Hypertension Center of Excellence. P.J. Blankestijn is a fellow of both the ERA-EDTA and of the American Society of Nephrology. In both cases, the fellow award is given as a sign of recognition by the society for the outstanding contributions to the nephrology field. He was and is member of Editorial Boards of J Hypertens and Nephrol Dial Transplant and reviewer for most journals in the cardiovascular field and some general medical journals including the New Eng J Med, the Lancet, and other.
- A.T. Lely has been invited to international and national conferences on talks of hypertension (and kidney) disease in pregnancy.
She will be in the lead of a multi-disciplinary guideline on the topic the coming years.
- A. Hoes was member of the cardiovascular guideline committee for Europe (*Piepoli MF, Hoes AW, Agewall S, et al. Eur Heart J. 2016;37(29):2315-2381*).
- A. Hoes and F. Visseren were member of the CVRM guideline development committee in the Netherlands.
- W. Spiering was Task Force member of the 2018 ESC/ESH Guidelines on Arterial Hypertension.

Selected examples for **Atherosclerosis:**

G. Pasterkamp was invited in advisory boards in meetings with private companies; both G. Pasterlamp and D. de Kleijn are frequently invited for lectures in Universities, companies and at annual international conferences.

4.6 Marks of recognition from societal groups

Selected examples for **Diabetes/Hypertension:**

- P.J. Blankestijn advised the minister of Health and the combined national health insurance companies on hypertension-related issues, and certified bodies on medical device related issues; also member of a committee ("Regiegroep Green Deal"), chaired by the director general of the Ministry of Health (VWS), on environmental impact of health care.
- H.W. de Valk is a member of the 'Ronde Tafel' (collaborative structure with various stakeholders including the 'Diabetes Vereniging Nederland', government, industry and Dutch Internist Society (NIV)) to shape and safeguard drug and device innovation in the Netherlands. He is also a member as representative of the national research collective BIDON Foundation and board member of the Dutch Diabetes Chamber, the policy making body regarding diabetes of the Dutch Internist Society (NIV). Other specific tasks (apart from general issues): scientific development and program contributor of the Diabetes chapter NWO Gender programme 2016.

Examples for **Atherosclerosis:**

- Funding was obtained for 3 projects that are related with grants from Health Holland with the aim to valorize scientific observations.

Table 5 – Open Science indicators High Risk - Diabetes, Hypertension and Atherosclerosis

5.1 Openness of the research agenda & stakeholder involvement

Stakeholders:

- Patient organisations ("Harteraad"; "Zorginstituut Nederland (ZIN)).
- (Inter)national funding organisations (Dutch Heart Foundation, Dutch Kidney Foundation, ZonMW, NWO, H2020, ERA, LeDucq).
- Healthcare payers (ZilverenKruis, Achmea).
- Researchers, primary care physicians and medical specialists as well as specialized nurses.
- Professional societies such as the Dutch Internist Society (NIV), ESC.
- (Pharmaceutical) companies: U-Protein, SkylineDx, AMGEN, MEDIS, Abbott, Lilly, U-PACT, ENCARE, ORTEC, Amgen.



5.2 Openness of data and protocols

Diabetes/Hypertension

- We have limited experience with publication of raw data. An example is: *Peters SA, Bots ML, Canaud B, et al. Nephrol Dial Transplant 2016;31(6):978-984*, although this is not hypertension-related research. These data can be analysed by outside parties.
- Microarray data from human or animal studies are always accessible. For example see: *Koeners MP, Wesseling S, Sanchez M, et al. Am J Hypertension 2016;29(1):123-131; Jie KE, Van der Putten K, Wesseling S, et al. PLoS One 2012;7(9):e41339*.
- If necessary, access is granted to the data used for primary analyses. We are currently cooperating in several large scale meta-analyses using individual patient data or adding our data to national consortia such as "Parelsnoer". We have experience with analysis of combined data sets of multiple centers, both initiated by other groups as by ourselves. Examples are: *Persu A, Jin Y, Baelen M, et al. Hypertension 2014;63(6):1319-1325; De Jager RL, Sanders MF, Bots ML, et al. Clin Res Cardiol 2016;105(9):755-762*.
- All trials are registered.
- Clinical studies have been published as rationale and design:
 - Sanders MF, Blankestijn PJ, Voskuil M, et al. Safety and long-term effects of renal denervation: rationale and design of the Dutch registry. *Neth J Med. 2016;74(1):5-15*.
 - Asselbergs FW, Visseren FJ, Bots ML, et al. The Utrecht Cardiovascular Cohort. *Eur J Prev Cardiol. 2017;24(8):840-847*.
 - Hooghiemstra AM, Bertens AS, Leeuwis AE, et al. Heart-Brain Connection Consortium. The missing link in the pathophysiology of vascular cognitive impairment: design of the heart-brain study. *Cerebrovasc Dis Extra. 2017;7(3):140-152*.
- We recently reproduced the common finding that HbA1c relates to increased cardiovascular morbidity and mortality but added that this finding seems dependent on the presence of cardiovascular disease (*Kranenburg G, Van der Graaf Y, Van der Leeuw J, et al. Diabetes Care 2015;38(10):1930-1936*), that is dependent on baseline risk for cardiovascular disease (*Bots SA, Van der Graaf Y, Nathoe HM, et al. Cardiovasc Diabetol 2016;15(1):101*) while there are some other important effect modifiers which make it difficult to delineate a population which may benefit most from stringent glycemetic control (*Van Munster SN, Van der Graaf Y, De Valk HW, et al. Diabetes Obes Metab 2016;19(3):320-328*).
- All trials are published including those with unexpected neutral findings (e.g. PANACEA study; *Westerink J, Deanfield JE, Imholz BP, et al. Atherosclerosis 2013;227(1):118-124*).

Atherosclerosis

- Projects in our unit have a data management plan.
- Our unit stimulates and enables the publication of raw research data but since often GWAS data are involved we are restricted to the provision of summary data.
- Our unit shares laboratory protocols whenever a collaborative partner asks for that. We also published a protocol for automated image analyses software in PLoS-One that can be downloaded upon request.

5.3 Open Access publications (1)

The UMC Utrecht stimulates open dissemination of scholarly publications (e.g. doctoral theses) via the platform NARCIS (<https://www.narcis.nl/>).

Examples of open access publications of our unit:

- Jie KE, Van der Putten K, Wesseling S, et al. Short-term erythropoietin treatment does not substantially modulate monocyte transcriptomes of patients with combined heart and renal failure. *PLoS One 2012;7(9):e41339*.
- De Jager RL, Sanders MF, Bots ML, et al. Renal denervation in hypertensive patients not on blood pressure lowering drugs. *Clin Res Cardiol 2016;105(9):755-762*.
- Sanders MF, Blankestijn PJ, Voskuil M, et al. Safety and long-term effects of renal denervation: rationale and design of the Dutch registry. *Neth J Med. 2016;74(1):5-15*.
- Hooghiemstra AM, Bertens AS, Leeuwis AE, et al. Heart-Brain Connection Consortium. The missing link in the pathophysiology of vascular cognitive impairment: design of the heart-brain study. *Cerebrovasc Dis Extra. 2017;7(3):140-152*.
- Bots SA, Van der Graaf Y, Nathoe HM, et al. The influence of baseline risk on the relation between HbA1c and risk for new cardiovascular events and mortality in patients with type 2 diabetes and symptomatic cardiovascular disease. *Cardiovasc Diabetol 2016;15(1):101*.
- Nelissen BG, Van Herwaarden JA, Moll FL, et al. SlideToolkit: an assistive toolset for the histological quantification of whole slide images. *PLoS One. 2014;9(11):e110289*.

Atherosclerosis

G. Pasterkamp represents the UMC Utrecht as member of the platform Open Science at the Utrecht University. Sander van der Laan is a junior representative for the UMC Utrecht in the Utrecht University open science discussions. So, it is evident that we play an active role in these discussions.



Appendix G: Expertise area Genetics

Table 3 – Process indicators Genetics

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment	The majority of cardiovascular traits and diseases is highly heritable. Recent studies suggest that even the diseases that were formerly known as “Mendelian” or “monogenic” have a polygenic component that potentially explains the reduced penetrance and phenotypic heterogeneity between and within families. Our cardiogenetics team has a strong basis in both the monogenic and complex disease fields. Through national and international collaborations, we are able to successfully study the genetic mechanisms causing a range of life-threatening cardiovascular disorders in large numbers of individuals. Identification of novel loci within “druggable genome” using Mendelian Randomisation approaches can lead to novel treatment options that may target the underlying mechanisms of the disease. Within our group expertise is available for functional follow-up of found targets (cell, small and large animal models). Moreover, we focus on identifying effect modifiers (both (epi-) genetic and non-genetic) to explain phenotypic variability and develop predictive analytics to inform patients and their family members regarding diagnosis and prognosis.
3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made	One of the main topics of the research agenda of the Dutch Heart Foundation is “early detection”. Our major research projects (Bio4Care; CVON eDETECT, CVON DOSIS, Leducq Foundation CurePLaN, DETECTIN-HF (ERA-CVD)) specifically address this topic, which is also a major theme within Circulatory Health. CVON DOSIS is aimed at unraveling the pathophysiology of genetic cardiomyopathies, CVON eDETECT focuses on early detection of disease in mutation carriers and ERA CVD DETECTIN-HF aims to develop a personalized risk model for heart failure and sudden cardiac death in genetic DCM patients, taking into account biomarkers and clinical risk factors. Our institute invested heavily the last couple of years in attracting experts in the field of cardiogenetics to become a leading center both nationally and internationally (prof. dr. J. Bakkers, prof. dr. E. van Rooij, prof. dr. P. van Tintelen, prof. dr. F. Asselbergs), as clearly reflected by obtained funding and research and societal outputs.
3.3. Stakeholders are involved in formulating the main research questions	Our unit is in close contact with several patient organisations including (but not limited to) the PLN Foundation, “Harteraad”, and HEARTZ. In collaboration with those patient groups we organized several public events (PLN, ACM and HCM patient days; yearly crowdfunding initiatives) and involved patients actively in grant proposal writing and patient information outlets (https://www.erfelijkehartziekten.nl for example). In the IMI BigData@Heart consortium, we work closely with industry partners Bayer, Vifor and Servier to enhance implementation of potential drug targets that we identify through our genetic analyses.
3.4. The research questions are feasible and are pursued using optimal and efficient design	In our unit we have structural collaborations with bioinformaticians, data scientists, statisticians, epidemiologists and methodologists, but also basic scientists for functional experiments of found targets. All types of experiments including iPSC, 4C, single-cell RNA seq, small (zebrafish, mice) and large (pig) animal models are available. Moreover, our unit is part of multiple global genetic consortia that host a wide range of expertise's if not available within our own institute.
3.5. What is ‘the next step’ if the project delivers positive results	a. We continuously identify novel targets for treatment or biomarker development. The next step is to find partners to develop small molecules to test those targets. b. To implement positive results within routine care to impact patients daily care. Specifically, to evaluate impact of incorporating genetics for diagnoses and predictive analytics (including pharmacogenetics) within our electronic health record to inform patients regarding risk of developing disease or progression of disease that can guide intervention.



Table 4 – Output indicators Genetics

4.1 Research products for peers	<p>a. The mission of our research unit is to improve the survival and quality of life of patients with heart failure by prevention, risk stratification, early diagnosis, Selected peer-reviewed publications related to the genetics of cardiovascular disease internationally:</p> <ul style="list-style-type: none">• Van Setten J, Brody JA, Jamshidi Y, et al. PR interval genome-wide association meta-analysis identifies 50 loci associated with atrial and atrioventricular electrical activity. <i>Nat Commun.</i> 2018;9(1):2904.• Gladka MM, Molenaar B, de Ruiter H, et al. Single-cell sequencing of the healthy and diseased heart reveals cytoskeleton-associated protein 4 as a new modulator of fibroblasts activation. <i>Circulation.</i> 2018;138(2):166-180.• Laarman MD, Vermunt MW, Kleinloog R, et al. Intracranial aneurysm-associated single-nucleotide polymorphisms alter regulatory DNA in the human circle of willis. <i>Stroke.</i> 2018;49(2):447-453.• Cadrin-Tourigny J, Bosman LP, Nozza A et al. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. <i>Eur Heart J.</i> 2019;40(23):1850-1858.• Van der Laan SW, Siemelink MA, Haitjema S, et al. Genetic susceptibility loci for cardiovascular disease and their impact on atherosclerotic plaques. <i>Circ Genom Precis Med.</i> 2018;11(9):e002115.• Van der Laan SW, Fall T, Soumaré A et al. Cystatin C and cardiovascular disease: a Mendelian randomisation study. <i>J Am Coll Cardiol.</i> 2016;68(9):934-45. <p>Researchers from our unit set up a patient cohort enabling prospective research on HCM, DCM, ACM and/or PLN. and development of novel treatments aimed at providing optimal personalized, evidence-based patient management.</p>
4.2 Research products for societal target groups	<p>Selected examples of unit researcher involvement in practice & policy guideline generation:</p> <ul style="list-style-type: none">• Elliott PM, Anastasakis A, Asimaki A, et al. Definition and treatment of arrhythmogenic cardiomyopathy: an updated expert panel report. <i>Eur J Heart Fail.</i> 2019. doi: 10.1002/ejhf.1534.• Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. <i>Heart Rhythm.</i> 2019. doi: 10.1016/j.hrthm.2019.05.007.• Authors/Task Force members, 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). <i>Eur Heart J.</i> 2014;35(39):2733-2779.• Perrino C, Barabási AL, Condorelli G et al. Epigenomic and transcriptomic approaches in the post-genomic era: path to novel targets for diagnosis and therapy of the ischaemic heart? Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart. <i>Cardiovasc Res.</i> 2017;113(7):725-736. <p>Selected examples of unit researcher contributions for patient groups:</p> <ul style="list-style-type: none">• Organizing patient information days: "Harteraad", PLN, HCM.• Lectures for patient organisations world-wide (ACM, HCM, PLN, aortic disease, congenital heart disease). <p>As part of CVON eDETECT we created the website https://www.erfelijkehartziekten.nl to inform both clinicians and patients on inherited cardiac diseases. In addition, we have a website to inform researchers, medical specialists, patients, and the general public about our research on solid organ transplantation. This website is available in many languages including Dutch (igenetrain.nl) and English (igenetrain.org).</p> <p>In 2016, we did a crowdfunding campaign (https://steunmijnonderzoek.hartstichting.nl/project/van-setten/) together with the Dutch Heart Foundation to collect funding for research on heart transplantation. € 36,000 was successfully collected, and another € 36,000 was matched by the Dutch Heart Foundation.</p>
4.3 Use of research products by peers	<p>Selected examples of the use of our research products by peers:</p> <ul style="list-style-type: none">• ACM risk-calculator tool for calculating risk for sudden death in patients with ACM.• As listed in section 5.2 we made our protocols including electronic case report forms publicly available for clinicians and scientists to use for their own registries and to facilitate collaborative future projects. <p>Selected examples of publications frequently used by peers:</p> <ul style="list-style-type: none">• Van Setten J, Isgum I, Smolonska J, et al. Genome-wide association study of coronary and aortic calcification implicates risk loci for coronary artery disease and myocardial infarction. <i>Atherosclerosis.</i> 2013;228(2):400-405. (76 citations).• Van der Harst P*, van Setten J*, Verweij N, et al. 52 Genetic Loci Influencing Myocardial Mass. <i>J Am Coll Cardiol.</i> 2016;68(13):1435-1448. (41 citations).
4.4 Use of research products by societal groups	<p>Selected examples of the use of our research products by societal groups:</p> <ul style="list-style-type: none">• ACM risk-calculator tool for calculating risk for sudden death in patients with ACM.• Organisation of several public events (PLN, ACM and HCM patient days; yearly crowdfunding initiatives).• Lectures are given regularly to patient groups to inform them about ongoing research initiatives in the field of genetics and in particular in the field of genetic cardiomyopathies.



4.5 Marks of recognition from peers	<p>In 2018, the NFU recognized UMC Utrecht as expertise center for inherited cardiovascular disease (https://www.UMC Utrechtrecht.nl/nl/Ziekenhuis/Afdelingen/Hart-en-vaatcentrum/Ziektebeelden,-onderzoeken-en-behandelingen/Centrum-voor-erfelijke-hart-en-vaatziekten). In 2019, we will apply to the European Reference Network http://guardheart.ern-net.eu/.</p> <p>Invited lectures have been listed in domain specific research sections.</p> <p>We participate and founded several large global genetic consortia. Few example those are led by UMC Utrecht researchers:</p> <ul style="list-style-type: none"> • Patel R, Tragante V, Schmidt AF, et al. Subsequent event risk in individuals with established coronary heart disease: design and rationale of the GENIUS-CHD consortium. <i>Circ Genom Precis Med</i>. 2019. doi:10.1161/CIRCGEN.119.002470. • www.igenetrain.org: International Genetics & Translational Research in Transplantation Network (iGeneTRaiN). Design and Implementation of the International Genetics and Translational Research in Transplantation Network. <i>Transplantation</i>. 2015;99(11):2401-2412. <p>Selected awards:</p> <ul style="list-style-type: none"> • J. van Setten (2016): Charles J. Epstein Trainee Award – Semifinalist 66th Annual Meeting of the American Society of Human Genetics, Vancouver, Canada. • J. van Setten (2014): Lodewijk Sandkuijl Award (€500): European Human Genetics Conference, Milan, Italy. • Personal Dekker fellowships (Dutch Heart Foundation), all related to genetic cardiomyopathies: J. Groeneweg (2013), F. Asselbergs (2014), A. te Riele (2014), A. Baas (2016). • E. van Rooij. Ammodo Science Awards KNAW.
4.6 Marks of recognition from societal groups	<p>The PLN Foundation, a patient organisation that represents patients that carry the PLN mutation at high risk for genetic cardiomyopathies, has recognized the UMC Utrecht as expert center and together with the PLN foundation member researchers at UMC Utrecht obtained funding from both the PLN foundation itself and external funding agencies to create a risk calculator to predict progression, find novel targets for treatment with the overall aim to cure this severe genetic disease.</p>

Table 5 – Open Science indicators Genetics

5.1 Openness of the research agenda & stakeholder involvement	<p>Stakeholders:</p> <ul style="list-style-type: none"> • Patient organisations are involved in all grant proposals including PLN foundation, “Harteraad” section Inherited cardiac diseases, transplant patient organisation “Hartentwee”, and HEARTZ. • (Inter)national funding organisations (Dutch Heart Foundation, Dutch Kidney Foundation, ZonMW, NWO, H2020, ERA, LeDucq). • (Inter)national collaborating researchers, primary care physicians and medical specialists.
5.2 Openness of data and protocols	<p>We founded the UNRAVEL research data platform at UMC Utrecht that is embedded in routine practice using data collected in routine care to facilitate research in genetic cardiomyopathies. All protocols are shared on http://www.unravelrdp.nl and publicly available. Same applies for Arrhythmogenic cardiomyopathy registry: http://www.acmregistry.nl/ and cardio-oncology registry http://www.oncor.nl, both founded by our cardiogenetics team.</p> <p>Our cardiogenetics team is involved in several consortia that embraces the vision of open science:</p> <ul style="list-style-type: none"> • CVON eDETECT (P. van Tintelen/F. Asselbergs): https://www.durrercenter.nl/e-detect/# • ERA-CVD DETECTIN-HF (F. Asselbergs): https://www.durrercenter.nl/detectin-hf-era-cvd/ • LeDucq CURE-PLaN (P. Doevendans): https://www.cure-plan.online <p>Genetic summary results are shared with the community when possible, for instance through Zenodo (e.g. https://zenodo.org/record/2591375#.XOWAZi17H1I and https://zenodo.org/record/1422824#.XOWAoC17H1I)</p> <p>Pipelines and software are made available for the scientific community on Github. Scripts and datasets are orderly kept on the HPC to allow other researchers to work with the datasets and replicate results.</p>



5.3 Open Access publications (1)

The majority of our publications are open access according to policies of funding bodies.

Selected examples of open access publications (one was funded by the UU Open Access fund):

1. Van Setten J, Warmerdam EG, Groot OQ, et al. Non-HLA Genetic Factors and Their Influence on Heart Transplant Outcomes: A Systematic Review. *Transplant Direct*. 2019 ;5(2):e422.
 2. Van Setten J, Verweij N, Mbarek H, Niemeijer MN, et al. Genome-wide association meta-analysis of 30,000 samples identifies seven novel loci for quantitative ECG traits. *Eur J Hum Genet*. 2019. doi: 10.1038/s41431-018-0295-z
 3. Van Setten J, Brody JA, Jamshidi Y, et al. PR interval genome-wide association meta-analysis identifies 50 loci associated with atrial and atrioventricular electrical activity. *Nat Commun*. 2018;9(1):2904.
 4. Groenhof TKJ, Asselbergs FW, Groenwold RHH, et al. The effect of computerized decision support systems on cardiovascular risk factors: a systematic review and meta-analysis. *BMC Med Inform Decis Mak*. 2019;19(1):108. doi: 10.1186/s12911-019-0824-x.
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Appendix H: Expertise area Imaging

Table 3 – Process indicators Imaging

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment	<p>a. The unit strives to deliver the best possible imaging services for patients with cardiovascular diseases. We try to achieve this by incorporating guideline-recommended current state-of-the-art methods as well as developing new imaging techniques and methods and bringing these to the clinic.</p> <p>b. The questions being pursued concern both common and uncommon cardiovascular diseases for which UMC Utrecht is a tertiary referral center. These include but are not limited to ischemic and non-ischemic hereditary and acquired cardiomyopathies, congenital heart disease, heart failure, aorta, complex peripheral arterial disease, brain aneurysms, hemorrhagic stroke, ischemic stroke, multisystem aspects of cardiovascular disease such as heart-brain and bone-cardiovascular interactions. In addition, we study specific groups with elevated cardiovascular risk such as women with reproductive disorders. Finally, we study cardiovascular risk in healthy athletes. In all of these areas there is a need for fast, reliable and comprehensive imaging. As such, there is a strong focus on development of new cardiac and vascular CT and MR imaging techniques and post-processing methods and bringing these to the clinic.</p>
3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made	<p>Imaging research closely follows the top-priorities and agenda of the Netherlands Heart Foundation. Senior imaging researchers from UCM Utrecht have been involved in stakeholder meetings to set this agenda. The Imaging Division of UMC Utrecht contributes expertise on development and introduction of new imaging techniques as well as application of innovative multi-organ imaging protocols and analysis methods. Also, Imaging research is closely embedded in the research priorities of the Circulatory Health strategic research program.</p>
3.3. Stakeholders are involved in formulating the main research questions	<p>Almost all research proposals and projects require input and support from patient organisations. Imaging researchers are in close contact with the cardiovascular patient organisation (“Harteraad”) as well as other relevant patient organisations such as the one allied to the Netherlands Kidney Foundation, the organisation for patients with Arrhythmogenic CardioMyopathy (ARVC/ACM) and PseudoXanthoma Elasticum (PXE). The Ministry of Public Health (VWS) supports ongoing research (MARC-2 study) involving the development and understanding of coronary artery disease in athletes.</p>
3.4. The research questions are feasible and are pursued using optimal and efficient design	<p>In the Imaging Division we have our own research committee and trial bureau including methodologists who can advise. In addition, we work closely with cardiovascular epidemiologists and statisticians from the Julius Center. All projects are reviewed prior to submission.</p>
3.5. What is ‘the next step’ if the project delivers positive results	<p>a. In many of our technical development projects we work closely together with referring clinicians as well as companies such as Philips Healthcare, Medis Medical Imaging Systems, Pie Medical and others to ensure that new technical developments reach routine healthcare.</p> <p>b. The Imaging Division is in close contact with Utrecht Holdings and has a dedicated contact person. Over the past years several inventions have been patented and a start-up company Quantib-U (https://www.quantib.com/) has been founded.</p> <p>c. Cardiovascular imaging research in the Imaging Division obtains funding from a variety of clinical and technical funding schemes (e.g. Netherlands Heart Foundation, Applied and Engineering Sciences, Netherlands Organisation for Scientific Research (NWO) as well as companies and charities). Most projects involve public-private partnerships.</p> <p>d. Cardiovascular Imaging researchers are closely involved in National and International professional and scientific societies and are on various policy making and funding agency panels, also outside of the imaging field.</p>



Table 4 – Output indicators Imaging

4.1 Research products for peers	<p>Selected examples of research products for peers:</p> <ul style="list-style-type: none">• Researchers of our unit patented and licensed a novel technique for assessing vessel obstruction based on machine learning (US patent 10,176,575; http://patents.com/us-10176575.html).• The Imaging Division set up a research image storage and management platform (Research Imaging Architecture; RIA).• Researchers of our unit are responsible for imaging datasets (e.g. the Dutch ACM registry; https://www.acmregistry.nl) and for investigating the value of (new) imaging techniques (e.g. in heart failure and cardiomyopathy, hemorrhagic and ischemic stroke, family screening in (un)ruptured cerebral aneurysms, and imaging in potentially high risk groups [women with reproductive disorders, patients with potential cardiotoxic oncology treatment and healthy athletes]). <p>Key publications:</p> <ul style="list-style-type: none">• Aengevaeren VL, Mosterd A, Braber TL, et al. Relationship between lifelong exercise volume and coronary atherosclerosis in athletes. <i>Circulation</i>. 2017;136(2):138-148.• Zoet GA, Benschop L, Boersma E, et al; CREW Consortium. Prevalence of subclinical coronary artery disease assessed by coronary computed tomography angiography in 45- to 55-year-old women with a history of preeclampsia. <i>Circulation</i>. 2018;137(8):877-879.• Bourfiss M, Prakken NHJ, Van der Heijden JF, et al. Diagnostic value of native T(1) mapping in arrhythmogenic right ventricular cardiomyopathy. <i>JACC Cardiovasc Imaging</i>. 2019; doi: 10.1016/j.jcmg.2019.01.023.• Bourfiss M, Vigneault DM, Aliyari Ghasebeh M, et al. Feature tracking CMR reveals abnormal strain in preclinical arrhythmogenic right ventricular dysplasia/ cardiomyopathy: a multisoftware feasibility and clinical implementation study. <i>J Cardiovasc Magn Reson</i>. 2017;19(1):66.• Hartevelde AA, Van der Kolk AG, Van der Worp HB, et al. Detecting intracranial vessel wall lesions with 7T-magnetic resonance imaging: patients with posterior circulation ischemia versus healthy controls. <i>Stroke</i>. 2017;48(9):2601-2604. <p>Researchers from our unit, in collaboration with other units, set up several imaging patient cohorts; e.g. SMART ORACLE, patients with different cardiomyopathies, patients undergoing cardiotoxic oncology treatment, patients with unruptured and ruptured cerebral aneurysms, patients with acute ischemic stroke, women with reproductive disorders, as well as a cohort of healthy athletes, among others. In addition, unit researchers contributed to intracranial vessel wall MRI method development and translation to patients care and products on Philips MRI scanners.</p>
4.2 Research products for societal target groups	<ul style="list-style-type: none">• T. Leiner co-wrote a policy report used by the government to decide on abdominal aortic aneurysm screening in The Netherlands (“Gezondheidsraad”).• T. Leiner has created an electronic textbook to educate physicians about cardiac anatomy (https://doradiology.com/product-clinical-anatomy.html).• B. Velthuis co-wrote a <i>Circulation</i> paper on increased risk of coronary plaques in life-long athletes (see 4.1). These results and collaboration with Radboud MC enabled permission from the Ministry of VWS to perform a follow-cardiac CT screening study (MARC-2) to further understand the development of coronary atherosclerosis in athletes.
4.3 Use of research products by peers	<ul style="list-style-type: none">• Several machine learning algorithms are used on external datasets via national and international collaborations.• Use of the UMC Utrecht ARVC/ACM imaging and clinical database is shared through long-term collaboration with the North American ARVC registry (John Hopkins Hospital, Baltimore).• Ongoing research in coronary artery disease in athletes is an important collaboration with Prof. Sharma’s group (St. George’s Hospital in London).• Intracranial vessel wall MRI has become standard part of clinical diagnostic MRI protocols on Philips MRI scanners worldwide.
4.4 Use of research products by societal groups	<ul style="list-style-type: none">• Several of the machine learning algorithms we developed were licensed by Pie Medical B.V.• The follow-up data provided from coronary CT screening in healthy athletes (MARC-2 study) will be reported back to the Ministry of VWS and used in future (national and international) advisory boards and guidelines.• Etidronate is now reimbursed for PXE patients and professional societies dealing with PXE patients have changed their guidelines for treatment based on research by our unit.
4.5 Marks of recognition from peers	<ul style="list-style-type: none">• T. Leiner was awarded a senior fellowship from the International Society for Magnetic Resonance in Medicine and was elected to the Presidency of the same Society for 2020-2021.• B. Velthuis is a board member of the European Society of Cardiovascular Radiology (ESCR).• P.de Jong has held a keynote lecture on calcific aortic disease at the European Association for Nuclear Medicine Congress in Duesseldorf.• J. Hendrikse: ERC Starting grant HEARTOFSTROKE about technical developments and translation of intracranial vessel wall MRI methods in patients with cerebrovascular disease or cardiovascular risk factors.



4.6 Marks of recognition from societal groups	<ul style="list-style-type: none">• T. Leiner is scientific co-founder of Quantib-U (https://www.quantib.com/), a machine learning start-up company that managed to obtain a substantial amount of external valorisation funding.• National best PhD thesis award in Medical Imaging (Frederik Philipsprijs), awarded in 2013, 2015 en 2016 to cardiovascular research PhD theses from the UMC Utrecht Imaging department (respectively Habets, Van der Kolk, Willeminck).
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Table 5 – Open Science indicators Imaging

5.1 Openness of the research agenda & stakeholder involvement	<p>Stakeholders:</p> <ul style="list-style-type: none">• Organisations for patients with cardiovascular disease (“Hartenraad”), kidney disease, ARVC/ ACM, PXE, cerebral aneurysms and cerebral ischemic stroke.• Companies, e.g. Quantib-U, Pie Medical Imaging BV, Philips Healthcare, Medis Medical Imaging Systems.• Funding agencies, e.g. Netherlands Heart Foundation, Applied and Engineering Sciences, Netherlands Organisation for Scientific Research (NWO).• Scientists: national and international collaborators.
5.2 Openness of data and protocols	<p>a. Projects in our unit have a data management plan. These are stored at the Trial Bureau of the Imaging Division.</p> <p>b. The Imaging Division stimulates and enables the storage and release of raw research data through its dedicated Research Imaging Architecture (RIA) platform. External access is under construction and data are made available upon reasonable request to other researchers.</p> <p>c. Our unit stimulates the registration of protocols for clinical trials. Examples:</p> <ul style="list-style-type: none">• https://www.trialregister.nl/trial/4956• https://www.trialregister.nl/trial/5147• https://clinicaltrials.gov/ct2/show/NCT03139006• https://www.trialregister.nl/trial/5406 <p>d. All clinical trials that are instigated from our unit are registered and the results are always published (https://ichgcp.net/clinical-trials-registry/NCT00880113).</p>
5.3 Open Access publications (1)	<p>The Imaging Division aims to publish open access as much as it can. We are in close contact with Utrecht University Library which provides support and has arranged open access publishing on behalf of researchers at UU/UMC Utrecht for many journals.</p> <p>Examples of open access publications of our unit:</p> <ul style="list-style-type: none">• Van Hamersvelt RW, Isgum I, De Jong PA, et al. Application of speCtrAL computed tomogrAphy to impRove specificity of cardiac compuTEd tomographY (CLARITY study): rationale and design. <i>BMJ Open</i>. 2019;9(3):e025793.• Sprenk J, De Vos BD, Lessman N, et al. Coronary calcium scoring with partial volume correction in anthropomorphic thorax phantom and screening chest CT images. <i>PLoS One</i>. 2018;13(12):e0209318.• Kofink D, Muller SA, Patel RS, et al; on behalf of the SMART Study Group. Routinely measured hematological parameters and prediction of recurrent vascular events in patients with clinically manifest vascular disease. <i>PLoS One</i>. 2018;13(9):e0202682.



Appendix I: Expertise area Cardiovascular Clinical Epidemiology

Table 3 – Process indicators Cardiovascular Clinical Epidemiology

<p>3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment</p>	<p>a. Cardiovascular diseases have a major impact on our society. The number of patients suffering from e.g. a heart attack, stroke or heart failure is still increasing. It is the <i>mission</i> of our unit to perform internationally recognized and societally well-embedded research to improve the early recognition, prevention and treatment of various cardiovascular conditions. Among these conditions are heart failure, stroke, heart attack, aneurysms, peripheral artery disease and venous thrombotic conditions. To accomplish our objectives fundamental, applied and translational research are incorporated which could result in promising technology (e.g. X-ray reducing surgery techniques), new treatments and improved personalized care (e.g. prediction rules).</p> <p>b. Cardiovascular Clinical Epidemiology is structured in three sub-themes: (1) Brain; (2) Heart; and (3) Vasculature and Precursor Conditions. The questions being pursued are specific for each sub-theme. The theme <i>Brain</i> focuses on research into determinants and functional consequences of vascular and neurodegenerative changes in the brain that occur with aging and that have a major impact on patients, healthcare and society. The emphasis is on normal and accelerated brain aging and on both macro- and microvascular changes. The sub-theme <i>Heart</i> focuses on subclinical and clinical heart conditions that have important consequences for patients, health care and society. Clinical topics include heart failure, atrial fibrillation, ischemic heart disease and acute coronary syndrome. Emphasis is on normal and accelerated heart aging and on both macro- and microvascular changes. The strategic research program focuses on improvement of early detection of new disease and progression of disease. Furthermore, focus is on the importance of co-morbidity in the development, recognition, prognosis and treatment of heart diseases and on innovative ways to improve prognosis, such as eHealth and Big Data analysis techniques. In addition, we aim to clarify underlying mechanisms, including genetic susceptibility. The theme <i>Vasculature and Precursor Conditions</i> focuses on increasing knowledge on (potentially) modifiable causes, consequences and treatment options of accelerated development of precursor conditions and abnormalities in vascular structure and function. Among precursor conditions are overweight, hypertension, dyslipidemia, renal dysfunction, and (type 2) diabetes. Among vascular abnormalities are plaques and thickened wall thickness of the carotid artery, thickened muscles in the heart, and the presence of calcium in the arteries in the body. Among the causes that we address are genetic factors, environmental exposures, biomarkers, nutritional factors, factors in and around pregnancy and reproduction, lifestyle factors and early in life exposures.</p>
<p>3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made</p>	<p>Our research roadmap is based on:</p> <ul style="list-style-type: none"> • Strategic focus within the UMC Utrecht strategic theme Circulatory health. • Strategic agenda of the Netherlands Heart Foundation based on patient plus researchers priorities; gender, early detection of cardiovascular disease, better treatment and management of cardiovascular diseases, healthy ageing. • Mission statement of the Dutch Cardiovascular Alliance; early recognition of cardiovascular disease. • Netherlands Organisation for Scientific Research (NWO); Vascular Medicine second phase. <p>thereby considering the National Research Agenda of the Netherlands.</p>
<p>3.3. Stakeholders are involved in formulating the main research questions</p>	<p>In some of our projects patient representatives from the diseases under study are invited to discuss our research lines. For several grants we involved clinicians (UMC Utrecht), epidemiologists (UMC Utrecht), basic scientists (UMC Utrecht), and patient organisations (e.g. "Harteraad", Brain Aneurysm Patient Platform, hartsichting.nl). Within the Utrecht Cardiovascular Cohort (UCC), the strategic research program closely collaborates with all UMC Utrecht divisions that are involved in care of patient at risk or with vascular disease. The UCC steering committee meets monthly to discuss progress. The individual members of the Circulatory Health research themes we collaborate with discuss individually with other stakeholders; e.g. for grant proposals the individual members of the Aneurysm theme discuss with stakeholders like the Dutch Heart Foundation, NWO, ZonMw and (within Europe) H2020, ERA-CVD.</p>
<p>3.4. The research questions are feasible and are pursued using optimal and efficient design</p>	<p>Methods are applied from the total range of statistical and epidemiological study designs, ranging from multi-center randomized controlled studies into the effects of preventive and therapeutic interventions to large and small cohorts, case control and cross-sectional studies into determinants and prognosis of vascular conditions. Cardiovascular Clinical Epidemiology is an integrated part of the Julius Center and in our research we closely and intensely collaborate with other disciplines of the Julius Center (e.g., methodology group). PhD candidates have or are obliged to follow the Master of Epidemiology at UMC Utrecht. We also collaborate with researchers and clinicians in the UMC Utrecht within Circulatory Health among which the departments of Imaging, Cardiology, Experimental Cardiology, Vascular Surgery, Neurology, Women & Baby, Nephrology & Hypertension, Geriatrics, Endocrinology (diabetes) and Vascular Medicine. Our researchers have access to part of the pan-European EPIC studie (EPIC-NL, EPIC-InterACT, EPIC-CVD), the Utrecht Health Project ("Leidsche Rijn Gezondheidsproject"; LRGP) with a general population sample of > 12,000 inhabitants, UCC-SMART, UCC-CVRM, UCC-UHP (a starting initiative with phenotypic enrichment of 1000 UHP participants) and several Global Health studies. Furthermore, researchers have access to the Julius General Practitioners Network (a general practitioner-based routine clinical care registry among around 325.000 patients).</p>



3.5. What is 'the next step' if the project delivers positive results

- a. In our projects we have collaborations with multiple stakeholders among which clinicians, researchers, patient organisations and interest groups and knowledge centers. Large pharmaceutical companies are also involved in projects related to external validity of randomized trials in e.g. the field of heart failure: Servier, Bayer, Vifor, Novartis, or in the area of atherosclerosis imaging (METEOR-China).
- b. Within U-Trial (UMC Utrecht) a dedicated clinical trial developer will be assigned to Circulatory Health.
- c. We rely on a diversity of funders (e.g. Dutch Heart Foundation, NWO, ZonMw, H2020, ERA-CVD), in cases we combine public-private funds to strengthen our valorisation efforts. In our unit researchers participate in various national (e.g. I. Vaartjes ; Dutch Health Council commission screening AAA) and international (guideline) committees. Several of our researchers (e.g. Y. van der Schouw, A. Hoes) contribute to position statements:
- Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-2381.
 - Stute P, Ceausu I, Depypere H, et al. A model of care for healthy menopause and ageing: EMAS position statement. *Maturitas*. 2016;92:1-6.
 - Dimopoulou C, Ceausu I, Depypere H, et al. EMAS position statement: Testosterone replacement therapy in the aging male. *Maturitas*. 2016;84:94-99.
 - Neves-E-Castro M, Birkhauser M, Samsioe G, et al. EMAS position statement: The ten point guide to the integral management of menopausal health. *Maturitas*. 2015;81:88-92.
 - Seferović PM, Petrie MC, Fillipatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20(5):853-872.
- d. Our work is presented in professional literature and at professional society conferences. We emphasize the dissemination of results to patients, care givers, patient organisations, funders and healthcare professionals.

Table 4 – Output indicators Cardiovascular Clinical Epidemiology

4.1 Research products for peers

Key publications:

- Seferović PM, Petrie MC, Fillipatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20(5):853-872.
- Blankestijn PJ, Bots ML. Renal denervation in uncontrolled hypertension: the story continues to unfold. *Lancet*. 2018;391(10137):2300-2302.
- De Jager RL, Van Maarseveen EM, Bots ML, Blankestijn PJ; SYMPATHY investigators. Medication adherence in patients with apparent resistant hypertension: findings from the SYMPATHY trial. *Br J Clin Pharmacol*. 2018;84(1):18-24.
- De Jager RL, De Beus E, Beeftink MM, et al; SYMPATHY Investigators. Impact of medication adherence on the effect of renal denervation: The SYMPATHY Trial. *Hypertension*. 2017;69(4):678-684.
- Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-2381.
- Greving JP, Wermer MJH, Brown RD, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol*. 2014; 13(1): 59-66.
- Rutten FH, Groenwold RH. β -Blocker use for patients with or at risk for coronary artery disease. *JAMA*. 2013;309(5):438-439.

Researchers from our expertise area set up several cohorts (2013-2018):

- Utrecht Cardiovascular Cohort (ongoing, n > 5000).
- Dutch Heart Foundation facts and figures database of all Dutch inhabitants (I. Vaartjes).

The investigators of our expertise area intensively collaborate with researchers of the Circulatory Health research themes and consequently contribute to their research products; for specifics see the information provided by the different themes.



4.2 Research products for societal target groups	<p>Selected examples of lectures given by unit researchers to general audiences;</p> <ul style="list-style-type: none">• S.A.E. Peters (2018): UMC Utrecht Public Lecture, “Man-vrouw verschillen in risicofactoren voor hart- en vaatziekten”.• M.L. Bots: participant of Meet the Professor (outreach to primary schools).• Y.T. van der Schouw (2016): UMC Utrecht Public Lecture, “Hart- en vaatziekten: voor man en vrouw verschillend”. <p>Other research products for societal groups:</p> <ul style="list-style-type: none">• Involvement in generation of guidelines: Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). <i>Eur Heart J.</i> 2016;37(29):2315-2381.• Researchers from our unit (I. Vaartjes, M. Bots) contribute to the Annual report of ‘Facts and figures on cardiovascular disease in the Netherlands’ for the Netherlands Heart Foundation.
4.3 Use of research products by peers	<p>Selected examples of publications with the total number of citations (Google Scholar, June 28 2019):</p> <ul style="list-style-type: none">• Greving JP et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms. <i>Lancet Neurol</i> 2014. PMID:24290159. (471 citations).• De Beus E, Bots ML, Van Zullen AD, et al. Prevalence of apparent therapy-resistant hypertension and its effect on outcome in patients with chronic kidney disease. <i>Hypertension</i> 2015;66(5):998-1005. (25 citations)• De Jager RL, Beus E, Beeftink MMA, et al. Impact of medication adherence on the effect of renal denervation. The Sympathy trial. <i>Hypertension.</i> 2016;69(4):678-684 (43 citations). <p>Publication for which we made the dataset publically available through the journal:</p> <ul style="list-style-type: none">• Peters SA, Bots ML, Canaud B, et al. HDF Pooling Project Investigators. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. <i>Nephrol Dial Transplant.</i> 2016;31(6):978-984. <p>Our datasets have been made available to others for analyses and generation of knowledge. For example, EPIC-NL in several GWAS consortia; UCC-SMART in PROG-IMT studies; UHP in several GWAS studies; CONTRAST in the IPD meta analysis on HDF pooling project. Moreover, researchers from other groups have worked with data from cohorts of the Julius Center.</p>
4.4 Use of research products by societal groups	<ul style="list-style-type: none">• Use of datasets for the annual report of ‘Facts and figures on cardiovascular disease in the Netherlands’ for the Netherlands Heart Foundation.• The interactive website https://www.u-prevent.com with various lifetime cardiovascular risk calculators for patients with diabetes, patients with clinical manifest vascular disease, apparently healthy people and elderly subjects/patients.
4.5 Marks of recognition from peers	<p>Selected examples of recognition marks from peers:</p> <ul style="list-style-type: none">• J. Greving: Senior Postdoc Dekker fellowship (Dutch Heart Foundation; 2013); Rudolf Magnus Young Talent fellowship (2013); CVON (Dutch Heart Foundation) Young Talent fellowship (2017).• I. Vaartjes (2018): grant Dutch Heart Foundation for the project ‘Earlier Recognition’ (2018); Dutch Health Council, commission screening abdominal aortic aneurysm (AAA) (2019).• A. Algra (2016): invited lecture European Stroke Organisation Conference: Teaching course on management of asymptomatic intracranial aneurysms.• M. Bots (2014, 2017): invited lectures 1) KL University Hospital, Kuala Lumpur, <i>Malaysia: The cardiovascular polypill: a simple strategy helping to solve a complex problem?</i>; 2) EUROPREVENT, Amsterdam: <i>What have we learned from CIMT measurements.</i>• S. Peters (2017): invited lectures 1) Innovations in Research and Health Care Symposium, Peking University Health Science Center and UNSW Sydney, Beijing, China: Sex differences in chronic disease; 2) Gender Summit, Berlin, Germany: <i>Sex differences in risk factors for cardiovascular disease: large-scale meta-analyses summarising all available evidence.</i>• Y.T. van der Schouw (2017): invited lecture EMAS congress Amsterdam on <i>Ovarian aging and cardiometabolic disease.</i>



Table 5 – Open Science indicators Cardiovascular Clinical Epidemiology

5.1 Openness of the research agenda & stakeholder involvement	<p>Stakeholders involved:</p> <ul style="list-style-type: none">• collaborating, both nationally as internationally, clinicians, epidemiologists, scientists, etc.• Patient organisations, among which “Harteraad”, Brain Aneurysm Patient Platform, hartsichting.nl.• Funding organisations among which Dutch Heart Foundation, NWO, ZonMw and (within Europe) H2020, ERA-CVD.• The investigators of our expertise area intensively collaborate with researchers of the Circulatory Health research themes and consequently contribute to their research products; for specifics regarding pharmaceutical or device companies see the information provided by the different themes.
5.2 Openness of data and protocols	<ul style="list-style-type: none">• All material is stored on central drives of the UMC Utrecht following a standard format and data are shared generally through contacting the steering committee of the specific study through websites, e.g. https://www.epicnl.eu.• We have limited experience with publication of raw data. An example is: <i>Peters SA, Bots ML, Canaud B, et al. Nephrol Dial Transplant 2016;31(6):978-984</i>. These data can be analysed by outside parties.• A clinical study was published as rationale and design: Asselbergs FW, Visseren FJ, Bots ML, et al. The Utrecht Cardiovascular Cohort. <i>Eur J Prev Cardiol. 2017;24(8):840-847</i>. <p>All trials are registered in national (Netherlands Trial Registry) or international registries (e.g. https://clinicaltrials.gov). Rationale and design are generally published (selected examples are given below):</p> <ul style="list-style-type: none">• Vergouwen MD, Rinkel GJ, Algra A, et al. Prospective Randomized Open-label Trial to evaluate risk faCTOR management in patients with Unruptured intracranial aneurysms: Study protocol. <i>Int J Stroke. 2018;13(9):992-998</i>.• Vos A, Tempelman H, Devillé W, et al. HIV and risk of cardiovascular disease in sub-Saharan Africa: Rationale and design of the Ndlovu Cohort Study. <i>Eur J Prev Cardiol. 2017;24(10):1043-1050</i>.• Sanders MF, Blankestijn PJ, Voskuil M, et al. Safety and long-term effects of renal denervation: rationale and design of the Dutch registry. <i>Neth J Med. 2016;74(1):5-15</i>.• Valk MJ, Hoes AW, Mosterd A, et al. Rationale, design and baseline results of the Treatment Optimisation in Primary care of Heart failure in the Utrecht region (TOPHU) study: a cluster randomised controlled trial. <i>BMC Fam Pract. 2015;16:130</i>.• Greving JP, Diener HC, Csiba L, et al; Cerebrovascular Antiplatelet Trialists’ Collaborative Group. Individual patient data meta-analysis of antiplatelet regimens after noncardioembolic stroke or TIA: rationale and design. <i>Int J Stroke. 2015;10 Suppl A100:145-150</i>.• Vink EE, de Beus E, de Jager RL, et al. The effect of renal denervation added to standard pharmacologic treatment versus standard pharmacologic treatment alone in patients with resistant hypertension: rationale and design of the SYMPATHY trial. <i>Am Heart J. 2014;167(3):308-314.e3</i>.• Verloop WL, Beeftink MM, Nap A, et al. Renal denervation in heart failure with normal left ventricular ejection fraction. Rationale and design of the DIASTOLE (Denervation of the renal Sympathetic nerves in heart failure with normal Lv Ejection fraction) trial. <i>Eur J Heart Fail. 2013;15(12):1429-1437</i>.



5.3 Open Access publications (1)

Our general approach is to publish in online, open access journals for wider dissemination as much as possible. The UMC Utrecht stimulates open dissemination of scholarly publications (e.g. doctoral theses) via the platform NARCIS (<https://www.narcis.nl/>).

In the period between January 1st, 2016 and December 31st, 2018, we had 54 publications in either BMC journals or PLoS One co-authored by one of our cardiovascular epidemiologists. Selected examples:

- Boateng D, Wekesah F, Browne JL, et al. Knowledge and awareness of and perception towards cardiovascular disease risk in sub-Saharan Africa: a systematic review. *PLoS One*. 2017;12(12):e0189264. doi: 10.1371/journal.pone.0189264.
 - Addo J, Cook S, Galbete C, et al. Differences in alcohol consumption and drinking patterns in Ghanaians in Europe and Africa: The RODAM Study. *PLoS One*. 2018;13(11):e0206286. doi: 10.1371/journal.pone.0206286.
 - Van der Hoeven T, Browne JL, Uiterwaal CSPM, et al. Antenatal coffee and tea consumption and the effect on birth outcome and hypertensive pregnancy disorders. *PLoS One*. 2017;12(5):e0177619. doi: 10.1371/journal.pone.0177619.
 - Wang X, Dalmeijer GW, den Ruijter HM, et al. Clustering of cardiovascular risk factors and carotid intima-media thickness: The USE-IMT study. *PLoS One*. 2017;12(3):e0173393. doi: 10.1371/journal.pone.0173393.
 - De Kat AC, Dam V, Onland-Moret NC, et al. Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. *BMC Med*. 2017;15(1):2. doi: 10.1186/s12916-016-0762-8.
 - Koopman C, Vaartjes I, van Dis I, et al. Explaining the decline in coronary heart disease mortality in the Netherlands between 1997 and 2007. *PLoS One*. 2016;11(12):e0166139. doi: 10.1371/journal.pone.0166139.
 - Hwong WY, Bots ML, Selvarajah S, et al. Use of antihypertensive drugs and ischemic stroke severity - Is there a role for angiotensin-II? *PLoS One*. 2016;11(11):e0166524. doi: 10.1371/journal.pone.0166524.
 - Hwong WY, Bots ML, Selvarajah S, et al. Use of a diagnostic score to prioritize Computed Tomographic (CT) imaging for patients suspected of ischemic stroke who may benefit from thrombolytic therapy. *PLoS One*. 2016;11(10):e0165330. doi: 10.1371/journal.pone.0165330.
 - Eikendal AL, Bots ML, Haaring C, et al. Reference values for cardiac and aortic magnetic resonance imaging in healthy, young caucasian adults. *PLoS One*. 2016;11(10):e0164480. doi: 10.1371/journal.pone.0164480.
 - Vos AG, Idris NS, Barth RE, et al. Pro-Inflammatory markers in relation to cardiovascular disease in HIV Infection. A systematic review. *PLoS One*. 2016;11(1):e0147484. doi:10.1371/journal.pone.0147484.
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Appendix J: Expertise area Global Cardiovascular Health (A) and Diversity (B)

Table 3 – Process indicators (A) Global Cardiovascular Health

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment	<p>3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment</p> <p>a. Global health focuses on the improvement of health around the world and reduction of health disparities between countries and populations. The mission of our unit is to promote cardiovascular health, equality in health and well-being worldwide by generating the best evidence in order to guide health decision-making; to bridge epidemiology and public health; and to build high impact global cardiovascular health research capacity. Through internationally recognized and societally well-embedded research our unit contributes to the prevention and management of cardiovascular diseases globally.</p> <p>b. Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. The contribution of low- and middle-income countries to the global burden of cardiovascular disease is estimated at 80%. This is characterized by higher mortality rates and high burden of morbidity due to sub-optimal care, partially related to health system challenges. Our work therefore aims to: (1) study cardiovascular risk factors and disease outcomes internationally; (2) to develop, implement and scale-up cost-efficient approaches; and (3) to support clinical decision making for primary and secondary prevention of cardiovascular diseases globally.</p>
3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made	<p>United Nations <i>Sustainable Development Goal 3 – ensure healthy lives and promote wellbeing for all at all ages</i> specifically calls for reduction of premature mortality from non-communicable diseases, including cardiovascular diseases, by one third by 2030 through promotion of well-being, prevention and treatment.</p> <p>Our main focus to generate evidence for primary and secondary prevention of cardiovascular diseases globally aligns with international policy initiatives (World Heart Federation, World Health Organisation) and networks (Global Alliance for Chronic Disease Research) and draws on our local, national and international networks and our own expertise for research agenda setting.</p>
3.3. Stakeholders are involved in formulating the main research questions	<p>For co-creation of our strategic research programme we liaise with:</p> <ul style="list-style-type: none">• patient organisations nationally and internationally (such as the Ghana Action on Preeclampsia);• practitioners (such as Ghana Medical School / Ghana Health Service practitioners, providing primary and specialized patient care);• scientists;• governmental (such as the Ghana Health Service) and non-governmental organisations (such as the World Heart Federation or the Global Alliance for Chronic Diseases); and• funders (such as the European Union), <p>thereby considering the National Research Agenda of the Netherlands.</p>
3.4. The research questions are feasible and are pursued using optimal and efficient design	<p>In our unit we draw on the structural collaboration and expertise of fellow statisticians and methodologists at the Julius Center, UMC Utrecht and Utrecht University with regard to the design and conduct of our (international) studies and adequate statistical analysis of our research projects.</p>
3.5. What is 'the next step' if the project delivers positive results	<p>Our projects are generally interdisciplinary including colleagues from various disciplines, such as epidemiology, public health, health policy and systems, clinical sciences, social sciences, research ethics, anthropology and include stakeholders such as patient organisations, governmental, non-governmental and funding organisations. Application, implementation and scale-up of our research findings for population-based prevention and clinical practice is supported through:</p> <ul style="list-style-type: none">• collaboration with e.g. public health services in the countries we work, such as the Ghana Health Service in Ghana or the Department of Health in South Africa;• contributions to practice and policy guidelines nationally and internationally;• broad dissemination of results by use of presentations and publications (scientific journals, reports, printed and social media) for professional societies, patient organisations, department / ministries of health and at international conferences.



Table 4 – Output indicators (A) Global Cardiovascular Health

4.1 Research products for peers	<p>Selected peer-reviewed publications relating to determinants, prevention and management of cardiovascular disease internationally:</p> <ul style="list-style-type: none">• Selak V, Webster R, Stepien S, et al. Reaching cardiovascular prevention guideline targets with a polypill-based approach: a meta-analysis of randomised clinical trials. <i>Heart</i>. 2019;105(1):42-48.• Zhao M, Vaartjes I, Graham I, et al. Sex differences in risk factor management of coronary heart disease across three regions. <i>Heart</i>. 2017;103(20):1587-1594.• Takeuchi F, Akiyama M, Matoba N, et al. Interethnic analyses of blood pressure loci in populations of East Asian and European descent. <i>Nat Commun</i>. 2018;9(1):5052.• Boateng D, Agyemang C, Beune E, et al. Migration and cardiovascular disease risk among Ghanaian populations in Europe: The RODAM study (Research on Obesity and Diabetes among African Migrants). <i>Circ Cardiovasc Qual Outcomes</i>. 2017;10(11).• Van der Linden EL, Browne JL, Vissers KM, et al. Maternal body mass index and adverse pregnancy outcomes: a Ghanaian cohort study. <i>Obesity</i>, 2016;24(1):215-22. <p>Researchers affiliated with Global Cardiovascular Health at the University Medical Center Utrecht set up research infrastructure and patient / population cohorts in the Netherlands and internationally, such as:</p> <ul style="list-style-type: none">• Global Geo Data Health Center https://globalgeohealthdatacenter.com/• Survey of Risk Factor Collaboration https://surfriskfactor-audit.com/• Ndlovu Cohort Study (doi: 10.1177/2047487317702039).• BRAVO Breastfeeding Optimisation Trial, Jakarta, Indonesia (https://doi.org/10.1186/s13063-016-1397-y)• The Polypill SPACE consortium infrastructure (e.g., Selak V, Webster R, Stepien S, et al. <i>Heart</i>. 2019;105(1):42-48)• GENetics of sUbSequent Coronary Heart Disease (GENIUS-CHD) consortium. <p>Various patient cohorts in Ghana, Uganda, Tanzania, Suriname, South Africa contribute to e.g. the Global Pregnancy Collaboration (CoLab, https://pregnancycolab.tghn.org/) and International Prediction of Pregnancy Complication Network (ICPIP) and further international networks.</p>
4.2 Research products for societal target groups	<p>a. Selected examples of unit researcher involvement in practice & policy guideline generation:</p> <ul style="list-style-type: none">• Mancía G, Fagard R, Narkiewicz K, et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). <i>J Hypertens</i>. 2013;31(7):1281-1357.• Brown MA, Magee LA, Kenny LC, et al; on behalf of the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive Disorders of Pregnancy ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. <i>Hypertension</i>. 2018;72(1):24-43.• Brown MA, Magee LA, Kenny LC, et al; on behalf of the International Society for the Study of Hypertension in Pregnancy (ISSHP). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. <i>Pregnancy Hypertens</i>. 2018;13:291-310. <p>b. Selected examples of unit researcher involvement in practice & guideline committees:</p> <ul style="list-style-type: none">• D.E. Grobbee (ongoing): Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC); Task Force for the management of diabetes mellitus of the European Society of Cardiology (ESC).• R. Lamptey (since 2018): (Ghana Medical School, Accra, Ghana): National policy guidelines for the management of cardiovascular diseases in Ghana.• F. Wekesah (since 2018): (African Health and Population Research Center, Nairobi): National Non-communicable Disease prevention and treatment guidelines, Kenya. <p>c. Selected examples of media & outreach activities by unit researchers:</p> <p>M. Zhao (2018): Reuters Health; http://www.mdalert.com/news/article/women-with-heart-disease-less-apt-to-reach-treatment-targets-than-men.</p> <p>J. Browne (since 2014): Dutch Royal Academy of Science (KNAW) initiative 'Faces of Science': blogger and public engagement activities; https://www.nemokennislink.nl/facesofscience/wetenschappers/joyce-browne</p> <p>S. Peters (on-going): https://www.georgeinstitute.org.uk/people/sanne-peters</p> <p>F. Asselbergs (2018): 4Chambers interview; https://www.youtube.com/watch?v=ZFPVVOrupMs&feature=youtu.be</p> <p>d. Selected examples of unit researcher contributions for health professionals and general public:</p> <p>K. Klipstein-Grobusch (2017, 2019): SCUBY – Scale Up Diabetes and Hypertension Care; https://www.scuby.eu/blog/scuby-successful-start-in-ljubljana; launch event including public discussion; coverage in https://www.healtheuropa.eu/scuby-project-hypertension/91119/; Wits NCD Research Leadership Training Program: https://researchfeatures.com/2017/09/18/non-communicable-disease-research-african-continent/; https://www.youtube.com/watch?time_continue=10&v=mxFNbNIXIMM</p> <p>J. Browne / D. Boateng (2017, 2018): Dutch Global Health film festival www.globalhealthfilmfestival.nl – documentaries & discussions about Global Health related issues.</p>



4.3 Use of research products by peers	<p>Selected examples of the use of our research products by peers:</p> <ul style="list-style-type: none">• Our data and scientific contributions are considered for practice and guideline generation such as Mancia G, Fagard R, Narkiewicz K, et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). <i>J Hypertens.</i> 2013;31(7):1281-1357. [Citations: 3853]• Our data sets contribute to international consortia, such as the Polypill SPACE consortium. Pregnancy cohort data from Ghana contribute to e.g. the Global Pregnancy Collaboration (CoLab, https://pregnancycolab.tghn.org/) and International Prediction of Pregnancy Complication Network (ICCIP).• Research infrastructure such as the Global Geo Data Health Center is available to the scientific community.
4.4 Use of research products by societal groups	<p>Selected examples of the use of our research products by societal groups (and peers):</p> <ul style="list-style-type: none">• Implementation of sex and gender editorial policy guidelines (SAE Peters, R. Norton. Sex and gender reporting in global health: new editorial policies. <i>BMJ Glob Health.</i> 2018;3(4):e001038.• Re-evaluation of the classification, diagnosis & management recommendations for hypertensive disorders of pregnancy : Brown MA, Magee LA, Kenny LC, et al; on behalf of the International Society for the Study of Hypertension in Pregnancy (ISSHP). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. <i>Pregnancy Hypertens.</i> 2018;13:291-310.• Revision of management guidelines for arterial hypertension: Mancia G, Fagard R, Narkiewicz K, et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). <i>J Hypertens.</i> 2013;31(7):1281-1357.
4.5 Marks of recognition from peers	<p>Selected examples of recognitions marks from peers:</p> <p><i>a. Science awards/ Scholarly prizes:</i></p> <ul style="list-style-type: none">• J. Browne (2017): Innovation Award of the Netherlands Association for Community Genetics and Public Health Genomics (NACGG) for research on prenatal screening of pregnant women for placental disorders.• M. Zhao (2017): Young Investigator Award, Europrevent.• E. Nonterah (2018): International Early Career Investigator Award by the American Heart Association. <p><i>b. Bursaries:</i></p> <ul style="list-style-type: none">• F. Wekesah (2018): Harvard T. Chan School of Public Health's Lown Scholars Program on Cardiovascular Health. <p><i>c. Visiting professor / honorary appointments:</i></p> <ul style="list-style-type: none">• D. Grobbee: Honorary Professor University of Sydney, Australia & University of Kuala Lumpur, Malaysia.• F. Asselbergs: Adjunct Professor of Epidemiology, Dartmouth Medical School, USA.• K. Klipstein- Grobusch: Visiting Professor of Epidemiology, University of the Witwatersrand, Johannesburg, South Africa. <p><i>d. Committees:</i></p> <ul style="list-style-type: none">• D. Grobbee: Fellow of the Royal Dutch Academy of Sciences, The Netherlands; Honorary fellow of the Indonesian Heart Association and of the Romanian Society of Cardiology; Member Board European Society of Cardiology.• K. Klipstein-Grobusch: Chair Dutch-Flemish Accreditation Higher Education Review (Global Health), The Netherlands; Technical Advisory Committee, DELTAS Sub-Saharan Africa Consortium for Advanced Biostatistics Training, South Africa.• S. Peters: Member of Management Committee on Global Women's Health, The George Institute for Global Health; Program Committee Organisation for the Study of Sex Difference.• F. Asselbergs: Executive Committee GENIUS-CHD. <p><i>e. Editorial boards:</i></p> <ul style="list-style-type: none">• Global Heart: D. Grobbee (editor-in-chief); K. Klipstein-Grobusch, J. Browne.• European Journal Preventive Cardiology: D. Grobbee, M. Bots.• BMJ Global Health: S. Peters. <p><i>f. Selected invited lectures:</i></p> <ul style="list-style-type: none">• D.E. Grobbee (2017-2018): 1) Hong Kong Heart Foundation: <i>The environment and cardiovascular health</i>; 2) European Society of Cardiology Congress, Munich: <i>Legacy effects in cardiovascular trials</i>; 3) World Congress of Cardiology, Dubai: <i>Global burden of cardiovascular disease</i>.• M. Bots (2014, 2017): 1) KL University Hospital, Kuala Lumpur, Malaysia.; <i>The cardiovascular polypill: a simple strategy helping to solve a complex problem?</i>; 2) EUROPREVENT, Amsterdam: <i>What have we learned from CIMT measurements</i>.• F. Asselbergs (2017): 1) American Heart Association's annual Scientific Sessions "<i>Session Precision Medicine: Rapid Fire Reports from the Front Line</i>"; 2) European Society of Cardiology, Big Data@Heart Educational Event "<i>Genetic epidemiology: Back to Basics</i>."• S. Peters (2017): 1) Innovations in Research and Health Care Symposium, Peking University Health Science Center and UNSW Sydney, Beijing, China: <i>Sex differences in chronic disease</i>; 2) Gender Summit, Berlin, Germany: <i>Sex differences in risk factors for cardiovascular disease: large-scale meta-analyses summarising all available evidence</i>.• K. Klipstein-Grobusch (2015, 2017): 1) Noguchi Memorial Institute for Medical Research, Accra, Ghana: <i>Cohort studies; challenges and opportunities in Africa. Advancing non-communicable disease research in West Africa: building cohorts for multidisciplinary research including genomics studies</i>; 2) Fogarty International Center for Advanced Study in the Health Sciences, Bethesda, USA: <i>Research Capacity Building in Non-Communicable Disease in South Africa: The Wits Non-Communicable Disease Research Leadership Program</i>.



