# UMC Utrecht Research Evaluation

2019 - 2024

UMC Utrecht

# Foreword

Dear reader,

As it happens, my term as dean more or less overlaps with the period under review for this research evaluation. When I started as dean in 2019, the site visit of the previous review committee was one of the major and most inspiring events during my first year. It certainly helped me to better understand where and how our research could be improved further.

The world, at that time, was unknowingly on the eve of a pandemic that would affect all domains of life and work. COVID-19 unequivocally demonstrated the societal importance of scientific research with a vaccine being developed at breakneck speed based on the new technology of mRNA vaccination and a myriad of trials, in many of which UMC Utrecht was involved, providing evidence of the effects of possible therapies. The urgency of exchanging knowledge about a deadly infectious disease also upended traditional peer-reviewed scientific publishing and proved a boost for so-called preprints and data sharing. Regrettably, it also spiralled into the mainstream distrust in science and conspiracy theories. These changes, like so many other corona-related changes, will not go away. Many UMC Utrecht researchers contributed to research, national policy advice, and seemingly never-ending public engagement about COVID-19, which is amply evidenced in this report.

Now, with the end of my dean's term nearing, it would appear that the geopolitical situation is even more momentous than in 2019. International agreements, norms, and collaborations that since World War II have been the bedrock of democratic and scientific institutions are crumbling, with uncertainty being the only certainty. Scientific values of optimism and openness are evidently at stake.

And that is even without the disruptive influence of Artificial Intelligence on all of society, including scientific research (and the other core tasks of university medical centers, education, and care). Of course, UMC Utrecht also tries to harness this development for the good of health research. But here again, uncertainty about the potential of AI, for good or for worse, is rife.

My term as dean ends in December 2025 and the one thing I am certain of is that UMC Utrecht researchers have made large and significant contributions to understanding, preventing, and treating diseases and in general, in the wording of UMC Utrecht's strategy Connecting Worlds, to adding value to the lives of people. I will not single out examples, as I expect this report to speak for itself. But I am proud of all UMC Utrecht researcher teams working to the best of their ability to do meaningful and impactful scientific research. I hope this report and review by the evaluation committee helps us to improve even further. I am under no illusion about the existential questions scientific research will keep facing, but I also know for sure that scientific research and the people working at UMC Utrecht will continue its mission to improve society.

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

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# General

# General

## 1 - Research strategy and governance at UMC Utrecht

The mission of UMC Utrecht is to improve people's health and create tomorrow's healthcare. Our strategy 'Connecting Worlds' 2020-2025 describes how we realize our mission. Key elements include multidisciplinary collaboration with network partners, innovation at the intersection of research themes and a focused approach to activities. Research at UMC Utrecht is organized into six multidisciplinary strategic programs, each with a limited number of disease targets: Brain, Cancer, Child Health, Circulatory Health, Infection & Immunity, and Regenerative Medicine & Stem Cells.

*Figure 1: Visualization of the six strategic programs.*

These programs integrate the four mandated, interdependent functions of UMC Utrecht: patient care, research, teaching, and valorization. Interaction with patients and society creates an 'innovation loop', where societal issues guide scientific research and where scientific results quickly move from bench to bedside.

**Research governance: leadership**
The executive board of UMC Utrecht consists of four members: (1) prof. C. (Carina) G.J.M. Hilders MD, PhD, chair. (2) Prof. A. (Arno) W. Hoes, MD, PhD, dean and vice-chair. (3) J.W.R. (Remco) van Lunteren, MSc. (4) Drs. J. (Josefien) C.E. Kursten, MSc.

The dean is responsible for all matters related to research and education. A vice-dean of research, prof. Elly Hol, was installed in 2024. The vice-dean of research is primarily responsible for all internal and campus research policies and the vice-dean research chairs, amongst others, the monthly research meeting with the divisions. Representatives of early career researchers are structurally present. The vice-dean of education, prof. Marc Bonten (who succeeded prof. Berent Prakken in 2025), leads the education center that coordinates teaching, performs educational research, and guides innovation in education. The creation of the strategic programs started in 2010 and their position in UMC Utrecht research governance has matured over time. The leadership for each program consists of a chair, additional board members (so-called 'core team') and a program manager. Although all programs have their own focus areas, there is also overlap in the research(ers) associated to each program. In Chapter 2 of this report, more information per strategic program is presented.
The programs are linked to budget-holding divisions where (research) personnel is employed. Each division is led by a division management team consisting of two members, complemented by a 'leadership team' that includes, amongst others, a research manager and an education manager. In addition, every division has several research supporting structures in place such as policy officers, quality coordinators and trial bureaus. Central research policy and support services are organized through the Research Office. The Research Office focuses on strategic advice, science policy, and the (local, regional, national and international) positioning of UMC Utrecht in the field of research. Further, it advises and supports researchers in finding valorization opportunities and supporting them with research and innovation grants. As of 2021, the Research Office is led by dr. Esther van 't Riet (head of the department) and Merel-Marlijn Sondervan (Cluster lead Funding & Support).

### Research governance: key meetings

- U-team (weekly): Executive Board, division managers and directors
- Strategic programs meeting (monthly): chairs of strategic programs with dean and/or vice-dean research participating every other month (*)

- Research meeting (monthly): Research managers of divisions and vice-dean research (*)
- Advisory Council on Promotions (monthly): Dean (chair), vice-dean research, all chairs of strategic programs, three divisional managers research
- Strategic meetings on a regular basis with executive board of UMC Utrecht, division managers, directors and chairs of strategic programs

** Since 2024, these include representatives of early career researchers.*

## 2 - Follow-up from previous evaluation

The recommendations from the previous SEP review 2019 and the UMC Utrecht response can be found online. Below we concisely recapitulate the main recommendations and responses found in 'UMC Utrecht response to assessment report from SEP research evaluation (2013-2018)'. In Chapter 2, all six strategic programs respond to their specific recommendations.

**The mandate of the programs (strategy) and the divisions (execution) needs to be clear, to avoid ongoing negotiations around budgets and appointments; strategic choices need to be made by academic researchers +ring-fence funds for research including seed money for new initiatives for program leaders.**
The strategic programs have received a limited budget for programming activities and for seed grants, in addition to existing funding for leadership and management. Furthermore, the strategic programs have become an obligatory passage point for all academic promotions. New associate and full professorships are assessed by the strategic programs and the chairs make up the majority of the Advisory Council on Promotions, which advises on all central promotions.
Currently, a major principal change in UMC Utrecht (research) governance is taking shape. An entirely new governance, aiming to integrate financial and strategic research decision-making, is being developed and will be implemented starting 2026. This will increase strategic and budgetary mandate of the research programs. See section 'SWOT analysis & strategy for the next six years' for more information.

**With respect to personal grants (Veni-Vidi-Vici and ERC), there appear to be possibilities to improve the success rates (based on the quality of the young scientists). Coordinate activities to help researchers submit competitive grants.**
Research funding support has greatly expanded and professionalized (see section 1.7), with increased earning capacity as a result.

**Integrated research support (including Technology Transfer Office (TTO) functions) is not present at the UMC Utrecht level. Create an accessible, integrated central support office.**
Integrated research support is on the horizon in the new UMC Utrecht governance per 2027. There will be a dedicated center for Research & Innovation Services and Expertise (RISE). This will integrate, strengthen and professionalize all forms of research support. In line with the starting point of better collaboration through centralization, most of research support personnel will hierarchically be positioned in this new center, allowing for more efficient and strategic employment of resources. The technology transfer functionality primarily resides in Utrecht Holdings, which is a shared entity with Utrecht University, but dedicated technology transfer personnel will be part of RISE too. RISE will include support for clinical trials. Next to RISE there will be a Core technologies hub, combining management and support for technologies. See section 'SWOT analysis & strategy for the next six years' and paragraph about Innovation and valorisation support for more information.

**UMC Utrecht is ideally positioned on the Utrecht Science Park campus, in the national environment and globally. Formulate specific goals and timelines concerning ongoing and new collaborations.**
Collaborations at Utrecht Science Park have expanded and intensified, witness for example Utrecht Cancer and Utrecht Brain (see section 1.6)

**Formulate a uniform and structured UMC Utrecht policy on talent programs, tenure tracks and a mentoring system, and create clarity regarding career assessment.**
A talent program has been introduced, and the academic career profiles should improve clarity regarding career assessment (see section 1.4). A tenure track system was deemed not fitting UMC Utrecht research governance as it does not align well with the existing procedures for career advancement.

**Time allotted for research by clinician-scientists is not clearly defined, and a vision on the positions of non-MD scientists is unclear. Also, the PI role lacks a definition.**
The role of Clinical Scientist, with protected research time, has been introduced (see section 1.4). For non-MD scientists, the normal academic positions are available. The Principal Investigator role never featured in UMC Utrecht central research governance, so a definition was not relevant. The closest equivalent, which is more used, is probably the role of research group leader.

**Considering the focus on Open Science with fewer metrics: consult the staff and broaden the support base with respect to specifics and the impact the new science evaluation approach has on research areas and individual researchers.**
The six academic career profiles (see section 1.4) were based on a UMC Utrecht wide consultation. Comparable national and international developments have gained traction, but debate about new forms of research evaluation remains ongoing.

**Across UMC Utrecht, there appear to be distributed pockets of ICT and data science. Create a coordinated approach across UMC Utrecht.**
UMC Utrecht has made a major effort to organize, bring together, and streamline data infrastructure and AI for health research (see section 1.6).

### Recommendations from the societal stakeholder committee

**Define the societal value which the UMC Utrecht aims for, determine objectives and organize activities that contribute to these objectives.**
The societal value from UMC Utrecht research has in general terms been defined by the overall strategy, mission and vision and is in local research contexts translated to (efforts to create) tangible patient and societal benefits.

**Implement a policy on patient involvement regarding representation, reimbursement, remuneration, training, communication, and feedback.**
The strategic program patient participation developed policies like this, supporting and professionalizing patient involvement in research, education and care (see section 1.8).

**Provide more opportunities for researchers to learn from each other, both within and across strategic programs, on patient involvement practices and efforts to enhance societal impact.**
The strategic program patient participation created many of these learning opportunities and more (see section 1.8).

## 3 - Data sharing

### Open Science

The transition to Open Science is widely regarded as necessary to adapt scientific practices to the great societal challenges we are facing today. This is reflected in Utrecht University's strategy towards Open Science, the Dutch National Program for Open Science, the EU Open Science policy, and the UNESCO Open Science recommendation.
In line with these developments, UMC Utrecht facilitates and promotes Open Access publishing, FAIR (Findable, Accessible, Interoperable and Reusable) data sharing, public engagement/stakeholder involvement and Recognition & Rewards. Governance takes place through the multidisciplinary Open Science team, chaired by the dean. This team convenes five times per year to discuss and advise on relevant policies.
Recognition & Rewards are mainly operationalized through the six diverse academic career profiles (see 'Career profiles' under section 1.4). Open Access publishing is stimulated and until two years ago was also financially supported. The percentage of Open Access publications has risen from 53% in 2015, to 74% in 2019 and 82% in 2024. A UMC Utrecht-wide publication strategy is under development by the Library Committee and the Open Science team.

### Data management

Findable, Accessible, Interoperable and Reusable (FAIR) data sharing and research data management are facilitated by the IT directorate. The Research Data Management (RDM) policy, effective since 2019, specifies how UMC Utrecht researchers manage data in the entire research data life cycle: during processing, validation, cleaning, preparation for analysis, archiving and sharing data. For specific study processes, the policy prescribes certain methodologies and (preferred) systems. Special attention is paid to transparent scientific practices. Researchers are required to make data "as open as possible, as closed as necessary" and to ensure that data adhere to the FAIR principles. In 2021, the Data Sharing Guidelines were introduced to provide practical guidance, taking into account different types of data sharing scenarios, and relevant laws and regulations regarding privacy and data processing.

#### Sharing data

To complement these policies, the UMC Utrecht adopted DataverseNL as its centrally supported repository for datasets. Since its launch, uptake has gradually increased (see Appendix D). To map the usage of other dataset repositories, such as those tailored to specific research domains, a pilot with Elsevier's Datamonitor was performed in 2023. However, due to the differing types of datasets included in the output (including sets of graphs, PDFs, instead of actual datasets), it is difficult to unambiguously interpret these numbers. A point of future improvement is to increase our insights into our center's open data sharing (e.g. to make transparent how many studies publish their datasets), and to expand support for repository services beyond DataverseNL.
To facilitate RDM, the UMC offers data management and RDM courses. Each division has one or more data managers available for consultation by researchers. There is a continuous effort to improve the RDM and Open Science support for researchers. Researchers are expected to self-evaluate their adherence to their own data management plan and RDM policy. The maturing of the data governance model, as well as the upcoming central organization of research activities, offer the possibility to introduce a stricter control mechanism.

### Data infrastructure

Other technical facilities to support FAIR data include myDRE, Archivematica, and Molgenis. In the Secure Processing Environments (SPEs) of myDRE, researchers can provide dataset access to external parties while remaining in control over copies. Archivematica is the research archive of the UMC, where previously composed datasets are stored in a findable and accessible way post-study. Lastly, in Molgenis, the UMC has started to index the metadata of clinical cohorts, as a start to the formation of the Health Data Space Utrecht (HDSU). Metadata in Molgenis can be exchanged with the national catalog in the Netherlands, under the European Health Data Space (EHDS) obligation. Reuse of healthcare data for scientific research is facilitated at UMC Utrecht by a specially designed data platform. This platform ensures that healthcare data from the patient file is available to researchers anonymously. Of course, such reuse is only permitted under the applicable legal conditions, which are guaranteed in the platform.

## 4 - Recognition & Rewards

### Recognition & Rewards and career profiles

UMC Utrecht has been one of the frontrunners in the Dutch national 'Recognition & Rewards' movement, analogous to the European 'Coalition to the Advancement of Research Assessment' (CoARA). Over the years, this resulted in regular national media attention. The aim of these initiatives is to develop forms of research evaluation that recognize the various activities and outputs needed to achieve scientific and societal impact.
To diversify the reward system in relation to career advancement, UMC Utrecht implemented in 2022 six academic career profiles, each representing a different pathway to scientific and societal impact. Since then, 40 associate professors have been appointed in one of those profiles. The six profiles are: Academic educator (5 appointed since 2022), Clinical researcher (17), Exploratory researcher (9), Implementation researcher (3), Methodology & technology researcher (6). The valorization research profile was introduced in 2013 already, four appointments have been made since then. An extensive description of the profiles can be found online. Discussion about certain aspects of the career profiles is ongoing, but in the Netherlands all universities and university medical centers are committed to developing and implementing diverse career profiles.

### Clinical scientists

UMC Utrecht believes that clinicians who are also active in translational research embody our mission as they bridge the clinical and scientific environments. However, given the immediacy and urgency of clinical duties, it is often hard to protect research time. To balance this, UMC Utrecht started recognizing so-called 'clinical scientists' in 2021. When supported by both divisions and strategic programs these clinicians/researchers are formally recognized by the dean for their translational research and are granted at least 0.4 FTE research time from their division. As of Q1 2025, 43 clinical scientists have been appointed. Surveys indicate a generally positive effect of clinical scientist recognition but also suggest that pressures on research time in certain cases continue to exist.

> Joris de Graaf – appointed as clinical scientist in 2024:
> *"The position of Clinical Scientist allows me to optimally combine my two passions – patient care and research on brain injuries. My clinical work and scientific research reinforce each other, enabling me to truly bridge the gap between practice and science. Now that I have structural time allocated for research, I have more 'headspace' to initiate new projects, establish collaborations, and invest in my development as a researcher. This position also contributes to my visibility and positioning both within UMC Utrecht and beyond: colleagues (from both healthcare and research) are more easily able to find me with research ideas and for potential collaborations."*

### Talent programs for academics

The development of academic talent is a priority for UMC Utrecht. Since 2022, talent development programs have been made available for all academic levels, from PhD and postdocs to full professors. Current funding secures the programs at least until the end of 2027.

UMC Utrecht aims to be the place where:
- The retention and progression of the most talented researchers is prioritized
- Researchers are attracted to develop as research talent
- Diversity is actively promoted
- Open Science, Recognition & Rewards and "The New Utrecht School" are integral parts of development and career paths and personal ambitions

Our four Talent Programs are based on these principles, aiming to support talented researchers to contribute to the strategic objectives of UMC Utrecht, both now and in the future:
1. PhD Boost Program
2. Research Career Development Program (Post-doc / assistant professor)
3. Talent Development Program Associate Professors
4. New Professor Program

Talent programs strengthen participants in the impact they have with their work and accelerate their teamwork and personal leadership skills. As one of the participants mentioned: *"The program gives you the space to focus on your vision and ambitions, something we often do not have time for in our day-to-day lives. And that is something I truly appreciate."* They also strengthen the internal network in UMC Utrecht and between participants and create a community of talented young researchers that reflects the elements of Recognition & Rewards. Participants of the talent programs are invited to familiarize themselves with the career profiles and develop their expertise and activities according to one of those. Importantly, all programs have been rated eight or higher by the previous participants.

*The selection process*
The programs are broadly communicated to ensure that all researchers have the opportunity to express interest. Final participation is determined through a nomination process where division management holds a key role, complemented by input from the strategic programs (The New Professor Program is excluded from the selection process, they are invited to participate upon appointment). To ensure a well-balanced selection, candidates must complete a qualification form corresponding to their level. During the selection process, diversity criteria are taken into account: at least 50% women and at least 1/3 of participants with a culturally diverse or international background. The number of candidates typically exceeds the number of available places. This implies that the selection process requires renewed attention. Divisions could adopt a more selective approach when nominating candidates in future, in order to manage expectations and avoid potential disappointment. A key question is how talent can be made visible. One way would be by organizing a talent assessment or talent review. In addition, the communication processes surrounding the talent programs will be reviewed to ensure they run efficiently and effectively.

**Perspective from early-career researchers**
The UMC Utrecht Young Academy is a group of early- to mid-career researchers that work to promote an open, supportive and internationally competitive research environment for young investigators. In 2024, the UMC Utrecht Young Academy carried out a survey among researchers about their career goals, prospects, and support at UMC Utrecht. Across all strategic programs and divisions, 212 researchers participated in the survey: 30% PhDs, 14% postdocs, 28% assistant professors, 15% associate professors and 5% full professors.

The Young Academy identified the following themes:
- There is a need for clarity regarding what is required to advance to a next career step: 50% of respondents stated that it was not clear to them how to achieve promotion. There is also a need for a more transparent and unified process for promotion and overall career support across parts of UMC Utrecht. A common theme among respondents is that they feel the effects of "the X-factor", "internal politics" and "being male" as troubling biases that may affect their careers.
- There is an urgent need for one-on-one coaching or mentoring expressed by 95% of responders. Many respondents (37%) prefer an independent mentor who has no direct influence on their career path.

- There is high pressure on acquiring external funding: 62% of responders are paid from external grants. Many responders (48%) have had positive experience with the Research Support Office in applying for grants.
- Most researchers (82%) know about the six career profiles, and some have had positive experience with promotion based on them (20%), but some have had trouble achieving promotion with the career profiles (17%).

## 5 - Academic culture

### Research training and integrity

UMC Utrecht promotes a research culture based on the values of honesty, scrupulousness, transparency, independence, and responsibility. These values are described in the Netherlands Code of Conduct for Research Integrity, which UMC Utrecht strongly endorses (see here). This Code has also been translated into UMC Utrecht's own Guidance on Research Integrity (2024), which offers a practical elaboration of the national Code and refers to relevant policies, procedures, and service desks available to researchers, students, support staff, supervisors, and others involved in research.
To support a responsible research environment, all new researchers follow the e-module 'Introduction for researchers' which addresses research integrity. Furthermore, training on research integrity is a mandatory part of our PhD training program. Currently, we are developing a Responsible Conduct of Research training (RCR) for PhD supervisors.
To encourage a research culture that endorses integrity and minimizes the risk of misconduct, UMC Utrecht has adopted policies promoting good mentorship and supporting an open, safe, stimulating and inclusive research culture. Trainings and programs have been established to implement these policies for researchers and staff alike. Outreach activities are organized and tools are made available to spark dialogue on research integrity.

*Figure 2: UMC Utrecht wheel of integrity.*

**'UMC Utrecht guidance research integrity meetings'**
This guidance outlines the setup for scientific integrity meetings within research groups. The guidance details the structure of the meetings and offers tools and topics to start up conversations.

**'UMC Utrecht wheel of integrity'**
From the UMC Utrecht Guidance on Research Integrity, the wheel has been made into a conversation-starting game. By giving the pointer a little spin, one of its 14 topics is chosen as the topic of conversation. This tool aims to get feedback from researchers about our research policy and to get informed about research culture at various departments and research groups. It also guides researchers towards finding information on research policies and helpdesks. It is an outreach tool that can be used during research events, as well as on a small scale within departments and for education purposes.

**'The Dilemma Game app'**
The Dilemma Game app has been developed by Erasmus University Rotterdam (EUR) to stimulate awareness of, and to have an open and critical conversation about integrity and professionalism in research. The Dilemma Game confronts researchers with dilemmas in the context of a critical dialogue, supporting them in further developing their own 'moral compass'. The app can be used individually by researchers at any time, or together with peers and colleagues.

Our aim is that everyone working in research who has a question pertaining to research integrity talks about it with their colleagues and supervisors, knows where to find more information and reaches out when they witness something that is in violation of research integrity.

### Diversity and inclusion

UMC Utrecht strives to be an inclusive and diverse academic environment. In line with EU requirements, UMC Utrecht formulated a 'gender equality plan' in 2021, which gives a full overview of the gender and diversity policies. In addition, within the HR department, a full-time Diversity & Inclusion (D&I) officer has been hired, and a D&I core team has been established. This core team includes representatives from HR, healthcare, education and research, who all actively work to address issues of diversity and inclusion within UMC Utrecht. UMC Utrecht also started the 'This Is Us' campaign, which addresses social safety within the entire organization, with coffee talks and lectures for all interested employees.
Both 'This Is Us' and the D&I Core team recognize that the current pathways to address issues in social safety are in need of further development. Although UMC Utrecht, for example, has an ombuds office and counselors, not all employees are aware of their options to speak up/speak out in a safe way. HR is working to set up a plan to improve this.
Through the 'D&I in education' research group, headed by Prof. Gönül Dilaver, bias trainings have been developed for the UMC Utrecht staff, with specific versions for staff in healthcare, research or teaching. 60% of our education staff has already participated in the training, aided by the fact that it has been a management KPI.
The research training is currently being finalized, aimed at associate and assistant professors. Additionally, Prof. Dilaver's group has developed an active bystander training for the UMC Utrecht, and the Funding & Support team at the Research Office has developed a training on D&I in research proposals.
D&I as a policy topic is relatively new, which means that the governance is still under development, with overlapping initiatives from different domains of UMC Utrecht. As the continuing importance of D&I is beyond doubt, governance consolidation in UMC Utrecht seems the most relevant future issue.

## 6 - Research Infrastructure

### Facilities

The UMC Utrecht houses many essential research facilities and technology platforms for both internal and external clients. These facilities are essential for the research spanning the entirety of the different research programs. Research facilities in the UMC Utrecht can be broadly divided into four categories: core technologies, advanced technology platforms, expertise centers, and the sample management hub.

While a precise definition can be challenging, **core technologies** are in general more mature, with a well-developed pay-per-service business model, and a broad user base within UMC Utrecht. Currently, these include the Cell Microscopy Core, Core Flow Facility, and Utrecht Sequencing Facility.
**Advanced technology platforms** often work on a more collaborative basis, are evolving, and usually provide their services to a smaller group of researchers. They have the potential to grow into core technologies if the respective technologies see broad adoption across the UMC Utrecht. The current advanced technology platforms include Biofabrication Facility Utrecht, Cellular Screening Technologies, iPSC Facility, Luminex Multiplex Facility, Medical Metabolomics Facility, Multi-scale Spatial Omics Platform, Olink Targeted Proteomics Platform, PamGene kinome activity platform, Proteomics Facility, and the Utrecht Platform for Organoid Technology.
**Expertise Centers** are individual research groups that utilize complex technology or analyses requiring continuous R&D input from lab managers or lead scientists. This technology is only available to others on a collaborative basis and there usually is no intent of developing into a facility model. The current expertise centers are: Bioinformatics, the Center for Image Sciences, and the UMC Utrecht Artificial Intelligence labs.
**The sample management hub** includes the Central Biobank Facility and the Pathology Tissue Facility.
The research facilities are accessible online via Technologies Archive - Research at UMC Utrecht, which provides an overview of available services, equipment, and contact information.

Most research facilities and technology platforms in the UMC Utrecht have evolved organically into their current form

and have different organizational structures aligned with the role and function of the facility. The heterogeneous organizational structure is necessary to enable the facilities to function optimally and to keep them up to date with developments in the field. However, recent impactful developments in biotechnology and data science, a shortage of skilled personnel and a general decline in national funding for knowledge institutes have directly impacted UMC Utrecht research programs. Due to the growth in research FTE (see also table X) of 20% over the last 5 years, several departments indicate a lack of (laboratory) space. By developing the current research infrastructure into a centralized "Research & Innovation Center," UMC Utrecht commits to long-term strategic planning for infrastructure investments and staffing. This centralization of research facilities and technology platforms will help to maximize resources, streamline research, improve education & training and promote collaboration across the campus and beyond.
In addition, with central funding, an investment plan for positions that both (i) stabilize current research facilities (sectorgelden; 6 FTE fixed appointments of facility staff), and (ii) acts as a catalyst for new innovative technologies (seed money; 4 FTE for 4 years) has been rolled out.

### AI in health research

Information about the data infrastructure is described in *subchapter 1.2 Data Sharing*. Here we will describe the Artificial Intelligence (AI) research in UMC Utrecht. To promote and integrate grassroots AI health research efforts, five Health AI-labs have been established. These labs align with the UMC Utrecht strategic priorities, the thematic communities of the Utrecht Life Sciences (ULS), and the broader themes of the EWUU AI Hub (see *Collaborations – National* p.8 for more information on the EWUU alliance). The Health AI-labs focus on clinical care, scientific research, and academic education. Each lab has appointed dedicated directors and coordinators with deep expertise in both AI and the lab's thematic domain, ensuring a clear strategic direction and coordination of AI-related activities. The initial development of these labs was supported by TKI funding (Top Consortia for Knowledge and Innovation), enabling a strong start with both top-down and bottom-up project selection and fostering rapid collaboration and implementation of AI innovations.
The five Health AI Labs work closely with the 10 AI Labs that UU has developed and implemented. All the Labs are organized in the same way and several joint initiatives have been developed to promote knowledge and experiences between the knowledge institutes and establish a campus-wide community. To further embed AI within UMC Utrecht, the 3AI program was launched in 2023. It focuses on three pillars: (1) Data & Infrastructure; (2) Research (via the AI-labs); (3) Implementation. The full 3AI program team comprises nine experts and works closely with initiatives such as Health-RI, AI Coalition 4 NL (AIC4NL), EWUU, and regional networks to ensure integrated development across research, data, and implementation. Together, they pursue a shared mission: data- and impact-driven healthcare, work, and education that is safer, more effective, efficient, and sustainable, bringing care closer to the patient and citizen.

### Selected collaborations

In this subchapter, we present an overview of selected, impactful collaborations. A more extended overview of our strong multidisciplinary and interdisciplinary networks at global, European, national, and regional levels can be found here.

### Regional

#### Utrecht Science Park

At Utrecht Science Park, a unique combination of various public and private partners can be found within one square mile. There are two national institutes of the Royal Academy of Sciences, the Hubrecht Institute in molecular sciences and the Westerdijk Fungal Biodiversity Institute. Unique is also the presence of the only Dutch Faculty of Veterinary Medicine, an international leader in the field. There is the national Children's Oncology Center Prinsess Maxima with more than 30 independent research groups that perform pre-clinical and clinical research on childhood cancer. The efforts of Utrecht University of Applied Sciences complement the academic environment. Adding to that is the official opening of the National Institute for Public Health and the Environment (RIVM), at the end of 2025, and the presence of various private partners such as MERUS, Genmab, and Nutricia Research.

#### Strategic Theme Life Sciences

The UMC Utrecht is part of the Strategic Theme Life Sciences (STLS), which connects the research groups and education of the Faculties of Medicine, Veterinary Medicine, and Science with the broader life sciences community within the Utrecht Science Park. The STLS focuses on interdisciplinary research and applications in the life sciences, comprising innovations in the medical, biological and technical domain for innovative solutions for societal challenges in health

and care. It is about achieving excellent science in the service of a healthier society. Six Thematic Communities establish scientific connections between over 4,500 life sciences researchers. Together, they contribute to nine focus areas that create societal impact through the Societal Challenges (see figure 3). Two of these Societal Challenges are Utrecht Cancer and Utrecht Brain (started in 2024), which aim to unite all cancer and neuroscientific research on campus and enhance the visibility of Utrecht's expertise nationally and internationally.

*Figure 3: Visualization of the Thematic Communities, Focus areas, and Sociatal Challanges of Strategic Theme Life Sciences.*

## National

### EWUU alliance (TU/e, WUR, UU and UMC Utrecht)

In the EWUU alliance University Medical Center Utrecht, Eindhoven University of Technology, Wageningen University & Research and Utrecht University connect their scientific knowledge in research and education. The four institutions cooperate, since 2020, on a cross-disciplinary basis in the areas in which they complement each other. In this way, EWUU contributes to urgent societal transitions.
The alliance of TU/e, WUR, UU and UMC Utrecht challenges new generations of researchers and students to cooperate right across disciplines without setting prior limitations, in seven different areas like Preventive Health, Circular Society, Living Technologies, Roadmap Artificial Intelligence, Education, Collaboration and overarching ambitions.

### National growth fund projects

With the National Growth Fund (NGF), the Dutch government invests over €11 billion in 50 very large projects that contribute to the structural and sustainable economic and societal growth of the Netherlands. UMC Utrecht participates in multiple of those projects. The total UMC Utrecht budget in these projects is about 180-200 million euro, the government investment constitutes 110 million euro of that budget.

- **Oncode-PACT:** Infrastructure for innovative models and methods to develop effective cancer drug candidates faster and cheaper for specific patient groups. UMC Utrecht plays a prominent role as one of the coordinating partners in accelerating new treatments and medicines in oncology. Our researchers will specifically focus on patient cohorts, biologics and cell & gene therapy.
- **RegMed XB:** Establishes a national pilot factory for regenerative medicine in the Netherlands, supporting companies and research institutions in developing and valorizing new therapies, production technology, and services. In Utrecht, the Innovation Center for Advanced Therapies (ICAT) aims to improve and accelerate the translation of research into healthcare solutions for the development of regenerative treatments, and Advanced Therapy Medicinal Products including cell therapy, and disease models.

- **Center for Animal-Free Biomedical Translation (CPBT):** To continue improving the health of humans and animals, a radically different approach is needed: making the step to humans and animals better and faster without relying on animal testing as the golden standard. The development of transition knowledge will not only contribute to a significant acceleration in the development of efficient drugs for conditions such as ALS and Cystic Fibrosis in the lab (both coordinated by UMC Utrecht), but it will also ensure that these medicines become available to patients more quickly. In 2025, the CPBT is officially launched under it's new name: Ombion, Center for Animal-free Biomedical Translation.
- **Digital United Training Concepts for Healthcare (DUTCH):** Works on a novel approach for training and development of healthcare professionals in hospitals. It transforms healthcare education in the Netherlands to reduce current staff turnover, increase intake and training capacity, and ensure sufficient ongoing education.
- **Health-RI:** Facilitates and stimulates data-driven research, policy and innovation with an integrated health data infrastructure. This infrastructure is accessible for researchers, citizens, care providers and industry. This enables optimal re-use of health data, samples and images to foster a learning healthcare system and accelerate personalized health. UMC Utrecht is one of the eight regional Nodes, which are part of the governance of Health-RI.
- **NXTGEN HIGHTECH:** Develops ultra-precise, high-tech machines and equipment that contribute to the competitiveness and earning capacity of the Netherlands, addressing societal challenges like energy transition, health, safety, and food. UMC Utrecht is involved in projects related to the development of artificial kidneys (coordinating) and cell production technology.

### Collaborations and top research areas from the last five years

*Figure 4: Recent external collaboration on country/territory level.*

**International**

UMC Utrecht is engaged in a wide array of international collaborations spanning institutions around the world. Based on the PURE profiles of our researchers, recent external collaborations on the country/territory level can be visualized on this map. Explore the details by clicking on the dots or selecting a country/territory from the list, where shared research outputs with international institutions are accessible.

Global Health

UMC Utrecht Global Health conducts high-impact (clinical) epidemiologic and public health research that generates evidence contributing to improved individual and public health and to educate new generations of researchers and health care professionals across the globe. Our global health research activities are concentrated in Asia, Oceania and Africa, carried out in collaboration with a range of local and international partners and are rooted in our expertise in (clinical) epidemiology and public health sciences in the areas of circulatory health, cancer, infectious disease, maternal and child health, as well as environmental health at the Julius Center for Health Sciences and Primary Care.

European Reference Networks for Rare Diseases

UMC Utrecht has over 30 expertise centers for rare disorders (ECZAs). In the Netherlands, more than one million children and adults have a rare disorder. A disorder is rare if it occurs in less than 1 in 2,000 people. The mission of expertise centers is to share expertise and experiences in health care and perform research. Collaboration is the key word in rare diseases, both in the Netherlands and in Europe. Therefore, European Reference Networks (ERNs) have been established. UMC Utrecht participates in around 20 and coordinates the ERN-RITA for Immunodeficiency, Autoinflammation and Autoimmune Diseases.

Advancing collaborations

The UMC Utrecht Internationalization Committee advises on the policy for international affairs and is responsible for the internal calls that promote research collaboration, such as the EU Consortium Grant, the Strategic Network Development Grant, and the Incoming Clinical Research Fellows Grant.

The Networks and Partnerships team within the Research Office plays a key role in facilitating connections in the research and innovation field. They facilitate collaborations with strategic partners (both in consortia and bilateral collaborations), such as other academic partners, governments and private parties. Our strategic international institutional networks & platforms are e.g. League of European Research Universities (LERU), the COIMBRA group, European University Association (EUA), International Association of Universities (IAU), the Utrecht Network, the Eureka Institute for translational medicine, Challenge-driven Accessible Research-Based and Mobile European University Alliance (CHARM-EU), and the European Association of Research Managers & Administrators (EARMA).

## 7 - Research and innovation support

### Quality management

UMC Utrecht aims for relevant clinical research that adheres to current safety and integrity standards and guidelines. All medical research that meets the criteria of the 'Medical Research Act with human subjects' (WMO) is assessed by the national Central Committee on Research Involving Human Subjects. This committee protects subjects while taking into account the interests of medical progress. All clinical research at UMC Utrecht can only be carried out with the consent of the Executive Board. Research with human biological material requires a positive recommendation of the Biobank Research Ethics Committee and in case of collection of human biological material an approval of the Executive Board. The Research Office is responsible for Quality Assurance, Training, Expertise Centre and UMC-wide procedures and policies (Quality Manual Research), in collaboration with the research quality coordinators. All divisions have dedicated research quality coordinators who report to division management. The research quality coordinator has an advising and controlling task to promote quality and safety and works in close cooperation with division support staff for data management, privacy and legal affairs. The research quality coordinator performs quality checks on the non-scientific aspects of a research proposal before it can start or be submitted to the review committee.