4.6 Marks of recognition from societal groups	<ul style="list-style-type: none">• D. Grobbee: Fellow of the Royal Dutch Academy of Sciences, The Netherlands; Chair Prevention Route, Dutch National Science Agenda; Knight in the Order of the Dutch Lion (2017).• K. Klipstein-Grobusch (2016): Prince Claus Chair for Development and Equity Committee.• J. Browne: Board member Netherlands Society Tropical Medicine and International Health (NVTG); Member of the Supervisory Board Simavi.• M. Bots: Advisory board for the working party on 'Cardiovascular disease: figures and facts' of the Dutch Heart Foundation; Management Board 'Queen of Hearts' consortium on women specific drivers and heart failure.
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Table 5 – Open Science indicators (A) Global Cardiovascular Health

5.1 Openness of the research agenda & stakeholder involvement	<p>Selected stakeholders, exemplary shown for our international collaboration on hypertensive disorders in pregnancy in Ghana:</p> <ul style="list-style-type: none">• Patient organisation: Ghana Action on Preeclampsia (GHAPEC).• Practitioners: Ghana Medical School / Ghana Health Service practitioners, providing primary and specialized care to pregnant women.• Scientists: colleagues at UMC Utrecht, further Dutch scientific organisations (Royal Tropical Institute, Free University Amsterdam) and international colleagues from e.g. Ghana, USA, Canada.• Governmental organisations: Ghana Health Service.• Non-governmental health organisations: Netherlands Network on Sexual and Reproductive Health and Rights - Share-Net International and the International Federation of Obstetricians and Gynecologists (FIGO).• Funders: Bill & Melinda Gates Foundation, Dutch Scientific Organisation.
5.2 Openness of data and protocols	<p>a. Projects in our unit have a data management plan in line with policies of the Julius Center, UMC Utrecht and Utrecht University; data are stored accordingly on protected Julius Center servers, respectively Utrecht University (for the Global Geo Data Health Center) servers.</p> <p>b. Our unit stimulates the registration of protocols for clinical trials, and ensures registrations of trial and publishing of results of clinical trials (clinicaltrials.gov, trialregister.nl, clinicaltrialsregister.eu), such as for the BRAVO Breast Feeding Optimisation Trial ClinicalTrials.gov, NCT01566812 or the UMPIRE trial clinicaltrials.gov NCT01057537 contributing to the SPACE collaboration.</p>
5.3 Open Access publications (1)	<p>Our general approach is to publish in online, open access journals for wider dissemination including in low- and middle-income countries. Funding for open access to be partially covered by the Utrecht University 'Open Access Fund', funders and facilitated by the VSNU initiative on open access publishing.</p> <p>Below some examples of open access publications:</p> <ul style="list-style-type: none">• Qanitha A, Uiterwaal CSPM, .Henriques JPS, et al. Characteristics and the average 30-day and 6-month clinical outcomes of patients hospitalised with coronary artery disease in a poor South-East Asian setting: the first cohort from Makassar Cardiac Center, Indonesia. <i>BMJ Open</i>. 2018;8(6):e021996.• Boateng D, Wekesah F, Browne JL, et al. Knowledge and awareness of and perception towards cardiovascular disease risk in sub-Saharan Africa: A systematic review. <i>PLoS One</i>. 2017;12(12):e0189264.• Hwong WY, Abdul Aziz Z, Sidek NN, et al. Prescription of secondary preventive drugs after ischemic stroke: results from the Malaysian National Stroke Registry. <i>BMC Neurol</i>. 2017;17(1):203.



Appendix K: Expertise area Global CV Health (A) and Diversity (B)

Table 3 – Process indicators (B) Diversity

3.1. The unit of assessment has a mission and the mission-derived targets guide the work of those working within the unit of assessment	<p>a. Through internationally recognized and societally well-embedded research the Circulatory Health strategic research program adds to the improvement of the health of patients with cardiovascular diseases, with an important focus on women.</p> <p>b. The disease burden from diseases of the circulatory system is high. Globally, 32% of all deaths had a cardiovascular cause in 2017, of which 85% was attributable to coronary heart disease and stroke (<i>GBD 2017 causes of death collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736-1788</i>). Of all disability-adjusted life years, cardiovascular diseases account for 15.6% in men (of which 50% due to ischemic heart disease and 34% due to stroke) and 13.4% in women (of which 42% due to ischemic heart disease and 38% due to stroke) to form the second and third leading causes of disability-adjusted-life-years (DALYs) in both sexes (<i>GBD 2017 DALYs and HALEs collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392:1859-1922</i>).</p>
3.2. How research questions relate to existing knowledge is well described and this knowledge is transparently incorporated in the choices made	<p>Our main focus is in line with several knowledge agenda's:</p> <p>The Dutch Cardiovascular Alliance has the ambition to reduce cardiovascular disease by 25% in 2030. The NWA route of healthcare, prevention and treatment predicts 7 million people with chronic conditions (which is 40% of our society). This will increase pressure on our healthcare system and research to revise, adapt and improve diagnostic tracks are crucial, as cardiovascular disease is the second field of medicine with the most healthcare costs. The NWA route specifically addresses attention to <i>differences between people</i> and researching current healthcare pathways to directly implement in clinical practice. The knowledge routes prevention and personalized medicine refer to innovations in e-Health, biomarkers, and improving diagnoses as areas of investments.</p> <p>Our strategy is in line with these ambitions and dedicated to improve knowledge on heart disease in women. By investigating current paths of healthcare, by identifying women who have remained underdiagnosed, or that have a poor prognosis, and by understanding diversity, we aim to improve quality of care in women.</p>
3.3. Stakeholders are involved in formulating the main research questions	<p>Our strategic research program team annually meets with patient representatives from the diseases we study to discuss our research lines. For several grants we involved clinicians (UMC Utrecht), epidemiologists (UMC Utrecht), basic scientists (UMC Utrecht), patient organisations (“Harteraad”) and interest groups (WomenInc), and knowledge centers (University of Applied Sciences Utrecht, Clinical Health Sciences UU).</p> <p>Within the Utrecht Cardiovascular Cohort (UCC), the strategic research program team closely collaborates with all UMC Utrecht divisions that are involved in care of patient at risk of or with vascular disease. The UCC steering committee meets monthly to discuss progress, also involving the topics on female-specific risks and risk factors. Data from UCC patients are linked to the Julius General Practitioners Network (JGPN) database, covering all patients in the region of the UMC Utrecht. Cardiovascular risk management is evaluated with separate analyses for women and women after reproductive disorders.</p>
3.4. The research questions are feasible and are pursued using optimal and efficient design	<p>In our unit we have structural collaboration with statisticians and/or methodologists, they are involved in all projects based on knowledge of the content and methodology.</p> <p>In addition, for specific projects, involving big data, omics, text mining and/or machine learning, expertise is sought in the University Utrecht with the group of D. Oberski (Associate Prof. of methodology of Data Science), and outside in collaboration with UMC Groningen and Amsterdam UMC (CVON Artificial Intelligence consortium), the group of D. Boomsma (Prof. of Biological Psychology at Amsterdam UMC), and the group of B. Heijmans (Associate Prof. of Population Epigenomics at LUMC).</p>



3.5. What is 'the next step' if the project delivers positive results	<p>In the RED-CVD project we work in close collaboration with patient care groups ("Harteraad"), representatives of national organisations for practice nurses and general practitioners (GPs), including GPs specifically trained in cardiovascular diseases and medical directors of large GP cooperations. We organise regular meetings with a users' committee during the study, also to discuss feasibility and identify barriers and facilitators of implementation of the programme in everyday clinical practice.</p> <p>Within the UCC and specifically women after reproductive disorders with vascular disease the next step will be intervention. Preventive strategies should be taken and this fits within the hospital aim to focus on preventive strategies the coming years.</p> <p>Position statements through Board membership of the European Menopause and Andropause Society (Y.T. van der Schouw):</p> <ul style="list-style-type: none">• Stute P, Ceausu I, Depypere H, et al. A model of care for healthy menopause and ageing: EMAS position statement. <i>Maturitas</i>. 2016;92:1-6.• Dimopoulou C, Ceausu I, Depypere H, et al. EMAS position statement: Testosterone replacement therapy in the aging male. <i>Maturitas</i>. 2016;84:94-99.• Neves-E-Castro M, Birkhauser M, Samsioe G, et al. EMAS position statement: The ten point guide to the integral management of menopausal health. <i>Maturitas</i>. 2015;81:88-92. <p>Memberships (guideline) committees:</p> <ul style="list-style-type: none">• A.T. Lely (2018-2020): Guideline committee Otterloo (perinatologist) and multi-disciplinary guideline on Kidney Disease and pregnancy.• A.T. Lely (2016-current): Off-Road committee ZonMW.
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Table 4 – Output indicators (B) Diversity

4.1 Research products for peers	<p>Key publications:</p> <ul style="list-style-type: none">• Van der Meer MG, van der Graaf Y, Schuit E, et al. Added Value of Female-Specific Factors Beyond Traditional Predictors for Future Cardiovascular Disease. <i>J Am Coll Cardiol</i>. 2016;67:2084-2086.• Paauw ND, van der Graaf AM, Bozoglan R, et al. Kidney Function After a Hypertensive Disorder of Pregnancy: A Longitudinal Study. <i>Am J Kidney Dis</i>. 2018;71:619-626.• Bots SH, den Ruijter HM. Recommended Heart Failure Medications and Adverse Drug Reactions in Women. <i>Circulation</i>. 2019;139:1469-1471.• Pasterkamp G, den Ruijter HM, Libby P. Temporal shifts in clinical presentation and underlying mechanisms of atherosclerotic disease. <i>Nat Rev Cardiol</i>. 2017;14:21-29.• Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. <i>BMJ</i>. 2018;363:k4247. <p>Researchers from the Julius Center created a dataset with genome-wide association study data, that is also used by researchers within and outside the UMC Utrecht.</p>
4.2 Research products for societal target groups	<p>Selected examples of lectures for general audiences:</p> <ul style="list-style-type: none">• Y.T. van der Schouw (2016): UMC Utrecht Public Lecture, "Hart- en vaatziekten: voor man en vrouw verschillend".• H. den Ruijter (2016): UMC Utrecht Public Lecture, "Hart- en vaatziekten: voor man en vrouw verschillend".• H. den Ruijter (2018): UMC Utrecht Public Lecture, "Onderzoek naar hart- en vaatziekten bij vrouwen".• A.T. Lely (2016): UMC Utrecht Public Lecture, "Nierziekten en zwangerschap".• A.T. Lely (2016): Lecture "Lotgenotendag antifosfolipiden syndroom (APS)" on APS and pregnancy.• S. Peters (2018): UMC Utrecht Public Lecture, "Man-vrouw verschillen in risicofactoren voor hart- en vaatziekten".• K. Groenhof (2018): UMC Utrecht Public Lecture, "Zwangerschap en hart- en vaatziekten". <p>Selected examples of media & outreach activities by unit researchers:</p> <p>H. den Ruijter (2015-2018):</p> <ul style="list-style-type: none">• Newspaper Volkskrant, "Hebben mannen een ander hart dan vrouwen?".• Newspaper Volkskrant, "Vrouwen overlijden vaker na hartaanval".• Newspaper Telegraaf, "De feiten over hart- en vaatziekten op een rij".• Newspaper Telegraaf, "APK voor geneesmiddelen".• Television Eva Jinek, Sex differences in cardiovascular disease.• Television RTL4 Koffietijd, Sex differences in cardiovascular disease.
4.3 Use of research products by peers	<ul style="list-style-type: none">• One of our papers (Brand JS, Rovers MM, Yeap BB, et al. Testosterone, sex hormone-binding globulin and the metabolic syndrome in men: an individual participant data meta-analysis of observational studies. <i>PLoS One</i>. 2014;9(7):e100409) gathered 84 citations and 6,614 page views.• Colleagues from Amsterdam UMC used our samples to perform GWAS study on dizygotic twinning.• Colleagues from Cambridge University used our data.



4.4 Use of research products by societal groups	<p>Selected examples of the use of our research products by societal groups (and peers):</p> <ul style="list-style-type: none"> • Implementation of sex and gender editorial policy guidelines (Peters SAE, Norton R. Sex and gender reporting in global health: new editorial policies. <i>BMJ Glob Health</i>. 2018 Jul 26;3(4):e001038). • Research line on cardiovascular disease after reproductive disorders has led to a guideline in 2014.
4.5 Marks of recognition from peers	<p>Selected examples of recognitions marks from peers:</p> <ul style="list-style-type: none"> • Y.T. van der Schouw (2012-2017): Board membership European Menopause and Andropause Society. • Y.T. van der Schouw (2007-now): Editorial Board member <i>Maturitas</i>. • A.T. Lely (2014): Clinical Fellowship ZonMw – personal career grant. • S. Peters (2018-now): Associate editor <i>BMJ Global Health</i>. • S. Peters (2019): Guest editor <i>Circulation</i>. • S. Peters: Member of Management Committee on Global Women's Health, The George Institute for Global Health; Program Committee Organisation for the Study of Sex Difference • H. den Ruijter (2017-2022): Member of the Young Academy of the Royal Netherlands Academy of Sciences. <p>Selected examples of invited lectures:</p> <ul style="list-style-type: none"> • S. Peters (2015, 2017): 1) Innovations in Research and Health Care Symposium, Peking University Health Science Center and UNSW Sydney, Beijing, China: <i>Sex differences in chronic disease</i>; 2) Gender Summit, Berlin, Germany: <i>Sex differences in risk factors for cardiovascular disease: large-scale meta-analyses summarising all available evidence</i>. • H. den Ruijter (2017-2019): <ul style="list-style-type: none"> - Symposium organizer Sex differences in prescription, efficacy and adverse drug reactions of commonly prescribed drugs OSSD (Washington). - Invited speaker International symposium on Biomechanics in Vascular biology and Cardiovascular disease (London). - Keystone (Taos, New Mexico) Lessons Learned and Concepts Challenged. - EHRA conference (Barcelona) Let's talk about sex session with Women Inc. - Frontiers in Biomedicine (Université de Genève). - Congress of the Organisation of the Study of Sex Differences OSSD (Montréal). - Kongress der Deutschen Gesellschaft für Innere Medizin (Mannheim). - Paris Diderot: Gender in research: A new kind of scientific excellence (Paris). • A.T. Lely (2018): International Society on Hypertension in pregnancy and maternal health: update on pregnancy and renal transplantation. • Y.T. van der Schouw (2017): EMAS congress Amsterdam <i>Ovarian aging and cardiometabolic disease</i>.
4.6 Marks of recognition from societal groups	<ul style="list-style-type: none"> • H. den Ruijter (2019): assigned initiator by the Dutch Heart Foundation for new research on cardiovascular disease in women, initiator for implementation research and initiator for knowledge network on sex and gender in cardiovascular disease (budget 3ME).

Table 5 – Open Science indicators (B) Diversity

5.1 Openness of the research agenda & stakeholder involvement	<p>Selected stakeholders:</p> <ul style="list-style-type: none"> • Patient organisations: Nierpatiënten Vereniging Nederland (NVN), HELPP stichting, "Harteraad". • Interest group: WomenInc. • Scientists: colleagues at UMC Utrecht, knowledgecenters (University of Applied Sciences Utrecht, Clinical Health Sciences UU) and international colleagues from e.g. the University of Cambridge. • National organisations for practice nurses and GPs, including GPs specifically trained in cardiovascular diseases and medical directors of large GP cooperations.
5.2 Openness of data and protocols	<p>All material is stored on central drives of the UMC Utrecht following a standard format and data are shared generally through contacting the steering committee of the specific study through websites, e.g. https://www.epicnl.eu.</p>



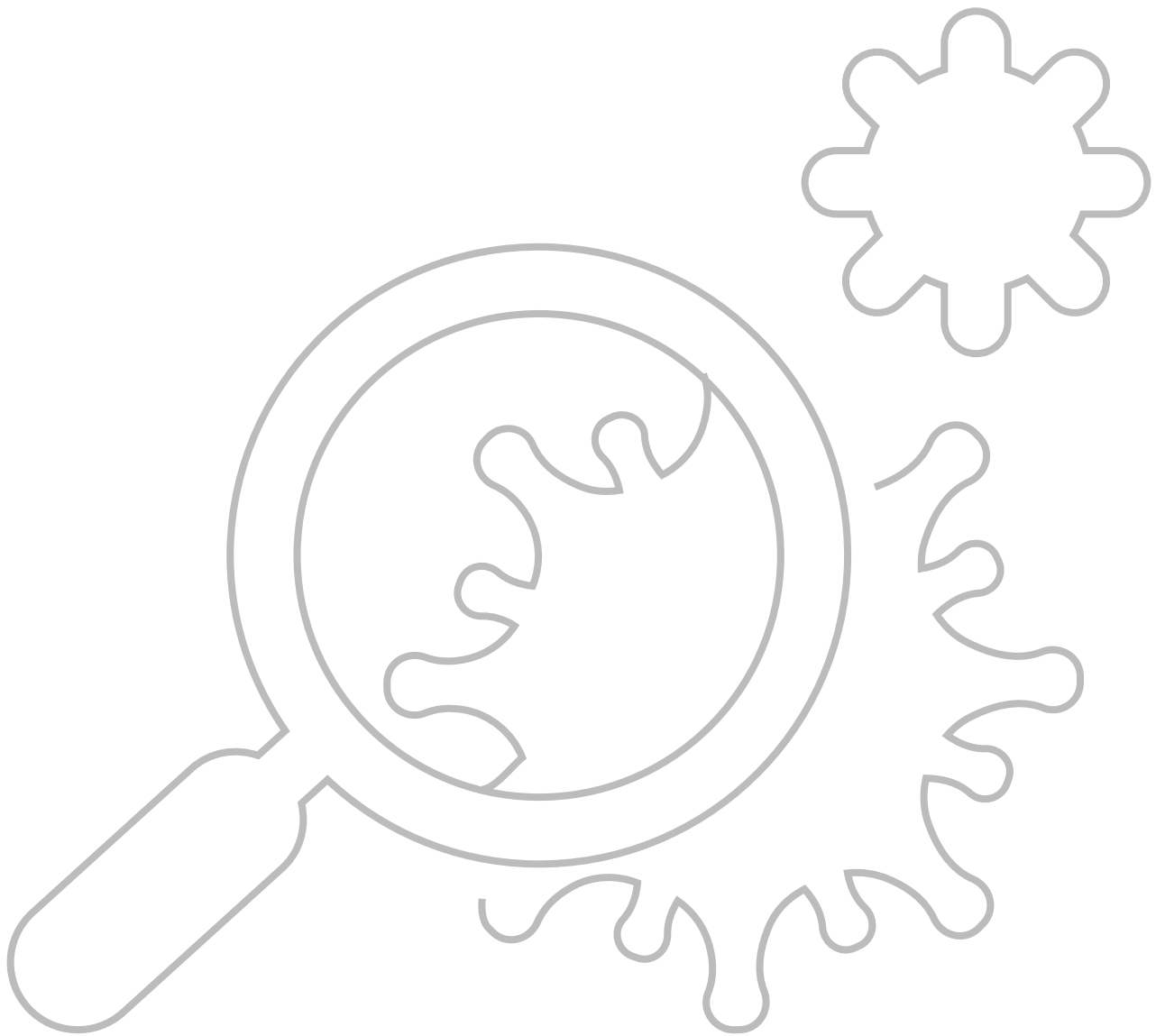
5.3 Open Access publications (1)

Selected examples of open access publications of our unit:

- Dam V, Van der Schouw YT, Onland-Moret NC, et al. Association of menopausal characteristics and risk of coronary heart disease: a pan-European case-cohort analysis. *Int J Epidemiol*. 2019. doi: 10.1093/ije/dyz016.
 - Baart SJ, Dam V, Scheres LJJ, et al; CREW consortium. Cardiovascular risk prediction models for women in the general population: A systematic review. *PLoS One*. 2019;14:e0210329.
 - De Kat AC, Verschuren WM, Eijkemans MJ, et al. Anti-Müllerian Hormone Trajectories Are Associated With Cardiovascular Disease in Women: Results From the Doetinchem Cohort Study. *Circulation*. 2017;135:556-565.
 - De Kat AC, Dam V, Onland-Moret NC, et al. Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. *BMC Med*. 2017;15:2.
 - De Kat AC, Van der Schouw YT, Eijkemans MJ, et al. Back to the basics of ovarian aging: a population-based study on longitudinal anti-Müllerian hormone decline. *BMC Med*. 2016;14:151.
 - Heida KY, Franx A, van Rijn BB, et al. Earlier Age of Onset of Chronic Hypertension and Type 2 Diabetes Mellitus After a Hypertensive Disorder of Pregnancy or Gestational Diabetes Mellitus. *Hypertension*. 2015;66:1116-1122.
 - Groenhof TKJ, Zoet GA, Franx A, et al; PREVEND Group. Trajectory of Cardiovascular Risk Factors After Hypertensive Disorders of Pregnancy. *Hypertension*. 2019;73:171-178.
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Self-evaluation report strategic research program **Infection & Immunity**





Abbreviations	296
1. Strategic research program infection & immunity	298
1.1 Vision and strategy	298
1.2 Organisation	299
1.3 Composition	300
1.4 Funding	302
1.5 SWOT analysis	304
1.6 Evaluation practices and/or policies	304
1.7 Open Science activities	305
1.8 Patient involvement	306
1.9 Teaching	306
2. Research theme: preventing antimicrobial resistance	308
2.1 Mission, urgency and/or relevance of the research questions	308
2.2 Relation to existing knowledge	308
2.3 Collaborations with stakeholders	309
2.4 Research design	310
2.5 The next steps	310
2.6 Results highlights	311
2.7 Two examples of patient involvement	313
2.8 Ten most important scientific publications	314
2.9 Two most important societal contributions	316
3. Research theme: preventing inflammation	318
3.1 Mission, urgency and/or relevance of the research questions	318
3.2 Relation to existing knowledge	318
3.3 Collaborations with stakeholders	319
3.4 Research design	320
3.5 The next step	321
3.6 Results highlights	321
3.7 Two examples of patient involvement	324
3.8 Ten most important scientific publications	325
3.9 Two most important examples of societal contributions	327
4. Research theme: elucidating host-pathogen interactions	328
4.1 Mission, urgency and/or relevance of the research questions	328
4.2 Relation to existing knowledge	328
4.3 Collaborations with stakeholders	329
4.4 Research design	329
4.5 The next step	330
4.6 Results highlights	331
4.7 Two examples of patient involvement	333
4.8 Ten most important scientific publications	334
4.9 Two most important examples of societal contributions	335



5. Research theme: developing immune-mediated therapy & prevention	337
5.1 Mission, urgency and/or relevance of the research questions	337
5.2 Relation to existing knowledge	337
5.3 Collaborations with stakeholders	339
5.4 Research design	339
5.5 The next step	340
5.6 Results highlights	341
5.7 Two examples of patient involvement	344
5.8 Ten most important scientific publications	345
5.9 Two most important examples of societal contributions	346
6. Appendix I. Professors and associates in I&I	348



Abbreviations

ADCARE	Atopic Dermatitis Center of Reference and Excellence	EASYM	European Association for SYstems Medicine
AIDS	Acquired ImmunoDeficiency Syndrome	EBMT	European Group for Blood and Marrow Transplantation
ALTANT	ALternatives-To-ANTibiotics	EBV	Epstein-Barr-virus
AMR	Anti-Microbial Resistance	EC	European Commission
APS	Anti-Phospholipid Syndrome	ECDC	European Centre for Disease Prevention and Control
CAP	Community Acquired Pneumonia	ECRAID	European Clinical Research Alliance on Infectious Diseases
CAPiTA	Community Acquired Pneumonia immunisation Trial in Adults	EFPIA	European Federation of Pharmaceutical Industries and Associations
CART	Chimeric Antigen Receptor T cell	EMA	European Medicines Agency
cART	Combination Antiretroviral Therapy	EMBO	European Molecular Biology Organisation
CCMO	Dutch Clinical Research Foundation	Epi	Epidemiology of Infectious Diseases
CDC	Centers for Disease Control and Prevention	ERAD	ER-Associated protein Degradation
CFF	Central Flow cytometry Facility	ERC	European Research Council
COMBACTE	COMBating AntimiCrobial resisTance in Europe	ESAR	European Society for translational Antiviral Research
COMBACTE-CARE	COMBACTE-CARbapenem-REsistance	ESBL	Extended Spectrum Beta-Lactamase
COMBACTE-CDI	COMBACTE-Clostridium Difficile Infection	ESCMID	European Society of Clinical Microbiology and Infectious Diseases
COMBACTE-MAGNET	COMBACTE-Molecules Against Gram-NEgative infecTions	ESICM	European Society of Intensive Care Medicine
COMBACTE-NET	COMBACTE NETWORKs	EULAR	EUropean League Against Rheumatism
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats	EVOTAR	EVOLution and Transmission of Antibiotic Resistance
CVID	Common Variable Immunodeficiency Disorders	FDA	Food and Drug Administration
CVID	Daily Board	FOCIS	Federation of Clinical Immunology Societies
DB	Division Imaging and Oncology	GMP	Good Manufacturing Practices
dB&O	Division Imaging and CancerOncology	GSLS	Graduate School of Life Sciences
dH&L	Division Heart and Lungs	HEMATON	Dutch hematology patient organisation
dHS	Division Surgical Specialties	HIV	Human Immunodeficiency Virus
dIGD	Division Internal Medicine and Dermatology	HLA	Human Leukocyte Antigen
dJC	Division Julius Center for Health Sciences and Primary Care	HSV	Herpes Simplex Virus
dKind	Division Pediatrics	IAS USA	International Antiviral Society USA
dLAB	Division Laboratory, Pharmacy and Biogenetics	IBD	Inflammatory Bowel Disease
DMTR	Dutch Melanoma Treatment Registry	ICI	Immune Checkpoint Inhibitors
dVF	Division Vital Functions	ICU	Intensive Care Unit
E.N.T.	Ear-Nose-Throat	IMI	Innovative Medicines Initiative
EAACI	European Academy of Allergy and Clinical Immunology	IMID	Immune-Mediated Inflammatory Disease
EACS	European AIDS Clinical Society	IRAS	Institute for Risk Assessment Sciences



ISO	International Organisation for Standardisation
ITN	Innovative Training Networks
JIA	Juvenile Idiopathic Arthritis
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
KNAW	Royal Netherlands Academy of Arts and Sciences
KNVM	Royal Dutch Association for Microbiology
KWF	Dutch Cancer Society
LMIC	Low and Middle Income Countries
LPS	Lipopolysaccharide
LTI	Laboratory for Translational Immunology
MARS	Molecular diagnosis and Risk stratification of Sepsis
MDRE	Multi-Drug Resistance Enterococci
METC	Medical Ethics Committee
MMB	Laboratory of Medical Microbiology
MRSA	Methicillin-Resistant Staphylococcus aureus
NADP	Netherlands Antibiotic Development Platform
NCOH	Netherlands Center for One Health
ND4BB	New Drugs for Bad Bugs
NIH	American National Institutes of Health
NOS	Dutch Broadcast Foundation
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NVK	Dutch National Society for Pediatric Oncology
NVKR	Dutch Society for Pediatric Rheumatology
NVVI	Dutch Society for Immunology
NWO	Dutch Research Council
OA	Osteoarthritis
OCW	Ministry of Education, Culture and Science
PERISCOPE	PERTussIS COrrelates of Protection Europe
PI	Principle Investigator
PMC	Princess Máxima Center for Pediatric Oncology
PMT	Program Management Team
POC	Point-Of-Care
PREPARE	Platform for European Preparedness Against (Re-)emerging Epidemics
PreS	European Society for Pediatric Research
PROCARE	PROfiling Consortium of Antibody Repertoire and Effector functions
R&D	Research and Development

REPO-TRIAL	REPOurposing TRIALs
RESCUE	REspiratory Syncytial virus Consortium in Europe
R-GNOSIS	Resistance in Gram-Negative Organisms: Studying Intervention Strategies
RIVM	National Institute for Public Health and the Environment
RSV	Respiratory Syncytial Virus
SATURN	Studying impact of Specific Antibiotic Therapies on prevalence of hUMAN host Resistant bacteria
SCT	Stem Cell Transplantation
SDD	Selective Decontamination of the Digestive tract
SEP	Standard Evaluation Protocol
SLE	Systemic Lupus Erythematosus
SOD	Selective Oropharyngeal Decontamination
SOP	Standard Operating Procedure
SSc	Systemic Sclerosis
STARCS	Selection and Transmission of Antimicrobial Resistance in Complex Systems
TEG	T cells engineered to Express a defined Gamma delta T cell receptor
TNF	Tumor Necrosis Factor
TTO	Technology Transfer Office
TTW	Applied and Engineering Sciences
UBC	Utrecht Bioinformatics Center
UCAN CANDU	Canada-Netherlands Personalized Medicine Network in Childhood Arthritis and Rheumatic Diseases
UCQI	Center for Quantitative Immunology
UDAIR	Utrecht Center for Diagnostic Advances in Immunology Research
ULS	Utrecht Life Sciences
UMC Utrecht	University Medical Center Utrecht
UU	Utrecht University
VITAL	Vaccines and Infectious diseases in the Ageing population
VRE	Vancomycin-Resistant Enterococci
VWS	Dutch Ministry of Health, Welfare and Sport
WHO	World Health Organisation
WKZ	Wilhelmina Children's Hospital
ZiN	Dutch National Health Care Institute
ZonMw	Netherlands Organisation for Health Research and Development



1. Strategic research program infection & immunity

1.1 Vision and strategy

The incidence of inflammatory diseases and of opportunistic infections caused by microorganisms resistant to our current therapies are both increasing and call for a coordinated multidisciplinary scientific and healthcare response. At the same time, harnessing the immune system appears to be a powerful therapeutic approach in prevention and treatment of infection and cancer. These research themes, therefore, are integrated in the Strategic Research Program Infection & Immunity (I&I).

Antimicrobial resistance, especially of bacteria against antibiotics, is increasing worldwide. As the number of newly-developed antibiotics has declined over the last decades, a scenario of untreatable bacterial infections has become realistic in many parts in the world. For high-income countries this threatens the successful prevention and treatment of bacterial infections in patients requiring immune compromising treatments. In low and middle-income countries even community-acquired infections in previously healthy subjects may become untreatable. Antibiotic resistance is now considered a global health crisis, necessitating an international and diverse response. Researchers in the UMC Utrecht contribute to this response through investigating the complex dynamics of antibiotic resistant bacteria and their resistance genes, through developing and testing new approaches for infection prevention and antibiotic stewardship, through developing new (non-antibiotic) treatment options and through establishing a European clinical trial network to better (and more efficiently) evaluate new antimicrobial agents.

Immune-mediated inflammatory diseases (IMIDs) denote a spectrum of >30 chronic diseases, which can affect virtually every organ. About 10% of the population suffers from an IMID, making this class of diseases a huge health care problem. Some IMIDs are iatrogenic or infectious, but most have unknown etiology. At the UMC Utrecht we study the regulation and dysregulation of the immune system across different diseases in multidisciplinary teams. To understand disease, we also strive to understand how a healthy immune system develops from newborn to the elderly. Integrated studies of the immune system will allow for the classification of patients on the basis of underlying mechanism and the identification of treatable traits for IMIDs. Optimal treatment of patients with diseases resulting from failing or derailed immunity and/or infection requires a shift from typically “organ-driven” to personalized “immune activation pattern-driven”. Furthermore, we use our knowledge to harness the immune system to prevent and fight inflammation, infection and cancer.

Mission and ambition

The strategic research program I&I aims for a national and international leading role in obtaining and disseminating knowledge and innovations in the field of inflammatory and infectious diseases and immune-mediated therapy. Our aim is to improve treatment in patients with difficult-to-manage infections, immune diseases or cancer. Our doctors and researchers closely collaborate to deliver high-quality care and cutting edge research, where possible together with patients. We ensure our knowledge and expertise by training talented people to become the future generation of experts.

Objectives and research themes

The program aims to contribute to solutions for diseases with large societal impact, with a focus on tertiary patient care, with strong research facilities, with strong connection in the region and beyond, continuously responding to new developments and with an effective talent policy. More specific, our objectives are:

- To provide innovative, improved and affordable treatment options for patients with complex and/or rare IMIDs;
- To classify and monitor patients with IMIDs in order to select the right therapy for each patient;
- To prevent antimicrobial resistance becoming a problem for patients in the Netherlands;
- To better use the immune system in the treatment of cancer, inflammatory diseases and difficult to treat infections (including those caused by drug-resistant bacteria);
- To better prevent opportunistic infections in patients at risk for such infections as a result of underlying disease and/or treatment for that disease (hospital-acquired infections);
- To develop and evaluate vaccination strategies;
- To develop new treatment strategies for complex infections.



To pursue these objectives, I&I is organized in four connected research themes (Figure 1); (1) preventing antimicrobial resistance, (2) preventing inflammation, (3) elucidating host-pathogen interactions, and (4) developing immune-mediated therapy and prevention. Each theme had distinct research lines, and clinicians, researchers and research groups are often active in several themes.

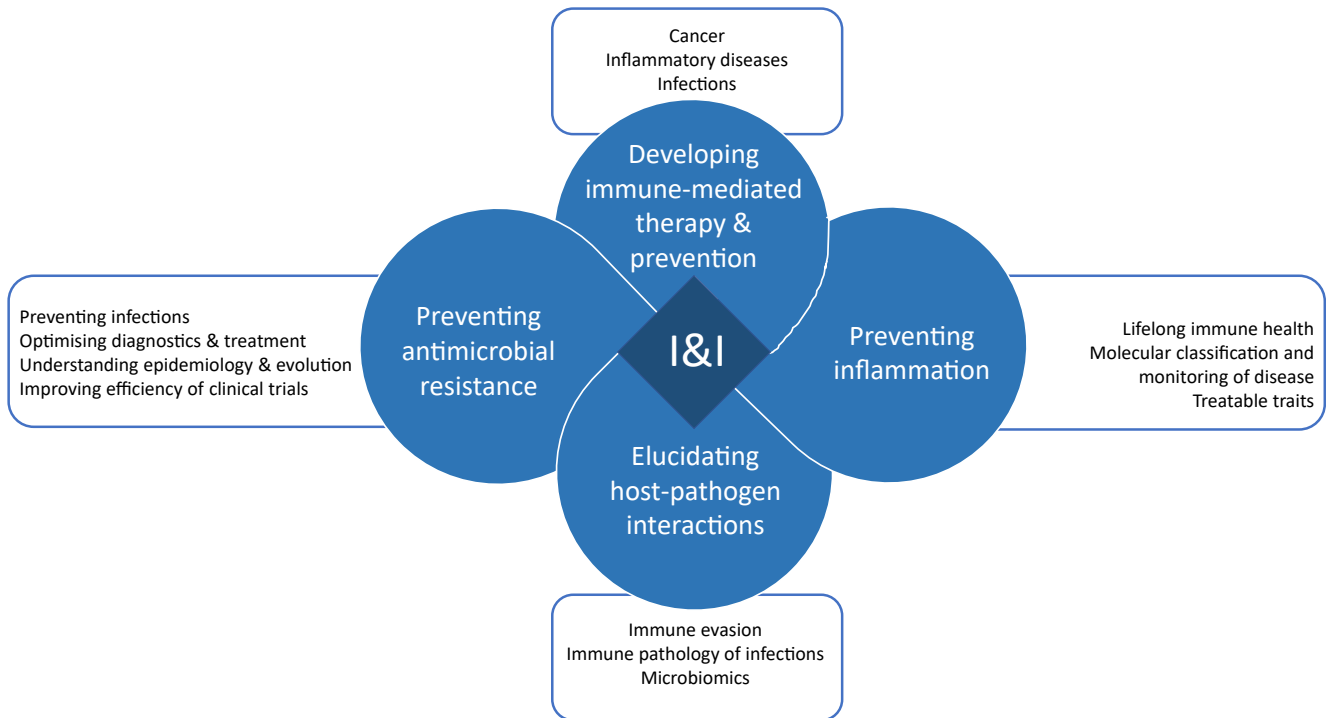
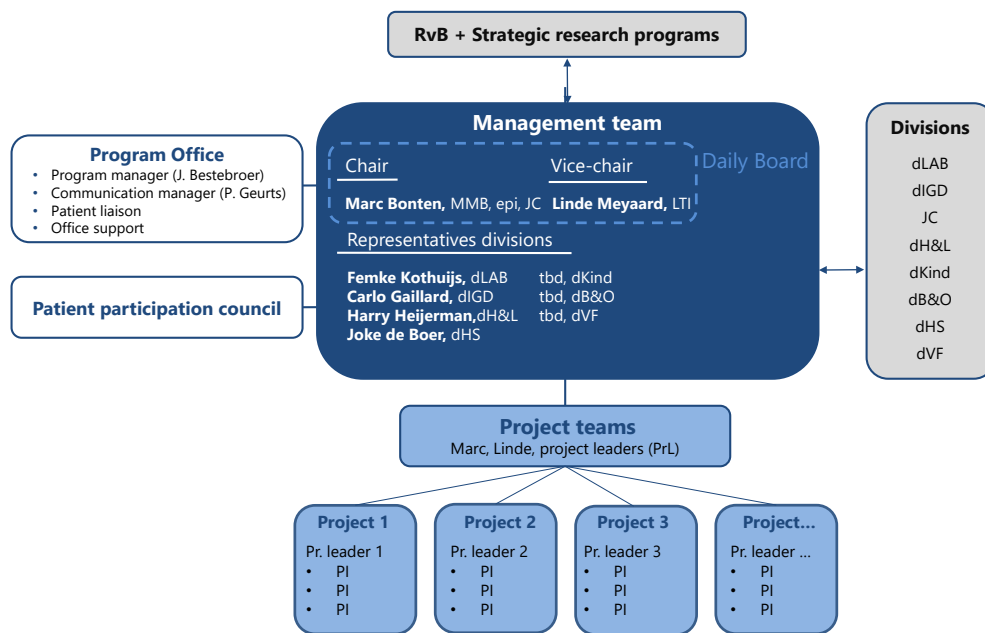


Figure 1. Strategic research program I&I is organized in four closely connected research themes.

1.2 Organisation

The governance of the I&I program is schematically represented in Figure 2.



Projects: I&I cohort, Clinical mycology, Patient participation, ...

Figure 2. Governance of strategic research program I&I.



Program Management Team Infection & Immunity (PMT)

The program is governed by the PMT, chaired by prof. Marc Bonten, who reports to the UMC Utrecht Executive Board. The PMT develops the long-term research strategy and sets annual targets to realize its ambitions. As the resources, such as research staff, clinicians and support staff, are positioned in the divisions (actually in individual departments) the targets need to be agreed (and negotiated) with the Management Teams of the participating divisions. The PMT has an annual budget of around 250K€, to be used for the Program Office and outreach activities. This budget does not allow for strategic funding of research activities. The PMT meets at least 4 times a year; typically every other month.

Daily Board I&I (DB)

For specific tasks within the focus area the Daily Board can appoint Project teams, led by a project leader. Project groups have a defined task to be realized in a defined time period. Examples of such projects include strategy development for an I&I cohort, implementing medical mycology and realizing patient participation.

Program Office

The PMT is supported by a Program Support Office, which consists of at least the program manager and a communication manager.

1.3 Composition

The strategic research program I&I collaborates with eight (out of ten) UMC Utrecht divisions. The research is primarily executed by three large departments, i.e. the Laboratory for Translational Immunology (LTI) and Laboratory of Medical Microbiology (MMB) at dLAB, and Epidemiology of Infectious Diseases (Epi) at dJC, in close collaboration with clinical research groups (dKind, dIGD, dH&L, dHS, dB&O, dVF). Please refer to Table 1 for all research staff for all divisions participating in the four I&I research themes. The program currently holds 37 professor positions (Appendix 1) and had 249 PhD theses in 2013-2018 (list available during site visit).

	FTE	% of div	% of I&I	Preventing AMR	Preventing inflammation	Elucidating host-pathogen interactions	Immune-mediated therapies & prevention
Research divisions							
dLAB, Dept. Medical Microbiology	68	31%	28%	x		x	x
dLAB, Lab. Transl. Immunology					x	x	x
dJC, Epidemiology of inf. diseases	35	28%	14%	x		x	x
Clinical divisions							
dIGD (Internal Med. & Dermat.)	76	55%	31%	x	x		x
dH&L (Heart & Lung)	23	23%	9%	x	x		
dHS (Surgical Specialties)	19	20%	8%		x		
dB&O (Imaging & Oncology)	10	5%	4%	x			x
dVF (Vital Functions)	7	33%	3%	x			
dKind (Pediatrics)	6	18%	3%		x	x	x
Total	244		100				

Table 1. Participating divisions in I&I. Two research and six clinical divisions collaborate in the four I&I research themes. Research staff at program level is provided in full-time equivalents FTE and percentage for different divisions. dLAB: division Laboratory, Pharmacy and Biogenetics; dJC: division Julius Center for Health Sciences and Primary Care. FTE: full time equivalent. % of div: percentage of FTE within a division that is I&I. % of I&I: percentage of FTE of a division within strategic research program I&I.

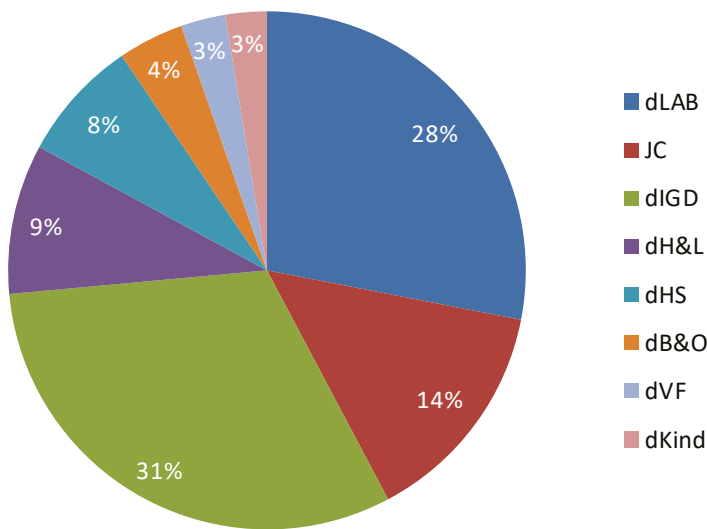


Figure 3. Ratio divisions participating in strategic research program I&I.

The Laboratory of Translational Immunology (LTI) was established in 2013 and integrated 9 separate immunology research groups in the UMC Utrecht. Previously these groups were embedded in different clinical and non-clinical departments and had their own lab facilities. Integration of all immunology labs in the LTI has effectively resulted in (1) implementing key technologies in core facilities, (2) a unified quality control system, (3) close interaction of clinicians and researchers from different divisions in- and outside meetings, and (4) immunology research across different diseases. As of 2019 not all research laboratories could be physically unified and remain somewhat scattered throughout the UMC Utrecht/WKZ, but efficiency and collaboration has immensely increased.

The operational transition from 9 independently operating labs into the LTI has not yet been fully finalized. The ultimate goal is to have all staff (including lab technicians and scientists) appointed at dLAB, and to have clinician-researchers that interact with lab-based LTI researchers appointed at the respective clinical divisions. This model optimizes efficiency, governance and research quality. Currently, technicians and researchers from some research groups are still appointed at their respective clinical division, despite their research projects being fully integrated in the LTI with full access to core facilities. This is managed by annual “bench fee” payments to the LTI by different divisions.

Microbiological research is concentrated in the Department of Medical Microbiology (MMB), where MMB research staff collaborates with clinician-researchers from the clinical divisions and epidemiologists. Epidemiological research (including mathematical modelling, public health, primary care research and biostatistics) is concentrated in the Julius Center for Health Sciences and Primary Care. As in LTI and MMB, epidemiologists collaborate with clinician-researchers from the clinical divisions and lab-based researchers in MMB and LTI.

I&I research is embedded in the larger research theme Utrecht Life Sciences (ULS) of the Utrecht University (UU). The goal of ULS is “to intensify cooperation in the areas of education, research & innovation by providing state of the art shared infrastructures, scouting & educating talented people, creating access to scarce expertise and databases, and increasing access to external grants & funds for its partners.” I&I researchers are active in the research domains “Personalized Medicine & Health”, “One Health” and “Science for Life”. ULS has 67 core research facilities located in close proximity (see <https://www.utrechtlifesciences.nl/facilities>) at the campus. The individual research groups in I&I are well connected to these research facilities and some are located in UMC Utrecht (fig 4).

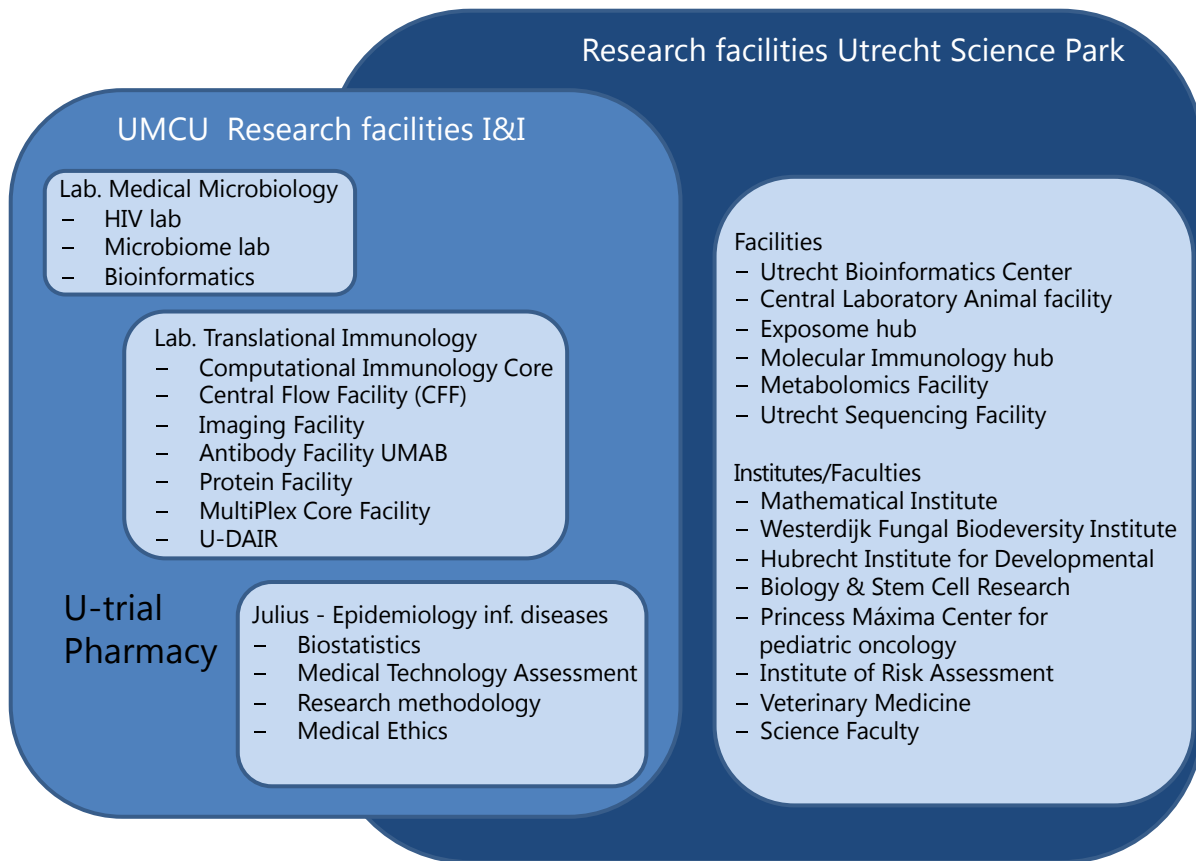


Figure 4. The core research facilities within the research departments of I&I and the connected research facilities at the Utrecht Science Park.

1.4 Funding

	2018	2017	2016	2015	2014	2013
National grants (2)	€ 1,311,570	€ 3,814,841	€ 2,344,361	€ 3,842,218	€ 3,701,705	€ 3,562,295
External grants (3)	€ 17,481,309	€ 12,963,928	€ 6,500,119	€ 16,586,142	€ 11,688,963	€ 14,265,786
Contract research (4)	€ 3,921,197	€ 14,143,464	€ 5,426,932	€ 7,942,817	€ 3,773,936	€ 3,949,428
Total Funding	€ 22,714,076	€ 30,922,233	€ 14,271,412	€ 28,371,177	€ 19,164,604	€ 21,777,509

Table 2. Recruited external funding I&I period 2013-2018. Amounts reflect correction for funding shared with other strategic research programs.

1 Research grants obtained in national scientific competition (e.g. grants from NWO and the Royal Academy);

2 Research grants obtained from external organisations, such as European Commission and charitable organisations;

3 Research contracts obtained from industry.

The recruited external funding of I&I research is depicted in Table 2 and Figure 5a-d. In brief, the average external funding over the past 6 years is 24 M€/year, totaling 145.5M€ (Figure 5a). This makes up 24% of the total external funding of the UMC Utrecht. 19% is shared with strategic research programs Cancer (7%), Child Health (7%) and Regenerative Medicine & Stem Cells (4%) (Table 2 accounts shared funding). The ratio between the divisions that participate in I&I is depicted in Figure 5d; the divisions Laboratories, Pharmacy & Biogenetics (dLAB), Internal Medicine & Dermatology (dIGD) and Julius Centre were responsible for 90% (30% each) of external funding within I&I. Research grants from non-industry organisations, e.g. EU and charity organisations, accounted for 58% of the funding in the last six years (Figure 5b). This was mainly due to IMI projects and EU projects for antibiotic resistance (40M€) and to a lesser extent to several EU projects in the field of immune diseases (6 M€). The largest charity organisations are the Dutch funding organisations ReumaNederland (Dutch Arthritis foundation; 5M€) and KWF (Dutch Cancer Society; 5M€). Funding from industry makes up 28% of the total amount, mainly in the field of chronic immune diseases (dIGD). National governmental funding (NWO/ZonMw) include Veni, Vidi and Vici grants (Table 3 for prestigious personal grants).



Fig. 5a Yearly external funding (146M euro)

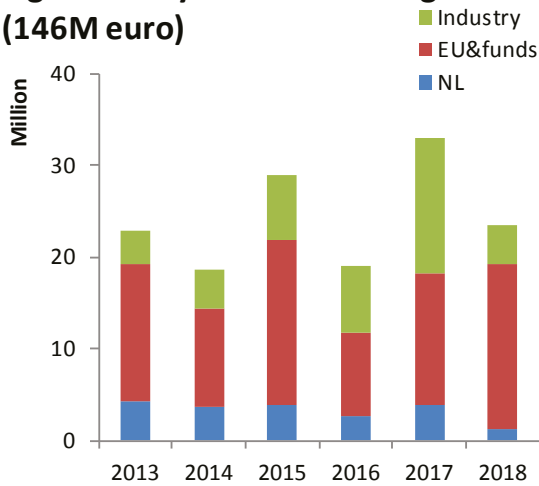


Fig. 5b External funding type 2013-2018

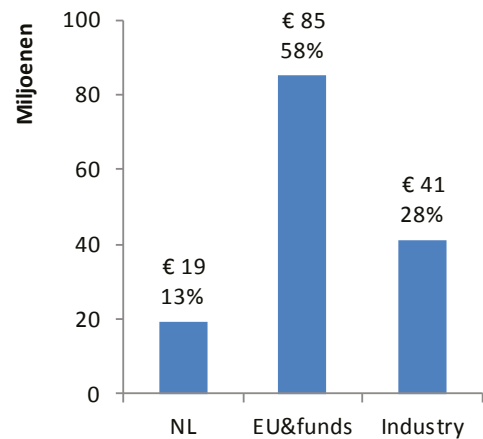


Fig. 5c External funding divisions 2013-2018

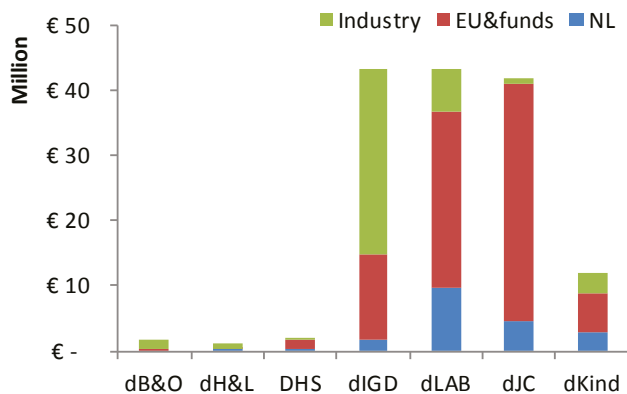


Fig. 5d Ratio external funding 2013-2018

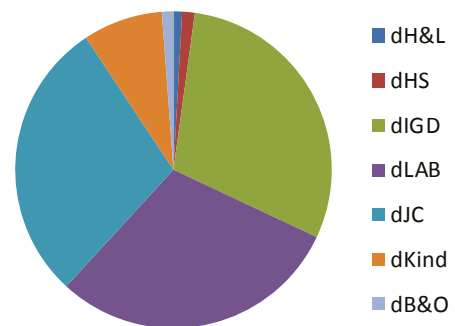


Figure 5. Recruited external funding I&I 2013-2018. NL: Research grants obtained in national scientific competition (e.g. grants from NWO and the Royal Academy); EU&Funds: Research grants obtained from external organisations, such as European Union and charitable organisations; Industry: Research contracts obtained from industry.

Grant	Year	Name
Veni (NWO)	2013	Broen (LTI), Peperzak (LTI), Prado Sanchez (LTI)
	2014	Jongorius, Loosdregt (LTI), van der Vlist (LTI)
	2015	Bruijning-Verhagen, Marut (LTI), van Zoelen (Epi)
	2016	Pandit (LTI)
	2017	Kuiper (LTI), Schipper (LTI), Venekamp (Epi)
	2018	Willemen (LTI)
	Vidi (NWO)	2013
2014		Bogaert (dKind)
Vici (NWO)	2014	Meyaard (LTI)
Marie Curie Fellowship (EC)	2013	Marut (LTI), Rossato (LTI)
ERC Starting Grant (EC)	2015	Rooijackers (MMB)
ERC Proof of Concept Grant (EC)	2015	Radstake (LTI)
Bas Mulder Award (KWF)	2015	Peperzak (LTI)
	2016	Plantinga (LTI)

Table 3. Laureates personal grants I&I period 2013-2018.



1.5 SWOT analysis

Internal organisation	External context
<p>STRENGTHS</p> <ol style="list-style-type: none"> 1. Presence of large UMC Utrecht patient cohorts which allow rapid evaluation of pathogenic mechanisms across multiple (>30) infectious-immune-inflammatory diseases. 2. Multidisciplinary research infrastructure with laboratories organized in core facilities (<i>examples</i> CFF, UDAIR, Bioinformatics, microbiome), successful collaborations between theoretical sciences (mathematicians, theoretical biologists), epidemiologists, (micro) biologists and physicians, and availability of clinical, laboratory and immunology-microbiology databases. 3. Embedding of I&I program in Utrecht Life Science campus (cooperation of I&I program with Faculty of Veterinary Medicine, Faculty of Pharmaceutical Sciences, Science Faculty, KNAW), and access to state-of-the-art facilities at the Utrecht Science Park. 4. Prominent position in national and international research networks such as for clinical research (COMBACTE consortia, RESCUE, PREPARE, R-GNOSIS, EVOTAR, VITAL) and in European Reference Networks (TRANSCHILD, RITA, ReCONNECT; ophthalmology uveitis; ADCARE). 5. Excellent teaching infrastructure with medical and biomedical curricula (master & PhD tracks) with I&I and epidemiology focus. 	<p>OPPORTUNITIES</p> <ol style="list-style-type: none"> 1. High (and rising) prevalence of I&I diseases with large unmet medical need for innovative treatment and prevention. 2. Increasing emphasis on prevention of infections and inflammation, necessitating large-scale clinical studies. 3. Global threat of antimicrobial resistance. 4. Increasing referral of specific patient groups to tertiary centers because of complex diseases and expensive current treatments. 5. Current successful developments in cancer treatment with immunotherapy.
<p>WEAKNESSES</p> <ol style="list-style-type: none"> 1. Physical dispersion of (clinical) immunology research groups throughout UMC Utrecht/WKZ, though with central coordination "LTI". 2. Appointment of LTI scientists at multiple divisions. 3. Limited laboratory space is increasingly prohibitive for hosting/attracting high-quality research groups. 4. Lack of a developed policy of nurturing talent plan (<i>talentbeleid</i>) and declining trend in personal funding for young research staff. 5. Limited possibilities for clinicians to allocate time for research activities. 	<p>THREATS</p> <ol style="list-style-type: none"> 1. Planned (hospital-wide) budget cuts in 2020-2022. 2. Limited budget for the use of expensive biologicals by health insurance companies may increase the costs of care of I&I patients in UMC Utrecht and put research budgets under pressure. 3. Limited public recognition of I&I diseases with absence of major funding institutes. 4. Declining R&D activities in pharmaceutical industry for new antibiotics.