The UMC Utrecht quality system is consistent with the Guideline Quality assurance of research involving human subjects which has been prepared by the Dutch Federation of University Medical Centers. A new Quality Manual Research was implemented in 2022, providing researchers and staff with a clear overview of the agreed standard procedures and associated work instructions per type of research. It also outlines roles, responsibilities, and internal and external quality monitoring processes aimed at continuous improvement.
Part of the quality system is the mandatory monitoring for all research subjects to the 'Medical Research Act with human subjects'. The Basic Course Regulations and Organization for Clinical Investigators (eBROK) deals with laws and regulations when conducting clinical research and is compulsory for all researchers involved in human-based scientific research. 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 tracers on research leadership. Through research tracers, the implementation of the UMC-wide research policies is checked. The tracer on leadership focuses primarily on the organization of the research over the whole division and on the management and support processes.
Critical incidents are reported hierarchically. Depending on the impact on subject safety/data integrity, reporting can include the Ethical Review Board, department head, research quality coordinator, division management and the Executive Board.
In 2022, UMC Utrecht introduced Vidatum, a centralized research management application. This unified system for registering all medical scientific research supports internal approval workflows, financial monitoring, and budgeting for grant proposals.

### Funding Support

Since the last SEP research evaluation, the Funding and Support team (formerly the Research Support Office (RSO) of the Research Office) at UMC Utrecht has significantly developed its services, growing into an established in-house team that provides full-cycle and all-round support to externally funded research projects. The team development has focused specifically on professionalization of the services and its team structure. They have established a pre-award, post-award and project support team. The pre-award team focuses on the development of personal grants and grant writing services. Each of the strategic programs is linked to two grant writers from the pre-award team: one for nationally funded projects and one for internationally funded projects. The post-award service ensures high-quality project delivery and reduces risks in our externally funded portfolio. All teams work closely together. For example, an experienced project manager will give implementation advice on proposals that are co-written by the grant writers. Also, in the team composition there is room for expertise areas, adhering to the specific needs of funding schemes, for example the Dutch Talent Program. Further, experts do not only work closely together within the team, to promote knowledge transfer internally, but the Funding and Support service also commits to sharing knowledge within the organization and within (inter)national networks.
The services have been expanding, accommodating the full funding landscape: the national and European funding programs, both on collaborative and within the personal programs. With the introduction of large-scale funding programs, like the National Growth Fund and KIC LTP, the Funding & Support team has provided manpower to adhere to the new developments and to form a dedicated team on large-scale funding.
In 2021, the Funding and Support team became an independent team within the Research Office, growing to 25 professionals led by three coordinators and a cluster lead. The growth in personnel has been made possible by the strategic use of specific Dutch governmental funding for universities and university medical centers aimed at increasing support for EU grants. This growth has proven highly successful. In funding programs where specialized support is offered, the success rates are currently up to 50% higher than the EU/NL average (see Figure 5 and 6).
Also, the Funding and Support Team has established a leading role in the (inter)national research management community.

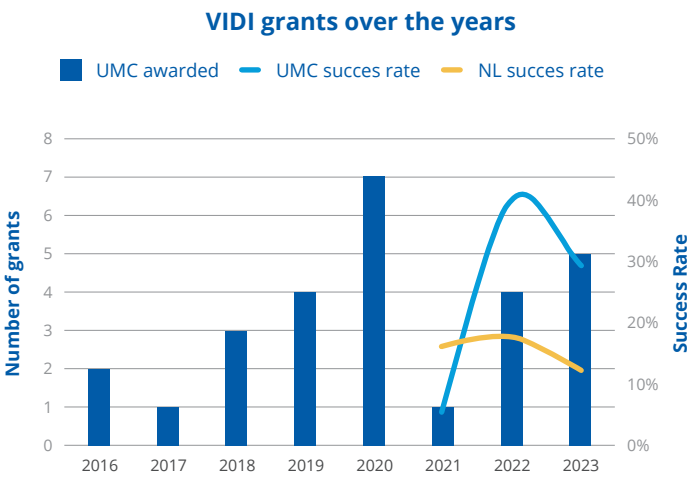



*Figure 5: UMCU success rate in VIDI grants over the years compared to national average*

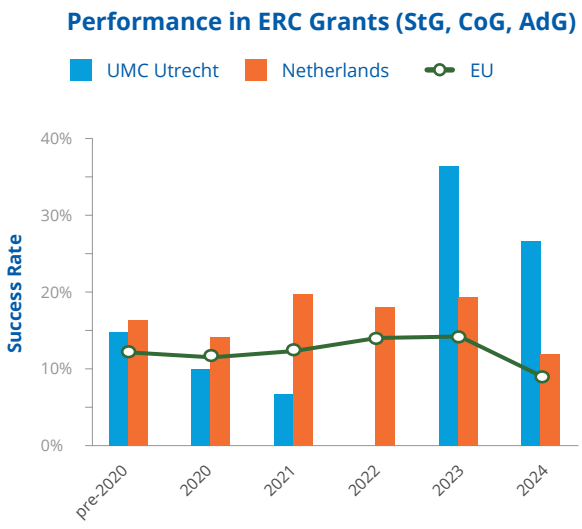



*Figure 6: UMCU success rate in VIDI grants over the years compared to national and European average*

When capacity limits are reached or in cases where external consultants can provide more specialized expertise (e.g. in the case of more business or education-oriented grants), researchers can apply for professional development grants to hire external support. This hybrid model accommodates the team's and UMC Utrecht organization's needs.
In line with the organization's transformation efforts, our funding support services will be further centralized and optimized, including ways of working with continuously stricter requirements from multiple funding bodies.

### Innovation and valorization support

As a university medical center, we have the knowledge, experience and responsibility to contribute to solutions for societal challenges in the field of healthcare and health. Our unique combination of specialist care, scientific research and innovation makes it possible to quickly identify clinical needs, develop new knowledge, realize innovative solutions, implement them in healthcare practice, and make them widely accessible. This also includes creating awareness and contributing to societal debate.
At UMC Utrecht, we embrace a broad definition that does justice to all forms of valorization and its role as a catalyst for the three other core tasks (care, education, and research): *Valorization is the process in which knowledge, innovation and expertise of UMC Utrecht from care, research and education are converted into concrete impact for society.*

Different innovation and valorization activities are supported within UMC Utrecht:

- *Hands-on support, stakeholder engagement, and public-private partnerships*
  Staff within the Research Office and on site within divisions are a first point of contact for researchers with questions about valorization. For example, they help with creating a business case, finding a private partner for joint research funding, and writing an impact paragraph in grant proposals. The annual UMC Utrecht innovation contest – the Ureka Mega Challenge – also provides a support platform for those with an innovative idea.
- *Business development and entrepreneurship*
  To help researchers with economic valorization, specialized support is provided by Utrecht Holdings. Utrecht Holdings is the Knowledge Transfer Office (KTO) of Utrecht University and UMC Utrecht. Utrecht Holdings focuses on the commercialization of academic research and supports researchers in development, protection, and exploitation of IP through spin-off companies and/or out licensing. UtrechtInc is the platform on campus to support university-linked entrepreneurship as a start-up incubator.

*Academic entrepreneurship*
Since 2017 the UMC Utrecht has implemented a procedure 'academic entrepreneurship'. In this procedure, Utrecht Holdings, the legal department, and HR (academic entrepreneurship committee) evaluate situations where UMC Utrecht staff would like to be involved in a startup company on a case-by-case basis. In most cases, this means that the UMC Utrecht staff member wants to obtain shares in the startup and remain employed by the UMC Utrecht at the same time. Since 2017, many cases have been evaluated and advised. Although equity share is often part of the advice, it mainly involves mitigating actions to prevent conflict of interest. This approach enables us to maintain a balance between incentivizing valorization of research results while safeguarding our other three core tasks: care, research and education.

- *Specialized translation and implementation support*
  For certain research areas, hubs with expertise on innovation and valorization in that specific field are created. For example, for advanced therapies (Innovation Center for Advanced Therapies), MedTech (Department of Medical Technology and Clinical Physics), AI (3AI, AI labs) and oncology (Oncode Institute).
- *Outside-in: contract research*
  To support researchers in contract research, trial centers/trial coordinators are working within divisions. They provide on-site support in the set-up, conduction, and close-out of clinical trials. In addition, U-TRIAL aims to strengthen the clinical trial climate at UMC Utrecht by being a first point of contact for clinical research organizations (CROs), pharmaceutical companies and medical device companies, and by offering knowledge and expertise for internal and external research partners.

Since the landscape for support on valorization is fragmented across the UMC Utrecht, the Research Office works in 2025 on creating a strategy concerning valorization, including a fitting organization structure (governance) and a more structured support landscape for researchers. UMC Utrecht also contributes to the Netherlands Federation of University Medical Centres (NFU) trajectory on Impact and Innovation that aims to develop standardized, obligatory policies and frameworks across all UMCs to streamline and facilitate valorization efforts.

## 8 - Stakeholder engagement

### Patient involvement

Patient involvement in all aspects of research is stimulated through a dedicated program and a Patient Engagement Office. Although many researchers at UMC Utrecht collaborate with patients, for others this is still relatively unfamiliar territory.

#### Training

In consultation with researchers, patients, and others, an e-learning for researchers was developed in 2022. This e-module (30 minutes) focuses on the initial stages of research, specifically writing about collaborating with patients in a research proposal. An e-module on collaboration during research projects became available mid-2025. In addition, a lecture on patient involvement is an integral part of the Clinical Scientific Research (KWO) course, which teaches third-year medical students how to set up and conduct scientific research. From September 2023, patients also provide feedback on the research proposals that students prepare in small groups. These patients are recruited by the Patient Engagement Office. To train researchers in collaboration with patients there is a one-day training course consisting of two parts. First researchers learn theory, concrete examples and case histories, then participants practice some situations with patient partners. At the end of the course, participants will have an understanding of the added value of involving patients. They know how and at what stage they can optimally involve patients.

#### National policy

Members from the UMC Utrecht program on patient involvement participated at a national level to promote patient participation in research. The national Central Committee on Research Involving Human Subjects (CCMO) since 2023 asks clinical researchers how they involved patients, local Medical Research Ethics Committees follow up on that. Prof. Van Delden was ethics advisor to the workgroup that revised the Helsinki declaration.

### Science communication

Science communication is one of the core activities of the Department of Marketing and Communication of the UMC Utrecht. Within this department, the team *Science and Community* was established in 2021. In this team, six science communicators are working on internal and external communication about science. They work closely together with the strategic programs, every science communication officer has a strategic program in his or her portfolio. In addition, a research communication service has been established in 2024 within the Funding and Support team to specifically support research projects. Other important developments of the last year were:

- A new corporate website for Research. In 2024, www.umcutrecht.nl/research was launched.
- An annual UMC Utrecht Research Day in the Utrecht Science Week, showing impactful research for an internal and external audience.

## 9 - Graduate School of Life Sciences

The training and supervision of PhD candidates is assigned to the Graduate School of Life Sciences (GSLS), the collective responsibility of the Faculty of Medicine (UMC Utrecht), Faculty of Veterinary Medicine (Utrecht University), and Faculty of Science (Utrecht University). The GSLS hosts a vibrant academic community with 1800 active master students and over 2000 PhD candidates (± 1500 in UMC Utrecht) across 17 master's and 15 PhD programs, plus a new continuing education program for professionals. Most PhD programs are linked to master programs and are rooted in Utrecht University's Life Sciences research theme and UMC Utrecht's strategic programs.

The Graduate School of Life Sciences aims to improve life by offering an inspiring and innovative academic environment that prepares graduates to thrive in the life sciences and society. This mission is realized through four strategic principles:

1. **Future-proof programs:** GSLS offers master's, PhD, and Continuing Education programs aligned with societal and scientific needs, grounded in Utrecht Life Sciences research communities. It includes 15 PhD programs with thematic training and supportive communities. The GSLS website is being updated based on feedback from the 2024 Communication Survey.
2. **Competence development:** GSLS fosters personal and professional growth to prepare PhD candidates for diverse career paths. For the development of diverse competences, a PhD Course Centre was established in 2015. It offers free training based on the PhD Competence Model. Since 2022, teaching training is mandatory for teaching PhD candidates. Writing courses are organized in-house by the Communication Skills Academy. For career development, an annual Life Sciences Career Week, attended by ~120 PhD candidates, and activities like the PhD Day and Supervisor of the Year award are organized. Further, the biweekly PhD Update (> 1950+ subscribers) shares important information, events, and news.
3. **Academic environment:** GSLS offers an inspiring, innovative and safe academic environment. You can read more about this under section *1.5 Academic Culture*. To specifically monitor PhD well-being a PhD Survey is organized annually by the PhD Council. Confidential advisors, dedicated to PhD candidates, were appointed in 2021 and they meet once every six weeks with a PhD team to discuss recent developments. To increase awareness of, and start the conversation about, inappropriate behavior Utrecht University and UMC Utrecht together hosted a theatre play 'Mindlab' for all academics in 2021. As a follow up UMC Utrecht developed the previously described *This is Us* program. The GSLS endorses this program, though it is difficult to reach all PhD candidates, and the PhD survey still indicates an invariably high stress level among PhD candidates.
4. **Teaching and supervision:** GSLS ensures high-quality teaching and supervision through structured guidance and support. PhD candidates must register in the MyPhD system at the start of their track, where they list their supervisors and mentor, and upload a Training and Supervision Agreement outlining task division, meeting frequency, and their intended training plan. In 2021, new guidelines were introduced defining expected attitudes and behaviors for both PhD candidates and supervisors. To further support supervisors, GSLS provides mandatory supervision training for new supervisors and a toolbox of advanced training options. To improve supervisor support further, GSLS conducted the first PhD Supervisor Survey in 2023, which received more than 350 complete responses.

### Current developments

Efforts are ongoing to close remaining gaps and establish a fully functioning Plan-Do-Check-Act cycle throughout the entire PhD trajectory. This involves coordination with key stakeholders, including the dean's office, research support, HR, and PhD programs. In this context, the transformation of the "MyPhD" system by Utrecht University and UMC Utrecht into a monitoring tool is a welcome development, offering essential data such as the rate of annual progress meetings.
Additionally, support for PhD supervisors is being strengthened, including peer support initiatives. In parallel, the pilot initiative of the UU Doctoral Advisory Board, which aims to integrate feedback from PhD candidates and colleagues into the annual assessment of PhD supervisors, is regarded as a promising development.
Further, a new PhD program is being considered to accommodate approximately 300 (mainly clinical) PhD candidates not currently covered by existing programs.
A key challenge ahead is the projected budget reduction of 5% in both 2026 and 2027. These cutbacks may pose a risk to maintaining the current level of quality across the program.

## 10 - The Education Center and Life Sciences Education Research

### Education Center

The Education Center holds final responsibility for a range of educational programs, including university degree programs, the PhD Course Center, the UMC Utrecht Academy, and postgraduate medical training. The Expertise Center and various supporting departments in the Education Center contribute to quality assurance and the implementation of these programs. In addition to its primary role in delivering and facilitating education, the Education Center also has a responsibility for policy development and for overseeing and organizing education and training within UMC Utrecht.
The division's leadership consists of the Director and Vice Dean of Education and the Division Manager. They are supported by the leadership team, which includes program directors, the Director of the Department of Professionals in Healthcare, department heads, the student assessor, and policy advisors from the management team.
The educational strategy is embedded in *The New Utrecht School*, which forms an integral part of UMC Utrecht's strategic vision. This approach enables us to educate (future) professionals who are capable of solving complex problems creatively and taking responsibility for themselves, their patients, and society at large. UMC Utrecht focuses on educational innovation and initiatives within six themes: (1) interprofessional and interdisciplinary learning, (2) patient participation, (3) inclusion and diversity, (4) translational medicine and life sciences, (5) resilience and well-being, and (6) planetary health.

### Life Sciences Education Research

Research at the Education Center takes place in the *Life Sciences Education Research* (LSER) program. Its mission centers on developing adaptive, creative, and socially responsible health professionals by studying learning and professional development across both academic and clinical environments. As healthcare professionals are key drivers of future health systems, LSER investigates how (life-long) learners evolve and how best to support them in complex, dynamic settings. The program is driven by and feeds into UMC Utrecht's *Connecting Worlds* strategy and the educational strategy of *The New Utrecht School*. The program's research agenda is wide-ranging and transdisciplinary, addressing major themes that reflect contemporary challenges in healthcare education. Key topics for research include: adaptive expertise, inter- and transdisciplinary learning, education with emerging technologies (e.g. AI and VR), diversity, equity and inclusion (DEI), feedback, translational medicine, patient participation, and well-being. These topics are explored using varied methodologies, including qualitative, quantitative, mixed-methods, and design-based research, ensuring findings are both rigorous and contextually relevant.
Collaboration, team science, and open science are core principles of the LSER program. It plays a central role in the educational research efforts of the EWUU alliance and contributes to Utrecht University's research themes such as *Dynamics of Youth and Institutions for Open Societies*. LSER has also been instrumental in shaping the university's *Professional Performance* (2014–2022) and *Higher Education Research* focus areas.
Altogether, the program promotes the formation of health professionals who not only possess high levels of knowledge and skill, but are also capable of solving complex problems collaboratively, creatively, and with social responsibility. This integration of education, research, and healthcare practice strengthens both learning/work environments and the health system.

## Main research accomplishments

A milestone for LSER is the establishment of its interdisciplinary PhD program in 2021 within the Graduate School of Life Sciences. This program has grown rapidly, currently supporting over 50 PhD students, and includes a co-led doctoral program with University of California, San Francisco (UCSF), which fosters international research exchange and collaboration. PhD candidates (> 10 since 2022, see appendix D) have defended their theses, covering cutting-edge topics such as patient participation, interprofessional feedback, translational medicine, and learning analytics. It has an average of around 80 peer-reviewed publications annually, along with many contributions to or organizing international conferences, invited lectures and book(s) (chapters). It has secured a range of competitive grants from funders such as ZonMw, NRO, NWO, the EU-projects (including a Marie-Curie ETN), and the Dutch Ministry of Health (VWS). Leading projects include studies on adaptive expertise, DEI, patient involvement, faculty development, translational medicine. An example is the continuing success with founding scientific directorship of the EUREKA Institute, which focuses on training translational scientists, mirroring LSER's commitment to bridging education, science, and practice. Researchers within the program also contribute significantly to international organizations such as the Association for Medical Education in Europe (AMEE) and the Dutch Society for Medical Education (NVMO), playing key roles in thought leadership and agenda setting. Several LSER researchers are recipients of prestigious Comenius grants and active members of the Comenius Network of the Royal Netherlands Academy of Arts and Sciences (KNAW) (see appendix B). A notable example is the 2023 Comenius Leadership Fellowship for a large project using games and art to foster open-mindedness in higher education. The program is also active in and chairing Utrecht University's incentive fund (USO) consistently leading successful proposals for educational innovation.

By combining rigorous research with strong partnerships and societal relevance, the LSER program contributes significantly to advancing health professions education. Its work ensures that future healthcare professionals are not only well-trained but also equipped to meet the complex, interdisciplinary, and human-centered demands of modern complex healthcare systems.

# Appendix

## Appendix A - Research staff

### Research staff (numbers)

| | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|---|
| Full professors | 202 | 206 | 208 | 214 | 210 | 212 |
| Associate professors | 151 | 157 | 172 | 175 | 194 | 173 |
| Assistant professors | 424 | 465 | 475 | 500 | 524 | 536 |
| Post-docs | 279 | 257 | 285 | 296 | 258 | 273 |
| PhD students | 763 | 749 | 760 | 775 | 810 | 864 |
| Technicians & other support | 254 | 347 | 316 | 292 | 295 | 299 |
| Visiting scientists | 93 | 3 | 2 | 28 | 41 | 325 |
| **Total research staff** | **2.166** | **2.184** | **2.218** | **2.280** | **2.332** | **2.682** |

Increase in 2024 compared to 2019: **24%**

*Note: the number of full professors is based on information from the Academic Careers database. The other numbers are based on information from divisions and Pure research information as compiled by directorate IT. Numbers indicate persons, not FTE.*

### Clinical Scientists per program (numbers)

| | Brain | Cancer | Child Health | Circulatory Health | I&I | RM&SC |
|---|---|---|---|---|---|---|
| Clinical scientists | 10 | 6 | 12 | 4 | 8 | 3 |

*Note: the number of clinical scientists is based on information from the Academic Careers database. Since 2022, 43 clinical scientists have been recognized at UMC Utrecht (as per March 2025). Distribution over the 10 divisions is unequal.*

# Appendix B - Earning capacity

## Externally acquired research funding (per program)

| | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|---|
| Brain | € 14,485,113 | € 18,851,201 | € 13,873,470 | € 16,679,038 | € 25,442,785 | € 34,842,515 |
| Cancer | € 24,281,931 | € 22,307,366 | € 28,323,076 | € 25,875,847 | € 38,040,878 | € 53,261,232 |
| Child Health | € 14,425,322 | € 5,370,674 | € 11,771,582 | € 11,132,624 | € 14,245,003 | € 17,331,751 |
| Circulatory Health | € 26,337,818 | € 16,226,868 | € 17,571,844 | € 627,555 | € 22,218,191 | € 21,292,933 |
| I&I | € 28,430,216 | € 46,439,354 | € 63,092,453 | € 22,603,836 | € 11,600,182 | € 34,544,713 |
| RM&SC | € 9,693,373 | € 8,569,964 | € 22,016,735 | € 6,764,571 | € 19,732,235 | € 14,968,555 |
| Other research | € 5,845,781 | € 5,547,108 | € 997,202 | € (296,961) | € 728,819 | € 6,840,220 |
| **Total budget** | **€ 123,499,555** | **€ 123,312,535** | **€ 157,646,362** | **€ 83,386,510** | **€ 132,008,092** | **€ 183,081,920** |

*Note:*
- *The complete amount of funding awarded for a project is registered in the year of reception, regardless of the duration of the project.*
- *When a project is linked to multiple strategic programs, the funding is administratively divided equally among them.*
- *Negative amounts can occur if reimbursements had to be made, e.g. when fewer patients were included than expected and the initially awarded budget was not realized. This is the case, for example, for two large Circulatory Health projects (Genius' II and Trials@Home) in 2022. Acquired research funding of Circulatory Health is therefore € 7,575,204 in 2022.*
- *Due to various reasons, the financial administration sometimes takes more time than expected, which is why some projects have not yet been incorporated in the table above. Some examples of large projects that have been awarded in the period 2019-2024 are:*
  - *NGF RegMed XB pilot factory ICAT*
  - *NGF OnCode accelerator (partial)*
  - *NGF CPBT (partial)*
  - *NGF NXTGEN Hightech (partial)*
  - *NWO Summit DRIVE-RM*
  - *ZonMW CEMMRI*
  - *VWS RZN - Antimicrobiële Resistentie*
  - *Spieren voor Spieren' funding*
  - *NWO KIC-LTP IMAGINE*

## Earning capacity per year per funding stream

| | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|---|
| 2nd (national research funders) | € 27,350,912 | € 25,414,907 | € 26,353,426 | € 17,069,074 | € 38,807,220 | € 35,363,228 |
| 3rd (health charities, EU) | € 71,824,389 | € 74,702,200 | € 102,208,301 | € 42,004,418 | € 69,913,767 | € 111,323,424 |
| 4th (private parties) | € 23,967,709 | € 23,195,428 | € 29,921,565 | € 24,283,147 | € 23,287,076 | € 36,395,267 |
| **Total budget** | **€ 123,143,011** | **€ 123,312,535** | **€ 158,483,292** | **€ 83,356,639** | **€ 132,008,063** | **€ 183,081,920** |

*Note: Due to rounding issues, small differences may occur between this table and the one above.*

## Composition of UMC Utrecht overall budget

| | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|---|
| **Reimbursed patient care** | € 669,041,000 | € 738,111,000 | € 779,683,000 | € 795,860,000 | € 847,161,000 | € 868,305,000 |
| **Direct government funding for academic tasks of UMC** | € 92,349,502 | € 93,148,767 | € 97,963,109 | € 105,456,201 | € 114,771,137 | € 123,390,156 |
| **Direct government funding** | € 158,655,000 | € 163,882,000 | € 171,270,000 | € 182,173,000 | € 198,278,000 | € 205,979,000 |
| **Funding for secondary medical training (medical specialists)** | € 58,902,000 | € 59,284,000 | € 60,561,000 | € 62,030,000 | € 66,058,000 | € 68,804,000 |
| **External research funding** | € 123,143,011 | € 123,312,535 | € 158,483,292 | € 83,356,639 | € 132,008,063 | € 183,081,920 |
| **Other services** | € 139,804,487 | € 181,512,698 | € 170,995,599 | € 250,977,160 | € 228,291,800 | € 220,889,924 |
| **Total budget** | **€ 1,241,895,000** | **€ 1,359,251,000** | **€ 1,438,956,000** | **€ 1,479,853,000** | **€ 1,586,568,000** | **€ 1,670,450,000** |

*Note: To appreciate the relative share of external research funding to the overall UMC Utrecht budget and the overall multiplicity of funding sources for the various missions of UMC Utrecht, the table above gives insight in the composition of UMC Utrecht total budget for the period 2019-2024. (Source: Directorate of Information & Finance (dIF))*

# Appendix C - PhD candidates

## Graduation rate

Faculty of Medicine

| | Enrollment (N / %) | | | Graduation rate (N, cumulative) in relation to PhD duration (D) | | | | | Success rate N (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Starting year | Total | Female | Male | D ≤ 4 years | D ≤ 5 years | D ≤ 6 years | D ≤7 years | D >7 years | Graduated | Not yet graduated | Stopped |
| 2016 | **289** | 169 (58%) | 120 (42%) | 110 | 159 | 193 | 214 | 236 | 236 (82%) | 26 (9%) | 27 (9%) |
| 2017 | **297** | 182 (61%) | 115 (39%) | 61 | 136 | 188 | 227 | 237 | 237 (80%) | 46 (15%) | 14 (5%) |
| 2018 | **232** | 141 (61%) | 91 (39%) | 38 | 92 | 147 | 162 | | 162 (70%) | 58 (25%) | 12 (5%) |
| 2019 | **278** | 182 (65%) | 96 (35%) | 35 | 117 | 155 | | | 155 (56%) | 107 (38%) | 16 (6%) |
| 2020 | **256** | 159 (62%) | 97 (38%) | 37 | 66 | | | | 66 (26%) | 172 (67%) | 18 (7%) |
| 2021 | **259** | 175 (68%) | 84 (32%) | 25 | | | | | 25 (10%) | 221 (85%) | 13 (5%) |
| 2022 | **274** | 181 (66%) | 93 (34%) | 2 | | | | | 2 (1%) | 266 (97%) | 6 (2%) |
| 2023 | **299** | 202 (68%) | 97 (32%) | 0 | | | | | 0 (0%) | 295 (99%) | 4 (1%) |
| 2024 | **240** | 183 (76%) | 57 (24%) | 0 | | | | | 0 (0%) | 240 (100%) | 0 (0%) |

# Appendix D - Dataset repositories

## Numbers of UMC Utrecht datasets deposited in DataverseNL

| | 2015-2019 | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|---|
| Number of datasets deposited | 9 | 5 | 11 | 26 | 27 | 35 |
| Cumulative number of datasets deposited | 9 | 14 | 25 | 51 | 78 | 113 |

# Strategic Program Brain

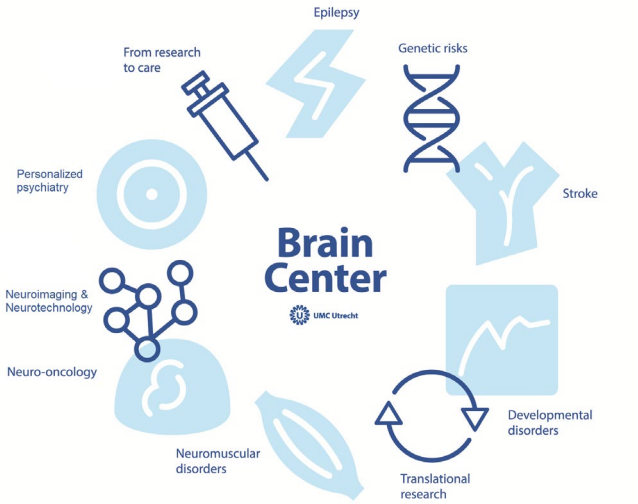
Self-evaluation report 2019-2024

# Strategic Program Brain

## 1 - Mission, governance, and main research topics

### Mission

The strategic program Brain, also known as the UMC Utrecht Brain Center, is an internationally recognized research center in clinical and experimental neuroscience. We conduct comprehensive research in the full translational range, bridging fundamental studies and healthcare innovation to advance neurological, neurosurgical, and psychiatric patient care. Our work involves developing and directly applying (personalized) treatments in clinical practice. Several of our focus areas are registered as national centers of expertise for rare disorders (ECZAs) and are part of European Research Networks (ERNs). We collaborate with academic, institutional, industrial, and societal partners, while fostering education and training our future researchers and caregivers. Additionally, we engage in public outreach activities to share knowledge about brain health and diseases. There are around 500 people related to our program, including both clinical and preclinical researchers across over 50 research groups, as well as support staff. We have a total of 40 full professors and approximately 35 associate professors, 30 assistant professors, 80 postdocs, and 250 PhD students.




### Research focus

The strategic program consists of six different disease areas: developmental disorders, epilepsy, neuromuscular disorders, neuro-oncology, personalized psychiatry, and stroke. All disease areas aim to translate basic science and patient-driven research questions into clinical diagnostic methods, prediction models, and novel treatments. Underlying these disease areas, we have four different research approaches: genetic risks, from research to care, translational research, and neuroimaging & neurotechnology. Together, the disease areas and research approaches form the focus of the strategic program Brain (figure 1).

*Figure 1: Visualization of the strategic program Brain.*
*Matrix includes our six disease areas (light blue) and four research approaches (dark blue).*

#### Developmental disorders

The 'Developmental Disorders' area aims to understand brain development, predict, treat, and prevent developmental disorders. We integrate fundamental, translational, and clinical research to distinguish between normal and abnormal brain development. Our researchers study brain-based developmental disabilities (BBDD) and work to identify at-risk individuals as early as possible. We monitor brain activity and behavior inside and outside the clinical setting and incorporate e-health solutions in standard practice. UMC Utrecht is a national center of expertise for neonatal neurology, collaborating with Utrecht University faculties and the strategic programs 'Child Health' and 'Dynamics of Youth.'

#### Epilepsy

Our epilepsy researchers focus on understanding the causes of epilepsy and how the disease can be better managed or treated. We study genetic predispositions and explore new therapies that enhance patients' quality of life. Our research has two key focus areas: precision medicine and advanced presurgical neurophysiological techniques.

'Precision medicine' aims to develop personalized methods for diagnosing, treating, and predicting outcome in epilepsy. Researchers in the second focus area study the pathophysiology of epilepsy to improve diagnosis and optimize neurosurgical treatment. By capturing epileptic and physiological activity using non-invasive EEG-fMRI and invasive EEG, we delineate epileptic tissue, characterize networks, and assess the cognitive impact of epilepsy. These methods help optimize treatment strategies and improve surgical outcomes. The UMC Utrecht is the national center of expertise for complex epilepsies and part of the European Reference Network EpiCare.

### Neuromuscular disorders

'Neuromuscular disorders' provides excellent clinical care for patients with all forms of neuromuscular disorders and performs outstanding research on motor neuron disease, neuropathy, and neurotechnological innovations to improve quality of life. We aim to elucidate the dynamics between genetic predispositions and environmental influences that contribute to neuromuscular disorders. Our goal is to transition from understanding these conditions towards therapeutic interventions and tailor-made therapies for patients with rare genetic neuromuscular disease. We closely collaborate with patients and their families, patient organizations and funding bodies. The UMC Utrecht is the national center of expertise for neuromuscular disorders and is part of the European Reference Network EURO-NMD.

### Neuro-oncology

UMC Utrecht's neuro-oncology researchers perform innovative research in the field of brain tumors, with a special focus on gliomas. Our mission is to advance understanding, improve patient outcomes, and pioneer treatments through a multidisciplinary approach combining clinical excellence with innovative research. As one of the largest tertiary referral centers for neuro-oncology in the Netherlands, UMC Utrecht is recognized as a center of expertise. We are developing personalized treatment strategies that aim to extend patient survival and enhance quality of life. Our research prioritizes understanding the mechanisms of tumor growth and resistance, exploring new ways to effectively deliver drugs to the brain, and tailoring treatments to individual patient profiles. We do this in close collaboration with researchers from the Princess Máxima Center.

### Personalized psychiatry

The 'Personalized Psychiatry' disease area aims to optimize psychiatric treatments by integrating patient perspectives with biological and psychological research. We focus on three key questions: how biology and genetics influence mental health, what outcomes matter most to patients, and how prediction models and biomarkers can improve mental health and recovery. Our research utilizes methods such as EEG, genetics, data science, and big data analysis to enhance psychiatric diagnosis and treatment. By personalizing care based on an individual's biological and psychological profile, we strive to improve treatment precision and patient outcomes.

### Stroke

At the UMC Utrecht Brain Center, we conduct (pre)clinical research to improve the treatment of cerebrovascular diseases, such as acute ischemic stroke, aneurysmal subarachnoid hemorrhage, and neonatal hypoxic-ischemic brain damage. Our mission is to improve prevention, diagnosis, and treatment of cerebrovascular diseases through integration of basic, translational, clinical, and epidemiological research with state-of-the-art methods. We strive to identify early biomarkers of cerebrovascular disease, develop innovative treatment approaches, and improve patient outcomes through precision medicine. By combining large-scale data analysis with clinical research, we aim to refine stroke prevention strategies and improve recovery processes.

### Research approaches

Our research is driven by four key research approaches, with patient participation embedded across all disease areas. 'Genetic risks' plays a crucial role in understanding both familial and complex neurogenetic diseases like epilepsy, ALS, and cerebrovascular disorders. By analyzing extensive DNA and RNA sequencing data, researchers uncover disrupted gene networks, leading to better diagnostics and treatment strategies. 'Translational research' bridges the gap between laboratory studies and clinical application. Using humanized genetic animal or human in vitro models, scientists explore disease onset and mechanisms under controlled conditions, paving the way for new therapies. 'Neuroimaging and neurotechnology' enable advanced brain function analysis and manipulation. Cutting-edge MRI innovations, from hardware development to computational modeling, help assess neuronal and vascular functions, refining diagnosis and treatment evaluation. Finally, 'clinical trials' are essential for testing novel therapies, ensuring that research translates into real-world patient care.

## Strategy 2021-2025

The strategic program Brain has developed a five-year strategy (see figure 2) that is in line with the UMC Utrecht 'Connecting Worlds' strategy. For the period 2021-2025, the program focuses on four major topics: synergy of neuroimaging research (1), prevention, personalized care, and precision medicine (2), realization of a strategic program laboratory (Center for Translational Neuroscience) (3), and the strengthening of our collaborations, both national and international (4). Additionally, we stimulate the incorporation of artificial intelligence, data science, and e-health as research approaches in our work. Besides the program specific strategy, all six disease areas have developed their own five-year strategy with individual goals (available upon request).