Based on the SWOT analysis we intend to put more emphasis on our "weaknesses" in the coming years. The physical dispersion of research groups cannot be changed in the current setting. Yet, the UMC Utrecht has an ambitious plan to restructure the hospital, which includes a new research and laboratory building. We are confident that this new building, being part of the hospital infrastructure, will allow the integration of all I&I research facilities and will alleviate the currently perceived pressing lack of laboratory space.

We will also strive to realize dedicated research time for young talented and ambitious clinical scientists that can bridge patient-oriented clinical science with laboratory-based science. The first steps towards research time allocation in clinical divisions have been set.

1.6 Evaluation practices and/or policies

Performance and goals

All employees in the UMC Utrecht plan and evaluate their activities with their supervisor in planning and control cycles "Performance & goals".



I&I researchers

I&I does not have specific evaluation practices and/or policies. PIs are indicated by the collaborating departments and divisions, not solely by the strategic research program I&I. Professors and associate professors are regarded as PI but further criteria are typically being a researcher who

- has his/her own research group (including one or more PhD students);
- has his/her own research line;
- has independently acquired one or more research grants;
- has (inter)national recognition for his/her expertise evidenced by invitation for e.g. lectures, reviews.

A list of professors and associates (including clinical) can be found per research theme in Appendix I.

(Associate) professor appointments

As of 2018-2019, the Strategic Research Programs – thus also I&I - are instrumental in appointing new professors (as defined in a 5-year-spanning document that is updated yearly) and associate professors (yearly) in collaboration with the divisions.

Accreditation

ISO 9001: The LTI research laboratories are ISO 9001 accredited. This process-oriented and system-oriented approach forms a solid foundation for continuously maintaining a consistent level of quality. For instance, the lab uses SOPs for all standard procedures, training and qualification of personnel is monitored and equipment is monitored and maintained according to schedules. Improvements are planned, implemented and controlled. The lab is yearly audited and evaluated. The central flow facility of the LTI is ISO 1859 certified, which are standards that allow for diagnostic care.

1.7 Open Science activities

Openness of the research agenda & stakeholder involvement

Twice a year a public lecture is organized by I&I to highlight focus themes to the general public. At a regular base, the research strategy is discussed with representatives of patient organisations through specific research groups to inform and gain from their expertise. Research agenda is further exemplified through lectures and courses to students at bachelor, master and PhD level. Various professionals are involved in a variety of public representation activities, e.g. (social-) media, articles in general public magazines, Open Hospital Days and visits to primary schools (e.g. Meet the Professor). Specific examples are included for each research topic under “research products”.

Our research agenda is regularly discussed with our collaborators, among others:

- Utrecht Science Park: partners within Utrecht Life Sciences (Hubrecht Institute, Westerdijk Institute, Faculty of Veterinary Medicine, Faculty of Beta-Sciences, PMC, Danone, Genmab);
- National: regional and national (academic) hospitals, National Institute for Public Health and the Environment (RIVM), Netherlands Center for One Health, Netherlands Antibiotic Development Platform, funds (e.g. ReumaNederland, Dutch Cancer Foundation, AIDSfonds), Oncode Institute, pharmaceutical and technical companies.

Openness of data and protocols

The general UMC Utrecht SEP report describes the UMC Utrecht policy on Open Science activities. I&I supports these activities and sees high quality data infrastructure as indispensable for research and innovation, which should be embedded centrally. Researchers must be supported to generate standardized and harmonized data to secure quality and reproducibility and in order to increase future societal impact. Therefore, we stimulate:

- science conform FAIR (Findable, Accessible, Interoperable, Re-usable) principles (e.g. all research labs use electronic lab notebooks (iLabber);
- departments have specialists for data management and analysis;
- execution, storage and sharing of human samples according to the Biobank protocol;
- GCP-compliant phase I/II research by a dedicated professional team;
- implementation of trial offices and U-Trial for execution of clinical research (advise, quality control, teaching, monitoring, registration of studies in public database)



I&I-specific examples include

- Online software www.PIRCHE.org for HLA matching in stem cell- and organ transplantation developed by Spierings group (free to use for research, commercial for clinical application);
- National BioDay Registry (www.bioday.nl) for moderate-severe atopic dermatitis patients to follow (for at least 5 years) efficacy, safety, and patient satisfaction of the novel drug dupilumab in daily practice, developed by de Bruin-Weller lab (biomaterials are stored within the UMC Utrecht central biobank).
- After publication of the core genome sequence-based typing method for *Enterococcus faecium* (de Been et al. J Clin Microbiol 2015) by Willems group and the availability of the public repository at <https://www.cgmlst.org/ncs/schema/991893/>, >11.000 strains have been submitted to the database.
- Clinical trials that are instigated are registered on www.clinicaltrials.gov and the results are always published (see research output I&I themes).

Open Access publications

I&I stimulates Open Access publishing. Financial support can be requested from the UMC Utrecht/Utrecht University Open Access Fund (50%; max. € 1000) that partly reimburses article processing charges. This financial support is by far not sufficient to cover the costs of the publications and open science publication imposes a financial problem on the research groups, for which we currently do not have a solution.

1.8 Patient involvement

I&I patient sounding board

The I&I program had a patient liaison (2017-2018) as part of the Support Office who was responsible for patient involvement in the strategic research program I&I (current vacancy will be filled in 2019). A Patient Sounding Board (PSB) was established to take advantage of the unique experience and expertise of patients to enhance the quality of care, research and education within I&I. In addition to patients, health care providers partake in the panel; all from fields of rheumatology, clinical immunology, ophthalmology, E.N.T., gastro-enterology, dermatology, and infectious diseases. The PSB was initially focused on advise for the then-to-be-established Centre for Immune Diseases but has since also been contacted for input for research projects (e.g. Immunity out of balance - on molecular classification of immune diseases), the I&I cohort (e.g. patient information form to participate in this research), evaluation of multidisciplinary care, improving availability of information about scientific research, and image representation of 'patients with immune diseases' (e.g. information movie).

Several departments and divisions collaborating within I&I have specific patient participation programs (e.g. dIGD on rheuma and arthritis) and strong relationships with several external patient organisations. A number of specific patient involvement initiatives are exemplified in the 'patient involvement' sections of the 4 research themes.

1.9 Teaching

The Utrecht Graduate School of Life Sciences (GSLs) combines training and education for Master's students and PhD candidates, thus incorporating theory and practice at both levels and allowing overall quality control and consistency. Our students participate largely in MSc and PhD programs of I&I and Epidemiology.

The master's program I&I is one of the 16 in this school and selects every year 30 students for the 2 years research master (60 students in total). Key component of this biomedical master are 1) a 9 months hands-on internship, which trains future scientists and 2) 10 weeks of theoretical training in different disciplines within I&I. Upon graduation, two thirds of the students have already found a job, which increases to 90-95% after six months. 80% of the students choose for a PhD position in the Netherlands or at prestigious international institutes (e.g., Stanford, Rockefeller, Karolinska Institute, Imperial College). The remainder pursue for a career in consultancy, biotech companies, teaching or as CRA. Additionally, several modules for Infectious Disease epidemiology, including mathematical modeling are offered within the master's program Epidemiology.

The PhD program I&I is the second largest out of 14 programs in the GSLs enrolling 180 PhD candidates in Infection and Immunity. Around 68% of these PhD students are within the UMC Utrecht. Both PhD and Master program are chaired by the scientific director Prof. van Strijp. Student representatives participate in the Board of both the master's and PhD programs. Both programs have a shared website enabling selection of internships for master students.



The MSc and PhD Epidemiology programs are also part of GSLS and are organized by the following faculties and institutes: Julius Center for Health Sciences and Primary Care, Faculty of Veterinary Medicine, Faculty of Science, Department of Pharmaceutical Sciences, Division of Pharmacoepidemiology and Pharmacotherapy, and Institute for Risk Assessment Sciences, Division Environmental Epidemiology. The Master's program provides students with extensive knowledge and practical skills in patient-oriented research design, implementation, quantitative analysis and its application to clinical medicine and public health. The post-graduate master is mostly followed by PhD candidates, but there is also a PhD program Epidemiology. The PhD program is aimed at optimal preparation of PhD fellows to become independent researchers, research consultants, or continue their career at an academic level in (non)governmental institutions or the pharmaceutical industry. The Master's and PhD program are both accredited by the Dutch Epidemiology association as leading to a registration as an Epidemiologist.

Through participation in the Utrecht Life Sciences, the I&I program has access to many high-tech shared facilities, shared PhD training courses and educational programs, such as the 'Infection meets Immunity' Summer School, and shared meetings. Thus, the I&I educational program has a strong embedding in the Utrecht Science Park.



2. Research theme: preventing antimicrobial resistance

2.1 Mission, urgency and/or relevance of the research questions

Antimicrobial resistance is considered a major global healthcare threat. The remarkable increase in antibiotic resistance results from complex dynamics driven by antibiotic use (in humans and agriculture), failing transmission control, travel of humans, transport of animals, interspecies transmission, and more. Historically, the Netherlands have managed to maintain low prevalence of antibiotic resistance among human bacterial pathogens, despite the direct presence of extensive agricultural industry with intensive antibiotic use and high prevalence of resistant bacteria among animals. As antibiotics are used in humans and animals and disperse across species and into the environment, antibiotic resistance is a typical “one health” issue.

The focus of research activities in this theme during 2013-2018 were:

- to quantify and understand the relationship between antibiotic use and antibiotic resistance in and in-between humans and animals;
- to determine the population structure and evolution of multidrug-resistant opportunistic pathogens in humans and animals;
- to develop and scientifically evaluate infection prevention measures in hospitalized patients and community-dwelling subjects;
- to optimize diagnosis and treatment of infections, in order to minimize unnecessary antibiotic use in hospitals and in primary care;
- to better understand infection pathogenesis among those patients experiencing the highest burden of antibiotic selective pressure, i.e., intensive care unit patients;
- to develop tools and to quantify the burden of antimicrobial resistance;
- to develop an European-wide clinical research infrastructure to increase efficiency of clinical evaluation of new antimicrobial therapies.

2.2 Relation to existing knowledge

Antibiotic resistance has been recognized as a global health threat by the United Nations, the WHO, the G7, G20 and many more international organisations. As such our research questions fit in the current existing knowledge. Here, we list some initiatives to demonstrate how UMC Utrecht interacts nationally and internationally to execute different parts of the research agenda.

MARS cohort

In MARS (Molecular diagnosis and risk stratification of sepsis) all clinical data of ICU patients are (automatically) collected in a data warehouse on a daily basis (since 2011 in UMC Utrecht and 2011-2014 also in Amsterdam UMC). Each day, presence of infection is registered and left-over blood samples are biobanked. The cohort currently contains more than 14,000 patients (40% with sepsis) and more than 400,000 stored blood samples. With these data different aspects of sepsis and infections are studied. Since 2012, the MARS cohort has yielded >55 scientific peer-reviewed publications (Nature Imm, JAMA, Lancet, BMJ, Blood, PLoS Med, AJRCCM, CID, ICM, CCM) and 9 PhD thesis.

Netherlands Center for One Health (NCOH)

In 2016 UMC Utrecht was founding partner of the Netherlands Center for One Health (NCOH) and took leadership for the research theme “tackling AMR”. For this theme a scientific research agenda (SRA) was developed, defining 6 solution sets, supported by epidemiological and ecological research. All UMC Utrecht research subthemes mentioned in section 2.1 fit within the NCOH Solution Sets for AMR:



Problem chain and accompanying Solution Sets

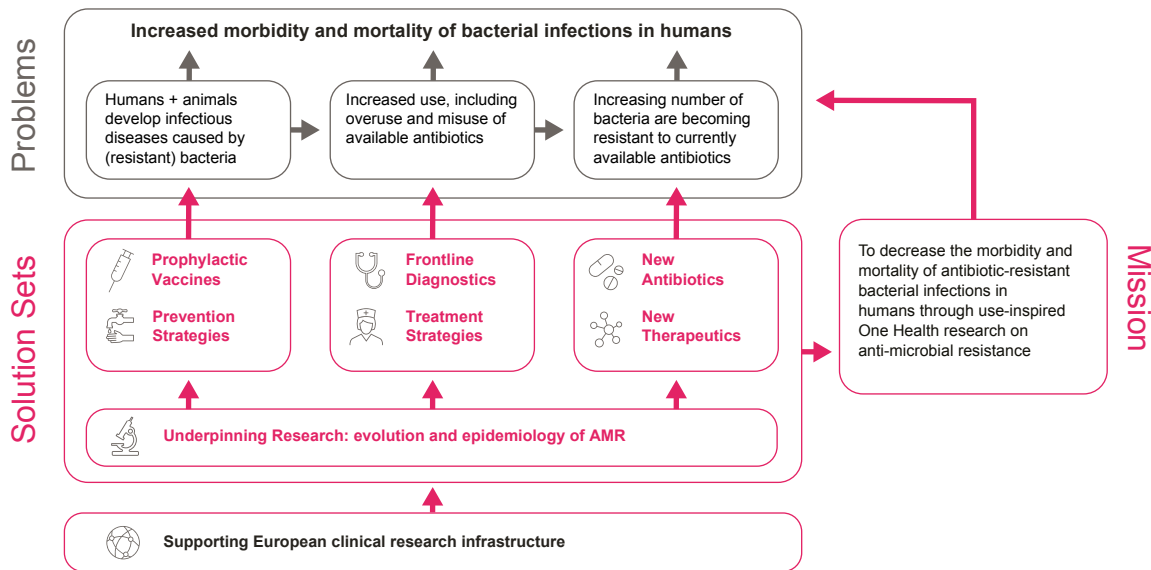


Figure 6. Problem chain and solution sets of NCOH-AMR.

European networks

UMC Utrecht coordinates four projects (COMBACTE-NET, COMBACTE-CARE, COMBACTE-MAGNET, COMBACTE-CDI) in the New Drugs for Bad Bugs (ND4BB) program of the Innovative Medicine Initiative (IMI). The major aim is to develop a European-wide clinical research infrastructure to optimize clinical evaluation of new antibacterial agents. COMBACTE stands for Combatting Antibiotic resistance in Europe (see www.combacte.com). Total budgets for the 4 COMBACTE projects are €214M for NET, €83M for CARE, €167M for MAGNET and €4,6M for CDI.

UMC Utrecht is also partner in PREPARE (Platform for European Preparedness Against (Re-)emerging Epidemics), an EU-funded network for harmonized large-scale clinical research studies on infectious diseases, prepared to rapidly respond to any severe ID outbreak, providing real-time evidence for clinical management of patients and for informing public health responses. For clinical studies in PREPARE, the trial infrastructure created in COMBACTE is used.

UMC Utrecht acquired HORIZON2020 funding to develop a business plan to sustain the network activities established in COMBACTE and PREPARE after the funding period (named ECRAID Plan, 2019-2020, 3M€), and leads an international consortium to apply for funding for an international clinical trial network based on the result of ECRAID Plan, to start in 2021. ECRAID stands for European Clinical Research Alliance on Infectious Diseases.

During the years 2013-2018 UMC Utrecht also coordinated the following EU-funded consortia:

- EVOTAR (Evolution and Transfer of Antibiotic Resistance; 2011-2015, 12M€);
- R-GNOSIS (Resistance in Gram-Negative Organisms: Studying Intervention Strategies; 2011-2017, 12M€);
- STARCS (Selection and Transmission of Antimicrobial Resistance in Complex Systems; 2017; JPIAMR);

and was partner in:

- SATURN (studying the impact of Specific Antibiotic Therapies on the prevalence of hUman host ResistaNt bacteria, EU 7th Framework Programme, 2010-2015);
- MODERN (Understanding and modelling reservoirs, vehicles and transmission of ESBL-producing Enterobacteriaceae in the community and long term care facilities; JPIAMR, 2017-2020).

2.3 Collaborations with stakeholders

Research collaborations are mainly with national and international peers, and national and international funding was acquired through responding to research questions derived from national and international research agendas. The IMI-funded consortia involve collaborations with 10 private partners (all from EFPIA) and 57 public partners in 14 European countries.



As most clinical research questions address acute infections, patient representatives are not that easy to identify. This is a recognized gap and we have started to organize patient involvement for our research activities in 2018. UMC Utrecht has acted, unofficially, as national reference center for vancomycin-resistant enterococci (VRE) between 2011-2018; in all 45 hospitals submitted 919 VRE isolates for genotyping.

The MARS data warehouse and biobank (section 2.2) is increasingly used to develop and validate new biomarkers and molecular technologies for early diagnosis and prognostication of critically ill patients with sepsis and/or inflammation. Many of these projects are conducted together with biotech companies (Dutch as well as international). In addition, the MARS framework supports the conduct of several EU- and/or industry sponsored trials.

2.4 Research design

Almost all research activities in the theme “Preventing AMR” are executed by collaborations between researchers of the departments of Medical Microbiology and/or infectious disease epidemiology together with clinicians from clinical departments.

Clinical research activities are fully embedded within the strategic research program infectious disease epidemiology to optimize and innovate study designs and data analysis. All PhD students with clinical research topics do a master Epidemiology during their PhD training (complementary).

All PhD students with microbiological research topics are part of the Infection & Immunity PhD program of the Utrecht Graduate School of Life Sciences. All PhD students have a daily supervisor and weekly meetings with the larger research group.

Statistical and methodological support is provided by the strategic research program infectious disease epidemiology, the strategic research program “methods of epidemiology at the Julius Center for Health Sciences and Primary Care” and the bioinformatics group within the microbiome hub (Department of Medical Microbiology).

2.5 The next steps

Here we report on the plans we have with the larger initiatives in this research theme:

European clinical research network

UMC Utrecht acquired H2020 funding to develop a business plan to sustain the network activities established in COMBACTE and PREPARE after the funding period (named ECRAID Plan, 2019-2020), and leads an international consortium to apply for funding for an international clinical trial network based on the result of ECRAID Plan, to start in 2021. The aimed next step, therefore, is the establishment of a new legal entity, coordinated through UMC Utrecht, for a European clinical trial network to improve efficiency of clinical trials related to prevention, diagnosis and treatment of acute, chronic and emerging infections.

MARS cohort

In sepsis research, to derive causal inference from observational data several advanced statistical modeling methodologies have been used, including structural equation models and multistate marginal structural models. In the coming years, these methods will be further refined and extended in close collaboration with the UU Department of Mathematics as well as PacMed, an Amsterdam-based health data analytics company. Over the next 4 years, we will enroll a total of 1800-2000 patients who are scheduled for elective high-risk surgery in the UMC Utrecht into a comprehensive, prospective cohort study. To this aim, blood and microbiological samples will be collected before and during surgery, allowing for post-hoc studies aimed at improved perioperative risk assessment.



Global health

Our own studies have provided the evidence that the burden of antibiotic resistance currently is – at most – modest in the Netherlands. This is in sharp contrast to the current situation in Low and Middle Income Countries (LMIC). Many practices successfully implemented in the Netherlands might also be beneficial for patients in LMIC, but our collaborations up till now have had a strong focus on the Netherlands and Europe. UMC Utrecht does not have a history of collaborations with LMIC with regard to antibiotic resistance research. In 2019/20 we will need to make a strategic decision whether to shift focus to LMIC, which would require either external start-up budget or reallocation of internal research funding.

2.6 Results highlights

2.6.1. Research products for peers

Cohorts, infrastructure

- COMBACTE (section 2.2)
- NCOH (section 2.2)
- MARS cohort (section 2.2)
- Dutch national Q fever database
- i-4-1-health project (One Health project on control of AMR in the Netherlands and Belgium)

Clinical trials

Several large and innovative investigator-initiated randomized clinical trials, both national and international, have been designed, managed and executed within this research theme:

- Acute otorrhea study in children (van Dongen et al. N Engl J Med 2014)
- MOSAR-ICU study (Derde et al. Lancet Infect Dis. 2014)
- SDD-SOD study (Oostdijk et al. JAMA. 2014)
- CAPITA study (Bonten et al. N Engl J Med. 2015)
- CAP START study (Postma et al. N Engl J Med. 2015)
- SATURN-ICU study (van Duijn et al. Lancet Infect Dis. 2018)
- R-GNOSIS study (Wittekamp et al. JAMA. 2018)

Each of these studies provided essential new information for national and international guidelines and databases are available upon request for additional analyses.

Assays, methods, models

- Willems' group developed mlplasmids (<https://gitlab.com/sirarredondo/mlplasmids>), a collection of machine learning classifiers that predict DNA sequences as chromosome or plasmid-derived (2018)
- Willems' group developed a core genome sequence-based typing method for *Enterococcus faecium*. This method is available through a public repository (<https://www.cgmlst.org/ncs/schema/991893/>).

Publications, theses

The principle researchers in this theme published >470 publications (Scopus) and 42 PhD theses in 2013-2018.

2.6.2. Research products for societal target groups

Policy

- Bonten and Verheij acted as scientific advisor for RIVM (National Institute for Health and the Environment) and contributed to the current national program of surveillance of antibiotic resistance and on Antimicrobial Stewardship in the Netherlands.
- Bonten and Kluytmans acted as advisors on infection control and antibiotic resistance for the Ministry of Health.
- Kretzschmar developed a software tool BCoDE-toolkit developed for public health policy makers in collaboration with ECDC, and software tool EUFRAT to quantify the risk of transmission of infectious diseases via blood donations in collaboration with ECDC.



Outreach

- Bonten regularly blogs on topics related to infection prevention and AMR on the international blogsite (<https://reflectionsipc.com>), which has 14.000 visits per month.
- Schürch is a Carpentries instructor, trainer and maintainer of the Data Carpentry Genomics Shell lesson. Software and Data Carpentry (The Carpentries) are volunteer organisations whose members teach foundational computational and data skills to researchers. All Carpentries' lessons are open source, with an open contribution model, and lessons are collaboratively created and maintained by volunteers. Schürch has instructed 7 two-days-workshops (of which 4 as lead instructor) and 4 instructor trainings to prepare people to teach as Software and Data Carpentry instructors. This was instrumental in building the Carpentries community in the Netherlands and in Europe.
- The department MMB organized (between 2013 and 2018) 14 one to 3-day international symposia in Utrecht with international faculty. Attendance ranged from 75 to 200 persons.

2.6.3. Use of research products by peers

Infrastructure

- MARS infrastructure has been successfully used to develop and validate multiple diagnostic biomarkers for patients with suspected sepsis (including the FAIM3/PLAC8-ratio, sNIP-score, and SeptiCyte LAB) as well as novel molecular methods for rapid pathogen detection (including multiplex PCR on whole blood).

Databases, tools

- mlplasmids, developed by Willems group, are machine-learning classifiers that predict DNA sequences as chromosome or plasmid-derived and have been warmly welcome and is widely used by the community. The publication for mlplasmids (2018) has an altimetric score of 40, the webserver of mlplasmids is frequently visited.
- After publication of the core genome sequence-based typing method for *Enterococcus faecium* by Willems' group (de Been et al. J Clin Microbiol 2015) and the availability of the public repository at <https://www.cgmlst.org/ncs/schema/991893/>, >11.000 strains have been submitted to the database coming from various groups from all over the world.
- Van Mourik has pioneered the use of electronic patient databases for semi-automated surveillance of hospital-acquired infections. This approach reduces subjective interpretation, inter-observer variability and workload, and is now adopted by others both nationally and internationally. Van Mourik is, despite her young age, considered an international expert, regularly receiving invitations for international meetings and she is leading a European task group to develop guidelines for implementing (semi-)automated surveillance of hospital-acquired infections (PRAISE; Providing a Roadmap for Automated Infection Surveillance in Europe, funded through JPIAMR).
- The software tool BCoDE toolkit (Kretzschmar group) has been used multiple times in different countries for estimating disease burden (Colzani et al. PLoS One. 2017, Cassani et al., Lancet ID 2019).

Courses

- Ekkelenkamp organizes a 3-day "antibiotic course" that is attended by 60 participants, mainly residents in internal medicine and clinical microbiology. The first course was in 2014, and runs with 3-4 courses per year. The course has a clinical focus but naturally includes the most recent relevant research findings from our teams. There is currently a 2-year waiting list for course attendance.
- Kluytmans and van Mourik organize the EUCIC (European Committee on Infection Control, part of ESCMID), 3-day advanced module for Epidemiology and Data Analyses in Infection Control.

2.6.4. Use of research products by societal groups

- Studies initiated and led by UMC Utrecht have changed the national and international guidelines (see 2.6.1) for treatment of patients in Intensive Care Units (ICU) (Oostdijk et al. JAMA 2014; Plantinga et al. CMI 2018), for treatment of patients hospitalized with community-acquired pneumonia (Postma et al. NEJM 2014) and with otitis media acuta (van Dongen et al. Pediatrics. 2015), for infection control strategies in hospital settings, including isolation strategies for AMR carriers and pre-operative decolonisation of *S. aureus* carriage to prevent surgical site infections.
- SeptiCyte™ LAB (Immunexpress, Seattle, WA) was validated on MARS data and represents the first (and only) gene expression assay that is cleared by the FDA in the United States to distinguish infectious from non-infectious causes of systemic inflammation in critically ill patients.
- A novel multiplex real-time PCR assay enabling detection of microbial DNA directly in whole blood was developed by Microbiome (Amsterdam) as part of the MARS project. Technical validation and clinical performance studies of this test in preparation of its bedside implementation on the Idylla platform (owned by Biocartis, Mechelen) were performed in the MARS cohort.



2.6.5. Marks of recognition from peers

Awards, personal grants

- Bonten received the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2015 Award for Excellence in Clinical Microbiology and Infectious Diseases .
- Bonten received an honorary fellowship of the Royal College of Physicians of Ireland (2017).
- Bonten was the DGHM (“Deutsche Gesellschaft für Hygiene und Mikrobiologie”) Lecturer 2018.
- Bonten served on the SEP committee of the Academic Medical Center Amsterdam in 2017.
- Verheij is visiting professor at the University of Southampton, UK.
- The intensive care department has been internationally recognized as a center of excellence in sepsis care and as such has been selected to host ESICM fellows each year as well as organize several ISICEM/ESICM masterclasses on infectious disease management in the ICU.

Board participation

- Bonten, Kluytmans, Willems, Kretzschmar and Cremer/Derde/de Lange (Sepsis & Inflammation research group) have been invited frequently as faculty members (including keynote lectures) by major international meetings, such as the European Society of Intensive Care Medicine (ESICM), ESCMID, Epidemics, ID-week, ASMicrobe.
- Willems was elected chair of the division of molecular typing of the Royal Netherlands Society for Microbiology in 2017.
- Kretzschmar is member of PLoS Medicine editorial board since 2014.
- Bonten (2016-2019) and Rooijackers (>2019) are board members of the Netherlands Antibiotic Development Platform (NADP), founded by the Ministry of Public Health, Welfare, and Sport and the Top Sector Life Sciences & Health. The mission of NADP is to bring companies and research groups together to accelerate research into the development of new antibiotics and alternatives to antibiotics.

2.6.6. Marks of recognition from societal groups

- Theo Verheij is member of the advisory group Public Health of the Dutch Health Council and member of the Supervisory board of IZER, a large cooperation of general practitioners in Rotterdam.
- Venekamp was a member of the Board of Directors of the International Society of Otitis Media and served as expert referee ‘High-quality and reliable diagnostic, treatment and rehabilitation’ call of the Research Council Norway.
- Kretzschmar was Chief Science Officer for Mathematical Disease Modelling at RIVM, where she contributed to the communication of scientific results to policy makers in public health.

2.7 Two examples of patient involvement

- Cremer closely collaborates with members of IC Connect (the primary organisation of former ICU patients and their relatives in the Netherlands) and the Dutch foundation for Family and Patient Centered Intensive Care as part of an R&D program that aims to develop low-anticoagulant heparin as a novel therapy to reduce histone-mediated organ injury in sepsis patients. To this end, the chairperson of IC Connect has already provided valuable input during the preparation phase of a recent ZonMw grant application. Furthermore, a representative (i.e., former sepsis patient) has agreed to attend investigator meetings if issues of patient recruitment are to be discussed and will co-author all patient information materials that are to be drafted for a planned clinical phase I/IIa study with this new drug.
- For the ongoing ZonMw-funded trial comparing the effectiveness of oral and topical antibiotics in children with acute otitis media and ear discharge due to a spontaneous perforation of the tympanic membrane, Venekamp and Verheij brought together a panel of eight parents. They helped shape the application during a focus group meeting. The parent panel is involved throughout all phases of the trial; they work with us throughout the research, e.g. on patient information, recruitment issues and reporting of trial results, and will be key to pull the evidence into mainstream practice.



2.8 Ten most important scientific publications

1. Postma DF, van Werkhoven CH, van Elden LJ, Thijsen SF, Hoepelman AI, Kluytmans JA, Boersma WG, Compajen CJ, van der Wall E, Prins JM, Oosterheert JJ, Bonten MJ; CAP-START Study Group. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med*. 2015 Apr 2;372(14):1312-23.
This UMC Utrecht-funded multicenter study used an innovative cluster-randomized cross-over design to demonstrate the non-inferiority of a strategy of empiric therapy with narrow-spectrum antibiotics, compared to 2 strategies with broad-spectrum antibiotics, in 2,283 patients hospitalized with community-acquired pneumonia.
2. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, van Werkhoven CH, van Deursen AM, Sanders EA, Verheij TJ, Patton M, McDonough A, Moradoghli-Haftvani A, Smith H, Mellelieu T, Pride MW, Crowther G, Schmoelle-Thoma B, Scott DA, Jansen KU, Lobatto R, Oosterman B, Visser N, Caspers E, Smorenburg A, Emini EA, Gruber WC, Grobbee DE. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med*. 2015 Mar 19;372(12):1114-25.
In this investigator-initiated randomized placebo-controlled double-blind trial we enrolled 84,496 healthy subjects in the Netherlands to accurately determine the vaccine effectiveness of the 13-valent pneumococcal conjugate-vaccine against pneumococcal pneumonia and invasive disease. The results have been used worldwide by public health authorities in designing national immunisation programs for elderly.
3. Van Dongen TM, van der Heijden GJ, Venekamp RP, Rovers MM, Schilder AG. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *N Engl J Med* 2014;370(8):723-33.
This ZonMw-funded trial conducted by our research group demonstrates that topical antibiotics are more effective than oral antibiotics and initial observation in children with tympanostomy tubes who develop acute ear discharge. These findings have informed the relevant primary care guideline recommends general practitioners to prescribe topical antibiotics to children with tympanostomy tubes who develop acute ear discharge as new standard of care.
4. Oostdijk EAN, Kesecioglu J, Schultz MJ, Visser CE, de Jonge E, van Essen EHR, Bernards AT, Purmer I, Brimicombe R, Bergmans D, van Tiel F, Bosch FH, Mascini E, van Griethuysen A, Bindels A, Jansz A, van Steveninck FAL, van der Zwet WC, Fijen JW, Thijsen S, de Jong R, Oudbier J, Raben A, van der Vorm E, Koeman M, Rothbarth P, Rijkeboer A, Gruteke P, Hart H, Peerbooms P, Winsser LJ, van Elsacker-Niele AW, Demmendaal K, Brandenburg A, de Smet AMGA, Bonten MJM. Notice of Retraction and Replacement: Oostdijk et al. Effects of Decontamination of the Oropharynx and Intestinal Tract on Antibiotic Resistance in ICUs: A Randomized Clinical Trial. *JAMA*. 2014;312(14):1429-1437. *JAMA*. 2017 Apr 18;317(15):1583-1584.
In this cluster-randomized cross-over study, executed in 16 Dutch ICUs and 12,000 patients, Selective Digestive Decontamination (SDD) appeared to better prevent day-28 and hospital mortality than Selective Oropharyngeal Decontamination (SOD). Until this study, both interventions were considered equally beneficial. Based on this study, SDD is now recommended for all ICU patients with an expected ICU-stay of at least 48 hours in Dutch guidelines and has been implemented in almost all Dutch ICUs.
5. Wittekamp BH, Plantinga NL, Cooper BS, Lopez-Contreras J, Coll P, Mancebo J, Wise MP, Morgan MPG, Depuydt P, Boelens J, Dugernier T, Verbelen V, Jorens PG, Verbrugghe W, Malhotra-Kumar S, Damas P, Meex C, Leleu K, van den Abeele AM, Gomes Pimenta de Matos AF, Fernández Méndez S, Vergara Gomez A, Tomic V, Sifrer F, Villarreal Tello E, Ruiz Ramos J, Aragao I, Santos C, Sperring RHM, Coppadoro P, Nardi G, Brun-Buisson C, Bonten MJM. Decontamination Strategies and Bloodstream Infections With Antibiotic-Resistant Microorganisms in Ventilated Patients: A Randomized Clinical Trial. *JAMA*. 2018 Nov 27;320(20):2087-2098.
In this cluster-randomized cross-over trial, executed in 13 ICUs in 6 EU countries and 9,000 patients, we investigated whether SDD and SOD were also effective in reducing ICU-acquired bacteremia and hospital mortality in settings with higher prevalence levels of antibiotic resistance than Dutch ICUs. This appeared not the case.
6. Derde LPG, Cooper BS, Goossens H, Malhotra-Kumar S, Willems RJL, Gniadkowski M, Hryniewicz W, Empel J, Dautzenberg MJD, Annane D, Aragão I, Chalfine A, Dumpis U, Esteves F, Giamarellou H, Muzlovic I, Nardi G, Petrikos GL, Tomic V, Martí AT, Ståmmet P, Brun-Buisson C, Bonten MJM; MOSAR WP3 Study Team. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. *Lancet Infect Dis*. 2014 Jan;14(1):31-39.



In this interrupted time series study and cluster randomised trial, executed in 3 ICUs in 7 EU countries and 14,000 patients we demonstrated that implementation of WHO hand hygiene protocol and universal body washing were associated with lower acquisition rates of AMR bacteria (especially MRSA) and that addition of screening and isolation of carriers of AMR bacteria at the time of ICU-admission did not further reduce acquisition rates.

7. van Duijn PJ, Verbrugghe W, Jorens PG, Spöhr F, Schedler D, Deja M, Rothbart A, Annane D, Lawrence C, Nguyen Van JC, Misset B, Jereb M, Seme K, Šifrer F, Tomić V, Estevez F, Carneiro J, Harbarth S, Eijkemans MJC, Bonten M; SATURN consortium. The effects of antibiotic cycling and mixing on antibiotic resistance in intensive care units: a cluster-randomised crossover trial. *Lancet Infect Dis.* 2018 Apr;18(4):401-409.
In this cluster-randomized cross-over trial, executed in 8 ICUs in 4 EU countries and 9,000 patients, we investigated whether antibiotic cycling and antibiotic mixing differently affected the unit-wide prevalence of AMR carriage. This appeared not the case.
8. de Been M, Lanza VF, de Toro M, Scharringa J, Dohmen W, Du Y, Hu J, Lei Y, Li N, Tooming-Klunderud A, Heederik DJ, Fluit AC, Bonten MJ, Willems RJ, de la Cruz F, van Schaik W. Dissemination of cephalosporin resistance genes between *Escherichia coli* strains from farm animals and humans by specific plasmid lineages. *PLoS Genet.* 2014 Dec 18;10(12):e1004776.
The intestinal tract of poultry is an important reservoir for drug-resistant *Escherichia coli*. Previous studies, using low-resolution genetic typing methods, found that resistant *E. coli* from humans and poultry were indistinguishable from each other, suggesting dissemination of these bacteria through the food-chain to humans. By applying whole-genome sequencing methods, we did not find evidence for such transmission in this study. Instead, we discovered, for the first time, that genetically unrelated *E. coli* from humans and animals carried nearly identical plasmids that encode third-generation cephalosporin resistance determinants, suggesting dissemination of these determinants mainly via the transfer of mobile genetic elements.
9. Klein Klouwenberg PM, van Mourik MS, Ong DS, Horn J, Schultz MJ, Cremer OL, Bonten MJ; MARS Consortium. Electronic implementation of a novel surveillance paradigm for ventilator-associated events. Feasibility and validation. *Am J Respir Crit Care Med.* 2014 Apr 15;189(8):947-55.
Using the existing infrastructure of the MARS database we could immediately validate a newly introduced – by CDC – electronic surveillance paradigm for ventilator-associated events (VAE). Our analysis demonstrated that concordance between the novel VAE algorithm and ventilator-associated pneumonia was poor. Incidence and associated mortality of VAE were susceptible to small differences in electronic implementation. It was concluded that more studies were needed to characterize the clinical entities underlying VAE and to ensure comparability of rates from different institutions.
10. Cassini A, Colzani E, Pini A, Mangen MJ, Plass D, McDonald SA, Maringhini G, van Lier A, Haagsma JA, Havelaar AH, Kramarz P, Kretzschmar ME, On Behalf Of The BCoDE Consortium. Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. *Euro Surveill.* 2018 Apr;23(16).
This publication was the final result of a European consortium to develop methodology for estimation of disease burden for infectious diseases and to provide these estimates for many infectious diseases in Europe. The project delivered a software tool that can be used by policy makers for disease burden estimation. The project has led to many spin-off projects related to disease burden, such as the disease burden prevented by vaccination by the national immunisation program in the Netherlands and of AMR in Europe (both published in *Lancet Infect Dis*).



2.9 Two most important societal contributions

The better understanding of the dynamics of antibiotic resistance

The remarkable increase in antibiotic resistance results from complex dynamics driven by antibiotic use (in humans and agriculture), failing transmission control, travel of humans and transport of animals, interspecies transmission, and more. UMC Utrecht has provided important insights on several aspects related to this complexity. The Willems group initially focused on multi-drug resistance enterococci (MDRE), following the global emergence of vancomycin-resistant enterococci (VRE). His group developed several new typing schemes for tracking transmission of MDRE that have been implemented worldwide, and has established and curate international databases for sequence-based typing results that is used by researchers from literally all over the world (Europe, USA, Australia, Asia, South-America). In the Netherlands his group has acted, unofficially, as reference center for VRE, which has helped multiple Dutch hospitals in controlling VRE outbreaks. Studies into the population structure of *E. faecium* revealed the existence of a genetic subpopulation responsible for the vast majority of reported clinical infections and hospital outbreaks globally. The identification of this specific clinically relevant subpopulation has helped hospitals to better control outbreaks with VRE. Gradually the research activities focused on the question to what extent the high prevalence of AMR bacteria in agriculture in the Netherlands, most notably VRE, MRSA and ESBL-producing Enterobacterales, represented a health threat for humans in the Netherlands. The short answer to this question is NO for all three bacteria. The dominant lineage of *E. faecium* important for human infections is different from enterococci in detected animals and even the plasmids carrying the vancomycin resistance genes had host-specificity, suggesting the existence of distinct ecological niches. The typical animal-associated MRSA (clonal lineage ST398, clearly distinct from the well-known MRSA clones associated with human disease) is not a good colonizer in humans, is not transmitted efficiently between humans and is hardly ever causing hospital outbreaks. And also for ESBL-producing Enterobacterales our studies have provided clear evidence for distinct population structures in men and animals, although the studies on cross-species transfer of plasmids are currently executed. Furthermore, we also demonstrated how excretion of AMR genes from our hospital into the sewage system, was effectively diluted and cleared in waste water plants, yielding non-detectable levels of resistance genes when waste water left the waste water plant and entered open surface waters. At the patient site, we have quantified the disease burden caused by AMR in Dutch patients and concluded that – currently – it is highly unlikely that AMR is creating significant disease burden in the Netherlands. The insights derived from the molecular studies are combined with the results from our epidemiological studies in mathematical models that have helped us in better understanding the dynamics and to better predict the potential effectiveness of interventions. To summarize, our studies have demonstrated that – in contrast to ruling opinions – the current epidemiology of AMR in the Netherlands is dynamically stable and is not critically influenced by the presence of AMR in the animal reservoir.

Establishment of a European clinical trial network for infectious diseases

Clinical studies, such as observational studies and randomized trials, remain the best method to provide solid scientific evidence for medical care. Within this research theme considerable expertise and capacity has been built to design and successfully execute challenging clinical studies for the prevention and treatment of infectious diseases. Some of these could be considered as landmark studies, such as;

- The CAPiTA study (Bonten et al. NEJM 2015), a randomized placebo-controlled double-blind trial with 84,496 healthy subjects in the Netherlands that were recruited through >2,000 GPs. In this study we determined vaccine effectiveness of the 13-valent pneumococcal conjugate-vaccine against pneumococcal pneumonia and invasive disease, with endpoint detection in 47 hospitals across the country during a 4 year follow-up;
- Five cluster-randomized cross-over studies in ICUs testing several infection control strategies (published in NEJM (de Smet et al. 2009), JAMA (Oostdijk et al. 2014; Wittekamp et al. 2018) and Lancet Infectious Diseases (Derde et al. 2014; van Duijn et al. 2018) with total enrolment of about 46,000 patients. The innovative aspect of these studies was the design that prevented patient dependency in hospital settings and allowed a waiver for informed consent to test interventions in real-world settings;
- Two successive national multicenter studies on antibiotic treatment strategies in patients hospitalized with a clinical suspicion of CAP in Dutch hospitals. In the first cluster-randomized study, we demonstrated that a strategy based on beta-lactam monotherapy was non-inferior to strategies based on beta-lactam plus macrolide therapy or a fluoroquinolone (Postma et al. NEJM 2015). This study was followed by a cluster-randomized study in which we demonstrated non-inferiority of a strategy based on penicillin or amoxicillin compared to more broad-spectrum beta-lactam antibiotics (paper submitted).



UMC Utrecht has had (and still has) important roles in international research consortia studying different aspects of AMR, such as GRACE (Genomics to Combat Resistance against Antibiotics in Community-Acquired Lower Respiratory Tract Infection in Europe), EVOTAR (Evolution and Transfer of Antibiotic Resistance), R-GNOSIS (Resistance in Gram-Negative Organisms: Studying Intervention Strategies), STARCS (Selection and Transmission of Antimicrobial Resistance in Complex Systems), and SATURN (studying the impact of Specific Antibiotic Therapies on the prevalence of hUman host ResistaNt bacteria). The experience, capacities and networks built by these collaborations put UMC Utrecht in “pole position” to lead the IMI-funded clinical trial initiatives in their program New Drugs for Bad Bugs, that should lead to a high-quality clinical trial network for evaluating new assets for diagnosing, preventing and treating infections. Currently, clinical evaluation of new antibiotics is inefficient and (too) expensive, creating significant delays in approving new treatment options for patients and reducing the willingness of pharmaceutical companies to enter clinical evaluation with new assets. Our ambition is to reduce the phase of clinical evaluation (phase 2 and 3) from 5-10 years to 2-3 years. The societal relevance of the network is to foster the rapid availability of new treatment (or prevention) options for patients, to maintain labor and scientific activities in clinical trials in Europe and to motivate pharmaceutical companies to evaluate new assets. The higher efficiency will reduce costs for these expensive studies and prolong the period of patent protection after drug approval. Both will (partly) restore the current unattractive economic model for antibiotic development.



3. Research theme: preventing inflammation

3.1 Mission, urgency and/or relevance of the research questions

Homeostasis is key to health. Ideally a disturbance is dealt with as quickly as possible and homeostasis restored with the least amount of resources spent and as little damage done as possible. The purpose of our immune system is to deal with external disturbances. Ideally it eliminates a pathogen quickly, efficiently and without damage to the host to return to homeostasis. However, removal of pathogens can be accompanied by an inflammatory response which causes immunopathology - collateral damage - to the host. Furthermore, there are many diseases that result from disturbance of the immune system without an identified outside disturbance or in response to harmless substances such as food components. Immune-Mediated Inflammatory Diseases (IMIDs) such as atopic dermatitis, psoriasis, rheumatoid arthritis, inflammatory bowel diseases, asthma, chronic obstructive pulmonary diseases, sarcoidosis, multiple sclerosis, uveitis, vasculitis, lupus, scleroderma, Sjögren's disease, and allergic conditions have quite diverse clinical manifestations. Hence, these are traditionally considered to be separate disease entities. However, it has become increasingly clear that the clinical symptoms result from organ damage by common underlying inflammatory reactions. Integrated study of IMIDs will allow for the classification of patients on the basis of the underlying mechanism and the identification of treatable traits for IMIDs. Furthermore, it is to be expected that the occurrence of IMIDs increases due to aging. To better understand IMIDs, we need to elucidate how a healthy immune system develops from newborn to the elderly.

This research theme is fully embedded in the Laboratory of Translational Immunology (LTI). The LTI vision is to harness the immune system to cure infection, inflammatory disease and cancer. The mission of the LTI is to impact people's lives (1) by understanding the essence of life-long immune health, classifying and monitoring inflammatory diseases and identifying their treatable traits (as presented in this theme "Preventing inflammation"), and (2) by developing immune-mediated therapy for infection, inflammation and cancer (as presented in theme "Developing immune-mediated therapy and prevention"). We do this by working in multi-disciplinary teams of clinicians and researchers, stimulating the flow from fundamental immunological insight to improvement of care, and by closely linking education, research, diagnostics and care, and by training students and professionals to obtain a broad career perspective.

The focus of research activities in this theme during 2013-2018 were:

- understanding immune health: to gain fundamental understanding of neutrophil function and subtypes, lymphocyte dynamics, transcriptional regulation in immune cells, immune regulation by immune checkpoint receptors, tissue immunity and mechanisms of resolving inflammatory pain;
- lifelong immune health: by studying newborns, children and elderly next to the adult age group;
- classifying inflammatory disease: by systems medicine approaches;
- disease monitoring: by standardized cohort research to identify new biomarkers to diagnose immune-mediated disorders and monitor treatment strategies, and by point-of-care (POC) technology to predict infectious complications in patients with acute inflammation;
- identification of treatable traits: the aforementioned research activities form the basis for the identification of common traits among patients with different clinical phenotypes, providing putative treatment strategies on these common traits rather than solely on clinical phenotypes.

3.2 Relation to existing knowledge

Understanding the essence of life-long immune health

To understand disease, we need to understand health. Important insight on our immune system has come from studies in mice, which allows for in vivo studies and genetic manipulation. Albeit useful, translation to the human immune system is not always valid. Therefore, fundamental research on immunological processes in humans is required, including studies of the immune system in neonates, children and elderly. For practical and ethical reasons most studies on the human immune system are done ex vivo on peripheral blood. It is imperative to include immune cells in the tissues. Furthermore, human in vivo models are emerging: immune cell kinetics in humans can now be studied with non-toxic in vivo labeling techniques and in vivo LPS challenge models allow for studying acute inflammation. Lastly, transcriptional mechanisms or receptor function studies are often performed on cell lines as model for immune cells.



Although useful for initial exploration, such experiments should be accompanied or be confirmed by studies in human primary cells.

Classifying and monitoring inflammatory diseases

With about 10% of the population suffering from an IMID, this class of diseases reflects a huge health care burden. Treatment includes non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids or immune suppressive agents, which attenuate inflammatory reactions at the risk of (severe) side effects. Biologics targeting a single inflammatory mediator with unprecedented specificity, such as tumor necrosis factor (TNF)-inhibitors, are effective across various IMIDs, but typically not all patients respond. This illustrates that a single IMID can be caused by multiple molecular mechanisms, while a single mechanism can be involved in multiple IMIDs. A reclassification of IMIDs based on underlying molecular processes is urgently needed to optimize therapy for individual patients.

This requires large clinically well-defined patient cohorts covering a multitude of IMIDs, followed longitudinally with stored biological samples. Application of systems biology facilitates identification of molecular signatures of inflammatory processes in circulating immune cells that change upon successful treatment of IMID or during development of IMID. Standardized and validated technological platforms for immune monitoring are needed to identify biomarkers for molecular signatures of inflammatory processes in individual patients, to guide personalized treatment.

The patient mix in a university medical center is often characterized by acute disease: multiple trauma patients, extensive surgery, acute viral infections etc.. Disease pathology in these patients is often dual, including the primary cause of disease and infectious complications as secondary cause. These latter infections can be life-threatening and require fast interventions. Early identification of patients at risk is crucial for implementing preventive measures. Therefore, the LTI will develop 24/7 automated point-of-care technology that will enable monitoring these inflammatory conditions and will allow early intervention in the patients at risk.

Identification of treatable traits

The concept of treatable traits is relatively new in the field of inflammation and builds on the molecular classification of disease. The basic idea is that multiple diseases can share certain (genetic/pathogenic) traits that are involved in their pathogenesis. Some of these traits (e.g. fibrosis) are difficult to treat and some can be better targeted (certain immune responses). The concept of treatable traits is developed to prioritize novel treatment towards those traits that can be targeted. For instance, in injury/trauma induced infectious complications the concept is tested whether neutrophilia/shift in neutrophil phenotypes is a diagnostic and prognostic factor. While neutrophils are not yet a treatable trait, it is to be expected that neutrophilia ("bad" cells) can be targeted while preserving homeostatic levels of 'good' cells (Hellebrekers et al. Eur J Clin Invest 2018).

3.3 Collaborations with stakeholders

Within this research theme we have built strong bonds with:

- *Patient organisations*: Patient advocacy is increasingly important in the design of research strategies. Within the LTI patients with different clinical conditions are frequently part of the weekly research meetings where they tell their patient journey and researchers can ask questions. In addition, twice a year the LTI organizes a patient advocacy day. During this event, patients and partners visit the lab and co-perform several immunological techniques such as cell separations, DNA isolation and flow-cytometry. In the afternoons, we have discussion groups in which patients, partners and research(clinicians) form and shape novel research strategies around unmet clinical needs. In this way, patients are not only partners in research design but also become aware of the life on the lab which helps them during the course of their role of patient's advocates.
- *Public-private partnerships* play an important role in the translation of results residing from the lab. Moreover, clinical trials performed by pharma are a useful resource of human materials for translational studies. We have a substantial number of investigator-initiated studies with different biotech and pharma partners (AbbVie, Pfizer, Takeda, Janssen, GSK, MedImmune, Nextcure, Boehringer Ingelheim etc) embarking on the unique knowhow and knowledge of these partners.
- *International and national organisations* (e.g. EULAR) embody a powerful platform for dissemination of research results. Several PIs have key positions in such organisations (EULAR / EAACI / FOCIS etc). By these roles the LTI has a clear vantage point on the international and national podia.



3.4 Research design

All PhD students within the domain of Life Sciences are part of the Infection & Immunity PhD program of the Utrecht Graduate School of Life Sciences. All PhD students have a daily supervisor and weekly meetings with the larger research group. Although the supervision of junior researchers is primarily carried out by their direct supervisor(s), regular meetings with other researchers in the department during all stages of research projects guarantee timely independent feedback.

The LTI research laboratories are ISO 9001 accredited. In addition, the Central Flow cytometry Facility is ISO 15189 certified, operating according to the standards required for diagnostics. The LTI has several core facilities that provide for optimal and efficient design of research questions.

Core facilities providing technical support

The LTI has multiple core facilities providing technical and logistic support to all its research groups. The *Central Flow Facility* (CFF) has state-of-the-art flow cytometers, cell sorters and image stream and provides quality control (calibration and maintenance), expertise (mandatory introduction on the equipment for all employees, courses, advise on antibody panels etc) and technical support (sort-operators etc). Currently, the CFF not only serves LTI employees but supports >400 researchers from the UMC Utrecht and other institutes on campus. The *Imaging Facility* supports quality control and technical advice on the imaging equipment (confocal microscopy, Incucyte and two-photon intravital imaging). The goal of the *Antibody Facility UMAB* is to work closely with investigators to develop new monoclonal antibodies, suited for specific basic research or clinical applications, depending on the needs of the customer. To generate new antibodies to cell surface molecules, UMAB employs a new and very efficient cellular immunisation method in mice, which is developed within the Immunotherapy group of the UMC Utrecht. The Protein Facility provides technical advice and support on design and expression of recombinant proteins.

The *MultiPlex Core Facility* (MPCF) offers multiple immune-assays based on color coated microspheres. Over 160 mediators can be measured in less than 200 µl blood, plasma, serum, synovial fluid, culture supernatant, liquor, eye moisture, urine, dry bloodspots and middle ear effusion. The analytes include cytokines, chemokines, adipokines, grow factors and matrix proteins. All multiplexes are sensitive, accurate, optimized and validated. *U-DAIR*, is the intramural immune monitoring laboratory of the LTI facilitating translational research in 30+ clinically well-defined cohorts of patients suffering from inflammatory and immune-mediated diseases. U-DAIR develops, optimizes and validates an immunomonitoring program to enable standardized cohort research and thereby identifies new biomarkers to diagnose immune-mediated disorders and explores potential treatment strategies. The LTI core facilities CFF, MPCF, UDAIR and UMAB are used beyond the LTI, by researchers in the UMC Utrecht, the Utrecht campus and internationally.

Statistical and computational support

The interdisciplinary nature of our research team plays a crucial role in ensuring the use of optimal research design. Statisticians in our team are involved from the earliest steps of research design until the final steps of data interpretation. Within the LTI a dedicated statistician is available for questions and support. Twice a year an applied statistics workshop is provided for all researchers in the LTI. Statisticians in the team are part of the *Computational Immunology Core*, currently consisting of 3 permanent employees and 7 fixed-term positions. The Computational Immunology Core supports data interpretation, develops new mathematical models and bio-informatic pipelines for "big data" analyses and aims to train every member of the LTI to have at least a basic level of understanding of computational immunology. The Core is currently setting up an educational program in computational immunology for young scientists and supervisors, and is linked to other bioinformatics groups at the UU campus via the Utrecht Center for Quantitative Immunology (UCQI) and the Utrecht Bioinformatics Center (UBC). Although the supervision of junior researchers is primarily carried out by their direct supervisor(s), regular meetings with other researchers in the department during all stages of research projects guarantee timely independent feedback.



3.5 The next step

Understanding the essence of life-long immune health

Only 10% of the lymphocyte population can be found in circulation. Besides the presence of lymphocytes in lymphoid organs, it has become clear in recent years that every organ and tissue in the body harbors a population of resident T cells. These resident T cells play a central role in both tissue protection (e.g. against pathogens in the barrier tissues) as well as homeostasis and locally interact with other immune and non-immune cells. Interestingly, the tissue environment dictates functional programming of T cells and can even completely change their phenotype and function. In the case of (chronic) inflammation, immune responses are mostly localized in target tissues such as the gut in Crohn's disease or the joints in arthritis. Not surprisingly, tissue resident T cells have been implicated in the persistence of chronic inflammatory conditions and local disease relapses. We are only beginning to understand the dynamics and functional differentiation of T cells in human tissues and other compartments outside the blood, both in health and inflammation. This knowledge is crucial to design early intervention/prevention strategies that may be able to halt the perpetual loop of inflammation in patients with chronic inflammatory disorders. Furthermore, understanding changing T cell dynamics, compartmentalisation and function with age will provide insights in healthy aging and strategies to optimize vaccination and prevention strategies.

Classifying and monitoring inflammatory diseases and identifying treatable traits

Currently, we have clear results showing that diseases share molecular overlap and hence similar drugs need to be targeted to only certain subjects with given diseases. We are currently translating these observations into

- Clinical bucket trial approaches. Drug development is challenged by drug failure and subsequent high costs of drug development. We are designing and testing new clinical trial methodologies by harnessing multiple cell subsets and their molecular (OMICS) layers to predict response to therapy. In addition, so-called bucket trials are designed, based on our data with patients with different diseases but shared molecular pathways.
- The extremely high costs of the type of research (molecular profiling of diseases) is challenging and mostly require collaboration with large pharma partners. Most of these investigator-initiated studies (ISS) are combined with public-private funds. Tofapredict (a randomized intervention trial in patients with arthritis psoriatica) is one the clearest examples where an ISS is topped with 30% funding by Health Holland (Top Sector Life Sciences & Health).
- Currently we are applying "big data" originating from research (molecular profiling of disease) into electronic patient files to improve quality of care. Two examples of those are 1) prediction of intra-ocular tumors in patients with intra-ocular inflammation and 2) prediction of the risk at Sjögren's Syndrome in patients at risk for pSS by using big data from circulating cell subsets assessed for multiple OMICS layers.
- The mainstay in the future management of chronic diseases such as T2-eosinophil asthma is the prevention of exacerbations. Here it will be essential to identify the treatable traits underlying disease pathogenesis. The lack of knowledge on, and dedicated analysis of exacerbations is at least partly caused by the compartmentalisation of promising approaches. Our view is that an orthogonal approach will circumvent this compartmentalisation. The resulting 'big data' will be reduced to intuitive profiles associated with unique processes causing and/or predicting acute exacerbations. This approach will lead to home monitoring applications for all inflammatory pulmonary diseases. The spot on the horizon is the development of handheld devices that will enable the individual patient to monitor their own disease at home. This will empower the individual to optimal self-management in telemetric collaboration with the specialist.

3.6 Results highlights

3.6.1 Research products for peers

Cohorts, biobanks, databases

- Selection of patient cohorts collected in the context of this theme and stored in UMC Utrecht Central Biobank facility: the UMC Utrecht Infection and Immunity (U-I&I) cohort (700 patients); Osteoarthritis (OA) and pain cohort (OA patients with detailed pain analysis and tissue samples (with St Antonius) (Eijkelkamp); "skin" and "gut" biobanks (cells, plasma, serum, and tissue biopsies) (van Wijk, Oldenburg, de Bruin); juvenile dermatomyositis (national prospective study for that is including all new onset patients in the Netherlands) (van Wijk, van Rooijen); SYSCCLASS cohort encompassing >1200 patients with an IMID followed longitudinally (covering 13 diagnoses) (Radstake); Common Variable Immunodeficiency Disorders (CVID) cohort, now being expanded towards a national cohort (Leavis); UCAN-CANDU holding blood samples of all Juvenile idiopathic arthritis (JIA) patients in Canada and The Netherlands (van Loosdregt, Vastert); National Bioday registry for moderate-severe atopic dermatitis patients treated with the novel



drug dupilumab in daily practice (de Bruijn).

- Otten leads the PROCARE (Profiling Consortium of Antibody Repertoire and Effectorfunctions) consortium in which since 2014 all 8 University Medical Centers in the Netherlands have joined forces to redefine the matching strategy currently used for organ allocation by performing a comprehensive analysis of immunological risk factors for rejection and graft loss. This consortium includes analysis of more than 6.000 kidney transplantations with all clinical and laboratory data in one database accessible to all colleagues.
- Van Loosdregt group has generated various large epigenetic and transcriptomic datasets from immune cells isolated from patients with JIA. All sets are made publically available for other researchers to use.

Assays, technologies, models

- Strategy to assess allergenicity of novel food protein products was developed by Knulst/Houben group (Verhoeckx, Reg Toxicol Pharmacol. 2016).
- Vriskoop/Koenderman have developed tools to determine granulocyte kinetics in vivo with the use of stable isotope labeling with ^2H -glucose as well as 2-photon microscopy (Prunier C et al. Methods. 2017).
- Vriskoop/Hietbrink/Leenen/Koenderman have developed an immune monitoring infrastructure with the use of automated 24-7 flow cytometry by AQUIOS combined with dimension reduction software to intuitively present flow data for clinicians (Folcarelli et al. Sci Rep. 2018).

Publications, theses

The principle researchers in this theme published >1300 publications (Scopus) and 133 PhD theses in 2013-2018.