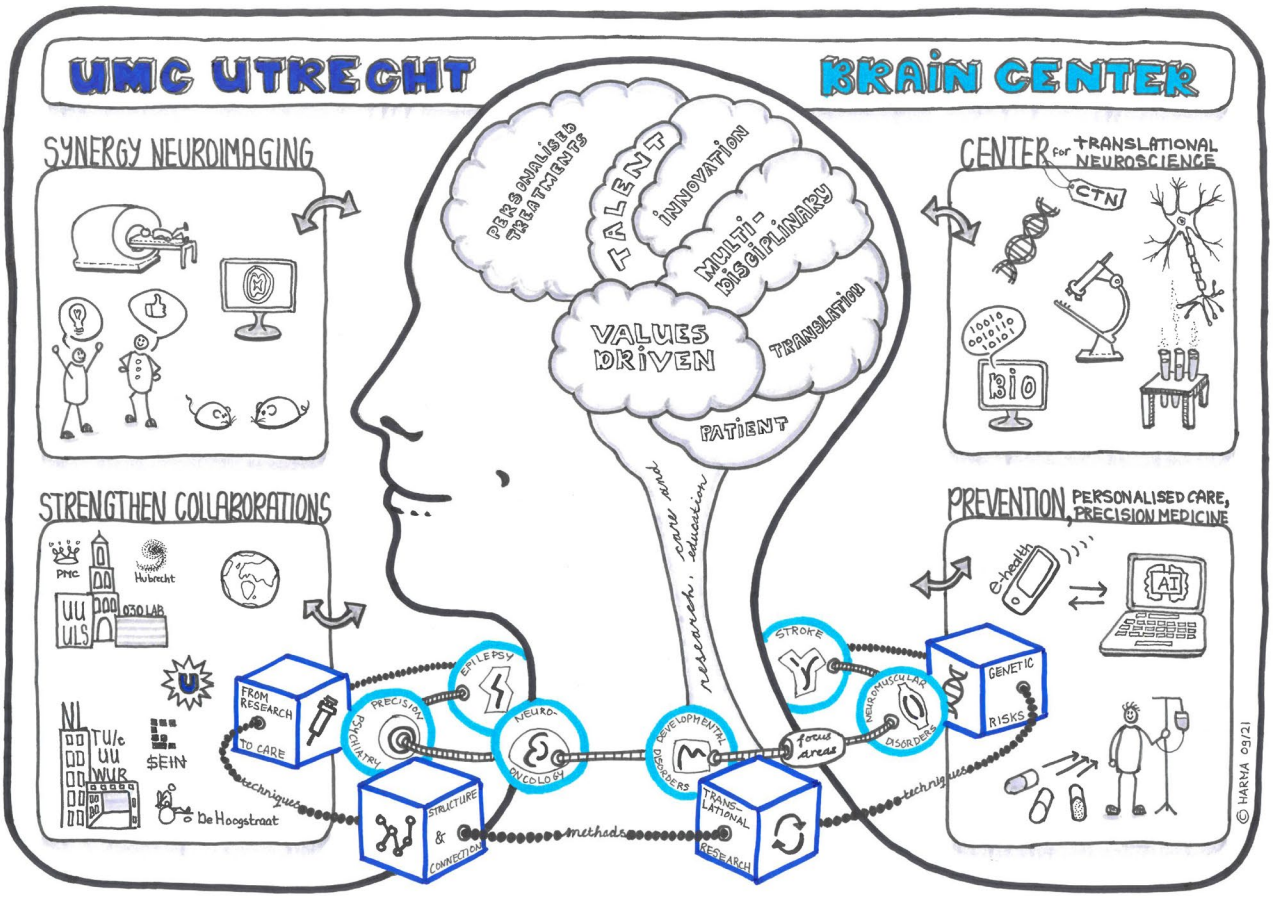



*Figure 2: Visualization of the five-year strategy (2021-2025) of the strategic program Brain.*

## Governance

The strategic program Brain consists of researchers located in four divisions: Brain (1), Imaging & Oncology (2), Surgical Specialties (3), and Woman & Baby (4). Furthermore, we collaborate closely with other partners on campus, such as the Prinses Máxima Center and the Central Military Hospital (CMH). In 2024, we started 'Utrecht Brain' to unite all neuroscience partners on campus and make optimal use of expertise and facilities. The management team consists of a chair (Jeroen Pasterkamp), program managers (Marjolein Sneeboer & Tinka Louter), communication advisor (Jerwin de Graaf), and representatives from the different divisions. The management team is responsible for vision & strategy, talent management & promotions, and day-to-day activities. Furthermore, each member of the management team holds a specific portfolio, e.g. valorization, clinical care, and education. Additionally, the chairs of the disease areas and research approaches form the advisory board. Each disease area is co-chaired by one basic and one clinical researcher. The advisory board advises the management team on strategy and is the direct link with the researchers.

## 2 - Concise reflection on program-specific recommendations from the previous evaluation

The strategic program Brain was reviewed as excellent during the former SEP evaluation. In the past years, we have been implementing the recommendations of the committee, subdivided into five categories: clinical scientist (i), career development (ii), relevance for society (iii), structure of the center (iv), and integration of research facilities (v). Please find below an overview of accomplishments per category.

### Clinical scientist

The strategic programs jointly designed a procedure for the implementation of Clinical Scientist positions to provide talented clinicians with dedicated research time. From 2021 onwards, the Brain program appointed 12 Clinical Scientists, distributed over the different collaborating divisions.

### Career development

The SEP committee noticed an exodus of (young) talented researchers from the UMC Utrecht, mainly due to the absence of a talent program. To further strengthen the collaboration between clinical and fundamental research, as well as between different departments and laboratories of the program, we transformed our personal fellowships into duo grants. This new initiative resulted in many new and out-of-the-box collaborations for young researchers and has proven successful, with many of the fellowship winners becoming Veni and Vidi laureates. Furthermore, many researchers from the strategic program Brain participate in the UMC Utrecht talent programs every year.

### Relevance for society

In 2020, 2022, and 2024, we organized a large outreach event in collaboration with New Scientist, a popular scientific platform, in TivoliVredenburg, Utrecht (see appendix D-2). These events highlighted the potential of artificial intelligence, virtual reality, and data science in neuroscientific research and care and, despite increasing ticket availability with each edition, they were fully sold out every time. Another topic of interest was further improvement of patient involvement in research. Nowadays, a course on patient involvement in research is part of the Clinical & Experimental Neuroscience PhD program. PhD students can also decide to follow a more in-depth course on this topic, which provides practical tools to involve patients in their research. Finally, we decided to integrate the methodological line 'From research to care' into the six disease areas and appointed specific ambassadors to support this topic in all research fields.

### Structure of the center

One of the recommendations of the committee was to renew our five-year strategy. More information about the new strategy can be found above. The committee also concluded that the research focus regarding psychiatric disorders was not clear. We assigned two new coordinators and restructured the focus area into 'personalized psychiatry' (former: psychotic disorders) to better align with the current vision of the Department of Psychiatry. 'Personalized psychiatry' is incorporating different data sources, tools, and methods together with patient involvement to develop prediction models and provide personalized treatment.

### Integration of research facilities

One of the ambitions of the program was to unite all fundamental-, animal-, and translational research within the Brain program in a Center for Translational Neuroscience (CTN). From 2022 onwards, the CTN was founded as a virtual center and the chairs of the five brain laboratories meet regularly. Together with the PhD program, we organize the Rudolf Magnus seminar series to facilitate more interaction between researchers and provide in-depth knowledge on fundamental neuroscience. In 2024, the first annual CTN meeting was organized, which was well attended by researchers from laboratories within the Brain strategic program.

## 3 - Main research accomplishments in the period 2019-2024

### ALS Home-monitoring and Coaching to improve self-control

In co-creation with patients, their caregivers, and healthcare professionals, the telehealth service ALS Home-monitoring and Coaching was developed to provide responsive and personalized care with more self-control over the care and less

burden of care for patients and their caregivers. With the newly developed ALS Home Monitoring and Coaching app, patients at home record data about their functioning (such as swallowing, motor function, and breathing), body weight, and wellbeing. The app allows patients to chat with healthcare professionals and monitoring of their data is performed by a nurse specialist, preventing patients from coming to the hospital unnecessarily. Adoption and satisfaction among patients and healthcare professionals is high. The app is implemented in twelve multidisciplinary ALS teams of the ALS Care Network.

### More personalized treatments of mental health problems with innovative technologies

Innovative technologies, such as big data, artificial intelligence, and virtual reality, are now integrated into psychiatric research, making treatments more personalized, accessible, and effective. In collaboration with the Central Military Hospital, we explore virtual reality for conditions like post-traumatic stress disorder, creating immersive environments where patients confront fears and engage with therapists. Furthermore, we developed a predictive model to assess the effectiveness of electroconvulsive therapy (ECT) for depression. By analyzing data from 1,900 patients, we identified key factors predicting ECT success, allowing for more informed decision-making and improved outcomes for patients with depression.

### Epilepsy surgery – the sooner the better

A large-scale European study into the effectiveness of epilepsy surgery in over 9000 patients, led by the UMC Utrecht and the University Hospitals of Erlangen, showed that one year after surgery, 72% of patients are seizure-free. After two years, this percentage is still 68% and after five years 66%. Short- and long-term outcomes are now provided for each specific epileptogenic pathology. The study convincingly demonstrates that early surgery improves the chance of reaching seizure-freedom. Previous studies by our researchers have shown that early medication withdrawal after pediatric epilepsy surgery is safe and has cognitive benefits. Our work has contributed to a better understanding of the importance of early surgical treatment for seizure and developmental outcomes. In this context, we have advocated – as one of the first centers – that epilepsy surgery may even be offered in children with non-eloquent lesional epilepsies who are well-controlled with medication. Findings of our studies have changed treatment practice worldwide.

### Research leads to first genetic treatment for Spinal Muscular Atrophy (SMA)

After Spinraza®, a second medicine for children with SMA became available. Zolgensma® is a genetic treatment that rebuilds the SMN1 gene in the DNA of affected infants. When administered at an early stage, the treatment can significantly improve clinical outcome. The coordination of this innovative medical treatment (which patient is eligible for receiving the treatment) was led by UMC Utrecht. The SMA team mapped the severity of symptoms of each child and decided, based on this information, whether treatment would lead to improvement. Furthermore, the SMA center advised the RIVM to add SMA to the Dutch perinatal screening program (hielprik), allowing newborns to be diagnosed early on and to receive timely treatment. From 2022 onwards, SMA is included in the screening program, a major achievement.

### Focused ultrasound (fUS) to open the blood-brain barrier

Researchers form the strategic program, together with colleagues from other institutes, explore the use of focused ultrasound (fUS) to open the blood-brain barrier temporarily and safely, facilitating drug delivery to the brain. This non-invasive, MRI-guided technique employs precise sound waves and microbubbles to locally open brain blood vessels without surgery. Initial studies target children and adults with malignant brainstem tumors, aiming to enhance treatments for various brain disorders by improving drug penetration into the brain. This is one of the first non-invasive techniques to administer drugs directly into the brain and provides hope for patients with a brain tumor and their families.

### Project MinE: largest resource of genetic data on ALS

Project MinE, founded by three patients with ALS and coordinated by our researchers of the UMC Utrecht, is the largest database in the world for genetic data on ALS. The project's mission is to find genetic variants that contribute to the development and progression of ALS. So far, DNA of ~14000 patients and ~4500 controls has been sequenced. The Project MinE dataset is accessible to all researchers working in the health domain and complies with FAIR principles. Also, Project MinE data will be harmonized with UK Biobank data in 2025 and 2026 and will also be accessible to the global academic and for-profit community at DNA Nexus. Lastly, through intensive collaboration with the department

of clinical genetics at the WKZ, we are now able to whole genome sequence (WGS) our own UMC Utrecht samples, and samples from external collaborators.

### Stem cell therapy to improve outcome for newborns with brain injury

Researchers at UMC Utrecht have developed a novel stem cell therapy to treat brain injuries in newborn children. The treatment involves administering mesenchymal stem cells via nasal drops, aiming to stimulate the brain's natural repair mechanisms. Preclinical studies demonstrated that stem cells can reduce inflammation and promote tissue regeneration. After promising results in a safety study with ten infants, the team recently received a large grant (~€5 million) to treat 162 infants with stem cells and monitor them for 24 months. Based on the results of the study, it will be determined whether the therapy will be a standard treatment in Dutch neonatal care. This study is the perfect example of how basic neuroscience can lead to clinical trials and implementation in daily care and has a direct impact on the quality of life of the young patients and their families.

### B-STARS trials to improve recovery after stroke

Despite improvements in acute stroke treatment and rehabilitation strategies, many stroke patients experience long-term motor impairment in their upper limbs. The B-STARS research program aims to develop effective non-invasive brain stimulation treatments to promote upper limb recovery through close collaboration between basic scientists, technology experts, neurologists, and rehabilitation doctors. The B-STARS phase 2 trial, executed together with De Hoogstraat Rehabilitation, showed that inhibitory repetitive transcranial magnetic stimulation (rTMS) in combination with upper limb training, initiated within three weeks after a stroke, promotes upper limb motor recovery. The study has received significant attention from patients, providing hope that further recovery is possible. This is further tested in an ongoing phase 3 trial involving over 450 patients across 16 Dutch rehabilitation centers.

### Online available prediction models for epilepsy

Our epilepsy researchers, together with EpilepsieNL, have developed prediction models that are freely available online for physicians and patients. The prediction models are available to calculate individualized chances of an epilepsy diagnosis after first seizures in children (1); seizure relapse after medication withdrawal (2); relapse after postoperative withdrawal in children (3); refractory JME and post withdrawal relapse in JME (4); and cognitive outcomes after pediatric epilepsy surgery (5). The tools are not part of the medical guidelines, but can supplement standard care with additional information, www.epilepsypredictiontools.info

### Advancing sleep research: understanding brain development, recovery, and growth

Researchers at UMC Utrecht, in collaboration with sleep experts from the Princess Máxima Center (PMC), De Hoogstraat Rehabilitation, and Kempenhaeghe, have established the Sleep Discovery Lab to explore the fundamental role of sleep in brain development, recovery, and growth. This initiative aims to bridge basic neuroscience with clinical applications, providing insights into how sleep supports neurodevelopment and optimizes recovery following early-life brain injury. The lab studies the consequences of disrupted sleep on brain maturation, neuronal plasticity, and behavioral outcomes, shedding light on the critical window in which sleep influences developmental trajectories and early-life neuroprotection. Additionally, the team has organized multiple international workshops.

### Mapping vascular cognitive impairment after stroke

Within the disease area 'stroke' we focus on identifying brain lesions associated with vascular cognitive impairment (VCI). Through the MetaVCIMap consortium, which we initiated and lead, we harmonized imaging and cognitive data from over 40 cohorts, encompassing 25,000 participants worldwide. This effort resulted in strategic maps for infarcts and key tracts affected by white matter hyperintensities, alongside detailed normative curves for small vessel disease (SVD). Over this period, our VCI group published more than 150 papers, including seven in The Lancet Journals, and secured several prestigious grants.

## 4 - Specific questions for the research committee

1. Does the committee see any developments or opportunities we should respond to?
2. Are there areas where we can further support our researchers?

# Appendix

## Appendix A - Key scientific outputs

1. Bakker, M. K., Van Der Spek, R. A. A., Van Rheenen, W., Morel, S., Bourcier, R., Hostettler, I. C., Alg, V. S., Van Eijk, K. R., Koido, M., Akiyama, M., Terao, C., Matsuda, K., Walters, R. G., Lin, K., Li, L., Millwood, I. Y., Chen, Z., Rouleau, G. A., Zhou, S., ... Ruigrok, Y. M. (2020). **Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors.** *Nature Genetics, 52*(12), 1303–1313. https://doi.org/10.1038/s41588-020-00725-7
   Citations: 188
   This study is the largest genome-wide association study on intracranial aneurysms in which 17 risk loci for intracranial aneurysms were identified, including 11 novel discoveries. It highlighted a strong genetic correlation between ruptured and unruptured aneurysms and implicated a role for endothelial cells in disease development. The research underscored the genetic contribution of smoking and hypertension and reveals potential drug targets, advancing therapeutic strategies for aneurysm management.

2. Weaver, N. A., Kuijf, H. J., Aben, H. P., Abrigo, J., Bae, H., Barbay, M., Best, J. G., Bordet, R., Chappell, F. M., Chen, C. P. L. H., Dondaine, T., Van Der Giessen, R. S., Godefroy, O., Gyanwali, B., Hamilton, O. K. L., Hilal, S., Wajer, I. M. C. H., Kang, Y., Kappelle, L. J., ... Biessels, G. J. (2021). **Strategic infarct locations for post-stroke cognitive impairment: A pooled analysis of individual patient data from 12 acute ischaemic stroke cohorts.** *The Lancet Neurology, 20*(6), 448–459. https://doi.org/10.1016/S1474-4422(21)00060-0
   Citations: 184
   After stroke, almost half of the patients suffer from post-stroke cognitive impairment (PSCI). By analyzing data from 2,950 patients across 12 cohorts, researchers created a comprehensive map that predicts the risk for cognitive impairment based on the location of the stroke. The development of a "location impact score" from this map enables clinicians to better predict PSCI risk on an individual level, facilitating targeted interventions and improved patient care.

3. Zweiphenning, W., Van 't Klooster, M. A., Van Klink, N. E. C., Leijten, F. S. S., Ferrier, C. H., Gebbink, T., Huiskamp, G., Van Zandvoort, M. J. E., Van Schooneveld, M. M. J., Bourez, M., Goemans, S., Straumann, S., Van Rijen, P. C., Gosselaar, P. H., Van Eijsden, P., Otte, W. M., Van Diessen, E., Braun, K. P. J., Zijlmans, M., ... Dankbaar, J. (2022). **Intraoperative electrocorticography using high-frequency oscillations or spikes to tailor epilepsy surgery in the Netherlands (the HFO trial): A randomised, single-blind, adaptive non-inferiority trial.** *The Lancet Neurology, 21*(11), 982–993.https://doi.org/10.1016/S1474-4422(22)00311-8
   Citations: 54, open access
   Previous research showed that high-frequency oscillations (HFOs) could function as a new biomarker for defining epileptic tissue. This unique HFO trial evaluated the effectiveness of using HFOs versus traditional interictal spikes in intraoperative electrocorticography to guide epilepsy surgery. The study showed that HFO-guided surgery was non-inferior to spike-guided approaches in achieving seizure freedom one year post-surgery. These findings support the use of HFOs as a reliable biomarker for tailoring epilepsy surgeries, potentially leading to better patient outcomes.

4. Hop, P. J., Zwamborn, R. A., Hannon, E., Shireby, G. L., Nabais, M. F., Walker, E. M., Van Rheenen, W., Van Vugt, J. J., Dekker, A. M., Westeneng, H., Tazelaar, G. H., Van Eijk, K. R., Moisse, M., Baird, D., Khleifat, A. A., Iacoangeli, A., Ticozzi, N., Ratti, A., Cooper-Knock, J., ... Mill, J. (2022). **Genome-wide study of DNA methylation shows alterations in metabolic, inflammatory, and cholesterol pathways in ALS.** *Science Translational Medicine, 14*(633). https://doi.org/10.1126/scitranslmed.abj0264
Citations: 32
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with an estimated heritability of 40-50%. DNA methylation is seen as a potential mechanism for mediating genetic and environmental risks in ALS. This genome-wide DNA methylation study identified 45 differentially methylated positions linked to genes involved in metabolism, inflammation, and cholesterol pathways. These findings enhance the understanding of ALS pathogenesis and may inform the development of biomarkers and therapeutic targets for this neurodegenerative disease.

5. Hoogstrate, Y., Draaisma, K., Ghisai, S. A., Van Hijfte, L., Barin, N., De Heer, I., Coppieters, W., Van Den Bosch, T. P., Bolleboom, A., Gao, Z., Vincent, A. J., Karim, L., Deckers, M., Taphoorn, M. J., Kerkhof, M., Weyerbrock, A., Sanson, M., Hoeben, A., Lukacova, S., ... French, P. J. (2023). **Transcriptome analysis reveals tumor microenvironment changes in glioblastoma.** *Cancer Cell, 41*(4), 678-692.e7. https://doi.org/10.1016/j.ccell.2023.02.019
Citations: 90, open access
This study, comparing the molecular profile of primary with recurrent glioblastoma, showed that glioblastomas primarily evolve through reorganization of the tumor microenvironment rather than changes within the tumor cells themselves. Notably, an increase in extracellular matrix-associated genes, predominantly expressed by pericytes, was observed at tumor recurrence. This shift is linked to poorer patient survival, highlighting the critical role of the microenvironment in glioblastoma progression and suggesting potential therapeutic targets.

6. Wang, X., Trabatti, C., Weeke, L., Dudink, J., De Veye, H. S., Eijsermans, R. M. J. C., Koopman-Esseboom, C., Benders, M. J. N. L., & Tataranno, M. L. (2023). **Early qualitative and quantitative amplitude-integrated electroencephalogram and raw electroencephalogram for predicting long-term neurodevelopmental outcomes in extremely preterm infants in the Netherlands: a 10-year cohort study.** *The Lancet Digital Health, 5*(12), e895–e904. https://doi.org/10.1016/S2589-7500(23)00198-X
Citations: 8, open access
This paper is scientifically relevant for its potential impact on personalized neonatal care and long-term outcomes for extremely preterm infants. By analyzing early amplitude-integrated electroencephalogram (aEEG) data with machine learning, the study aimed to identify predictive markers of neurodevelopmental outcomes at individual level. Findings indicated that specific qualitative and quantitative aEEG-EEG features obtained within the first postnatal days can predict long-term neurodevelopmental outcomes. These results underscore the utility of early EEG monitoring in identifying infants at risk for neurodevelopmental impairments, facilitating timely interventions and improve long term outcome.

7. Van Rheenen, W., Van Der Spek, R. A. A., Bakker, M. K., Van Vugt, J. J. F. A., Hop, P. J., Zwamborn, R. A. J., De Klein, N., Westra, H., Bakker, O. B., Deelen, P., Shireby, G., Hannon, E., Moisse, M., Baird, D., Restuadi, R., Dolzhenko, E., Dekker, A. M., Gawor, K., Westeneng, H., ... Veldink, J. H. (2021b). **Common and rare variant association analyses in amyotrophic lateral sclerosis identify 15 risk loci with distinct genetic architectures and neuron-specific biology.** *Nature Genetics, 53*(12), 1636–1648. https://doi.org/10.1038/s41588-021-00973-1
Citations: 180, open access
Through a comprehensive genome-wide association study on Project MinE data, involving 29,612 patients with ALS and 122,656 controls, researchers identified 15 risk loci associated with ALS. The study revealed 15 genetic risk factors for ALS, involved in glutamatergic neuron-specific biological pathways and protein degradation. Furthermore, the study showed that the role of neuroinflammation is limited. These insights enhance the understanding of ALS pathogenesis and may inform the development of targeted therapeutic strategies.

8. Stevelink, R., Campbell, C., Chen, S., Abou-Khalil, B., Adesoji, O. M., Afawi, Z., Amadori, E., Anderson, A., Anderson, J., Andrade, D. M., Annesi, G., Auce, P., Avbersek, A., Bahlo, M., Baker, M. D., Balagura, G., Balestrini, S., Barba, C., Barboza, K., ... Ali, Q. Z. (2023). **GWAS meta-analysis of over 29,000 people with epilepsy identifies 26 risk loci and subtype-specific genetic architecture.** *Nature Genetics, 55*(9), 1471–1482. https://doi.org/10.1038/s41588-023-01485-w
Citations: 31, open access
Researchers from UMC Utrecht, along with colleagues of the International League Against Epilepsy, have discovered specific changes in our DNA that increase the risk of developing epilepsy. This is the largest genetic study in epilepsy so far. The researchers identified 26 distinct genes in the DNA that appear to be involved in epilepsy. The strongest genetic signals were found for generalized forms of epilepsy for which 19 genes were unique. These findings significantly enhance our understanding of the origins of epilepsy and can contribute to the development of new and/or more personalized treatments.

9. Robinson, R. A., Griffiths, S. C., Van de Haar, L. L., Malinauskas, T., Van Battum, E. Y., Zelina, P., Schwab, R. A., Karia, D., Malinauskaite, L., Brignani, S., Van Den Munkhof, M. H., Düdükcü, Ö., De Ruiter, A. A., Van Den Heuvel, D. M., Bishop, B., Elegheert, J., Aricescu, A. R., Pasterkamp, R. J., & Siebold, C. (2021). **Simultaneous binding of Guidance Cues NET1 and RGM blocks extracellular NEO1 signaling.** *Cell, 184*(8), 2103-2120.e31. https://doi.org/10.1016/j.cell.2021.02.045
Citations: 25, open access
During cell migration or differentiation, cell surface receptors are simultaneously exposed to different ligands (signaling proteins). The general assumption was that when two signaling proteins with opposite downstream functions arrive at the same time at the nerve cell receptor, either one or the other protein binds. This study showed for the first time that instead of competing, the signaling proteins both bind. This temporarily "switches off" the cell, which offers opportunities for all kinds of new therapies.

10. Sentner, T., Wang, X., De Groot, E. R., Van Schaijk, L., Tataranno, M. L., Vijlbrief, D. C., Benders, M. J. N. L., Bartels, R., & Dudink, J. (2022). **The Sleep Well Baby project: an automated real-time sleep–wake state prediction algorithm in preterm infants.** *SLEEP, 45*(10). https://doi.org/10.1093/sleep/zsac143
Citations: 15, open access
Sleep is important for brain development. However, sleep is often disturbed in preterm children on the neonatal intensive care unit. This study developed a non-invasive algorithm to classify sleep–wake states in preterm infants using routinely monitored vital signs such as heart rate, respiratory rate, and oxygen saturation. The algorithm achieved reliable performance in real-time classification, particularly in identifying wake states. Implementing this tool in neonatal intensive care units could enhance individualized care by aligning medical interventions with infants' sleep–wake cycles, thereby promoting optimal brain development. The software has made several follow-up studies possible including a study showing the positive impact of sleep on white matter development in preterm infants.

11. Van Arnhem, M. M. L., Van Den Munckhof, B., Arzimanoglou, A., Perucca, E., Metsähonkala, L., Rubboli, G., Khinchi, M. S., De Saint-Martin, A., Klotz, K. A., Jacobs, J., Cross, J. H., Morales, I. G., Otte, W. M., Van Teeseling, H. C., Leijten, F. S. S., Braun, K. P. J., Jansen, F. E., Jansen, A., Lagae, L., ... Ramantani, G. (2023). **Corticosteroids versus clobazam for treatment of children with epileptic encephalopathy with spike-wave activation in sleep (RESCUE ESES): a multicentre randomised controlled trial.** *The Lancet Neurology, 23*(2), 147–156. https://doi.org/10.1016/S1474-4422(23)00409-X
Citations: 8
Epileptic encephalopathy with sleep-activated epileptic activity (EE-SWAS) is an underdiagnosed form of childhood epilepsy. Developmental issues in EE-SWAS are often concerning. The RESCUE ESES trial compared the efficacy of corticosteroids and clobazam in treating children with EE-SWAS. Results indicated that corticosteroids led to greater improvements in IQ scores compared to clobazam, although no significant difference was observed in overall cognitive function. For families navigating the challenges of EE-SWAS, these findings represent a significant step forward in managing this complex condition and potentially preserving cognitive function.

12. Vansteensel, M. J., Leinders, S., Branco, M. P., Crone, N. E., Denison, T., Freudenburg, Z. V., Geukes, S. H., Gosselaar, P. H., Raemaekers, M., Schippers, A., Verberne, M., Aarnoutse, E. J., & Ramsey, N. F. (2024). **Longevity of a Brain–Computer Interface for Amyotrophic Lateral Sclerosis.** *New England Journal Of Medicine, 391*(7), 619–626. https://doi.org/10.1056/NEJMoa2314598
Citations: 3
Brain-Computer Interfaces (BCIs) are promising solutions for communication impairments of people with severe paralysis. Long-term effectiveness in progressive disease, however, remains unclear. This article reports on seven years of unsupervised at-home use of a fully implantable BCI as a communication tool by an individual with advanced ALS. Initially, BCI use increased as other assistive communication technology became unusable. For years, the BCI was the only way the user could alert her caregiver. Several years after implantation, BCI use declined due to reduced reliability, likely caused by ALS progression. These findings highlight the value and potential limitations of implanted BCI technology.

13. Linders, L. E., Patrikiou, L., Soiza-Reilly, M., Schut, E. H. S., Van Schaffelaar, B. F., Böger, L., Wolterink-Donselaar, I. G., Luijendijk, M. C. M., Adan, R. A. H., & Meye, F. J. (2022). **Stress-driven potentiation of lateral hypothalamic synapses onto ventral tegmental area dopamine neurons causes increased consumption of palatable food.** *Nature Communications, 13*(1). https://doi.org/10.1038/s41467-022-34625-7
Citations: 16, open access
Stress can increase the intake of high caloric food, which can contribute to obesity and (binge) eating, but the neurobiology underlying this process is not clear. This study describes how stress changes the strength of synaptic contacts between specific neuron types within the Lateral Hypothalamus and the midbrain dopamine system, and it shows that these neuroadaptations causally contribute to binge eating behavior. The study, by studying causative mechanisms at the micro-scale, complements recent correlative imaging studies reporting links between (at the macro-scale) hypothalamus-midbrain dysfunction and binge eating in eating disorder patients.

14. Baak, L. M., Wagenaar, N., Van Der Aa, N. E., Groenendaal, F., Dudink, J., Tataranno, M. L., Mahamuud, U., Verhage, C. H., Eijsermans, R. M. J. C., Smit, L. S., Jellema, R. K., De Haan, T. R., Ter Horst, H. J., De Boode, W. P., Steggerda, S. J., Prins, H., De Haar, C. G., De Vries, L. S., Van Bel, F., ... Benders, M. J. N. L. (2022). **Feasibility and safety of intranasally administered mesenchymal stromal cells after perinatal arterial ischaemic stroke in the Netherlands (PASSIoN): a first-in-human, open-label intervention study.** *The Lancet Neurology, 21*(6), 528–536. https://doi.org/10.1016/S1474-4422(22)00117-X
Citations: 64
Perinatal arterial ischaemic stroke (PAIS) can lead to neurodevelopmental disabilities. In this first-in-human study, UMC Utrecht researchers tested the feasibility and safety of intranasally administered mesenchymal stromal cells in ten neonates with MRI-confirmed PAIS. The treatment was well tolerated, with no serious adverse events and only one mild transient fever in patients followed up until three months of age. Follow-up MRIs showed no unexpected abnormalities, and early motor assessments were promising. These findings suggest that intranasal mesenchymal stromal cell therapy is safe and feasible. Larger placebo-controlled trials are needed to assess its therapeutic benefits for neonates with PAIS.

15. Van Kessel, E., Snijders, T. J., Baumfalk, A. E., Ruis, C., Van Baarsen, K. M., Broekman, M. L., Van Zandvoort, M. J. E., & Robe, P. A. (2019). **Neurocognitive changes after awake surgery in glioma patients: a retrospective cohort study.** *Journal Of Neuro-Oncology, 146*(1), 97–109. https://doi.org/10.1007/s11060-019-03341-6
Citations: 36, open access
The neurosurgery department of the UMC Utrecht is specialized in performing awake brain tumor surgery to preserve neurocognitive and motor functions through advanced mapping techniques and multidisciplinary expertise. In this study, researchers evaluated neurocognitive functioning (NCF) in 168 glioma patients before and 3-6 months after awake craniotomy. The findings indicated that, except for psychomotor speed, cognitive functions were generally preserved post-surgery. However, psychomotor speed was vulnerable for surgery and showed a notable decline with a significant increase of impairments.

## Appendix B - Most important collaborations

### 1. BRAINSCAPES

In September 2019, the BRAINSCAPES consortium was awarded with a Gravitation Award (€19 million) from the Netherlands Organization for Scientific Research. BRAINSCAPES aims to fully map the genetic landscape of several psychiatric and neurological disorders and provide insight into the cell types and brain circuits that are affected in these disorders. BRAINSCAPES is a large consortium of different research institutes including UMC Utrecht, and brings together geneticists, molecular biologists, translational researchers, and bioinformatics specialists. BRAINSCAPES facilitates an innovative and close collaboration between all those disciplines.

### 2. The ALS Triangle in the Netherlands

A globally unique and successful collaboration is the so-called 'ALS triangle' (figure 3) that focusses on the diagnosis, treatment and research of ALS, progressive spinal muscular atrophy (PSMA), and primary lateral sclerosis (PLS). This partnership consists of the Dutch ALS Patients' Association (APV), the Dutch ALS Center (UMC Utrecht), and the Dutch ALS Foundation (SAN). Each organization contributes its own expertise to improve research and patient care. The APV advocates for patients, promoting quality of life measures and care while navigating complex regulations. They work closely with 35 rehabilitation centers to provide optimal support. The Dutch ALS Foundation performs research and coordinates national and international efforts to improve diagnosis, care, and treatment. Meanwhile, SAN raises funds for research and patient support. Together, these organizations align projects and initiatives to maximize impact, aiming to find effective treatments and enhance patients' quality of life.

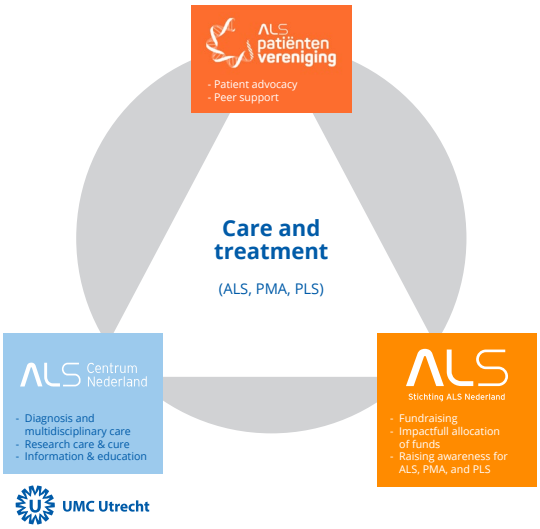



*Figure 3. ALS Strength through collaboration*

### 3. NeuroTech-NL

NeuroTech-NL was initiated by researchers, engineers, and clinicians at major research universities, technical universities, and academic hospitals, recognizing the need to further develop the Dutch neurotechnology ecosystem into a network that bridges research, industry and patient care. UMC Utrecht is one of the founding partners. The mission of NeuroTech-NL is to mitigate the handicaps caused by neurological disorders by developing the best interfaces with the brain and nervous system. The consortium brings together leading institutes, patient organizations, and companies across the neurotechnology field to perform groundbreaking, multidisciplinary, large-scale R&D and translate the results into solutions for patients and economic activity. The consortium is very successful and was awarded a Gravitation Award in 2022 (see appendix C).

### 4. CONTRAST consortium for acute stroke

The CONTRAST consortium (Collaboration for New Treatments for Acute STroke) is a collaborative initiative in the Netherlands dedicated to enhancing outcomes for patients with acute stroke. It unites experts from various medical centers, including UMC Utrecht. It aims to conduct preclinical studies and large-scale randomized clinical trials to develop and evaluate new treatment strategies for acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). Researchers from the strategic program Brain play a pivotal role in this consortium as leaders of the work packages 1, 2 and 7, contributing to preclinical and translational studies that inform clinical practices. This multidisciplinary collaboration is unique in its comprehensive approach, integrating laboratory research with clinical applications to improve patient outcomes. The consortium was so successful that CONTRAST 2.0 started in 2023.

**5. Epilepsy researchers participate in European Reference Network EPiCARE**

UMC Utrecht epilepsy researchers play a key role in ERN EPiCARE, a European Reference Network focused on rare and complex epilepsies. We contribute expertise in advanced neuroimaging, genetics, and precision medicine to improve diagnosis and treatment. Our team develops innovative presurgical evaluation techniques, such as EEG-fMRI and invasive EEG, to better localize epileptic networks. Additionally, we support knowledge-sharing initiatives, helping to standardize care across Europe. By collaborating with ERN EPiCARE, we aim to enhance personalized treatment strategies, optimize surgical outcomes, and improve the quality of life for patients with complex epilepsies.

**6. Utrecht Brain**

Utrecht Brain is a collaborative initiative, started in 2024, uniting all neuroscience partners at Utrecht Science Park (USP). Its goal is to bring together neuroscience research on campus and highlight Utrecht's expertise in neuroscience both nationally and internationally. By fostering multidisciplinary and multi-institutional collaboration, Utrecht Brain ensures optimal use of expertise and state-of-the-art facilities at USP. The initiative also focuses on structural profiling and strategic marketing to enhance visibility and impact. Its official launch will be in September 2025 with a first event during the Utrecht Science Week.

**7. Participatie in Perspectief (PiP) project**

The 'Participation in Perspective' (PiP) project was a research initiative for and with young people (12-17 years) with cerebral palsy (CP). It focused on sharing personal experiences about school, sports, and healthcare. Twelve CP ambassadors were actively collaborating with the UMC Utrecht researchers, advising on recruitment, analyzing interviews, and raising awareness to combat misconceptions about CP. The project generated qualitative and quantitative data, scientific publications, and the website Wij&CP, featuring information and personal stories. Collaboration between youth, researchers, healthcare providers, and policymakers made PiP a success in improving understanding and representation of CP.

## Appendix C - Grants and prizes

1. **GoALS: Research program for a breakthrough in the cure of ALS**
   The Dutch ALS Patients' Association, Dutch ALS Foundation, and Dutch ALS Center have launched GoALS, an ambitious five-year, €60 million research initiative aimed at accelerating the development of ALS therapies. GoALS optimizes the entire drug discovery pipeline by uniting the research lines: target discovery, preclinical validation, and patient-centric studies in one program. By restructuring financial support, researchers can build on each other's work more efficiently, driving faster and more impactful breakthroughs. GoALS also partners with industry through co-financing and strategic collaborations, ensuring that the most promising ALS treatments move efficiently from research to real-world application.

2. **Four ERC grants**
   In 2019, Ynte Ruigrok received an ERC Starting Grant for her project PRYSM, which focuses on the early recognition of intracranial aneurysms to prevent life-threatening brain hemorrhages. Five years later, she also received an ERC Proof of Concept grant to translate her research findings into practical applications, improving early detection and treatment strategies for brain aneurysms. Maeike Zijlmans received an ERC Proof of Concept in 2023 to design a special high-density grid for the brain to improve epilepsy surgery and outcome. In 2024, Alberto De Luca was awarded with an ERC Starting Grant to develop advanced MRI technologies for mapping the cerebral cortex, enhancing our understanding of brain disorders like Alzheimer's.

3. **Center for Animal-Free Biomedical Translation – National Growth fund 2024**
   The National Growth Fund invested €124.5 million in the Centre for Animal-Free Biomedical Translation (CPBT). Part of the CPBT program is the ALS transition project. The goal of this project is to accelerate the shift from traditional animal models to innovative, human-relevant technologies. This includes the use of patient-derived cells, organoids, and advanced computational models to better mimic ALS biology and accelerate therapy development. By fostering collaboration between researchers, clinicians, and industry, the project aims to improve the predictability of preclinical studies, reduce animal use, and ultimately speed up the development of effective treatments for ALS patients.

4. **Two gravitation grants (BRAINSCAPES; The Dutch Brain Interfaces Initiative)**
   The BRAINSCAPES (€19.6 million) and Dutch Brain Interfaces Initiative (DBI2; €21.9 million) neuroscientific research consortia have been awarded with a prestigious Gravitation grant. BRAINSCAPES aims to map brain activity across multiple scales, from individual neurons to whole-brain networks, enhancing our understanding of cognition and behavior (more information, see appendix A-1). DBI2 focuses on developing advanced brain-computer interfaces to restore lost functions in patients with neurological disorders. UMC Utrecht participates in both projects, contributing its expertise in brain research and clinical applications.

5. **Personal grants: 10 Veni; 5 Vidi; 3 Vici**
   From 2019-2024, ten researchers were honored with a Veni grant, five with a Vidi grant, and three with a Vici grant. All research fit well within the focus of the strategic program Brain. Some examples: stem cell therapy as treatment for neonatal brain damage (Cora Nijboer, Vici); advanced neuroimaging to study brain plasticity (Alex Bhogal; Vidi); the effect of stress on decision making (Frank Meye, Vidi); the effect of the environment in brain tumors invasiveness (Emma van Bodegraven, Veni).

6. **Brain researchers became members of the KNAW and the European Academy**
   Two UMC Utrecht Brain researchers (Leonard van den Berg, 2019; Elly Hol, 2022) became members of the KNAW. The research of Leonard van den Berg combines clinical, genetic, lifestyle, and imaging data to unravel the cause of ALS and motor neuron degeneration. He is the founder of the ALS Center and chair of the European Network to Cure ALS (ENCALS). Elly Hol was recognized for her pioneering research on glial cells and their relation to brain diseases, such as brain tumors and epilepsy. Furthermore, she strongly supports female researchers in their careers. Also, Elly Hol and Jeroen Pasterkamp were selected as members of the European Academy (Academia Europaea).

**7. PREMSTEM project was granted by EU Horizon 2020**

In 2020, the PREMSTEM project was honored with a grant within the EU Horizon 2020 research and innovation program. The study aims to develop new regenerative therapies for brain injuries in preterm babies. The therapies are focusing on using mesenchymal stem cells, administered through, among others, nasal drops, to promote neurodevelopment and repair. The goal of the project is to improve quality of life for affected children and reduce long-term problems, such as cerebral palsy.

**8. Two educational prizes**

Two of our researchers have been awarded with the Hijmans van den Bergh educational prize. Geert Ramakers and Rahul Pandit were honored for their outstanding educational skills and integration of current research into the bachelor's, master's, and PhD (bio)medical curricula of the next generation of neuroscientists. Rahul has, due to his international background, an eye for supporting minorities, whereas Geert was praised for his talent to provide students with a complete vision of study route possibilities.

## Appendix D - Key outputs or activities aimed at a professional of wider audience

1. **ALS research wins Klokhuis Science Award**
   In 2021, UMC Utrecht researchers Marion Sommers-Spijkerman and Anita Beelen won the Klokhuis Science Award for their project "My father has ALS, what now?". This award, presented by the educational children's program 'Het Klokhuis', recognizes research that is interesting and relevant to children aged nine to twelve years. Their project focuses on providing support and information to children whose parents have been diagnosed with amyotrophic lateral sclerosis (ALS), aiming to help them understand and cope with the disease's impact on their families. The recognition highlights the importance of addressing the needs of young caregivers in medical research.

2. **Three outreach events with New Scientist**
   To give back to society and increase transparency around publicly funded research, the UMC Utrecht Brain Center partnered with *New Scientist* to organize a major outreach event titled *New Scientist LIVE - Hersenziekten* at TivoliVredenburg in 2020, 2022, and 2024. Several brain scientists offered a glimpse into their fascinating research and the innovative neuro-technologies of the future. The event was sold out three times and was part of the 'Knowledge and Debate' program, highlighting the interest of society for this topic.

3. **Utrecht Brain Conference: where academia meets industry**
   Every two years, the Brain program organizes the Utrecht Brain Conference. The goal of the conference is to unite brain researchers and industry professionals to promote public-private partnership. Every edition, the conference focuses on a specific topic. So far, we have covered 'neuro-oncology and brain disease product development' (2019), 'neuroimaging and neuroanatomy' (2022), and 'early life brain development' (2024).

4. **Lectures at various editions of the Betweter Festival**
   The Betweter Festival is an annual event where science and creativity meet, connecting researchers with the public through interactive talks and experiments. UMC Utrecht Brain Center researchers have contributed to several editions in the past years. In 2019, Jeroen Dudink explored how sleep impacts life. In 2021, Tanja Nijboer conducted a virtual reality experiment on brain injury games, while Frank Meye talked about the link between stress and poor eating habits. That year, Floortje Scheepers also challenged the audience to think critically about the traditional mental health approaches. In 2022, Sarah Durston delved into the mysteries of human consciousness, discussing how meditation, yoga, and psychedelics can alter our understanding of the mind. In 2023, Max van den Boom explained how fast the brain processes information and in the 2024 edition, Jim van Os advocated for a renewed focus on meaning in mental healthcare. Through our contributions to the Betweter Festival, we open up our research to the public, fostering dialogue, transparency, and trust in science.

5. **Contribution to 3FM Serious Request 'Glazen Huis' for ALS**
   In 2023, 3FM Serious Request dedicated its annual 'Glazen Huis' campaign to raising funds for Stichting ALS Nederland. From December 17 to 24, three 3FM DJs were locked in a glass house, playing song requests in exchange for donations. This edition raised around €7.5 million, supporting ALS research and providing essential tools for patients. Beyond fundraising, the event significantly increased awareness about ALS, highlighting the urgent need for better treatments and support for those affected. Many of the UMC Utrecht researchers working on ALS participated, from giving live interviews in the 'Glazen Huis' to making videos explaining their research. This large-scale outreach event brought national attention to the fight against ALS.

6. **Book informing how to cope with a brain tumor**
   Anne Luteijn, nursing specialist at the Neurology & Neurosurgery department, contributed to a book "Zullen we samen...?' with a collection of open, moving, and educational stories from patients with a brain tumor, their loved ones, and caregivers. The aim of this book is to inform, comfort, and inspire people as well as to break taboos and start conversations about living with a brain tumor. The book is a great example of existential treatment (e.g. exploring fundamental life questions) which is part of the neuro-oncological care we provide. The book is distributed in hospices and hospitals but can also be purchased.

# Strategic Program Cancer

Self-evaluation report 2019-2024

# Strategic Program Cancer

## 1 - Mission, governance, and main research topics

Cancer is acknowledged to be one of the most complex diseases, involving a variety of factors including intracellular processes, tissue-specific mechanisms, and tumor microenvironmental influences that contribute to its origin and dissemination. Cancer is the second leading cause of death globally and the major cause of death in the Netherlands. **The mission** of the Strategic Program Cancer is to be a world-leading, cross-disciplinary, platform for research and innovation with the ultimate goal of improving the outcome of those at risk or affected with cancer. To fulfill this mission, we focus on innovations in fundamental, translational, clinical, and applied sciences that are connected in the so-called innovation cycle. This innovation cycle covers the whole patient journey – from prevention, early diagnosis, individualized treatment to supportive and palliative care. Multi- and interdisciplinary collaboration within and outside UMC Utrecht is essential to advance research at all levels.

Our **Research strategy** is focused on **three main themes, each with two topics** and closely connected to the main UMC Utrecht strategy, 'Connecting Worlds'.

| Cancer Themes | Cancer Topics | Alignment to the UMC Utrecht Connecting Worlds strategy |
|---|---|---|
| 1. Molecular and cellular science & therapy | • Molecular science of cancer<br>• Immune- and cellular therapies | Molecular science & therapy<br>Biofabrication & disease modelling |
| 2. Risk Stratification for individualized interventions | • Prevention & prediction<br>• Survivorship & palliation | Molecular science & therapy<br>Healthy living |
| 3. Image science & image guided therapies | • Image guided therapies<br>• Minimal invasive techniques | Image guided interventions |

A multi- and cross-disciplinary interaction between the scientific topics and the subsequent translation in patient care is established through the clinical Tumor working groups. Vice versa, questions from the Tumor working groups feed the research performed by the various research groups, thus maintaining the innovation cycle. At a local level, cancer research greatly benefits from Utrecht Cancer, a unique collaboration at Utrecht Science Park between five public partners that was launched in October 2024. The regional network with the surrounding teaching hospitals, called ONCOMID, supports regional collaborative cancer care in various disciplines and is also partner in clinical research. Our (inter-)national collaborations are presented in the appendix.

### Governance

The UMC Utrecht Cancer community currently consists of:

- More than 1000 researchers from seven UMC Utrecht divisions contributing to the Strategic Program Cancer.
- 82 Cancer-related research groups (UMC Utrecht research website)
- 80 professors (32 primary Cancer, 17 secondary Cancer, 31 external professors; 36% female).
- 61 associate professors (31% female) and 10 clinical scientists (40% female).
- Assistant professors, postdocs, PhD candidates, and support research staff.

The Program is led by a General Board with representatives from each of the themes:

Elsken van der Wall, chair
Erna Erdtsieck-Ernste, manager

**Theme 1**
Susanne Lens
Jurgen Kuball

**Theme 2**
Sjoerd Elias
Gerlof Valk, vice-chair

**Theme 3**
Nico van den Berg
Jeroen Hagendoorn

The General Board is supported by a management assistant, a dedicated communication manager, two grant officers, and a clinical trial specialist. Junior representatives of the OncoCareer Board join the regular biweekly meeting of the Board once every two months. Three advisory boards have been installed for interaction and advice: 1) management of the divisions, 2) heads of (cancer) departments, and 3) three advocates for patients.
Every two months the chair of the Board meets with the Board of Directors of the Princess Máxima Children's Oncology Center (PMC) as well as the Antoni van Leeuwenhoek Hospital/Netherlands Cancer Institute to discuss collaborative research strategy and talent development.

## 2 - Concise reflection on program-specific recommendations from the previous evaluation

*Recommendation 1*
**Overall strategy: the program would benefit from more specifically defined targets (i.e. needs more detail) and better coordination with UMCU's vision at research and alignment with the broader UMC Utrecht strategy.**
We continued to reinforce our overall strategy and definition of our research and innovation profile. As indicated in our research strategy, we focus on three main themes each with two main topics, which are linked to the UMC Utrecht 'Connecting Worlds' Strategy. In order to strengthen our (inter-)national position, our themes are heavily involved in large national and international programs (see annexes).

*Recommendation 2*
**Viability strategic planning: The Translational Program, capitalizing on the organoid technology in concert with strong genomic approaches, can become a true goldmine for the UMCU Cancer program. This is a pretty unique set-up, difficult to copy for any institute. Strong features include genomic and proteomic technology and the presence of the PMC and Hubrecht Institute on campus.**
- The Utrecht organoid technology platform (U-PORT) is transformed into a national platform (N-PORT).
- Merck KGaA's acquisition of HUB organoids technology aims to accelerate drug development.
- Utrecht Science Park (USP) hosts a unique mix of public and private partners offering an ideal environment for new cancer research initiatives and collaborations, now represented by Utrecht Cancer.

*Recommendation 3*
**Global trends: The SWOT analysis and the discussions of the committee members with PIs in the program provided a good picture of strengths and weaknesses. Elements that were missing related to broader global trends in cancer research and how UMCU Cancer relates to them.**
Our current research strategy aligns with the recently published IHE report 'Comparator Report on Cancer in Europe 2025', where the areas have been identified that will dominate cancer research in the coming five years. This includes e.g. cell-based & immune therapies, radioligand based interventions, AI-guidance in diagnostics & precision medicine, RWD & Survivorship.

*Recommendation 4*
**Strengthen coordination within and across divisions: This should ensure that best practices, for example related to ICT and data management, are shared and not developed in parallel.**
Across divisions we innovated on sustainability of organoid technology, physics, clinical trial support, and AI for our research, care, and education:
- Start of a UMC Utrecht broad open innovation platform for treating patients faster and more effectively using the latest minimally invasive techniques. (IMAGINE; Chair: Prof Nico van den Berg).

- Clinical research has been strengthened:
  - Broad informed consent, implemented in the radiotherapy department (Prof. Lenny Verkooijen)
  - Methodology and new trial methods e.g. trial within cohorts design (Prof. Lenny Verkooijen, Prof. Miriam Koopman, Prof. Anne May, Dr. Peter van de Ven, Dr. Marijke Kars, Dr. Sjoerd Elias, Dr. Ewoud Schuit).
  - Transition from HIX (Electronic health record) to the new application 'standard content HIX' with ample implementation of research questionnaires (Dr. Carla Pieterman).
  - Funding Tool to support clinical researchers in their budget negotiations with industry.
- 3AI: 3AI refers to Data, Research, and Implementation in AI. Five Health AI labs have been installed (involved cancer PIs: Prof. Nico van den Berg, Prof. Paul van Diest, Prof. Jeroen de Ridder, Prof. Karijn Suijkerbuijk, Prof. Roel Vermeulen). Examples: implementation of AI algorithms in radiology and radiotherapy (Dr. Veldhuis, Dr. Alessandro Sbrizzi, Dr. Fast), in pathology (Prof. Paul van Diest, Dr. Carmen van Dooijeweert) and development of AI in education (Dr. Wilbert Bartels, Dr. Maud Verhoef-Jurgens).

*Recommendation 5*

**Career and talent management: Concerns were raised with respect to the lack of tenure-track policies, and the requirements for career advancement are undefined and left to individual divisions. The need to recruit and retain top-level scientists will be important and require sufficient financial support. A major threat is the erosion of research capacity in the clinical setting (helping with trials, nurse support, imaging support). To ensure that human capital (i.e. researchers and PhD candidates) is appropriately employed we ensured the following advancements:**

- In 2019 we initiated the OncoCareer Board, a team of young cancer scientists, mainly junior Postdocs, in order to identify the needs of junior (temporary) scientific staff to guide them in their career. From 2022 (after COVID-19) onwards representatives of this board join our Daily Board meetings on a regular basis.
- In 2021, a clinical scientist profile was created to enable doctors to lead research projects (minimal 0,4 FTE). Currently, 10 clinical scientists are appointed in Cancer. In 2021 we started live streamed 'UHD' lectures for newly appointed associate professors.
- The new career profiles, developed by the Research Office, were implemented: eight Experimental, seven Clinical, one Valorization and six Methodology & Technology researchers (no Educational researchers).
- As of 2022 a yearly PhD-event is organized focusing on general topics such as 'Burn-out', 'Diversity in Career paths', and 'How to deal with AI'.
- Members of the Strategic Program Cancer are heavily involved in the various related PhD-programs of the Graduate School of Life Science of Utrecht University, such as CTO, Epidemiology, Imago etc.
- In 2023 we implemented three dedicated Phase I/II research nurses on additional budget from the government (Sectorgelden), one with a dedicated cancer profile.

*Recommendation 6*

**Research support office (RSO): was reported as insufficient (with respect to grants, a tech office, and research support) and should be strengthened.**

The RSO has improved/professionalized significantly over the past five years. Two dedicated grant officers have been assigned to the Strategic Program Cancer (specialization in EU policy and agenda and National grants). This has contributed to our successes in acquiring major grants/funding, including National Growth Funds, European Horizon and IHI grants, implementation of NWO-Large research infrastructures and a public-private NWO Long-term partnership grant.

*Recommendation 7*

**Lack of dedicated budget and decision making: the research program has no dedicated research budget in place. Lack of transparency of the decision-making process within the divisions of how research money is allocated is a concern.**

A new organizational governance will be implemented as of January 1, 2026, that should support the research strategy of the UMC Utrecht by combining financial means with scientific strategic execution.

## 3 - Main research accomplishments in the period 2019-2024

### MOLECULAR & CELLULAR SCIENCE AND THERAPY

**TOPIC MOLECULAR SCIENCE OF CANCER – clinical translation of knowledge from organoid technology**
**Drug-repurposing screen Colon Cancer:** A drug-repurposing library is used to screen patient-derived organoids of colorectal cancer (CRC). A microscopy-based screen accurately scores drug-induced cell killing of 414 putative anti-cancer drugs. One of these drugs, vinorelbine, is consistently independent of RAS mutational status. Its combination with EGFR/MEK inhibition induces apoptosis at all stages of the cell cycle and shows tolerability and effective anti-tumor activity in vivo, setting the basis for a clinical trial to treat patients with metastatic RAS-mutant CRC.

**Urinoids as a model for Bladder Cancer:** A recent study from the UMC Utrecht demonstrated that bladder cancer organoids can be cultured directly from urine. Researchers have established 12 so-called urinoid lines from 22 patients. These urinoids serve as a non-invasive platform that advances precision medicine in bladder cancer. They facilitate detailed study of tumor pathogenesis, allow for longitudinal monitoring of drug responses, and support therapy adaptation.

**TOPIC IMMUNE- AND CELLULAR THERAPIES – model systems and target discovery in immuno-oncology**
**Multiplex Tissue Imaging:** The tumor microenvironment is a complex ecosystem containing various cell types, such as immune cells, fibroblasts, and endothelial cells, which interact with the tumor cells. In recent decades, the cancer research field has gained insight into the cellular subtypes that are involved in tumor microenvironment heterogeneity. Functional interactions between cytotoxic immune cells and their tumor targets are central to anti-cancer immunity. Identifying proteins in these intercellular communication events is essential for next generation immunotherapy drug discovery. Spatial omics developed at the Center of Molecular Medicine of the UMC Utrecht and combined with other high-end technologies are applied to characterize intercellular communication dynamics between interacting cells. This enables antigen and target discovery for cell therapy through immune cell mediated killing.

**Immune organoid interaction models** allow us to assess the impact of the immune system / immune modulatory drugs on solid cancers. In Utrecht, BEHAV3D has been developed to study the dynamic interactions of immune cells and patient cancer organoids by means of imaging and transcriptomics. Recently, models have been refined to study more complex cancer cell and stroma interactions to identify immune modulatory mechanisms and enabled the identification of new immune-associated targets in clinically relevant patient populations. This allows us to develop new models and tools to accelerate CAR-T cell developments within the national growth fund OncodeAccelerator and NextGen-Hightech.

**Novel targets and carrier: γδT cells** display potent cytotoxicity towards a large array of hematological and solid tumors, while preserving normal tissues. Such target cell recognition usually does not rely on specific peptide presentation by HLA molecules, rendering them applicable to a broad patient population. At UMC Utrecht, γδT cell receptor (abbreviated TEGs) has been introduced into the conventional αβT cell with exciting preclinical results. The first reports on the clinical studies show this approach is well tolerated. Further studies on novel designs are even more promising. One company spun out (GADETA) and had a successful exit. Another company is currently being set up.

**Antibody therapy with IgA:** IgA has the unique capacity over IgG to activate neutrophils to kill cancer cells. In the group of Prof. Jeanette Leusen IgA was engineered to meet clinical criteria in stability and half-life. The Spin-off company TigaTx was recently awarded >$35 million to proceed with engineered IgA to GMP production and clinical trials in colon cancer patients with the lead antibody Tiga-001.

## RISK STRATIFICATION FOR INDIVIDUALIZED INTERVENTIONS

### TOPIC PREVENTION & PREDICTION – innovative diagnostics and prediction

**Dense Tissue and Early Breast Neoplasm Screening (DENSE):** Dense breast tissue increases breast cancer risk and hampers detection with mammography. Studies suggest MRI alongside mammography improves cancer detection, but its impact lacks randomized trial scrutiny. The DENSE trial of the UMC Utrecht is pioneering, being the first RCT on supplemental screening for women with dense breasts. It shows MRI's added value for women with dense breasts in Dutch biennial mammography screening: breast cancer is detected in an earlier stage in a cost-effective way. Results have been published in the New England Journal of Medicine, led to adaptation of the EUSOBI guidelines for breast imaging. In the Netherlands, under great societal pressure, Secretary of State Karremans has given the National Institute of Public Health the assignment to investigate how MRI screening can be implemented. At the same time, the government (through ZonMw) has invested in the DENSE-2 trial to investigate potentially cheaper and less cumbersome ways of supplemental screening (abbreviated MRI and contrast-enhanced mammography). The DENSE-2 trial is coordinated by the same UMC Utrecht principal investigators as the DENSE trial.

**AI identification of brain tumor:** Rapid nanopore sequencing combined with a new 'deep-learning algorithm', speeds up the identification of a specific brain tumor type. Yearly, 1,400 adults and 150 children are diagnosed with a tumor in the brain or spinal cord. Surgery is often the first step taken in treatment. Brain tumor characterization normally takes a week, but this new technology, developed by UMC Utrecht and Princess Máxima Center, allows neurosurgeons to adjust their surgical strategies in real-time.

**AI models for breast cancer pathology:** AI has been shown to improve diagnostic accuracy in pathology. In the CONFIDENT-B trial, real-time assistance of an IVD-approved algorithm for detection of breast cancer metastases in sentinel lymph nodes proved to be safe, cost-effective, and fast, thereby significantly reducing pathologists' workload. This algorithm is now being used in daily clinical practice. UMC Utrecht is at the forefront of AI validation and implementation to improve cancer diagnostics and treatment strategies.

### TOPIC SURVIVORSHIP & PALLIATION – impact of exercise on survivorship

**Exercise for women with metastatic breast cancer:** The international consortium conducting the PREFERABLE-EFFECT study has now started a new study, again led by UMC Utrecht. In PREFERABLE II a live-remote exercise intervention training program will be offered. The researchers will evaluate whether training helps the patients to recover faster after curative cancer treatment and suffer less from the side effects of treatment. Targeted side effects include symptoms of fatigue, poor physical fitness, chemotherapy-induced neuropathy (nerve condition, such as tingling hands and feet) as well as elevated levels of distress. If the live-remote intervention will be effective, this will be an additional exercise option for patients with cancer.

## IMAGE SCIENCE & IMAGE GUIDED THERAPY

### TOPIC IMAGE GUIDED THERAPIES – local treatment without surgery

**MRI-radiotherapy (MR-Linac):** Radiotherapy under real-time MRI guidance (MR-Linac) enables a more precise treatment of tumors, for example prostate cancer, resulting in improved tumor control and less side effects. Both contribute to better outcomes and quality of life for patients. The need for surgery is reduced, because this treatment can be done in an outpatient setting. This reduces the need for hospital stay and requires less staff, aiding in reducing health care expenses. Currently, applications in childhood cancer are being investigated.

**High Intensity Focused Ultrasound:** Princess Máxima Center and UMC Utrecht collaborate in the development of MR-guided focused ultrasound (MR-HIFU) in combination with microbubbles in the bloodstream to open the blood-brain barrier in a controlled manner, resulting in improved treatment of intra-cranial tumors. In addition, UMC Utrecht coordinates a trial in which MR-HIFU and radiotherapy are compared for pain palliation in patients

with bone metastases (FURTHER) in breast cancer. New trials are planned for drug delivery in pediatric and adult brain tumors as well as veterinary applications.

**Radionuclide therapeutics:** Theranostics, radioactively labeled medicines, combines diagnosis and therapy. Following confirmation of radionuclide-accumulation in the various tumor-sites in diagnostic exams, a larger amount of a radioactive element is administered for tumor-eradication as actual therapy. Proof-of-concept clinical studies with new tracers for head-and-neck cancer and neuroendocrine tumors. Another promising nuclear therapy, radioembolization, uses radioactively labeled spheres (such as Holmium) that are administered via the hepatic artery for local and internal irradiation of liver cancer or liver metastases, but also in combination with liver surgery.

**TOPIC MINIMAL INVASIVE TECHNIQUES – more precise surgery**

**Robotic surgery:** UMC Utrecht was the first UMC in the Netherlands to employ robotic surgery. Our surgeons have developed numerous robotic programs in the last 25 years and helped implement those nationwide. In a UMC Utrecht study (in collaboration with Amsterdam UMC) the nationwide implementation and outcomes of robotic liver surgery (RLS) in the Netherlands have been evaluated. From 2014 to 2021, the nationwide use of RLS in the Netherlands has increased rapidly with currently one-tenth of all liver resections and one-fourth of all minimally invasive liver resections being performed robotically. The learning curve required at least 33 major RLS procedures. Identification of anatomical structures based on real-time x-ray, echo or optical images, would become the 'Google maps navigation' for surgeons. A comprehensive overview of current literature on the accuracy of anatomy recognition algorithms in intrathoracic and -abdominal surgery showed that this is an upcoming research discipline, but still at its infancy. Larger datasets and methodological guidelines are required to improve accuracy and clinical applicability in future research.

A novel avenue is to navigate even more precisely by integrating image guiding with AI techniques. This study shows that deep learning-based semantic segmentation has the potential for anatomy recognition in RAMIE video frames. The inference time of the algorithm facilitated real-time anatomy recognition. Clinical applicability should be assessed in prospective clinical studies.

## 4 - Specific questions for the research committee

Based on the recommendations of the previous SEP-committee, we have chosen to focus our research in three main themes with two topics each.

1. Does the Committee approve of this research strategy? More specifically: are these the correct focus areas considering our expertise and the future developments in cancer science? Should there be more focus, meaning should we skip certain areas?
2. Does the Committee consider the current Cancer program inviting and attractive for talents? What would be your recommendation to strengthen the attractiveness?
3. How does the Committee consider our profiling, especially Utrecht Cancer, considering the national and international competition?

# Appendix

## Appendix A - Key scientific outputs

### MOLECULAR & CELLULAR SCIENCE AND THERAPY

1. Bollen, Y., Stelloo, E., Van Leenen, P., Van Den Bos, M., Ponsioen, B., Lu, B., Van Roosmalen, M. J., Bolhaqueiro, A. C. F., Kimberley, C., Mossner, M., Cross, W. C. H., Besselink, N. J. M., Van Der Roest, B., Boymans, S., Oost, K. C., De Vries, S. G., Rehmann, H., Cuppen, E., Lens, S. M. A., . . . Snippert, H. J. G. (2021). **Reconstructing single-cell karyotype alterations in colorectal cancer identifies punctuated and gradual diversification patterns.** *Nature Genetics, 53*(8), 1187–1195. https://doi.org/10.1038/s41588-021-00891-2
Citations: 40, open access
In this study the evolution of aneuploidy (abnormal chromosome number) in colorectal cancer was examined using patient-derived tumor organoids (PDTOs). Live-cell imaging was combined with single-cell whole-genome sequencing to track and link chromosome mis-segregation events to chromosomal copy number alterations (CNAs) across cell generations. The study reveals that CNAs arise frequently, with both gradual and punctuated patterns of diversification. A link between specific mitotic errors and CNA types was revealed, and although many CNAs have a negative impact on fitness, some cells with novel karyotypes remain proliferative. Finally, the findings in organoids are validated by examining CNAs in fresh colorectal cancer biopsies.

2. Kimman, T., Slomp, A., Martens, A., Grabherr, S., Li, S., Van Diest, E., Meeldijk, J., Kuball, J., Minnema, M. C., Eldering, E., Bovenschen, N., Sebestyén, Z., & Peperzak, V. (2023). **Serpin B9 controls tumor cell killing by CAR T cells.** *Journal For ImmunoTherapy Of Cancer, 11*(3), e006364. https://doi.org/10.1136/jitc-2022-006364
Citations: 13, open access
This study investigates the role of serpin B9 in mediating resistance to chimeric antigen receptor (CAR) T-cell therapy. Serpin B9 inhibits granzyme B (GrB), a key effector molecule in T-cell-mediated cytotoxicity. The researchers found that enforced serpin B9 expression in melanoma cells reduces GrB sensitivity. Serpin B9 is uniformly expressed in B-cell lymphomas, especially diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). Silencing serpin B9 in DLBCL cells enhanced their sensitivity to CAR T-cells, while serpin B9-high CLL cells resisted killing. These findings suggest that targeting serpin B9 could improve CAR T-cell therapy outcomes.

3. Gui, T., Fleming, C., Manzato, C., Bourgeois, B., Sirati, N., Heuer, J., Papadionysiou, I., Van Montfort, D. I., Van Gijzen, M., Smits, L. M., Burgering, B. M., Madl, T., & Schuijers, J. (2023). **Targeted perturbation of signaling-driven condensates.** *Molecular Cell, 83*(22), 4141-4157.e11. https://doi.org/10.1016/j.molcel.2023.10.023
Citations: 6, open access
Biomolecular condensates are essential for cell organization, but their behavior is not well understood. The authors find that disrupting WNT-activated β-catenin condensates can block oncogenic signaling. Using a live-cell condensate imaging method in human cancer cells they identify specific peptides that prevent β-catenin from forming condensates on DNA. This disruption stops β-catenin's role in activating genes and slows down colorectal cancer cell growth. These peptides work by blocking the usual protein domain interactions that drive condensate formation. Based on these principles, the authors also successfully design peptides that affect YAP and TAZ condensates in the Hippo pathway. Their 'monomer saturation' model proposes that short interacting peptides can target and block harmful gene activation in diseases. **Patent:** Schuijers J., Burgering B.M.T., Fleming C.F., Gui T. 'Live cell imaging platform for condensates'. PCT/NL2022/050596

4. Van Soest, D. M. K., Polderman, P. E., Toom, W. T. F. D., Keijer, J. P., Van Roosmalen, M. J., Leyten, T. M. F., Lehmann, J., Zwakenberg, S., De Henau, S., Van Boxtel, R., Burgering, B. M. T., & Dansen, T. B. (2024). **Mitochondrial H2O2 release does not directly cause damage to chromosomal DNA.** *Nature Communications, 15*(1). https://doi.org/10.1038/s41467-024-47008-x
Citations: 19, open access
This study challenges the dogma that mitochondrial release of reactive oxygen species (ROS in the form of hydrogen peroxide/ H2O2) damages DNA in the cell nucleus. The authors developed an innovative way to induce localized H2O2 production in cells and find that only nuclear H2O2 causes DNA damage, mutations, and a p53-dependent cell cycle arrest. Conversely, H2O2 released by mitochondria, even in large amounts, does not directly damage nuclear DNA. Thus, H2O2 from mitochondria is unlikely to contribute significantly to DNA mutations, cancer development and aging.

5. Hernández-López, P., Van Diest, E., Brazda, P., Heijhuurs, S., Meringa, A., Van Heyningen, L. H., Riillo, C., Schwenzel, C., Zintchenko, M., Johanna, I., Nicolasen, M. J. T., Cleven, A., Kluiver, T. A., Millen, R., Zheng, J., Karaiskaki, F., Straetemans, T., Clevers, H., De Bree, R., … Kuball, J. (2023). **Dual targeting of cancer metabolome and stress antigens affects transcriptomic heterogeneity and efficacy of engineered T cells.** *Nature Immunology, 25*(1), 88–101. https://doi.org/10.1038/s41590-023-01665-0
Citations: 6 (patent family)
This study demonstrates that γδ T-cell receptor (γδ TCR)-based cancer targeting can be enhanced by incorporating chimeric co-receptors that target cancer-associated stress antigens. Engineered αβ T-cells expressing γδ TCR (TEGs) with chimeras improved tumor cell killing, proliferation, and persistence. The NKG2D-CD28WT chimera controlled liquid tumors, while the NKG2D-4-1BBCD28TM chimera extended persistence and enhanced control of both liquid and solid tumors. The CD277-targeting 103-4-1BB chimera showed the best outcomes, eradicating both tumor types. Single-cell transcriptomics revealed that these chimeras reprogram TEGs via NF-κB, enhancing proliferation, cytotoxicity, and reducing exhaustion, particularly shaping CD8+ TEGs into a proliferative state. **Patent**: submitted 2024 and Spin off company in set up

## RISK STRATIFICATION FOR INDIVIDUALIZED INTERVENTIONS

6. Bakker, M. F., De Lange, S. V., Pijnappel, R. M., Mann, R. M., Peeters, P. H., Monninkhof, E. M., Emaus, M. J., Loo, C. E., Bisschops, R. H., Lobbes, M. B., De Jong, M. D., Duvivier, K. M., Veltman, J., Karssemeijer, N., De Koning, H. J., Van Diest, P. J., Mali, W. P., Van Den Bosch, M. A., Veldhuis, W. B., & Van Gils, C. H. (2019). **Supplemental MRI Screening for Women with Extremely Dense Breast Tissue.** *New England Journal Of Medicine, 381*(22), 2091–2102. https://doi.org/10.1056/nejmoa1903986
Citations: 471
This Dutch multicenter randomized trial evaluated supplemental MRI screening for women aged 50–75 with extremely dense breast tissue and normal mammograms. Among 40,373 participants, the MRI-invitation group showed a significantly lower interval cancer rate (2.5 vs. 5.0 per 1000 screenings; 0.8 in those who actually underwent MRI screening after invitation) over two years compared to mammography-only screening. The MRI-detection rate was 16.5 per 1000 screenings, with a false-positive rate of 79.8 per 1000. About 59% accepted MRI invitations and adverse events were rare (0.1%). The study concluded that MRI screening effectively reduces interval cancers in this high-risk group, though it carries higher false-positive rates. Improvement of screening for women with dense breasts, who since the beginning of breast cancer screening are at disadvantage because sensitivity of mammography is much lower in this group, whereas at the same time their breast cancer risk is higher. MRI screening for extremely dense breasts has been included in the European EUSOBI guidelines. Based on the results of this trial women ask for notification of breast density (which is a federal law in the USA, but not in all other countries) and for supplemental screening.