3.6.2 Research products for societal target groups

Patient organisations

- van Loosdregt/Vastert group intensively collaborates with patient organisations such as the jeugdremavereniging. Also, we collaborate with a dedicated patient representative (Casper Schoemaker). In addition, we have a strong collaboration with the Dutch Arthritis Society which appointed us as research center of excellence (2019-2024). We are currently developing a national research agenda for juvenile arthritis for which we use the James Lind alliance methodology.
- Oldenburg participated in several guideline working groups (ECCO, Dutch), yearly patient seminars. Radstake and Kruize participated in multiple patient seminars from National Sjögren's Society.

Guidelines

- Radstake group participated on multiple (disease) guideline papers including on Sjögren's Syndrome (Fisher et al. Standardisation of labial salivary gland histopathology in clinical trials in primary Sjögren's syndrome. Ann Rheum Dis. 2017; Shiboski et al. International Sjögren's Syndrome Criteria Working Group. 2016 Ann Rheum Dis. 2017)
- Proposals for safe doses of food allergens derived under co-responsibility of Prof. Houben (Taylor et al, Food and Chemical Toxicology, 2014) were developed into a guidance for food allergen management in Australia-New Zealand (VITAL).

Outreach

- Borghans gave a Public Lecture on "The Maths of Memory" in Maynooth, Ireland, explaining importance of immunological memory, covering recent public discussions on vaccination coverage, and explaining how mathematical models contribute to our understanding of immunological memory.
- "Klokhuis", an educational TV program broadcasted on the Dutch national television, with weekly outreach in most elementary schools in the Netherlands as well, and directed for children aged 8 years and older (and their parents) highlighted research van Loosdregt/Vastert group in a dedicated broadcasting (20 minutes) on how it is to deal with JIA.

3.6.3 Use of research products by peers

Datasets, methods

- Researchers at MD Anderson Cancer Institute use newly developed fusion protein of anti-inflammatory cytokines (IL4-10 synerkine) developed by Eijkelkamp group for their research.
- Radstake group has been involved in the development of standards for flow cytometry (Cossarizza A, et al. Eur J Immunol. 2017) and involved by NIH initiatives of newly identified primary immunodeficiency disorders in respectively 2015 (Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease, Zhou et al. Nat Gen) and 2017 (CD55 deficiency, early-onset protein-losing enteropathy, and



thrombosis, Ozen et al. NEJM), gathered resp. 146 and 26 citations.

- Meyaard group's publication on a method to measure netosis (van der Linden et al. 2017. Scientific Reports) was cited 14 times and led to multiple requests for protocols by peers.

Infrastructure

- Stable-isotope labeling infrastructure and expertise Borghans/Tesselaar group is used by various internal and external partners, including Center for Human Drug Research, Karolinska Institute (Sweden) and Central Veterinary Institute (Lelystad).
- The LTI (PI Radstake) has an ongoing bilateral collaboration with Guangdong University, Guangzhou, China. They use our research facilities for the training of their PhD students, the first of which just arrived. This collaboration has already resulted in two scientific publications (one in revision & Meng Xu et al. Theranostics 2019).

3.6.4 Use of research products by societal groups

Guidelines

- Otten's publication (Kamburova et al. Am J Transplant. 2018) has led to implementations in all Dutch kidney transplant centers and are used to assess risk stratification for kidney graft when a donor kidney is offered. Additionally, Belgian colleagues with their own TEMPLATE kidney transplant consortium validate their findings with our database, and request received from peers to setup a sequel for the PROCARE study. The Dutch Ministry of Health, Welfare and Sport (VWS) has acknowledged that the results from the PROCARE study (Otten group) should be implemented in a novel kidney transplantation allocation system (update from Eurotransplant) and will provide financial support for that.
- Guidance on early introduction of allergenic foods to infants was developed in Meijer/Houben group and has been the basis of an opinion of the Dutch National Society for Pediatric Oncology (NVK, 2017).
- Proposals for safe doses of food allergens derived by Houben group (Taylor et al, Food and Chemical Toxicology, 2014) are currently used as a benchmark for food allergen management by many food companies worldwide as well as food safety authorities in north-west Europe.
- Leavis has contributed to reimbursement of biologic treatments for rare immunologic disorders (i.e. rituximab for vasculitis, TNF inhibitors for rare inflammatory disorders, anakinra for autoinflammatory disorders) by the Dutch National Health Care Institute (Zorginstituut Nederland).

Outreach

- Multiple PIs participated in programs to bring science to schools, such as "Meet the professor", "Slimme Gasten", Junior college Utrecht, in the University Museum Utrecht and the Conference for highly gifted children
- Under supervision of Koenderman/Vrisekoop, two PhD students entered a competition to pitch their research to laymen. Drs. Van Staveren became second in the final national round and was invited by the Museum of Natural History to pitch her research to laymen in London.
- Vrisekoop/Koenderman were involved bringing immunology to societal issues. They were involved in the analysis of amateur cyclists participating in the Tour for Life (cycle tour from Italy to The Netherlands) with the use of a mobile laboratory. (van Staveren et al. PLoS One. 2018). Similar field work was performed in Indonesia with a clinical trial focused on parasitic infection. Again the samples were taken in the field and analyzed later. (de Ruiter et al. Cytometry A. 2018).
- Meyaard reported on her experience with retraction of a research paper on two occasions: in 2013 on a Tulips-organized session on scientific honesty at the Dutch Pediatrics Society, Veldhoven and in 2017 in a "Lessons learned" symposium at Utrecht University. This yielded press coverage and discussion on scientific integrity. The first occasion was filmed and being used in lectures and classes on scientific integrity (i.e. by Prof. J. de Haes, Scientific integrity counselor at Amsterdam University).
- Kruize is advisory board member of the National Society of Sjögren's Patients (NVSP).

Private partners

- Many of the PIs in this theme also participate in theme 5 (Developing immune-mediated therapy and prevention) and as such collaborate with industry. Valorisation efforts are listed under 5.4.



3.6.5 Marks of recognition from peers

Awards

- Liset Westera (Borghans/Tesselaar group) won the Best PhD Thesis Award from the Dutch Society for Immunology (NVVI; 2014).
- Raoof (Eijkelkamp group) won a Bright Spark Award at the European Congress of Immunology in 2018 for his work on involvement of macrophages in the resolution of inflammatory pain.

Board participation, lectures, symposia

- Several PIs (a.o. Eijkelkamp, Oldenburg, Leavis, van Wijk, Otten, Koenderman, Houben, Knol, Radstake and Meyaard) have frequently been invited as faculty members (including keynote lectures) by major national and international meetings and societies, such as the European Academy of Allergy and Clinical Immunology; Brain, Behaviour, and Immunity; Federation of Clinical Immunology Societies, Dutch Initiative on Crohn and Colitis; Dutch Working party on Immunodeficiencies (WID) and the Dutch interuniversity working party on autoinflammation (IWA); international eosinophil society; and Dutch Society for Immunology.

3.6.6 Marks of recognition from societal groups

Funding, contract research

- Eijkelkamp group: our ReumaNL funded research to identify inflammatory mediators in liquor of osteoarthritis patients linked to pain was used in the fund raising brochure of November 2016.
- van Wijk/van Royen, Oldenburg, and de Bruin have received funding from the “innovatiefonds zorgverzekeraars”.
- van Wijk/van Royen have received funding from patient organisations ‘Bas stichting’ (Netherlands) and CureJM (USA) for research on juvenile dermatomyositis.
- PhD student Lotte Nijhuis was awarded by the French Patient Organisation Kourir for the most relevant research from a patient perspective on the congress of the Paediatric Rheumatology European Society (PReS) (2018).

Board participation

- Several PIs participate(d) as members or chairs of different societal associations, e.g. Oldenburg is chairman of national ‘Initiative Crohn and Colitis’, Radstake is member of the national society of Systemic lupus erythematosus (SLE) and Anti-phospholipid syndrome (APS) patients, Meyaard of the Scientific Advisory Board of the Dutch Arthritis Foundation (now ReumaNederland), Houben of the Scientific Working Group on Food Safety of the European Technology Platform ‘Food for Life’, Vriskoop of the Young Investigator Board of the Netherlands Respiratory Society, and Knol of the Scientific Advisory Board of the National Lung Foundation.

Training and education

One of the most important societal contributions of scientists is the training and education of young professionals (PhD and MD). This is not limited to scientific skills and also includes a plethora of other skills and competencies. In 2017 van Wijk has been awarded the PhD supervisor (co-promotor) of the year award from the Graduate School of Life Sciences Utrecht (GSLs), representing >1800 PhD students. She is also member of the advisory board of GSLs to develop a PhD competency program. Immunology is confronted with an increasing need for quantitative approaches, including mathematical modelling, biostatistical and bio-informatic approaches. The next generation immunologists need to be trained appropriately, in order to be prepared for these challenges. The LTI provides this training via different routes, varying from interdisciplinary training of PhD students in EU Innovative Training Networks (ITN) training networks (both in our own research group and through different training events for other PhD students in these EU networks), by teaching this interdisciplinary approach to students at the universities of Delft, Utrecht and Rotterdam, by giving lectures at summer schools for (bio-)medical students, but also by giving lectures for the general public.

3.7 Two examples of patient involvement

- Van Wijk/Oldenburg group has initiated the inflammatory bowel disease “TWIN study” to determine the first signs of (pre-clinical) Inflammatory Bowel Disease (IBD). In this study, monozygotic and dizygotic twin pairs are included, concordant or discordant for Crohn’s disease and/or colitis. Initially a small group of patients and their twin siblings were consulted about the idea of a TWIN study. Since they were very positive and also expressed motivation to participate, the study design was subsequently discussed with the patient organisation “Crohn en Colitis Ulcerosa Vereniging Nederland”.



After ethical approval, a movie on the TWIN-IBD study was recorded together with a patient and his twin brother (<https://www.youtube.com/watch?v=L7-EQH8b3Eg&feature=youtu.be>) and information about the study was published in *Chroniek* (Dutch initiative on Crohn's and Colitis) June 2017, and *IBD MDL-life* 2018. Currently more than 60 twins have been included. To update patients about the progress of the study a patient day for participating twins is organized. This day consists of presentations and question sessions.

- Radstake group is tightly linked to patient advocacy groups. To this aim we organize patient – lab days during which patients spend a day on the lab with researchers to highlight how a day in the lab looks like. Conversely, during this day researchers feel free to ask patients about their patient journey. One clear outcome of this was an invited review with a patient as co-author (Miss Mosterman). (Cossu et al. *Clin Rev Allergy Immunol*. 2018). Another example is the testing of a placebo pill for a clinical trial before initiation. This led to a summary for patients with clear instructions how to take this placebo successfully. Finally, Dept. Rheumatology and Clinical Immunology organizes science days involving clinicians, researcher and support staff and patients with IMIDs, to provide an overview of ongoing scientific projects as well as participation of patients, clinicians and scientists in lively discussions on particular diseases.

3.8 Ten most important scientific publications

1. Willemen HLDM, Kavelaars A, Prado J, Maas M, Versteeg S, Nellissen LJJ, Tromp J, Gonzalez Cano R, Zhou W, Jakobsson ME, Małecki J, Posthuma G, Habib AM, Heijnen CJ, Falnes PØ, Eijkelkamp N. Identification of FAM173B as a protein methyltransferase promoting chronic pain. *PLoS Biol*. 2018 Feb 14;16(2):e2003452.
The molecular mechanisms of chronic pain development are poorly understood, limiting the development of highly needed novel analgesics. This manuscript is important because genetic variations in the genomic region encoding FAM173B have been linked to chronic pain in humans. In this study, we identify the role and function of the hitherto unknown FAM173B in the development of pathological inflammatory pain. Therefore, this manuscript provides an important conceptual framework to explain why persistent inflammatory pain can develop in humans and it opens the possibility for new ways to treat chronic pain. Based on this study CD3 is now developing small molecules to inhibit FAM173b to treat chronic (inflammatory) pain.
2. Petrelli A, Mijnheer G, Hoytema van Konijnenburg D, van der Wal M, Giovannoni B, Mocholi E, Vazirpanah N, Broen J, Hijnen D, Oldenburg B, Coffey P, Vastert S, Prakken B, Spierings E, Pandit A, Mokry M, van Wijk F. PD-1+CD8 T-cells are clonally expanding effectors in human chronic inflammation. *J Clin Invest*, 2018;128(10):4669-4681.
By demonstrating that in chronic autoimmune inflammation PD1 expressing cells are clonally expanding effector and not exhausted cells we introduce a novel view on PD1 expression and T-cell exhaustion. The probable pathogenic role of these CD8 effector cells makes them potential targets in chronic inflammation. Furthermore, our data imply that in cancer, anti-PD1 therapy may not only rescue exhausted CD8 T cells, but may further unleash effective effectors leading to both tumor and tissue destruction. This paper was highlighted in: Bernard NJ. Some PD-1+ CD8+ T-cells are not exhausted. *Nat Rev Rheumatology* 2018 Sep 26.
3. Peeters JGC, Vervoort SJ, Tan SC, Mijnheer G, de Roock S, Vastert SJ, Nieuwenhuis EES, van Wijk F, Prakken BJ, Creighton MP, Coffey PJ, Mokry M, van Loosdregt J. Inhibition of (super-)enhancer activity in autoinflammatory site-derived T cells reduces disease-associated gene expression. *Cell Reports*, 2015;12(12):1986-96.
This the first study that demonstrates that the (super-)enhancer landscape is altered in primary immune cells of patients with an autoimmune disease. It also shows that inhibition of (super-)enhancer activity preferentially reduces the expression “disease-specific” genes. This study provides a better understanding of disease pathogenesis, and proposes a novel therapeutic strategy for the treatment of autoimmune diseases.
4. Kamburova EG, Wisse BW, Joosten I, Allebes WA, van der Meer A, Hilbrands LB, Baas MC, Spierings E, Hack CE, van Reekum FE, van Zuilen AD, Verhaar MC, Bots ML, Drop ACAD, Plaisier L, Seelen MAJ, Sanders JSF, Hepkema BG, Lambeck AJA, Bungener LB, Roozendaal C, Tilanus MGJ, Voorter CE, Wieten L, van Duijnhoven EM, Gelens M, Christiaans MHL, van Ittersum FJ, Nurmohamed SA, Lardy NM, Swelsen W, van der Pant KA, van der Weerd NC, Ten Berge IJM, Bemelman FJ, Hoitsma A, van der Boog PJM, de Fijter JW, Betjes MGH, Heidt S, Roelen DL, Claas FH, Otten HG. Differential effects of donor-specific HLA antibodies in living- versus deceased-donor transplantation. *Am J Transplant*. 2018 Sep;18(9):2274-2284.
The results of this study have been implemented in all Dutch kidney transplant centers and are used to assess risk stratification for kidney graft when a donor kidney is offered. Some centers even refuse specific kidney offers as they are considered high risk for graft loss according to this multi-center evaluation.



5. Janssen WJM, Grobarova V, Leleux J, Jongeneel L, van Gijn M, van Montfrans JM, Boes M. Proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1) controls immune synapse stability in human T cells. *J Allergy Clin Immunol.* 2018 Dec;142(6):1947-1955.
This paper has several elements incorporated that exemplify our translational research on chronic inflammation. We executed a genetic screening of immunodeficiency patients, and identified two distinct mutations in a cytosolic protein in lymphocytes called PSTPIP1 (proline-serine-threonine phosphatase interacting protein 1). The patients had immunodeficiency without signs of inflammation, although one already had a pre-activated T-cell status. Experiments using primary patients' T-lymphocytes showed that PSTPIP1 controls immune synapse formation and cell adhesion. This work shows that a pre-activated polymerized F-actin status, such as seen PSTPIP1 T274M patient T-cells, sets the stage towards the development of chronic inflammation.
6. Blom, W.M., Michelsen-Huisman, A.D., van Os-Medendorp, H., van Duijn, G., de Zeeuw-Brouwer, M.-L., Versluis, A., Castenmiller, J.J.M., Noteborn, H.P.J.M., Kruizinga, A.G., Knulst, A.C., Houben, G.F., 2018. Accidental food allergy reactions: Products and undeclared ingredients. *Journal of Allergy and Clinical Immunology*, 142(3), pp. 865-875.
This was the first prospective study showing the high frequency and impact of unexpected allergic reactions due to sub-optimal food allergen labeling legislation.
7. Tak T, Wijten P, Heeres M, Pickkers P, Scholten A, Heck AJR, Vriskoop N, Leenen LP, Borghans JAM, Tesselaar K, Koenderman L. Human CD62Ldim neutrophils identified as a separate subset by proteome profiling and in vivo pulse-chase labeling. *Blood.* 2017 Jun 29;129(26):3476-3485.
This study provides the first data supporting our long term vision that neutrophils belong to a heterogeneous population of cells. Using stable isotope labeling and multiplex proteomics, at least three different stable subtypes of neutrophils were found in humans.
8. Blokland SLM, Hillen MR, van Vliet-Moret FM, Bikker A, de Jager W, Pandit A, Kruize AA, Radstake TRDJ, van Roon JAG. Salivary gland secretome: a novel tool towards molecular stratification of patients with primary Sjögren's Syndrome and non-autoimmune sicca. *RMD Open.* 2019 Jan 11;5(1):e000772.
Primary Sjogrens syndrome (pSS) is difficult to diagnose. In this paper we describe the identification a method to molecularly stratify patients with and without Primary Sjogrens syndrome. This work represents the first successful attempt to molecularly stratify patients with and without this disease.
9. Kumar D, Puan KJ, Andiappan AK, Lee B, Westerlaken GH, Haase D, Melchiotti R, Li Z, Yusof N, Lum J, Koh G, Foo S, Yeong J, Alves AC, Pekkanen J, Sun LD, Irwanto A, Fairfax BP, Naranbhai V, Common JE, Tang M, Chuang CK, Jarvelin MR, Knight JC, Zhang X, Chew FT, Prabhakar S, Jianjun L, Wang Y, Zolezzi F, Poidinger M, Lane EB, Meyaard L, Röttschke O, Meyaard, L * and Rotzschke, O*. A functional SNP associated with atopic dermatitis controls cell type-specific methylation of the VSTM1 gene locus. *Genome Med.* 2017 Feb 20;9(1):18.
In this study we identified a SNP in the promotor region of the immune checkpoint receptor SIRL-1 that leads to loss of expression of this receptor in monocytes and demonstrate that this SNP is associated with atopic dermatitis. This finding initiated the studies leading to the identification of SIRL-1 as an inhibitory pattern recognition receptor.
10. van den Broek T, Borghans JAM, van Wijk F. The full spectrum of human naïve T cells. *Nat Rev Immunol.* 2018 Jun;18(6):363-373.
Recently the paradigm of "static" naïve T cells has been shifted. The lab of Dr. van Wijk has contributed to this novel concept by showing that human naïve T cells are unexpectedly dynamic and plastic in function (JCI 2016), which builds on previous findings by the lymphocytes dynamics group led by Dr. Borghans of the CTI (Blood 2011). In this comprehensive overview in Nature Reviews Immunology, we highlight recent insights on human naïve T cell development, function, and dynamics, and discuss implications for immune aging and senescence, vaccination and immune reconstitution in hematopoietic stem cell transplantations. Within one year following publication, the paper has already been cited 32 times.



3.9 Two most important examples of societal contributions

Preventing inflammation

Chronic inflammatory diseases are molecularly complex, difficult to treat and, therefore, leading to complications and disability to participate to society in terms of work. To overcome this, immunology researchers in the UMC Utrecht have embarked on the effort to molecularly re-classify inflammatory diseases based on their molecular fingerprint rather than applying the currently adhered diagnostic strategies. It is envisioned that this approach will lead to three important societal contributions. First, inflammatory diseases usually present themselves in different organs, most often in a temporal matter. For instance, patients with ankylosing spondylitis (AS) develop inflammatory bowel disease and/or non-infectious uveitis in 20-30% of the cases. UMC Utrecht studies (Radstake group) demonstrated that patients with isolated cases of AS display a different molecular fingerprint compared to those that develop inflammatory bowel disease and/or uveitis. This may allow early recognition (and treatment) of patients at risk for this complicated presentation of AS, which will reduce its impact on quality of life and workability. Secondly, the majority of drug candidates fail in phase II/III clinical trial. This is likely due to inclusion of patients on diagnostic grounds, whereas molecular characterisation may identify distinct subgroups. Hence, basket (or bucket) trials like the field of oncology – where patients are included based on the presence of a molecular signature – need to be initiated. Molecular signatures determined in >800 patients covering >12 different inflammatory conditions allows such studies to be performed in UMC Utrecht. Finally, UMC Utrecht investigators used molecular fingerprinting to assess whether certain medicines are effective for inflammatory diseases. Proof of principle was recently achieved by the execution of a clinical trial in patients with primary Sjögren's disease (pSS) using the combination of two existing drugs, leflunomide and hydroxychloroquine, which were predicted to be effective for this disease. This combination was most effective for pSS so far, with >40% of the patients reaching clinical response. Molecular fingerprinting at baseline predicted treatment response with clinically useful certainty. These data suggest that up to 40% of the patients with pSS can be treated with this combination of drugs which costs roughly 400 euro per year in contrast to the biological therapies currently in development that average out at 15,000-20,000 euro per year.

Redefining matching strategy for kidney transplantation

The Dutch society is well acquainted with kidney transplantation. The topic regularly hits the news, such as recently when the Dutch Law changed to approving the opt-out system. Kidney transplantation is the best option for end-stage kidney failure. However, transplant rejection is still a major complication. The multicenter collaboration aims to prevent kidney transplantation with a high risk for graft loss, leading to a longer average half-life of transplanted kidneys. This diminishes a return to hemodialysis and renewed (on average 2.5 years) waiting time for a deceased kidney donor. In the Netherlands, approximately 65 patients with end-stage renal failure die per year while waiting for a donor kidney, while more than a hundred are removed from the waiting list due to their poor physical condition. Within the Eurotransplant region, the current method to evaluate whether a donor kidney has a suitable match with the recipient patient is (in addition to human leukocyte antigen (HLA) typing) by measuring the presence of donor-specific HLA antibodies. Upon transplantation such antibodies bind to the cells in the transplant and destroy these by activating the complement system. The classical test to measure anti-HLA antibodies is the crossmatch assay, which measures the level of anti-HLA antibodies as well as their complement activating properties. Whereas implementation of the crossmatch assay in clinical practice has virtually ruled out hyperacute rejection of the transplant, it is not sensitive enough to detect low levels of HLA antibodies that activate the complement system.

Since 2014, all 8 University Medical Centers in the Netherlands have joined forces in the PROCARE consortium (led by PI Otten) to redefine the matching strategy currently used for organ allocation by performing a comprehensive analysis of immunological risk factors for rejection and transplant loss. This consortium is funded by the Dutch Kidney Foundation. Amongst others, the PROCARE consortium showed that the pre-transplant presence of donor-specific HLA antibodies (DSA) detected by the Luminex technique, but not by the crossmatch test, increased the risk of rejection. Based on these findings the Luminex DSA test is currently implemented by all Dutch centers for risk stratification, which is a major valorisation success of the PROCARE consortium.



4. Research theme: elucidating host-pathogen interactions

4.1 Mission, urgency and/or relevance of the research questions

The mission of this theme is to understand the intricate relationship between host and pathogen at the molecular level in order to design future therapeutic approaches. Through internationally-recognized and societally well-embedded research, the theme adds to the improvement of patients health through better understanding of bacterial (staphylococcal, streptococcal) and viral (herpes simplex virus (HSV), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), respiratory syncytial virus (RSV)) interactions with the human immune system. The focus of research activities in this theme during 2013-2018 were:

- *Immune evasion*: Bacteria and viruses are not innocent bystanders during attack of the immune system. They have evolved highly specific ways to overcome destruction by the immune system and these immune evasion molecules are key virulence factors. This topic aims to better understand these at the molecular level, which holds the key to novel smart therapeutic approaches.
- *Immune pathology of infections*: The way an infectious agent causes disease or specific disease states is essential in order to design and develop the best strategy for therapeutic intervention. This topic aims to understand cellular and molecular mechanisms of immune-mediated collateral damage caused in the process of pathogen elimination.
- *Microbiomics*: The bacteria that live together on the skin, in the gut or airways are of crucial importance in health and disease. This topic aims to understand the balance between composition of the microbiome and diseases and disease states.

4.2 Relation to existing knowledge

Immune evasion

In the last two decades, we have revealed a plethora of secreted bacterial immune evasion molecules in mainly *Staphylococcus aureus*. In the last few years we have focused mainly on Staphylococcal toxins and their role in pathophysiology of infection. By discovering all receptors for the diverse staphylococcal leucocidins and hemolysins (such as Pantone Valentine Leucocidin), we proved in vitro and in vivo that these toxins specifically kill phagocytes and thus are part of the arsenal of immune evasion strategies of *S. aureus*. This impacted the whole view on the role of bacterial toxins in infections, which was extensively reviewed in Spaan AN et al. (Nat Rev Microbiol 2017) and Spaan AN et al. (Annu Rev Microbiol 2013).

Research on viral immune evasion focuses on the elucidation of strategies used by large DNA viruses, such as herpesviruses and poxviruses, to elude the cellular immune response. Often, viral evasion mechanisms involve basic cellular processes and can be used as tools to unravel key players in these reactions. This is illustrated for ER-associated protein degradation (ERAD), a process involved in a broad range of diseases. Cutting-edge technologies, including genome-wide CRISPR/Cas screens, are used to identify virus and host factors critically involved in viral infections. CRISPR/Cas technology is also used to edit viral genomes; nucleases can also be used to inactivate viral genomes, thus offering a novel treatment modality. This research is embedded in various national and international funding schemes and networks.

Immune pathology of infections

Immunopathology is an important component of infections with the highest burden, including HIV, respiratory infection and sepsis. We aim to develop drugs which target and regulate the immune system to improve outcome of these infections. For respiratory viral immune pathology collaborations have increased access to cutting-edge technologies to study neutrophil-mediated airway disease, including high throughput functional assays, development of animal models, lung organoids and reporter cells.

In the last few years we gained novel insights in the HIV reservoirs in immune cells and potential HIV eradication strategies including immune interventions. These insights were obtained through the international HIV eradication platform IciStem and the national NL4Cure platform and fueled the HIV research field and the very active HIV community.



They developed ultra-sensitive methods for the detection of HIV variants that circulate worldwide and developed several in vitro and ex vivo system for the evaluation of curative strategies. For evaluation of longevity of immune cells, viral immune reservoirs and immune activation and pathology a long-standing collaboration exists between research groups in the MMB and the LTI.

Microbiomics

Despite the global explosion of reported microbiome research, UMC Utrecht has only recently developed this infrastructure. Microbiome research within the UMC Utrecht focusses on changes in the human microbiome related to chronic infectious diseases, immunologically mediated diseases and antibiotic resistance, as well as functional microbiomics dissecting microbiome-host interactions in human intestinal organoids. Within Utrecht Life Sciences UMC Utrecht partners in the Utrecht Exposome Hub, in which research on the external and internal exposome is integrated. The internal exposome focuses on the role of the microbiome in health and disease (see: <https://www.uu.nl/en/research/utrecht-exposome-hub>), and is hosted by the department of Medical Microbiology. For this, it has built an efficient laboratory pipeline, as well as a bioinformatic infrastructure with bioinformaticians and high-performance computing to facilitate and guide (meta)genomics-based research.

4.3 Collaborations with stakeholders

Immune evasion

There is a constant interaction with clinicians, international collaborators as well as the major pharmaceutical industries. Because of the potential of application in therapy, our work is part of the national One Health program (NCOH) and the national alternatives-to-antibiotics program (ALTANT). Immune evasion molecules are targets for therapy, and here we work with different vaccine and antibody companies to incorporate these targets in existing or new programs (AstraZenica, GSK (Sienna, IT) and MSD-animal health (Boxmeer, NL). As evasion molecules are also the perfect anti-inflammatory molecules, we collaborate on this topic with Pepsan Systems (Lelystad, NL).

Immune pathology of infections

This research topic finds its stakeholders in academia, society and industry. UMC Utrecht researchers work interdisciplinary with other EU institutes in academic networks (e.g. RESCEU, PERISCOPE, PERFORM) as part of the H2020 or IMI programs, and Bill & Melinda Gates Foundation projects. To ensure focus on the highest need, societal involvement exists with continuous collaboration with patients who review research grants and actively participate in research networks, joint appointments with the Dutch National Public Health Institute (RIVM), collaboration with European Medicines Agency (ECDC), European Medicines Agency (EMA), European AIDS Clinical Society (EACS), and the Dutch HIV Society, participation in working parties of the World Health Organisation (WHO) and other international collaborations such as European Society for translational antiviral research (ESAR) and IciStem. Finally, the research theme actively furthers the development of preventive and therapeutic medical interventions through public-private partnerships.

Microbiomics

Important stakeholders for the microbiome facility are clinicians and researchers within and outside the UMC Utrecht. The launch of the microbiome facility already fueled interdisciplinary collaborations between different research teams and medical specialists. Further research collaborations within the domain of microbiomics are mainly with national and international academic peers.

4.4 Research design

The department of Medical Microbiology participates in all three subtopics of this theme. All PhD students within the domain of Life Sciences are part of the Infection & Immunity PhD program of the Utrecht Graduate School of Life Sciences. All PhD students have a daily supervisor and weekly meetings with the larger research group. Furthermore, since 2015, the department of Medical Microbiology has built a bioinformatic infrastructure by hiring two bioinformaticians and investing in high performance computing to facilitate and guide (meta)genomics-based research. Molecular research is supported by solid state-of-the-art chemical and biophysical approaches and determinations nuclear magnetic resonance, crystallography, surface plasmon resonance, Cryo-Electron Microscopy, Cryo-Electron Tomography, etc.) in collaboration with colleagues at the science faculty and at the Bijvoet Center for Biomolecular Research (Utrecht University). Furthermore, multidisciplinary research teams enhance research quality.



An example is the development of vaccines in collaboration with the veterinary faculty (Utrecht University), Dept. of Pharmacy and Chemistry (Science Faculty, Utrecht University) and the Hubrecht Institute (KNAW, Utrecht). The same holds for global collaborations; e.g. a five-year successful project with the university of Lyon and New York University to identify ALL human receptors for the most important staphylococcal toxins. The structural and molecular studies on viral evasion proteins have been one of the working themes of a European consortium: the Innovative Training Network, providing cutting-EDGE knowLEDGE on herpes virology and immunology (EDGE). EDGE has brought together European academic and biomedical industry facilities with the aim of training early career researchers and narrowing the gap between fundamental herpesvirus knowledge and prospective clinical applications. The Department of Medical Microbiology (Wiertz/Lebbink) is work package leader and employs two PhD students from the consortium. The LTI participates in the subtopics immune evasion and host-pathogen interactions. The core-facilities providing statistical, computational and technical support in the LTI are outlined in section 3.4 of this document.

4.5 The next step

Immune evasion

In bacterial immune evasion, the next step is to implement the knowledge into future therapeutics within the Research Theme “Developing immune-mediated therapy and prevention”. We will apply specific monoclonal antibodies to immune evasion molecules (in this case leukotoxins) with Medimmune (Astra Zeneca). We are also involved in vaccine development for staphylococci in collaboration with Merck and GSK. LTI and MMB labs actively collaborate on the identification of bacterially-encoded ligands for immune checkpoint receptors. This led to the identification of SIRT-1 as an inhibitory pattern recognition receptor, recognizing both pathogen-encoded molecular patterns (PAMPs) as well as danger associated molecular patterns (DAMPs).

For viral immune evasion, genome-wide CRISPR/Cas screens performed in our laboratory have identified novel viral and host factors essentially involved in virus infection and replication. These factors represent novel targets for vaccine and drug development. Furthermore, knowledge of (structural) details of inhibition of MHC class I presentation employed by several viral proteins contributes to the development of counteracting strategies. In addition, elucidating how viral evasins interfere with cellular processes (e.g. ER-associated protein degradation) may point toward new treatment strategies for diseases resulting from disturbances in those cellular pathways (e.g. diseases associated with excessive or diminished protein degradation, such as type 1 diabetes, cystic fibrosis, neurodegenerative diseases, muscle dystrophies, metabolic disorders, etc.).

Immune pathology of infections

Collaboration between respiratory viral and bacterial infection research groups of the LTI and MMB will be further intensified, also on the Utrecht Science Park, the National Institute for Public Health and the Environment (serology, animal models, respiratory microbiome studies) and many international collaborations (e.g. University of Edinburgh, Oxford University, Chinese University of Hong Kong). The organoid model will be further developed to study immune pathology by studying the complex interaction between host epithelium, immune cells and invading pathogens. How immune-tolerance to commensals is regulated and whether break of tolerance can lead to disease is an open area of research. Through a Vici grant (Meygaard) by ZonMw, studies into mechanisms of atopic dermatitis related to *Staphylococcus aureus* colonisation are boosted with clear potential to lead to novel treatment target.

Regarding HIV research, the next step will be to further develop in vitro and ex vivo model systems, including cerebral organoids, for the evaluation of new curative strategies. The most successful strategy involving both virological and immune-based interventions will be evaluated in a clinical phase I trial (NL4Cure Bridge study funded by ZonMw and Afdonds and coordinated by UMC Utrecht, Nijhuis/Wensing). This project will further intensify the collaborations within the UMC Utrecht (LTI: Borghans, Tesselaar, Kuball), Translational Neurosciences (Lot de Witte), Internal Medicine (Andy Hoepelman) and within the UU campus (Social Science, John de Witte; Theoretic Biology, Rob de Boer).

Microbiomics

The recent establishment of microbiome research group and facility responded to a growing request from researchers and clinical researchers within the Utrecht Science Park. The next step is to further strengthen collaborations with the aim to acquire funding for microbiome-based research. As a first step two research positions (assistant and associate professor) have been created to sustain the microbiome facility and to further invest in functional microbiomics.



4.6 Results highlights

4.6.1 Research products for peers

Methods, technologies, models

- Van Strijp/Rooijackers developed a large series of in vitro methods to assess antibody and vaccine efficacy and serve as correlates of protection in clinical studies for bacterial infections.
- Van Sorge developed an assay to study human antibodies present in patient plasma/serum directed against glycopolymers of *Staphylococcus aureus* that circumvents sensitivity limitations and precludes need for IgG affinity purification (van Dalen R. et al. Nature 2019).
- Lebbink/Wiertz developed the use of CRISPR/Cas technology as a novel treatment against viral infections (Diemen et al. PLoS Pathog 2016) and human genome-wide genetic screens with shRNA and CRISPR/Cas libraries (Van de Weijer et al. Nat Commun 2014).
- Rozhnova/Kretzschmar team developed a mathematical model to investigate the impact of Pre-exposure Prophylaxis on the HIV epidemic in the Netherlands (Rozhnova et al. AIDS. 2018).
- Kretzschmar led a large European consortium that developed methodology and software for estimating the burden of infectious diseases in terms of DALYs (Cassini et al. Euro Surveill. 2018; Kretzschmar et al. PLoS Med. 2012).

Infrastructure, cohorts

- As part of the Exposome Hub, Leavis/Paganelli/van den Wijgert/Willems developed a microbiome facility with standardized protocols for collection, processing and storage of fecal samples, 16S-based and shotgun sequencing-based microbiome community profiling and bioinformatic analyses. Methods were developed to apply 16S rRNA gene sequencing data to clinical research questions, to incorporate them into classical biostatistical models and new patient cohorts were attracted.
- van Sorge (with St. Antonius Hospital, RIVM and Academic Medical Center Amsterdam) has set up a prospective surveillance system in the Netherlands for invasive infections caused by Group A Streptococcus. In a second stage, a retrospective clinical study of the cases will be performed.
- Borghans/Tesselaar group has built the infrastructure to measure and interpret enrichment levels from in vivo stable isotope labeling experiments. This consists of the infrastructure in the laboratory as well as the development of the mathematical tools to interpret the data.
- Nijhuis/Wensing group has built the largest cohort world wide of HIV-positive patients with a hematological malignancy who have undergone an allogeneic stem cell transplantation: IciStem cohort (www.icistem.org).

Publications, theses

The principle researchers in this theme published >360 publications (Scopus) and 53 PhD theses in 2013-2018.

4.6.2 Research products for societal target groups

Outreach

- Research by Nijhuis and Wensing (IciStem program; HIV remission/cure after allogeneic stem cell transplantation), Lebbink and Wiertz (CRISPR/Cas9-Mediated Genome Editing of Herpesviruses), Bont (relationship between RSV and asthma development), Meyaard (sex-differences in infections) and van de Wijgert (vaginal microbiome) had wide societal outreach through various news outlets in the Netherlands (e.g. NOS, RTL) and abroad (e.g. NY Times, NNBC, CNN, Nature news, Scientific American, The Scientist).
- Van Sorge, Paganelli, Borghans, van der Vlist, Boes, Rooijackers, Meyaard, Bont and van Strijp presented research at societal meetings for e.g. journalists, press officers, general public, primary schools and during annual conference for highly gifted children.

Policy, application

- Kretzschmar contributed to the policy advice to the government on whether or not to implement population based screening for chlamydia infections in the Netherlands (in the context of the CSI project).
- Borghans group (Arends) developed the Happi-App (Health Appi, see happiapp.nl), an app for HIV-infected individuals aiming to make their lives easier, by providing a personal overview of their latest blood measures, treatment schedule and hospital visits as well as general information.



- Nijhuis/Wensing group: HIV SPREAD Surveillance Program and Dataset as part of the European Society for translational antiviral research (ESAR). In this program clinicians, virologist and epidemiologist from 28 European countries are actively involved in collecting representative data to reliably determine the incidence of transmitted drug resistant HIV within different patient groups and to identify risk factors in transmission of drug resistant HIV in Europe. Within the SPREAD program we developed a European database of HIV-drug resistant strains; published Scientific Surveillance Reports in peer reviewed medical journals; Generated viral panels, representative for the resistant viruses circulating in Europe and we developed for public health and research purposes an open European web platform to map the spread of drug resistant HIV.

4.6.3 Use of research products by peers

Datasets, methods

- Van Sorge's dataset produced in van Hensbergen et al, PLoS Pathogens 2018 was used by Natalia Korotkova (Kentucky University) to identify a function of GacH, a phosphoglyceroltransferase, in the context of host-pathogen interaction. This resulted in a joint publication in 2019 (Edgar R et al. Nat Chem Biol 2019).
- Microbiome facility Willems groups provided support for microbial community profiling to eight clinical research groups within (Leavis, Radstake, Oldenburg, Suijkerbuijk, Kranenburg) and outside (Catharina ziekenhuis, Eindhoven; Institute for Risk Assessment Sciences, Utrecht University; Franciscus Hospital, Rotterdam) UMC Utrecht.
- The software tool BCoDE (Burden of Communicable Disease in Europe) toolkit has been used multiple times in different countries for estimating disease burden (Colzani et al. PLoS One. 2017)
- Nijhuis's combinational CRISPR/Cas9 gene-editing approach can halt HIV replication and prevent viral escape (Scientific Reports, 2017) has been applied by several groups not only to combat HIV but also for other infectious diseases.

Publications, recommendations

- Wensing is chair of International Antiviral Society–USA Drug Resistance Mutations Group (independent, volunteer panel of experts charged with delivering accurate, unbiased, and evidence-based information on HIV Drug Resistance mutations to HIV clinical practitioners).

4.6.4 Use of research products by societal groups

- Kretzschmar group's methods for calculating disease burden are used by RIVM for regular reporting to the ministry of health on the state of infectious diseases in the Netherlands (Staat van Infectieziekten) and in similar reporting to the ministry of agriculture on the burden of foodborne infections population health.
- van de Wijgert discussed promising research results of a study evaluating incorporation of point-of-care tests in urogenital infection management in resource-poor settings with Rwanda Minister of Health and WHO, likely leading to improved clinical guidelines.
- Nijhuis/Wensing demonstrated high rates of transmission of drug-resistant HIV in Aruba (2017) resulting in reduced susceptibility to the WHO recommended first-line regimen in nearly half of newly-diagnosed HIV-infected patients (CID, 2017: 64(8):1092-1097). Following our findings, local and regional public health authorities have been informed. Local guidelines have reinforced baseline resistance testing and replaced the WHO recommended first-line regimen by an integrase inhibitor-based regimen.
- Bont wrote a UMC Utrecht blog about negative consequences of requiring a minimum of 4 first author original publications on the quality of PhD-led research (www.UMC Utrechtrecht.nl/nl/Nieuws/Minimaal-vier-artikelen-in-je-proefschrift) which was picked up internally and externally (www.dub.uu.nl/nl/blog/minimaal-vier-artikelen-je-proefschrift-helemaal-niet-nodig).

4.6.5 Marks of recognition from peers

Awards

- Bont received the International Congress of Pediatric Pulmunology (CIPP) Award for Contribution to Understanding Childhood Respiratory Disease and Global Medical Education.
- Rumpret (Meygaard group) received the Bright Spark Award 2017 from the Dutch Society for Immunology for his work on S1RL-1 as a pattern recognition receptor.

Board participation

- Several PIs participate(d) as members or chairs of (inter)national associations, e.g. Wiertz is chair of the board of the Virology Division of the Royal Dutch Association for Microbiology (KNVM), board member of the International Association for Research on EBV and Associated Diseases, and Scientific Advisory Board of the Georg Speyer Institute in Frankfurt; Wensing is advisor for the WHO HIV resistance network, chair of the international Panel that assesses



HIV-1 Drug Resistance mutations (IAS-USA), board member of the European AIDS Clinical Society (EACS) and Chair of the European HIV drug resistance surveillance program SPREAD; Kretzschmar is member of the board of PLoS Medicine.

- Tesselaar is member of the internal review committee of the Biobank UMC Utrecht; Bont is chair of the internal ethics committee (METC).
- Nijhuis and Wensing are Honorary Professors at University of the Witwatersrand (Johannesburg, South Africa).

4.6.6 Marks of recognition from societal groups

Awards

- Lebbink/Wiertz group was awarded two grants by F.P. Fischer Foundation for application of CRISPR/Cas technology for development of treatment alternatives for HSV-induced keratitis, in collaboration with the department of Ophthalmology of the UMC Utrecht.

Contract research

- Van Strijp received a grant on the development of anti-inflammatory peptides with the commercial partner Pepscan Systems 2016, Eurostars BAIT.
- Lebbink/Wiertz group is involved in a large-scale AstraZeneca-funded research project/consortium INFORM, in collaboration with Bont (coordinator) and Julius Clinical. The project aims to study the molecular epidemiology of RSV infections worldwide and to monitor for escape mutants of the novel antibody nirsevimab.

Board participation

- Kretzschmar served as member of Prevention Africa Data and Safety Monitoring Board of the NIAID (Division of AIDS, USA) and was Chief Science Officer for Mathematical Disease Modelling at RIVM, where she contributed to the communication of scientific results to policy makers in public health.
- Borghans, Nijhuis and Kretzschmar were/are member of the Scientific Advisory Board of AIDS Fonds Netherlands.
- Bont was a member of the Scientific Advisory Boards of the Dutch Lung Foundation (Longfonds) and Muscle Foundation (Spierfonds).
- Bont is regular advisors of national and international public health institutes (RIVM, CDC, ECDC) and global health bodies (WHO), international regulators (EMA, FDA) and decision makers (Dutch Health Council).
- Nijhuis is member of the IAS HIV Cure International Scientific Working Group consisting of physicians, scientist and community members. She is also part of the Towards an HIV Cure Research Academy and mentors two young HIV investigators in resource limited settings

4.7 Two examples of patient involvement

- There is strong involvement of patients in the respiratory syncytial virus (RSV) research group of Louis Bont. Nicole Derksen is employed by the UMC Utrecht as the chairperson of the Dutch Patient Advisory Board (PAB) and the EU PAB for RSV infection. She is supported by Inge Oliemans, who was recently appointed by UMC Utrecht as a communication expert of the PAB. The RSV PAB is involved in all parts of the research, including prioritizing research questions, drafting grant applications, writing patient information and communicating with various stakeholders. An international RSV PAB has been set up by Nicole Derksen and is currently functioning.
- In the IciStem project (www.icistem.org) developed by Nijhuis/Wensing, HIV positive individuals who suffer from a hematological malignancy for which they require an allogeneic transplant are being investigated. In this project people living with HIV are represented by the CAB (Community Advisory Board) which include patients who have undergone an allogeneic transplantation, active community members and experts in socio-behavioral aspects of HIV Cure research. The CAB is involved in the different steps of the project and especially the intervention studies. They will also ensure that the project and the whole process is communicated with the people living with HIV and is in line with the MIPA criteria (Meaningful Involvement of Patients living with HIV/AIDS).



4.8 Ten most important scientific publications

1. Spaan AN, Vrieling M, Wallet P, Badiou C, Reyes-Robles T, Ohneck EA, Benito Y, de Haas CJ, Day CJ, Jennings MP, Lina G, Vandenesch F, van Kessel KP, Torres VJ, Henry T* and van Strijp JA*. The staphylococcal toxins γ -haemolysin AB and CB differentially target phagocytes by employing specific chemokine receptors. *Nat Commun.* 2014 Nov 11;5:5438. and Tromp AT et al. Human CD45 is an F-component-specific receptor for the staphylococcal toxin Pantone-Valentine leukocidin. *Nat Microbiol.* 2018 Jun;3(6):708-717.
Van Strijp group identified all receptors for the most important group of toxins from staphylococci. This was done in a collaborative effort with the university of Lyon and New York University.
2. N.M. van Sorge*, #, Jason N. Cole*, Kirsten Kuipers, Ramy K. Aziz, Ana Kasirer-Friede, 12 authors, Mark J. Walker, Sanford J. Shattil, Patrick M. Schlievert, Biswa Choudhury, Victor Nizet#. The classical Lancefield antigen of Group A Streptococcus is a virulence determinant with implications for vaccine design. *Cell Host Microbe.* 2014; 15 (6): 729-40.
Here we identified the genetic basis of the classical Lancefield antigen, which historically defines groups of medically-relevant streptococcal pathogens. The genetic identification allowed functional studies that highlighted that these structures are not merely structural components of the cell wall but contribute to virulence and represent safe vaccine targets (patent PCT/US12/049604).
3. van Diemen FR, Kruse EM, Hooykaas MJ, Bruggeling CE, Schürch AC, van Ham PM, Imhof SM, Nijhuis M, Wiertz EJ, Lebbink RJ. CRISPR/Cas9-Mediated Genome Editing of Herpesviruses Limits Productive and Latent Infections. *PLoS Pathog.* 2016 Jun 30;12(6):e1005701.
This publication highlights that the CRISPR/Cas9 genome editing technology can be effective in blocking the replication of different herpesviruses. Its potential as a treatment strategy for HSV-1-induced keratitis is being explored in a collaboration with the Department Ophthalmology of the UMC Utrecht, with the financial support of the Dr. F.P. Fischer Foundation.
4. Hendrickx AP, Top J, Bayjanov JR, Kemperman H, Rogers MR, Paganelli FL, Bonten MJ, Willems RJ. Antibiotic-Driven Dysbiosis Mediates Intraluminal Agglutination and Alternative Segregation of *Enterococcus faecium* from the Intestinal Epithelium. *MBio.* 2015 Nov 10;6(6):e01346-15.
In this study we have investigated the processes that occur in the gut during antibiotic treatment that result in intestinal microbial dysbiosis, and the effects on intestinal epithelial cell lining architecture. This information has provided clues on how antibiotic treatment leads to intestinal overgrowth and translocation of potential pathogens.
5. Berbers RM, Nierkens S, van Laar JM, Bogaert D, Leavis HL. Microbial Dysbiosis in Common Variable Immune Deficiencies: Evidence, Causes, and Consequences. *Trends Immunol.* 2017 Mar;38(3):206-216.
This UMC Utrecht review serves as the basis for further characterisation of microbiome and immunologic profiles of Common variable immunodeficiency (CVID) patients with and without immune dysregulation, as a basis of a research line. It poses an important role for microbial dysbiosis as a driver of immune dysregulation in CVID.
6. Kretzschmar ME, Schim van der Loeff MF, Birrell PJ, De Angelis D, Coutinho RA. Prospects of elimination of HIV with test-and-treat strategy. *Proc Natl Acad Sci U S A.* 2013 Sep 24;110(39):15538-43.
This publication was a starting point of several research projects on the impact of antiretroviral treatment on the HIV epidemic. We received funding from the AIDS fonds for a project on the impact of treatment on HIV incidence in the Netherlands, and for a project on HIV transmission patterns in the Dutch Caribbean populations. We also received funding from ZonMw for several projects on implementation and impact of PrEP on HIV transmission.
7. Vriskoop N, Drylewicz J, Van Gent R, Mugwagwa T, Van Lelyveld SF, Veel E, Otto SA, Ackermans MT, Vermeulen JN, Huidekoper HH, Prins JM, Miedema F, de Boer RJ, Tesselaar K, Borghans JAM (2015) Quantification of naive and memory T-cell turnover during HIV-1 infection. *AIDS* 29, 2071-80.
This paper yielded two important insights: 1) It provides direct evidence that naive T cells in healthy individuals are extremely long-lived, with expected lifespans of 6-9 years. The longevity of naive T cells has long been disputed. The insight that naive T cells in humans are that long-lived has important implications for our understanding of different diseases and interventions, including HIV-infection, stem-cell transplantation and thymectomy. 2) By quantifying the change in naive and memory T-cell turnover in HIV-infected individuals we show that there is no lack of T-cell production in HIV-infection.



- Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, Bont L; Dutch RSV Neonatal Network. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med*. 2013 May 9;368(19):1791-9.

This study - considered a game-changer in the RSV field – demonstrated a causal link between RSV infection and wheeze, which has now been prioritized for research by the World Health Organisation. The potential impact of preventing asthma has boosted the field of RSV vaccine development.

- R.J. Geerdink, M.P. Hennis, G.H.A. Westerlaken, A.C. Abrahams, K.I. Albers, J. Walk, E. Wesselink, R. Janssen, L. Bont* and L. Meyaard*. 2018. LAIR-1 limits neutrophil extracellular trap formation in viral bronchiolitis. *J Allergy Clin Immunol*. 141:811-814.

Tracheal aspirates from mechanically ventilated children suffering from RSV bronchiolitis, are full of activated neutrophils, that have an enhanced propensity to form neutrophil extracellular traps. The immune checkpoint receptor LAIR-1 limits this, providing a possible therapeutic target to limit lung damage due to neutrophil-mediated immune pathology.

- Hermans LE, Moorhouse M, Carmona S, Grobbee DE, Hofstra LM, Richman DD, Tempelman HA, Venter WDF, Wensing AMJ. Effect of HIV-1 low-level viraemia during antiretroviral therapy on treatment outcomes in WHO-guided South African treatment programmes: a multicentre cohort study. *Lancet Infect Dis*. 2018 Feb;18(2):188-197.

This large-scale study shows that low-level viraemia occurs frequently and represents an important threat to virological success. Current WHO-guided clinical practice in low-income and middle-income countries is not geared towards early recognition and management of low-level viraemia. This study urges the policy makers and clinicians to incorporate management of low-level viraemia in their efforts to control the HIV epidemic

4.9 Two most important examples of societal contributions

Improving vaccine development

Global burden of disease estimates identified respiratory infection as the leading cause of infant mortality. Following malaria, respiratory syncytial virus (RSV) infection is the second most common cause of death in children under the age on one year. There is a concentration of RSV research at the Utrecht Science Park of which a substantial part is led by the Bont-Meyaard translational research group. At the LTI, this group has studied patient-derived airway neutrophil biology leading to identification of novel therapeutic targets on neutrophils, which are studied with support of pharmaceutical industry. The immune response of epithelium in RSV infection is studied in primary epithelial culture models with the Beekman lab of the Hubrecht laboratory. At the MMB, a large-scale molecular virology study is underway to measure the prevalence and global distribution of escape mutants to an extended half-life antibody against RSV (nirsevimab), which is soon expected to be introduced as a “passive vaccine” in the national vaccine schemes throughout the world. In this molecular surveillance study, UMC Utrecht is working closely with research at the World Health Organisation and the National Institute of Health (NIH). At the patient level, vaccine development is further facilitated by studying burden of disease (IMI-funded RESCEU consortium) in childhood as well as in older adults. At the end of the translational medicine pipeline, this research theme performs clinical trials. UMC Utrecht researchers collaboratively developed a nasal application of an RSV-specific antibody which is currently tested in a phase 2b trial. The overarching aim of this affordable prophylactic drug is to provide access to high-risk babies in developed as well as low-and-middle income countries. To optimize patient impact, all RSV research grants are reviewed before submission by an independent RSV patient advisory board. Taken together, this research theme uses the full translational medicine pipeline, from discovery to introduction, to understand immunopathogenesis, develop treatment targets and improve vaccine development against one of the most deadliest viral infections during infancy.

Immune evasion research for antibacterial strategies

Infections with drug-resistant bacteria pose a major threat to human health and result in massive increases in health care costs. Especially the ‘ESKAPE pathogens’ (i.e. *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*) are organisms that are increasingly difficult to treat with conventional antibiotics and understanding host-pathogen interactions will aid in tackling the urgent need for novel treatment options to fight the growing number of drug-resistant pathogens.

Frontier studies on host-pathogen interactions by the groups of Prof. Van Strijp and Prof. Rooijackers revealed that successful pathogenic bacteria only survive in the human host if they have ways to block the immune system, and we discovered over 50 these immune evasion molecules in the past decade. When bacteria enter the human body, they are



confronted by the human innate immune system (neutrophils, complement, antimicrobial peptides) that try to eradicate the infection as soon as possible and the immune evasion molecules counteract that attack. The immune evasion molecules not only suppress natural immunity but also hamper the current attempts to create effective vaccines as they are also vaccine evasion molecules. From our work on Staphylococci in humans, we have learned that even sufficient amounts of antibacterial antibodies do not work in vivo when such molecules are produced locally. A vaccine cannot work when neutrophils or complement do not reach the site of infection or are inactivated. Together with GSK in Siena we will increase vaccination efficacy by including evasion molecules in vaccines. Alternatively, we also explore ways to inactivate immune evasion molecules by monoclonal antibodies.

Antibody-based biologicals are considered an attractive alternative route to clear infections. Because of our unique expertise and functional assays to study immune activation on bacteria, we plan to develop new anti-bacterial antibodies that potently trigger immune activation. Major advantages include rapid activity and requirement of only basic (non-adaptive) immune functions (e.g. complement, phagocytes) that are retained even in immunocompromised patients. Progress in antibody therapies against bacteria is hampered by limited knowledge of the processes underlying antibody-dependent immune activation on bacterial cells. We aim to identify new antibodies with strong immune-activating potential using a non-biased approach, in which our functional assays drive the antibody selection process. For this we developed functional assays that measure bacterial killing, complement pore formation and phagocytic killing in a high throughput fashion and combine this with B-cell sequencing on smart-selected relevant B cells. These antibody candidates are then produced recombinantly and characterized in our functional assays and in vivo models of infection. With our detailed knowledge of the complement system and collaboration with Genmab (shared patent), we showed that antibodies require organisation into hexameric structures to induce potent complement activation. This provides a unique opportunity to potentiate the capacity of antibody therapies.



5. Research theme: developing immune-mediated therapy & prevention

5.1 Mission, urgency and/or relevance of the research questions

The immune system is designed to protect us from threats from outside and ideally does this with causing the least damage. The power of the immune system is underlined by “old” approaches such as passive and active vaccination and recent advances in cancer therapy, where blockade of immune checkpoints leads to tumor reduction and even removal by the body’s own defense system. The groups in this theme aim to harness our immune system to fight infection and cancer and to restore immune balance in the case of inflammatory disease. The scientific basis of these approaches often stems from work in the themes “preventing inflammation” and “elucidating host-pathogen interactions”. The tumor immunology work is also part of the strategic research program Cancer.

The focus of research activities in this theme during 2013-2018 were immune mediated therapy and prevention in:

- *Cancer (tumor immunology)*: Aims to provide next generation (personalized) immune therapies to patients with (hematological) malignancies by finding novel targets for cancer immune therapies (e.g. extend the scope chimeric antigen receptor T cell (CAR T) therapies, thromboelastography concept), developing intelligent combinations with targeted therapies, and developing personalized transplantation care and next generation immune checkpoint inhibitors (ICI) (assess predictors and analyze underlying mechanisms of toxicity, resistance, role with microbiome).
- *Inflammatory diseases*: Aims to provide personalized care to patients with Immune mediated inflammatory diseases (IMIDs) based on (immune) molecular profiling of these conditions. Furthermore, since there is growing evidence for different IMIDs sharing molecular profiles, we focus on developing intelligent clinical trial designs and readouts, as well as early clinical pipeline developmental programs in close collaboration with pharmaceutical industries. Chronic inflammation is often accompanied by chronic pain. We develop novel treatment modalities for the treatment of pain, with aim to bring this to the clinic.
- *Infectious diseases*: Aims to guide the development and implementation of rational and evidence-based vaccination programs for medically vulnerable patients, and for the society at large, in order to reduce the disease burden from vaccine preventable diseases. In addition, through internationally-recognized and societally well-embedded research, we aim to improve treatment of (hospitalized) immunocompromised patients suffering from difficult-to-treat bacterial infections, through developing therapeutic antibodies for drug-resistant bacterial infections. (*S. aureus*, *K. pneumoniae*, *S. pneumoniae*, *P. aeruginosa*).

5.2 Relation to existing knowledge

Cancer

Within the last 5 years cancer immune therapy became a game changer in cancer therapies, and today three major drug pipelines entered clinical practice: cancer specific antibodies, checkpoint inhibitors and living drugs (e.g. CAR T cells). Within the theme hematology and tumor immunology, we have been involved during the last decade in developing these three branches.

We have a strong and long-standing pipeline in developing IgA as potential backbone for cancer immune therapy (Group Leusen), which has the power to complement IgG-based immune therapies in collaboration with commercial partners. In addition, we have discovered novel checkpoint inhibitors and generated clinical cohorts to test efficacy and toxicity parameters connected to checkpoint inhibitor treatments (Groups Meyaard & Suijkerbuik). We also developed different so-called advanced therapy medicinal products (ATMPs), such as mesenchymal stromal cells that entered clinical practice for the treatment of graft versus host disease after stem cell transplantation and next generations of CAR T (see example of development: TEGs, metabolic cancer targeting Goups Kuball & Sebestyen). In addition, we also explored whether for the most successful cellular therapy to date, namely the allogenic stem cell transplantation, further harmonisation is possible as progress is mainly hampered by historical approaches that have been grown over decades in stem cell transplantation centers world-wide. We have also connected and harmonized the allogeneic stem cell transplantation programs between the UMC Utrecht and PMC through a comprehensive biobank (Groups Nierkens, Lindemans, Kuball) and on young adult cohorts with harmonized treatment schedules as fundament for innovative drugs generated (Groups Vormoor, Kuball).



Thereby, we created a unique position of the UMC Utrecht for future development of novel therapies in Europe. Finally, exploring the combination of novel small molecules with immune therapy based concept, particularly in B cell malignancies, is a new development and will be used to cross-fertilize the strategic research programs Cancer and I&I (Group Peperzak & Minnema) and allow developing overarching themes for the next wave of drugs and a more structured patient journeys from the age of 0 to 100 (see also <http://www.tumor-immunology-utrecht.nl>).

Inflammatory diseases

The development of novel therapeutic modalities for IMIDs has surpassed every expectation over the past few years. The discovery of TNF α inhibitors for rheumatoid arthritis (RA) has led to a major breakthrough for patients with RA, psoriasis and inflammatory bowel diseases. We have now come to a point where clinical trials have become a challenge because of the large number of drug targets entering phase II and III clinical trials leading to a shortage of patients that fit the criteria for such trials. Yet, despite some exceptions (e.g. anti-IL-23 for psoriasis and anti IL4/IL-13 for atopic dermatitis) true progression in treatment efficacy has been absent after the introduction of TNFi. Hence, the time has come to develop more personalized treatment approaches. As drugs work via molecular mechanisms, re-classifying IMIDS on the basis of molecular fingerprints is a rational approach. Within the UMC Utrecht we have the unique opportunity to embark on this unmet need by bringing all immunological research covering >20 different IMIDs and >10 different clinical disciplines under one roof. Hence, multiple immune cell subsets and OMICS layers are currently collected from >1000 patients that are followed longitudinally and spanning from early childhood till the elderly. In addition, combining multiple IMIDs opens the opportunity to focus on disease over-arching phenotypes (interstitial lung disease, cardiovascular risk, sex bias, chronic fatigue, pain). In collaboration with the computational biology department of Utrecht University we are currently developing novel computational programs and machine learning algorithms to apply the gained molecular data for drug design (CXCL4), drug repurposing (RepurpSS-I/II) and improvement of daily clinical practice.

Infectious diseases

Work on the development of therapeutic antibodies and alternatives to antibiotics builds on 20 years of research in the Department of Medical Microbiology (Rooijackers, van Strijp; also see Research Theme "Elucidating host-pathogen interactions"). We increase vaccination efficacy by including evasion molecules in vaccines, develop alternative model systems next to mice (e.g. human skin) and develop strong opsonic antibodies with use of our functional immunoassays.

Antibody-based biologicals are considered an attractive alternative route to clear infections. We aim to identify new antibodies with strong immune-activating potential. Targets for these antibodies are the same as in vaccination. We aim for highly potent opsonic antibodies combined with evasion molecule/toxin neutralizing antibodies. Using B-cell sequencing in human volunteers and patients and production of antibodies against our targets in vitro helps us, combined with functional in vitro analysis to design the most potent antibodies that we further enhance using state of the art patented technology (shared patent with Genmab).

In this topic we also investigate vaccine strategies (Bruijning-Verhagen, van Baarle, Bont). This research addresses major topics in the National Research Agenda Prevention; which preventive strategies can be designed and implemented that aid in specific improvement in health of vulnerable groups in short, middle and long term? And how can implementation of existing effective prevention strategies be improved in order to reach large groups and specific (vulnerable) target groups, also and in particularly before and during target moments.



5.3 Collaborations with stakeholders

Many stakeholders are involved in formulating research questions.

Cancer

Within this topic, we have close links with:

- Patient organisations, e.g. for all clinical trials and translational research, we created a quarterly interaction with HEMATON (Dutch hematology patient organisation) and Stichting Melanoom and we involve the organisation during grant submission as well as follow up of project;
- Societies of health care professionals and reference networks, e.g. for solid tumors through quarterly meetings with the WIN-O (working group immune-oncology) and scientific board of DMTR (Dutch Melanoma Treatment Registry). All parties involved collaborate with the Dutch Cancer Registry for clinical care and research;
- Companies, e.g. collaboration with companies is critically reflected in development programs with different industrial partners such as Gadeta, Miltenyibiotec, Medixciventures, Synthron, Genmab and Nextcure taken along for the valorisation of findings from our translational research.
- We participate in Oncode Institute, with the aim to translate basic knowledge on immune checkpoint receptors into clinical application without delay. Oncode is an independent institute in the Netherlands dedicated to outsmarting cancer and impacting lives. Meyaard is Oncode investigator.

Inflammatory diseases

The involvement of patients ('organisations) in the LTI is highlighted in section 3.3. For public-private partnerships: they play an important role in the translation of results residing from the lab. Investigator initiated studies in collaboration with biotech and pharma companies to develop novel strategies to restore immune balance include work with AbbVie, Pfizer, Takeda, Janssen, GSK, MedImmune, ArgenX, Boehringer Ingelheim, Janssen, Ono Pharmaceuticals, and Nutricia. Synerkine Pharma originated at the LTI and is now collaborating with several groups in the LTI.

Infectious diseases

For vaccine development, there is constant interaction with clinicians, RIVM and major pharmaceutical industries (e.g. vaccine manufacturers) in order to guide the research into therapeutics with a high medical need. For several grants on immune-mediated therapies, we partner with Genmab (located at the campus), an international company developing antibody therapeutics for treatment of cancer and strong track records in antibody biology research and antibody engineering. The UMC Utrecht Technology Transfer Office (TTO) supports in patent writing and formulating research contracts with companies, and ultimately with licensing and developing the intellectual property.

5.4 Research design

Research groups in this theme are embedded in LTI, MMB and Julius Center. LTI and MMB host core-facilities providing computational and technical support as outlined in sections 1.3 and 3.4. The Julius Center hosts expertise in clinical epidemiology, statistics and mathematical modelling. The UMC Utrecht biobank facility is the backbone for all biobanks to allow standardized collection of material collected during clinical trials or general biobanking initiatives.

Specific for subtopics:

Cancer

- We may refer to our strategic set up of complementary research groups connected to harmonized treatment journeys (see 5.2). These groups are meeting through the Strategic Research Program I&I (LTI) as critical think tank and allow e.g. the critical discussion of an experimental Setup of Translational Studies. Thus by utilizing the Tumor Immunology Utrecht Platform located at the Strategic Research Program I&I (LTI), within the Cancer Center, the joint UU-UMC Utrecht Utrecht Molecular Immunology HUB, Hubrecht Institute, and PMC we connect leading experts in the field providing peer support during the development of the next generation of studies.
- Given our unique expertise in ATMP development, the ATMP facility of the UMC Utrecht is an additional key ingredient and provides support during designing and execution of studies dealing with cellular therapies.



Inflammatory diseases

- Experimental Setup of translational clinical studies: Critical discussion with peers from the field during EU projects like NECESSITY, HARMONICSS (HARMONisation and integrative analysis of regional, national and international Cohorts on primary Sjögren's Syndrome), REPO-TRIAL (REpurOsing TRIALs), partners on initiator investigated studies from the industry and the clinical trial unit (Department of Rheumatology);
- OMICS: within the I&I center, unique expertise is present on the OMICS we currently apply such as; microbiome, transcriptome, epigenome, imaging (radiology), exposome (Dutch exposome center, I&I), metabolomics, cell phenotyping (flow cytometry core facility, LTI) and proteomics (U-DAIR, LTI);

Infectious diseases

- Our research on development of immune-mediated therapies is well embedded in the context of several other research projects in the Rooijackers and van Strijp groups at the department MMB, for example ongoing research funded by European Research Council and Utrecht University Molecular Immunology Hub to study basic mechanisms of antibody-mediated immune activation on bacteria. Our research on vaccines is embedded in e.g. VITAL consortium that examines the immunology of ageing and vaccination programs in elderly.

5.5 The next step

Cancer

- IgA development: We initiated the startup company TigaTX which will further utilize IgA as backbone for novel therapies.
- Checkpoint development: LAIR-1 based anti-cancer therapy is developed with an US based biotech company, with the ambition of IND filing in 2020. This would bring a receptor discovered by Meyaard in 1997 and studied ever since, into clinical application. We also invested in clinical cohorts and a novel computational pipeline to identify potential checkpoint receptors encoded in our genome, of which still hundreds are available. We will now select lead candidates for further characterisation and will generate antibodies in our in-house facility that can serve as blockers. This effort is embedded in Oncode and with the aim to explore this concept with commercial partners or also spin out the platform given its high potential.
- Next generation of CART, the TEG pipeline: The patient organisation is involved in academic clinical trial designs and next steps during the dose escalation study. For further valorisation key stakeholders (Gadeta, KITE, Gilead) are involved in the project. For the TEG pipeline we expect that the startup company will perform a next series of clinical trials while we will focus within academia on novel targets as well as bispecific projects and aim to potentially open a second company on the GAB concept.

Inflammatory diseases

Designated molecular fingerprints shared by different IMIDs will be taken forward in novel design of clinical trials – bucket trials – in which patients with diverse clinical conditions are given a similar therapeutic target based on their molecular signature and irrespective of their diagnosis. We have collaborations with big pharma partners considering such novel trial design approach (e.g. AbbVie, Roche, Jansen). These designated molecular signatures form a solid basis for early (pre) clinical drug design trajectories. Before entering such trajectories with pharma or biotech, our valorisation department will be consulted and a fast-track program will be followed to spin-out a company or engage in a collaborative research agreement with big pharma. Finally, molecular classification of disease brings about the unprecedented opportunity for drug repurposing. This is exemplified with our recently executed clinical trial in patients with primary Sjögren's Syndrome (RepurpSS-I) in which we re-purposed two existing drugs (leflunomide and hydroxychloroquine) reaching high efficacy (~50%). These initial results, as well as validation of our predictive molecular algorithm for therapy response, will be further tested with funding from ZonMw (RepurpSS-II).

Infectious diseases

For the development of therapeutic antibodies, in our NACTAR project from TTW (Dutch Research Council domain Applied and Engineering Sciences), we involve several partners that are involved in bringing antibodies to the end users (patients): we include clinical microbiologists to join bi-annual user committee meetings, and the main commercial partner, Genmab, has expressed interest to bring our research finding into practice. Genmab provides in-kind contributions to setting-up antibody sequencing and helps to design our research questions. We already have a patent together with Genmab for the use of engineered antibodies for treatment of infectious diseases. Novel findings from NACTAR project may lead to further patent applications.



The second user Hycult Biotech is involved for potential commercialisation of anti-bacterial antibodies for diagnostic laboratory assays, which will improve diagnostic tools to detect *Klebsiella* infections in patients. Bas Nagelkerken (Technology Transfer Office) and the legal department of UMC Utrecht was involved in the design of the IP agreement. In another project directly funded by Genmab, Genmab fully funds researchers in the lab to identify antibodies against *S. aureus*.

Projects with evaluation of (new) vaccination programs for special target groups will be essential for evidence-based and more personalized vaccine policies. With the increasing number of infant vaccines that become available in the near future, this approach is essential to maintain the trust of the general public in vaccination programs. Through the RIVAR project, we have an extensive collaborative network of hospitals involved in care for vulnerable pediatric populations and close links with pharma involved in vaccine development and production (GSK, MSD, Pfizer, Sanofi Pasteur). The UMC Utrecht takes a leading role in designing and executing vaccine studies in these special pediatric populations. For the coming years; additional target vaccines will include influenza and pertussis, as well as diseases for which vaccines are expected to become available in the near future (norovirus, RSV). Another major challenge is to improve vaccine efficacy in elderly and to define clear vaccination strategies to protect ageing adults against infectious diseases. Through the VITAL project (with 17 academic and public institutes and 7 private partners), we will assess the burden of vaccine preventable diseases, explore the mechanisms of immunosenescence in ageing adults, compute the clinical and economic impact of vaccination strategies, across different age and risk groups, and develop educational resources for stakeholders. The aim is to provide evidence-based knowledge to develop targeted vaccination strategies.

5.6 Results highlights

5.6.1 Research products for peers

Patents

- Several PIs are inventors on a number of patents. E.g. Kuball/Grunder for methods to mediate anti-tumor or anti-infectious response, Leusen on development of therapeutic IgA antibodies, Peperzak on a novel technology to improve the killing machinery of engineered T cells for use in cancer immunotherapy, Radstake on treatment of systemic sclerosis, Eijkelkamp/Willemsen on chronic pain treatment, Rooijackers/van Strijp treatment infectious diseases (details not to be disclosed)

Methods, technology

- Peperzak group developed highly reproducible 3D hydrogel culture methods that allow culture of patient cells (including multiple myeloma bone marrow cells) and can be used to test cellular behavior during cancer progression and upon treatment.

Cohorts, datasets

- UNICIT-cohort encompassing all ICI treated patients in UMC Utrecht to assess predictors and analyzing underlying mechanisms of toxicity, identify ways to modulate microbiome improving ICI outcomes, identify novel targets for ICI and develop algorithm for predicting ICI non-response using CT-scans and histology slides (nationwide).
- The stem cell transplantation biobank (UMC Utrecht, PMC) as well as the leukemia, myeloma and lymphoma (LML) biobank (Parel) allow collecting material from harmonized patient journeys (Kuball/Minnema/Lindemans) and resulted e.g. in the novel dosing of ATG during stem cell transplantation as reflected in the new European Group for Blood and Marrow Transplantation (EBMT) guidelines.
- Radstake group (van Roon, Radstake, Kruijze) designed and executed the first drug repurposing trials in patients with Sjogrens Syndrome which has led to the first ever effective trial for this condition.
- Pain clinic-Rijsdijk/van Dijk participate in the International PAIN OUT network (<http://pain-out.med.uni-jena.de/>) aiming to reduce postoperative pain and setup a cohort of postoperative patients with detailed pain analysis to predict the development of neuropathic pain.
- Bruijning group set up a collaborative research network for vaccine studies in medically vulnerable pediatric populations. Collaborations were set up with pediatric/neonatology departments of 13 secondary and tertiary care hospitals across the country. Thus far, two infant cohorts have been set up through this network; the RIVAR cohort to study rotavirus vaccination effectiveness in risk-group infants, and the PRIEMA cohort on the immunogenicity of national immunisation program vaccines in preterm infants.
- Van Baarle group set up a unique healthy elderly cohort in which CMV-specific immunity and healthy ageing biomarkers are investigated.



Publications, theses

The principle researchers in this theme published >270 publications (Scopus) and 21 PhD theses in 2013-2018.

5.6.2 Research products for societal target groups

Guidelines, implementation, policy

- Introducing abT cell depletion as standard of care in allo SCT in 2018 and achieving reimbursement from 2020. Based on the work of Kuball group, the abT cell depletion was introduced in the guidelines of EBMT and guidelines of HOVON, which resulted in reimbursement of the procedure by the Dutch insurances from 01/2020.
- Nierkens group developed an assay to measure active antithymocyte globulin in children (a form of serotherapy given to patients undergoing hematopoietic cell transplantation (Admiraal et al. Lancet Haematol 2015) and was translated into the adult population (Admiraal et al. Lancet Haematol. 2017) and is reflected in the new EBMT guidelines (Kuball, Nierkens, Lindemans).
- Aneasy-to-use nomogram was designed to define the optimal dose of ATG for individual patients based on weight and absolute lymphocyte counts. This has been implemented in standard-of-care for ATG conditioning in the UMC Utrecht and PMC and several international centers.

Software, tools

- Bovenschen group has developed a software tool (together with KonJoin and UU) to better connect researchers and clinician-scientists with each other and with society/students, also to facilitate research internships (2017).
- Bruijning/de Hoog developed the Research Follow-App; an IT application for improved detection and registration of participant reported outcomes in medical research. Used in several research projects at WKZ and RIVM, and available as a service to third research parties. The application consist of a software platform from which custommade research Apps can be designed, with specific focus on data that require longitudinal and repeated reporting by participants.

Outreach

- Bruijning has been invited on several television shows, radio broadcasts, newspaper interviews and articles for popular magazines as an expert on immunisations and immunisation policy. Together this involves > 20 public outreach contributions in the past year.
- Bruijning organized the 5th European Expert Meeting on Rotavirus Vaccination (Utrecht, March 20-22, 2017)
- Bovenschen, Nierkens and Boelens made movies to explain their research to general public (Dendritic cell vaccination: <https://youtu.be/tT8wBN1HvEo>; Neuroblastoma: <https://youtu.be/ly1zlyQbWz0>, <https://www.youtube.com/watch?v=VAJOeUpOZIM>)
- Meyaard/Suijkerbuijk: Dutch language chapter for general public in publication from Biomedical sciences and society: "Checkpointblokkers: Doorbraak in kankertherapie" (with K. Suijkerbuijk) in "Ons Afweersysteem" Biocahier Biowetenschappen en Maatschappij, nr 3, 2018.
- Kuball provided multiple interviews by using the EBMT platform as well as communications to connect the community and distribute novel ideas on how to deal with novel transplantation concepts (>10 contributions)

5.6.3 Use of research products by peers

Models, analyses

- The antibody core facility U-MAB of the LTI (Moerer/Leusen) has successfully completed several antibody-generation projects for internal peers, external academic groups (UU, AMC, PMC), or industry (Synthon, Aristi, U-protein, ONO Pharmaceutical). As example, the antibodies generated for Synthon in 2016, have been selected to be clinically developed as an ADC (antibody Drug Conjugate), and are at the moment tested in Cynomolgous Monkeys (2019), and will go into clinical trials for AML patients in 2020.
- CXCL4 that is identified as biomarker in systemic sclerosis (SSc) by Radstake group is currently used as disease activity marker in multiple international clinical trials (van Bon et al. NEJM 2014).
- Spierings' group developed online software (www.pirche.org) for HLA matching in stem cell- and organ transplantation, free to use for research, commercial for clinical application. The PIRCHE web portal contains 380 registered users worldwide. For these users, a total of more than 200000 PIRCHE analyses were performed for approximately 75000 individuals/patients. Forty-one users executed 30 match runs or more. The first transplant center outside Utrecht started to use the PIRCHE model (Spierings group) for clinical use in 2018.



Assays

- Nierkens group set up an assay to detect ADA2 activity to diagnose ADA2 deficiency. We receive samples from multiple international centers for analyses (Astrid Lindgren's Children Hospital, Stockholm; Klinik für Immunologie UniversitätsSpital, Zürich; Klinik für Kinder- und Jugendmedizin Universitätsklinikum, Aachen; etc) for description in case reports. The results van the novel ATG dosing scheme that we have developed for children has also been adapted for adults, and changed clinical care in both populations.
- Rooijackers's novel assay methods to measure the activity of complement enzymes is now used by colleagues in the complement field to study the activity of complement regulators. Our methodology can be used to develop therapeutic inhibitors of complement. (Berends et al. BMC Biology 2015)

Other

- Bovenschen has founded the concept Bachelor Research Hubs, an (UU-wide) initiative to improve undergraduate research. Within the UMC Utrecht, the Bachelor Research Hub is a dedicated laboratory space positioned in the middle of ongoing research and healthcare where bachelor students (biomedical sciences, medicine) can meet researchers, clinicians and clinician-scientists, and have the opportunity to do biomedical and clinical research, also on patient cases. This not only stimulates interdisciplinary learning but also creates synergy between teaching, research, patientcare, and society. A novel laboratory course where students work on an actual research problem of one of the PIs has been implemented (2017). A paper describing this novel educational approach has been conditionally accepted for publication in *Nature Biotech.* (also see: 'Micha (4) verbindt zorg, onderzoek en onderwijs'. UMC&ZO dec, 2018; UMC Utrecht Twitter, LinkedIn, Facebook; and 'Studenten zoeken de oorzaak van Micha's ziekte'. UMC Utrecht. Connect. Dec 2018.

5.6.4 Use of research products by societal groups

Valorisation

- Research from a few groups resulted in establishment of spin-off companies. E.g. Gadeta was established in 2015 for valorisation of a first set of gdTCRs. Kuball is scientific co-founder and inventor on all key patents. Named as one of the top 10 spin-offs of 2016 worldwide by Nature Biotechnology (Bouchie et al. 2017). In 2018 the company started a strategic partnership for the clinical exploration of main leads with KITE and GILEAD; spin-off Synerkine Pharm was established to develop IL4-10 synerkine for the treatment of chronic pain. Combined research from Hack, Eijkelkamp and Lafeber (e.g. Eijkelkamp et al. J Neurosci. 2016) led to the granting of a patent in Europe and Japan for the a fusion protein of anti-inflammatory cytokines IL-4 and IL-10. TigaTx is a company founded by Leusen and aims to employ IgA antibodies in tumor therapy.
- Many research group perform contract research or gained PPP grants; e.g Leusen group has >13 research contracts with industry (e.g. Synthon, Argenx, Genmab, Nutricia), Eijkelkamp group has several contracts with Max Planck institute (Germany) to test novel compounds to treat type 2 diabetes; Raymakers/Peperzak performed contract research with Philips Research BV; van Strijp received a grant to develop Staphylococcal vaccines together with MSD Animal Health and to develop vaccines with the commercial partner GSK; Boes lab collaborates with Bunyavax and ISA Therapeutics B.V; Meyaard collaborated with Ono, Janssen, Nextcure and Boehringer Ingelheim; Rooijackers's work on antibody therapies was supported by Genmab, Nierkens group valorized the ATG measurements and immune monitoring technology by performing assays for SME and pharmaceutical companies (Kiadis, GamidaCell).

Guidelines

- Minnema contributed to the use of CD38-specific antibody Daratumumab for Multiple Myeloma in the Dutch national clinical guidelines.
- Bruijning: A rotavirus vaccination cost-effectiveness evaluation conducted by our research group was used by the Dutch Health Counsel to formulate the advisory statement and was instrumental in the decision making process by the Minister of Health on the chosen rotavirus vaccination strategy (universal versus targeted rotavirus vaccination).
- Spierings was invited to write the chapter on Histocompatibility of "The EBMT Handbook" as first authors (published in 2019). This handbook provides guidelines to clinicians for hematopoietic stem cell transplantation.

5.6.5 Marks of recognition from peers

Awards, grants

- Rooijackers was selected for the prestigious EMBO Young Investigator Program (2016), and was awarded a Young Investigator award by the international Complement society (2014). Minnema received a Spafima research grant (2018) entitled: Predicting multiple myeloma therapy response using a 3D organoid bone marrow model.



- Van Baarle/Bonten received an IMI grant (€6M) as scientific Lead for VITAL program, research on vaccines and infectious diseases in the ageing population. This is a public-private consortium consisting of 24 partners in 13 countries.

Board participation

- Radstake is executive board member and chair of investigative rheumatology within the European League Against Rheumatism (EULAR), associate editor of Arthritis and Rheumatology and Editor EU of Expert reviews of Clinical Immunology. Radstake and Kuiper are chair and board member, respectively, of the European Association for Systems Medicine (EASYM).
- Kuball has been executive member of the EBMT and is now chairing the legal regulatory advice committee of EBMT which is key in implementing novel drugs (e.g. ATMPs) to the European market (<https://www.ebmt.org/legal-regulatory-affairs-committee>).
- Spierings is co-chair of the 18th International HLA & Immunogenetics Workshop and co-chair for the 35th Conference of the European Federation for Immunogenetics 2021.

5.6.6 Marks of recognition from societal groups

Board participation

- Minnema is member of the medical advisory board of patient organisation Amyloidosis and HEMATON.
- Radstake is Advisory board member of the National society of SLE and APS patients (www.NVLE.org)
- Bruijning served as external advisor for the Dutch Health Counsel committee on immunisations (2017/2018) and serves as expert and representative of the Dutch Pediatric Association on the multidisciplinary guideline committee on immunisations coordinated by RIVM

Awards, grants, contract research

- Spierings group received the UMC Utrecht Ureka Mega Challenge Award 2013 for innovation.
- Bovenschen has been appointed as Senior Fellow of the Center of Academic Teaching of Utrecht University (2017) and rewarded with a NWO Comenius Teaching Fellow grant (2018). As such he has been appointed as a member of the KNAW Comenius Network that advises the minister and Ministry of Education, Culture and Science (OCW). Bovenschen has been rewarded (also by students) with the titles: 'Teacher of the Year 2018' of the Faculty of Medicine and as 'Teacher of the year 2018-2019' of the whole Utrecht University.
- Rooijackers received grants for two PPP-research consortia (grants from NWO-TTW (TTW-NACTAR) and TTW-Industrial doctorate

5.7 Two examples of patient involvement

- The Department of Hematology has meetings three times a year with the patient organisation HEMATON to discuss their needs and research projects developed at the UMC Utrecht. This includes clinical studies with novel therapies for treatment of multiple myeloma, such as the BCMA-BiTe study. Other examples are the target study, developed in collaboration with Kuball/de Witte and the patient organisation (http://www.hovon.nl/studies/studies-per-ziekte-beeld/sct.html?action=showstudie&studie_id=151&categorie_id=11) and the TEG001 study (<https://www.trialregister.nl/trial/6357>). In addition, in 2018 a visit ("werkbezoek") by HEMATON took place in order to assess whether the clinical branch covers the needs of the patients. This platform has been awarded by HEMATON (waarderingsprijs: [https://www.hematon.nl/nieuwsberichten/waarderingsprijzen+voor+UMC Utrecht-team+stamceltransplantatie+en+bestuurder+groene+kruis](https://www.hematon.nl/nieuwsberichten/waarderingsprijzen+voor+UMC+Utrecht-team+stamceltransplantatie+en+bestuurder+groene+kruis)).
- Nierkens group developed a dendritic cell vaccination strategy that has been (re-) submitted to the Dutch Clinical Research Foundation (CCMO; NL65115.000.18/ U-DANCE-anti-AML). The VOKK (society for parents of children with cancer) was consulted from the beginning and provides valuable input to reduce potential discomfort for the children. More specifically, the VOKK has the experience that young patients are often concerned that the intradermal injections may be painful. Since we do not want patients to refuse further vaccination because of this, the VOKK pointed out the option of using lidocaine/tetrocaine 70mg/70mg (Rapydan®) plasters at the marker injection site 1 hour before vaccination, which in their experience reduced discomfort. This has been implemented in the protocol. The VOKK was also part of the team that made the movie about the dendritic cell vaccine (<https://youtu.be/tT8wBN1HvEo>).



5.8 Ten most important scientific publications

1. Sebestyén Z, Scheper W, Vyborova A, Gu S, Rychnavska Z, Schiffler M, Cleven A, Chéneau C, van Noorden M, Peigné CM, Olive D, Lebbink RJ, Oostvogels R, Mutis T, Schuurhuis GJ, Adams EJ, Scotet E, Kuball J. RhoB Mediates Phosphoantigen Recognition by V γ 9V δ 2 T Cell Receptor. *Cell Rep.* 2016 May 31;15(9):1973-85.
This paper elucidates the crucial role of a small GTPase in the inside out recognition mechanism of a tumor cell by a g9d2T cell receptor and has been critical to implement toxicity and safety studies for TEG001 and allow entering the phase I clinical trial. In addition, we have submitted a patent for the MoA in combination with TEG001.
2. Brandsma AM, Schwartz SL, Wester MJ, Valley CC, Blezer GLA, Vidarsson G, Lidke KA, Ten Broeke T, Lidke DS, Leusen JHW. Mechanisms of inside-out signaling of the high-affinity IgG receptor Fc γ RI. *Sci Signal.* 2018 Jul 24;11(540).
This paper addresses the issue how the high affinity Fc receptor for IgG, Fc γ RI of CD64, can function. Because of its high affinity, this receptor is always occupied by its ligand, human IgG, under physiological conditions. We elucidated the mechanism how immune complexes or opsonized targets can bind to this important receptor for infection, inflammation and immunotherapy. We made use of super-resolution imaging and D-storm microscopy to reveal the clustering of this receptor. Our results imply that nanoscale reorganisation of Fc γ RI, by inside-out signaling enhances Fc γ RI cellular effector functions, that may impact inflammation and immunotherapy.
3. Peperzak V, Vikstrom I, Walker J, Glaser SP, LePage M, Coquery CM, Erickson LD, Fairfax K, Mackay F, Strasser A, Nutt SL, Tarlinton DM. Mcl-1 is essential for plasma cell survival. *Nature Immunology* 2013; 14(3): 290-297.
This paper describes the crucial role of pro-survival protein MCL-1 in the survival of plasma cells. Partly based on this publication, multiple pharmacological companies (including Amgen, Servier/Novartis, AstraZeneca and AbbVie) initiated development of MCL-1-specific inhibitors to target malignant plasma cells for treatment of Multiple Myeloma (MM). MCL-1 inhibitors from Amgen (AMG 176), Servier/Novartis (S63845) and AstraZeneca (AZD5991) are currently being tested in clinical phase I trials with MM, Acute Myeloid Leukemia (AML) and other haematological malignancies.
4. Oostvogels R, Jak M, Raymakers R, Mous R, Minnema MC. Efficacy of retreatment with immunomodulatory drugs and proteasome inhibitors following daratumumab monotherapy in relapsed and refractory multiple myeloma patients. *Br J Haematol.* 2018 Oct;183(1):60-67.
This manuscript shows that myeloma patients refractory to IMiDs and/or proteasome inhibitors can respond again to those drugs after they are treated with daratumumab. This finding is clinically important and offers new therapeutic possibilities in relapsed-refractory myeloma patients.
5. van Bon L, Affandi AJ, Broen J, Christmann RB, Marijnissen RJ, Stawski L, Farina GA, Stifano G, Mathes AL, Cossu M, York M, Collins C, Wenink M, Huijbens R, Hesselstrand R, Saxne T, DiMarzio M, Wuttge D, Agarwal SK, Reveille JD, Assassi S, Mayes M, Deng Y, Drenth JP, de Graaf J, den Heijer M, Kallenberg CG, Bijl M, Loof A, van den Berg WB, Joosten LA, Smith V, de Keyser F, Scorza R, Lunardi C, van Riel PL, Vonk M, van Heerde W, Meller S, Homey B, Beretta L, Roest M, Trojanowska M, Lafyatis R, Radstake TR. Proteome-wide analysis and CXCL4 as a biomarker in systemic sclerosis. *N Engl J Med.* 2014 Jan 30;370(5):433-43. (cited over 200 times)
This study led to the identification of CXCL4 as a biomarker in systemic sclerosis. Moreover, this research initiated a research line that led to a wealth of knowledge on CXCL4 as a crucial molecule in the immune system (multiple papers in revision). We have now two filed patents on this molecule for the treatment of systemic sclerosis.
6. Geneugelijk K, Niemann M, Drylewicz J, van Zuilen AD, Joosten I, Allebes WA, van der Meer A, Hilbrands LB, Baas MC, Hack CE, van Reekum FE, Verhaar MC, Kamburova EG, Bots ML, Seelen MAJ, Sanders JS, Hepkema BG, Lambeck AJ, Bungener LB, Roozendaal C, Tilanus MGJ, Vanderlocht J, Voorter CE, Wieten L, van Duijnhoven EM, Gelens M, Christiaans MHL, van Ittersum FJ, Nurmohamed A, Lardy JNM, Swelsen W, van der Pant KA, van der Weerd NC, Ten Berge IJM, Bemelman FJ, Hoitsma A, van der Boog PJM, de Fijter JW, Betjes MGH, Heidt S, Roelen DL, Claas FH, Otten HG, Spierings E. PIRCHE-II Is Related to Graft Failure after Kidney Transplantation. *Front. Immunol.* 2018 9:321.
This UMC Utrecht-funded PROCARE-supported retrospective multicenter study on the effect of PIRCHE-II matching in kidney transplantation is the first study to show that the PIRCHE-II score is the strongest HLA-related factor that associate with graft survival. This study proved that this association is in a non-linear fashion. The study also indicated that the effect is most pronounced in first transplants. Data from this study were key for subsequent allocation simulation studies, to show the feasibility of PIRCHE-II matching, and for the health economics study.



7. Eijkelkamp N, Steen-Louws C, Hartgring SA, Willems HL, Prado J, Lafeber FP, Heijnen CJ, Hack CE, van Roon JA, Kavelaars A. IL4-10 Fusion Protein Is a Novel Drug to Treat Persistent Inflammatory Pain. *J Neurosci*. 2016 Jul 13;36(28):7353-63.

In the manuscript we describe the development of a novel immune-based therapy (a fusion protein of anti-inflammatory cytokines) to treat chronic inflammatory pain. The manuscript is important because the data provided is the fundament of the start of a spin-off company for the clinical development of this molecule for the treatment of chronic pain. Moreover it provides more basic insights into how cytokines regulate pain.

8. de Koning C, Gabelich JA, Langenhorst J, Admiraal R, Kuball J, Boelens JJ, Nierkens S. Filgrastim enhances T-cell clearance by antithymocyte globulin exposure after unrelated cord blood transplantation. *Blood Adv*. 2018 Mar 13;2(5):565-574.

In this study we provide an explanation why patients receiving cord blood transplantation are showing more adverse effects from ATG than patients receiving bone marrow transplantation. We show that use of Filgrastim, commonly given to CB-transplanted patients to accelerate immune reconstitution, activates neutrophils with killing of other PBMC as a result, thereby dramatically reducing immune reconstitution in patients that have residual ATG levels. After this finding, the dosing of Filgrastim is adapted in clinical care: it is never given to patients with potential residual ATG exposure.

9. Wensink AC, Kemp V, Fermie J, García Laorden MI, van der Poll T, Hack CE, Bovenschen N. Granzyme K synergistically potentiates LPS-induced cytokine responses in human monocytes. *Proc Natl Acad Sci U S A*. 2014 Apr 22;111(16):5974-9.

This paper shows for the first time that anti-bacterial cytokine responses are enhanced by killer cell proteases. This mechanism constitutes a potential target for anti-inflammatory diseases such as sepsis.

10. Bruijning-Verhagen P, Mangen MJ, Felderhof M, Hartwig NG, van Houten M, Winkel L, de Waal WJ and Bonten MJM. Targeted rotavirus vaccination of high-risk infants; a low cost and highly cost-effective alternative to universal vaccination. *BMC Medicine* 2013 (April):11;112.

This paper was the first health economic evaluation of an alternative rotavirus vaccination strategy for infants. We demonstrated that a targeted approach to rotavirus vaccination in which infants with medical risk conditions (i.e. prematurity, low birth weight or severe congenital conditions), are selected for vaccination is a highly cost-effective approach and much more favourable than universal vaccination of all infants nearly all scenarios analysed. This publication led to paradigm shift in policy decisions analysis for rotavirus vaccination in the Netherlands and beyond, where targeted vaccination is now considered and evaluated as one of two alternative strategies next to the conventional universal infant vaccination approach.

5.9 Two most important examples of societal contributions

Translating preclinical concepts into the clinic and real-world data generation

Kuball group has been instrumental in implementing targeting cancer as metabolic disease into the field of chimeric antigen receptor (CAR) T cells therapies, so-called TEGs (T cells engineered to express a defined gamma delta T cell receptor). In the near future this will allow to target cancer independently of its mutational load and offer a new avenue towards novel targets of cancer immune therapy. We developed the concept during the last 10 years from basic biology to the final product, developed engineering techniques which are fully compatible to good manufacturing practices (GMP) criteria and started a first in human study in 2018 at the UMC Utrecht. Most importantly, the patient organisation HEMATON has been part of the steering committee during the whole development, allowing to fine-tune the design of the academic clinical study. During the process, we wrote patents to secure a potential valorisation of the concept and this resulted in the UMC Utrecht spin-off company Gadeta (www.gadeta.nl), which has been acknowledged as one of the top 10 spin outs world-wide by Nature Biotechnology in 2016 (Bouchie et al.). Gadeta started an exclusive partnership with one of the biggest players in cancer cell immune therapy (KITE/GILEAD) in 2018 that is further developing the concept towards a potential market authorisation.

Due to the fundamental interest of the group in developing novel treatment modalities, the group developed, in close collaboration with the Department of Hematology and additional international partners, a novel concept to reduce toxicity after allogeneic stem cell transplantation platform (so-called graft engineering).



This concept mainly reduces substantially long-term toxicity and will allow to early introduce additional compounds after allogeneic stem cell transplantation to reduce the relapse rate. This exciting development allowed for the first time to harmonize [Dutch stem cell transplantation guidelines](#) as well as to introduce the reimbursement of graft engineering by the Dutch payers.

Through his activities at European Group for Blood and Marrow Transplantation (EBMT), Kuball also changed the way how novel drugs will be assessed after market-authorisation by promoting to European Medicines Agency (EMA) the cellular therapy registry of EBMT as platform for all CART products entering the market which resulted in a [qualified opinion by EMA](#) (2019). In the future this will allow to generate real-world data that will be used for safety assessments of novel CART products as well as provide valuable information to health technology assessment bodies and payers.

Chronic pain

Chronic pain is a major societal problem with more than 20% of population affected. Until now treatment options are very limited, and those options that exist are often ineffective or cause major side effects (e.g. opioid addiction). The latter is highlighted by all news about the current 'opioid crisis' that indicates that many people die because of opioids overuse (USA >130 people/day). Because our current understanding of chronic pain is limited the UMC Utrecht adds to solving this huge societal challenge by providing important new insights on the mechanism of chronic pain, and developing completely new potential immunotherapies to treat pain.

Pain has predominantly been studied from a neurological perspective. Frontier studies on the interaction between the immune system and the nervous system by the Eijkelkamp group, however, have identified important 'immunological' contributors to the development of chronic pain. Besides the identification of pain genes and novel roles of immune cells in regulating pain, we have identified that anti-inflammatory cytokines are key regulators of the resolution of pain and translated these findings together with several other LTI groups (Prof Hack, Prof Lafeber, Dr van Roon) into the idea of a novel therapeutic to treat chronic pain. This approach consists of fusing anti-inflammatory cytokines into one molecule to overcome limitation of individual cytokines. In pre-clinical model, a fusion protein of interleukin-4 and interleukin-10 shows remarkable efficacy in treating chronic inflammatory, neuropathic and osteoarthritis pain. This research has led up to 5 patent applications. These valorisation efforts have further led to a new collaboration with The Centre for Drug Design and Discovery (CD3) to develop small molecules aimed at inhibiting the newly identified pain gene FAM173b. More importantly, the research has been at the basis of an exciting start of a UMC Utrecht spin-off company (Synerkine Pharma) that will clinically develop a fusion protein of the anti-inflammatory cytokines IL4 and IL10 (IL4-10 synerkine) for the treatment of chronic pain. Synerkine Pharma recently raised EUR 3.3 million euro in a Series A financing to execute its plans.

In order to fill the gap in translation of preclinical pain research into the clinic, we are developing a chronic pain phone app with Prof Wulffraat to, in a patient-friendly way, quantify and qualify pain in children in order to obtain better pain data in study cohorts and to provide more information to patients on their pain. In the translation of preclinical pain research to the clinic, we have setup with our clinical partner Rijdsdijk an outpatient clinic for patients suffering from post-herpetic neuralgia with the aim to improve phenotyping of the pain syndrome by studying inflammatory parameters combined with sensory information obtained with quantitative sensory testing. Rijdsdijk has setup the first outpatient clinic in the Netherlands counselling postoperative patients on opioid use in the first month after surgery to reduce opioid use and pain. Patients are additionally screened early on the development of neuropathic pain to further decrease opioid consumption by treating pain of neuropathic origin with the appropriate drugs. By investigating factors that contribute to the risk of developing neuropathic pain in the early postoperative phase, a prediction rule is being developed to ultimately reduce pain and opioid use.



6. Appendix I. Professors and associates in I&I

Preventing antimicrobial resistance

Professors	Associates (incl. clinical)
Prof. Bonten, MJM	Dr. Bootsma, M
Prof. Damoiseaux, RAMJ	Dr. Boel, CHE
Prof. Eijkemans, MJC	Dr. Cremer, O
Prof. Jong, PA de	Dr. Ekkelenkamp, M
Prof. Kluijtmans, JAJW	Dr. Fluit, AC
Prof. Kretzschmar, MME	Dr. Kessel, CPM van
Prof. Schilder, AGM	Dr. Kusters, H (moved 2018)
Prof. Verheij, TJM	Dr. Oosterheert, JJ
Prof. Willems, RJL	Dr. Schaik, W van (moved 2018)
	Dr. Venekamp, RP

Preventing inflammation

Professors	Associates (incl. clinical)
Prof. Boer, JH de	Dr. Balak, DMW Dr. Tesselaar, T
Prof. Bont, LJ	Dr. Bijlsma, JWJ (retired 2018) Dr. Vastert, SJ
Prof. Bruijnzeel-Koomen (retired 2018)	Dr. Boes, ML Dr. Vlist, M van der
Prof. Grutters, JC	Dr. Borghans, JAM Dr. Vrisekoop, N
Prof. Hack, CE (retired 2018)	Dr. Bruin-Weller, MS de Dr. Wijk, van F
Prof. Heijerman, HGM	Dr. Eijkelkamp, N
Prof. Houben, GF	Dr. Hamann, D
Prof. Imhof, SM	Dr. Hoppener, JWM
Prof. Knulst, AC	Dr. Knol, EF
Prof. Koenderman, L.	Dr. Kuiper, JJW
Prof. Laar, JM van	Dr. Loosdregt, J van
Prof. Lafeber, FPJG	Dr. Marut, W
Prof. Lammers, JWJ (retired 2018)	Dr. Nijboer, CHA
Prof. Leenen, LPH	Dr. Oldenburg, B
Prof. Meyaard, L	Dr. Otten, HG
Prof. Miedema, F	Dr. Pandit, A
Prof. Prakken, ABJ	Dr. Reedquist, KA
Prof. Radstake, TRDJ	Dr. Roon, JAG van
Prof. Wulffraat, NM	Dr. Spierings, J



Elucidating host-pathogen interactions

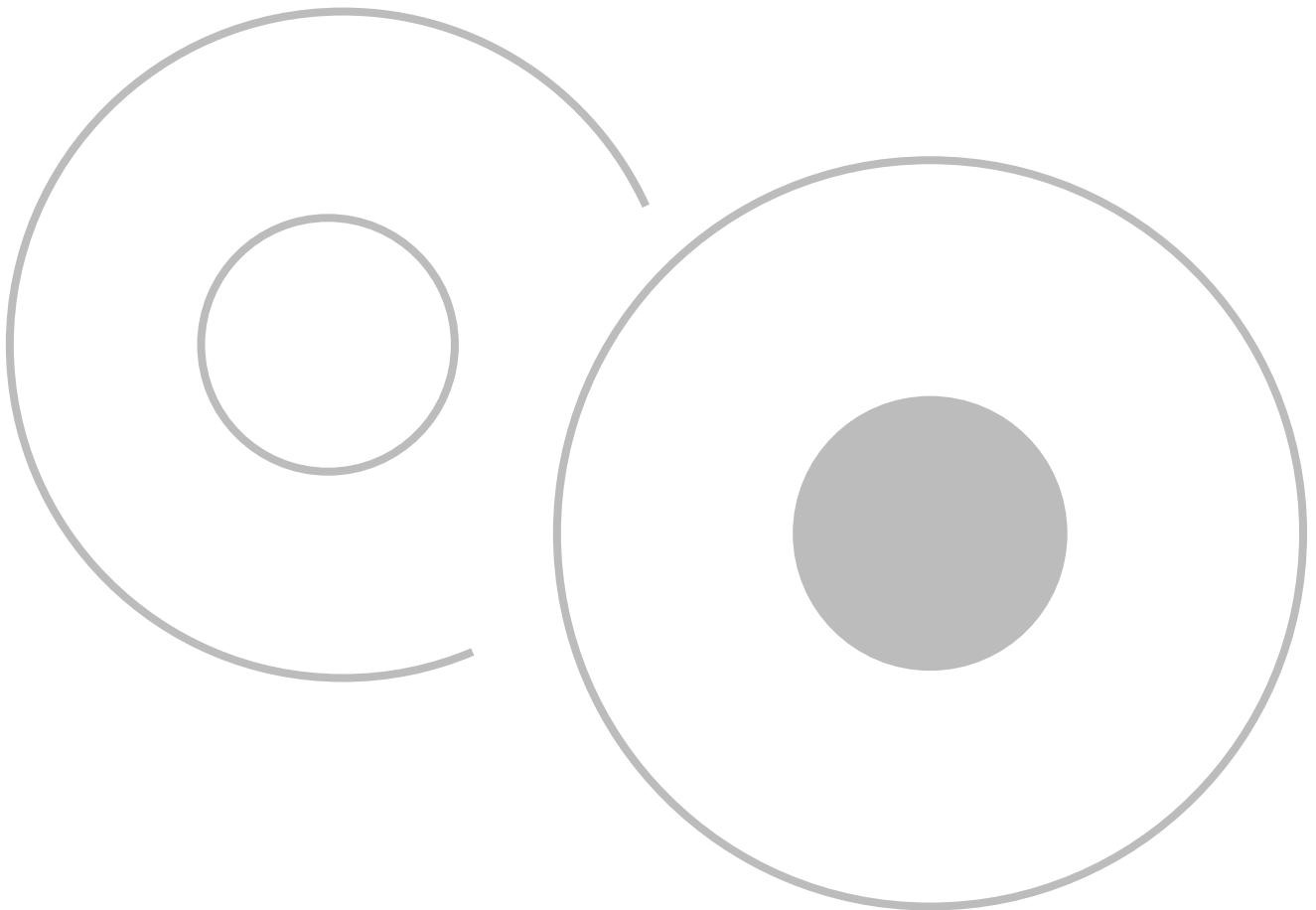
Professors	Associates (incl. clinical)	
Prof. Bont, LJ	Dr. Boes, ML	Dr. Tesselaar, K
Prof. Coutinho, RA (retired 2018)	Dr. Bogaert (moved 2017)	Dr. Wensing, A
Prof. Hoepelman, IM	Dr. Borghans, JAM	Dr. Wolfs, T
Prof. Meyaard, L	Dr. Haas, PJ	
Prof. Rooijackers, SHM	Dr. Kessel, CPM van	
Prof. Sanders, EAM	Dr. Leavis, H	
Prof. Strijp, JAG van	Dr. Lebbink, RJ	
Prof. Wiertz, EJHJ	Dr. Nijhuis, M	
Prof. Wijgert, JHHM van de	Dr. Rensing, M (moved 2016)	
Prof. Willems, RJL	Dr. Sorge, NM van	

Developing immune-mediated therapies & prevention

Professors	Associates (incl. clinical)	
Prof. Baarle, D van	Dr. Arends, JE	Dr. Mutis (moved)
Prof. Boer, JH de	Dr. Balak, DMW	Dr. Nierkens, S
Prof. Bont, LJ	Dr. Bartels, M	Dr. Oostvogels, R
Prof. Bruijnzeel-Koomen (retired 2018)	Dr. Boelens, J	Dr. Peperzak, V
Prof. Hack, CE (retired 2018)	Dr. Boes, ML	Dr. Raijmakers, RAP
Prof. Houben, GF	Dr. Bovenschen, AN	Dr. Reedquist, KA
Prof. Kuball, JHE	Dr. Bruijning-Verhagen, PCJL	Dr. Roon, van JAG
Prof. Lafeber, FPJG	Dr. Bruin-Weller, MS de	Dr. Schipper, HS
Prof. Meyaard, L	Dr. Eijkelkamp, N	Dr. Schutgens, REG
Prof. Oldenburg, B	Dr. Hietbrink, F	Dr. Sebestyen, Z
Prof. Radstake, TRDJ	Dr. Jak, M	Dr. Spierings, J
Prof. Rooijackers, SHM	Dr. Knol, EF	Dr. Spierings, HT
Prof. Sanders, EAM	Dr. Kruize, AA	Dr. Suijkerbuijk, KPM
Prof. Strijp, JAG van	Dr. Kuiper, JJW	Dr. Trzcinski, KP (moved 2017)
Prof. Winkel, JGJ van	Dr. Leavis, HL	Dr. Vastert, SJ
Prof. Wulffraat, NM	Dr. Leusen, JHW	Dr. Verhage, L
	Dr. Limper, M	Dr. Vlist, M van der
	Dr. Loosdregt, van J	Dr. Wagen, LE van de
	Dr. Marut, W	Dr. Wijk, F van
	Dr. Minnema, MC	Dr. Witte, M de
	Dr. Montfrans, JM van	
	Dr. Mous, R	



Self-evaluation report strategic research program **Regenerative Medicine & Stem Cells**





1. Objectives and research area	353
2. Composition and funding	355
2.1 Composition	355
2.2 Funding 2013-2018	358
3. Research environment & collaboration	360
3.1 Research agenda	360
3.2 Scientific collaboration	361
3.3 Patients	361
3.4 Industry	362
3.5 Ethics	363
4. Education & Training	364
5. Open access & FAIR-data	367
6. SWOT analysis	369
7. Conclusion	371
Appendix 1	372
Theme 1 Musculoskeletal tissue regeneration	374
Theme 2a Cardiovascular and Renal regeneration Heart Regeneration	385
Theme 2b Cardiovascular and Renal regeneration Kidney Regeneration	394
Theme 3 Stem cell-based therapies: Organoids and Stem Cells	404



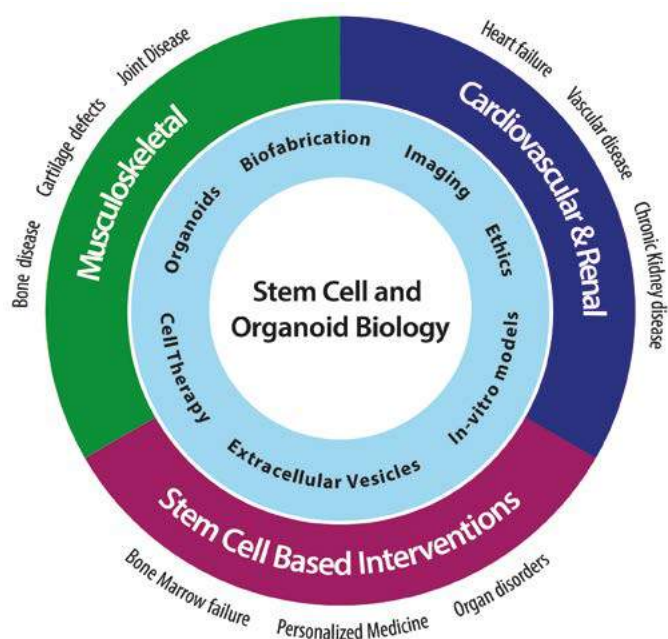
1. Objectives and research area

Regenerative medicine (RM) is one of the strategic themes of the UMC Utrecht (UMC Utrecht) and within the campus-wide Utrecht Life Sciences (ULS). Collaboration between RM researchers from the faculties of medicine, veterinary medicine and science is strong. In November 2015, a majority of UMC Utrecht RM investigators relocated to the Regenerative Medicine Center Utrecht (RMCU), integrated into the new building of the Hubrecht Institute, followed by the RM research groups of the Faculty of Veterinary Medicine in January 2019. This center now houses about 250 RM researchers, shared equipment and facilities, including the Utrecht Biofabrication Facility. We see that daily interactions between fundamental and translational scientists, engineers and clinicians stimulates creativity and cross-pollination of knowledge, fostering new approaches to rapidly bring regenerative medicine in the form of personalized care to our patients.

Our three focus areas are centered around translational research and focus on three patient-oriented themes:

- (1) musculoskeletal tissue regeneration
- (2) cardiovascular and renal regeneration: a) heart regeneration, b) kidney regeneration
- (3) stem cell-based interventions

These are supported by a variety of technologies such as biofabrication, organoids, organ-on-chip, in vitro models, biomaterials, cell therapy, stem cell biology, single-cell analysis, imaging and ethics. Scientific findings are combined with these advanced technologies to create new therapeutic benefit for both human and animal patients. The entire bench-to-bed capacity is available in Utrecht. The collaboration in Utrecht is unique, both in terms of volume (Utrecht has the most RM researchers in the Netherlands) and multidisciplinary.



Vision:

To improve our understanding of stem cell biology, to develop innovative technologies, and to translate our findings into novel regenerative therapies.

Mission:

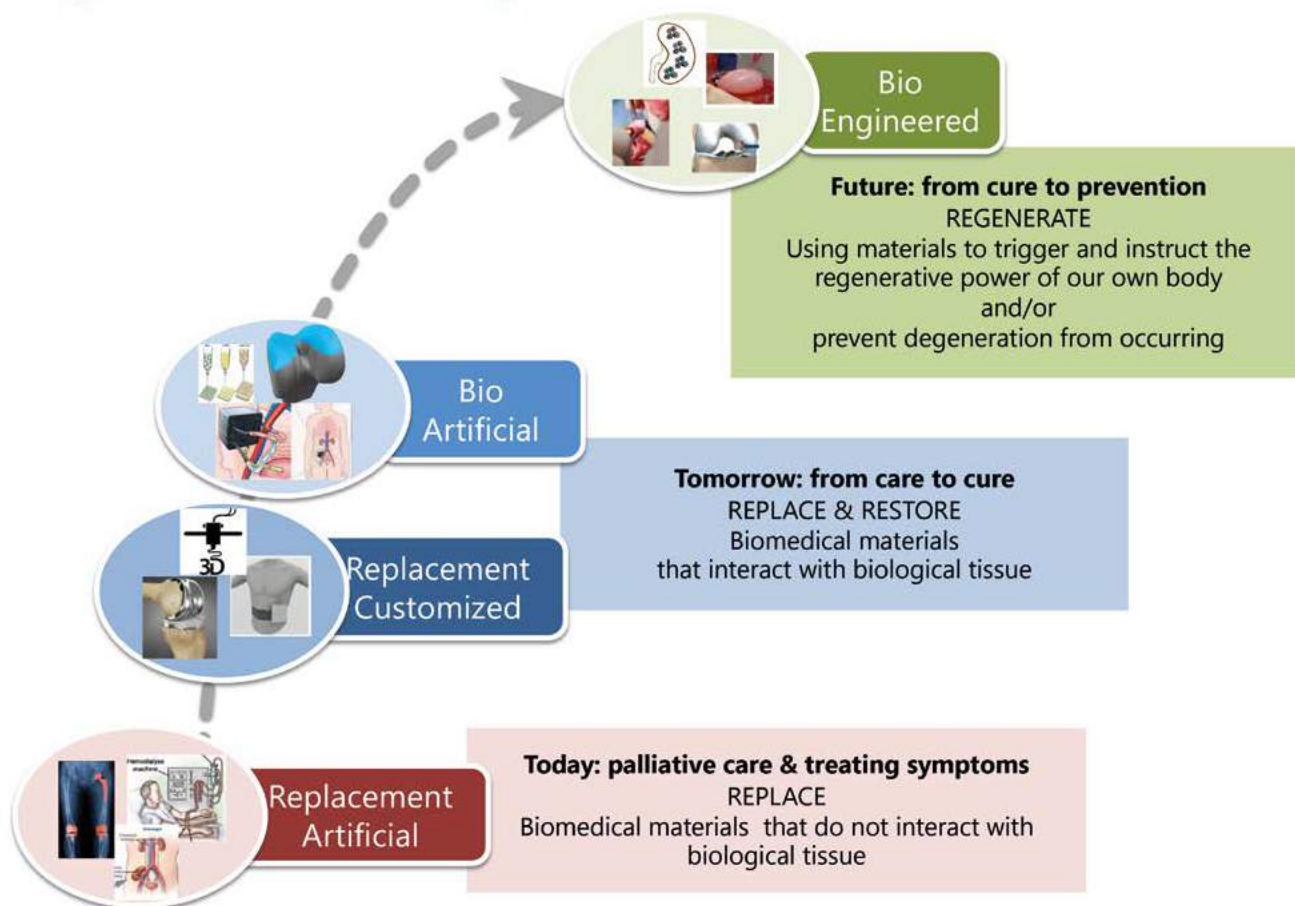
1. To bring novel regenerative treatments for patients to standard clinical care.
2. To provide a center of excellence for biomedical, technological and stem cell-based research.
3. To attract, train and educate the next generation of investigators and caregivers to develop and implement regenerative therapies.
4. To incorporate societal perspectives through active connections to patient (societies) and relevant stakeholders.
5. To actively foster (international) collaboration with academia, government and industry.



Regenerative medicine is a dynamic and rapidly advancing life sciences field, in which a variety of biomedical and biotechnical research areas and clinical care converge with the aim of developing novel therapies to restore or regenerate living tissues as part of treatments related to tissue degeneration, organ failure, ageing or trauma. The Regenerative Medicine & Stem Cells (RM&SC) program brings together fundamental, translational and clinical scientists to create momentum in this field and inspire innovative solutions to clinical problems.

Clinical problems with high societal relevance, for example, heart and kidney failure and osteoarthritis are targeted. At the core of the program, increased understanding of the basic principles of stem cell and organoid biology is pursued in order to develop regenerative therapies for a variety of human diseases. In the translational steps towards the three patient-oriented themes, overall research efforts focus on the complexity and spatial organisation of biological tissues and organs, as well as on the multifactorial approach of tissue re- and degeneration, which is an interplay of many catabolic and anabolic factors, growth factors, cells, biomaterials and mechanical and physical stimuli.

Regenerative Medicine promises to transform healthcare





2. Composition and funding

2.1 Composition

The strategic research program is comprised of researchers from different hospital divisions, which maintain responsibility for oversight, management and finances of their respective research activities and researchers. Thus, the strategic research program strives to create synergy between researchers and division goals without compromising scientific discovery and clinical application.

In the spirit of cooperation, the leadership and management of the RM&SC is diverse. It consists of the RM&SC Executive Committee, the RMCU Scientific Board and the RM&SC support staff. Extending beyond the immediate management teams are liaisons to our various stakeholders (e.g., UMC Utrecht divisions, corporate communications, Utrecht University departments, ULS business ventures, patient societies and foundations, national alliance partners and international cooperation initiatives).

The Executive Committee consists of 8 senior members (a mixture of fundamental scientists, engineers and physician-scientists) from participating divisions who represent the themes and main clinical areas. This committee meets every 4 weeks for 2 hours, and bi-annually for 3-4 hours for large programmatic strategic planning.



Marianne Verhaar
Head of the department of Nephrology & Hypertension
Prof. Experimental Nephrology

Chair of Strategic program RM&SC



Jos Malda
Head research Orthopaedics
Prof. Orthopaedics UMCU/ Translational Regenerative Medicine Vet. Faculty
Vice chair speerpunt RM&SC
Member program board ULS



Paul Coffey
Prof. Cell Biology
Manager Research dLaboratoria, Apotheek & Biomedische Genetica

Director PhD program RM



Joost Sluijter
Prof. Cellular & Translational Cardiology



Jeffrey Beekman
Prof. Cellular disease models
Pediatric Pulmonology



Debby Gawlitta
Associate Professor
Oral and Maxillofacial Surgery



Moyo Kruijt
Orthopaedic Surgeon
Associate Prof. Orthopaedic

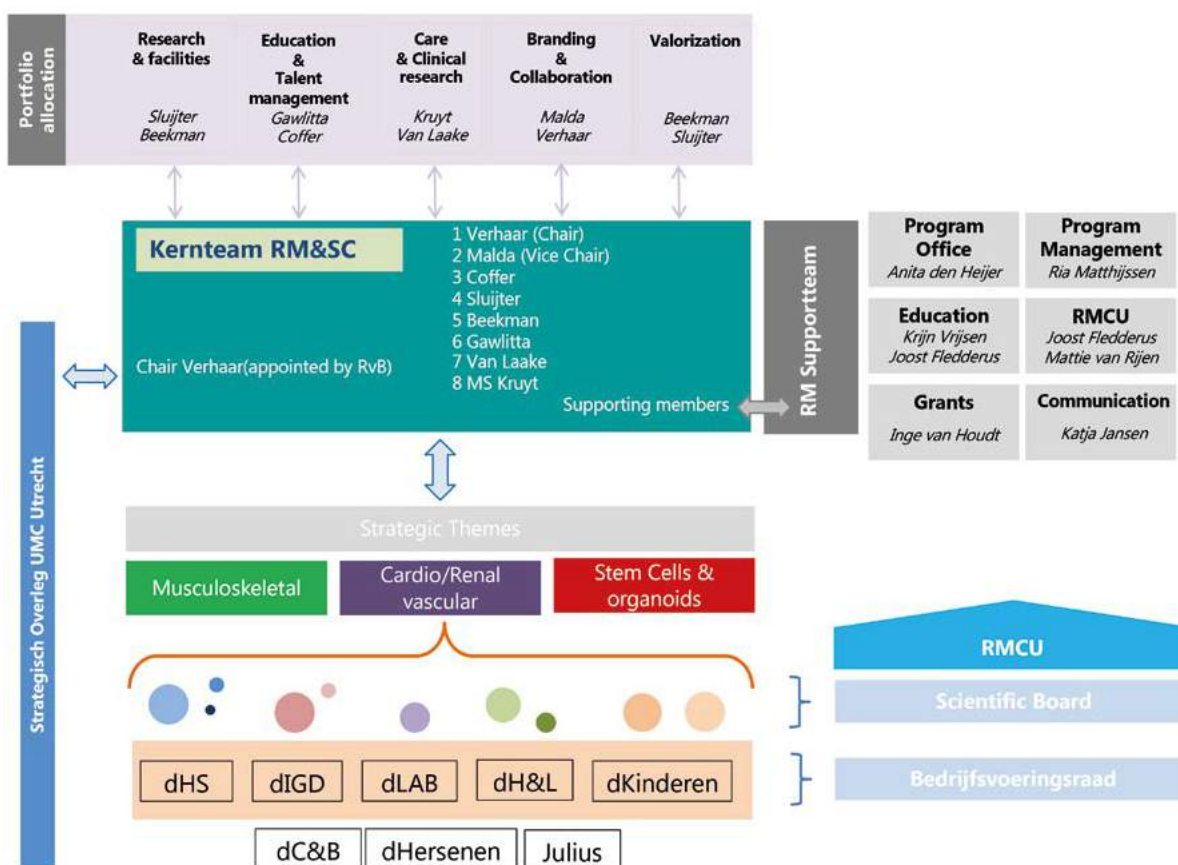


Linda van Laake
Cardiologist
Associate Prof. Cardiology

The Executive Committee is supported by a Program Manager, a Communications-, Education- and Grant-Coordinator and a secretary, all who work closely with the Director of Administration of the RMCU. This team is key to supporting and implementing the RMSC strategy, under the direction of the Executive Committee.