7. Kopper, O., De Witte, C. J., Lõhmussaar, K., Valle-Inclan, J. E., Hami, N., Kester, L., Balgobind, A. V., Korving, J., Proost, N., Begthel, H., Van Wijk, L. M., Revilla, S. A., Theeuwsen, R., Van de Ven, M., Van Roosmalen, M. J., Ponsioen, B., Ho, V. W. H., Neel, B. G., Bosse, T., ... Clevers, H. (2019). **An organoid platform for ovarian cancer captures intra- and interpatient heterogeneity.** *Nature Medicine, 25*(5), 838–849. https://doi.org/10.1038/s41591-019-0422-6
Citations: 580
This study presents a protocol for efficiently deriving and expanding ovarian cancer (OC) organoids, enabling the creation of 56 organoid lines from 32 patients representing all major OC subtypes. These organoids closely replicate the histological and genomic features of the original tumors, reflecting intra- and interpatient heterogeneity. They can be genetically modified and used in drug screening assays to assess responses to platinum-based chemotherapy, including the development of chemoresistance in recurrent disease. Additionally, OC organoids can be xenografted for in vivo drug-sensitivity testing, demonstrating their potential for research and personalized medicine applications.
*Note: the first author of this paper is not from the UMC Utrecht, yet the clinical contribution of the UMC Utrecht researchers to this paper was essential.*

8. Smits, F. J., Henry, A. C., Besselink, M. G., Busch, O. R., Van Eijck, C. H., Arntz, M., Bollen, T. L., Van Delden, O. M., Van Den Heuvel, D., Van Der Leij, C., Van Lienden, K. P., Moelker, A., Bonsing, B. A., Rinkes, I. H. B., Bosscha, K., Van Dam, R. M., Derksen, W. J. M., Dulk, M. D., Festen, S., ... Zeh, H. (2022). **Algorithm-based care versus usual care for the early recognition and management of complications after pancreatic resection in the Netherlands: an open-label, nationwide, stepped-wedge cluster-randomised trial.** *The Lancet, 399*(10338), 1867–1875. https://doi.org/10.1016/s0140-6736(22)00182-9
Citations: 99
The algorithm for the early recognition and minimally invasive management of complications after pancreatic resection considerably improved clinical outcomes compared with usual care. This difference included an approximate 50% reduction in mortality at 90 days. This provision will considerably improve clinical outcomes and decrease the failure to rescue rate, which is an international priority in surgical practice and among policy makers. Our simple to use and low-cost algorithm, and the method for its implementation, can be modified easily for use in other types of surgery.

9. Van Dooijeweert, C., Flach, R. N., Ter Hoeve, N. D., Vreuls, C. P. H., Goldschmeding, R., Freund, J. E., Pham, P., Nguyen, T. Q., Van Der Wall, E., Frederix, G. W. J., Stathonikos, N., & Van Diest, P. J. (2024). **Clinical implementation of artificial-intelligence-assisted detection of breast cancer metastases in sentinel lymph nodes: the CONFIDENT-B single-center, non-randomized clinical trial.** *Nature Cancer, 5*(8), 1195–1205. https://doi.org/10.1038/s43018-024-00788-z
Citations: 7, open access
This clinical trial evaluated the effectiveness of an AI-assisted workflow for detecting breast cancer metastases in sentinel lymph nodes (SNs). Conducted from September 2022 to May 2023, 190 SN specimens were divided into intervention (AI-assisted) and control arms. Expert pathologists assessed digital images of SN specimens, with AI assistance in the intervention arm. Results showed a significant reduction in the use of immunohistochemistry (IHC) and cost savings of approximately €3,000. Additionally, AI assistance improved sensitivity by up to 30% and reduced assessment time, demonstrating the potential for cost and time savings while maintaining diagnostic safety.

10. Hiensch, A. E., Depenbusch, J., Schmidt, M. E., Monninkhof, E. M., Pelaez, M., Clauss, D., Gunasekara, N., Zimmer, P., Belloso, J., Trevaskis, M., Rundqvist, H., Wiskemann, J., Müller, J., Sweegers, M. G., Fremd, C., Altena, R., Gorecki, M., Bijlsma, R., Van Leeuwen-Snoeks, L., ... May, A. M. (2024). **Supervised, structured and individualized exercise in metastatic breast cancer: a randomized controlled trial.** *Nature Medicine, 30*(10), 2957–2966. https://doi.org/10.1038/s41591-024-03143-y
Citations: 8, open access
The PREFERABLE-EFFECT trial evaluated the impact of a nine-month supervised exercise program on physical fatigue and health-related quality of life (HRQOL) in 357 patients with metastatic breast cancer (MBC) across Europe and Australia. Compared to usual care, exercise significantly reduced physical fatigue and improved HRQOL at six months, with moderate effect sizes. The intervention was safe, with only two unrelated adverse events. These findings highlight the value of incorporating supervised exercise into supportive care for MBC patients to alleviate fatigue and enhance overall quality of life. Related publication.

## IMAGE SCIENCE & IMAGE GUIDED THERAPY

11. Braat, A. J. A. T., Bruijnen, R. C. G., Van Rooij, R., Braat, M. N. G. J. A., Wessels, F. J., Van Leeuwaarde, R. S., Van Treijen, M. J. C., De Herder, W. W., Hofland, J., Tesselaar, M. E. T., De Jong, H. W. A. M., & Lam, M. G. E. H. (2020). **Additional holmium-166 radioembolisation after lutetium-177-dotatate in patients with neuroendocrine tumour liver metastases (HEPAR PLuS): a single-centre, single-arm, open-label, phase 2 study.** *The Lancet Oncology, 21*(4), 561–570. https://doi.org/10.1016/s1470-2045(20)30027-9
Citations: 52

In patients with metastatic neuroendocrine neoplasms, the liver is often affected, impacting prognosis and survival. Peptide receptor radionuclide therapy (PRRT) can extend progression-free survival. The HEPAR PLuS study investigated the safety and efficacy of adding holmium-166 (166Ho) radio-embolisation after PRRT in patients with metastatic liver neuroendocrine neoplasms. Thirty-one patients received 166Ho-radioembolisation within 20 weeks after four PRRT cycles. At three months, 43% of patients showed an objective response in the treated liver volume. Common adverse events included abdominal pain, increased γ-glutamyl transpeptidase, and lymphocytopenia. One fatal treatment-related event occurred. The study concluded that 166Ho-radioembolisation is safe and effective, warranting further investigation in a randomized controlled trial.

12. Van Der Veen, A., Brenkman, H. J. F., Seesing, M. F. J., Haverkamp, L., Luyer, M. D. P., Nieuwenhuijzen, G. A. P., Stoot, J. H. M. B., Tegels, J. J. W., Wijnhoven, B. P. L., Lagarde, S. M., De Steur, W. O., Hartgrink, H. H., Kouwenhoven, E. A., Wassenaar, E. B., Draaisma, W. A., Gisbertz, S. S., Van Der Peet, D. L., May, A. M., Ruurda, J. P., ... Van Laarhoven, H. W. M. (2021). **Laparoscopic Versus Open Gastrectomy for Gastric Cancer (LOGICA): A Multicenter Randomized Clinical Trial.** *Journal Of Clinical Oncology, 39*(9), 978–989. https://doi.org/10.1200/jco.20.01540
Citations: 159

This multicenter randomized clinical trial was conducted as the oncological efficacy and safety of laparoscopic gastrectomy were under debate. This publication showed that postoperative complications and oncological efficacy did not differ between laparoscopic- and open gastrectomy in a Western population with predominantly advanced gastric cancer. In addition, median hospital stay also did not differ between both groups. For laparoscopic gastrectomy, the median blood loss was less, whereas the mean operating time was longer, as compared to open gastrectomy.

13. Kontaxis, C., Woodhead, P. L., Bol, G. H., Lagendijk, J. J. W., & Raaymakers, B. W. (2020). **Proof-of-concept delivery of intensity modulated arc therapy on the Elekta Unity 1.5 T MR-linac**. *Physics in Medicine And Biology, 66*(4), 04LT01. https://doi.org/10.1088/1361-6560/abd66d
Citations: 23, open access

This paper demonstrated the technical feasibility of arc therapy on the Elekta 1.5T MR-Linac for faster and more conformal radiation therapy. Radiation dose and MRI performance were evaluated and shown to be passing the clinical acceptance criteria. This work demonstrates the dynamic capacities of the system and de-risked new delivery modes for the MR-Linac system. Currently, in 2025, this delivery mode is being investigated by the manufacturer of the MR-Linac.

14. Vermeulen, C., Pagès-Gallego, M., Kester, L., Kranendonk, M. E. G., Wesseling, P., Verburg, N., De Witt Hamer, P., Kooi, E. J., Dankmeijer, L., Van Der Lugt, J., Van Baarsen, K., Hoving, E. W., Tops, B. B. J., & De Ridder, J. (2023). **Ultra-fast deep-learned CNS tumour classification during surgery.** *Nature, 622*(7984), 842–849. https://doi.org/10.1038/s41586-023-06615-2
Citations: 92, open access

Central nervous system tumors, especially in children, are highly lethal. Primary treatment involves neurosurgical resection, balancing tumor removal with minimizing neurological damage. Surgeons often lack precise tumor type knowledge before surgery, relying on preoperative imaging and intraoperative histological analysis, which can be inconclusive. We developed Sturgeon, a transfer-learned neural network, using rapid nanopore sequencing for intraoperative molecular subclassification. Sturgeon accurately diagnosed 45 out of 50 retrospectively sequenced samples within 40 minutes. In 25 real-time surgeries, it achieved correct diagnoses in 18 cases within 90 minutes. In conclusion, machine-learned diagnosis based on low-cost intraoperative sequencing can assist neurosurgical decision-making, potentially preventing neurological comorbidity and avoiding additional surgeries.

15. Teunissen, F. R., Willigenburg, T., Tree, A. C., Hall, W. A., Choi, S. L., Choudhury, A., Christodouleas, J. P., De Boer, J. C., De Groot-Van Breugel, E. N., Kerkmeijer, L. G., Pos, F. J., Schytte, T., Vesprini, D., Verkooijen, H. M., & Van Der Voort van Zyp, J. R. (2022). **Magnetic Resonance-Guided Adaptive Radiation Therapy for Prostate Cancer: The First Results from the MOMENTUM study—An International Registry for the Evidence-Based Introduction of Magnetic Resonance-Guided Adaptive Radiation Therapy.** *Practical Radiation Oncology, 13*(3), e261–e269. https://doi.org/10.1016/j.prro.2022.09.007
Citations: 22, open access
This study reports on the 12-month outcomes of patients with localized prostate cancer treated with MR-guided radiation therapy (MRgRT) using a 1.5T MR-Linac system. The study included 425 patients, with follow-ups at 3, 6, and 12 months. Results showed a significant decline in prostate-specific antigen levels and a peak in genitourinary and gastrointestinal toxicity at three months. For patients without androgen deprivation therapy (ADT), there was a significant increase in erectile dysfunction at 12 months. The findings suggest that MRgRT is effective and safe, providing valuable data for patient education and future studies.

16. Meulen, L. W. T., Bogie, R. M. M., Siersema, P. D., Winkens, B., Vlug, M. S., Wolfhagen, F. H. J., Baven-Pronk, M., Van Der Voorn, M., Schwartz, M. P., Vogelaar, L., De Vos Tot Nederveen Cappel, W. H., Seerden, T. C. J., Hazen, W. L., Schrauwen, R. W. M., Herrero, L. A., Schreuder, R. M., Van Nunen, A. B., Stoop, E., De Bruin, G. J., ... Moons, L. M. G. (2024). **Standardised training for endoscopic mucosal resection of large non-pedunculated colorectal polyps to reduce recurrence (*STAR-LNPCP study): a multicentre cluster randomised trial.** *Gut, 73*(5), 741–750. https://doi.org/10.1136/gutjnl-2023-330020
Citations: 6
Endoscopic mucosal resection (EMR) is effective for large (≥20 mm) non-pedunculated colorectal polyps (LNPCPs) but has a high early recurrence rate. A multicenter cluster randomized trial evaluated whether standardized EMR training could reduce recurrence rates in Dutch community hospitals. 59 endoscopists were assigned to either an intervention group (e-learning and hands-on training) or a control group. Among 1412 LNPCPs, recurrence rates were lower in the intervention group (13% vs 25%) with similar complication rates. The benefit was significant for 20-40 mm LNPCPs but less evident for ≥40 mm LNPCPs. The study supports a national training program for endoscopists performing EMR on large LNPCPs.

# Appendix B - Most important collaborations

## GENERAL

**Research collaboration agreement UMC Utrecht – Princess Máxima Center** (2019-2022)
*Prof. Jurgen Kuball, Prof. Marnix Lam, Prof. Chrit Moonen*

**Project 1:** Ultrasound in high-grade glioma: crossing the blood-brain-barrier,
**Project 2:** Immunotherapy: target identification across different tumor types
**Project 3:** Theranostics: image-guided personalized cancer care.

**Scientific: Real world data cohorts**
*Prof. Miriam Koopman, Prof. Lenny Verkooijen, Prof. Karijn Suijkerbuijk, Prof. Gerlof Valk, Prof. Roel Vermeulen, Dr. Richard Meijer, Dr. Rhode Bijlsma.*

At UMC Utrecht, real-world data cohorts of nearly all types of cancer are available, with a strong focus on evaluating innovative systemic (drug)- and technological (image guided) treatments. Some of these cohorts include adolescent and young adult (AYA) cancer survivors, Dutch multiple endocrine neoplasia (MEN), MRI-Linac (Momentum), colorectal cancer (PLCRC), melanoma (UNICIT), breast cancer (UMBRELLA) cohorts, Prospective Bladder Cancer Infrastructure (proBCI), European Prospective Investigation Into Cancer and Nutrition (EPIC) and real world data of patients in palliative phase (Sympal database).

**Utrecht Life Sciences**
*Public partners: University Utrecht, University Medical Center Utrecht, Hubrecht Institute, Princess Máxima Center, Westerdijk Institute, University of Applied Sciences.*

Utrecht Life Sciences connects public and private partners at the Utrecht Science Park for interdisciplinary research, valorization, and education. This network of approximately 6000 Life Sciences researchers is organized in six interconnected thematic communities. With their interdisciplinary research they create impact on major societal health challenges for future generations, e.g. Utrecht Cancer.

**TU Eindhoven, Wageningen University, Utrecht University, University Medical center Utrecht (EWUU)**
*Prof. Carl Moons, Prof. Nico van den Berg, Prof. Jelle Ruurda.*

Artificial Intelligence: The goal of the four partners is to develop new AI techniques that enable better and greater impact in the field of prevention and care. Think of developing better techniques for early diagnosis or creating the possibility to tailor medicines to individual patients. Together the partners have the data, technology, knowledge, and facilities to realize these solutions. The alliance facilitates existing collaborations and promotes new initiatives by bringing together involved researchers.

## MOLECULAR & CELLULAR SCIENCE AND THERAPY

**Oncode Institute**
*Prof. Boudewijn Burgering, Prof. Susanne Lens, Prof. Madelon Maurice, Prof. Linde Meyaard (I&I), Prof. Jeroen de Ridder, Dr. Maria Rodriguez Colman, Dr. Hugo Snippert.*

Oncode Institute unites over 800 researchers at 13 partnered research institutes across the Netherlands, all dedicated to achieving the same mission: to drive breakthrough discoveries and accelerate their translation into new diagnostics and treatments for cancer patients.

### European Lobular Breast Cancer Consortium (ELBCC)

*Prof. Patrick Derksen, Prof. Paul van Diest, Prof. Elsken van der Wall, Prof. Sabine Linn.*

The intention of this consortium is to create a platform that brings together basic scientists, translational researchers, and clinical experts in the field of Invasive Lobular Breast Cancer. The ultimate goal is to better understand, diagnose, and treat this form of recurrent breast cancer to improve the prognosis of women who suffer from it. Invasive Lobular Breast Cancer (ILC) affects 25,000 patients in Europe every year and thus has a significant social impact.

### National Growth Fund: RegmedXB: Utrecht - Innovation Center for Advanced Therapies (ICAT)

*Prof. Jurgen Kuball, Dr. Joost van Duin, Dr. Trudy Straetemans, Dr. Zolt Sebestyen, Prof. Jos Malda, Prof. Marianne Verhaar*

ICAT aims to improve and accelerate the translation of research into healthcare solutions by bringing together all relevant expertise and infrastructure for the development of regenerative treatments, Advanced Therapy Medicinal Products (ATMPs) including cell therapy, and disease models. ICAT will also provide the infrastructures for part of additional National Funds like Oncode-PACT and NXTGEN HIGHTECH. Spin off grants are e.g. https://www.certainty-virtualtwin.eu, https://ctgct.si/en/partners/

### Allogeneic stem cell transplantation for patients with hematological myeloid malignancies.

*Dr. Moniek de Witte together with EBMT, HOVON*

As a board member of the Dutch SCT working party and a participant in the Myeloproliferative Neoplasm (MPN) working group, as well as in two European Society for Blood and Marrow Transplantation (EBMT) committees, she is actively engaged in shaping the future of SCT treatment through the development of national and international guidelines, contributing to retrospective studies, and leading collaborative research initiatives. Additionally, her work with HOVON includes delivering annual updates on MPN, supporting the integration of the latest research into clinical practice.

## RISK STRATIFICATION FOR INDIVIDUALIZED INTERVENTIONS

### ENDO-ERN and FORCE

*Prof. Gerlof Valk, Prof. Hanneke van Santen, Dr. Rachel van Leeuwaarde*
*Various European (ENDO-ERN) and National partners, including Dutch Federation of Cancer Patient Organizations (FORCE)*

ENDO-ERN: This European Reference Network on rare endocrine conditions aims to improve access to high-quality healthcare for patients with rare hormonal disorders. For this purpose, the education of Reference Centers (RCs) across Europe will be supported and developed to ensure that the best possible care is made available to patients locally. Due to the intrinsic features of hormone action and the genetic basis of some conditions, the consequences of endocrine conditions are usually not restricted to a single organ, but instead overlap in multiple organs.

FORCE aims to improve knowledge about rare cancers by collecting patient data and materials to create a 'data and biobank' for scientific research. Rare cancers affect one in five cancer patients, who have lower survival rates compared to those with common cancers. Challenges include late detection due to unrecognized symptoms, fewer treatment options, difficulties in research due to limited patient data, and fewer fellow sufferers. FORCE's efforts address these issues to enhance understanding and treatment of rare cancers.

### GENAYA - 'A national database of GENome data of Adolescent and Young Adult cancers'.

*Dr. Rhode Bijlsma*

Each year, around 3900 young adults (AYAs) aged 18-39 in the Netherlands are diagnosed with cancer. They receive multidisciplinary care from specialists to ensure optimal treatment outcomes. Complete DNA testing of tumors can refine diagnoses and reveal new treatment options. Research shows genetic characteristics of tumors vary by age, highlighting the need for age-specific treatment paths for AYAs. More scientific research is needed to understand these differences. Hartwig is building this database with anonymous genetic data and treatment histories with 35 participating hospitals to support this effort.

### Institute for Preventive Health - oncology (Eindhoven, Wageningen, Utrecht)

*Prof. Roel Vermeulen (director), Prof. Anne May.*

The Institute for Preventive Health focuses on evidence-based, innovative solutions to support healthy lifestyles through multidisciplinary research. They unite professionals from various fields to explore the intersection of lifestyle, environment, and technology. Their research is organized into four themes:

- Healthy Start: Identifying effective lifestyle interventions for disadvantaged youth.
- Preserving Health: Investigating environmental changes and lifestyle interventions to help adults maintain good health, especially in vulnerable neighborhoods.
- Living with Disease: Improving the quality of life for people with chronic diseases.
- Health@Home: Assessing the effectiveness of technology tools in helping older adults live independently at home.

### OPTIMISM (KWF-funded database)

*dr. Everlien de Graaf*

OPTIMISM Implementation of symptom monitoring (SM) can help reduce complaints. SM involves patients indicating how severe their symptoms are felt, allowing healthcare providers to quickly intervene. Benefits are seen in fewer complaints, fewer visits to the emergency room, and fewer hospital admissions, improving overall quality of life. Collaboration with Dr. Jurrian van der Werf (IKNL) and dr. Rudolf Fehrmann (University Medical Center Groningen).

### National Program Palliative Care (NPPZ), National Institute Palliative Care (PZNL), Academic Workplace for Primary Palliative Care (AWPZ).

*Prof. Saskia Teunissen, Dr. Marijke Kars, Dr. Everlien de Graaf, Dr. Matthew Grant*

NPPZ The UMC Utrecht method 'palliative reasoning' and the validated PROM 'Utrecht Symptom Diary-multidimensional' are integrated in the Quality Framework and palliative care specific guidelines (quality framework). The Advance Care Planning method IMPACT is integrated in the palliative care guideline for children. AWPZ aims to achieve future-proof individualized care in the context of remaining survival and to understand the complexity of palliation to develop scientifically substantiated appropriate care available in the palliative phase.

Partners involved: Health Center de Bilt, Academic Hospice Demeter, Leidsche Rijn Julius Health Centers, Johannes Hospice Vleuten, the regional palliative care networks (Consortium Septet), and Utrecht University of Applied Sciences. Dutch Ministry of Health, Welfare and Sport.

## IMAGE SCIENCE & IMAGE GUIDED THERAPY

### Hybrid MRI radiotherapy system: MRI-Linac

*Prof. Bas Raaymakers, Dr. Martin Fast*

The department of Radiotherapy of UMC Utrecht collaborates with Elekta, a manufacturer of radiotherapy equipment and treatment control software, for decades. The joint aim is to progress image guided radiotherapy to deliver more precise treatments that yield better tumor control with fewer complications. A successful and very concrete outcome of this collaboration is the hybrid MRI radiotherapy system. This was proposed, designed, built, and clinically introduced within this collaboration. This system is sold as the Elekta 1.5 T Unity system since 2018, with over 100 systems treating patients all over the globe. This system has brought MRI in the daily adaptive treatment, and we are continuously raising the bar with better and quicker treatment workflows to enable real-time adaptive treatments in which patient motion is entirely mitigated. The benefits of adaptive treatments are explored also for conebeam CT guided treatments. Together with Elekta we are investigating and developing new workflows for adaptive treatments to enable daily, and where possible real-time adaptive treatments for all radiotherapy patients.

### MR-STAT collaboration (2020)

*Dr. Alessandro Sbrizzi, Prof. Nico van den Berg*

During ISMRM 2020, UMC Utrecht and Philips kicked off a research partnership to advance precision diagnosis through breakthrough quantitative MRI technology MR-STAT. The exclusive, multi-year research partnership will establish a global clinical research network with the aim of fully commercializing the technology, which has initially been developed here at UMC Utrecht.

MR-STAT is a paradigm shift in MR, relying on a new smart acquisition scheme and machine-assisted reconstruction. MR-STAT delivers multiple quantitative MR parameters in a single fast scan, and represents a significant advance in MR tissue classification, fueling big data algorithms, and AI-enabled integrated diagnostic solutions.

### University Medical Center Utrecht Named Focused Ultrasound Center of Excellence (2021)

*Prof. Chrit Moonen, Prof. Karijn Suijkerbuijk, Dr. Clemens Bos, Dr. Roel Deckers*

UMC Utrecht has been recognized for their innovative vision and for increasing synergy among image-guided therapies – incorporating focused ultrasound, nuclear medicine, radiotherapy, radiology, and oncology into a single division. By recognizing UMC Utrecht as a Center of Excellence and supporting their work, the Foundation will expedite the translation of image-guided focused ultrasound treatment modalities to the clinic. Current projects include using focused ultrasound to treat bone metastases, breast cancer, and uterine fibroids. The team is also exploring focused ultrasound for targeted drug delivery, immunomodulation, and opening the blood-brain barrier.

### UGIRA the upper GI international Robot association

*Prof. Richard van Hilligersberg, Prof. Jelle Ruurda*

UGIRA aims to advance robotic esophageal and gastric surgery globally. Its key focuses include creating training programs with experienced surgeons, ensuring safe implementation through proctoring, conducting international studies via a web-based registry, and establishing standardized guidelines for robotic procedures. The society will serve as a platform to set up training pathways, appoint proctors worldwide, and support collaborative research on robotic esophagogastric surgery. The guidelines will cover robotic surgery for both benign and malignant conditions, excluding bariatric procedures.

# Appendix C - Grants and prizes

## GENERAL

### Personal EU & KWF Young Investigator grants

- Dr. Aniek Janssen (ERC Starting 2019), Prof. Hugo de Jong (ERC PoC 2020), Prof. Hugo Snippert (ERC Consolidator 2023), Prof. Jeroen de Ridder (ERC Consolidator 2023), Dr. Aniek Janssen (ERC Consolidator 2024).
- NWO Veni: 2x 2019, 2x 2020, 3x 2023. NWO Vidi: 1x 2019, 4x 2020, 2x 2023. NWO Vici: 1x 2019, 1x 2024.
- KWF YIG: 1x 2021, 3x 2022, 1x 2023

## MOLECULAR & CELLULAR SCIENCE AND THERAPY

### Prize: Ammodo Science Award and Organ-on-chip Award Health Holland

*Dr. Hugo Snippert (2024, 2019)*

Recent scientific research has advanced our understanding of cancer and therapies, but fundamental questions remain. Snippert's work focuses on the behavior of tumor cells, using microscopy and molecular genetics. He developed the 'confetti' mouse model to study stem cell competition and applied microscopy to organoids. This revealed new insights into tumor diversity and drug responses. Additionally, Snippert is studying the transition of benign tumors to malignant ones using mini-organs, aiming to predict tumor behavior for personalized treatments in the future.

### KWF Grant – DARE-NL

*Dr. Trudy Straetemans (2022)*

DARE-NL (5300 k€ consortium budget) is a collaboration among Dutch academic developers of Advanced Therapy Medicinal Products (ATMPs), aiming to revolutionize cancer treatment. Funded by the Dutch Cancer Society, it seeks to accelerate clinical testing and ensure timely access to new therapies. DARE-NL connects scientists, clinicians, pharmacists, regulatory agencies, and patient advocates, centralizing knowledge and harmonizing protocols. This initiative focuses on developing raw materials, biologics, assays, and technologies, while also facilitating implementation and patient outreach. The ultimate goal is to improve survival, quality of life, and cure rates for cancer patients.

### National Growth Fund (NGF) – OncodeAccelerator

*Prof. Miriam Koopman, Dr. Jeanine Roodhart, Prof. Jurgen Kuball, Prof. Jeanette Leusen, Prof. Onno Kranenburg, Dr. Sjoerd Elias, Dr. Peter van de Ven (2022)*

OncodeAccelerator aims to collaboratively optimize and accelerate the development of new cancer therapies for the benefit of patients of all ages. We do this by integrating patient data and materials, including patient-derived organoid models at early stages in preclinical therapy development. Our world-class toolbox of state-of-the-art technologies is available through Demonstrator Projects to anyone globally that has a target of interest, and will result in more effective, personalized cancer therapies. This will bring us closer to our overarching goal: to outsmart cancer and impact lives. Oncode Accelerator has six coordinating partners: Leiden University, Leiden University Medical Center, the Netherlands Cancer Institute, Princess Máxima Center, UMC Utrecht, and the Oncode Accelerator Foundation. NGF will invest 325 million euros in supporting the initial eight years

## RISK STRATIFICATION FOR INDIVIDUALIZED INTERVENTIONS

### Prize: Dutch Applied-AI awards

*Prof. Jeroen de Ridder (2024)*

Prize for the development of Sturgeon. Sturgeon, developed in partnership with CMM and Oncode Institute, enables fast brain tumor classification necessary to help brain surgeons with real-time decision-making.

### KWF Grant: The development of the Corsano EndoWatch

*Prof. Hanneke van Santen (2022)*

Children with hypothalamic tumors often survive but suffer from poor quality of life due to hormonal imbalances, leading to issues like overweight and chronic fatigue. In collaboration (1.083 k€) with TU/e, PMC and Corsano Health, a smartwatch will be developed to act as an 'external hypothalamus'. This device will monitor body temperature, stress, sleep, daily activity, and sodium concentration, helping to detect and address hormonal imbalances quickly. This innovation aims to improve the quality of life for children with hypothalamic tumors.

### Horizon-EU Grant: PREFERABLE-II

*Prof. Anne May, Dr. Anouk Hiensch, Prof. Elsken van der Wall (2022)*

The PREFERABLE-II consortium (6.011 k€): Personalised Exercise-Oncology for improvement of supportive care: a super umbrella trial to demonstrate the (cost)effectiveness of live-remote exercise in cancer survivors.
Grant to develop and evaluate a personalized and live-remote exercise program for cancer patients. With this new intervention, they aim to resolve current problems in the implementation of exercise programs. Existing exercise interventions are designed in a one-size fits all fashion and leave only limited room for personalization. This program is going to design an exercise program that improves overall quality of life and one out of four major long-term side effects: fatigue, low physical fitness, neuropathy or psychological symptoms, in order to personalize the program to the survivor's main side effect. Spin off grants on fatigue and metastatic breast cancer and on the effect of yoga in women with a breast cancer diagnosis who suffer from joint pain and stiffness caused by hormone therapy.

### Horizon-EU Grant: ARTILLERY

*Prof. Lenny Verkooijen, Dr. Sophie Gernaat (2022)*

The ARTILLERY project, funded by Horizon Europe (6.000 k€), aims to develop AI systems to automatically detect chronic disease risks in breast cancer patients using these routine CT-images. This could improve quality of life and survival rates. Breast cancer is the most common cancer in women worldwide, with survivors at higher risk of chronic diseases like cardiovascular disease, weight gain, and osteoporosis. This increased risk is due to treatment-induced toxicity and shared risk factors such as overweight and lack of exercise. Radiotherapy CT-images, used for planning, contain valuable information on disease risk factors but are not systematically assessed.

### KWF Grant: REDUCE

*Dr. Lodewijk Brosens (2024)*

REDUCE investigates prognostic molecular markers to optimize and reduce the individual follow-up of operated neuroendocrine tumors of the pancreas (1.606 k€). Each year, about 200 people are diagnosed with pancreatic neuroendocrine tumors (pNETs). While most are surgically removed and don't recur, 20-40% are malignant and do recur. The study aims to identify genetic markers (ATRX, DAXX, menin, DNA changes) to predict tumor behavior, potentially reducing unnecessary follow-ups. By examining stored tissue from 800 pNETs, researchers will develop a model to predict recurrence. The goal is to tailor follow-up plans, reducing anxiety and medical interventions for patients with benign tumors, while ensuring safety and quality of life improvements.

## IMAGE SCIENCE & IMAGE GUIDED THERAPY

**Prize: The William and Francis Fry Award, International Society for Therapeutic Ultrasound (ISTU).**
*Prof. Chrit Moonen (2029)*

This lifetime achievement award is given annually to an individual who has made outstanding contributions to therapeutic ultrasound. Potential recipients of this award are nominated by the Organizing Committee of each annual ISTU symposium and ratified by the Board.

**Prize: Klaas Breur Award ESTRO**
*Prof. Jan Lagendijk (2022)*

This special tribute from the European Society for Radiotherapy and Oncology has been awarded due to the role Lagendijk played in the development of the MR-Linac. He is considered a key figure in the invention of this device, which brings a 'revolution in radiotherapy'. UMC Utrecht is the place where the MR-Linac was developed and a pioneer in applying the new technique. Meanwhile, the third MR-Linac has been installed in Utrecht, and the devices are in use in various radiotherapy departments worldwide.

**KWF Grants: PET scans with FAPI tracer**
*Prof. Onno Kranenburg, Dr. Sjoerd Elias, Prof. Marnix Lam, Dr. Jeroen Hagendoorn, Dr. Bart de Keizer, Dr. Miangela Lacle, Dr. Jeanine Roodhart (2023)*

Two grants of translational research with high potential clinical impact (383 k€ and 594 k€). Based on tumor biological insights we identified FAP as a promising biomarker for two clinical challenges: 1) to better assess colorectal cancer peritoneal disease extent, and 2) to detect the unfavorable and heterogenous CMS4 colorectal cancer subtype. In these two clinical studies, FAP expression is visualized with a FAPI-PET scan, which we were the first to use in the Netherlands. Both studies are highly interdisciplinary with extensive imaging-molecular tissue comparisons. Expected outcomes include the proof of concept of using a FAPI-PET for better pre-surgical assessment of peritoneal disease extent and CMS4 load, thereby enabling better medical decisions in the future

**IHI-Europe Grant: Illuminate**
*Prof. Dennis Klomp (2024)*

The ILLUMINATE project aims to improve the use of Lutetium-177-PSMA (Lu-177-PSMA) in treating advanced prostate cancer. Lu-177-PSMA targets prostate-specific membrane antigen (PSMA) on cancer cells, delivering radioactive Lutetium-177 to these cells. While it helps most patients, about 30% do not benefit. The project focuses on identifying those who will respond best to the treatment and improving manufacturing methods to prevent shortages, ensuring more effective and widespread use (total budget 21.000 k€; UMC Utrecht: 2.500 k€ EU funding)

**NWO-LTP Award: IMAGINE**
*Prof. Nico van den Berg, Prof. Lenny Verkooijen, Dr. Maarten van Kouwen (2024)*

Integrating advanced imaging technology into cancer care allows for more sophisticated, targeted, and effective treatment. So-called image-guided interventions (IGI) have a similar impact that GPS navigation has had on mobility. The interventions have minimal side effects and ensure rapid recovery, reducing dependence on scarce healthcare resources. The IMAGINE project realizes new treatment options and applies new organizational models. An important part of the project is the involvement of all stakeholders (total budget 54.000 k€).

**ZEGG Grant: CROSSROADS**
*Dr. Leon Moons (2024)*

The research is aimed at determining whether follow-up or complementary surgery after local excision of a (pT1) colon carcinoma is best for the patient. The goal is to investigate in a multicenter, observational de-escalation study whether the implementation of intensive follow-up and the omission of complementary surgery – through a guideline revision – is indeed safe for patients with less than a 15% chance of lymph node metastases. Additionally, for the intermediate-risk group (15-25% chance of LNM), it will be investigated whether follow-up is also an option and if it can be done safely (total budget 1.800 k€).

# Appendix D - Key outputs or activities aimed at a professional of wider audience

## GENERAL

### Patents & Spin-offs (2019-2024)

37 Cancer-related patents have been filed in the period of 2019-2024. A list of these patents (confidential) can be shown during the side visit. The following Cancer-related spin-off companies have been established:

- Nanocell Therapeutics, Prof. Raymond Schiffelers (2020)
- LaigoBio, Prof. Madelon Maurice (2022)

### UHD-Lectures (2020-2024, started during COVID-19)

32 lectures published on our Strategic Program Cancer YouTube channel
If one of our researchers is appointed as Associate Professor, he or she can give a lecture, which is recorded in the studio of the UMC Utrecht. A separate pitch is recorded for social media. The pitch and lecture can be used to disseminate the research subject and to make students enthusiastic.

### KWF tours (2022-2024, cancelled during COVID-19)

Volunteers and heritage keepers (groups of 12-50 participants) are given 2-5 times yearly a tour at UMC Utrecht to see the latest innovations in prevention, early diagnosis, treatment, and survivorship care.