Governance Speerpunt Regenerative Medicine & Stem Cells



Supporting the RMCU, a Scientific Board is installed, consisting of Principal Investigators (PIs) of the RMCU. The Scientific Board meets 6 times annually. The Scientific Board oversees all aspects of governance and organisation within the RMCU and is supported by the Director of Administration, who is the liaison to the UMC Utrecht divisions and outside parties. Together with the Executive Committee, they manage all aspects of the center, including finances, FTEs, logistics, flex-space and laboratory oversight.



 Regenerative medicine & stem cells	
 Circulatory health	<ul style="list-style-type: none"> • heart failure • aneurysm • chronic kidney disease • peripheral arterial diseases
 Brain	<ul style="list-style-type: none"> • brain, stem cells and organoids
 Regenerative medicine & stem cells	<ul style="list-style-type: none"> • bone & cartilage • chronic kidney diseases • peripheral arterial diseases • organ disorders
 Child health	<ul style="list-style-type: none"> • organoids • congenital and hereditary disorders (cystic fibrosis, liver, kidney, metabolic)
 Cancer	<ul style="list-style-type: none"> • organoids • stem cells
 Infection & immunity	<ul style="list-style-type: none"> • cell therapy • immune defects • immunology wound healing & tissue regeneration

An integrated RM community is key for the ambitions and key goals. Within the RM&SC strategic research program, we collaborate with 8 of the current 10 UMC Utrecht divisions: Surgical Specialties (DHS), Internal Medicine and Dermatology (DIGD), Hart and Lungs (DHL), Laboratories & Pharmacy (DLAB), Pediatrics (KIND) all have researchers in the RMCU. Participation of the other divisions is essential, and researchers from Imaging & Cancer, Neurosciences and Julius Center are also closely involved. Interactions with divisions occur both formally and informally: the RM&SC chair and program manager present updates to each division management team every year; the RM&SC chair is part of the monthly Strategic research program Chairs committee and of “UMC Utrecht Strategisch Overleg”. More informal interactions happen throughout the year, when support from both a division and the RMSC program are needed, for example, “hooglerarenplan”, UHD positions and other nomination of candidates, or to apply for internal research funding.

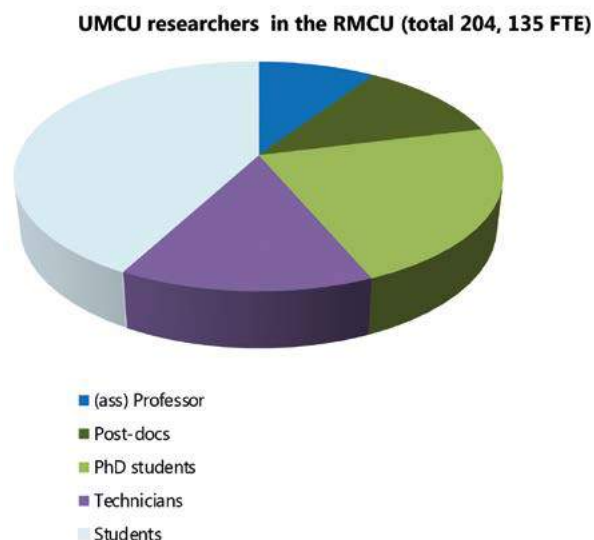
Many of our PIs are affiliated with more than one strategic research program and joint activities have increased, both in research and education. Cardiovascular RM is embedded in both the RMSC and Circulatory Health programs, with extensive cross-collaboration in stem cell biology, extracellular vesicle biology, tissue engineering and stem cell-based therapies. We cooperate with the Cancer Care program on organoid and stem cell biology. Together with Child Health, we are investigating the use of novel organoid technologies and their clinical transition, genetic disorders and gene-editing. With Infection and Immunity, we focus on osteoarthritis and tissue regeneration, immunotherapy and bone marrow transplantation and graft-versus-host disease. The Brain program is closely involved in induced pluripotent stem cells research and neural stem cell biology, along with neonatal hypoxia and tissue regeneration.

Translating our results into clinical application is done with the cooperation of patient centers (Mobility Clinic, Hart & Vaat Centrum) and other resources, such as the Cell Therapy Facility, Biofabrication Facility, iPS Cell Facility, Julius Center Clinical Trial Support, cluster Medical Technology & Clinical Physics, Ethics and Center for Imaging Sciences. Over-arching all of our research and education are themes of valorisation, grant support, talent management, research ICT, ethics, biobanking and outreach, where we collaborate together in numerous initiatives, programs and activities.

To connect the activities and strategic choices in the field of RM between the three faculties and the Hubrecht Institute that are incorporated in the RMCU, we are organizing a RM Utrecht Board. This RMU Board has two delegates in the ULS Program Board, who advise ULS directors on strategic issues. Together, these teams aim to accelerate programmatic progress through developing research lines, cultivating talent, stimulating joint grant applications, raising awareness and aligning our program with (inter)national aims.



division/department	research FTE (including students)
dLAB	11,5
CMM	11,5
dHL	17,3
Cardiology	16,3
Cardiothoracal surgery	1,0
dHS	62,7
maxillofacial	6,1
Orthopedic	54,3
Urology	2,3
dIGD	19,6
Nephrology	18,2
Rheumatology	1,4
dKinderen	23,8
Pediatric Gastroenterology	11,5
Pediatric Pulmonology	12,3
total	134,9



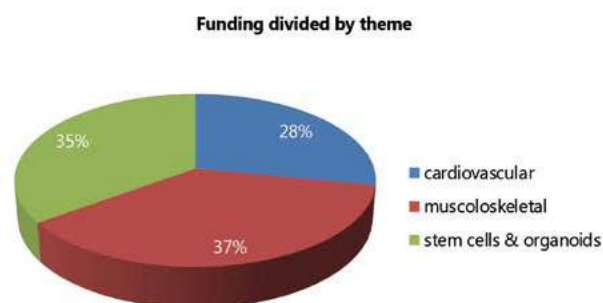
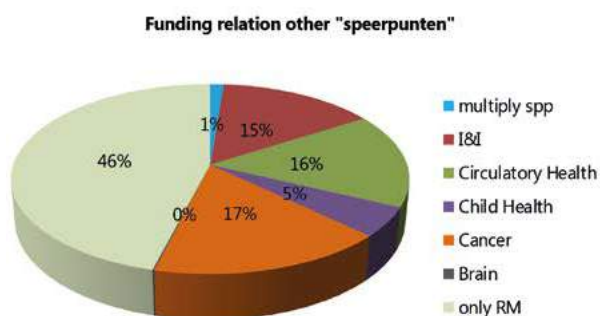
2.2 Funding 2013-2018

There are two important issues to mention:

1) Many of our research activities overlap with the other UMC Utrecht and (inter)national strategic research programs and the Research Office's system of assigning funding (in table) does not visualize this.

Funding from external organisations is about €13 million annually. Many of our PIs are affiliated with more than one strategic research program so about half of the subsidies are shared, resulting in approximately €8.4 million for RMSC annually; funding is distributed roughly equally across our three themes.

External Funding	2018 (€)	2017 (€)	2016 (€)	2015 (€)	2014 (€)	2013 (€)
Research grants (2)	1,186,422	2,716,089	1,165,692	1,775,286	2,197,318	2,686,106
Contract research (3)	4,259,474	3,383,714	6,633,556	5,159,550	4,726,931	3,714,171
Other (4)	2,691,930	1,364,728	1,445,325	2,206,997	1,021,052	2,150,567
Total Funding	8,137,826	7,464,531	9,244,573	9,141,832	7,945,301	8,550,844





2) not all external funds received by our program can be included in our UMC Utrecht system. Therefore, we have created an additional list of funding.

- NWO Zwaartekracht (Gravitation, 2017): award of €18.8 million to our Materials-Driven Regeneration (MDR) consortium together with Eindhoven University of Technology (TU/e) and Maastricht University supporting our research on the regeneration of tissue and organ function with intelligent, life-like materials. Financed by the Dutch Ministry of Education, Culture and Science, this prestigious grant awards research consortia that have the potential to belong to the absolute world top in the field of research or have already achieved that level.
- Regenerative Medicine Crossing Borders (RegMedXB, 2017): award of €25 million. We are leaders in the Kidney Moonshot (creating a functioning subunit of a bioengineered kidney), the Osteoarthritis Moonshot (taking steps towards a bioengineered joint) and the Heart Moonshot (regeneration of the heart).
- Horizon 2020 Marie S. Curie COFUND Grant (2018): coordinator, award of €3 million. This grant stimulates excellence of research training, mobility and career development. The RESCUE-COFUND (see section on Education) program supports 29 PhD students in the RMCU.
- Strategic alliance between Utrecht University (UU) and TU/e: €535,000 annually to our program. This alliance further strengthens and stimulates research in the NWO Gravitation project.
- Strategic alliance between the UMC Utrecht, UU with the MIRA institute, Technical University Twente (2015): €600,000 to our program.
- Utrecht Advanced In Vitro Models Hub, U-AIM (2017): co-chair, €400,000. One of four hubs funded by the ULS, we are building a center of excellence that focuses on the co-creation, application and valorisation of advanced and predictive regenerative in vitro models, whilst at the same time reducing animal experimentation.
- Utrecht Platform for Organoid Technology (UPORT), €1,2 million. UPORT 1) provides a framework for rapid and standardized acquisition and processing of patient-derived tissues for the generation of organoids; 2) supports the generation and analysis of novel organoid-based model systems with valorisation potential and clinical relevance; and 3) connects clinicians, researchers, patients, education and industry across the Utrecht campus and beyond to promote organoid-based applications.
- Utrecht Additive Tissue Manufacturing and Tissue Farming Facility (2012): €515,000 for a period of 4 years. This biofabrication facility is currently up and running.
- We have had the privilege of being selected by the Utrecht University Alumni group, the Hofvijverkring, The Hague, as their fundraising (€125,000) focus for a period of 5 years (2015-2020). Together, we have established the Hofvijverkring (HVK) Visiting Scientist program. The HVK Visiting Scientist is chosen for his/her accomplishments as a translational researcher in the RM field, ability to inspire young talent, and with the aim of strengthening the cooperation between Utrecht and the visitor's university. Through the Hofvijverkring Visiting Scientist (HVK) program, our community is exposed to top-level translational scientists as Loren Field, Indiana University; Paul Dalton, University of Wurzburg; April Pyle, University of California, Los Angeles; Yu Shrike Zhang, Harvard; and Roel Nusse, Stanford University. Our community benefits from both formal and informal interactions with the HVK scientist, and there is always follow-up through student/researcher exchanges and joint projects.



3. Research environment & collaboration

We are in a unique position of having the entire range of bench to bedside at our fingertips; we draw upon our strong relationships with the Hubrecht Institute, the Medical Departments in UMC Utrecht and Julius Center, an internationally renowned center for biostatistics and epidemiology. We can run an entire project from early fundamental investigation to pre-clinical studies on small and large animal models to preparing GMP-grade materials for clinical trials and clinical implementation.

3.1 Research agenda

Our research roadmap is based on and prepared in consultation with:

- National strategic agenda of the “Nationale Wetenschaps Agenda” (NWA)
- Moonshot programs of Regenerative Medicine Crossing Borders (RegMedXB)
- Strategic agendas of medical professionals and health foundations and patient organisations

Nationally and beyond, we provide input into the Dutch Research Agenda (NWA), where RM is, and has been, a key area. This signifies that our members have a positive impact on patient societies and foundations, as well as through public speaking engagements. The Agenda aligns research questions with societal and economic issues as it prioritizes national scientific funding, based on research questions the Dutch society feels are most important. National funding agencies rely on the NWA to help determine where financial support should be allocated. For the coming period, the NWA is focusing on building bridges across the spectrum of science, and cooperation of researchers across boundaries of disciplines and sectors, and RM, prevention and treatment, personalized medicine and materials (made in Holland) are four of the 25 routes. Our research falls within these overarching questions:

- how can we use (stem) cells and biomaterials to promote formation and repair;
- can we design models using smart technology;
- can we design (bio) electronics devices that communicate directly with our bodies to restore/support bodily functions? Both on a general patient population or for specific patient groups, e.g. a specific cardiomyopathy.

In 2017, RegMedXB (Regenerative Medicine Crossing Borders) was initiated between Utrecht, Eindhoven, Leiden, Leuven and Maastricht. This new, virtual, institute calls upon academia, industry and government to invest together with the aim of accelerating the translation of research into health care solutions, technology transfer and new businesses. This model is drawing inspiration from already successful programs, such as CIRM (California Institute for RM), the Wyss Institute and Flemish Institute for Biotechnology (VIB), and our program is part of the leadership driving this forward. RegMedXB is currently in Phase 1, where four projects are funded: taking steps toward a bioengineered joint, a first subunit of a bioengineered kidney, a proof-of-concept therapy for type 1 diabetes and regeneration of the human heart. <https://regmedxb.com>

The Dutch Health Foundations (Nierstichting, Hartstichting, ReumaNederland, Nederlandse Cystic Fibrosis Stichting) as well as the patient organisations (Hareraad, Nierpatienten Vereniging Nederland, Samenwerkende Reuma Patiëntenorganisaties Nederland, Nederlandse Cystic Fibrosis Stichting) are strong partners and are well-organized with large patient participation, and they are great supporters of our efforts. For example, the ReumaNederland has appointed 15 university research groups as Research Centers of Excellence (RCE) and has allocated a budget of €3.8 million/coming 5 years for research; 3 of these groups are from Utrecht and focus on osteoarthritis. ReumaNederland supports this long-term scientific research because it offers the prospect of concrete breakthroughs for better treatment of osteoarthritis, the most common form of rheumatism that affects nearly 1.4 million people. Another example of global alignment is in the field of kidney disease, where environmental and socioeconomic differences greatly influence kidney health and care. The World Health Organisation published a report illustrating how every United Nations sustainable development goal has some relevance to kidney health (<https://www.who.int/bulletin/volumes/96/6/17-206441/en/>). With this in mind, we are developing off-the-shelf technologies, methods and products, and taking them a step further by personalizing them for every single patient.



One of our principal investigators, Annelien Bredenoord, is also a member of the Dutch Senate (Eerste Kamer) and is closely involved in the medical ethics of regenerative medicine, and in particular, the ethical considerations of how clinical trials are conducted. She investigates these topics together with our researchers, in order to improve quality of life by interweaving politics, ethics, science and technology.

Through our stakeholders, we validate that our research questions are important to the health of our society. And through our scientific and industry collaborators, as well as our ability to obtain funding, we can be confident that our questions are interesting, feasible and of great potential. Stakeholders involved in our research processes range from scientific collaborators to patients to industry to government agencies to caregivers. We strive to include the relevant stakeholders in a project as early as possible, and after setting expectations and making a plan, we meet with particular stakeholders on a regular basis for updates, discussion, input/feedback and to consider the overall direction of our research.

3.2 Scientific collaboration

The multidisciplinary collaboration of (stem cell) biologists, material scientists and doctors ensures an improved understanding of stem cell biology, the development of innovative technologies and the translation into regenerative therapies. Where possible, we try to structure our research teams with complementary expertise.

To give some examples; in the artificial kidney project the group consists of physicians, chemists (organic, polymer and electrochemistry), a part-time financial program manager and a technical department that helps with documentation and regulations. Another example is the vascular graft group that has biologists, engineers and vascular surgeons working side-by-side. When the biologists and engineers develop a graft prototype, they hand it over to the surgeons who determine whether or not it may work – how does it handle, is it suturable, is it size-appropriate.

In cases where we cannot employ someone with a particular expertise, we seek advice, partnerships and collaborations. We are fortunate to be located in the Utrecht Science Park, where more than 108 businesses, institutes and facilities are housed in close proximity. We have a wealth of knowledge at our fingertips that is easily shared among our researchers. Close collaboration with RM researchers from the Faculty of Sciences and of Veterinary Medicine that illustrates the recognition of the “One Health” principle, that allows for the unique and fruitful collaboration of researchers from both the medical and veterinary fields, to benefit the target species of both professions. Moreover, important strategic alliances with the technical universities of Eindhoven and Twente have been established, facilitating the merger of excellent regenerative engineering competencies and technological novelties. We are complementary via biotechnology and biomedical expertise.

We collaborate closely with other researchers, both in Utrecht and outside, and are leaders in a number of consortia, for example,

WEAKID: clinical validation of miniature wearable dialysis machine

ERKNet: The European Rare Kidney Disease Reference Network

CHECK: The Cohort Hip and Cohort Knee (CHECK) study with early symptomatic osteoarthritis (OA)

APPROACH: Applied Public-Private Research enabling OsteoArthritis Clinical Headway

MDR: Materials-Driven Regeneration

TECHNOBEAT: Tools and TECHNOlogies for Breakthrough in hEArt Therapies

RegMedXB: Regenerative Medicine Crossing Borders

3.3 Patients

Health Foundations and Patient Organisations

The Dutch Health Foundations (Nierstichting, Hartstichting, ReumaNederland, Nederlandse Cystic Fibrosis Stichting) and patient organisations (Harteraad, Nierpatienten Vereniging Nederland, Samenwerkende Reuma Patiëntenorganisaties Nederland, Nederlandse Cystic Fibrosis Stichting) are strong partners. In addition to funding, the foundations assist with publicity and active links to patients. Other organisations such as NeoKidney and the Netherlands Heart Institute are also strongly involved. Patient involvement is not only restricted to patient organisations. As leaders in RegMedXB, we encourage and support the patient’s perspective, which occurs at every level of the organisation. In addition, patients or patient organisations are involved per department or project. Below we list a few select examples.



Musculoskeletal: has an extensive pool of trained Patient Research Partners (PRPs; including osteoarthritis patients), involved both in clinical care as well as research projects. PRPs are selected based on their interest and involvement in other related projects. Patients highly value our focus on joint preservation, an important feature for patients. For each research proposal, two patients are identified who review the first draft of a proposal; thereafter, a larger patient panel is involved throughout the entire project also in collaboration with the patient societies.

Heart: A relatively new research line was initiated by a patient foundation, the PLN Foundation. Phospholamban (PLN) regulates the flow of calcium into and out of the heart, and mutated PLN has been identified as a cause of cardiomyopathy within the Dutch population. We were asked by the foundation to establish a scientific program around PLN. The foundation contributes funds and facilitates public interest in this area. We meet every 3-4 months with members of the foundation, alternating between the UMC Utrecht activities (i.e., lab tours, updates) and their events (i.e., National PLN day, which has now created a network with other groups in the Netherlands). Moreover, in 2018 a PLN LeducQ grant was granted in which a transatlantic network will work to cure this devastating disease.

Kidney: regular meetings with the Dutch Kidney Foundation and Dutch Kidney Patient platform are held. We involve patient foundations such as the Dutch Kidney Patient Association (NVN) early in our research projects. Focus groups consist of patients and patient representatives who had been involved in earlier discussions related to our projects, and they have done their homework. Before we meet, they read up on current literature, which allows us to have a productive and high-level conversation. Based on feedback, we have been able to adjust some particular aspects in a timely manner. This has helped better shape our research, prototypes (in particular the patient interface) and clinical trial design. These groups are critical during development phases, and this type of critique gives us great insight into criteria for market acceptance; this also allows better expectation management on both sides.

Organoids & Stem Cells: program development together with the Cystic Fibrosis Patient Foundation in the Netherlands (NCFS) for the past five years. Through their organisation, we sit down with leading labs in the Netherlands, including all of the major academic hospitals, and develop a strategy to raise funds together. In addition, the NCFS screens patient needs and so that as a collective, we determine the current strengths our Dutch research network and how we can fill any gaps. This interactions has led to 10M Euro in shared research funding in the last 8 years.

Overall: For the development of the advanced in vitro models through the U-AIM Hub, patient organisations will be part of the advisory board and patient involvement is envisioned in the development of specific in vitro models. Throughout our research, patients are also involved, and are sometimes co-authors, in considering the ethics of certain topics, for example through qualitative interview studies, in focus groups.

3.4 Industry

We are also fortunate to have the support of Top Sector Life Science & Health, one of the nine top sectors in the Netherlands designated by the Dutch Ministry of Economic Affairs, which initiates and stimulates interdisciplinary research and private-public partnerships.

We partner with various types and sizes of companies, depending on our project needs. These include:
Industrial partners within RegMedXB: 300MICRONS, Access2Bone, CytoSMART, CARTECH, Fujifilm, Galapagos, HCM Medical, Innophysics, InSciTe, Kuros BioSciences, LifeTec Group, Materiomics, MIMETAS, Ncardia, Nestegg Biotech, Ntrans, Osteo-Pharma, Scinus, Starfish/LRMP, STENTiT, Suprapolix, Veldlaser, Visualsonics, Xeltis
Industrial partners in RESCUE CoFUND project are: Ocello 3D screening, Pepscan, Delmic BV, InteRNA technologies BV, Noviocell BV, Mead Johnson Nutrition, Histogenetics, Chiesi farmaceutici S.P.A., LifeTec group BV, Micronit Microtechnologies BV, Pharmahungary 2000 Ltd, Mimetas BV, Viscofan Bioengineering, Nordic Bioscience, Orhtros TR, KiOmed pharma, RegenHU, K2M, Philips Healthcare, Philips, Global Stem cell Technology, Kuros Biosciences BV, AO Spine Knowledge Forum Tumor International, 20Med Therapeutics BV, MRI Guidance BV, Hubrecht Organoid Technology.



3.5 Ethics

A dedicated group of researchers within our program provides input from an ethics perspective in order to increase societal awareness and opportunities for future translation of research results. The contribution of the medical ethics team aims to identify and evaluate the ethical issues raised by translational research, particularly in regenerative medicine, stem cells, genetics/genomics and biobanking, and to develop ethical guidelines for responsible innovation and translation in those fields.

Current advances in biotechnology open up unprecedented possibilities to transform human tissues into complex, valuable tissue products, such as organoids. We proposed consent for governance as a leading paradigm for the derivation, storage and use of complex human tissue products to ensure adjustment to changing ethical requirements. We published several key opinion articles in this field in leading journals such as *Science* (Bredenoord et. al., 2017) and *Nature Cell Biology* (Boers and Bredenoord, 2018), indicating the need for ethical reflections on this topic. In another article in *Biofabrication* (Otto et. al., 2016), we aimed to highlight important points of existing ethical discussions, as well as to call attention to emerging issues specific to 3D biofabrication in bench and bedside research and the translation to society.

We also described ethics with respect to the FAIR data principles in *Eur J Hum Genet* (Boeckhout, et al. 2018). The FAIR guiding principles for research data stewardship (findability, accessibility, interoperability, and reusability) look set to become a cornerstone of research in the life sciences. A critical appraisal of these principles in light of ongoing discussions and developments about data sharing is in order. The FAIR principles point the way forward for facilitating data sharing more systematically-provided that a number of ethical, methodological, and organisational challenges are addressed as well.

We think that the solution lies in part in what Annelien Bredenoord refers to as ethical parallel research. This entails that the medical ethicist is involved in the very first stages in the process of medical or biomedical research. The ethicist works together with the researcher in the lab, the data scientist at the computer, with patients and test subjects and with the physician who wants to begin a clinical trial. For instance, while a new organoid application was being developed for CF, we also conducted ethical studies in parallel to learn about the impact on and expectations of patients (Boers et al, JCF 2017). Knowing the societal interpretation and consequences is paramount for a successful implementation of new technologies into practice and requires a tight collaboration between disciplines.



4. Education & Training

Our discoveries will not come to fruition without a prepared future generation. Thus, over the past years, we have continued to broaden and improve our educational activities and we still have the only full-range of higher education RM program in the country, including summer schools to attract and inspire (inter)national students. In addition, we have increased our efforts to engage the public, including children.

We offer courses and programs at different levels within the Graduate School of Life Sciences at Utrecht University:

Bachelor level

We offer various elective courses in Regenerative Medicine and Stem Cells in the curricula of Biomedical Sciences, Veterinary Medicine, Medicine 'CRU' (traditional medical degree) and the technology track of the Selective Utrecht Medical Master (SUMMA-Tech); these courses focus on basic stem cell-, organ- and tissue-biology, principles of de- and regeneration, biomaterials and tissue engineering. Highlights include meet-the-patient sessions, practical lab work, excursions to technical universities and biotech companies and writing/presenting research results.

Master level

The RM program has developed two Master's programs on Regenerative Medicine & Technology (RMT) and Biofabrication and 3D printing (BIOFAB). These research masters focus primarily on lab-based internships but also include a writing assignment, as well as in-house developed elective courses on stem cells basics, the fundamentals of biofabrication, vascular- and vascularized tissue engineering, and cardiac regenerative medicine. The master programs offer great freedom for students to mold their program to their own specific needs. In the courses, we use various teaching formats such as expert lectures, peer teaching, journal clubs, essay writing, and a group assignment to write a research proposal, supervised by tutors from our research groups.

Master's program RMT

The RMT program aims to train multidisciplinary scientists and combines fundamental disciplines such as stem cell biology, materials science and biomechanics with more applied disciplines such as cell therapy, implantology and imaging. The master's program is a cooperation between the UU, the UMC Utrecht and the Faculty of Biomedical Engineering at TU/e. The combined expertise, various state-of-the-art laboratories and research groups equip you with an understanding of processes ranging from specific cell culturing techniques, the use of biomaterials to computer models and imaging modalities.

Master's program BIOFAB

BIOFAB program was the first Master's programme in additive manufacturing for biomedical applications. Our long-term goal is to provide students with the necessary skills to perform, innovate and lead this next revolution in manufacturing. BIOFAB attracts students from all walks of life – medicine, physics, chemistry, mathematics and biology, and trains them in essential skills for working in additive manufacturing industries. The mobility component of BIOFAB allows the international placement of students so they understand international expectations while appreciating cultural differences. Our double degree consists of both coursework and research – building up the necessary skills for students while allowing them to put their experiences into practice. BIOFAB provides an opportunity for Australians and Europeans to understand each other's culture: crucial for achieving a global perspective and strengthen ties between our two communities.

Elective courses RMT/BIOFAB

- Vascular(ized) tissue engineering (online course):
This course provides in-depth and hands-on knowledge on developmental and adult blood vessel formation in health and disease and the current clinical treatments for which vascular(ized) tissue engineering (TE) is thought to be eligible. Moreover, state-of-the-art techniques of vascular(ized) TE, including the use of biomaterials and cell sources for bioreactor-cultured and in situ applications are addressed. The course contains group and individual assignments, as well as active participation and peer interactions in group discussions.



- **Fundamentals of Biofabrication (online course):**
This course provides students with fundamental knowledge on the various aspects of biofabrication, including 3D printing techniques, biomaterials, tissue engineering, applications, translation and ethics. The course contains group and individual assignments, as well as active participation and peer interactions in group discussions.
- **Cardiac Regenerative Medicine:**
In this course, students are acquainted with the application of regenerative medicine in cardiac diseases. Subjects like cardiac development, reprogramming, RM treatment options including non-cell-based therapies and translational cardiac RM are addressed. In addition, students are introduced interpretation and processing of study data, and become acquainted with the impact of research on society, in particular, on patients. The course consists of lectures, interactive meetings, an exam and a group assignment, supervised by experts and laymen.
- **Introduction to stem cells:**
This course addresses both fundamental mechanisms regulating stem cell function as well as considerations concerning the use of stem cell therapies in the clinic.

PhD program in Regenerative Medicine:

Our PhD Program offers an inspiring, multidisciplinary and translational education program in the area of Regenerative Medicine for PhD students. Located within the Utrecht University Graduate School of Life Sciences, students graduate with a PhD degree from Utrecht University. The PhD Program encompasses a broad range of research and education areas, including fundamental and developmental biology, processes and mechanisms of disease, technical innovation and clinical application. Complementing the specific education and training in regenerative medicine, are courses that build and enhance general skills, such as communication, statistics, and laboratory animal techniques. A unique hallmark the Utrecht RM Program is the partnership with the Faculty of Veterinary Medicine at Utrecht University. This provides an integrated approach in which basic scientists and clinicians from both human and veterinary medicine work side-by-side. In addition, the emphasis on translational aspects for both human and veterinary medicine offer students the availability of large animal models and the possibility to translate new treatments to veterinary and human patients. The PhD Program strongly encourages interaction with colleagues and peers within this highly multidisciplinary field and PhD students will be acquainted with the international perspective of the field of regenerative medicine through frequent contacts with colleagues from abroad, regularly invited international guest speakers and the encouragement to participate in international meetings. At this moment 99 people (including RESCUE) are in the RM PhD program.

In 2015, our PhD program was awarded an NWO Graduate Programme Fellowship (800k EUR), supporting 4 selected PhD students in the period 2015-2019. The aim of the Graduate Programme is to create an excellent educational and research environment for highly talented young researchers by strengthening the system of doctoral training.

In 2019, the RESCUE-RM (REgenerative Medicine & Stem Cells in UtrEcht) training program was awarded to us by the EU H2020 Marie S. Curie COFUND funding program. This unique international doctorate program aims to enhance the potential and future career perspectives of researchers by providing a global training network including over 50 excellent academic and industrial partner organisations, creating a new generation of research experts, empowering them to take leading positions in the field of Regenerative Medicine world-wide. Together, the UMC Utrecht (coordinator), the UU and the Hubrecht Institute offer 29 PhD positions. We have designed a well-rounded training program, including entrepreneurship, knowledge transfer and translating science into clinical practice, that will prepare them to become the smart leaders of the future in the field of regenerative medicine.

Utrecht Summer School (largest summer school in Europe):

The Utrecht Summer School is a cooperation of the Utrecht University, HU University of Applied Sciences and University of Hong Kong (HKU) University of the Arts. These institutions of higher education offer high quality, fully accredited summer courses in English on the bachelor, master, PhD and Post-Academic level to broaden student's horizons in an inspiring international environment. The RM program offers 4 different summer courses:

Regenerative Medicine

In this interactive course at a beginner Masters level, we teach the basics of regenerative medicine, stem cell biology and technologies as well as how this science is translated and implemented into patient care. The course combines lectures, tutorials with hands-on experiments, demonstrations and tours.



3D Printing and Biofabrication

This course provides insight into the opportunities of additive manufacturing technologies and 3D printing in biomedical applications. It provides the basics of 3D printing, including a hands-on Ultimaker workshop and introduction to 3D design software. In addition, it also provides insight into the specific challenges encountered when translating 3D printing to biofabrication, such as the development of specific bioinks and the required control over processing conditions. Finally, it provides state-of-the-art examples of how biofabrication is currently translated from bench to bedside.

Introduction to Organoid Technology

This intensive 3-day course provides an overview on current organoid technology and the application of organoids in basic research, disease modelling, drug development, personalized medicine and regenerative medicine.

Advanced In Vitro Models

This course teaches the best practices of advanced in vitro models, regulatory aspects, (stem) cell biology and technologies for testing medicine and/or substance safety testing as well as how the results can be validated, translated and implemented into human medicine.

Public engagement:

The RM program participates in activities that inform the general public about our research activities, such as the National Weekend of Science (lab tours and fun educational activities) and organizing tours for patient organisations and national charity funds (e.g. Dutch Heart Foundation, Dutch Kidney Foundation, ReumaNL). In addition, we provide supervision for high school students for writing assignments and science projects.

For the broader RM community at Utrecht University, we host several (inter)national courses and conferences in the field of regenerative medicine and stem cells (e.g. Utrecht Stem Cell Conference in Cardiology, Annual meeting for Dutch Society for Stem Cell Research, Biofabrication 2015, CUHK Musculoskeletal Regenerative Medicine Symposium 2016) and a monthly seminar series with international speakers at the RMCU.



5. Open access & FAIR-data

The UMC Utrecht is one of the initiators of “Science in Transition”: research must provide added value and societal parties must participate in decisions about the production of knowledge. We firmly believe in dissemination of knowledge and that transparency is key to systematic progress, as well as serendipitous “Eureka!” moments. Our ambitions are therefore appropriately coupled with our consideration of how they may impact the field as well as society. Thus, we participate in scientific and layman lectures, publications, policy reports, workshops, interviews, media appearances and focus group studies; and are also involved in creating videos and animations to describe our research and findings to our stakeholders.

Science in Transition has further developed into “Open Science,” which aims to make research accessible (publications, data, technology, software, materials) to both the public and professionals. Our goal is to publish in Open Access journals when possible, although this does occasionally become a cost balance issue, even though the UU gives a financial compensation of up to €1000 (some journals charge much more than that, e.g., \$5000 *Nature, Cell*; \$3500 *Biofabrication*). Another point of view is that access doesn’t mean it is comprehensible, for example, to the public. For a layperson, a scientific article is very difficult to read and understand. They rely on the media and other means of dissemination. There are other ways to make information accessible. For example, for the CF Foundation, our researchers need to write a lay version of their publications. This is translated into Dutch by the foundation and posted on their website and distributed to their members.

We align ourselves where possible with policies generated by the UMC Utrecht, the Netherlands Federation of Dutch University Medical Centers (NFU) or by the greater community. Below are areas where we strive to make our research plans and findings as transparent and accessible as possible.

Data management: in scientific research, data management is fundamental to high quality research and academic integrity. We strive to have a Data Management Plan at the start of each project to ensure that good scientific practice is followed according to the FAIR principles: data should be ‘Findable, Accessible, Interoperable and Re-usable’. The Data Management Plan is an integral part of the research protocol and describes a standardized way for how research data are collected, how data are used and stored during research and how to make data accessible for others after the research has been completed. Our data (arrays, proteomics with patient materials, meta analyses) is locally stored and patient information kept confidential. We are in the process of transitioning to electronic lab journals, which will make access and sharing of our data easier. The digital lab journals we use are GLP-approved and the Beekman group is working toward a data sharing platform with Dutch CF Foundation and a group in the US: a public database that has collected registry data from 80-90% of all pts; users can enter a mutation and find data and can generate an organoid profile.

Commercialisation: Bringing our science in the form of a tool, method or therapy to the market is our ultimate goal. The UMC Utrecht provides valorisation offers types of support such as the Utrecht Holdings, Pontes Medical, UtrechtInc, THINC.Healtcare (Julius), Mikrocentrum.

To promote transparency in *preclinical research*, one of our research groups has taken the initiative to set up a pre-clinical trial database. In light of their publication (Eur J Clin Inves 2014), they developed and recently launched www.preclinicaltrials.eu to promote transparency in all areas of preclinical research.

Animals in research: The Utrecht animal experiments committee (DEC Utrecht) supervises conduct of research on animals. The committee consists of experts who advise researchers on animal experiments for scientific research and education, and also identify alternatives. One of our research groups is the co-creator of the Utrecht Advanced In Vitro Models (U-AIM) hub. U-AIM is a “one-stop-shop” where high potential in vitro models are developed, validated and transitioned to stakeholders. Through a strong cooperation between scientists, students, regulators and industry, U-AIM aims to increase market potential of innovative models and thereby reduce animal experimentation.



Human subjects: The Medical Ethics Assessment Committee Utrecht (METC Utrecht) is an independent committee that is recognized by the Central Committee on Research Involving Human Subjects (CCMO). Research that falls under the Medical-Scientific Research with People Act (WMO) must be assessed by an independent committee of experts. The investigation may not start without a positive assessment from this committee. Our scientists have a direct link with the clinic and access to patient materials, clinical trials and patient support groups. We are involved registered clinical trials, of which we are the Principal Investigator, trial Chair, or a participant hospital. Below are some of our key trials.

- IMPACT: Instant MSC Product accompanying Autologous Chondron Transplantation for focal articular cartilage lesions of the knee; feasibility and safety
- SUMMIT Superiority of Matrix-induced autologous chondrocyte implant versus Microfracture for Treatment of symptomatic articular cartilage defects
- KNEEREVIVER: Knee Joint Distraction, Prospective follow-up of clinical efficacy of knee distraction as treatment for knee OA by use of 'ArthroSave's Knee-Reviver
- SinusBCP: Micro-structured BCP granules as bone graft substitute in maxillary sinus floor augmentation with two-stage implant placement
- Maxillo-2: Micro-structured Beta-Tricalcium Phosphate for Repair of the Alveolar Cleft in Cleft Lip and Palate Patients
- MAXA: a Randomized Controlled Trial of Magnetos ceramic granules vs. Autograft in Instrumented Posterolateral Spinal Fusions
- BIPOWR: limited-efficacy testing of Spring Distraction System (SDS) and bilateral one-way rod for early onset scoliosis
- REPEAT: bone marrow mononuclear cells for ischemic heart disease
- BAMl: acute myocardial infarction
- WEAKID to validate a miniature wearable dialysis machine in a clinical setting and to prepare the system for CE-marking
- JUVENTAS: Effect of repetitive intra-arterial infusion of bone marrow mononuclear cells in patients with no-option limb ischemia: a randomized, double-blind, placebo-controlled trial
- MANUS to assess the safety of intramuscular administration of allogeneic mesenchymal stromal cells for digital ulcers in systemic sclerosis
- ABBA: intervention study with B2-agonist in defined subgroup of patients based on preclinical studies in organoids

Cell Therapy Facility: For clinical studies in which mesenchymal stem cells are used, we depend on the Cell Therapy Facility (CTF) of the UMC Utrecht. In 2017 the CTF had a temporary loss of GMP certificate (due to lack of central investment). This has resulted in the delay & cancelation of clinical trials with the use of cell products. Innovations in regenerative medicine such as 3D printing, organoids and tissue engineering are emerging technologies and we want to maintain a leading role in fundamental and translational research to accelerate these innovation to the benefit of patients. The CTF will need to facilitate and accelerate these research projects. CTF will be instrumental in cell therapy innovations in UMC Utrecht and investments in the CTF are needed to maintain the competitive position in research and healthcare.



6. SWOT analysis

Strengths

1. **Position:** Strong (inter)national position and large critical mass with multidisciplinary collaborations and excellent campus-wide embedding within Utrecht Life Sciences. Leading in organoid technology, biofabrication, stem cell-based therapies, extracellular vesicle (exosome)-orientated technologies and imaging.
2. **Infrastructure:** The large majority of Utrecht RM researchers are located at the Regenerative Medicine Center Utrecht which facilitates multidisciplinary collaborations and sharing state-of-the-art facilities, also with scientists at the Hubrecht Institute and Faculty of Science and Veterinary Medicine. Located at the Utrecht Science Park, which houses a diverse range of organisations, facilities and expertise, fostering an ecosystem of innovation and collaboration. Close proximity of both human and animal patients in the hospital (UMC Utrecht) and Faculty of Veterinary Medicine.
3. **Collaboration:** Strategic alliances with Technical Universities of Eindhoven and Twente (complementarity biotechnological and biomedical expertise). Participation in many (inter)national consortia (RegMedXB, NWO-Zwaartekracht, H2020) or programs (ZonMW Translational Adult Stem Cell).
4. **Education & Training:** The only academic center in the Netherlands with a complete range of RM education & training (Bachelor, Master, PhD, summer school) and the recently initiated H2020 COFUND RESCUE training program, including both human and animal oriented programs.
5. **Patient-centered research themes:** Three patient-centered themes with high societal relevance and close relationships with health funds and patient organisations. Access to patient materials, clinical trials and patient support groups.
(Inter)national expertise center: Osteochondritis of the Knee and OA Spine reference center, advanced heart failure patients. Largest reference center for cystic fibrosis (CF) patients (also leads European Research Network for CF) and a major center for bone marrow transplantation in children in the Netherlands, novel clinical uses of hematopoietic stem cells and mesenchymal stem cells. Mobility Clinic and Hart & Vaat Centrum are multidisciplinary, tertiary referral expertise center for patients with complex problems.

Weaknesses

1. Research governance is divided between budget-responsible divisions and strategic research programs and research support for grant applications, innovation and valorisation, and also for regulatory compliance, is fragmented and insufficient.
2. Temporary loss of GMP certificate related to CTF (due to lack of central investment) and the delay & cancelation of clinical trials with the use of cell products.
3. Limitation in crucial infrastructure, such as availability operation theater needed for novel therapies and ISO certified department medical technology.
4. Lack of a central talent policy and talent programs in the UMC Utrecht.
5. Lack of central marketing- and communication strategy in the UMC Utrecht.

Opportunities

1. Well-equipped to take the next steps towards implementation of novel regenerative therapies, all elements needed are present. Supporting facilities; Julius Clinical, Utrecht Holding, ISO 13485 certified MTKF. Collaboration with companies
2. Advanced in vitro models provide great opportunities for improving basic science research and drug development so that translational efficacy towards clinical practice improves, and new alternatives that replace, reduce, refine laboratory animal use can be developed. One health policy, in Utrecht there is a unique opportunity together with veterinary faculty for patients, both animals and humans.
3. Upcoming Strategic alliances UMC Utrecht- TU-Eindhoven and Wageningen University provides interesting collaborative options in the Regenerative Medicine and Stem Cells field.
4. The national Top sector Life Science & Health has regenerative medicine as one of the priority roadmaps for the National Science Agenda. The European Commission Horizon 2020 program includes the topic of regenerative medicine.



Threats

1. New policies from main Dutch research funder ('Inbeddingsgarantie', NWO) and government (WNRA) limit hiring practices with temporary contracts that are the norm in academia. Lack of means of the UMC Utrecht to meet increasing demands on financial matching of grants.
2. Lack of structural support of the Cell Therapy Facility (CTF) and Good Manufactory Practice (GMP) of compounds as key facilities for clinical trials.



7. Conclusion

Regenerative Medicine Utrecht converges the life sciences, engineering and physical sciences and comprises the largest mass of RM researchers (>250) in the Netherlands. Regenerative Medicine Utrecht has built an excellent infrastructure, offering access to a variety of large and small animal models, patient materials, novel technologies, shared high-tech facilities and multi-disciplinary expertise. We have a complete RM education program to educate and train the next generation of researchers and clinicians. There is ideal expertise and infrastructure for pre-clinical/clinical research, including a GMP-accredited Cell Therapy Facility and biobanks.

The Regenerative Medicine Center concentrates most RM investigators in Utrecht under one roof, integrating fundamental science, emerging technologies, translational research and clinical care to perform high-quality research with the aim of developing novel regenerative treatments. Regenerative Medicine Utrecht has all the elements to propel findings from bench to bedside and is enhanced by strategic alliances with technical universities and a strong valorisation focus. The Regenerative Medicine Center demonstrates a paradigm shift in how research is conducted in Utrecht; the synthesis of different backgrounds and approaches is already creating new discoveries for patient benefit.

Our quest to live long and healthy lives sparks our imaginations and goals. Regenerative medicine (RM) is associated with stem cell therapy and tissue engineering, and the ultimate goal of repairing, restoring or regenerating tissue. We have quickly learned that these concepts cannot be studied in isolation and in fact, the definition of RM continues to broaden. We pride ourselves on being able to draw upon the wealth of our diverse community and strive to understand the astonishing complexity of our bodies from many viewpoints. We are privileged to be at the forefront of this exciting and promising research area.



Visit our website: [link to our website](#)



Or take an preview by watching this short video about regenerative medicine collaboration at the Utrecht Science Park: [link to this video](#)



Or follow us at twitter @RMUtrecht



Appendix 1

RMSC principal investigators and Clinical Associates (MD=Medical Doctor)

Last name	First name	Theme	Division	Department	Title	MD
Alblas	Jacqueline	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Associate Professor	
Beekman	Jeffrey	Stem Cell & Organoid Biology	dKinderen	Pulmonology	Professor	
Bierings	Marcus	Stem Cell & Organoid Biology	dKinderen	Hemaotogie	Associate Professor	MD
Boelens	Jaap	Stem Cell & Organoid Biology	dKinderen	Oncology	Associate Professor	MD
Borst de	Gert-Jan	CardiovascularTissue Regeneration	dHS	Vascular Surgery	Full Professor	MD
Bredenoord	Annelien	Stem Cell & Organoid Biology	Julius	Medical Ethics	Full Professor	
Buikema	Jan Willem	Cardiovascular Tissue Regeneration	dH&L	Cardiology	Medical Resident	MD
Castelein	Rene	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Full Professor	MD
Chamuleau	Steven	Cardiovascular Tissue Regeneration	dH&L	Cardiology	Full Professor	MD
Cheng	Caroline	Cardiovascular Tissue Regeneration	dIGD	Nefrology	Associate Professor	
Clevers	Hans	Stem Cell & Organoid Biology	dLAB	Cell Biology	Full Professor	
Coffer	Paul	Stem Cell & Organoid Biology	dLAB	Cell Biology	Full Professor	
Creemers	Laura	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Associate Professor	
Custers	Roel	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Medical specialist	MD
Delden	Johannes	Stem Cell & Organoid Biology	Julius	Medical Ethics	Full Professor	
Doevendans	Pieter	Cardiovascular Tissue Regeneration	dH&L	Cardiology	Full Professor	MD
Fuchs	Sabine	Stem Cell & Organoid Biology	dKinderen	Pediatrics	Associate Professor	MD
Gawlitta	Debby	Musculoskelatal Tissue Regeneration	dHS	Oral and Maxillofacial Surgery	Associate Professor	
Gerritsen	Karin	Cardiovascular Tissue Regeneration	dIGD	Nephrology	Associate Professor	MD
Hjortnaes	Jesper	Cardiovascular Tissue Regeneration	dH&L	Cardiothoracic Surgery	Medical Resident	MD
Ito	Keita	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Full Professor	
Joles	Jaap	Cardiovascular Tissue Regeneration	dIGD	Nephrology	Associate Professor	
Jong de	Pim	Musculoskelatal Tissue Regeneration	dBeeld/Cancer	Radiology	Full Professor	
Klumperman	Judith	Stem Cell & Organoid Biology	dLAB	Cell Biology	Full Professor	
Kort de	Laetitia	Stem Cell & Organoid Biology	dHS	Urology	Full Professor	MD
Koudstaal	Stefan	Cardiovascular Tissue Regeneration	dH&L	Cardiology	Medical Resident	MD
Kranenburg	Onno	Stem Cell & Organoid Biology	dBeeld/Cancer	Oncology	Full Professor	
Kruyt	Moyo	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Associate Professor	MD
Kuball	Jurgen	Stem Cell & Organoid Biology	dBeeld/Cancer	Internal Medicine	Full Professor	MD
Laake van	Linda	Cardiovascular Tissue Regeneration	dH&L	Cardiology	Associate Professor	MD
Laar van	Jaap	Stem Cell & Organoid Biology	dIGD	Rheumatology	Full Professor	MD
Lafeber	Floris	Musculoskelatal Tissue Regeneration	dIGD	Rheumatology	Full Professor	
Lindemans	Caroline	Stem Cell & Organoid Biology	dKinderen	Pediatrics	Medical specialist	MD
Luijten	Peter	Musculoskelatal Tissue Regeneration	dBeeld/Cancer	Radiology	Full Professor	



Malda	Jos	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Full Professor	
Mastbergen	Simon	Musculoskelatal Tissue Regeneration	dIGD	Rheumatology	Associate Professor	
Maurice	Madelon	Stem Cell & Organoid Biology	dLAB	Cell Biology	Full Professor	
Middendorp	Sabine	Stem Cell & Organoid Biology	dKinderen	Gastroenterology	Associate Professor	
Moonen	Chrit	Musculoskelatal Tissue Regeneration	dBeeld/Cancer	Radiology	Full Professor	
Nieuwenhuis	Edward	Stem Cell & Organoid Biology	dKinderen	Gastroenterology	Full Professor	MD
Nijboer	Cora	Stem Cell & Organoid Biology	dV&B	Neuro Immunology	Associate Professor	MD
Oner	Cumhur	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Full Professor	MD
Pasterkamp	Jeroen	Stem Cell & Organoid Biology	dHersenen	Neuroscience	Full Professor	
Rooij	Eva	Cardiovascular Tissue Regeneration	dH&L	Cardiology	Full Professor	
Rookmaaker	Maarten	Cardiovascular Tissue Regeneration	dIGD	Nephrology	Associate Professor	MD
Rosenberg	Toine	Musculoskelatal Tissue Regeneration	dHS	Oral Maxillofacial Surgery	Full Professor	MD
Sakkers	Ralph	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Medical specialist	MD
Saris	Daniel	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Full Professor	MD
Seevinck	Peter	Musculoskelatal Tissue Regeneration	dBeeld/Cancer	Radiology	Associate Professor	
Sluijter	Joost	Cardiovascular Tissue Regeneration	dH&L	Cardiology	Full Professor	
Spil van	Erwin	Musculoskelatal Tissue Regeneration	dIGD	Reumatology	Medical Resident	MD
Suyker	Willem	Cardiovascular Tissue Regeneration	dH&L	Cardiothoracal surgery	Full Professor	MD
Teraa	Martin	Cardiovascular Tissue Regeneration	dIGD	Nephrology	Medical Resident	MD
Verhaar	Marianne	Cardiovascular Tissue Regeneration	dIGD	Nephrology	Full Professor	MD
Vonk	Lucienne	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Post doc	
Vulpen van	Lize	Musculoskelatal Tissue Regeneration	dIGD	Internal Medicine	Medical Specialist	MD
Weinans	Harrie	Musculoskelatal Tissue Regeneration	dHS	Orthopedics	Full Professor	
Welsing	Paco	Musculoskelatal Tissue Regeneration	dIGD	Reumatology	Associate Professor	
Witte de	Moniek	Cardiovascular Tissue Regeneration	dBeeld/Cancer	Internal Medicine	Medical Specialist	MD



Theme 1 Musculoskeletal tissue regeneration

Musculoskeletal theme

Brief description work field

In our aging population that only continues to grow, we must shift our focus from treating symptoms to innovations that can replace or restore affected tissues. In the musculoskeletal tissue regeneration theme we work closely together with the Faculties of Science and Veterinary medicine of the UU, and all three technical universities in the Netherlands (Eindhoven University of Technology, Technical University Delft and Twente University) and beyond (e.g., University of Würzburg, Queensland University of Technology, and Chinese University of Hong Kong). The multidisciplinary collaborations between (stem cell) biologists, material and imaging scientists, engineers and medical doctors ensure that our research activities are at the forefront of the field and foster a fruitful basis for innovation in musculoskeletal tissue regeneration. We are studying and improving various options to initiate our natural regeneration capacities, to design regenerative bone and cartilage implants and to create 3D printing techniques and novel biomaterials to create new tissue in.

Why we do what we do and how we pose the right questions

Mission	Injuries and disorders of the musculoskeletal system, including joints, bone, ligaments, muscles and other structures that support limbs, neck and back, are common, and have become a costly and increasing healthcare problem with prevalence rates going up to 80%. Aside from daunting healthcare costs (10% of total Dutch healthcare costs), such disorders have a major impact on quality of life and are accompanied with major socio-economic consequences. Our goal is to shift the focus from treating symptoms to innovations that can replace or restore affected tissues.
Cartilage & joints	Approximately 1.4 million people in the Netherlands and 250 million people worldwide suffer from cartilage degeneration in the knee joint and the underlying bone, also known as knee osteoarthritis. Patients experience severe pain accompanied by reduced movement and mobility. Although it is not yet clear how exactly knee osteoarthritis arises, there are known causes, including trauma and rheumatoid arthritis, as well as wear and tear with aging. Another important patient group consists of young patients with cartilage defects, which often result in osteoarthritis at a later stage. Once osteoarthritis is established, there is no cure, only management of symptoms.
Current state of care	Artificial joint reconstruction is currently the only successful long-term intervention, but has a number of disadvantages: approximately 20% of patients (mostly under the age of 65) have complaints after the procedure; the lifespan of a prosthesis is relatively short young patients (approximately 15 years, after which revision surgery is often required); and costs are high (€10,000 per initial treatment). The number of treatments in the Netherlands has doubled in the last 10 years. Considering the current demographic changes in our society, the numbers are expected to rise continuously and estimated to reach 60,000 in 2030. A prosthesis remains a last resort and combating symptoms does not solve the underlying cause of the problem.
RM offers options	Regenerative medicine can offer new treatment options, for example, with a cartilage repair intervention for young patients or in the future even a complete bio-engineered joint replacement; or new cartilage regenerative (local) drugs to be injected and slowly released in the joint. Our multidisciplinary research teams work closely together towards this goal: a lasting cure of osteoarthritis and other degenerative joint disorders.
Bone	Large bone defects can occur as a result of trauma, congenital malformations, infection or the removal of a tumor. Over 2.2 million bone substitutions are performed annually worldwide by surgical reconstruction using bone grafts from another body part of the patient, e.g., the iliac crest. However, the main disadvantages of autologous bone grafts include pain, an additional defect at the iliac crest and limited source material.



We aim to tailor bone repair	<p>Our goal is therefore to develop new treatments through the engineering of new bone from patient-derived cells and materials, biomaterial scaffolds and/or through the use of local drugs that can specifically stimulate bone repair. These approaches are inspired by naturally occurring mechanisms of bone growth and repair. For example, it was observed that bone is often stimulated to grow when there is a bone-related infection (Croes et al, 2017) and this is related to interaction between bone cells and the immune system. Hence, bone regenerative therapies are currently designed using immune modulating molecules produced by immune cells. Further, to produce functional bone tissue, the interplay between different cell types and scaffold materials is essential: interactions of bone forming cells, bone remodeling cells and immune cells with various implantable materials are studied. In addition, there is a focus on tissue engineering where cells, materials and/or stimulating factors are combined to form de novo tissue in the lab or in the patient. Here, the availability of enough nutrients to keep the engineered structures viable poses an additional challenge when engineering larger bone grafts containing living (stem) cells.</p>
The questions we ask	<p>Within the UMC Utrecht, the departments of Orthopedics, Rheumatology, Oral and Maxillofacial Surgery and Radiology are prominently involved in this RM theme. Together, we are studying and improving various options to initiate our natural regeneration capacities; designing regenerative bone and cartilage implants; and creating 3D printing techniques and novel biomaterials to increase mobility and functionality. We predominantly focus on three areas:</p> <ol style="list-style-type: none">1. Cartilage & Joints: how to reach a lasting cure of (knee)osteoarthritis2. Bone: how to heal (large) defects and achieve better interaction between bio-artificial components and the patient's cells and tissues3. Biofabrication: developing novel technologies for tissue engineered bone and cartilage <p>1. Cartilage & joint</p> <p>Knee pain is commonly treated by an injection that includes corticosteroids and hyaluronan in the knee joint, with a relatively short-term or no effect. We are therefore developing biodegradable microparticles or gels that are loaded with approved medication or with new experimental compounds. With one injection, long-term delivery can be established. For example, anti-inflammatory therapeutics or other innovative cartilage regenerative products are specifically delivered into the joint membrane of the knee or intervertebral disc without the occurrence of systemic side effects. The medication is gradually released, thereby eliminating the need for frequent injections.</p>
Osteo-arthritis	<p>Osteoarthritis (OA) affects both cartilage and subchondral bone, which is essential for the proper functioning of the joint. Often subchondral bone appears diseased, even in a very early stage of the disease and we hypothesized that in a subset of patients, bone deterioration is an important driver of disease progression. We are testing Zoledronate in patients that have bone marrow lesions in their painful osteoarthritic knee. As the bisphosphonate Zoledronic is known to reduce bone turnover, we anticipate slowing osteoarthritis progression as well as relieving pain. Advanced MRI imaging is combined with this clinical trial.</p>
Cartilage repair	<p><i>Improving cartilage regeneration</i></p> <p>Inflammation plays an important role in injury and regeneration; first, during injury in response to tissue damage, and then during the healing process. We've investigating the complex relationship between inflammation and regeneration, for example to reduce inflammation in the joint. Individual anti-inflammatory cytokines have the disadvantage that they are cleared quickly in the body. We have developed a fusion protein of IL4 and IL10, both anti-inflammatory cytokines. This fusion protein is stable and after injection it lasts longer in the joint. Preclinical research shows clear effects on inhibiting inflammation, stimulating cartilage turnover (cartilage matrix build-up) and an analgesic effect in a single treatment (Steen-Louws et al., 2019). If confirmed in clinical trials, this may be the first disease modifying OA drug.</p> <p>In addition, emerging evidence suggests that modulating the expression of several miRNAs can induce chondrogenesis of human mesenchymal stromal cells (MSCs). However, knowledge about miRNA regulation in MSC differentiation is limited and poorly understood. Therefore, we aim to identify microRNAs that play a role in chondrogenic differentiation of MSCs, and to validate their biological roles.</p>



Towards the clinic	<p><i>Clinical application</i></p> <p>We have completed and on-going clinical trials for cell-based therapies and examples are shown in the section “Use of research products by societal groups.”</p>
Bone	<p>2. Bone</p> <p>Cartilage and bone research are close intertwined, as exemplified in our project on the regeneration of bone tissue in a large bone defect. We’re investigating various methods that can stimulate bone regeneration, such as shock wave therapy, titanium foam carrying growth factors, and bone marrow-derived stem cells that have been differentiated towards hypertrophic chondrocytes (endochondral bone regeneration, Longoni et al., 2018). In normal bone growth and repair, bone tissue can develop from cartilage and this process is now being mimicked to regenerate bone in defects. We have previously demonstrated the ability to create a cartilage template with stem cells, which is subsequently converted into bone tissue following implantation in animal models. We are now using this method with devitalized cartilage, as this might be much easier and cheaper to use in the operating theater.</p>
Bone biology	<p><i>The biology of bone formation</i></p> <p>Studying the etiology of diseases allows us to improve treatment strategies. For example, we’ve discovered new evidence that scoliosis starts in the intervertebral disc (Schlosser et al., 2014) and not in the vertebral bodies and are better understanding how growth evolves in the normal healthy growing spine; this will lead to earlier detection and better correction mechanisms for bracing techniques. We have a close collaboration with the image analyses groups to further the use of non-radiation imaging modalities such as MRI and ultrasound, for following scoliosis in adolescents. One example, is spring distraction, an extendable device used to correct spinal deformity in children with scoliosis. Titanium rods are implanted in young children with severe back falsification to correct and support the spine. As they grow, these children currently undergo several stressful surgeries to extend the rod, with long recovery periods. Within the UMC Utrecht, we’ve developed a new technology, called MAGnetic Expansion Control or MAGEC, where the surgeon can extend the correction rod during an outpatient clinic visit with the help of an external, magnetically controlled remote control. This prevents curvature of the spine in a non-invasive manner, without having to have the child undergo multiple operations.</p>
Scoliosis	
Genetic disease	<p>Another example on bone disease etiology and clonical transfer is our research on Osteogenesis Imperfecta (OI), a rare but severe genetic disease also known as brittle bone disease. Although it is known to be caused by effects in the gene that makes collagen, it is not clear how mutations lead to the diminished bone quality and deformities. Several subtypes have been identified and for many of these, we have biobanked bone samples. These samples are tested for properties including collagen mineralisation (collaboration with Eindhoven University of Technology, TU/e), overall stiffness and strength, as well as the collagen cross-linking and glycosylations. We hypothesize that the latter is the key to the disease. The group is involved in a EU project (BOOSTB4; https://www.boostb4.eu) that aims to use stem cell therapy in newborns to introduce a healthy genome and correct the cause of disease as a therapy for severe OI. In this project, 6 patients will undergo stem cell therapy to test safety and efficacy of this advanced therapy.</p>
Implants and 3D printing	<p><i>Personalized implants and 3D printing</i></p> <p>We’re designing new methods to personalize bone implants for patients through image-guided surgeries and synthetic graft substitutes. In certain cases, surgery is the only option, and we strive to continuously refine and make complex surgeries easier with saw and drill guides. This requires a combination of optimizing imaging tools to improve musculoskeletal image reconstructions from both MRI and CT. We also make novel patient-specific implant designs, e.g., a personalized hip dysplasia implant and a deformable highly porous titanium pelvic implant for large bone defects. For patients with complicated anatomy, 3D models aid the training of surgeons in preparation of surgery. We’ve capitalized on the knowledge of our Biofabrication Facility and have added 3D printing infrastructure into our surgical suites. In particular, we’ve built an in-house 3D Face Lab, which is responsible for 3D planning of maxillofacial reconstructions. Not only are 3D models of the skeletal structures, saw guides and printed implants are used, but also a digital representation</p>



of the surgical outcome on the facial appearance of the patient can be predicted and used to better prepare the patient for the esthetical outcome of the surgery.

- Graft sub-stitutes *Biomaterial-based bone graft substitutes*
Spinal fusions require a piece of bone, which may come from a donor (allograft), the patient (autograft) or a graft substitute. We're using a synthetic graft substitute AttraX® (CE-557130), which is a bioresorbable tricalcium phosphate (TCP) mixed with a fast resorbing polymer carrier to improve spinal fusions without the need for an autograft. Once implanted, the optimized architecture of AttraX® stimulates the differentiation of mesenchymal stem cells into bone-forming osteoblasts without the need of additional growth factors. In collaboration with NuVasive, the manufacturer of AttraX®, we conducted a patient and observer blinded, controlled, randomized, multi-center clinical trial ([ClinicalTrials.gov ID: NCT01982045](https://clinicaltrials.gov/ct2/show/study/NCT01982045)) in 100 patients, in which clinical outcomes equate those of autografts. This product is a good replacement for an autologous graft with the advantage of unlimited material supply and the prevention of graft harvesting morbidity. However, this new product cannot provide the desired stabilisation for all patients and we continue to explore options to broaden this.
- What's next
Furthermore, the creation of large constructs for bone defect such as arise after infection, trauma or bone cancer requires the introduction of vascularisation in engineered bone tissue. Such prevascularized bone constructs could be applied in larger defects with limited vascular supply, including, for example, mandibular defects after oncological resections or in non-unions (failure of healing of a broken bone). We have established methods to create capillary-like networks in bioengineered bone tissues in novel biomaterials. For this, we combine several types of human stem cells in vitro. In order to functionally perfuse the capillary-like network, we stimulate our cultures in perfusion bioreactors in collaboration with the TU/e. We have also introduced larger channels connected to the self-assembled capillary network in those cultures, and developed small diameter blood vessels substitutes to complete our multi-scale vascular tree that can perfuse our vascularized bone constructs. These small diameter blood vessels are created by uniquely combining two different 3D printing techniques to create a bilayer that can spatially direct stem cell differentiation of our co-cultures. Current work is focusing on biomaterial optimisation, interconnection of the vascular structures at the multiple levels and functional perfusion, both in vitro and in vivo of our complex bone tissue models.
- Biofabrication **3. Biofabrication**
For larger defects, we depend on the development of regenerative tissue-engineered constructs. For this, materials and (stem) cells are combined in a 3D architecture that resembles the original tissue as much as possible. Within this field, new biomaterials, particularly hydrogels for cell printing and encapsulation, which are capable of mimicking the native environment of articular cartilage, are being developed, both within our center and in collaboration with industrial partners (e.g., Fujifilm). In this framework, our researchers have a prominent role in national and international consortia focusing on biomaterials and tissue printing, in particular the Dutch Gravitation initiative "Materials Driven Regeneration (MDR)" and the Regenerative Medicine across borders (RegMedXB) project.
- Cartilage-like tissue
In this relatively young field, the Utrecht Biofabrication Facility performs groundbreaking work. Our researchers are frontrunners in the field of Biofabrication and Bioprinting. Through the cooperative funding of the Dutch Arthritis Society and the UK Regenerative Medicine platform, our teams are establishing the foundation for the bioprinting of cartilage-derived progenitor cells, enabling the fabrication of cartilage-like tissue *in vitro* with zonal distribution of cells expressing zone-specific markers (i.e., lubricin in the superficial zone). The utilisation of bioprinting and multiple 3D printing technologies to address the complex biomechanical profile of articulating joints is also a primary target in our research, towards the goal of fabricating large, mechanically-competent cartilage replacements. In the 3D-Joint project, a new approach has been developed, where cartilage and bone regeneration are combined with biofabrication methods that allow cells to be printed together with micrometer and nanometer-sized fibers, which accurately mimic bone and cartilage tissue.



MEW	<p>Emerging technologies, such as the melt electrospinning, a 3D printing technique, are combined with expertise in (bio)materials science, e.g., by using biofunctional hydrogels and thermoplastic polymers. The new melt electrospinning writing (MEW) technology has been developed such that it can incorporate bio-inks, which was done in collaboration with leading companies in the field of 3D (bio)printing, such as RegenHu, Switzerland. We have combined MEW technology with a 3D printing device from regenHU, and created two custom-built MEW 3D printers. This novel technology is only present in a few countries world-wide, and has unique features that enable the fabrication of soft and flexible scaffolds with microscale structures.</p> <p>Similarly, in a collaboration with the AO Research Institute in Davos, Switzerland, efforts are undertaken to regenerate the fibrocartilage of the mandibular condyle using state-of-the-art 3D printing techniques mentioned before, combined with bioinks and dental pulp stem cells of the facial region (MACRON project).</p>
Facial reconstruction	<p>Osteochondral defects are hard to heal due to limited regenerative capacity of cartilage tissue. To fabricate implants that mimic native tissue and potentially replace damaged tissue, bioprinting is used to spatially arrange cells within soft hydrogels. The mechanical properties of these hydrogels can be increased by reinforcing scaffolds made by MEW. We recently incorporated MEW in the bioprinting process, which allows for control over deposition of MEW fibers and cells. We've implanted osteochondral plugs into Shetland ponies, a good model because of their strong biomechanical, biological and pathological resemblance to the human knee. These implants are 3D bioprinted from a porous, biocompatible, osteoconductive alpha-tricalcium phosphate based material (CaP).</p>
What's next	<p>Microfibers made of PCL (with MEW) were sufficiently anchored into this bone substitute, and provided a stable base for the chondral compartments that were seeded with articular cartilage progenitor cells (ACPCs).</p>
MEW+ Bio-printing	<p>The results are promising and have been recently translated to an ongoing pre-clinical investigation in an orthotopic defect model in large animals (horses, stifle joint focal, critical size osteochondral defects). Horses are well respected models, due to the challenging mechanical environment of their joint, as well as the biochemical composition of the hyaline cartilage, similar to human patients, as also highlighted by basic investigation performed by our researchers. This research effort, due to the strong representation of veterinary researchers within RM Utrecht, aims to tackle both a clinical problem in the equine veterinary clinic and, at the same time, facilitate translation towards human medicine ("One health, one medicine" principle).</p>
One Health	<p>Alongside cartilage printing and repair, our teams are further exploring bioprinting strategies for the preservation of healthy joint function, restoring or healing different tissues within the joint. For example, we are key partners in a recently initiated consortium on the biofabrication of regenerative meniscal implants, aimed at tackling the increasing incidence of post-meniscectomy induced OA (MEFISTO project EU-funded). In addition we are combining biofabrication with our knowledge about the influence of intra-articular environment (homeostasis) on cell growth, as well as the effects of growth factors.</p>
Meniscus repair; EV's	<p>The recent discovery that extracellular vesicles (EV) can stimulate regeneration and the role of microRNAs on chondrogenic differentiation or MSCs are also being investigated.</p>



Outcomes

Research products for peers

Year	# publications	# dissertations
2013	237	7
2014	207	14
2015	215	10
2016	227	3
2017	198	9
2018	206	10
Total	1290	53

Scientific output of this theme, in the table above; 99% are peer-reviewed publications. The most significant are described below.

Reinforcement of hydrogels using three-dimensionally printed microfibrils.

Visser J, Melchels FP, Jeon JE, et al. *Nat Commun.* 2015 Apr 28;6:6933

Despite intensive research, hydrogels currently available for tissue repair in the musculoskeletal system are unable to meet the mechanical, as well as the biological, requirements for successful outcomes. Here, we reinforce soft hydrogels with highly organized, high-porosity microfibril networks that are 3D-printed with a technique termed melt electrospinning writing. We show that the stiffness of the gel/scaffold composites increases synergistically (up to 54-fold), compared with hydrogels or microfibril scaffolds alone. Modelling affirms that reinforcement with defined microscale structures is applicable to numerous hydrogels. The stiffness and elasticity of the composites approach that of articular cartilage tissue. Human chondrocytes embedded in the composites are viable, retain their round morphology and are responsive to an in vitro physiological loading regime in terms of gene expression and matrix production. The current approach of reinforcing hydrogels with 3D-printed microfibrils offers a fundament for producing tissue constructs with biological and mechanical compatibility.

Allogeneic Mesenchymal Stem Cells Stimulate Cartilage Regeneration and Are Safe for Single-Stage Cartilage Repair in Humans upon Mixture with Recycled Autologous Chondrons

de Windt, T. S., Vonk, L. A., Slaper-Cortenbach, I. C. M., et al. Allogeneic Mesenchymal Stem Cells Stimulate Cartilage. *Stem Cells* (2017). 35(1), 256-264.

Traditionally, mesenchymal stem cells (MSCs) isolated from adult bone marrow were described as being capable of differentiating to various lineages including cartilage. Despite increasing interest in these MSCs, concerns regarding their safety, in vivo behavior and clinical effectiveness have restrained their clinical application. We hypothesized that MSCs have trophic effects that stimulate recycled chondrons (chondrocytes with their native pericellular matrix) to regenerate cartilage. Searching for a proof of principle, this phase I (first-in-man) clinical trial applied allogeneic MSCs mixed with either 10% or 20% recycled autologous cartilage-derived cells (chondrons) for treatment of cartilage defects in the knee in symptomatic cartilage defect patients. This unique first in man series demonstrated no treatment-related adverse events up to one year postoperatively.

Extracellular vesicles: New tool for joint repair and regeneration.

Malda, J., Boere, J., van de Lest, C. H. A., et al. (2016). *Nature Rev Rheumatology*, 12(4), 243-249.

Cell-derived extracellular vesicles (EVs), present in synovial fluid and cartilage extracellular matrix (ECM), are involved in joint development and in the regulation of joint homeostasis. Although the exact function of EVs in these processes remains incompletely defined, the knowledge already acquired in this field suggests a role for these EVs as biomarkers of joint disease, and as a new tool to restore joint homeostasis and enhance articular tissue regeneration. In addition to direct injection of therapeutic EVs into the target site, surface coating of scaffolds and embedding of EVs



in hydrogels might also lead to novel therapeutic possibilities. Based on the existing literature of EVs in synovial fluid and articular tissues, and investigation of the molecular factors (including microRNAs) active in joint homeostasis (or during its disturbance), we postulate novel perspectives for the implementation of EVs as a regenerative medicine approach in joint repair.

Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis

Wiegant, K., van Roermund, P.M., Intema, F.,; Cotofana, S.,; Eckstein, F.,; Mastbergen, S.C., Lafeber, F.P.J.G. (2013) *OSTEOARTHRITIS AND CARTILAGE*,21 (11). 1660-1667, DOI: 10.1016/j.joca.2013.08.006
Treatment of severe osteoarthritis (OA) in relatively young patients is challenging. Although successful, total knee prosthesis has a limited lifespan, with the risk of revision surgery, especially in active young patients. Knee joint distraction (KJD) provides clinical benefit and tissue structure modification at 1-year follow-up. The present study evaluates whether this benefit is preserved during the second year of follow-up.

Endochondral bone formation in gelatin methacrylamide hydrogel with embedded cartilage-derived matrix particles.

Visser J, Gawlitta D, Benders KE, et al. *Biomaterials*. 2015 Jan;37:174-82.
The natural process of endochondral bone formation in the growing skeletal system is increasingly inspiring the field of bone tissue engineering. However, in order to create relevant-size bone grafts, a cell carrier is required that ensures a high diffusion rate and facilitates matrix formation, balanced by its degradation. Therefore, we set out to engineer endochondral bone in gelatin methacrylamide (GelMA) hydrogels with embedded multipotent stromal cells (MSCs) and cartilage-derived matrix (CDM) particles. CDM particles were found to stimulate the formation of a cartilage template by MSCs in the GelMA hydrogel in vitro. In a subcutaneous rat model, this template was subsequently remodeled into mineralized bone tissue, including bone-marrow cavities.

3D printing of surgical implants: design and regulatory challenges

Koen Willemsen, Razmara Nizak, Herke Jan Noordmans, et al. *Accepted manuscript with The Lancet, Digital Health*. 2019 July
Additive manufacturing or so-called 3D printing of metal implants provides considerable opportunities to treat challenging patients, yet the legislation concerning such patient-specific implants makes it complex to implement these techniques in daily practice. In this paper, we share our acquired knowledge describing two consecutive semi-urgent spinal instability cases who received a 3D-printed patient-specific spine implant. We define the challenges that we encountered on the first case and how this gained knowledge that accelerated the process for the second case. This article could provide surgeons and engineers logistical and legal perspectives on how to introduce personalized implants in similar situations.

Research products for societal target groups

Knee Joint Distraction

By preserving the knee, patients may be able to avoid surgery. We've developed a novel form of knee distraction. The KneeReviver separates the upper and lower leg apart allowing native cartilage to regenerate. This treatment shows promising results: more than 70% of patients did not need a prosthesis until 5 years post treatment and 50% until 10 years after treatment (van der Woude, et al., 2017). The 'KneeReviver' is patented and marketed by the spin-off company ArthroSave.

In cooperation with the Dutch Orthopaedic Society and Patient Associations, an application for provisional reimbursement of knee joint distraction has been submitted to provide access to patients as well as to extend the evidence base for the clinical effects of this treatment and optimal indication for patients as well as society (reimbursement with evidence development). ArthroSave (UMC Utrecht) was one of 10 winners of the Academic Startup Competition 2019 in Amsterdam.



Improving OA diagnosis

A diagnosis is often late and there is still a lack of good disease and biochemical markers and O imaging procedures. A better definition of osteoarthritis can better delineate different phenotypes of the disease. Specific treatment for these phenotypes will lead to improved outcomes.

The international APPROACH consortium (coordinated in Utrecht, awarded €15M in EU funding) contributes to this by combining biomedical data for >10,000 patients and controls from eight existing cohorts into a unified bioinformatics platform. With the help of complex algorithms, bioinformaticians can comb through this central database to identify subtypes or phenotypes of OA. These subtypes can then be validated in a longitudinal clinical study (study started 2015 with first inclusion in 2018), using existing and newly-developed biological markers. The results of this 5.5 year program will be used to support the selection of patient cohorts for new disease modifying osteoarthritis drug clinical trials. The identification of disease subtypes will lead to improved diagnostic and prognostic tools and more effective, personalized treatments.

Patents:

2013: WO2013070076A1, Fusion protein comprising an interleukin 4 and interleukin

2016: WO2017209605A1, Implant, fitting plate and method of manufacturing an implant and fitting plate

2018: US20180221034A1, System for Connecting a Connecting Device, in Particular a Distractor, to a Bone

2018: US20180338782A1, Spinal distraction system

2018: US20180098791A1, Coupling device for in an orthopaedic system

Use of research products by peers

Biofabrication facility

The Utrecht Biofabrication Facility is a leading European knowledge center in the area of biofabrication, bringing together engineers, materials scientists, cell biologists, clinicians and commercial partners to create a fostering environment for development, evaluation and clinical translation of 3D tissue constructs. The opportunities range from small prototyping jobs to co-development of large research projects, facilitated by the presence of key technologies and expertise (researchers and technical staff).

Utrecht Advanced In Vitro Models (U-AIM)

The Utrecht In Vitro Models Hubs is a “one-stop shop” where high potential in vitro models are being developed, validated and transitioned to stakeholders. Through a strong cooperation between scientists, students, regulators and industry, the Hub aims to strongly reduce animal experimentation and increase market potential of innovative models. We develop adequate research models for (imaging) methods to detect early changes in joint degeneration and to test treatments in a clinical setting.

We have successfully developed a bioreactor platform to culture osteochondral explants and can culture them for long term (>56 days), preserving the viability of the bone and cartilage compartment. This device and ex vivo culture method have been established in the framework of the EU-funded HydroZONES project (2013-2017), in collaboration with industrial partners (Lifetec B.V.), which have now brought this device to the market as new tool to assess cartilage repair strategies prior to animal or human testing. Implementation of mechanical loading is also ongoing. Furthermore, the recently started EU-funded MEFISTO project will further extend this model to test engineered meniscal implants.

Mobility Clinic

The Mobility Clinic of the UMC Utrecht is the academic center of expertise for people with complex problems with the support and locomotor apparatus. Medical specialists from different departments work together in a multidisciplinary manner. As a result, almost all patients can already count on a clear diagnosis and clear treatment advice after the first visit to the clinic.



Patients are not only assured of a rapid diagnosis at the Mobility Clinic, they are also treated according to the latest insights and techniques that are often not yet available in other hospitals. The Mobility Clinic is also conducting research into new treatment methods and options for improving existing treatments. At this moment, the knee, spine, ankle and foot are included in research and patient care.

Use of research products by societal groups

Guidelines

- Essential contributions from the UMC Utrecht to the AOSpine classification of spinal trauma accepted as standard world-wide and are incorporated in many guidelines. National guidelines for spinal trauma are being prepared.
- Co-author of new guideline for treatment of cartilage damage in the knee joint for the Dutch Orthopedic Society 2019 (NOV standpunt kraakbeenletsel knie 2019).
- Co-author of comprehensive review for Dutch physical therapists regarding treatment of cartilage damage in the knee joint.
- The European multicenter RCT demonstrating the use of BMP-7 has become a key study world-wide on the subject of clinical application of bone regeneration technologies. (Delawi, Diyar, et al. "OP-1 compared with iliac crest autograft in instrumented posterolateral fusion: a randomized, multicenter non-inferiority trial." JBJS 98.6 (2016): 441-448.)

Cartilage repair: changing the standard of care

Our multi-center studies led to the registration of Chondroselect (TiGenix, Belgium), a somatic cell therapy product that contains characterized autologous cartilage cells for the repair of cartilage lesions in the knee. This has been successfully used in matrix-induced autologous chondrocyte implants (MACI, Genzyme) during a 2-step surgical procedure, during which cartilage cells are cultured in the lab and reintroduced into the patient several weeks later. Building on this, we further refined our approach and developed a new procedure called IMPACT (Instant MSC Product Accompanying Autologous Chondron Transplantation). Within a single surgical procedure, cartilage cells are removed, mixed with allogeneic MSCs and a fibrin glue cell carrier and replaced. Phase I and II trials have been successfully completed with 35 patients and also provided the first clinical evidence for the trophic function of MSCs. IMPACT research and subsequent trials have resulted in 2 publications in Stem Cells, a cum laude PhD project for Tommy de Windt, MD, and stimulated a side-project with MSC-derived extracellular vesicles that was published in Theranostics; this research was awarded with 3 ZonMw Translational Adult Stem Cell grants. We will start a phase III study in the fall of 2019 with 120 patients. This study was planned a year ago, but due to problems with the Cell Therapy Facility (CTF) in the UMC Utrecht, all clinical trials that use MSCs were suspended. We are further investigating, how the desired cells and biomaterials can be introduced arthroscopically by a surgeon in a more standardized manner using an airbrush technique.

Dutch Health insurance

The Mobility Clinic of the UMC Utrecht Utrecht has played a major role in the acceptance for autologous chondrocyte implantation (ACI) as treatment for large cartilage defects in the knee joint by Dutch health insurance companies. This was obtained by recognition of Zorgverzekeraars Nederland (an umbrella organisation of 10 health insurers in the Netherlands) for this therapy and incorporated into new guidelines by the Dutch Orthopedic Society for treatment of cartilage defects in the knee joint.



Marks of
recognition
from peers

Center of excellence

- Research Centres of Excellence-Artrose: ReumaNederland has appointed 15 university research groups as Research Centers of Excellence (RCE) and 3 of these groups are from Utrecht and focus on osteoarthritis.
- The UMC Utrecht Department of Rheumatology and Clinical Immunology is one of the European League Against Rheumatism (EULAR) Centres of Excellence.
- AOSpine reference: The UMC Utrecht Spine Unit is an integrated orthopedic and neurosurgical unit which provides care for spine patients of all ages. This unit is an AOSpine reference center and has a leading role in the global research activities of the AOSpine especially in spinal trauma and spinal oncology. The Spine Unit is also involved in the translational research especially in the areas of bone and intervertebral disc regeneration. National guidelines for spinal trauma are being prepared.
- International Cartilage Regeneration & Joint Preservation Society: We are the only Dutch ICRS Centers of Excellence.
- Dutch expertise center for cartilage repair of the knee joint (Dutch Orthopedic Society)
- NFU center of excellence for Osteochondritis Dissecans (European Reference Network application is pending)
- Center of Excellence in Congenital, Orofacial and Dental Anomalies.

Grants (selected list)

- Weinans: European Project APPROACH (2016) €15M; Stichting LSH-TKI IMIT (2017) €800K
- Malda: ERC 3dJoint (2015) personal grant €1,9 M; Malda: MEFISTO- EU NMBP-22 (2019) €600K
- Saris (ZonMw TAS), IMPACT(2013), €600k ; MSC-derived (2017) €300k; Impact to cartilage care (2017) €700k;
- Gwalitta: NWO Graduate program grant 'Integrating Regenerative Medicine and Technology' (2013) €800k
- Lafeber: Stichting LSH-TKI LSH SynerKine (2014) €750k
- Creemers: European Commission iPSpine (2019) total €15M, €300 UMC Utrecht

Awards (selected list)

- Kruyt: The presentation of the SDS received the best paper award at the at the AOTK (Technical innovations) meeting in Montreal (2018)
- Mastbergen: EULAR abstract award (Rome 2015)
- Vonk: Selected for the UMC Utrecht Steyn Parvé program for stimulating female talent (2018); Young Investigator Award, International Cartilage Repair Society (ICRS) World Congress; Top 3 best paper presentation in 'Arthroscopy and Sports Medicine' (AAOS); International Cartilage Repair Society (ICRS) Scientist Travelling Fellowship 2015; Biomet award for best scientific contribution, Netherlands Orthopedic Association (NOV) congress
- Malda: Annals of Biomedical Engineering, Editor's Choice Award (2018), Nanonica Prize for the breakthrough of the year in the field of nanotechnology, Nanonica Europe SL (2015)
- Levato: best oral presentation award at TERMIS-EU (2016)
- Dias Castilho, Wake Forest Institute for Regenerative Medicine (WFIRM) Young Investigator award (2017), European Society for Artificial Organs Young investigator exchange Award (2019), European Society of Biomechanics Conference travel Award (2019)

Membership (selected list)

- Malda: elected President of the International Biofabrication Society.
- Alblas: board member Netherlands society of Biomaterials and Tissue Engineering (NBTE) and member AO Research Review Commission; Editorial Board of Bioengineering; Member TERMIS
- Creemers: member of the International Reviewers Panel European Cells and Materials (eCM); JOR Spine; member Advisory Review Board,
- Gwalitta: General board member of the NVMB (Dutch Society for Matrix Biology); Member local organizing committee of the European Society for Biomaterials congress Maastricht, September 2018 (~1000 participants)
- Oner: Chair of the AOSpine Knowledge Forum Trauma and member of the AO research commission. He is the chairman of the national Guidelines commission of spinal trauma.



Marks of recognition from societal groups

Our researchers are all actively engaged in mentoring, teaching, public speaking, providing expertise to the media, organizing conferences and workshops, and writing for a lay audience. We are exploring media methods of communication, examples can be found here:

- Dutch media has highlighted the development of Knee Joint Distraction as a potential treatment for knee OA, highlighted, for example in de Volkskrant, Algemeen Dagblad, DE Gelderlander, Margriet, Tijd voor Max, Quest, EenVandaag, RTV Noord.
- 3D printing is an item that has been frequently in the news in recent years for example in Trouw, Volkskrant, NRC, AD, NOS, RTV-Utrecht, Nemokennislink
- Cartilage transplantation is also a topic that has frequently appeared in the news from the UMC Utrecht, for example in AD, Zin, Een vandaag, RTV-Utrecht, Nemokennislink
- Media attention was also paid to innovation for the UMC Utrecht about (vertebral) implants in RTL-nieuws, NOS, NRC, Volkskrant, AD, Nederlands Dagblad,
- Outreach activities like exhibition University Museum Utrecht 2016 (Joint distraction), Festival der beschaving (2015), 50+ beurs (2016)

We strive to make our (translational) research accessible to a wider audience through videos and animations. A few links as examples:

[RM and collaboration at the Utrecht Science Park](#)

[the challenge to create tissue in the lab](#)

[3D printing to create living joint replacements](#)

[osteocondral-bioprinting](#)

[3D printed joint implants](#)

[bone printing for spine](#)

[preparation for knee distraction](#)

[IMPACT one stage cartilage treatment](#)

[osteoarthritis-explained-by-dance](#)

Additional

Missing parts and or conclusions

The Musculoskeletal RM groups have a long tradition in multidisciplinary methodologies and translating basic research to the clinic. In the past five years, we have expanded our research considerably with enabling technologies on 3D printing, imaging sciences and immunology. Some of these newer research lines are somewhat at the boundary of what could be considered Regenerative Medicine, for example, etiology of osteoarthritis, scoliosis and implant infection. We believe that knowledge in these areas strengthen our program. Understanding the biology, consequences and peripheral effects on tissue damage and regeneration allows us to better design new therapies that can help the host tissue repair itself. In addition, we're witnessing increased daily interaction between scientists and medical staff such as surgeons, and the benefit to both standard of care and level of personalized treatment we can provide our patients. We expect that this trend will continue to grow further as the RM field matures with an increasing number of clinical applications in the next decade.



Theme 2a Cardiovascular and Renal regeneration

Heart Regeneration

Heart Regeneration

Helping patients with new solutions

The most common cause of death, world-wide, is heart disease, which accounts for 31% of all deaths. Heart disease is caused by a loss of cardiomyocytes, usually because of a heart attack or progression to heart failure. Despite advances in how we manage heart disease, heart disease is progressive, and current therapies, such as lifestyle changes, modern drugs, implanted devices only alleviate symptoms and prevent the disease from becoming worse. There is an obvious need for solutions to reverse or repair damaged heart muscle.

For centuries, we've been studying the heart, and over the years, assumptions have been over-turned by scientific observations and discoveries. One such assumption was that the heart was incapable of regenerating. While this is not entirely true, the heart cannot repair itself enough to be fully functional after trauma or disease-induced damage.

Another assumption was based on early scientific observations that patients' mononuclear cells can be used to repair the heart upon simple intramyocardial injections. In this report, we highlight a diverse group of researchers dedicated to finding new ways to repair, regenerate and restore healthy cardiac tissue.

Why we do what we do and how we pose the right questions

Mission The mission of our RM Cardiac Research program is to bring novel reparative strategies towards clinical trials by bringing together complementary strengths of developed technologies and biology, enhancing our understanding of these diseases via basic research, improving our translational approaches towards potential new therapies, and implement these into our essential preclinical models towards novel clinical trials in patients.

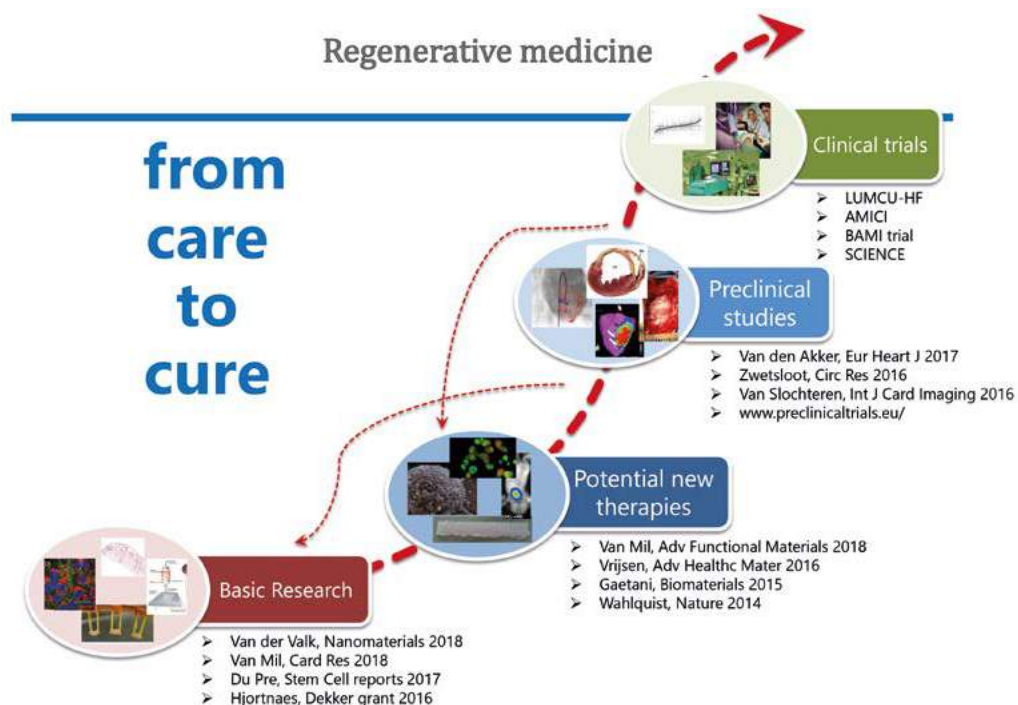


Figure 1: RM Cardiac Research line where basic findings lead to potential new therapies which are tested in preclinical studies toward new clinical trials in patients. (arrows: examples of key-output for each pillar in the pipeline).



The questions we ask

Heart failure creates a large healthcare problem, with ~200,000 patients living with heart failure in the Netherlands having no curative therapies. We therefore created a research pipeline, including

- Basic Research
 - Unravel the cellular and molecular mechanisms in natural regenerative cardiac processes
 - Develop advanced *in vitro* cell model systems (myocardial and valvular)
- Potential new therapies
 - Explore new directions for interventions
 - Improve methodology of existing small animal models
 - Develop potential new therapies in small animal models
- Preclinical studies
 - Improve methodology in existing large animal models
 - Improve imaging techniques
 - Test new intervention methods
 - Translate potential new therapeutic possibilities
- Clinical trials
 - Participate in (inter)national clinical trials
 - Develop and start new clinical trials

Since the cardiac regenerative arena is still a relatively young field, all aspects in this pipeline are essential to have continuous feedback from outcomes to new developments; moreover, the new developed products still need time for clinical trial implementation.

Basic Research

Basic Research

The experiences and methodologies developed in the regenerative field allow the development of advanced *in vitro* cell models to study processes more in details. Examples are:

- Van der Valk, *Nanomaterials* 2018: In this collaborative work with Profs Elana Aikawa and Robert Langer, we developed a 3D *in vitro* model of human cardiac aortic valve disease (CAVD) in which bioprinting with different hydrogels enabled us to mimic the extracellular matrix of native tissue and study biomechanical properties and cellular responses in a layer-specific manner. The model will allow us to explore potential new therapies for valve calcification *in vitro*.
- Van Mil, *Card Res* 2018: The use of specific cell types derived from induced pluripotent stem cells (iPSCs) has developed into a powerful approach to investigate the cellular pathophysiology of numerous diseases. Despite major advantages, still much progress is needed and pitfalls overcome. To gain a better understanding about different approaches and cardiomyopathy models, we generated an extensive overview of this expanding field.
- Du Pre, *Stem Cell Reports* 2017: Circadian (24-hr) rhythms are biorhythms regulated by molecular clocks that play an important role in (patho)physiology. In this work, we described the presence of a molecular circadian clock in adult-derived progenitor cells and a circadian rhythmicity in their function, including cell proliferation, stress tolerance and growth factor release. Improving our understanding of cellular behavior may improve our reproducibility and outcomes of potential therapies. (See also Crnko, *Nature Reviews Cardiology* 2019)
- Hjortnaes, Dekker NHS grant 2016: Dr. Jesper Hjortnaes received a Dekker grant from the Netherlands Heart Foundation to generate a heart-on-a-chip to better mimic the failing human myocardium. He focuses on the development of a fibrosis model that can represent the increased stiffening of the myocardial wall during heart failure. With this, he can test novel therapeutics to explore their effects in a 3D environment. (Sadeghi, *Adv Healthc Mat* 2017; Bracco Gartner, *Front Cardiovasc Med* 2019).

New Therapies

Development of potential new therapies:

- Wahlquist, *Nature* 2014: Heart failure is characterized by a decline in cardiac function, and improving the contractility of heart muscle cells by boosting intracellular calcium handling might be an effective therapy. In this collaborative work with Prof. Mark Mercola (Stanford), we found that inhibiting miRNA-25 can restore Ca levels in the myocardium via normalisations of SERCA2 pump levels and thereby facilitate a new therapeutic approach to restore cardiac function.



- Gaetani, *Biomaterials* 2015: Cardiac cell therapy suffers from limitations related to poor engraftment and significant cell death after transplantation. In this work, we used the previous developed 3D printed cardiac patch (Gaetani, *Biomaterials* 2012) and evaluated the therapeutic potential in a mouse model of myocardial infarction. The application led to a reduced adverse myocardial remodeling and preservation of cardiac performance and demonstrated an enhanced delivery of cells and actions in the heart.
- Vrijksen, *Adv Healthc Mat* 2016: Cellular transplantation therapy has not yet fulfilled its high expectations for cardiac repair due to cell retention problems. However, secreted paracrine factors among extracellular vesicles (EVs) are powerful natural communication mediators that have pro-angiogenic effects. Here, we demonstrated that these therapeutic effects are largely mediated via the presence of EMMPRIN on EVs. This work was also the basis for an ERC Consolidator Grant in 2018 for Prof. Joost Sluijter (EVICARE).
- Van Mil, *Adv Functional Mat* 2018: Cardiac tissue engineering is still challenged by the need to recapitulate fibrillary organisation and mechanical behavior, which can be used to repair damaged myocardium. Here, we used melt electrowriting (MEW) to generate controlled hexagonal microstructures that allowed biaxial deformations, unprecedented compliance and improved maturation of iPSC-derived cardiomyocytes. Interestingly, the designed scaffold allowed shape recovery after epicardial porcine delivery.

PreClinical

Preclinical studies are used to implement and bridge novel therapies toward clinical applications, examples:

- Van Slochteren, *Int J Card Ima* 2016: For cardiac regenerative therapy intramyocardial catheter-guided cell transplantations are targeted to the infarct border zone. For optimal therapeutic effect this area should be accurately identified. In this work, we developed a practical and accurate technique to fuse electromechanical mapping (EMM) with late gadolinium-enhanced magnetic resonance imaging (LGE-MRI) to guide intramyocardial injections. This 3D CartBox image registration toolbox enables registration of EMM data on pre-acquired MRI during the EMM-guided procedure; this enables easy guidance of injections to the most optimal injection location for cardiac regenerative therapy.
- Zwetsloot, *Circ Res* 2016; (two papers, editions of April and August): We understand the importance and potential use of meta-analyses for scientific research. In one paper, we defined a multivariable model to identify potential responders of human cell therapy and distinguish responders from non-responders. In the other, we evaluated the observed effects of cardiac stem cells in post-myocardial infarction models and observed that translational failure is also a major issue when using this more potent cell type.
- Van den Akker, *Eur Heart J* 2017: Although some beneficial effects on the heart have been reported for delivery of stem or progenitor cells, the magnitude of effect is moderate and cellular retention is consistently low. In this study, we visualized for the first time, the real-time dynamics of intramyocardial stem-cell injections. This shows a massive, immediate wash-out via venous drainage, accounting for the low retention. Moreover, the use of carriers reduces this outflow.
- Chamuleau, <https://www.preclinicaltrials.eu/>: In order to increase transparency, help avoid duplication, and reduce the risk of reporting bias by enabling comparison of the completed study with what was planned in protocols, we initiated and established the website Preclinicaltrials.eu. This initiative is the successor of the clinical registration database and is strongly supported by funders, research institutes and research groups; for example, The Royal Netherlands Academy of Arts and Sciences and the Netherlands Organisation for Scientific Research are involved to guarantee permanent access to the database, and the EU TACTICS consortium and the European Society of Cardiology working group on cardiovascular regenerative and reparative medicine (ESC WG CARE).



Clinical

Clinical trials

Participation in multicenter clinical (stem cell) trials

Participation, including RMSC PI and coordinator, in several multicenter clinical (stem cell) trials:

- PRECISE trial: Adipose-Derived Regenerative Cells in Patients with Ischemic Cardiomyopathy. PI: Prof. Emerson Perin (Texas, USA);
- AMICI: Allogeneic Mesenchymal precursor cell infusion in patients with acute myocardial infarction. PI: Dr. Eric Duckers (Rotterdam/Utrecht, Netherlands);
- BAM1: The effect of intracoronary reinfusion of Bone marrow-derived mononuclear cells (BM-MNC) on all-cause mortality in Acute Myocardial Infarction. PI: Prof. Anthony Mathur (London, UK), FP7 project;
- REPEAT: Repetitive progenitor cell (BMMNC) therapy in patients with advanced chronic heart failure. PI: Prof. Andreas Zeiher (Frankfurt, Germany);
- SCIENCE (H2020 project): European multicentre study on stem cell (allogeneic ADSC) therapy in ischemic non-treatable cardiac disease. PI: Prof. Marianne Kastrup (Copenhagen, Denmark), H2020 project;
- LUMC Utrecht-HF: Intramyocardial bone marrow cell injection in patients with chronic ischaemic heart failure. PI: Prof. Douwe Atsma (Leiden, Netherlands).
- Circadian Rhythms in Heart Failure: to investigate 24 hour-rhythms of physiological and molecular markers in heart failure patients & stem cells (van Laake)
- Fibrogenetic-CV: biobanking (iPS) cells from patients with cardiovascular disease and controls (van Laake)

What's next

For innovation and valorisation, our research unit is facilitated by the UMC Utrecht Holdings, which also participated in the previously-mentioned spin-of company Car-Tech (www.cart-tech.com), which is based on advanced imaging technology for adequate treatment planning and delivery strategies. All possible discoveries that might lead to valorisation are being discussed with these professionals. Several national valorisation grants were obtained in which industry co-develops new product lines with us (Chamuleau, MIGRATE (Mri Guided RegenerAtive ThErapy) LSH Impuls 2013; project, Sluijter, TOP-EV, Dutch Heart Foundation 2018).

A relatively new research line was initiated by a patient foundation, the PLN Foundation. The protein PLN regulates the flow of calcium into and out of the heart, and mutated PLN has been identified as a cause of cardiomyopathy within the Dutch population. We were asked by the foundation to establish a scientific program around PLN. The foundation contributes funds and facilitates public interest in this area. We meet every 3-4 months with members of the foundation, alternating between the UMC Utrecht activities (i.e., lab tours, updates) and their events (i.e., National PLN day, which has now created a network with other groups in the Netherlands). Moreover, in 2018 a PLN LeducQ grant was granted to Prof. Pieter Doevendans in which a transatlantic network will work to cure this devastating disease.

Outcomes

Research products for peers

For a selection and explanation of key publications, please see Figure 1 and its explanation

	# publications	# dissertations
2013	126	5
2014	114	12
2015	135	7
2016	112	10
2017	124	14
2018	94	7
total	705	55



Scientific output on this theme, in the table above, 98% are peer-reviewed publications. The 5 most appealing are described below

Circadian rhythms and the molecular clock in cardiovascular biology and disease

Sandra Crnko, Bastiaan C. Du Pré, Joost P. G. Sluijter, Linda W. Van Laake, Nature Reviews Cardiology, volume 16, pages437–447 (2019)

Inhibition of miR-25 improves cardiac contractility in the failing heart.

Wahlquist, C., Jeong, D., Rojas-Munoz, A., Kho, C., Lee, A., Mitsuyama, S., ... Mercola, M. (2014).. Nature, 508(7497), 531-535. DOI: 10.1038/nature13073

Epicardial application of cardiac progenitor cells in a 3D-printed gelatin/hyaluronic acid patch preserves cardiac function after myocardial infarction.

Gaetani, R., Feyen, D. A. M., Verhage, V., Slaats, R., Messina, E., Christman, K. L., ... Sluijter, J. P. G. (2015). Biomaterials, 61, 339-348. DOI: 10.1016/j.biomaterials.2015.05.005

Three dimensional fusion of electromechanical mapping and magnetic resonance imaging for real-time navigation of intramyocardial cell injections in a porcine model of chronic myocardial infarction.

van Slochteren, F., van Es, R., Gyöngyösi, M., van der Spoel, T. I. G., Koudstaal, S., Leiner, T., ... Chamuleau, S. A. J. (2016). The International Journal of Cardiovascular Imaging, 32(5), 833-843. DOI: 10.1007/s10554-016-0852-x

Intramyocardial stem cell injection: go(ne) with the flow.

van den Akker, F., Feyen, D. A. M., van den Hoogen, P., van Laake, L. W., van Eeuwijk, E. C. M., Hoefler, I., ... Sluijter, J. P. G. (2017). European Heart Journal, 38(3), 184-186. DOI: 10.1093/eurheartj/ehw056

Research products for societal target groups

Frebus van Slochteren has a background as a biomedical engineer and conducted his PhD thesis in the area of “technical solutions to improve cardiac regenerative therapy”. Based on this, he *patented* the core technology of a new spin-off company, established together with Steven Chamuleau, called CART-tech.

We’ve opened *a new line of research* as the request (and of course, careful consideration of our strategy) of the patient PLN Foundation. We’re extending this research line to collaborate with several institutes in the USA and China, on a PLN porcine model to mimic the human disease and investigation into potential therapeutic avenues.

Use of research products by peers

Due the potential and broad use of pluripotent cell-derived cardiomyocytes, we established a separate culture facility within the new Regenerative Medicine Center Utrecht for iPS cells. Within this facility we are able to generate and propagate iPS cell lines and differentiate them into cardiomyocytes (Castilho, M., van Mil, A. et al., *Adv Funct Mat* 2018). This facility is now used by many researchers within the RM Cardiac Research team for their projects and collaborations with both VU University Medical Center Amsterdam (Prof. Jolanda van der Velde), Groningen (Prof. Rudolf de Boer) and Maastricht (Prof. Paul Volders) have been established.

We find it important to perform systematic reviews and meta-analyses to *optimize current animal models* for myocardial infarction and cardiac regeneration. This is on-going, and we’ve received a ZonMW grant to support this. Our work cumulated in a publication, “Cardiac stem cell treatment in myocardial infarction: a systematic review and meta-analysis of preclinical studies” (Cir Res, 2016). We’re working to implement optimal use of animal models within the animal facility and hope that, over time, it will be followed by researchers in the field.

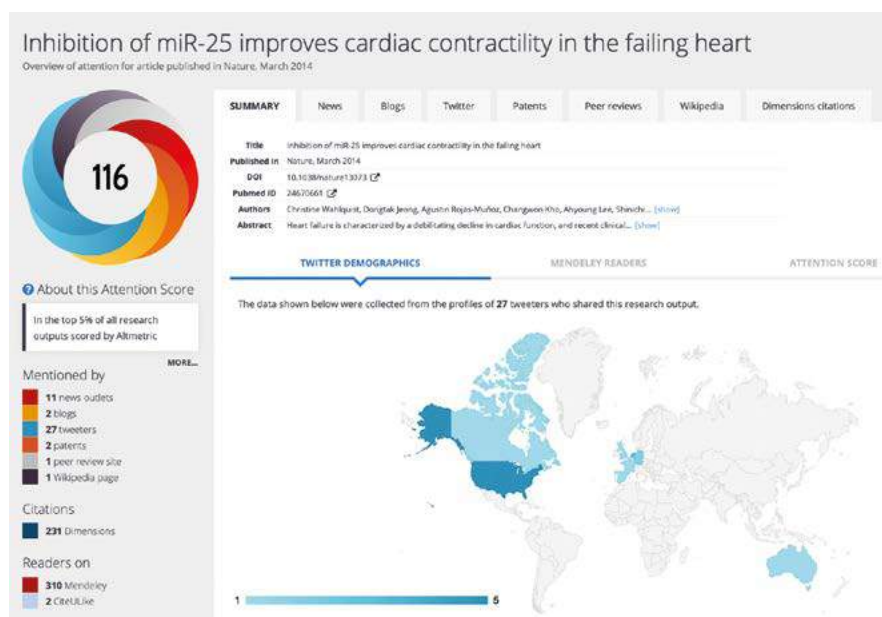


Hamid el Azzouzi, a post-doc in Pieter Doevendans' group has developed *a model that creates a transient narrowing of the aorta*. He can observe functional regeneration of the heart when this pressure is released. Dr. el Azzouzi is optimizing surgical parameters in Utrecht and plans to travel to the lab of Prof. Loren Field, University of Indianapolis, to perform these surgeries in a reporter mouse model. Prof. Field was the RMSC's first Hofvijverkring Visiting Scientist (funded mini-sabbatical of Prof. Field to Utrecht). The Field lab has a unique imaging system to quantitate the degree to which cardiomyocyte renewal contributes to the regeneration process.

Inhibition of miR-25 improves cardiac contractility in the failing heart.

Wahlquist C, Jeong D, Rojas-Muñoz A, Kho C, Lee A, Mitsuyama S, van Mil A, Park WJ, Sluijter JP, Doevendans PA, Hajjar RJ, Mercola M. *Nature*. 2014 Apr 24;508(7497):531-5.

This publication is based on findings from Joost Sluijter's group, and validated in collaboration with Mark Mercola's group in San Diego (who recently moved to Stanford, San Francisco). The figure below shows altmetrics for this paper.



Cardiovascular Research selected our work as Editor's Choice in 2013, 2014 and 2018 for: *most cited manuscripts*:

Derek J Hausenloy, Linda van Laake, Joost P.G. Sluijter, Michel Ovize. ESC WG Position Paper; Translating cardioprotection for patient benefit: The way forward. *Cardiovascular Research*, *Cardiovasc Res*. 2013 Apr 1;98(1):7-27.

most read manuscripts:

1. Sandrine Lecour, Joost P.G. Sluijter, Linda Van Laake, Derek J Hausenloy. Improving the pre-clinical assessment of novel cardioprotective therapies: A Position Paper by the ESC Working Group on Cellular Biology of the Heart. *Cardiovasc Res*. 2014 Dec 1;104(3):399-411.
2. Joost P.G. Sluijter. Microvesicles and exosomes for intracardiac communication. *Cardiovasc Res*. 2014 May 1;102(2):302-11.
3. Sluijter JPG, Van Laake LW. Extracellular vesicles in diagnostics and therapy of the ischaemic heart: Extracellular vesicles in diagnostics and therapy of the ischaemic heart: Position Paper from the Working Group on Cellular Biology of the Heart of the European Society of Cardiology. *Cardiovasc Res*. 2018 Jan 1;114(1):19-34.



Use of research products by societal groups

Researchers, led by Steven Chamuleau, have developed and recently launched a preclinical trial registration tool and are generating awareness at conferences and publications around the importance of transparency in preclinical research. The tool includes a website and preclinical study template. www.preclinicaltrials.eu

Video protocol: porcine myocardial infarction model - Myocardial infarction and functional outcome assessment in pigs. Koudstaal S, Jansen of Lorkeers S, Gho JM, van Hout GP, Jansen MS, Gründeman PF, Pasterkamp G, Doevendans PA, Hoefler IE, Chamuleau SA. *J Vis Exp*. 2014 Apr 25;(86). This video protocol describes (text and video) how to prepare and create a pig model of a myocardial infarction. It also discusses advantages of the model, expected outcomes, and tips for using the model. The figure below shows views of this publication.

Contribution to Guideline: Consensus Document "LVAD therapie" from the Workgroup Mechanical Circulatory Support (MCS) (Dutch foundations for thoracic surgery and cardiology; Nederlandse Vereniging voor Thoraxchirurgie (NVT) en Nederlandse Vereniging voor Cardiologie (NVC)), in press.

Steven Chamuleau and Joost Sluijter are actively involved in the international TACTICS initiative (Transnational AllianCe for regenerative Therapies In Cardiovascular Syndromes). This group of prestigious basic and clinical researchers is dedicated to promoting regenerative therapies as an alternative approach to circumvent current limitations of clinical practice in heart diseases. (www.tacticsalliance.org)

Recently, bone marrow mononuclear cell treatment for patients with refractory AP is now reimbursed by insurance in Leiden; we expect that this will promote the reimbursement of similar types of cell-based therapies.

Position paper

Cell-based therapies for cardiac repair: a meeting report on scientific observations and European regulatory viewpoints.

Schüssler-Lenz M, Beuneu C, Menezes-Ferreira M, Jekerle V, Bartunek J, **Chamuleau S**, Celis P, **Doevendans P**, O'Donovan M, Hill J, Hystad M, Jovinge S, Kyselovič J, Lipnik-Stangelj M, Maciulaitis R, Prasad K, Samuel A, Tenhunen O, Tonn T, Rosano G, Zeiher A, Salmikangas P. *Eur J Heart Fail*. 2016 Feb;18(2):133-41.

We contributed to a European Medicines Agency position paper on cell-based therapies for cardiac repair, which recommends considerations around improved understanding the underlying biological mechanisms of intended cell types; identifying appropriate animal models; principles and requirements for clinical-grade cell-based products and materials; the development of better methods for cell tracking and retention; on harmonizing standards of care among EU states for clinical trials; and frequent and transparent interactions with regulatory officials

Marks of recognition from peers

Boards

- Joost Sluijter: vice-chair (2014-2016) and chair (2016-2018) of the working group on Cellular Biology of the Heart (European Society of Cardiology); member of the TACTICS group (Transnational AllianCe for regenerative Therapies In Cardiovascular Syndromes - <https://www.tacticsalliance.org/>);
- Chamuleau (2016-2018): member of the European Society of Cardiology (ESC) working group on Cardiovascular Regenerative and Reparative Medicine, member of the TACTICS group (Transnational AllianCe for regenerative Therapies In Cardiovascular Syndromes - <https://www.tacticsalliance.org/>);
- van Laake (2012-2018): member of the working group on Takotsubo cardiomyopathy and the translational committee of the Heart Failure Association (HFA); the research Network 'Cardiolinc', www.cardiolinc.org; the working groups on Myocardial Function and Cellular Biology of the Heart of the ESC; selected member of the Utrecht Young Academy (2016).



Grants

ERC consolidator grant - Prof Joost Sluijter Horizon 2020 - ERC-2016-CoG – 725229: EVICARE: Extracellular Vesicle-Inspired CARDiac Repair, €2.0M
 Technology Of Protein delivery through Extracellular Vesicles to target PCSK9 (TOP-EV), Dutch Heart Foundation 2018B014, Prof Joost Sluijter €250,000 (total €500,000)
 COFUND Marie Skłodowska-Curie (EU FP Horizon 2020); PI (89 KE per PI)
 COST Action CardioRNA (prof van Rooij, EU FP Horizon 2020); co-applicant
 Jacob Jongbloed Talent Society grant, Circulatory Health Program UMC Utrecht (Dr van Laake, 100 KE)
 European Society of Cardiology Research Grant 2016-2017 (Dr van Laake 25 kE)
 Clinical Research Talent Fellowship, UMC Utrecht (Dr van Laake 60 KE)
 Novartis Europe personal grant for the Postgraduate Course in Heart Failure (Dr van Laake 5 KE)
 Netherlands Heart Foundation Dekker personal grant “Arts in Opleiding tot Specialist” (Dr van Laake 160 KE)
 European Society of Cardiology First Contact Initiative Grant (Dr van Laake 2.5 KE)
 Veni ZonMw grant, a personal grant of NWO (Dr van Laake 250 KE)
 Dutch Heart Foundation: CVON HUSTCARE (Prof Doevendans/Chamuleau/Sluijter 2013), CVON RECONNECT (Doevendans, 2015), CVON REMAIN (Prof van Rooij/Chamuleau 2016), NHS-Dekker (Dr Hjortnaes, 2017), NHS Private-Public (Prof Sluijter, 2018).
 NWO: CAS-NWO Program (Prof Doevendans, 2015), Gravitation Materials Driven Regeneration (MDR) (Prof Chamuleau, 2017), NWO-TOP (Prof van Rooij, 2017),.
 European funding: ERA-CVD network grant (2016), ERC consolidator (Prof van Rooij, Sluijter, 2014+2016), ESC Research Grant 2016 (Dr van Laake), Marie Skłodowska-Curie (Dr Feyen, 2016), , ESC First contact initiative grant 2013 (De Feyen), Horizon 2020; call PHC 15. SCIENCE (Prof Chamuleau).
 Dalijn foundation (Prof Doevendans, 2014+2016), Fondation Leducq Career Development Award (Dr Gaetani, 2013), Fondation Leducq network grant (Prof van Rooij/Doevendans, 2014+2018), MKMD, Marie-Curie grants (2016+2018).
 Eva van Rooij received an ERC Consolidator Grant and a Trans-Atlantic grant from the Leducq Foundation in 2013 to focus on endogenous stimulation of heart muscle repair through microRNAs.
 3- Steven Chamuleau received several grants including LSH Implule call (ZonMW) for MIGRATE (MRI guided regenerative therapy); a Horizon 2020 grant for SCIENCE for clinical research on regenerative medicine. He is also a work package leader for the CVON HUSTCARE (human stem cells for cardiac repair) grant.

Awards

Peter-Paul Zwetsloot is a physician-scientist who co-founded and coordinated the UAEM-Utrecht branch (Universities Allied for Essential Medicines), while conducting research after being awarded the Alexander Suerman Fellowship. He has also received several other awards and grants, including the Wijck-Stam-Caspers Grant and the American Heart Association CVSA Top 10 Abstract Travel Award. In addition, Peter-Paul has published several meta-articles analyzing current and past stem cell-based heart studies, which provide insightful overviews of how to improve this field.

Several researchers have also been awarded various UMC Utrecht Talent opportunities, including enrollment in the UMC Utrecht Talent Program (Sluijter, Eva van Rooij, Caroline Cheng); the Fellowship Klinische Onderzoekstalent (van Laake, Jan Willem Buikema); the young talent/leadership course, U RTP (van Schloteren); and an advanced mid-level leadership course (Sluijter).

Marks of recognition from societal groups

Importance of dissemination

It is evident that public opinion often sways the direction of funding, policy and acceptance. Therefore, our researchers find it extremely important to discuss the current and future directions of research in heart disease. Many researchers also volunteer their time to teach in a number of RM-related courses, and receive numerous invitations (for grants, consortia, talks, scientific and non-scientific journals for articles and as reviewer, outreach) and press (radio, tv, newspaper).



Examples:

- Sluijter: Special edition on national television via Omroep Max (2015), dedicated to the heart (<https://goo.gl/YZNHXL>), together with patients and other representatives;
- Chamuleau: Radio5 interview with Roberto Bolli (2015), a close collaborator and pioneer in this field which was invited by Utrecht University;
- Sluijter: Guest on the scientific radio program 'De kennis van nu' 2015: <http://www.dekennisvannu.nl/site/media/Hoe-je-een-stad-beter-niet-opwaardeert/209>;
- Chamuleau: interview for the Hart- en vaatgroep for their community (http://www.hartenvaatgroep.nl/uploads/media/In_dialoog_met_dr._Chamuleau.pdf);
- Sluijter: Radio BNR beter, 2017: <https://www.bnr.nl/player/archief/20180226155530120>;
- Publication in the national newspaper, Telegraaf, 13th June 2015: Organ printing;
- HartenTwee, interview with the heart and lung transplant patient organisation, 2018;
- De Cardioloog, double interview, 2018;
- NRC Handelsblad, interview national newspaper, 2012;
- Studium Generale lectures, Steven Chamuleau and Linda van Laake were invited to give these lectures at Utrecht University (2013 and 2014, respectively). Studium Generale is a platform for scientists and other leaders to present their latest research to an educated audience; events are open to the public.

Prizes

- Dr. Mira van der Naald, a PhD candidate, won the audience price for best poster at the Papendal course organized by the Dutch Heart Foundation, Hartstichting. Her poster discussed prospective registration of preclinical trials and the improvement of translation within the field of cardiac regeneration.
- Peter-Paul Zwetsloot won the Professor Frits de Waard Penning award for best and original epidemiological research. Peter-Paul published his findings on "Cardiac stem cell treatment in myocardial infarction; a systematic review and meta-analysis of preclinical studies" (Cir Res, 2016).
- Dries Feyen was awarded an ESC First Contact Initiative Grant that provides support to establish links from young scientists in European institutes to go abroad. The European Society of Cardiology is a non-profit organisation dedicated to disseminating evidence-based scientific knowledge.

Conclusions

In conclusion, we've illustrated the scientific and societal impact of the heart regeneration groups at the UMC Utrecht. The close interactions between fundamental scientists and clinicians, together with enabling technologies, represents the ability of this community to advance the field from various perspectives. The philosophy of proactively moving the field forward is exemplified in distinct areas, including efforts to establish preclinical trial registration as a standard; participation in developing guidelines for both research and clinical practice; responding appropriately to balance patient (and societal) expectations with feasibility of our science and technologies; and to inspire and open dialogue with the public about our position and progress in this exciting phase of cardiac repair and regeneration.



Theme 2b Cardiovascular and Renal regeneration

Kidney Regeneration

Kidney Regeneration

Brief description work field

Chronic kidney disease is a major health care problem with great economic impact. Worldwide, over 10% of the population has chronic kidney disease and ~2.6 million people receive renal replacement therapy. These numbers are expected to increase because of ageing and increasing prevalence of diabetes and cardiovascular disease. Regenerative medicine is an exciting therapeutic option to reduce the burden of kidney disease. Our research focuses on

1. Development of a portable/wearable (bio)artificial kidney;
2. Vascular regeneration, including in situ vascular tissue engineering for hemodialysis vascular access.
3. Kidney organoid technology to improve insight in kidney (patho)physiology and to generate functional kidney tissue;

Why we do what we do and how we pose the right questions

Our mission	<p>Kidney disease is often called the “silent killer.” Early stages can go undetected, and patients can lose up to 90% of their kidney function before any of a diverse array of clinical signs and symptoms manifest themselves. However, renal disease can lead to an up to 8-fold increase in cardiovascular mortality. Kidney disease may also progress to end stage kidney disease, requiring renal replacement therapy.</p> <p>Kidney transplantation is considered the best option for patients with end stage kidney disease. However, there is a shortage of donor organs and many patients are on transplant waiting lists requiring dialysis. Furthermore, kidney transplant patients are at risk for rejection and need to take medications which may have significant side effects. Approximately 1,000 kidney transplants take place every year in the Netherlands, half of which come from living donors. After 10 years, only about 45% of post-mortem donor kidneys are still functioning; for donor kidneys from a living donor, this average is 65%.</p> <p>In the Netherlands, more than 6500 people and two million people worldwide depend on dialysis, which has a major impact on quality of life, morbidity and mortality. It associated with very high costs, and these are among the highest that Dutch basic insurance policies reimburse.</p>
We can do better	<p>Regenerative medicine holds great promise to offer new therapeutic solutions for patients with kidney disease. We believe we can do better than the current standard of care, and our goal of improving the lives of kidney patients encompasses much more than medical treatment. We invest in research, technology, bedside care, our talent and our collaborators. And we do this while seeking the best ways to benefit our patients and their families and caregivers.</p> <p>Our mission is to improve care for patients with kidney disease by the development of novel regenerative strategies.</p>
The questions we ask	<p>Over the last five years, we have gained insight into this devastating disease and focused on building tools to help alleviate and hopefully, one day reverse kidney damage.</p> <p>These include:</p> <ol style="list-style-type: none">1. <i>Improving dialysis: can we make it portable, more consistent and amenable to a more normal lifestyle?</i> <i>Can we improve the low level of blood purification of standard dialysis (and improve health and well-being)?</i>2. <i>Novel strategies for in situ vascular tissue engineering for vascular access for hemodialysis.</i> <i>Can we use design intelligent materials for in situ vascular tissue engineering that can ultimately provide vascular access in dialysis patients whose veins are over-used, collapsing or clogging, minimizing complications and numbers of surgeries?</i> <i>Can we use Extracellular Vesicles to stimulate vascular regeneration?</i>



3. The development of patient-derived *kidney organoids*:

- Which kidney diseases can be modeled ex vivo by kidney organoids?
- Can patient-derived organoids be used for personalized medicine, i.e., can organoids derived from one patient be used to screen the efficacy of several different drugs ex vivo, before prescribing the patient a drug.
- Can organoids be used for high throughput drug screening, i.e., can promising pharmaceutical compounds be tested on a biobank of organoids from different patients to evaluate effectiveness?
- Can organoid-derived renal tissue applied in a bioartificial or bioengineered kidney provide auxiliary renal function?