### OncoMid meetings (from 2021 onwards)

Within Oncomid, specialists from different hospitals work together per tumor type in thirteen multidisciplinary expert teams (tumor working groups). The form and degree of collaboration vary per expert team. In addition to the weekly clinical discussions, most expert teams meet twice a year to share knowledge. This can be in the areas of treatments, research, latest developments, care pathways, and sharing indicators. Some expert teams are supported by IKNL by providing data. To involve the general public Oncomid organizes regular lectures and a yearly bike event (Staying active during and after cancer treatment).

### Stakeholder meetings

THINK Utrecht conference (2023): At the conference, various leading scientists will guide you through these innovations and how they will improve cancer care for patients in the future.

UTRECHT CANCER stakeholder dinner (2024): The Utrecht Science Park has hosted a unique combination of knowledge institutions, hospitals, and companies, all within walking distance of each other. During the Walking Dinner, it was shown how the collaboration between these partners significantly contributed to groundbreaking cancer research. This continuous improvement enhances the outlook for children, adults, and pets with cancer.

## MOLECULAR & CELLULAR SCIENCE AND THERAPY

### National public interviews

*Dr. Peter de Keizer (2029-2024)*

The aim of Peter de Keizer's group is to unravel the molecular mechanisms that cause cells to become senescent and to identify how these cells drive aging and age-related diseases. The role of senescence in late-stage therapy-resistant cancer is a major component of this research. The research has a strong translational component and a spearpoint of the group is to develop methods to target the deleterious effects of senescent and senescent-like cancer cells, for instance by eliminating them altogether.

Examples of interviews:
2019: www.oncologie.nu/nieuws/kanker-stoppen-door-senescente-cellen-op-te-ruimen
2020: www.nieuweleiders.nl/in-gesprek-met/peter-de-keizer/ouderdom
2024: www.telegraaf.nl/nieuws/1893746542/wetenschappers-willen-verouderingsproces-tegenhouden-over-vijftien-jaar-is-het-mogelijk-onze-biologische-klok-terug-te-draaien (national newspaper)

### Podcast Cell and gene therapy

*Dr. Trudy Straetemans (2021)*

Cancer is one of the world's most devastating diseases. Its treatment can be punishing and have several awful side effects. Fortunately, scientists have a better idea now of how to treat it, and the experimental techniques being used now may be commonplace in the future. At least, that's what many experts think. Host Rudy van Beurden has invited three guests for this podcast, who are experts in this field: Jacqueline Barry, Chief Clinical Officer at CT Catapult; Erik Manting, CEO at Immunicum AB and Trudy Straetemans, Assistant Professor at UMC Utrecht.

### National Geographic article - Sturgeon, AI tool for brain tumors

*Prof. Jeroen de Ridder, Prof. Eelco Hoving (2024)*

Meet Sturgeon, the AI tool that helps doctors identify brain tumors faster than ever. In the medical field, being fast, efficient, and correct can be the difference between life and death. This game-changing tool is helping cancer researchers and doctors save lives. A profile image of two men; they are standing near each other. The lighting is heavily blue with a slight glow around their faces. Bioinformatics professor Jeroen de Ridder and molecular pathologist Bastiaan Tops developed AI that expedites the diagnosis of brain tumors while patients' skulls are open during surgery. By Chris Gayomali, October 15, 2024

## RISK STRATIFICATION FOR INDIVIDUALIZED INTERVENTIONS

### Training program for healthcare professionals on comprehensible communication

*Prof. Margreet Ausems (2019-2021)*

Interventions are developed to make genetic research more accessible to patients with cancer and their families. She does so together with Pharos, the national expertise center for health inequalities, among others. For instance, she and her team initiated the erfo4all project and she developed a training program for oncological surgeons and nursing specialists in breast cancer care. The program consisted of a short online module and group training in the hospital. This involved using an actress to practice situations from everyday practice and then explain hereditary screening to patients in understandable language. Participants also learned how to check whether patients understood their explanations. The 'bespreekwijzer erfelijkheidsonderzoek bij borstkanker' was nominated (top 3) for the ZorgVoorZorg award.

### Local and National broadcasts and papers and FMS science & innovation award: screening Dense breasts

*Prof. Carla van Gils, Prof. Wouter Veldhuis (2021-2024)*

Radiologists want women with dense breast tissue to receive an additional MRI scan during breast cancer screening as soon as possible. They don't want to wait for new research results, as previous studies have shown significant health benefits and lives saved. The Dutch Society for Radiology (NVvR) emphasizes this in response to a recent article in the Volkskrant. 'This method truly works and is cost-effective', says Wouter Veldhuis of the NVvR. He believes extra screening should start immediately. 'Women are dying because we are not taking action'. Examples of regional and national publicity.

### e-Learning Molecular diagnostics in oncology

*Prof Miriam Koopman, Prof. Margreet Ausems (2023)*

Prof. Margreet Ausems (clinical geneticist) and Prof. Miriam Koopman (medical oncology) both UMC Utrecht, participated in the creation of e-learning 'Molecular diagnostics in oncology'. Based on a number of cases, experts are discussing the results of genetic research in the tumor. In addition, a number of mini lectures have been made. Through the case discussions and the mini-lectures, the participants learn the importance of molecular diagnostics

and how this can be used when starting a treatment for patients with (metastatic) cancer and when there's reason to refer a patient to a clinical geneticist. Molecular biology has an increasingly important role in oncology. Analysis of abnormalities in the DNA can provide insight into the diagnosis, prognosis, and treatment of cancer.

### Advanced colorectal neoplasia risk assessment tool to inform IBD surveillance

*Prof. Bas Oldenburg, Dr. Sjoerd Elias (2024)*

The risk-assessment tool enables advanced colorectal neoplasia risk assessment at multiple follow-up time points throughout the patient journey by integrating changes in patient characteristics and risk factors over time. Such dynamic modelling is critical in IBD, where the risk of a CRN evolves as disease duration and severity progress. The model was developed at the UMC Utrecht using data from six large, diverse cohorts across Canada, the Netherlands, the UK, and the USA. The model was published in 2024 and will be made available online and incorporated in the 2025 British Society of Gastroenterology Guidelines on Colorectal Surveillance in Inflammatory Bowel Disease (in press).

## IMAGE SCIENCE & IMAGE GUIDED THERAPY

### Pediatric radiotherapy

*Dr. Geert Janssens (2019)*

Dutch broadcast Waar gaat het geld van Maarten van der Weijden naartoe? Maarten van der Weijden supports pediatric radiotherapy with his action. He successfully completed his Elfstedenzwemtocht, a 195-kilometer swim to raise money for cancer research, with the total amount raised reaching 3.9 million euros. One of the supported research projects is 'Optimal treatment for children with metastatic cancer' by researchers Enrica Seravalli, Petra Kroon, and Geert Janssens

### Invited guest speaker Ministry of VWS information council

*Prof. Lenny Verkooijen (2020)*

During the Digital Meet Up, 'Learning from Implementation', organized by the Ministry of Health's Information Council, Lenny Verkooijen advocates for learning from every patient. Researchers are rapidly developing innovative cancer treatments, but it often takes time to see if these theoretical benefits translate into real patient advantages. Verkooijen's team in the Imaging and Oncology division developed a method to evaluate these innovations more efficiently and implement them faster if effective. She proposes an 'innovation clinic' to ensure no valuable information is lost, contributing to continuous patient outcome improvement as intended by the strategic Cancer research program. Video of the lecture (in Dutch) can be shared upon request.

### National broadcast MAX – MRI Linac radiation treatment for pancreas cancer

*Prof. Martijn Intven (2023)*

Cancer can sometimes strike unexpectedly, as it did for patient Ronald, who inherited a rare form of cancer through a genetic mutation. Treatment with the MR-Linac at UMC Utrecht provided a solution: precise high-dose radiation has made surgery unnecessary for now. Together with Prof. Martijn Intven he shares his remarkable story on the TV program Tijd voor MAX.

### Hospital of the Future

*Prof. Jelle Ruurda, Prof. Dennis Klomp, Dr. Jannie Wijnen, Prof. Nico van den Berg (2023)*

Guided tour for general public in 10 groups of 12 people. Demonstrations: VR-training and robotic surgery, Augmented reality during surgery, Telemonitoring wearables, MRI (self scan, quiet scan, quick scan), metabolic MRI, sustainability during surgery.

### Self check testicles

*Prof. Richard Meijer (2024)*

Men often discover abnormalities in their testicles themselves, for example, while showering. However, few go to the doctor. This is unfortunate because early detection can prevent intensive treatment for diseases like testicular cancer. To reduce discomfort and promote openness about testicular cancer, in a podcast and news article doctors at UMC Utrecht are urging men to perform self-examinations: 'check your testicles'.

# Strategic Program Child Health

Self-evaluation report 2019-2024

# Strategic Program Child Health

## 1 - Mission, governance, and main research topics

### Mission

The strategic program Child Health is an integrated framework for child-centered interdisciplinary research, aligning patients, clinicians, investigators, and resources in order to fill gaps to improve the lives of children with complex chronic diseases during childhood and thereafter.

### Governance and activities

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 (CF). He has been successful in leading his own research group and adheres to a holistic approach in clinical care. The chair is supported by a program manager, drs. Carolien Huizinga, a management assistant, Mariska Keizer, and a communication advisor, Renske Huijsing.

The Child Health Program consists of researchers working in 57 research groups. Currently, the Child Health Program has about 48 Principal Investigators (PIs) who are not professors and 38 PIs who are professors. They cover both the basic and clinical science fields as well as psychology, physiotherapy, ethics, and nursing. Additionally, we have 31 associate professors, 43 assistant professors and 120 PhD students. As a program, we collaborate with several divisions in the UMC Utrecht: Woman and Baby, Pediatrics, Images & Oncology, Heart & Lungs, Surgical Specialties, Brain, Internal Medicine & Dermatology, Julius Center (for Health Sciences and Primary Care), Laboratories, Pharmacy & Biomedical Genetics, and Anesthesiology, Intensive Care & Emergency Medicine. On campus, we strongly interact with the Princess Máxima Center and Dynamics of Youth program of Utrecht University to conduct innovative research that improves the treatment of diseases and quality of life and reduces damage to health of children and adolescents.

The Child Health Program has a program committee, consisting of senior scientists who are active in the program and represent both basic and clinical science.

Last five years there has been rejuvenation in the composition of the program committee. The current committee and program activities are shown in the images below.

### Program committee

**dChildren**
Prof. dr. C.K. van der Ent

**dWoman&Baby**
Prof. dr. M.J.N.L. Benders
Prof. dr. A.T. Lely

**DIGD**
Prof. dr. R.E.G. Schutgens

**dLAB**
Prof. dr. J.P. van Tintelen

**Vice-dean Education**
Prof. dr. A.B.J. Prakken

**Princess Máxima Center**
Prof. dr. L.H.J. Looijenga

**Prg Manager**
Drs. C.S.M. Huizinga

**Program commitee Child Health**

- Determining and monitoring the strategy of the Child Health Program
- Initiation and stimulation of new theme groups and symposia
- Career management: fleet review (vlootschouw), academic positions talent programs, coaching interviews with (principal) investigators
- Governance 030-Lab
- Links with Dynamics of Youth
- Marketing and Communication

**PIs Child Health**

- Network meetings about overaching themes, (UHD) lectures and events
- Grant application support
- Booster Grants
- Theme groups: 1) Innovative therapies, 2) Pain, stress & trauma and 3) Inflammation
- Participation in DoY communities
- Summer schools, for example Eureka
- Regular news letters and magazines. For example Be Real.

**Is and PhD's Child Health**

- Network meetings and events in collaboration with the science committee of the WKZ (PhDs). Examples: Next Generation Radio, 030-Lab day, speeddate events, Slimme Gasten, Meet the Professor
- Training
- Tulips
- Summer schools, for example Eureka
- Regular news letters and magazines. For example Be Real.

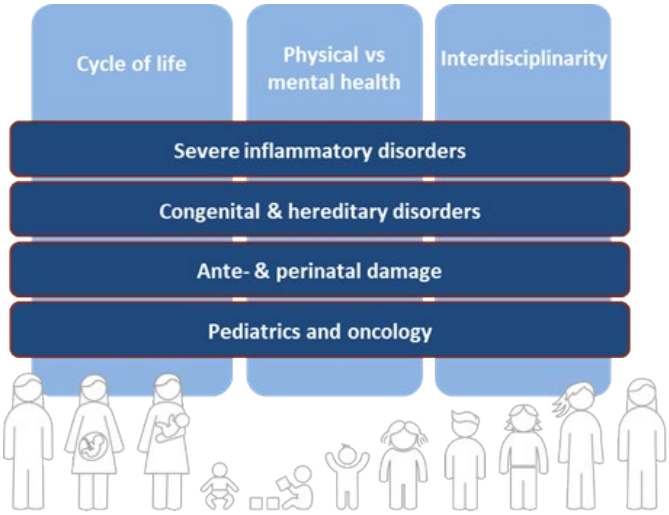
### Main research topics

Choosing an integral approach, the Child Health Program aims to push boundaries with regard to specific disease areas. All diseases in focus of the 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.

The main research topics are:

- Severe inflammatory disorders, like Juvenile Arthritis, and Respiratory Infections
- Congenital and hereditary diseases like cystic fibrosis, and diseases of the liver, kidney and blood
- Ante- and perinatal damage
- Pediatrics and oncology

Although these diseases are diverse, all researchers share the same perspective. They study diseases in a *life cycle perspective, they realize that physical and mental health interact continuously, and they strive for a highly interdisciplinary approach.*



## 2 - Concise reflection on program-specific recommendations from the previous evaluation

Based on the self-evaluation report and site visit in 2019, the program was reviewed as strong and vibrant with notable societal impact. The Child Health Program received some recommendations for the coming years, divided in five action categories:

### Unity of the program

The SEP committee noticed a chance to strengthen the unity of the program by renaming the strategic program to reflect the breadth of the research. We decided to use the subtitle 'Science for Life' more prominently. This subtitle adequately covers research from conception to adulthood and embraces the broad environment – mother, family, society – of the child. In the new organizational structure, the Child Health Program will be integrated into the theme of Mother and Child.

### Public health and prevention

Public health in the Child Health Program is translated as how a diseased child is influenced by their entire environment (family, society, exposome) and how this environment influences (or even creates) diseases in population-based cohorts. It was decided to strengthen research on this topic by starting the 030-Lab, where cohorts with healthy and diseased children are being followed and connected to a learning health care system and preventive lifestyle advice.

### PI criteria

The SEP committee was concerned about inequalities of becoming a PI. Every 1-2 years the Child Health Program committee organizes a review ('vlootschouw') of all PIs, associate professors and assistant professors. Also, annual coaching interviews with all researchers are conducted between members of the program committee and PIs. These coaching interviews are considered very positive and instructive by all involved. Furthermore, 44 researchers involved in the Child Health Program participated in a talent program of the UMC Utrecht, starting from 2022 onwards.

### Life-cycle care

Within the Child Health approach a strong life cycle perspective is adopted in all disease areas. This results in many long-term cohort studies in both diseased and healthy subjects, as well as strong collaborations between medical and social sciences and humanities within the Utrecht Science Park and beyond. Both children and young adults are seen at the 030-Lab, the connection between pediatrics and adult care is strengthened, with the Van Creveldkliniek as an example.

### U-trial infrastructure

In 2022, an adult physician was appointed as U-trialist for Child Health. Besides strengthening the Life Cycle approach, this comes with experience and knowledge about gene therapy trials. This is extremely important in the field of rare diseases in Child Health, such as metabolic diseases, hematology, and Cystic Fibrosis. The U-trialist has contributed to a professionalization of the 030-Lab, with increasing quality and efficiency regarding clinical trials and the start of first-phase gene therapy trials in 2024 as important results.

## 3 - Main research accomplishments in the period 2019-2024

### 1. Severe inflammatory disorders

**Juvenile arthritis** – an innovative biomarker guided multicenter intervention trial in sJIA

In collaboration with pediatric rheumatologists from several Dutch cities, we completed the first biomarker-guided multicenter intervention trial in systemic Juvenile Idiopathic Arthritis (sJIA). This study tested a biomarker-guided taper-and-stop strategy for first-line treatment with anakinra (IL-1 blockade) in new onset sJIA patients. Based on prior translational cohort studies from 2010-2018, which showed significant treatment responses, we focused on IL-18 levels (cut-off 1200 pg/ml) between three and nine months after treatment initiation to determine the timing for tapering and stopping anakinra. Funded by ZonMw, the trial included 65 patients from six academic hospitals between 2018-2022, with a two-year follow-up. The results showed that IL-18 is a valuable biomarker for monitoring disease course and treatment response, aiding decisions on safe tapering and stopping of treatment. Findings were presented at

the European Pediatric Rheumatology Society Meeting (PReS) and the American College for Rheumatology meeting in 2024. A manuscript is in preparation, and two follow-up studies were successfully funded. Additionally, a proposal for a follow-up study with a $2 million grant was recently submitted.

**Respiratory infections** – implementation of new vaccine programs in the Netherlands and worldwide
Our respiratory syncytial virus (RSV) study group had several high impact achievements in society and science. First of all, we contributed to RSV vaccine development used by the ministry of health of the Netherlands and the SAGE working group by WHO. Our burden studies in developing countries showed that RSV causes 25% of life-threatening episodes in infants under two years of age. We contributed to RSV vaccine development (three publications in *New Engl J Med* in 2023/2024). Besides that, the RSV group discovered how the environment shapes our respiratory microbiome (Odendaal Cell 2024). In children with cancer, we showed that two times weekly dosing of micafungin is equivalent to one time daily. The incidence of invasive aspergillus infections in children with acute lymphoblastic leukemia decreased from 5.8% to 1.2%. Besides on RSV, the group was active on e.g. rotavirus and COVID-19. The RIVAR-study on rotavirus vaccination for medical risk infants led to revision of the Dutch Health Council advice on infant rotavirus vaccination in the Netherlands in 2024. Epidemiological studies on COVID-19 directly informed policy decisions during the pandemic on NPIs and vaccination in children.

## 2. Congenital and hereditary diseases

**Cystic Fibrosis** – realizing treatment opportunities for patients with ultrarare genetic variants
The Cystic Fibrosis group was highly successful in bridging the gap between clinic and basic science. After introduction of CFTR-modulator therapy in about 85% of the patients, the group passionately focuses on treatment possibilities for patients with ultrarare variants. The group raised a new company based on fair medicine principles (Fair Therapeutics) to realize effective and accessible treatment in an extremely high cost monopoly market, using the patented intestinal stem cell organoid model, developed at our lab. The UMC Utrecht coordinated the initiative of the European Cystic Fibrosis Society to create access to modulators for patients with ultrarare variants and conducted the CHOICES trial in 11 EU countries, in close collaboration with EU patient organizations and EMA (What is HIT-CF Europe? - HIT CF). The group further supported moving treatment barriers for patients without any protein production by treating the world-first patient with inhaled CFTR-mRNA in lipid nanoparticles and by participating in the world-wide Phase I inhaled CFTR gene-therapy program. Besides the focus on ultrarare genetic variants, the group also impacted patients' lives by initiating prenatal treatment with modulators

**Liver** – personalized gene-correction therapy and organoid based disease modeling
Due to great collaborations at the Utrecht Science Park (teams from the KNAW Ammodo Science Award for Ground breaking Research, from NWA-ORC Nanospresso and the UMCU-TEAmRNA-Award), our researchers developed a personalized gene-correction therapy program based on a modular delivery system for base- and prime editing. The delivery system can be tailored to the specific mutation and the specific patient in an organ-specific context thanks to our organoid infrastructure and improved culturing system (Hepatocyte-like Liver Organoids (HeLLOs)). The latter led to a start-up company HeLLO R&D, which won numerous prizes. Importantly, HeLLO facilitates improved in vitro modeling of metabolic diseases, using for example mass spectrometry based stable isotope flux analyses developed in our group. PIs Fuchs and Jans acted as speaker on >30 occasions, e.g. for the Rolf Zetterström Lecture (Stockholm 2024), a plenary session at the SSIEM (Porto 2024: >2,700 attendees), as keynote speaker (Italian Society of Metabolism and Newborn Screening, Monterosso 2024 and at the Polymer Symposium, Düsseldorf 2022), at the Neuropediatric conference for rare disease (Salzburg, 2024), E-IMD (Porto 2024), United European Gastroenterology (UEG)-week (Copenhagen 2023: >10,000 attendees), the conference on genome medicine (King Faisal Specialist Hospital Riyad 2022), and the European Metabolic Group Conference (Innsbruck 2022).

**Blood** – novel bispecific antibody therapy for rare severe bleeding disorders
In collaboration with Hemab Therapeutics, we have designed and developed a novel treatment (HMB-001, bispecific antibody) for patients with rare, severe bleeding disorders in which treatment options to prevent bleeding have not been available before. Our study was published in Nature Cardiovascular Research, and results have been presented at various international meetings. More importantly, our pre-clinical work has been the starting point of a phase I/II clinical trial (we will be the only participating center in the Netherlands), and a long-term funded collaboration (with Hemab) to develop next generation compounds.

**Kidney** – GeNepher: an innovative data- and biobank for hereditary kidney disease
Our research group established GeNepher, an innovative data- and biobank for hereditary kidney disease that has grown to include over 400 participants. This biobank uniquely combines massively parallel sequencing data with biomaterials, enabling both gene discovery and treatment research. GeNepher has already facilitated breakthrough findings, including the discovery of NEK8 as a new cause of polycystic kidney disease, and the development of KidneyNetwork – a tool that leverages kidney-specific expression data to predict gene function. Our work has fundamentally changed genetic testing in nephrology, leading to national guidelines and establishment of a dedicated multidisciplinary clinic. The impact is evidenced by rapid growth in diagnostic testing (now 1000 samples annually) and the need to expand our clinical team. The biobank's infrastructure allows recontacting participants for research opportunities, making it a valuable resource for national and international collaborations, as demonstrated by the EU Horizon project Theracil (€8M; 470k to UMC Utrecht) and a 2024 Vidi grant.

### 3. Ante- and perinatal damage

**Antenatal** – improving prenatal diagnostics and postnatal care
We coordinated data collection and analysis within the International Network of Obstetric Survey Systems during the COVID-19 pandemic. At the start of the pandemic, no information on the COVID-19 infection in the vulnerable group of pregnant women and their offspring was available regarding prevention, outcomes and management, especially regarding medicine use and maternal vaccination. In 2019, the Health Council called for a study on the value of incorporating the first-trimester scan under the population act for prenatal screening in the Netherlands. This led to the nationwide IMITAS-study coordinated by PIs Bekker (UMC Utrecht) and Haak (LUMC). Within the nationwide TRIDENT-studies the introduction of the Non-Invasive Prenatal Test in the Netherlands was investigated. The UMC Utrecht has established a leading position in digital obstetric care in the Netherlands and internationally through its pioneering work in digital healthcare, such as the development and upscaling of the SAFE@home platform and the home telemonitoring program of the maternal and fetal condition.

**Neonatology / perinatology** – intranasal stem cell therapy for newborns after hypoxic brain injury
Our UMC Utrecht Center of Expertise for Neonatal Neurology developed a novel intranasal mesenchymal stem cell therapy for newborns with hypoxic-ischemic brain injury, successfully translating it from bench to bedside. This led to our first-in-human safety and feasibility study, published in The Lancet Neurology in 2022, cited 75 times and resulting in keynote invitations and collaboration requests. Before our forthcoming long-term outcome publication, we filed a patent on this innovative therapy, anticipating its broader benefits. Building on these achievements, we received a €5 million grant from Zorginstituut Nederland and partners to further test the therapy's efficacy in the upcoming iSTOP-CP study, collaborating with other NICUs and patient organizations. To enhance our impact, we work with partners like the Cerebral Palsy Alliance, University College London (UCL), and experts in our preclinical PREMSTEM-EU-project, including the European Society of Pediatric Research's Special Interest Group on Stem Cell Therapies.

### 4. Pediatrics and oncology

**Pediatrics and oncology** – hypothalamic dysfunction unraveled and treated
In collaboration with international colleagues from the University of Oldenburg in Germany we have developed a hypothalamic clinical score which is now used across the world to better recognize and diagnose hypothalamic dysfunction. With this score and by chairing the European craniopharyngioma group, we are now building large European consortia to improve hypothalamic outcomes for patients with acquired brain damage. Examples of outcomes of these collaborations are the HORIZON GRANT application 2024 (results expected 2025), a 2024 Vici grant, and the international trial with Setmelanotide in which we participate and have included the 2nd most patients of all participating centers. Times are truly changing for patients with hypothalamic dysfunction which is something that we could not imagine ten years ago. The PI of the study was invited to many international conferences to speak about new approaches to hypothalamic dysfunction (e.g. ESPE Liverpool 2024, ECE Stockholm 2024, ISPNO Philadelphia 2024).

### 5. Overarching themes

**Life Cycle & Mental and physical health** – PROactive cohort to identify risk and resilience factors for chronic illness
Children with chronic diseases or severe disorders often face psychosocial and mental health challenges, delays in autonomy, and difficulties participating in society. Both physical and mental health are interconnected, affecting their well-being and that of their families. This theme aims to understand these interactions, identify stressors and

protective factors, and raise awareness of the long-term impacts of chronic illness. It also focuses on developing interventions to improve both physical and mental health outcomes. Establishing long-term cohorts of chronically ill patients, tracking their health across the lifespan, and exchanging data with disease-specific and population cohorts helps identify risk and resilience factors for chronic illness. The PROactive cohort has started in 2016, but underwent professionalization in recruitment, logistics (management of the cohort), data storage, and data exchange between 2019 and 2024. Furthermore, the assessment rounds need a thorough evaluation directed at a more efficient use of questionnaires (generic PROMs for children), more connection to relevant data/parameters and questions from the specific disease cohorts, attention to healthy lifestyle, sensitive periods of life (transition periods), and extension of assessment into adulthood. Alignment with population cohorts (whistler, youth, piama, HBSC) is essential to identify specific risk and resilience factors for chronic illness.

**030-Lab** – 030-Lab as infrastructure for Child Health research

We initiated the 030-Lab, a core facility in the Wilhelmina Children's Hospital where researchers from all disciplines in the UMC Utrecht, Utrecht University, and the Princess Máxima Center work closely together. The goal is to perform innovative research which will improve the treatment of diseases and the quality of life of children and adolescents and to reduce health damage. This core facility consists of a:

- *Innovative trial office:* to support researchers with the design and conduct of studies. There is a strong focus on innovative treatments, like stem cell therapy, mRNA therapy and gene therapy.
- *Child Health Disease Cohort:* a large, diverse and constantly growing cohort in Utrecht that provides both biological and psychosocial data from over 10.000 healthy and diseased children and adolescents over an extended period.
- *Prevention desk* to offer children and parents support in lifestyle areas, like sleep, nutrition and physical activity.

## 4 - Specific questions for the research committee

1. Does the committee see any developments or opportunities we should respond to?
2. Are there areas where we can further support our researchers?

# Appendix

## Appendix A - Key scientific outputs

### Severe inflammatory disorders

Juvenile arthritis

1. Mijnheer, G., Lutter, L., Mokry, M., Van Der Wal, M., Scholman, R., Fleskens, V., Pandit, A., Tao, W., Wekking, M., Vervoort, S., Roberts, C., Petrelli, A., Peeters, J. G. C., Knijff, M., De Roock, S., Vastert, S., Taams, L. S., Van Loosdregt, J., & Van Wijk, F. (2021). **Conserved human effector Treg cell transcriptomic and epigenetic signature in arthritic joint inflammation.** *Nature Communications, 12*(1). https://doi.org/10.1038/s41467-021-22975-7
   Citations: 52

   Inflammation can transform human Treg cells into specialized effector Treg (eTreg) cells which are essential for immune balance. Through advanced transcriptional and epigenetic profiling, we have identified a distinct eTreg signature in the joint of JIA patients marked by key regulators like FOXP3, CTLA4, and the vitamin D receptor (VDR). These inflammation-tuned cells adapt via an altered (super-)enhancer landscape, overlapping with tumor-infiltrating Treg profiles. This pivotal insight reveals how Treg cells fine-tune their function in response to environmental cues, offering a new lens to explore immune modulation in health and disease.

Respiratory infections

2. We have developed a chatbot RSV Chatbot - ReSViNET with the ReSViNET Foundation. It received attention during the World Pneumonia Day (November 12, 2024) and is used globally, including the World Health Organization.

### Congenital and hereditary diseases

Cystic Fibrosis

3. Geurts, M. H., De Poel, E., Amatngalim, G. D., Oka, R., Meijers, F. M., Kruisselbrink, E., Van Mourik, P., Berkers, G., De Winter-De Groot, K. M., Michel, S., Muilwijk, D., Aalbers, B. L., Mullenders, J., Boj, S. F., Suen, S. W., Brunsveld, J. E., Janssens, H. M., Mall, M. A., Graeber, S. Y., Van Boxtel, R., Van der Ent, C.K., Beekman, J,M., & Clevers, H. (2020). **CRISPR-Based Adenine Editors Correct Nonsense Mutations in a Cystic Fibrosis Organoid Biobank.** *Cell Stem Cell, 26*(4), 503-510.e7. https://doi.org/10.1016/j.stem.2020.01.019
   Citations: 155

   This paper showcases the strength of the intestinal stem cell model for patients with Cystic Fibrosis, which was invented in our lab. The model is very useful for prediction of treatment response and disease severity in individual patients with unknown genetic variants. This paper shows that also innovative techniques like base editing create new hope for even patients with nonsense mutations. We are proud on this paper because it also is a nice example of close collaboration between the clinic and our lab, both parts are unmissable in this achievement.

Liver

4. *Establishment of the UMCU-Metabolic department as the center for innovative therapies for metabolic diseases.* We are not only the national center to provide hematopoietic stem cell transplantations (HSCTs) for metabolic diseases, but now also attract innovative trials to treat the very first patients in the Netherlands with gene-modified HSCTs (for MLD and Hurler), with systemic mRNA as enzyme replacement in the Moderna Phase I/II MMA-trial, and with tailored amino acid therapies for ARS1, ARS2-deficiencies and BCKDK. Moreover, we invest in the academic development of personalized gene-correction therapies (Schene ea. Nat Commun 2020/2022), supported by NWO Vici, ERC PoC, ERC Starting, and NWA ORC grants. This work was awarded the KNAW-Ammodo Science Award for Groundbreaking Research and the UMCU-TEAmRNA-Award.

Blood

5. Al-Samkari, H., Galactéros, F., Glenthøj, A., Rothman, J. A., Andres, O., Grace, R. F., Morado-Arias, M., Layton, D. M., Onodera, K., Verhovsek, M., Barcellini, W., Chonat, S., Judge, M. P., Zagadailov, E., Xu, R., Hawkins, P., Beynon, V., Gheuens, S., & Van Beers, E. J. (2022). **Mitapivat versus Placebo for Pyruvate Kinase Deficiency.** *New England Journal Of Medicine, 386*(15), 1432–1442. https://doi.org/10.1056/nejmoa2116634
   Citations: 64
   This study presents the results of the phase III trial with AG348, a pyruvate kinase activator and novel treatment for patients with pyruvate kinase deficiency (PKD). We are an international expert center for PKD and have had leading roles in many clinical trials with AG348 for patients with PKD (adults and children) as well as other rare anemias (ongoing).

Kidney

6. Gosselink, M. E., Snoek, R., Cerkauskaite-Kerpauskiene, A., Van Bakel, S. P., Vollenberg, R., Groen, H., Cerkauskiene, R., Miglinas, M., Attini, R., Tory, K., Claes, K. J., Van Calsteren, K., Servais, A., De Jong, M. F., Gillion, V., Vogt, L., Mastrangelo, A., Furlano, M., Torra, R., Bramham,K., Wiles, K., Ralston, E.R., Hall, M., Lio, L., Hladunewich, M.A., Lely, A.T., & Van Eerde, A. M. (2024b). **Reassuring pregnancy outcomes in women with mild COL4A3-5–related disease (Alport syndrome) and genetic type of disease can aid personalized counseling.** *Kidney International, 105*(5), 1088–1099. https://doi.org/10.1016/j.kint.2024.01.034
   Citations: 2, open access
   This paper addresses a critical knowledge gap in hereditary kidney disease care by providing evidence-based guidance for pregnancy counseling in Alport syndrome. Using data from our international PREGeNEPH registry, we demonstrated that pregnancy outcomes are better than previously assumed in mild cases. These findings directly impact patient care by enabling more personalized reproductive counseling. The paper exemplifies our commitment to addressing practical clinical questions that matter to patients.

## Ante- and perinatal damage

Antenatal

7. Bekker, M. N., Koster, M. P. H., Keusters, W. R., Ganzevoort, W., De Haan-Jebbink, J. M., Deurloo, K. L., Seeber, L., Van Der Ham, D. P., Zuithoff, N. P. A., Frederix, G. W. J., Van Den Heuvel, J. F. M., & Franx, A. (2023b). **Home telemonitoring versus hospital care in complicated pregnancies in the Netherlands: a randomised, controlled non-inferiority trial (HoTeL).** *The Lancet Digital Health, 5*(3), e116–e124. https://doi.org/10.1016/s2589-7500(22)00231-x
   Citations: 24, open access
   This non-inferiority trial shows the first evidence that telemonitoring might be as safe as hospital admission for monitoring complicated pregnancies. This study can highly influence current care protocols for pregnant women and prevent hospital admissions.

Neonatology/ perinatology

8. Wang, X., De Groot, E. R., Tataranno, M. L., Van Baar, A., Lammertink, F., Alderliesten, T., Long, X., Benders, M. J. N. L., & Dudink, J. (2023b). **Machine Learning-Derived Active Sleep as an Early Predictor of White Matter Development in Preterm Infants.** *Journal Of Neuroscience, 44*(5), e1024232023. https://doi.org/10.1523/jneurosci.1024-23.2023
   Citations: 2
   This is the first study connecting sleep to white matter development in humans. This paper is based on the award-winning Sleep Well Baby software, developed by the Department of Digital Health. This paper got high media attention and was positively commented on by the worldwide known Prof. JJ Volpe, the author of the book “Neurology of the Newborn”.

### Pediatrics and oncology

9. Müller, H. L., Tauber, M., Lawson, E. A., Özyurt, J., Bison, B., Martinez-Barbera, J., Puget, S., Merchant, T. E., & Van Santen, H. M. (2022b). **Hypothalamic syndrome.** *Nature Reviews Disease Primers, 8*(1). https://doi.org/10.1038/s41572-022-00351-z
   Citations: 69, open access
   In the review we described in depth the hypothalamic syndrome (HS). HS is characterized by intractable weight gain associated with severe morbid obesity, multiple endocrine abnormalities and memory impairment, attention deficit and reduced impulse control as well as increased risk of cardiovascular and metabolic disorders. Currently, there is no cure for this condition, but treatments for general obesity are often used in patients with HS, including surgery, medication, and counselling. However, these are mostly ineffective and no medications that are specifically approved for the treatment of HS are available. HS has specific challenges because the syndrome represents an adverse effect on different diseases, and that diagnostic criteria, etiology, pathogenesis, and management of HS are not completely defined.

### Overarching themes

Life cycle & Mental and physical health

10. Van Der Vlist, M. M. N., Hoefnagels, J. W., Dalmeijer, G. W., Moopen, N., Van Der Ent, C. K., Swart, J. F., Van de Putte, E. M., & Nijhof, S. L. (2022b). **The PROactive cohort study: rationale, design, and study procedures.** *European Journal Of Epidemiology, 37*(9), 993–1002. https://doi.org/10.1007/s10654-022-00889-y
    Citations: 8, open access
    This manuscript represents the result of our intensive interdisciplinary collaboration within the Wilhelmina Children's Hospital (WKZ), Princess Máxima Center, and Utrecht University. The PROactive cohort study operates with FAIR and Open Sciences principles. In this cohort, care and research are intertwined, focusing on the patient conversation about health in a broad holistic view. PROactive identifies children with a chronic disease at high risk of disabling fatigue, decreased daily life participation and psychosocial problems, as well as those who are resilient and thrive despite the challenges of growing up with a chronic condition. Children with chronic conditions and children with medically unexplained fatigue or pain in a broad age range (2-18 years) are included, as well as their parent(s). The first PhD student defended her thesis on data from this cohort in 2021.