Portable artificial kidney

1. Portable artificial kidney

There are two methods for dialysis: peritoneal dialysis (PD) and hemodialysis (HD).

We lead the development of miniaturized, mobile devices with better systems for fluid exchange and toxin removal. These provide patients with dialysis over a prolonged period of time, based on the continuous regeneration of a small volume of dialysate. Two portable devices are currently being developed, the WEAKID (Wearable Artificial KIDney) for peritoneal dialysis and the PAK (Portable Artificial Kidney) for hemodialysis (reviews on portable kidney devices: Wester M, et al., *Ned Tijdschr Geneesk* 2013; Wester M, et al., *Ned Tijdschr Geneesk* 2019; Kooman JP, et al., *Expert Rev Med Devices* 2015; van Gelder MK, et al., *Expert Rev Med Devices* 2018; van Gelder MK, et al., *Nephrol Dial Transplant* 2018, Braam B et al., *Nat Clin Nephrol* 2007, Legallais C, et al., *Adv Healthc Mater* 2018).

Currently, about 80% of hemodialysis patients must travel to a clinic or hospital setting, 3 times a week and sit for 4 hours per session, where trained clinical personnel administer dialysis treatment. It exerts a tremendous burden, physically and emotionally, on patients, caregivers and our healthcare systems. It is an intermittent treatment, that uses a large volume of water (~120 L of dialysate per session) and power, in an inadequate attempt to recapitulate a normally functioning kidney. This is time-consuming, inefficient and contributes to poor quality of life and high mortality.

We are leading efforts to build more efficient dialysis systems. We are involved in the development of a miniature, portable artificial kidney (PAK) for HD (the 'NeoKidney' initiative) that weighs less than 10 kg and uses 5-7 liters of dialysate removing dependence on large water and power supplies. Unlike other devices on the market, the device incorporates a recycling system comprised of a sorbent filtration system that removes toxic waste molecules, thereby reducing dialysate volume.

A miniature dialysis machine will allow patients to perform dialysis in the comfort of their home (even at night while asleep) or while on the go. The device has a friendly user interface, providing feedback to the patient and allowing remote monitoring of the patient and device by their physician. It allows personalisation of treatment and empowers a patient by giving him/her mobility, independence and an overall improved quality of life. Since dialysis can be done either frequently or over longer periods of time, fluctuations in toxin concentrations and body fluid will be reduced, and because dialysis is more consistent, it will reduce the risk of heart failure and other health problems often associated with these patients. We expect overall disease prognosis as well as condition of life to improve. This portable device is approximately 40% less costly compared to in-center HD, which will significantly reduce the economic burden on our healthcare systems.

This compact portable device can also reach many more patients, especially those who cannot travel for traditional dialysis treatments or in developing countries where availability of water is limited (publications on HD include Wester M, et al., *Nephrol Dial Transplant* 2017; Wester M, et al., *Am J Physiol Renal Physiol* 2018, Bonenkamp AA et al, *Neth J Med* 2018; van Loon I, et al., *Age Ageing* 2017).



In addition to the portable artificial kidney device for HD, we coordinate and are co-developing the WEAKID (WEArable Artificial KIDney, EC H2020 project, 3307k€; follow-up COPEDIS (Health Holland/ DKF) 1005k€), a miniaturized dialysis system for PD. PD is a dialysis technique that removes toxins and excess water by diffusion and osmosis, respectively, from the blood across the membrane into dialysis fluid in the abdominal cavity. The dialysis fluid is exchanged via a permanently implanted catheter 4-6 times a day, manually by the patient during the day, or automatically at night. Unfortunately, its clearance efficiency is low and high glucose concentrations are used for osmotic removal of water, which, in the long-term, can injure the peritoneum and contribute to cardiovascular disease and mortality. Large volumes of PD fluids (12 L/day) need to be stored at home and technique failure rate is high due to membrane failure and recurrent peritonitis. Within 4 years of treatment patients often have to switch to HD (complications of PD: Abrahams AC et al., *PLoS One* 2014; Abrahams, AC, et al., *Perit Dial Int* 2017).

WEAKID continuously regenerates and recirculates the intra-abdominal dialysis fluid, thereby maintaining a large diffusion gradient between plasma and intra-abdominal fluid and enhancing solute transport across the peritoneal membrane. WEAKID is expected to be 2-3x as efficient as current PD with only 1 exchange per day, thereby improving health and well-being and reducing peritonitis rate. It uses lower glucose concentrations, thus reducing functional deterioration of the membrane and improving technique survival. WEAKID may lead to a shift from HD to PD due to increased popularity of PD and longer technique survival. This may significantly reduce costs (cost savings ~40k€ per patient per year as compared to in-center HD).

Both artificial kidney models are built upon previous knowledge and technology developed in the EU FP7 Framework project, NEPHRON+ and have the potential to truly impact kidney patients, their families and our healthcare systems in multiple ways. In essence, they combine the flexibility of peritoneal dialysis and efficacy of hemodialysis in small devices. They offer continuous or prolonged therapy at home at a lower cost, reducing the amount of fluids and electrical power needed, while improving quality of life. They have the potential of changing the standard of care for kidney patients.

What's next?

In collaboration with a number of research groups, clinical nephrology departments and technology companies in the Netherlands, Italy, Spain, Switzerland and Singapore, we are planning to conduct a first-in-human clinical trial for evaluation of safety and efficacy of both the PAK for HD and WEAKID. The Dutch Kidney Foundation has initiated discussions with insurance agencies regarding reimbursement models. Given the potential and novelty of these device, the we will also initiate discussions with insurance agencies regarding reimbursement models and assess possible intellectual property options.

In the meantime, we are working on further miniaturisation and optimisation of the devices together with academic and industry partners, TTW, Health Holland and NeoKidney, a development enterprise initiated by the Dutch Kidney Foundation for the purpose of the realisation of a portable artificial kidney. One of the major challenges is removal of urea from dialysate. We are exploring several strategies, including polymeric sorbents (TTW OTP 14433, 744k€), electro-oxidation and membrane approaches (strategic alliance UMC Utrecht-UU-MIRA) (Tijink MS et al., *Biomaterials* 2013; Wester M, et al., *Nephrol Dial Transplant* 2013; Wester M et al., *Artif Organs* 2014; Wester M, et al., *Am J Physiol Renal Physiol* 2018). Another important challenge is removal of protein-bound uremic toxins (PBUTs) that are poorly removed from plasma by standard dialysis (Pavlenko D, et al., *Sci Rep* 2016; Pavlenko D, et al., *Sci Rep* 2017). Together with the Department of Pharmaceutics (UU) and the University of Twente we are developing a bioartificial kidney (BAK) containing hybrid "living membranes" with functional renal cells that are supported by an artificial functionalized hollow fiber membrane and are able to actively remove PBUTs. In addition, we are involved in the development of innovative mixed matrix membranes (MMM, LSH-TKI NOVAMEM 768k€), that combine diffusion and adsorption in one membrane by incorporation of adsorptive particles in a porous polymer, allowing further reduction of dialysate flow and volume and improving PBUT removal. For both the BAK and the MMMs proof of concept has been obtained in vitro and we aim for validation in vivo (rodents) within the near future.



In the majority of the projects, the Dutch Kidney Foundation, NeoKidney and/ or the Nierpatienten Vereniging Nederland (Dutch Kidney Patient Association) are involved. They connect us with their patients, who provide us with feedback, the ability to test new ideas and suggestions on our clinical protocols.

Vascular access

2. Vascular regeneration and vascular access

Prior to a first dialysis treatment, patients undergo surgery to create venous access. For hemodialysis, the most common practice is to surgically create an intersection of an artery and vein, called an AV fistula. For peritoneal dialysis, patients undergo a surgical procedure to implant a permanent catheter in the abdomen. Both are associated with surgical and post-op recovery risks, and repeated access to these locations is often accompanied by infection, fibrosis, collapse or clogging of the blood vessels, leakage and catheter malfunction.

For hemodialysis patients, whose veins are over-used, collapsing or clogging, we are investigating vascular access approaches to minimize complications and numbers of surgeries (reviews on vascular regeneration and in situ tissue engineering: Muylaert DEP, et al., *Tissue Eng Part B Rev* 2016, Huethorst E, et al. *Tissue Eng Part B Rev* 2016, de Jong OG, et al, *Front Immunol* 2014, Muylaert DE, et al., *Heart* 2014).

There are many challenges, such as how to achieve the desired long-term mechanical stability and associated matrix homeostasis in the demanding systemic circulation; how to attract and guide cells to build a layered arterial wall; how to avoid adverse developments such as thrombus formation and hyperplasia; and how to modulate the foreign body response and maintain functionality in patients with (risk factors for) cardiovascular disease.

Together with the Eindhoven University of Technology (TU/e), in the Strategic Alliance between TU/e/ Utrecht University and UMC Utrecht, as well as in a consortium, funded with €4 M from the Netherlands Organisation for Health and Research, and within the NWO Gravitation Programme, and based on earlier successes, we will exploit our supramolecular materials approach to tackle these challenges (Tlacua H, et al., *Tissue Eng Part A* 2015; Muylaert DE, et al., *Biomaterials* 2016). TU/e supplies materials knowledge and is responsible for design, and we analyze the biology and enable clinical application.

What's next

We aim to combine an off-the-shelf synthetic material that, when implanted, attracts a patient's own cells to replace the damaged tissue, and over time biodegrades. We are investigating several materials and one promising material is made by a TU/e spin-off company Xeltis that has FDA-approval for use in heart valve replacement. The ultimate goal is to create an implantable bio-compatible vascular graft with smart material(s) that slowly degrade and help the patient's own body repair and grow healthy tissue.

We have provided proof of principle in small animal models. At the end of June 2019, we will start experiments in a goat model and conduct a side-to-side anastomosis (from artery to vein) testing. This better models the human condition, with larger blood vessels and mimicking of an AV fistula. We will be studying the grafts for biofunction and cell retention (do they attract cells and does tissue formation develop) and durability (can it withstand repeated punctures, as patients undergo dialysis three times a week). In addition, we are preparing to use the uremic goat model that was established for the portable artificial kidney. What is currently available are synthetic grafts and these need to be replaced after about three years. We expect that our new graft will reduce or remove complications associated with vascular access for dialysis, reduce costs, and therefore improve overall treatment efficacy and quality of life.

Based on our previous work on extracellular vesicles (van Balkom BWM, et al., *Proteomics* 2018, van Balkom, et al, *Clin J Am Soc Nephrol* 2017) we are also exploring the role of extracellular vesicles in vascular (and renal) regeneration. We collaborate with industry and several other partners to develop advanced multi-organ-on-a-chip in vitro systems.



We are involved in EU- and global networks of scientists. In these networks, steps towards clinical application are discussed and communicated via position papers in international peer reviewed scientific journals (Reiner AT, et al, *Stem Cells Transl Med* 2017, Witwer KW, et al., *J Extracell Vesicles* 2019, They C, et al., *J Extracell Vesicles* 2018, Mateescu B, et al., *J Extracell Vesicles* 2017, Lener T, et al., *J Extracell Vesicles* 2015).

Kidney organoids **3. Kidney organoids (tubuloids)**

We capitalized on existing knowledge, mostly generated in Utrecht (Clevvers group), and adapted the organoid derivation methodology for the kidney. We have recently published a proof-of-principle in *Nature Biotechnology* (Schutgens F, et al., *Nature Biotechnology* 2019). With our modified procedure, we were able to take kidney tissue or a simple urine sample from a patient and create a robust kidney organoid model. We demonstrated that these kidney organoids provide an accurate representation of an infectious kidney disease (BK virus), malignant renal diseases (Wilms tumor, the most common kidney tumor in children) and genetic diseases (cystic fibrosis). Moreover, the renal organoid culture system allowed ex vivo evaluation of drug efficacy for the latter, demonstrating the potential of the model for personalized medicine. We are currently in the process of banking urine cells of patients for future application (reviews on kidney organoids: Schutgens F, et al., *Eur J Pharmacol* 2016, Rookmaaker MB, et al. *Nat Rev Nephrol* 2015).

The organoid culture system fundamentally differs from traditional cell culture models in that the organoids are self-organizing three-dimensional multicellular structures. In addition, the organoid culture system allows almost unlimited expansion of renal cells from patients that can be derived non-invasively, without genetic modification that interferes with the proliferation pathways. The latter is important for the investigation of malignancies and senescence, two conditions that are currently receiving a lot of attention. In addition, autologous non-genetically manipulated genetically stable expandable renal cells are promising for application in bioartificial and/or bioengineered kidneys.

What's next?

Although kidney organoids are a powerful model to study human development and disease, we still have a long way to go before they can be used in a therapeutic setting. Therefore, we are involved in a number of collaborations, using our research findings, that focus on various aspects, such as directed cell differentiation, architecture and supporting tissue elements, that need to be improved for organoids to recapitulate in vivo physiological functions. Examples of such collaborations include the NWO Gravitation project 'Materials Driven Regeneration: Regenerating tissue and organ function with intelligent, life-like materials' that focuses on materials-driven solutions for the regeneration of essential kidney functions; the RegMedXB consortium that includes a Kidney Moonshot focusing on the development of a bioartificial kidney. Furthermore, we collaborate with prof Roos Masereeuw, Department of Pharmacy, Utrecht University on cystinosis using kidney organoids and on the use of kidney organoids in the bioartificial kidney; with prof Hans Clevvers and dr Jarno Drost, Hubrecht Institute, on pediatric tumors using kidney organoids, with prof Ewout Hoorn and prof Joost Gribnau, Erasmus MC, on kidney organoids and polycystic disease and with prof Joost Hoenderop, Radboudumc Nijmegen on distal tubular transport functions.



Outcomes

Research products for peers

	# publications	# dissertations
2013	37	5
2014	50	1
2015	57	2
2016	50	4
2017	44	6
2018	69	4
total	307	22

Scientific output on this theme, in the table above, 96% are peer-reviewed publications. The 5 most appealing are described below

Tubuloids derived from human adult kidney and urine for personalized disease modeling.

Schutgens F, Rookmaaker MB, Margaritis T, Rios A, Ammerlaan C, Jansen J, Gijzen L, Vormann M, Vonk A, Viveen M, Yengej FY, Derakhshan S, de Winter-de Groot KM, Artegiani B, van Boxtel R, Cuppen E, Hendrickx APA, van den Heuvel-Eibrink MM, Heitzer E, Lanz H, Beekman J, Murk JL, Masereeuw R, Holstege F, Drost J, Verhaar MC, Clevers H.

Nat Biotechnol. 2019 Mar;37(3):303-313. doi: 10.1038/s41587-019-0048-8. Epub 2019 Mar 4

As an example of building upon existing knowledge, organoid technology established in Utrecht by Hans Clevers, we developed kidney organoids from human kidney tissue or urine that can be expanded over > 6 months while remaining genetically stable and represent proximal as well as distal nephron segments, as evidenced by gene expression, immunofluorescence and tubular functional analyses. We capitalized on existing knowledge and our strong interactions with the Hubrecht Institute and the Princes Maxima Center for Pediatric Oncology. The cumulation of our collaborative research can be seen in the recent Nature Biotechnology publication.

Troy/TNFRSF19 marks epithelial progenitor cells during mouse kidney development that continue to contribute to turnover in adult kidney.

Schutgens F, Rookmaaker MB, Blokzijl F, van Boxtel R, Vries R, Cuppen E, Verhaar MC, Clevers H.

Proc Natl Acad Sci U S A. 2017 Dec 26;114(52):E11190-E11198. doi: 10.1073/pnas.1714145115. Epub 2017 Dec 13. PMID: 29237753

We demonstrated that the Wnt target gene, Troy (TNFRSF19) marks the renal progenitor/stem cell population in the developing kidney and that these cells later contribute to homeostasis, predominantly in the collecting duct of the adult kidney and regeneration.

Early in-situ cellularisation of a supramolecular vascular graft is modified by synthetic stromal cell-derived factor-1 α derived peptides.

Muylaert DE, van Almen GC, Talacua H, Fledderus JO, Kluin J, Hendrikse SI, van Dongen JL, Sijbesma E, Bosman AW, Mes T, Thakkar SH, Smits AI, Bouten CV, Dankers PY, Verhaar MC.

Biomaterials. 2016 Jan;76:187-95. doi: 10.1016/j.biomaterials.2015.10.052. Epub 2015 Oct 23. PMID: 26524538

Efforts in in situ tissue engineering are focused on stimulating endogenous tissue repair. In this study, we incorporated SDF1-alpha-peptides, modified with UPy, into a UPy-modified polymer scaffold. We were able to show that a completely synthetic cell-free biomaterial has the capability to recruit and stimulate specific endogenous leukocyte populations in a rat model.



A regenerable potassium and phosphate sorbent system to enhance dialysis efficacy and device portability: a study in awake goats.

Wester M, Gerritsen KG, Simonis F, Boer WH, Hazenbrink DH, Vaessen KR, Verhaar MC, Joles JA. Nephrol Dial Transplant. 2017 Jun 1;32(6):951-959. doi: 10.1093/ndt/gfw108. PMID: 27220758 *Patients on dialysis suffer from fluctuations in potassium and phosphate levels. We conducted a study in goats on the efficacy of potassium and phosphate absorption in a wearable device. Our findings demonstrated clinically-relevant, concentration-dependent, pH-neutral potassium and phosphate removal with a small volume of dialysate using ion exchangers, providing continuous regeneration.*

Removal of urea by electro-oxidation in a miniature dialysis device: a study in awake goats.

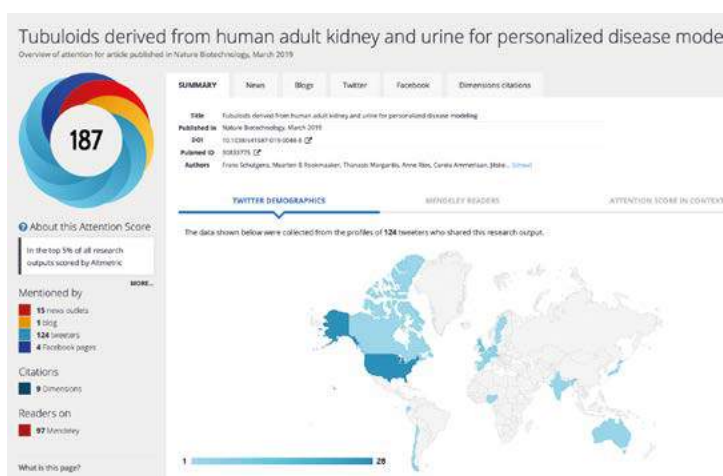
Wester M, van Gelder MK, Joles JA, Simonis F, Hazenbrink DHM, van Berkel TWM, Vaessen KRD, Boer WH, Verhaar MC, Gerritsen KGF. Am J Physiol Renal Physiol. 2018 Nov 1;315(5):F1385-F1397. doi: 10.1152/ajprenal.00094.2018. Epub 2018 Jul 11. PMID: 29993277 *Our kidneys filter and remove urea waste from our bodies and in this paper, we explored the efficacy of electro-oxidation (EO) for urea removal, and whether we could safely regenerate a small volume of dialysate in a closed-loop system. Using a hemodialysis goat model, we achieved clinically-relevant urea removal with a miniature dialysis device through EO.*

Research products for societal target groups

We are co-developing the WEAKID (Wearable Artificial Kidney), a miniaturized dialysis system for PD that improves survival of the peritoneum, uses a lower glucose concentration (and thus, fewer complications to the membrane and reduced peritonitis), is expected to be twice as efficient as current dialysis systems and will reduce overall costs of treatment

We have designed a miniature, portable artificial kidney (PAK) for hemodialysis that weighs less than 10 kg and uses 5-7 liters of dialysate removing dependence on large water and power supplies. It facilitates frequent and longer dialysis, thereby attenuating the fluctuations in water balance and waste solute levels, allowing personalisation of treatment. This dialysis machine will allow patients to perform dialysis in the comfort of their home (even at night while asleep) or while on the go. The device has a friendly user interface, providing feedback to the patient and allowing remote monitoring of the patient and device by their physician. This empowers a patient by giving him/her mobility, independence and an overall improved quality of life. Since dialysis can be done either frequently or over longer periods of time, kidney function will become more consistent, and because dialysis is more consistent, it will reduce the risk of heart failure and other health problems often associated with these patients. This portable device is also approximately 40% less costly compared to traditional HD, which will significantly reduce the economic burden on our healthcare systems.

Use of research products by peers



The Dutch Kidney Foundation (Nierstichting) is as strong partner. It's well-organized with a large patient base. In addition to funding, the foundation assists with publicity and active links to patients. They've recently created a private spin-off company, NeoKidney, with the sole aim of



funding and driving development of a portable artificial kidney, and they have become one of our grant partners on our project on improving vascular access for dialysis patients. Another patient foundation, the Dutch Kidney Patient Association (Nierpatiënten Vereniging Nederland) is closely involved in our peritoneal dialysis project. We are also closely involved in organisations focused on cardiovascular research, including the Dutch Heart Foundation and the Netherlands Heart Institute.

<http://www.neokidney.nl/index.php/en/>

Use of research products by societal groups

We have developed technology to culture adult stem cell-derived kidney organoids from human kidney tissue or urine that can be expanded for > 6 months remaining genetically stable. The kidney organoids represent proximal as well as distal nephron segments and can be used to model infectious, malignant and hereditary kidney diseases in a personalized fashion. Kidney organoids derived from a patient with cystic fibrosis allow ex vivo assessment of treatment efficacy. Kidney organoids cultured on microfluidic organ-on-a-chip plates adopt a tubular conformation and display active (trans-)epithelial transport function.

Currently the renal organoid model is applied in several collaborations focusing on a wide variety of renal disease including cystic renal disease, renal malignancies and genetic renal diseases. In addition, the functional capacity of organoid derived renal epithelial cells, has led to the current efforts to apply organoid renal cells in bioartificial and/or bioengineered kidneys in 2 large international consortia (RegMedXB and NWO Zwaartekracht).

Marks of recognition from peers

In 2017, we were awarded the prestigious NWO Zwaartekracht (Gravitation) grant (<https://mdrresearch.nl/>), together with Eindhoven University of Technology (TU/e) and Maastricht University (Applicants: Carlijn Bouten, Bert Meijer (TU/e); Verhaar, Clevers (UMC Utrecht, Hubrecht); Pamela Habibovic, Clemens van Blitterswijk (Maastricht UMC). Financed by the Dutch Ministry of Education, Culture and Science, this €18.8 million grant supports regeneration of tissue and organ function with intelligent, life-like materials. With our combined knowledge in the field of materials driven regeneration, and our multidisciplinary approach, the Materials-Driven Regeneration (MDR) consortium aims to tackle one of the biggest and costliest challenges of healthcare: the cure of chronic diseases, such as cardiovascular diseases, musculoskeletal disorders, and organ diseases such as kidney failure. We expect to generate IP and bring products to the market.

Karin Gerritsen was awarded a Horizon 2020 Treating and Managing Disease grant to validate WEAKID (Wearable Artificial Kidney); and Hans Clevers was awarded his second ERC Advanced Grant for organoid research.

Together with the Eindhoven University of Technology (TU/e), we have formed a consortium, funded with €4 M from the Netherlands Organisation for Health and Research. TU/e supplies materials knowledge and is responsible for design, and we analyze the biology and enable clinical application. We've built a biosynthetic graft based on an already existing bioartificial heart valve. The ultimate goal is to create an implantable bio-compatible vein with smart material(s) that degrade and help the patient's own body repair and grow healthy tissue.

We are also a leading partner in the Regenerative Medicine Crossing Borders (RegMed XB) Institute. RegMed XB brings together multiple health foundations, top scientists, entrepreneurs and governments to cooperatively tackle ambitious challenges in regenerative medicine. In RegMed XB, research and clinical translation are integrated to quickly and optimally bring research results into patient solutions and new businesses. In the RegMedXB Kidney Moonshot we work towards creating a functioning subunit of a bioengineered kidney.

Caroline Cheng was recruited by the RMSC strategic research program and awarded financial support to start up her lab at the UMC Utrecht (2013); she was also awarded a VIDI grant (2014) and is the scientific coordinator and WP leader of RECONNECT consortium, which is investigating the link between heart disease and kidney failure.



Marianne Verhaar serves on various (inter)national committees, including the Scientific Council of the Netherlands Heart Institute; the Scientific Advisory Board of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA); and as chair of Continuous Education and Professional Development of the ERA-EDTA. She is an elected member of the “AcademiaNet – Expert database of Outstanding Female Scientists and Scholars”, nominated by NWO (2012); International Fellow of the American Heart Association (FAHA) - Council on the Kidney in Cardiovascular Disease; and co-organizer of the route “Regenerative Medicine” of the Dutch National Science Agenda (“Nationale Wetenschapsagenda”).

Marks of recognition from societal groups

Hans Clevers received the Breakthrough Prize in Life Sciences in 2013 for describing the role of Wnt signaling in stem cells and cancer.

In 2018, Jaap Joles was awarded the Willem Birkenhäger Award, by the European Society of Hypertension for his achievements in international hypertension research.

Several policy documents have been developed by Linda van Laake and colleagues addressing “talent management and career tracks within the UMC Utrecht” (2016) that was provided to the Board of Directors; and reports, for example, on regenerative medicine in healthcare and implementation of technology in health care were written for the Young Health Council, an advisory committee for the Dutch government and parliament on current scientific knowledge and public health issues and research.

In addition, our researchers often present our research and results to the public; below are some select activities:

- Frans Schutgens (2017) presented at Universiteit van Nederland, where Dutch researchers give free online lectures: “How do you culture miniorgans”; <https://www.youtube.com/watch?v=Fxx2S8GxfPk>
- The *New Scientist* (2017) published a special edition showcasing Utrecht Life Sciences, in which several of our researchers and projects are highlighted: Madelon Maurice, cellular pathways; Marianne Verhaar, kidney regeneration; https://issuu.com/vbku/docs/ns_uls_special_lr
- Video (Cure kidney diseases) by the Dutch Kidney Foundation: Marianne Verhaar describing her research in kidney regeneration; this is done in partnership with RegMedXB; <https://www.nierstichting.nl/wat-wij-doen/nierziekten-genezen/>
- *MaxVandaag* (2017, television program, Wie maakt het verschil?): medical innovations in research; Marianne Verhaar and Maaïke van Gelder, PhD student describe the latest in kidney research; https://www.maxvandaag.nl/programmas/tv/wie-maakt-het-verschil/nierstichting/POW_03545861/
- Omroep Max (2018), Tour de Celeb: six Dutch celebrities cycled a stage of the Tour de France to raise funds for the Dutch Kidney Foundation; each cyclist was linked with a kidney patient, for whom they cycle; <https://www.maxvandaag.nl/programmas/tv/tour-de-celeb/>
- PodNL (2019), podcast about kidney organoids with Marianne Verhaar; <https://podcastluisteren.nl/ep/Focus-Wetenschap-Dit-kan-ook-Mini-niertjes-uit-je-eigen-urine#/>

News items on our *Nature Biotech* 2019 publication on generating kidney organoids from urine:

- UMC Utrecht news article (2019), <https://www.UMC Utrechtrecht.nl/nl/Nieuws/Onderzoekers-maken-mini-nieren-uit-urinecellen>
- RTL Nieuws (2019, Dutch television news), <https://www.rtlnieuws.nl/nieuws/nederland/artikel/4630551/umc-utrecht-kan-nierweefsel-maken-uit-urine>
- BNR, Wetenschap Vandaag (2019, Dutch all-news radio station), <https://www.bnr.nl/player/audio/10110581/10371428>



News items on portable artificial kidney:

- UMC Utrecht news article (2018), <https://www.UMC Utrechtrecht.nl/nl/Nieuws/Draagbare-kunstnier-in-ontwikkeling>
- Nemo Kennislink (2017), an online publisher of scientific research stories and every day life, <https://www.nemokennislink.nl/publicaties/de-ontwikkeling-van-de-draagbare-kunstnier/>
- Dutch Kidney Foundation has information and videos about research on this topic and how it will benefit patients, https://www.nierstichting.nl/wat-wij-doen/nierfalen-behandelen/draagbare-kunstnier/?gclid=EAlalQobChMljqfallfc4QIVIOd3Ch1DkwCtEAAYASAAEgKmlfD_BwE
- Home Dialysis Central (2018), medical education: Kidney IDEAS: The Future of Renal Replacement Therapy – Part 1; <https://www.homedialysis.org/news-and-research/blog/273-kidney-ideas-the-future-of-renal-replacement-therapy-part-1>
- Video (2017) on the WEAKID project; https://www.youtube.com/watch?v=XcnM_g4Z46o

News items about *in situ* tissue engineering for vascular access (collaboration with TU/e):

ZonMw interview (2018): ZonMW is the Netherlands Organisation for Health Research and Development, <https://publicaties.zonmw.nl/biedt-een-lichaamseigen-vaattoegang-de-dialyse-patient-meer-vrijheid/>

Additional

Missing parts and conclusions

We have all the components to make customized kidneys a reality, and to significantly advance the potential of regenerating renal and vessel tissue. We have chosen to actively contribute to the crosstalk between our stakeholders as it gives us insight into what it will take to truly be able to bring our innovations to the market and our patients.

Both artificial kidney models are built upon previous knowledge and technology developed in the EU FP7 Framework project, NEPHRON+ and have the potential to truly impact kidney patients, their families and our healthcare systems in multiple ways. In essence, they combine the flexibility of peritoneal dialysis and efficacy of hemodialysis in small devices. It offers continuous therapy at a lower cost, reduces the amount of fluids and electrical power needed, while improving quality of life.

Our research team covers an integrated perspective on renal medicine: from understanding the basics of renal (patho)physiology using organoid technology to complete artificial replacement of renal function using different dialysis modalities, with a team consisting of both fundamental biochemical and technical researchers as well as clinical nephrologists and patient representatives. Our findings are really encouraging. We have a wealth of current and previous knowledge that spans the entire project: biodegradable materials, tissue engineering, vascular and fundamental biology, kidney dialysis treatments and the know-how of integrating these aspects. A fully functional bio-degradable cost-effective material that is already FDA-approved that can stimulate and maintain a robust re-building of a new autologous vessel would improve current standard of care for dialysis patients.

We are extremely proud of our results thus far, and are excited about the potential of changing the standard of care for kidney patients.



Theme 3 Stem cell-based therapies: Organoids and Stem Cells

Organoids & Stem Cells

Brief description work field

We aim to understand stem cell biology in health and disease, and to develop novel diagnostic and treatment options for patients. Stem cells have the ability to both self-renew and differentiate into all cell types with tremendous potential for treatment and diagnosis of a wide range of disorders and diseases. Not only can these cells be used to repair or restore healthy tissue and function, they can also be used to stimulate the body's own repair mechanisms. In addition, living biobanks of stem cells support patient-specific research and personalized medicine.

Why we do what we do and how we pose the right questions

Our mission We are driven by clinical need and focus on patient-oriented research. Much of our insight stems from our relationships with patients or representative organisations such as patient foundations and medical practitioners. From these interactions, there are two general needs where RM&SC contributes: the development of regenerative therapies and precision tools for personalized medicine.

The questions we ask Our mission is to bring novel regenerative strategies to the clinic by bringing together complementary strengths of developed technologies and biology, by enhancing our understanding of these diseases through basic research, by improving our translational approaches towards potential new therapies, and by implementing these into our essential preclinical models towards novel clinical trials in patients and ultimately clinical implementation

Existing knowledge about organoids, pioneered and developed in Utrecht, offers enormous possibilities for the future. We want to further develop this knowledge and investigate how patients can benefit from it. This new knowledge also brings new ethical issues and we often lead and are fully engaged in these discussions.

Our primary research questions in the previous strategic period include:

1. *The biology of healthy and disease conditions*: How do cells interpret molecular signals and how does dysregulation lead to disease?
2. *Imaging our cells*: Can we improve upon technologies to visualize what's going on inside a cell?
3. *Organoid technology*: Can we further develop organoid technology for research and patient benefit?

Foundations of health and disease **1. The biology of health and disease** Understanding human biology and how this is deregulated under pathological conditions is a broad-ranging topic. In order to design appropriate therapies, no matter what type, it is first necessary to understand the molecular and cellular underpinnings of normal compared to dysfunctional cells. This research theme explores this using a variety of cellular systems and models, for example, we've demonstrated, using organoids, that location-specific identity is programmed in stem cells; that mutation profiles are tissue-specific and do not differ with age (Blokzijl F, et al., *Nature* 2016). Together, we are improving our understanding of stem cell biology, including how cells interpret signals from their environment and how to help repair, restore and replenish tissue. Below, we highlight several examples of our efforts in this area. To read about our research in kidney organoids, please see the Research Theme Kidney Regeneration document.



Wnt signaling	<p>There are many similarities between embryonic development and cancer, and one key signaling pathway in both is the Wnt pathway. Wnt is a driving force behind stem cell self-renewal and cell fate specification and has emerged as a significant contributor to human tumor progression. Although many components of the pathway have been described, the roles and functions of Wnt within the context of cancer are still only partially understood. In 2012, we discovered that particular mutations (RNF43/ZNRF3) drive Wnt hypersensitivity in cancer (Koo et al, <i>Nature</i> 2012; cited > 450 times).</p>
Extracellular Vesicle-Based therapeutics	<p>Improved understanding on cellular communication to repair organs introduced new directions within our institute, in which Extracellular Vesicles (EVs) are studied and used to facilitate reparative signals in various organs. Extracellular Vesicles are nano-sized vesicles released by all cells and present in all biological fluids and have emerged as important mediators of intercellular communication in (patho)physiological processes. Utrecht scientists are well-represented in the International Society of Extracellular Vesicles, past and current EU-COST Actions and are actively involved in organizing EV-focused (inter)national conferences and workshops. Importantly, current and future EV research in Utrecht is warranted by numerous individual and consortium grants, including personal ERC grants. Here, we aim to repair the myocardial tissue (Sluijter), the joint (Malda), the kidney (van Balkom) and modulate the immune system and thereby further stimulate organ repair (Lorenowicz/van Balkom/Vonk/Sluijter) via these key mediators of cell communication.</p>
Organoids to understand the brain models	<p>The brain is complex; it has about 100 billion neurons with associated connections. Since the brain is physically inaccessible and most models can only mimic it to a limited extent, it is challenging to study. In 2017, we opened the Utrecht MIND Facility (Multidisciplinary Investigation of Neural Disorders), a joint effort between the UMC Utrecht and the Faculty of Science, Utrecht University. This facility focuses on understanding the developing brain and builds human models of brain disease. Using patient cells, our researchers generate nerve cells (from induced pluripotent stem cells) and organoids, and simulate the developing brain in the lab. We can also genetically modify stem cells before they begin forming into tissue. This way, we can introduce a mutation common in individuals with autism spectrum disorder and compare organoids with and without the mutation at the cellular level. This is exciting as we can study conditions previously dominated by the field of psychology, for example, autism and psychiatric disorders. This also gives us a powerful tool to study the brain and to test potential treatments, for example, to better understand disease mechanisms of amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA).</p>
Organoids to understand genetic diseases	<p>Adult stem cell-derived intestinal organoids were first described in Utrecht and are simplified versions of organs that are cultured in vitro from stem cells. They have become a versatile powerful tool for basic biology, drug development and disease modeling. One focus is epithelial regeneration. The intestinal epithelium is the first barrier of defense against pathogens and intestinal stem cells are necessary for damaged-induced repair. Using co-cultures of immune cells and organoids, we identified that IL-22 promotes epithelial regeneration in the intestine, which indicates a contribution of the immune system to this process (Lindemans et al., <i>Nature</i> 2015). These findings provide us with a potential therapeutic target.</p>
Organoids to understand congenital intestine disorders	<p>Further demonstrating the power of organoids, we generated organoids from patients with congenital diarrhea disorders (CDD). CDD is a group of rare intestinal disorders that can be life-threatening and difficult to manage clinically. Treatment usually consists of life-long parenteral nutrition and eventually small intestine and/or liver transplantation. Using patient-derived organoids, we discovered that mutations in the STX3 and STXBP2 genes lead to microvillus inclusion disease (MVID) (Wiegerinck et al., <i>Gastroenterology</i> 2014 and Vogel et al., <i>JCI Insight</i> 2017, respectively). Using organoid cultures, we have also discovered that loss-of-function mutations in DGAT1 gene leads to fat intolerance and developed a lipid droplet formation assay and a lipotoxicity assay to study fatty acid metabolism in DGAT1-mutant organoids (van Rijn, et al., <i>Gastroenterology</i> 2018).</p>



Organoids to understand liver disorders

Another organoid application we are exploring are regenerative medicine approaches with liver organoids (Sabine Fuchs/Nieuwenhuis laboratory) in close collaboration with the Hubrecht Institute and veterinary faculty. We are now able to culture human liver organoids from remnants of diagnostic liver biopsies (1mmx1mm), resection or obduction material, and have set up various functional assays to investigate specific liver functions (including bile acid transport, drug metabolism, albumin synthesis, energy metabolism; see Huch M, Fuchs S et al. Cell 2015). Simultaneously, we aim to set up liver stem cell transplantations for children with liver disease. We are in the process of optimizing liver stem cell transplantations in mouse and dog models to scale up procedures and reach clinically relevant levels of engraftment. We prepare all culturing conditions for clinical use and we investigate ethical issues associated with first in man studies. To perform the first liver stem cell transplantation in human patients, we started a European consortium.

What's next?

The diversity and breadth of our scientific studies into normal and diseased conditions demonstrates our strength as a knowledge center for stem cell biology and regenerative medicine. Our focus for the next period is on furthering our understanding how cells respond to particular pathogens or stimuli, how to improve culture conditions towards cell-based therapies and how to advance the field of personalized medicine with our cell-based models.

2. Imaging our cells

Being able to observe cells in real-time, over extended periods of time or in deep recesses of a piece of tissue will provide more definitive explanations for our questions. Our theme has expertise in advanced imaging technologies as well as molecular tools, as highlighted below.

Light sheet microscopy

The MIND Facility has invested in two UltraMicroscope II lightsheet stations for research described above. This innovative imaging technology can create a 3D image of brain tissue, enabling digital visualisation of the exact composition of brain regions and the types of cells within them. This allows us to image development over long periods of time.

EM and CLEM

Electron microscopy (EM) is on the rise, as illustrated by the 2017 Nobel Prize in Chemistry that was awarded for cryo-EM. We are experts in EM and correlative light and electron microscopy (CLEM) – we are the national and international CLEM Flagship nodes within the Dutch Roadmap for EM Infrastructure and the European H2020 infrastructures EuroBioImaging and the Coordinated Research Infrastructures Building Life-science Services (CORBEL).

Molecular tags

We also investigate other methods for observing what goes on at the cellular level. One example is a functionally active internally-tagged Wnt protein that we generated to study paracrine Wnt signaling. This allowed us, for the first time, to visualize Wnt proteins at high resolution in complex tissues. We revealed the formation of Wnt gradients in the intestinal epithelium and that Wnt travels via cell division, not diffusion (Farin et al., *Nature* 2016; cited > 220 times).

What's next?

Our ambition is to become a world leader in imaging techniques for regenerative medicine and stem cells. We aim to make imaging techniques available to the broader research community and to advance innovations in biomedical research.

3. Organoid technology

Here, we highlight the success of combining our knowledge and converting scientific discoveries into a tool to help patients. As stated above, organoids are a promising tool to convert our basic knowledge into diagnostics and/or treatments.



Organoids as a diagnostic tool	<p>New developments in this field include the development of novel organoid-based culture technologies (e.g., Schutgens et al, <i>Nat Biotech</i> 2018; Sachs et al., <i>EMBO</i> 2019). Here we focus on the application of organoid technology in the context of human disease and care. For human applications, organoids can have a role as individual diagnostic for disease and therapy. Additionally, organoids or gene-corrected organoids can be used as source for cellular therapies. As shown in cystic fibrosis, rapid impact of organoids can be expected from their use as diagnostic, whereas their use as cell therapeutic will require new technologies involving safety (e.g., cell culture without animal components, and scalability). Below, we focus on the application of organoids for cystic fibrosis.</p>
Cystic fibrosis	<p>The variability in cystic fibrosis is immense - there are more than 1500 mutations identified so far in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which regulates the transport of fluid and electrolytes across the epithelial membrane. When the CFTR gene is mutated, the protein doesn't function properly, resulting in the accumulation of abnormally thick and sticky mucus. There are scores of patients with rare mutations who are difficult to diagnose, and we don't know how or if they'll respond to treatment as their genetics are often unclear or functionally not characterized.</p> <p>Treatment for cystic fibrosis (CF) is based largely on managing symptoms and treatment of respiratory complications. New drugs are emerging that target proteins affected by certain defects, but we need better ones that can also target a broader range of patients.</p> <p>Using cystic fibrosis intestinal organoids, we developed the first functional assay in any adult stem cell-derived organoid platform (Dekkers, et al., <i>Nat Med</i> 2013). This organoid swelling assay is now used in CF drug development for assessing preclinical efficacy and for conducting mode of action and exploratory studies.</p> <p>We aim to personalize diagnosis within the context of disease or treatment. Within the previous strategic period, we published seminal papers on drug mode of action studies (Okinoyeda et al., <i>Nat Chem Biol</i>, 2013) and a new type of treatment (a proof-of-concept) using CRISPR/Cas9 gene editing of human diseases stem cells (Schwank et al., <i>Cell Stem Cell</i> 2013). Our work is built upon the existing organoid technology and expertise in stem cell biology, tissue engineering, technology development (for example, imaging) and turning basic science into patient benefit.</p> <p>Based on a painless rectal biopsy, we generate patient-specific organoids (we're also just starting to set up a linked patient registry to organoid data). Together with our pharmaceutical partners, we test various drugs on each patient's organoids for their response, using our swelling assay. This allows us to quickly diagnose each individual patient, and make recommendations for a treatment plan before they even start treatment. We're currently seeking regulatory approval for this "living biomarker" with EMA as part of a large European study that is coordinated by UMC Utrecht.</p>
What's next?	<p>We bank our organoids within UMC Utrecht or with the Hubrecht Organoid Technology (HUB), which also has exclusive rights to our assay for commercial use and which licenses out our assays to commercial partners. Through our clinician counterparts, we gain access to primary patient cells. Our assay has been, and continues to be, incorporated into several drug discovery pipelines in the pharmaceutical industry (for example, screening for response to drug candidates). In addition, we continue to build our biobank of patient organoids that are available also to researchers. Because the CF swelling assay is quick, inexpensive and personalized for each patient, the hospital is using it to help determine patient response to treatment.</p> <p>We are currently expanding our technology base to develop similar, patient-based stem cell culture approaches for other diseases than CF. In addition to intestinal organoids, we're developing alternative airway cell-based systems that can be used to study cell differentiation, mucus hyperplasia, ciliary function and other epithelial defects in the context of congenital and acquired lung diseases.</p>



Outcomes

Research products for peers

	# publications	# dissertations
2013	172	8
2014	177	6
2015	185	15
2016	156	7
2017	166	2
2018	181	6
total	1037	44

Scientific output on this theme, in the table above, 99% are peer-reviewed publications. The 5 most significant publications from our program are described below.

A functional CFTR assay using primary cystic fibrosis intestinal organoids (cited 411 times)

Dekkers JF, Wiegerinck CL, de Jonge HR, Bronsveld I, Janssens HM, de Winter-de Groot KM, Brandsma AM, de Jong NW, Bijvelds MJ, Scholte BJ, Nieuwenhuis EE, van den Brink S, Clevers H, van der Ent CK, Middendorp S, Beekman JM.
Nat Med. 2013 Jul;19(7):939-45.

Cystic fibrosis (CF) is incurable with a life expectancy of 40 years; it is caused by mutations in the CFTR, a transmembrane regulator. We developed a new assay using patient-derived CF intestinal organoids that may facilitate diagnosis, functional studies and drug development. Our new assay is based on physical swelling of organoids (healthy controls), when exposed to forskolin, which is greatly reduced in CF patient-derived organoids, in mice carrying the Cftr F508del mutation (this is the most common mutation in CF patients), and is absent in Cftr-deficient organoids. This pattern is phenocopied by CFTR-specific inhibitors. Function of the CFTR F508del mutant protein is restored by incubation at low temperature, as well as by CFTR-restoring compounds. We have now patented this assay, and are encouraged by this first step towards tailored treatment for patients with cystic fibrosis.

An inducible mouse model for microvillus inclusion disease reveals a role for myosin Vb in apical and basolateral trafficking.

Schneeberger K, Vogel GF, Teunissen H, van Ommen DD, Begthel H, El Bouazzaoui L, van Vugt AH, Beekman JM, Klumperman J, Müller T, Janecke A, Gerner P, Huber LA, Hess MW, Clevers H, van Es JH, Nieuwenhuis EE, Middendorp S.
Proc Natl Acad Sci U S A. 2015 Oct 6;112(40):12408-13.

Microvillus inclusion disease (MVID) is a rare intestinal enteropathy that is seen within a few days to months after birth, resulting in persistent watery diarrhea. Although the exact pathophysiology is unclear, mutations in the myosin Vb gene (MYO5B) have been identified in the majority of MVID patients. We generated an intestine-specific conditional Myo5b-deficient (Myo5b^{fl/fl};Vil-CreERT2) mouse model, and analyzed intestinal tissues and cultured organoids. Our findings included several physiological changes and a new observation that loss of MYO5B disturbs both apical and basolateral trafficking on proteins that causes MVID in mice. Additionally, when compared to a novel MVID patient, our data showed that our mouse model completely recapitulates the intestinal phenotype of human MVID.



Interleukin-22 promotes intestinal-stem-cell-mediated epithelial regeneration (cited 326 times)

Lindemans CA, Calafiore M, Mertelsmann AM, O'Connor MH, Dudakov JA, Jenq RR, Velardi E, Young LF, Smith OM, Lawrence G, Ivanov JA, Fu YY, Takashima S, Hua G, Martin ML, O'Rourke KP, Lo YH, Mokry M, Romera-Hernandez M, Cupedo T, Dow L, Nieuwenhuis EE, Shroyer NF, Liu C, Kolesnick R, van den Brink MRM, Hanash AM. *Nature*. 2015 Dec 24;528(7583):560-564. doi: 10.1038/nature16460. Epub 2015 Dec 9.

Treatment with IL-22 in vivo after mouse allogeneic bone marrow transplantation enhanced the recovery of ISCs, increased epithelial regeneration and reduced intestinal pathology and mortality from graft-versus-host disease. ATOH1-deficient organoid culture demonstrated that IL-22 induced epithelial regeneration independently of the Paneth cell niche. Our findings reveal a fundamental mechanism by which the immune system is able to support the intestinal epithelium, activating ISCs to promote regeneration.

Visualisation of a short-range Wnt gradient in the intestinal stem-cell niche (cited 200 times)

Farin, H. F., Jordens, I., Mosa, M. H., et.al., (2016). *Nature*, 530(7590), 340-343. DOI: 10.1038/nature16937

We generated a functionally active internally tagged Wnt protein that allowed us for the first time to visualize Wnt proteins at high resolution in complex tissues. This approach led us to reveal the formation of Wnt gradients in the intestinal epithelium via cell division-mediated dilution of membrane-bound Wnt proteins.

Human tissues in a dish: the research and ethical implications of organoid technology.

Bredenoord AL, Clevers J, Knoblich J (2017) *Science*, 355(6322). pii: eaaf9414. doi: 10.1126/science.aaf9414.

The ability to generate human tissues in vitro from stem cells has raised enormous expectations among the biomedical research community, patients, and the general public. These organoids enable studies of normal development and disease and allow the testing of compounds directly on human tissue. Organoids hold the promise to influence the entire innovation cycle in biomedical research. They affect fields that have been subjects of intense ethical debate, ranging from animal experiments and the use of embryonic or fetal human tissues to precision medicine, organoid transplantation, and gene therapy. However, organoid research also raises additional ethical questions that require reexamination and potential recalibration of ethical and legal policies. In this review, we describe the current state of research and discuss the ethical implications of organoid technology.

Research products
for societal
target groups

Diagnostic assay

In 2015, a mere two years after the publication of our CF swelling assay, the first patient was treated based on this tool. Fabian, a young teenager, has an extremely rare CF mutation; he shares it with only one other person in the world, his aunt. His lung function was down to 30% but because his form of CF had not been tested on the only then successful drug on the market (produced by Vertex Pharmaceuticals). Because the cost of the drug was high, insurers refused to cover the cost without prior evidence of benefit for that particular patient. Fabian was thus ineligible to receive treatment.

Our research team generated organoids from Fabian and tested the drug on the swelling assay. If Fabian's organoids responded favorably to the drug, they should swell up, and they did. He was given the drug, and almost immediately felt its effects; he has not been hospitalized since.

Since then there is an agreement with Vertex. For patients with advanced CF and in great physical need – for those with disease severity of < 40% lung function - and not in a treatment program, meaning that their CF is rare, Vertex will provide medication to them based on our lab swelling assay results for free through a managed access program. This is an incredible step: we can quickly predict treatment response for a single patient and directly translate this into administration of the right therapy.



Patent applications:

2012 *patent application (granted 2014)* on the CF assay: A rapid quantitative assay to measure CFTR function in a primary intestinal culture model

2018: *Patent application* on Anti-low-density lipoprotein receptor related protein 5/6 antibodies (EP18200751.8)

Hypersensitivity in cancer: Our discovery that RNF43/ZNRF3 mutations drive Wnt hypersensitivity in cancer (Koo et al, Nature 2012, cited 450 times).

Use of research products by peers

The swelling assay (publication *Nat Med* 2013 is cited > 400 times) is a unique alternative to clinical trials, which are seldomly conducted for rare diseases as they are not economical, and overall outcome may not be beneficial to many patients. The Beekman group provides a method that can be performed by trained laboratory personnel, in either an academic or industry setting, that delivers a personalized readout for each patient. Currently, academic hospitals in Leuven, Lissabon, Campinas, Verona, Rotterdam, Cologne, Jerusalem, Moscow, Toronto, Sydney, Perth and Alabama use organoids for studying CF therapeutic response.

The Hubrecht Organoid Technology (HUB): this biobank houses more than 600 donors; this biobank includes almost everyone in the Netherlands with a rare genetic cystic fibrosis variant. This gives the research community an incredible resource for studying the biology underlying rare mutations in CF, gives patients contributing their cells an important role in moving science forward and heightens awareness through scientific meetings and the media about the potential of these technologies. The HUB holds our license and manages distribution of organoids and dissemination of knowledge to both academia and industry.

We have generated several organoid lines from patients with rare congenital intestinal disorders, and discovered that mutations in STX3 and STXBP2 lead to in microvillus inclusion disease and DGAT1 to fat intolerance. To better assess the genetic cause of severe diarrhea in newborns, we have generated a gene panel for congenital diarrheal disorders, containing 64 genes, that can be ordered by researchers at the Medical Genetics Department in the UMC Utrecht.

Due to their leading positions in the field, our researcher have contributed to many position papers and best-practices in the international EV societies. These include cardiovascular (Sluijter Cardio-vasc Res. 2018), immune-modulatory (van Balkom, JEV 2019), general EV (van Balkom, JEV 2015+2016+2018, Stem Cells Trans Med 2017, and cartilage (Vonk/Lorenowicz, Theranostics 2018) reparative directions.

Use of research products by societal groups

CF Center: About one-third of all Dutch patients with CF are treated in Utrecht. Our Center is a key partner of the Dutch Cystic Fibrosis Foundation and the Netherlands Cystic Fibrosis Foundation (NCFS), both of which have close-knit communities of patients, patient representatives, researchers and clinicians. Our Center is also part of the CF-core network of the European Reference Network for Rare Lung Diseases (ERN-LUNG). Because of our strong relationships, our research questions and goals are directly aligned with patient needs. And because we treat approximately 1/3 of all CF patients in the Netherlands, we have a long history of establishing and building upon knowledge gained in both the lab and clinic.

Insurance coverage: Together with the HUB, we're working with insurance companies to find a way to cover the cost of diagnosing and treating people with a single variant.



Marks of
recognition
from peers

Grants (selected list)

Flagship nodes within the Dutch Roadmap for EM Infrastructure and the European H2020 infrastructures EuroBioImaging and the Coordinated Research Infrastructures Building Life-science Services (CORBEL).

Klumperman accepted funding in 2018 the amount of €17 million as chairman and main applicant of the Netherlands EM Infrastructure from the Netherlands Organisation for Scientific Research (NWO) National Roadmap program.

UMC Utrecht has raised about € 12 million in the last 6 years for CF. This includes a Horizon 2020 grant of € 6.7 million that was awarded in 2018 of which, "HIT-CF: Personalised Treatment for Cystic Fibrosis Patients with Ultra-Rare CFTR Mutations", of which, we are the coordinator. Called the HIT-CF Project, our aim is to personalize treatments for patients with extremely rare types of CF.

Coffer: Marie-Curie Co-Fund application for 30 PhD students (ERC-ITN). Approximately €3M; consortium with 30 PIs. *Co-primary applicant*. (2018); Netherlands Cancer Society grants in 2013 and 2015, €570k each.

Maurice (coordinator): Marie Curie FP7 Initial Training Network (ITN) grant WntsApp (€4,000,000); UU Life Sciences Seed Grant (€100,000), together with Enrico Mastrobattista (Pharmaceutical Sciences); NWO VICI grant: Controlling the controller: Regulation of signals that guide stem and cancer cell growth and differentiation (€1,500,000); ECHO NWO grant (€260,000)

Middendorp: NWO-VIDI (2014) personal grant €800,000; NWO-Aspasia (2014) personal grant €100,000

Bredenoord: The Netherlands Organisation for Health Research and Development ZonMw grant "The Ethical and Legal Aspects of Personalised Medicine" (2018-2020) (€450,000) (role: PI of WP Learning Health Care Systems); The Young Academy project grant: "Breeding Brains? The ethics of cerebral organoids" (2017-2019) (€8000) (role: PI); Gravitation Grant "Netherlands Organ on Chip Initiative (NOCI)" (€18,833,678) (PI: Prof Christine Mummery, LUMC. (Role: lead WP Ethics); The Netherlands Organisation for Health Research and Development ZonMw grant: "The ethics of first-in-human organoid transplantation" (2016-2018) (€100,000) (role: PI); L'Oréal UNESCO: For Women in Science Award Committee (2016-2019)

Sluijter/van Balkom/Vonk/ Lorenowicz: 2x TKI-LSH (Health~Holland) grant € 500K, H2020 grants EXPERT (€15M) and ERC-EVICARE (€ 2M), Dutch Arthritis Foundation (ReumaNederland); €150K, Translational Adult Stemcell research (TAS) Game changer grant from ZonMW; €400K

Awards (selected list)

- Beekman; European Cystic Fibrosis Society: 2017 Person of the Year Award, ERS excellence award for CF research 2017, Willy Heuma prize for alternatives to animal experiments
- Klumperman 2015. Ratification as Dutch Flagship Node and Euro-BioImaging Node Candidate for Correlative Light Electron Microscopy
- Middendorp: Associate Professor competitive institutional award UMC Utrecht (2015) €125,000
- Bredenoord winner of Utrecht University "Publicity Award" for most visible researcher 2017; winner of the Dutch Association for Community Genetics and Public Health Genomics 2017 Innovation Prize
- Clevers: Breakthrough Prize in Life Sciences for discovery of tissue stem cells and cancer (2013); Körber European Science Prize (2016, €750k); Princess Takamatsu Award of Merit (Japan, 2017, approx. €412k); Order of Merit of the Federal Republic of Germany (2017).



Memberships

- Maurice, Kranenburg, Beekman are leaders of the Utrecht Platform for Organoid Technology (U-PORT) <https://www.uu.nl/en/research/life-sciences/research/hubs/utrecht-platform-for-organoid-technology>
- Bredenoord: Dutch Senate; her portfolio includes public health, medical ethics, privacy, data protection and family law; German Federal Ministry of Education and Research: expert panel on genome editing; International Society for Stem Cell Research (ISSCR): Chair of the Ethics; The Netherlands Organisation for Health Research and Development ZonMw: member of the Board (2018 - ongoing); The Royal Holland Society of Sciences and Humanities (De Koninklijke Hollandse Maatschappij der Wetenschappen): member (2018 – ongoing); The Royal Netherlands Academy of Arts and Sciences (KNAW): The Young Academy (De Jonge Akademie) (2014-2019)
- Coffe: study section member for both fundamental and translational applications for the Dutch Rheumatology Foundation (ReumaFonds); founding member of Dutch Society For Stem Cell Research (www.dsscr.nl) and chair of annual meeting; UMC Utrecht “Talent” steering committee (2010-2013); UMC Utrecht steering committee for Bachelor’s “Excellent” and Masters “Honors” programs for medical students (2010-2014)
- Maurice: member of the Young Academy Europe (YAE)
- Klumperman: Review panel, Cell Biology and Biophysics Unit European Molecular Biology Laboratory (EMBL), Heidelberg, Germany; Chair ad hoc committee scientific integrity UU; NWO-committee Grote Investerings/Big Investments (2015)
- Middendorp: ERC Expert Panel for IMI2 grant application 2019; Chair Utrecht Life Sciences advisory board VIDI applications (2016-2018)
- Clevers: National Academy of Sciences of the USA (2014); Member of the Academie des Sciences de l’Institut de France (2016)

Marks of recognition from societal groups

- As with all of our research activities and strong relationships with our stakeholders, we too, have strong connections with the media. We actively reach out to media (and they to us), in order to help move our research to the next level. Public awareness and understanding is a powerful tool, and we strive to relay our progress and findings in a timely, educational and transparent manner.
- Bredenoord is frequently in the news with ethical topics through television (Een vandaag, RTL nieuws, De Wereld Draait Door, Jinek, NTR) and radio (NPO Radio 1, BNR Nieuwsradio, Met het oog op morgen, de Kennis van Nu) appearances and newspaper interviews (NRC, Trouw, Volkskrant, Financieel Dagblad).
 - Beekman has been interviewed by the Associated Press, Nat Med, Cell Stem Cell and various lay media; podcast for BBC the Naked Scientists
 - Maurice: Interview with BNR national news radio station about publication on how cancer mutant proteins form small-sized aggregates to misregulate tissue growth (March 2016) <http://www.bnr.nl/radio/bnr-spitsuur/wetenschap-vandaag/10011393/hoe-eiwitklonters-kanker-kunnen-veroorzaken>; presentation on ‘The hype and hope of stem cells’ at the cultural festival ‘Science in the City’, Utrecht (April 2016); interview for magazine for stoma patients about publication of the lab on intestinal tissue renewal (June 2016)
 - Klumperman was interviewed by National Broadcast (NPO radio 1) on the occasion of the award of the Nobel prize in Medicine to Yoshinori Ohsumi for his discovery of autophagy; is in a Promotion movie Netherlands Electron Microscopy Infrastructure (NEMI) by Ministry of Education, Culture and Sciences; promotional movie Netherlands Electron Microscopy Infrastructure (NEMI) by Ministry of Education, Culture and Sciences. <https://www.youtube.com/watch?v=IAUV4cPg-8Vs&feature=youtu.be>
 - Clevers: TedxAmsterdam, Stem cells (2013); interview, The Scientist Magazine (2016)

Additional

Missing parts and or conclusions

Stem cells are powerful - they have the potential to become any cell type in our bodies which makes them promising for repair and regenerative strategies, and are often accompanied with ethical concerns. This makes them extremely complex and difficult to study. We are inspired by this challenge and excel in untangling the details underlying the molecular and cellular mechanisms driving both human health and disease. We are also experts in adapting various technologies such as imaging, iPS cells and organoid technology, in novel ways.



In addition, we lead discourse on ethical questions that arise from this research. Our continuous connection with the patient community and society yields valuable feedback that contributes to our progress. And finally, we're dedicated to ensuring that our future generations are properly trained and educated in order to maintain our momentum. Through this combination of fundamental science, technology and innovation, we're delivering on our promises of patient benefit.

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