## Appendix B - Most important collaborations

### Severe inflammatory disorders

Juvenile arthritis

UCAN CANDU, the Dutch-Canadian bi-national prospective cohort study, developing personalized treatment strategies for Juvenile Idiopathic Arthritis, a €5,3 million funded project by ZonMw, ReumaNederland, and the Canadian CIHR, running from 2017-2024. More than 2200 JIA patients were included in this prospective cohort study, connecting all academic pediatric rheumatology departments in the Netherlands and Canada, resulting in a new biology-integrated disease taxonomy for JIA, and paving the way for prospective targeted therapy trials necessary for developing personalized treatment strategies in JIA.

Respiratory infections

We have contributed to the fight against the COVID-19 pandemic. Our public health work is done in close collaboration with our national public health institute (RIVM). We perform our national studies (SPREAD during the pandemic) with 40 hospitals nationally. RIVM: joint research on COVID-19 epidemiology directly feeding into OMT advice to the ministry of health and policy decisions. Ministry of education: UMC Utrecht supported the evaluation and implementation of twice weekly self-testing in educational settings.
For RSV vaccine development, we have performed studies within EU-funded studies with many countries in Europe including ECDC. Globally, we lead the RSV GOLD network funded by the Bill&Melinda Gates Foundation in which we have performed prospective studies in about 15 developing countries.

### Congenital and hereditary diseases

Cystic Fibrosis

At UMC Utrecht, we play a leading role in advancing Cystic Fibrosis research and -care across Europe. We head the Cystic Fibrosis subnetwork of the ERN-LUNG, connecting with over 50 top Cystic Fibrosis centers across the EU to improve patient registries, advocate for patients, and establish high-quality standards of care. Additionally, we coordinate the European HIT-CF and Orgestra consortia, with top-notch laboratories and clinical centers all over Europe to drive innovative research. As an active member of the ECFS Clinical Trial Network, we also contribute to high-standard international clinical trials, ensuring that therapies reach Cystic Fibrosis patients across Europe.

Liver

Our research has greatly benefited from collaborations with leading experts and institutions. David Liu (Harvard/MIT), the inventor of prime and base editing, has supported our efforts by helping recruit talented postdocs from his team and supporting our NWO large infrastructure grant, INFRAGENE, a joint initiative between UMC Utrecht and LUMC to establish a national gene therapy platform. Sean Froese (Baumgartner group) has contributed to MMA gene correction, while Danny Incarnato (RUG) has provided expertise on RNA folding. Ruben van Boxtel (PMC) has guided our work on mutational profiling, ensuring both wanted and unwanted gene editing effects are carefully analyzed. Additionally, Tom de Koning (Lund University/UMCG) is collaborating with us to develop gene correction therapies for North Sea disease. Our partnership with Moderna (USA) has also been instrumental, as their pioneering work in mRNA therapies in the Netherlands lays the groundwork for future mRNA-based gene correction therapies.

Blood

The GenoMed4All and SYNTHEMA projects are two European initiatives (coordinated from the ERN EuroBloodNet) aiming to integrate multi-omics data from patients with rare hematological disorders across Europe using AI. By establishing robust and trustworthy AI algorithms, the management of a variety of rare (hematological) diseases can be personalized and improved (and acquired knowledge can be shared and beneficial for other applications). In SYNTHEMA this approach is extended by aiming to generate synthetic data to further enhance diagnostic capacity and improve disease management.

### Kidney

We have a strong European collaboration with ERKNet (European Reference Network for Rare Kidney Diseases). One of our researchers serves as Working Group chair and is a member of the Task Force Molecular Diagnostics. This collaboration has immense added value as it:

1. Connects us to >40 European expert centers, enabling knowledge exchange and patient referrals
2. Provides access to ERKReg, a registry of >19,000 rare kidney disease patients, vital for our research
3. Facilitates participation in European research consortia like Theracil (€8M EU grant)
4. Enables harmonization of genetic diagnostics and variant interpretation across Europe

Furthermore, we have a key partnership with the UMC Groningen genetics and bioinformatics teams (Franke, van der Velde). The added value of this collaboration includes:

1. Joint development of KidneyNetwork, an innovative tool using kidney-specific expression data to predict gene function
2. Access to advanced bioinformatics expertise and infrastructure through the VIP (Variant Interpretation Pipeline)
3. Complementary expertise in kidney genetics and large-scale data analysis
4. Strong track record of successful joint publications and grant applications

Finally, the Kidney Research Utrecht (KRU) informally unites all UMC Utrecht/UU kidney research groups, fostering interdisciplinary collaboration and innovation through regular meetings, shared projects, and joint grant applications. The collaboration that stands out most is with PI Prof Lely (OBGYN), with whom we established PREGeNePH, an innovative registry studying pregnancy outcomes in women with (genetic) kidney disease, enabling personalized counseling for this underserved patient group.

## Ante- and perinatal damage

### Antenatal

The COVID-19 infectiON and medicineS In preGNancy (CONSIGN) project aims to guide evidence-based decision-making about COVID-19 treatment options and vaccine indications for pregnant women. The project gathered evidence through the primary data collections of theCOVI-PREG and INOSS studies, and secondary use of data provided by the IMI-funded ConcePTION tools and network. The project was funded by the European Medicines Agency (EMA) and coordinated by PI B. Bloemenkamp.

The Pregnadigit-EU consortium is the European counterpart of Pregnadigit-NL. The consortium aims for implementing and optimizing digital obstetric care, addressing medical outcomes, implementation challenges, and cost/reimbursement issues. The consortium is led by PI Bekker (UMC Utrecht) and PI Ahaus (Erasmus University), with partners such as Vall d 'Hebron Hospital, Catsalut, Karolinska Hospital, Payor Region Stockholm, Aarhus Hospital, and ErasmusMC.

The TRIDENT consortium is a nationwide consortium investigating the introduction and test performance of the Non-Invasive Prenatal Testing (NIPT) in the Netherlands. PI Bekker is board member of this consortium. One of the studies performed within the consortium is the AFFIRM study, led by PIs Bekker and Scheffer.

The IMITAS consortium is a nationwide consortium investigating the introduction and test performance of the first-trimester anomaly scan in the Netherlands, led by PIs Bekker (UMC Utrecht) and Haak (LUMC)

The Pregnadigit-NL consortium is a nationwide consortium aiming for implementing and optimizing digital obstetric care within the Netherlands. IT brings together medical professionals, health policy makers, medtech partners, patient representatives, and health care insurance companies to address medical outcomes, implementation challenges and cost/reimbursement issues. The consortium is led by PIs Bekker (UMC Utrecht) and Franx (ErasmusMC).

### Neonatology/ perinatology

The ENSEMBLE project is a collaborative European research initiative aiming to establish a reliable early detection program for cerebral palsy (CP) before six months of age, compared to the current diagnosis age of 2–5 years. UMC Utrecht coordinates the project together with world-renowned experts in neonatal neurology and infant development. Utilizing methodologies like neuroimaging, electrophysiology, and machine learning, the project involves 15 partners across five countries. It emphasizes family partnership through a family advisory council and aims to improve clinical practice and quality of life for children with CP and their families including knowledge transfer and teaching.

## Pediatrics and oncology

Prof dr. H. van Santen is chair of the European Working Group for Craniopharyngioma (SIOP/ Brain Tumor Group). Within this working group, joint European Recommendations for treatment are made, difficult rare cases are discussed, and new collaborative research projects are developed.

## Overarching themes

### Partnership with Dynamics of Youth

The Child Health Program has a close partnership with Dynamics of Youth, one of the four research themes of the University of Utrecht. Besides joint memberships of the program committees and joint chairs of communities, we intensified our collaboration the last years by joint activities, for example:

- Annual Boost Grants since 2022: researchers are asked to submit research proposals in collaboration with one or more researchers with whom they have never worked before. The last two years we organized a draw among the applicants.
- Network events.
- The publication of a magazine, called Be Real, in 2023. Be Real is dedicated to the mutual, interdisciplinary collaboration in child and youth research in Utrecht.

### Life cycle and Mental and physical health

- National collaboration (Research Domain) within the UU Dynamics of Youth Strategic Theme: Domain Chair of Thriving and Healthy Youth (PI dr. Nijhof one of the three interfaculty chairs), focus on boosting health and resilience in children and young people
- Collaboration with Julius Center with specific dedication to epidemiology, as well as the pediatric palliative care research line of dr. M. Kars and dr. J. Fahner with Princess Máxima Center, with specific dedication to the psycho-oncology research line of Prof. dr. M.A. Grootenhuis, as well as neuro-psychology research line of dr. Marita Partanen, and the fatigue and sleep research line of dr. Raphaële Litsenburg.
- International collaboration on the evaluation and implementation of (eHealth) tools for children and their families, specifically CanChild, headed by Prof J.W. Gorter, McMaster University, Hamilton, Canada, and FitNet-UK, headed by Prof Crawley, Center for Academic Child Health, University of Bristol, UK.
- With patient/parent organizations and social partners (e.g. WKZ Kinderraad, Q-support, Reumafonds, NCFS, Jantje Beton, Kinderen met Long Covid) to improve patient participation in research (www.umcutrecht.nl/participatiematrix).

### The Child Health interactome

Besides the described collaborations above, our network is more extensive. Based on our collaborations we generated a Child Health interactome (see figure 3) and included the ERNs the Child Health is participating in.

## Collaborations and top research areas from the last five years

Recent external collaboration on country/territory level.

*Figure 3: Child Health interactome, including ERNs*

**UMC Utrecht and ERNs**

The UMC Utrecht is a member of the following ERNs

- Endo-ERN: the European network for hormonal disorders
- ERKNet: the European network for kidney diseases
- ERN BOND: the European network for bone disorders
- ERN CRANIO: the European network for abnormalities of the head, face and jaw and ear, nose and throat disorders
- ERN EpiCARE: the European network for epilepsy
- ERN EURACAN: the European network for solid tumors, malignant tumors of a clump of cells
- ERN EuroBloodNet: the European network for diseases in blood, bone marrow and lymph nodes
- ERN eUROGEN: the European network for diseases and disorders of the urinary tract and genitals
- ERN EURO-NMD: the European network for diseases of the nerves, muscles or nerve-muscle transition
- ERN GUARD-HEART: the European network for diseases of the heart
- ERNICA: the European network for hereditary and congenital disorders of the digestive organs (stomach, small intestine and large intestine)
- ERN LUNG: the European network for respiratory diseases
- ERN ReCONNET: the European network for diseases of connective tissue, bones, skeletal muscles, joints, capsules, cartilage and ligaments
- ERN RITA: the European network for immunodeficiency, autoinflammation and autoimmune diseases (the immune system does not work or works too well)
- ERN Skin: the European network for skin disorders
- ERN TRANSPLANT-CHILD: the European network for transplantation in children
- MetabERN: the European network for inherited metabolic diseases

# Appendix C - Grants and prizes

## Selected individual grants

| NWO Talent Program | |
|---|---|
| **Veni** | Dr. R.H. van Jaarsveld (2023),<br>Dr. L. Heskamp (2024) |
| **Vidi** | Prof. dr. P.C.J. Bruijning-Verhagen (2019),<br>Dr. Ir. J.P. Wijnen (2019),<br>Dr. K. Jongsma (2023),<br>Dr. N.M.T. Crombag (2024),<br>Dr. A.M. van Eerde (2024) |
| **Vici** | Prof. dr. F. van Wijk (2020),<br>Prof. dr. N. Eijkelkamp (2023),<br>Prof. dr. C.H.A. Nijboer (2023),<br>Prof. dr. S.A. Fuchs (2024) |
| **ERC Starting Grant** | Prof. dr. S.A. Fuchs (2024) |

## Selected collaborative grants

| | |
|---|---|
| **Government** | Center for Animal free Biomedical Translation: 124.5 M€<br>Together with a large number of national and international partners, the CPBT will work on the development and dissemination of animal-free biomedical innovations and expertise. Child Health scientists are involved in coordinating one of the transition projects focusing on the hereditary disease Cystic Fibrosis. Child Health researchers are also partners in the Asthma/COPD transition project. |
| **Marie-Curie (EU)** | Orgestra: 3.5 M€<br>Joint Doctoral network that will train thirteen doctoral candidates in developing personalized disease models using stem cell-derived organoids for rare diseases, including the lung and kidney diseases, Cystic Fibrosis and cystinosis. |
| **KWF/Kika** | EndoWatch/HERCules: 1.7 M€<br>The development of the Corsano EndoWatch; the smart wearable that helps to improve outcomes of children and young adults with hypothalamic dysfunction after surviving a suprasellar brain tumor and Effects of Radiotherapy and associations with Cognitive functioning; The HERCules Project. |
| **ZONMW** | TRACER consortium: 3 M€<br>TReating hereditary Anemias through stem CEll Research." Focus: Sickle Cell Anemia and Diamond-Blackfan Anemia syndrome. ZonMw PSIDER program. www.tracer-consortium.info |
| **H2020 (EU)** | PREMSTEM: 9 M€<br>Stem cell regeneration research network (PREMSTEM) is a global team focused on delivering a novel regenerative therapy to reduce the enormous emotional and economic implication of neurodevelopmental injury caused by brain damage associated with premature birth. |

## Appendix D - Key outputs or activities aimed at a professional of wider audience

### Severe inflammatory disorders

Juvenile arthritis

We generated the first national patient research agenda for juvenile idiopathic arthritis. Patients and carers were in the lead for developing a research agenda according to the James Lind alliance method. More than 600 questions from patients, family, and carers were prioritized in many sessions with all stakeholders. This resulted in a top 10 of the most relevant research questions according to Dutch patients with JIA.

Respiratory infections

We have advised the Dutch health council twice. Our SARS-CoV-2 vaccine work in **Down Syndrome** patients led to accelerated introduction of vaccination in this vulnerable population. For **RSV vaccines development**, we have led burden studies in Europe that were directly used by the Dutch health council in 2024 to prioritize nirsevimab for introduction in our national infant immunization program.

### Congenital and hereditary diseases

Cystic Fibrosis

- We organized regular webinars for patients and parents of children with CF, in collaboration with the Dutch CF Patient Society and a special meeting for grandparents (2024).
- Participation in EMA advisory board on biomarker use.
- Presence in national newspapers (e.g. NRC 2025) and TV programs (Het Kinderziekenhuis, 2024)

Liver

- Live national television: Documentary on metabolic diseases for NPO-VARA (19 December 2024), Het kinderziekenhuis 2024, Koffietijd 2022 (https://koffietijd.nl/videos/54731/fragmenten/gdl-dr.-sabine-fuchs-edward-nieuwenhuis), Tijd voor Max 2021 and 2019.
- National newspapers: Volkskrant (Wetenschapsbijlage 2024), Telegraaf (zeldzame ziekten dag 2024), de Groene Amsterdammer 2022 (https://www.groene.nl/lijsten/10-positieve-ontwikkelingen-van-2022), Trouw 2022, Telegraaf 2022.

Blood

Studies performed in the context of the PRIDES study (pregnancy and inherited bleeding disorders study) and related to severe menstrual bleeding in adolescents have provided important insights and have resulted in updated guidelines in primary, secondary and tertiary healthcare, thereby having large impact on female health and quality of life (e.g. PMID: 38077824, PMID: 33314402, PMID: 34343384).

Kidney

- Invited speaker for high-impact international online education sessions: KDIGO webinar “Genetic Testing in Kidney Disease” (2022) and American Society of Nephrology Kidney Week CME “Genetic Counseling: What Nephrologists Need to Know” (2023).
- Co-author of first multi-ERN guideline on Bardet-Biedl syndrome (2024) and European Alport guideline (2024), setting standards for diagnosis and care across Europe.
- Host and coordinator of monthly multidisciplinary nephrogenetic case discussions (2020-present), connecting specialists across the Netherlands.

### Ante- and perinatal damage

Antenatal

Advocacy for vaccination in pregnant women in national newspapers (‘Jonge, slanke vrouwen zonder vaccinatie’ AD.nl) and radio (NPO Radio 1)

Neonatology/ perinatology

- The BBC media channel published a podcast based on our work https://www.bbc.co.uk/programmes/w3ct6x3z.
- The Team Neo-BRAIN has received the 2024 UMC Utrecht Team Science Award for interdisciplinary research during the UMC Utrecht research week.

## Pediatrics and oncology

- For children treated with cranial irradiation, we have developed new surveillance recommendations for hypothalamic-pituitary dysfunction.
- For children with thyroid nodules and differentiated thyroid cancer, we have written the 1st European Treatment Recommendations.
- Development of a pediatric differentiated thyroid carcinoma registry within the EuRRECa project: rationale and protocol.

## Overarching themes

Life cycle & Mental and physical health

- Societal impact: Symposium 31st May 2022 organized by NJI (Nederlands Jeugd Instituut) on mental wellbeing in youth and COVID-19.
- Promotion of healthy lifestyle, also for chronically ill patients by generic or personal (with Ecological Momentary Assessments) advice. That means nutrition, exercise, sleep. Monitoring of progress within the cohort with annual measurements (PROfeel/Booster app and embedding of cohorts like PROactive and SMART-Youth in 'Leefstijlloket' (030-Lab).
- Sanne Nijhof: core team member from Medicine Faculty in development of interdisciplinary research master's: 'Youth Development & Social Change'. Faculties involved: FSW, GEO, GNK, REBO.
- Iva Bicanic is acting director of the center for Sexual Abuse in Children, very active as influencer on social media, national media, newspapers and television.
- In 2024 members of the Child Health Program initiated an 'burger-initiatief' about misuse and miscommunications on vaping, which resulted in interruptions and questions in the government.

# Strategic Program Circulatory Health

Self-evaluation report 2019-2024

# Strategic Program Circulatory Health

## 1 - Mission, governance, and main research topics

### Mission

Cardiovascular disease is the leading cause of death worldwide in both men and women. Our mission is to (inter) nationally reduce the burden of cardiovascular disease. To address this challenge, the strategic program *Circulatory Health* creates scientific and societal value by connecting cardiovascular researchers, clinicians, and educators within the UMC Utrecht and beyond. *Circulatory Health* therefore encompasses a wide range of activities in clinical, translational, and basic research, with applications in care, cure, and education.

### Governance

The daily board of *Circulatory Health* meets biweekly and is composed of professionals in the field of cardiovascular health. These professionals are also representatives of the divisions where close collaboration is necessary. The current members are:

Prof. dr. Gerard Pasterkamp (chair)
Prof. dr. Joost van Herwaarden (from October 2024)
Prof. dr. Frans Rutten
Prof. dr. Frank Visseren
Prof. dr. Pim van der Harst
Prof. dr. Hester den Ruijter
Dr. Pieter Vader (from February 2024)
Marco Houterman MSc

Former members of the daily board in the period 2019-2024 were prof. dr. Folkert Asselbergs (chair until August 2022) and prof. dr. Gert Jan de Borst (until November 2024).

### Program office

The program office initiates, facilitates, prioritizes, and partly executes the *Circulatory Health* program objectives. The program office consists of a program manager, management assistant, senior communications advisor, and policy and grant advisor. In addition, the *Circulatory Health* community has primary contacts at the UMC Utrecht Research Support Office for EU and national grants, where capacity is available for grant advice and grant writing.

### Main research topics and Circulatory Health community

The *Circulatory Health* community consists of approximately 700 members, of which 45 professors (33% female), 35 associate professors (40% female) and 4 clinical scientists (75% female). The remainder of the community consists of approximately 300 assistant professors, 50 postdocs, 300 PhD candidates, students, and support staff. For the period 2019-2024, *Circulatory Health* targeted four research focus areas which had a clear translation to patient groups within the broad field of cardiovascular disease. The focus for these patient groups is supported and strengthened by utilizing eight research approaches (Figure 1).

### Circulatory Health Community

'A community of researchers, clinicians and educators within the cardiovasculair domain'

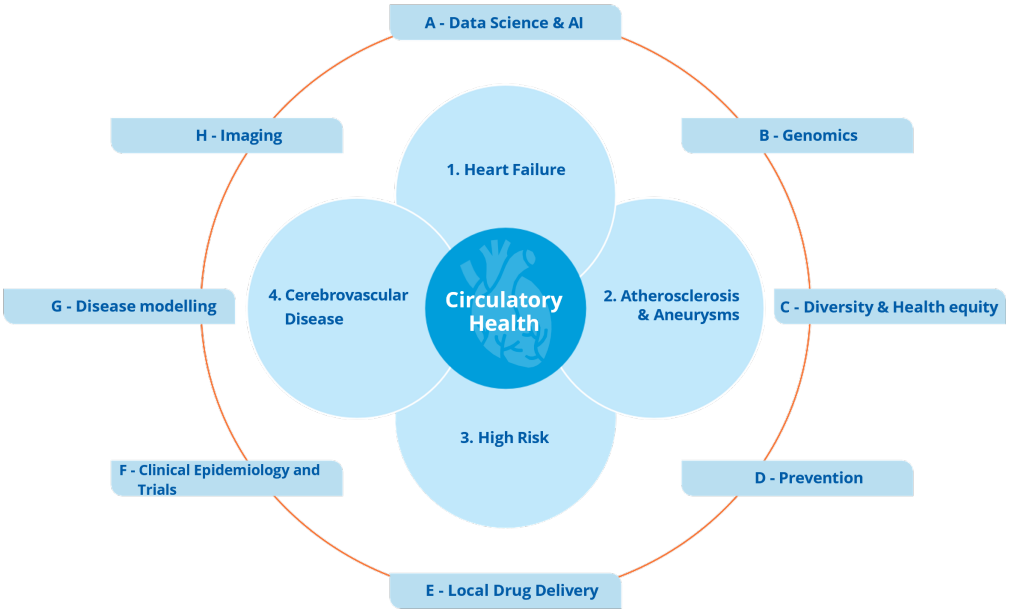



*Figure 1 – Circulatory Health community with four focus areas (1-4) and eight research approaches (A-H).*

## 2 - Concise reflection on program-specific recommendations from the previous evaluation

During the previous SEP review, the *Circulatory Health* strategic program received valuable recommendations. These recommendations resulted in 2020 into a 'UMC Utrecht response to assessment report from SEP research evaluation (2013-2018)' and an action plan specific for *Circulatory Health*. The following is a short, but concise reflection on the main recommendations by topic:

### 1. Centralization Data Science at UMC Utrecht level by creating core facility

To bridge the time until a core facility is established, two Data Science quartermasters were appointed within *Circulatory Health* to make an inventory of needs and questions and to develop a vision and strategy in the domain of Data Science. Moreover, as a strategic commitment, a new chair Data Science was appointed. In the meantime, in line with the SEP recommendations, a central facility has been established: the UMC Utrecht AI Labs.

### 2. Initiation of clinical trials with patient involvement

The appointment of a *Circulatory Health* clinical trial specialist and the presence of a central expertise center for trial initiation and support, U-Trial, has aided the initiation (with patient involvement) of numerous clinical trials, as exemplified in our key output (appendix A; # 1, 5, 9, 11 and 15).

### 3. Formulation and prioritization of research questions with patients

Within *Circulatory Health*, we have paid a lot of attention to involving patients in research (questions) and educating our researchers on this aspect. Regular contacts are maintained with patient organizations such as the Dutch Heart Foundation, Harteraad, Stichting Vrouwenhart, and the PLN Foundation. E-modules have been developed that assist researchers with patient involvement issues for research proposals, a symposium was held on patient involvement in education, a SCAD challenge, and a workshop were organized for researchers on how to involve patients in research and research proposal writing.

### 4. Clear career development plan for young researchers & dedicated research time for clinical scientists

This recommendation has been tackled by the Board of Directors themselves. From 2021 onwards four central UMC Utrecht talent programs are in place for (clinical) researchers and educators at different stages of their career.

Besides that, UMC Utrecht introduced six academic career profiles from 2023 onwards. Moreover, our Board provides the opportunity for clinicians to dedicate 40% of their time to research. Within *Circulatory Health*, four such clinical scientists have now been officially appointed.

**5. Interchange of PhD students between programs**

Within *Circulatory Health*, all kinds of get togethers are organized for cardiovascular PhD candidates, active in different PhD programs of the UU Graduate School of Life Sciences: educational lunch meetings, research cafés, grand rounds, lectures, education, and sports events. Around these get togethers there is sufficient opportunity for networking.

**6. Execution Laboratory for *Circulatory Health***

On April 8 2022, the Circulatory Health Research Center (the successor of the Laboratory for *Circulatory Health*) was officially launched. Although this center exists only virtually, its governance ensures a better collaboration between different research (wet lab) groups and finetuning of objectives and resources. Ideally collaboration, objectives, and resources would be served by having all *Circulatory Health* research groups in one physical center, but the plans for one UMC Utrecht Research & Innovation Center awaits implementation by the Board of Directors.

**7. Besides collaboration with Philips on FORS, have other attempts been made to valorize research economically?**

In the past years, UMC Utrecht has invested considerably (via the Research Support Office and Utrecht Holdings) in expertise on Public-Private Partnerships (PPP). The success rate of *Circulatory Health* in obtaining funding for PPP with Health Holland-TKI is relatively high and several spin-off companies are based on or make use of our inventions: e.g.: ORTEC (U-Prevent medical device for cardiovascular risk management), TargEd (improved treatment of thrombosis), Cordys Analytics (AI software for improved early detection of heart disease), and JAMA Therapeutics (extracellular vesicles as vehicles for better treatment targeting).

## 3 - Main research accomplishments in the period 2019-2024

Below are eight narratives as a selection of major achievements within the main research topics. The relationship to Figure 1 is shown in parentheses (focus areas 1-4 – research approaches A-H).

**U-Prevent medical device for personalized prevention of cardiovascular disease (3 - A, D, F)**

The Vascular Medicine research group has played a key role in developing and validating multiple European risk scores for predicting cardiovascular disease (CVD) risk. These include scores for patients with established CVD (SMART risk score), diabetes (SCORE2-diabetes), and the general population (SCORE2 and SCORE2-OP). The Utrecht Cardiovascular Cohort SMART (UCC-SMART) study provided a foundation for these analyses, which additionally incorporated data from millions of patients across international cohorts.

All risk scores were developed in collaboration with renowned institutions such as Harvard University, Cambridge University, Johns Hopkins University, and Karolinska Institutet. They were published in high-impact journals and endorsed by the European Society of Cardiology (ESC) Cardiovascular Risk Collaboration (e.g. doi: 10.1093/eurheartj/ehab309; cited 909 times up to date). These scores are now recommended in national and international guidelines (e.g. doi: 10.1093/eurheartj/ehab484; cited 3938 times up to date).
The research group has also pioneered statistical innovations in risk prediction, including lifetime risk estimation, causal-treatment effect estimation, competing risk adjustment, and flexible modeling of additional or missing data. These advancements have contributed to 13 successful PhD theses over the past 15 years.
To translate research into clinical practice, U-Prevent was developed—a CE-marked software device used by healthcare providers to estimate patient-specific CVD risk and the impact of preventive treatment. Originally developed by UMC Utrecht, U-Prevent was later transferred to ORTEC B.V. as part of a public-private partnership. Today, it is used by over 2,000 clinicians daily in the Netherlands and beyond.

**Expertise center for genetic hyperlipidemias (3 – B, D, F)**

The NFU expertise center for genetic dyslipidemias at the UMC Utrecht was founded in 2021 with the primary aim to

provide optimal care for patients and families with genetic dyslipidemias, especially Familial Dysbetalipoproteinemia. The center aims to advance knowledge about diagnosis, prognosis, and treatment of these diseases, and also to gain insight in the pathophysiology of the lipid derangements. The Vascular Medicine trial unit and the SMART cohort are important infrastructures for clinical studies (doi: 10.1016/j.jacl.2022.10.006) in these patients. International collaboration with the University of Cape Town resulted in the implementation of a specialized laboratory technique to separate lipoproteins, used in research, now made available for clinical practice to better diagnose and treat genetic lipid disorders (doi: 10.1016/j.cca.2022.11.035). The recent start of an observational registry for patients with Familial Dysbetalipoproteinemia further contributes to more knowledge for this rare lipid condition. Teaching and disseminating knowledge about rare genetic dyslipidemias are done during annual lipid teaching courses in the Netherlands and in 2024 also in Ethiopia for the African continent.

**Enabling technologies: innovations in image-guided therapies (IGT) in cardiovascular disease (1, 2, 4 - H)**
In recent decades, rapid progress in IGT has been made, leading to a remarkable transition from conventional open to endovascular techniques in (cardio)vascular surgery. Although these minimally invasive approaches offer advantages they are not without limitations. Most endovascular procedures require the use of fluoroscopy for visualization. Treatment of increasingly complex vascular diseases has led to longer procedure times, increasing radiation exposure for both patients and their treatment teams worldwide. Another challenge associated with the use of fluoroscopy is that endovascular guidewires and catheters are only displayed in 2D and only in grayscale images. This lack of information complicates navigation and increases the risk of procedural failures.
Since 2012, UMC Utrecht has collaborated with Philips (Philips Koninklijke N.V., Best, the Netherlands) on development of Fiber Optic RealShape (FORS) technology. FORS combines image fusion with specially designed endovascular guidewires, embedded with optical fibers, enabling the use of laser light instead of fluoroscopy for three-dimensional visualization of guidewires and catheters. This enhances spatial perception of devices and offers reductions in radiation. After execution of preclinical studies in UMC Utrecht also The First in Human clinical FORS study (doi: 10.1016/j.ejvs.2020.10.016) was conducted here (prof. dr. J. van Herwaarden). A remarkable success rate was achieved, with no less than 90.9% of navigation attempts executed successfully using FORS-enabled devices.
After CE label (2019) and FDA approval (2020) the results of use of FORS technology during aortic and peripheral procedures are now being evaluated in a global registry study executed in a limited number of centers of excellence in the USA and Europe, including UMC Utrecht.

**Diversity in atherosclerosis (2 - A, C, G)**
Over the past six years, our laboratories have made significant progress in unraveling the mechanisms underlying atherosclerosis, largely supported by the Athero-Express biobank (doi: 10.1038/s44161-022-00171-0). Within the Leducq consortium (appendix C, #3) in 2018 and more recently, the Dutch Heart Foundation (AtheroNeth program: appendix C, #10), we investigate the diversity of atherosclerosis. We have identified five molecular plaque types with distinct biological pathways and drug responsiveness. Using biobank data, we are developing predictive algorithms to assess drug efficacy across patient subgroups, with promising initial results. In collaboration with pharmaceutical companies, we are validating these models and advancing them with nuclear single-cell sequencing data. Additionally, in partnership with Utrecht Holdings, we are exploring the establishment of a service-oriented start-up to provide predictive models for drug efficacy in human atherosclerotic plaque data.

**Translational research in advanced heart failure & advancing gene therapies in cardiomyopathies (1 - B, G)**
At UMC Utrecht, our research bridges translational science and clinical application in advanced heart failure and inherited cardiomyopathies. Through UNRAVEL, we collect freshly isolated patient heart tissue from left ventricular assist device (LVAD) and heart transplant surgeries, enabling biomimetic culture of live myocardial slices. These models have proven instrumental in studying patient-specific responses to cardiotoxic chemotherapy and in testing gene therapies for genetic cardiomyopathies in collaboration with pharmaceutical partners. Our findings have been widely shared through international conferences (ISHLT, ESC), peer-reviewed journals, and invited lectures.
The Cardiogenetics Research Group is a key contributor to national and EU-funded consortia (GEREMY, PSIDER, Cure-PLaN, CVON PREDICT2, and CVON eDETECT) that develop gene- and variant-specific treatments for inherited cardiomyopathies. Our focus includes PLN, DSP, PKP2, RBM20, LMNA, and TNNI3 mutations, affecting thousands of individuals in the Netherlands. We integrate genotype-phenotype analyses with predictive risk calculators to optimize the timing and selection of gene therapies, using data from UNRAVEL. Our work is conducted in close collaboration

with patient organizations, including the PLN Foundation. To ensure responsible implementation, we address ethical, legal, and societal (ELSI) aspects, and a documentary on genetic heart disease and gene therapy is currently in post-production.
Beyond genetic interventions, our biobank also allows tracking of biomarkers. We identified sST2 as a predictor of right ventricular failure and mortality in LVAD patients, complementing our clinical work on the strong predictive value of peak oxygen consumption during CPET, which will support personalized follow-up and transplantation strategies. Our contributions to guidelines (e.g. doi: 10.1002/ejhf.3024 and doi: 10.1093/eurheartj/ehad194) reinforce our impact on patient care, while public-private collaborations such as Health Holland and the "Vrienden van UMC Utrecht" foundation support our work. Recognizing its importance, the first-ever Dutch chair in Advanced Heart Failure was established at UMC Utrecht in 2024 (prof. dr. L. Van Laake), further solidifying our leadership in this topic.

### Genetics of Cerebrovascular Diseases (4 – B, C)

The focus of the Genetics of Cerebrovascular Disease group is on aneurysmal subarachnoid hemorrhage (aSAH), an often fatal stroke caused by intracranial aneurysm (IA) rupture. Funded by an ERC Starting Grant (prof. dr. Y. Ruigrok, 2019), the group conducted the largest genome-wide association study (GWAS) on IA (prevalence: 3%; estimated 550,000 patients in the Netherlands) to date. This study uncovered a polygenic disease architecture, explaining over half of the disease heritability and highlighting the critical role of endothelial cells in pathogenesis. The findings were published in *Nature Genetics* (appendix A, key output #3; doi: 10.1038/s41588-020-00725-7), which was received as a landmark paper in IA genetics (13k article accesses, 206 citations). The summary statistics were made publicly available, with 2,176 downloads via DOI and over 50 studies citing or reusing the data. Building on this foundation, the group is currently conducting a follow-up GWAS with a fourfold larger patient cohort, now incorporating a sex-stratified approach—a method rarely applied in this field. These studies are part of an international IA genetics consortium within the International Stroke Genetics Consortium (ISGC), initiated by prof. dr. Y. Ruigrok.
Beyond IA/aSAH, the group also contributes to large-scale stroke genetics research within ISGC, including a GWAS meta-analysis of 110,000 stroke patients, which identified new drug targets for stroke. This study, published in *Nature* (doi: 10.1038/s41586-022-05165-3), received 126k article accesses, 252 citations, underscoring its impact. For her leadership in stroke genetics prof. dr. Y. Ruigrok received the ISGC Michele Sale Award for Women in Stroke Genetics (2020)—a prestigious mid-career award.

### Health equity and diversity in cardiovascular disease (1, 2, 3, 4 – C, F, G)

Within *Circulatory Health*, several research groups are dedicated to advancing our understanding of heart disease and stroke in women. Prof. dr. Y. Ruigrok's group is investigating the sex-specific factors contributing to the female predominance in intracranial aneurysms (IA) and aneurysmal subarachnoid hemorrhage (aSAH), conditions in which women account for 65% of cases. Supported by a Dutch Heart Foundation Clinical Established Investigator Dekker personal grant (2022) this research examines the interplay between genetic, clinical, and hormonal risk factors unique to women, aiming to deepen our understanding of IA pathogenesis and to improve risk prediction and prevention strategies. A pivotal component of the study involves a sex-stratified GWAS of 40,000 cases, an approach that is rarely employed in this area.
In parallel, dr. S.A.E. Peters received a ZonMw VIDI grant (2021) to explore whether sex differences in cardiovascular disease are shaped by nature or nurture. Her team's extensive publications on this topic, including a roadmap for sex- and gender-sensitive health research published in *BMC Medicine* (doi: 10.1186/s12916-023-03060-w), have made significant contributions to the field. Additionally, with support from a ZonMw grant, the team developed an eLearning module to promote sex- and gender-sensitive biomedical research, which is now being implemented in the UU Graduate School of Life Sciences (GSLS) and biomedical curriculum.
Prof. dr. H.M. den Ruijter coordinates several international and national consortia, including those funded by the Dutch Heart Foundation (IMPRESS; 2020) and LeDucq (2022) focused on heart disease in women. The team is pioneering new diagnostic approaches for coronary artery disease (CAD), specifically targeting the unique molecular regulation of female vascular tissues and cells. Their work has led to the discovery of a biomarker panel based on cell-free DNA methylation for diagnosing CAD in women (doi: 10.1093/eurheartj/ehae156), a breakthrough supported by two ERC Proof-of-Concept grants (appendix C, #2).

**Applied cardiovascular health in the primary care, public and global domain (1 – C, D, F)**
Multidisciplinary research is performed and focused on prevention, early diagnosis, and patient-centered treatment of patients with cardiovascular disease, with special attention for underserved populations within the public domain nationally and globally. In 2024, we received large EU grants as consortium leads for palliative care in heart failure (RAPHAEL), and the diagnosis management of patients with Metabolic Dysfunction-Associated Steatohepatitis (MASH). The General Practice Cardiovascular Health team within the Julius Center performed the largest ever investigator-driven randomized trial in primary care in the Netherlands evaluating the switch from vitamin K antagonist (VKA) to a non-vitamin K oral anticoagulant (NOAC) in frail elderly. Switching to a NOAC causes much more bleeding in this understudied and underserved population. The study has been published in Circulation in 2024 (appendix A, key output #15; doi: 10.1161/CIRCULATIONAHA) and is cited 101 times up to date. Results were presented in the hotline session of the ESC congress in Amsterdam in 2023, and findings have been incorporated in the 2024 ESC guidelines for the management of atrial fibrillation. We were subject of extensive media coverage, including a Dutch newspaper (Trouw) and a webinar. Finally, we received the Dutch General Practice Research Price 2024.

## 4 - Specific questions for the research committee

1. According to the evaluation committee, are the four chosen focus areas and eight research approaches of continued relevance to achieve scientific and societal impact?
2. According to the evaluation committee, are there any emerging cardiovascular topics and regional/extramural topics that should be prioritized within the *Circulatory Health* strategic program/Cardiovascular Theme in the (near) future?
3. From a governance perspective, what is the evaluation committee's opinion (both strengths and weaknesses) on topics overlapping with other strategic programs (such as the cardiovascular branch within Regenerative Medicine and stroke within Brain)?

# Appendix

## Appendix A - Key scientific outputs

Below the strategic program *Circulatory Health* has highlighted 15 key scientific articles published in the period 2019-2024.

1. Nidorf, S. M., Fiolet, A. T. L., Mosterd, A., Eikelboom, J. W., Schut, A., Opstal, T. S. J., The S. H. K., Xu, X-F., Ireland, M. A., Lenderink, T., Latchem, D., Hoogslag, P., Jerzewski, A., Nierop, P., Whelan, A., Hendriks, R., Swart, H., Schaap, J., Kuijper, A. F. M., ... Thompson, P. L. (2020). **Colchicine in Patients with Chronic Coronary Disease.** *New England Journal of Medicine, 383*(19), 1838–1847. https://doi.org/10.1056/nejmoa2021372
   Citations: 1427, (focus areas *Heart Failure and Atherosclerosis & Aneurysms*)
   In this randomized, controlled, double-blind trial the effect of colchicine (0.5 mg once daily) was investigated, with respect to reducing the risk of cardiovascular events, relative to matching placebo in a total of 5522 patients with coronary artery disease (CAD). It was shown that the risk of cardiovascular events was significantly less in CAD patients receiving colchicine as compared to those receiving placebo.

2. Groenewegen, A., Rutten, F. H., Mosterd, A., & Hoes, A. W. (2020). **Epidemiology of heart failure.** *European Journal of Heart Failure, 22*(8), 1342–1356. https://doi.org/10.1002/ejhf.1858
   Citations: 1313, open access (focus area *Heart Failure*)
   In this review evolving trends in the epidemiology of heart failure are described and discussed. Though the number of heart failure patients still continues to rise due to a growing and ageing population, over the years changing trends in the types of heart failure and the patient population can be seen. All these trends are discussed and placed into perspective.

3. Bakker, M. K., Van der Spek, R. A. A., Van Rheenen, W., Morel, S., Bourcier, R., Hostettler, I. C., Alg, V. S., Van Eijk, K. R., Koido, M., Akiyama, M., Terao, C., Matsuda, K., Walters, R. G., Lin, K., Li, L., Millwood, I. Y., Chen, Z., Rouleau, G. A., Zhou, S., ... Ruigrok, Y. M. (2020). **Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors.** *Nature Genetics, 52*(12), 1303–1313. https://doi.org/10.1038/s41588-020-00725-7
   Citations: 206, open access (focus areas *Cerebrovascular Disease and Aneurysms*)
   In this genome-wide association study in 10,754 patients with intracranial aneurysms and 306,882 controls (European and East Asian descent) 17 risk loci were identified, of which 11 were novel at the time. Evidence was provided that the majority of intracranial aneurysm heritability is polygenic of nature. Moreover, smoking and high blood pressure were identified as the main genetic risk factors for intracranial aneurysms.

4. Kamel, S. M., Van Opbergen, C. J. M., Koopman, C. D., Verkerk, A. O., Boukens, B. J. D., De Jonge, B., Onderwater, Y. L., Van Alebeek, E., Chocron, S., Pontalti, C. P., Weuring, W. J., Vos, M. A., De Boer, T. P., Van Veen, T. A. B., & Bakkers, J. (2021). **Istaroxime treatment ameliorates calcium dysregulation in a zebrafish model of phospholamban R14del cardiomyopathy.** *Nature Communications, 12*(1). https://doi.org/10.1038/s41467-021-27461-8
   Citations: 22, open access (focus area *Heart Failure*)
   In a knock-in zebrafish model of phospholamban R14del cardiomyopathy structural and functional characteristics were studied. Age-related remodeling, including inflammation and fibrosis, were noticed in adult hearts carrying this mutation. Moreover, before structural changes were obvious already $Ca^{2+}$-dysregulation was apparent, which could be ameliorated by istaroxime treatment.

5. Van Herwaarden, J. A., Jansen, M. M., Vonken, E-J. P. A., Bloemert-Tuin, T., Bullens, R. W. M., De Borst, G. J., & Hazenberg, C. E. V. B. (2021). **First in Human Clinical Feasibility Study of Endovascular Navigation with Fiber Optic RealShape (FORS) Technology.** *European Journal of Vascular and Endovascular Surgery, 61*(2), 317–325. https://doi.org/10.1016/j.ejvs.2020.10.016
Citations: 49, open access (focus area *High Risk*)
Fiber Optic RealShape (FORS) technology has been previously introduced for the 3D-visualization of endovascular devices in real time. In this study the use of the FORS technology was tested for the first time in humans: 14 Endovascular Aortic Repair (EVAR) and eight Endovascular Peripheral Lesion Repair (EPLR) patients. It was shown that the FORS technology was safe and feasible in the investigated patients, with the potential to improve image-guidance during operations and to reduce radiation exposure compared to standard fluoroscopy.

6. Hageman, S., Pennells, L., Ojeda, F., Kaptoge, S., Kuulasmaa, K., De Vries, T., Xu, Z., Kee, F., Chung, R., Wood, A., McEvoy, J. W., Veronesi, G., Bolton, T., Achenbach, S., Aleksandrova, K., Amiano, P., Amouyel, P., Andersson, J., Bakker, S. J. L., ... Di Angelantonio, E. (2021). **SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe.** *European Heart Journal, 42*(25), 2439–2454. https://doi.org/10.1093/eurheartj/ehab309
Citations: 909, open access (focus area *High Risk*)
In this study a model (SCORE2) was developed and validated in order to predict 10-year (non)fatal cardiovascular disease (CVD) risk in the general European population. The risk prediction model was developed using individual data from 45 cohorts in 13 countries (677,684 individuals; 30,121 CVD events); for validation, participant data were used from 25 additional cohorts out of 15 European countries (1,133,181 individuals; 43,492 CVD events).

7. Hartman, R. J. G., Owsiany, K., Ma, L., Koplev, S., Hao, K., Slenders, L., Civelek, M., Mokry, M., Kovacic, J. C., Pasterkamp, G., Owens, G., Björkegren, J. L., & Den Ruijter, H. M. (2021). **Sex-Stratified Gene Regulatory Networks Reveal Female Key Driver Genes of Atherosclerosis Involved in Smooth Muscle Cell Phenotype Switching.** *Circulation, 143*(7), 713–726. https://doi.org/10.1161/circulationaha.120.051231
Citations: 75, open access (focus area *Atherosclerosis & Aneurysms*)
In this study a systems approach is described providing for novel insights into molecular mechanisms underlying male-female differences in atherosclerosis. For that, sex-specific gene regulatory networks (GRNs) were compared, showing sex differences in activity of these networks in atherosclerotic plaques. This publication provides a major contribution and stimulus to put male-female differences even more prominently on the research agenda.

8. Uijl, A., Savarese, G., Vaartjes, I., Dahlström, U., Brugts, J. J., Linssen, G. C. M., Van Empel, V., Brunner-La Rocca, H-P., Asselbergs, F. W., Lund, L. H., Hoes, A. W., & Koudstaal, S. (2021). **Identification of distinct phenotypic clusters in heart failure with preserved ejection fraction.** *European Journal of Heart Failure, 23*(6), 973–982. https://doi.org/10.1002/ejhf.2169
Citations: 96, open access (focus area *Heart Failure*)
In this publication five distinct clusters of heart failure with preserved ejection fraction (HfpEF) patients (LVEF ≥ 50%) are identified that differ in clinical features, treatment and prognosis. These results indicate that HFpEF is heterogenous of nature and that study design should be tailored to personalized treatment of HFpEF patients.

9. Van den Berg, S. A., Uniken Venema S. M., Reinink H., Hofmeijer, J., Schonewille, W. J., Miedema, I., Fransen, P. S. S., Pruissen, D. M. O., Raaijmakers, T. W. M., Van Dijk, G. W., De Leeuw, F-E., Van Vliet, J. A., Kwa, V. I. H., Kerkhoff, H., Van 't Net, A., Boomars, R., Siegers, A., Lok, T., Caminada, K., .... Slotboom, M. (2022). **Prehospital transdermal glyceryl trinitrate in patients with presumed acute stroke (MR ASAP): an ambulance-based, multicenter, randomized, open-label, blinded endpoint, phase 3 trial.** *The Lancet Neurology, 21*(11), 971-981. https://www.sciencedirect.com/science/article/pii/S1474442222003337?via%3Dihub
Citations: 34, (focus area *Cerebrovascular Disease*)
In this phase 3 clinical trial, involving six Dutch ambulance services and 18 hospitals, it was investigated whether early administration (within three hours of symptom onset) of glyceryl trinitrate to patients with suspected acute stroke had a beneficial effect on disease progression. No evidence was found that transdermal administration of glyceryl trinitrate in the prehospital setting has a beneficial effect on patients with suspected acute stroke. However, there were indications of early harm from this treatment in patients with intracerebral hemorrhage, suggesting that glyceryl trinitrate should be avoided in this setting.

10. Mokry, M., Boltjes, A., Slenders, L., Bel-Bordes, G., Cui, K., Brouwer, E., Mekke, J. M., Depuydt, M. A. C., Timmerman, N., Waissi, F., Verwer, M. C., Turner, A. W., Khan, M. D., Hodonsky, C. J., Benavente, E. D., Hartman, R. J. G., Van den Dungen, N. A. M., Lansu, N., Nagyova, E., ... Pasterkamp, G. (2022). **Transcriptomic-based clustering of human atherosclerotic plaques identifies subgroups with different underlying biology and clinical presentation.** *Nature Cardiovascular Research, 1*(12), 1140–1155. https://doi.org/10.1038/s44161-022-00171-0
Citations: 29, open access (focus area *Atherosclerosis & Aneurysms*)
In this study, cluster analysis of gene expression profiles obtained from 654 human carotid plaques revealed five dominant plaque subtypes. The cellular composition of these plaque subtypes differed and were associated with severity of clinical presentation. The plaque subtype correlated with the most severe clinical phenotype was found to be associated with inflammatory and fibrotic cell lineages. It was concluded that plaques at risk for thrombotic events can be further subdivided by gene-expression profiling studies.

11. Blankestijn, P. J., Vernooij, R. W. M., Hockham, C., Strippoli, G. F. M., Canaud, B., Hegbrant, J., Barth, C., Covic, A., Cromm, K., Cucui, A., Davenport, A., Rose, M., Török, M., Woodward, M., & Bots, M. L. (2023). **Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure.** *New England Journal of Medicine, 389*(8), 700–709. https://doi.org/10.1056/nejmoa2304820
Citations: 125, (focus area *High Risk*)
A randomized controlled trial involving 61 research centers in eight European countries shows that a new method of dialysis, namely hemodiafiltration, is a better treatment for patients with kidney failure than hemodialysis. The chance of death for this patient group decreases by 23% with this new method. For kidney failure patients, this new treatment is an important breakthrough, and it is therefore expected that hemodiafiltration will be used more widely in the near future.

12. Nguyen, P. D., Gooijers, I., Campostrini, G., Verkerk, A. O., Honkoop, H., Bouwman, M., De Bakker, D. E. M., Koopmans, T., Vink, A., Lamers, G. E. M., Shakked, A., Mars, J., Mulder, A. A., Chocron, S., Bartscherer, K., Tzahor, E., Mummery, C. L., De Boer, T. P., Bellin, M., & Bakkers, J. (2023). **Interplay between calcium and sarcomeres directs cardiomyocyte maturation during regeneration.** *Science, 380*(6646), 758–764. https://doi.org/10.1126/science.abo6718
Citations: 20, (focus area *Heart Failure*)
Zebrafish hearts are known to regenerate after injury by generating new cardiomyocytes through cell division and differentiation. In the mammalian heart, however, damaged cardiac tissue is replaced by connective tissue after myocardial infarction, resulting in reduced cardiac function. Insight into the cardiac repair process in zebrafish may therefore be of therapeutic importance to induce recovery of mammalian cardiac tissue after myocardial infarction. In this article, the role of a novel regulator (LRRC10) in the proliferation and differentiation of zebrafish cardiomyocytes is described. An important finding is that the role of this regulator seems to be evolutionarily conserved, as it has a similar effect on mouse- and human cardiomyocytes.

13. Poorthuis, M. H. F., Hageman, S. H. J., Fiolet, A. T. L., Kappelle, L. J., Bots, M. L., Steg, P. G., Visseren, F. L. J., Bhatt, D. L., & De Borst, G. J. (2024). **Prediction of Severe Baseline Asymptomatic Carotid Stenosis and Subsequent Risk of Stroke and Cardiovascular Disease.** *Stroke, 55*(11), 2632–2640. https://doi.org/10.1161/strokeaha.123.046894
Citation: 1, open access (focus areas *High Risk, Cerebrovascular Disease and Atherosclerosis & Aneurysms*)
In this multidisciplinary approach, the diagnostic- and prognostic value of the Prevalence of Asymptomatic Carotid Artery Stenosis (PACAS) risk model was investigated for the detection of ACAS and the prediction of subsequent stroke and cardiovascular disease (CVD) after follow-up. After studying 26,384 patients it was concluded that the PACAS model was able to reliably identify patients at high risk for ACAS; moreover, high PACAS scores were significantly correlated with incidence of stroke and CVD.

14. Van de Wakker, S. I., Bauzá-Martinez, J., Rios Arceo, C., Manjikian, H., Snijders Blok, C. J. B., Roefs, M. T., Willms, E., Maas, R. G. C., Pronker, M. F., De Jong, O. G., Wu, W., Görgens, A., El Andaloussi, S., Sluijter, J. P. G., & Vader, P. (2024). **Size matters: Functional differences of small extracellular vesicle subpopulations in cardiac repair responses.** *Journal of Extracellular Vesicles, 13*(1), e12396. https://doi.org/10.1002/jev2.12396
Citations: 23, open access (focus area *Heart Failure*)
Small extracellular vesicles (sEVs) obtained from cardiac progenitor cells (CPCs) have been shown to possess cardiac repair properties. However, size heterogeneity within the sEV populations complicates determination of their regenerative abilities. In this study the functional consequences of size-selected sEV subpopulations in cardiac repair-related processes were investigated. It was shown that the middle- and smallest-sized sEV subpopulations exhibited the highest pro-angiogenic and anti-fibrotic activities. The sEV-based therapeutic potential for cardiac repair is further discussed.

15. Joosten, L. P. T., Van Doorn, S., Van de Ven, P. M., Köhlen, B. T. G., Nierman, M. C., Koek, H. L., Hemels, M. E. W., Huisman, M. V., Kruip, M., Faber, L. M., Wiersma, N. M., Buding, W. F., Fijnheer, R., Adriaansen, H. J., Roes, K. C., Hoes, A. W., Rutten, F. H., & Geersing, G-J. (2023). **Safety of Switching from a Vitamin K Antagonist to a Non-Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients with Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial.** *Circulation, 149*(4), 279-289. https://doi.org/10.1161/circulationaha.123.066485
Citations: 101, open access (focus areas *High Risk* and *Heart Failure*)
In this randomized controlled clinical trial in frail older patients with atrial fibrillation (FRAIL-AF) switching from vitamin K antagonist (VKA) treatment to a non-VKA oral anti-coagulant was associated with more bleeding complications compared to continuation with the VKA treatment. Therefore, without a clear indication, switching from VKA treatment to non-VKA oral anticoagulant treatment is not recommended for frail older patients with atrial fibrillation.

## Appendix B - Most important collaborations

The strategic program *Circulatory Health* harbors numerous partners and networks, from regional to (inter)national which are described on our website in more detail. Below some of these collaborations (and their eventual spin-offs) are elaborated on.

1. Andersen, C. R., Presseau, J., Saigle, V., Etminan, N., Vergouwen, M. D. I., & English, S. W. (2019). **Core outcomes for subarachnoid haemorrhage.** *The Lancet Neurology, 18*(12), 1075–1076.
   https://doi.org/10.1016/s1474-4422(19)30412-0
   Citations: 34, (focus area Cerebrovascular Disease)
   This letter resulted from a round table discussion that was held on June 25, 2019, in Amsterdam, the Netherlands, on the way(s) to improve outcome measurements in subarachnoid hemorrhage (SAH). The discussion was held between a group of SAH researchers (among which *Circulatory Health* PI M.D.I. Vergouwen), SAH survivors, healthcare providers, families, and foundation representatives. In the letter the components (core outcome domains, core outcome timeline, and core outcome measurement instruments) of a core outcome set for SAH were described.

2. Linschoten, M., & Asselbergs, F. W. (2020). **CAPACITY-COVID: a European Registry to determine the role of cardiovascular disease in the COVID-19 pandemic.** *European Heart Journal, 41*(19), 1795–1796.
   https://doi.org/10.1093/eurheartj/ehaa280
   Citations: 43, open access (overarching focus areas)
   The CAPACITY registry has been set up to clarify the role of cardiovascular disease in the COVID-19 pandemic. This can either provide more insight into cardiovascular complications in COVID-19 patients or into the clinical course of COVID-19 in cardiovascular disease patients. On May 19, 2025, the total number of inclusions was 13815 patients, with 72 centers from 13 different countries including patients. CAPACITY is endorsed by professional societies, patient organizations and companies. These include a.o. the Dutch Heart Foundation (DHF), the European Heart Network (EHN), the European Society of Cardiology (ESC), the British Heart Foundation (BHF), Harteraad, the Dutch CardioVascular Alliance (DCVA), Novartis, Novo Nordisk. The goal obviously is to improve the healthcare for (cardiovascular) COVID-19 patients.

3. Koop, Y., Wimmers, R.H., Bots, M.L., & Vaartjes, I. (2022). **Year numbers Cardiovascular Diseases in the Netherlands 2022.** Available from: https://www.hartenvaatcijfers.nl/jaarcijfers/jaarcijfers-hart-en-vaatziekten-2022-9a67f.
   open access, (overarching focus areas)
   Principal Investigators of the Julius Center, participating in *Circulatory Health*, are involved in producing the year numbers for cardiovascular diseases in the Netherlands; the numbers for 2022 are just an example of this. These numbers are the result of a collaboration between the Dutch Heart Foundation (DHF) and the Dutch Heart Registration (DHR) and directed at healthcare professionals, researchers, patients, and policy makers. Data are extracted from several sources, including Dutch Hospital Data (DHD), the Dutch Central Bureau of Statistics (CBS), and DHR. With this platform, the participating parties want to ensure that there is one central, joint and public environment where reliable and high-quality data can be found on cardiovascular diseases and related care in the Netherlands.

4. Dutch CardioVascular Alliance (DCVA)
   open access, (overarching focus areas)
   The DCVA is a national network facilitating and supporting collaborations between different research groups and centers by means of national consortia. The strategic program *Circulatory Health* is participating in several of these consortia, such as COVID@Heart, ECG project UMCU, DEFENCE, HEART4DATA, and MYDIGITWIN. The added value of these collaborations obviously is that serious cardiovascular problems are tackled on a national scale (such as 'Deltaplan Heart Failure'), by making use of the specific expertise of different academic centers and stakeholders.

5. Collaboration with professional soccer club FC Utrecht and the Dutch Heart Foundation (DHF)
(focus areas *Heart Failure* and *High Risk*)
During the last four years the Dutch Heart Foundation (DHF), professional soccer club FC Utrecht and UMC Utrecht joined forces via the "Carry that band"-campaign to emphasize the importance of cardiovascular health to a broader audience. Because high blood pressure is a silent but serious risk factor for cardiovascular disease, the focus is on measuring your blood pressure on a yearly basis. Clinicians from UMC Utrecht and ambassadors of FC Utrecht (including soccer players) work together in providing publicity and opportunity to measure blood pressure around one of the soccer games of FC Utrecht. Moreover, in the 2025 National Heart Failure week of DHF, Netherlands Heart Institute (NHI) and Dutch CardioVascular Alliance (DCVA) one of the soccer games of FC Utrecht will be used to focus the attention of the public on heart failure.
The added value of the collaboration with FC Utrecht is to generate public awareness for the importance of regular blood pressure measurements in the prevention of cardiovascular diseases and heart failure.

6. Women's Heart Challenge for medical students 2023.
(overarching focus areas)
In this Women's Heart Challenge- a Utrecht educational challenge - students were thinking along with researchers, clinicians, and patients about the rare heart disease Spontaneous Coronary Artery Dissection (SCAD), which mostly occurs in young women without apparent risk factors for cardiovascular disease. The kick-off for this event for over 400 (bio)medical students was in the FC Utrecht stadium. The best idea will be carried out by a limited number of students under supervision of experienced scientists/educators at the UMC Utrecht. In this way, (bio)medical students are already in an early stage of their career inspired to get involved in cardiovascular research.

7. ERN Guard-Heart
(focus area *Heart Failure*)
Principal investigators of *Circulatory Health* are participating as full members in the European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN Guard-Heart). In this network focused on genetically transmitted heart disease and specific procedures for pediatric patients, 44 expert healthcare providers from 16 European Member States bring in their specific expertise to tackle these diseases and highly specialized treatments. The added value of our input lies, amongst others, in extensive experience with providing multidisciplinary care to patients and relatives with suspected inherited cardiovascular disease, as well as in education and phenotyped cardiogenetic databases and patient registries (for further details see here).

8. AtheroNeth consortium
(focus area *Atherosclerosis & Aneurysms*)
To illustrate the collaboration on a national level AtheroNeth is used. AtheroNeth is a new consortium, funded by the Dutch Heart Foundation, that zooms in on three objectives (work packages): 1. The nature of different plaque types; 2. The identification of new blood markers and development of new imaging techniques; 3. The potential of personalized treatment. In this consortium all seven Dutch UMC's are participating.

9. Health Holland-TKI
(overarching focus areas)
*Circulatory Health* proves very successful in obtaining funding for public-private partnerships (PPP) via Health Holland-TKI (see as an example appendix C, #7). Several of these partnerships were already successful and the discoveries from those collaborations developed into spin-off companies (TargEd, Cordys Analytics, JAMA Therapeutics). TargEd focuses on the development of drugs designed to improve treatment of thrombosis. Cordys Analytics aims at the development of software for the early detection of heart disease. JAMA Therapeutics targets the delivery of genetic medicines to the heart.

## Appendix C - Grants and prizes

In the period 2019-2024 researchers from *Circulatory Health* acquired numerous (inter)national personal and collaborative grants, among which also Public Private Partnership (PPP) consortia grants. A selection of this is presented below.

### 1. NWO-Gravitation grant: Exposome-NL

The Exposome-NL consortium has been awarded with the NWO-Gravitation grant (€ 17.4 million) in 2019 to study the influence of non-genetic factors on health. Prof. Dr. R.C.H. Vermeulen and prof. dr. D.E. Grobbee are involved in this consortium as executive board members.

### 2. European Research Council (ERC) grants

In the evaluation period several *Circulatory Health* principal investigators received personal grants from the ERC:

- Prof. dr. H.M. den Ruijter (2019 and 2024): *ERC Consolidator* grant (Molecular basis of sex differences in atherosclerosis) and *ERC Proof of Concept* grant (Early detection of coronary artery disease).
- Dr. P. Vader (2019 and 2023): *ERC Starting* grant *(OBSERVE: extracellular vesicles for RNA drug delivery) and ERC Consolidator* grant (Unravelling extracellular vesicle heterogeneity to inspire improved therapeutic RNA delivery systems).
- Prof. dr. J.P.G. Sluijter (2024): *ERC Proof of Concept* grant (Delivering drugs in the body more effectively).
- Prof. dr. Y.M. Ruigrok (2019 and 2024): *ERC Starting* grant (PRYSM: early recognition of intracranial aneurysms to prevent life-threatening brain hemorrhages) and *ERC Proof of Concept* grant (Preventing brain hemorrhages non-invasively).

### 3. LeDucq Foundation grants

Four LeDucq Foundation consortium transatlantic grants were awarded that were/are executed in the evaluation period:

- Prof. dr. P.A. Doevendans (2018): Cure PhosphoLambaN induced Cardiomyopathy (CURE-PlaN).
- Prof. dr. G. Pasterkamp (2018): Defining the roles of smooth muscle cells and other extracellular matrix producing cells in late-stage atherosclerotic plaque pathogenesis.
- Prof. dr. H.M. den Ruijter (2022): Sex differences in atherosclerosis (AtheroGEN).

The above principal investigators are the European coordinators for these transatlantic consortia.

### 4. NWO-Vici personal grants

From 2019-2024 two of our researchers were honored with the prestigious Vici grant of NWO:

- Prof. dr. E. van Rooij (2020): Genetic cardiac diseases.
- Dr. J. Zwanenburg (2021): The heartbeat as source of information for brain health.

### 5. NWO-Vidi personal grants

Three of our researchers were awarded with the prestigious Vidi grant of NWO:

- Prof. dr. G.J. Geersing (2019): Vidi (Thrombophlebitis).
- Dr. P. Vader (2019): Vidi (Endogenous RNA couriers).
- Dr. S.A.E. Peters (2021): Vidi (Gender differences in heart disease explained).

### 6. Dutch Heart Foundation (DHF) personal Dekker grants

In the evaluation period several *Circulatory Health* researchers received personal Dekker grants from the DHF to support their research and career:

- Dr. P. Vader (2019): Cardiac-specific extracellular vesicle-mediated transport.
- Prof. dr. L. van Laake (2019): Prevention of chemotherapy-mediated cardiac damage.
- Dr. J. van Setten (2019): Genes underlying dilated cardiomyopathy.
- Dr. M.D.I. Vergouwen (2020; clinical established investigator): Prevention and treatment of stroke.
- Prof. dr. Y. Ruigrok (2022; clinical established investigator): Higher risk factors for brain aneurysms in women.
- Dr. B. Steensma (2022; postdoc): Development radiostethoscope for measuring blood flow through the heart.

- Dr. T. van de Hoef (2023): Diagnosis of chest pain with artificial intelligence.
- Dr. H. Westland (2023): Optimal support for heart failure.
- Dr. S. Hageman (2023): Digital decision aid for myocardial infarction.
- Dr. M. Bakker (2023): Causes of vertebral hemorrhages.
- Dr. N. Weaver (2024; clinical scientist): Development of a prediction model for mental problems after a stroke.

### 7. Public-Private Partnership (PPP) grants via Health Holland-TKI

Several of our (principal) investigators have proven successful in obtaining funding for public-private partnership (PPP) consortia grants via Health Holland-TKI. Some recent examples:

- Prof. dr. W. Suyker (2024): QUICK coronary bypass LINK with Octocon blood vessel connection technology (QUICK-LINK).
- Dr. R.W.M. Vernooij (2024): Choosing the right dialysis modality in clinical practice: hemodiafiltration or hemodialysis (CHAMPION).
- Dr. B. van Balkom (2024): Human Organ Models combined On Chips foR Assessment of Systemic diSease mechanisms and Unwanted Side effects *in vitro* (HOMO CRASSUS *in vitro*).

### 8. Consortia grants awarded for various programs

Within the evaluation period various consortia grants were awarded, of which the following are examples:

- NANOSPRESSO-NL (Local preparation of high-quality, personalized nucleic acid nanomedicines): 2022, prof. dr. R. Schiffelers, NWO-NWA ORC (€ 8.14 million).
- DRIVE-RM (New treatments for chronic diseases such as heart and kidney failure using implantable smart materials): 2024 prof. dr. M. Verhaar, NWO-SUMMIT (DRIVE-RM: New treatments for chronic diseases such as heart and kidney failure using implantable smart materials (€ 37.5 million).
- RAPHAEL (Integrating a palliative care approach for patients with heart failure): 2024, prof. dr. G.J. Geersing, Horizon Europe (€ 6.2 million).
- AtheroNeth (Differences in mechanisms in cause and progression atherosclerosis): 2024, prof. dr. G. Pasterkamp, Dutch Heart Foundation (€ 6 million).

## Appendix D - Key outputs or activities aimed at a professional of wider audience

The strategic program *Circulatory Health* has highlighted below 10 key outputs/activities over the period 2019-2024, which were aimed at a professional and/or wider audience.

1. Jaspers, N. E. M., Blaha, M. J., Matsushita, K., Van der Schouw, Y. T., Wareham, N. J., Khaw, K-T., Geisel, M. H., Lehmann, N., Erbel, R., Jöckel, K-H., Van der Graaf, Y., Verschuren, W. M. M., Boer, J. M. A., Nambi, V., Visseren, F. L. J., & Dorresteijn, J. A. N. (2020). **Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people.** *European Heart Journal, 41*(11), 1190–1199. https://doi.org/10.1093/eurheartj/ehz239
   Citations: 92, open access (focus area *High Risk*)
   In this article the development and validation are described of the LIFEtime-perspective CardioVascular Disease (LIFE-CVD) model. This model allows estimation at the individual level of cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation effects on healthy people. To make this model easily accessible to patients and medical doctors, it was developed into an interactive online tool available via www.U-Prevent.com. It allows patients and healthcare professionals to calculate individual cardiovascular risk and the effect of preventive measures.

2. Collet, J-P., Thiele, H., Barbato, E., Barthélémy, O., Bauersachs, J., Bhatt, D. L., Dendale, P., Dorobantu, M., Edvardsen, T., Folliguet, T., Gale, C. P., Gilard, M., Jobs, A., Jüni, P., Lambrinou, E., Lewis, B. S., Mehilli, J., Meliga, E., Merkely, B., ... Siontis, G. C. M. (2021). **2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.** *European Heart Journal, 42*(14), 1289–1367. https://doi.org/10.1093/eurheartj/ehaa575
   Citations: 3723, open access (focus areas *Heart Failure* and *Atherosclerosis & Aneurysms*)
   As a member/author of the European Society of Cardiology (ESC) Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, prof. dr. F.H. Rutten participated to produce the 2020 ESC guidelines for this patient group.
   For dissemination of knowledge on the causes of heart failure, how to live with this disease, and all other questions patients, families or their caretakers may have, a website (heartfailurematters.org) has been created by the ESC in 11 different languages. To maintain and update knowledge on this website, healthcare professionals voluntarily contribute their time and expertise, including experts from *Circulatory Health*.

3. Visseren, F. L. J., Mach, F., Smulders, Y. M., Carballo, D., Koskinas, K. C., Bäck, M., Benetos, A., Biffi, A., Boavida, J-M., Capodanno, D., Cosyns, B., Crawford, C.A., Davos, C. H., Desormais, I., Di Angelantonio, E., Franco, O. H., Halvorsen, S., Hobbs, F. D. R., Hollander, M., ..., Williams, B. (2021). **2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.** *European Heart Journal, 42*(34), 3227–3337. https://doi.org/10.1093/eurheartj/ehab484
   Citations: 3938, open access (focus area *High Risk*)
   Publication of the new European guidelines for the prevention of cardiovascular diseases with the aim of better patient care and thus impactful for all citizens. This directive is implemented in general practices and with this, according to the most recent scientific insights, (preventive) risk management of cardiovascular diseases can be applied. Prof. dr. F.L.J. Visseren was chairman of this international task force.

4. Arbelo, E., Protonotarios, A., Gimeno, J. R., Arbustini, E., Barriales-Villa, R., Basso, C., Bezzina, C. R., Biagini, E., Blom, N. A., De Boer, R. A., De Winter, T., Elliott, P. M., Flather, M., Garcia-Pavia, P., Haugaa, K. H., Ingles, J., Jurcut, R. O., Klaassen, S., Limongelli, G., ..., Kaski, J. P. (2023). **2023 ESC Guidelines for the management of cardiomyopathies.** *European Heart Journal, 44*(37), 3503–3626. https://doi.org/10.1093/eurheartj/ehad194
   Citations: 1012, open access (focus area *Heart Failure*)
   As a member/author of the ESC Task Force for the management of cardiomyopathies, prof. dr. J.P. van Tintelen participated to produce the 2023 ESC guidelines for this patient group.

5. Kharlamov, A., Sherriff, N., Delles, C., & Van der Harst, P. (2024). **Tackling cardiovascular healthcare disparities for the LGBTQIA+ population: a call to action in the European Society of Cardiology.** *European Heart Journal, 45*(15), 1291–1294. https://doi.org/10.1093/eurheartj/ehad882
Citation: 1, open access (focus area *Heart Failure*)
In this *European Heart Journal* Global Spotlight, Kharlamov et al provide an overview of the LGBTQIA+ equality index among European countries, indicating that the rights and freedom of LGBTQIA+ people differ within Europe, including inequalities in (cardiovascular) health status. Moreover, they present the challenges that LGBTQIA+ communities and clinicians are facing, as well as strategies to address those issues.

6. Open Science Community Utrecht (OSCU)
(overarching focus areas)
Several principal investigators of *Circulatory Health* (e.g. Y.T. van der Schouw, R.C.H. Vermeulen, M.L. Bots, A.W. Hoes, S.W. van der Laan, M.K. Bakker, S. Hageman) are active as members of the Open Science Community Utrecht (OSCU). With regard to Open Science, OSCU aims at (1) promoting transfer of knowledge; (2) inspiring researchers to start with Open Science practices; and (3) providing input on policies, infrastructure, and support services. In 2021 *Circulatory Health* investigators G. Pasterkamp and S.W. van der Laan were involved in organizing the *Open Science Symposium* in the Faculty of Medicine of UMC Utrecht.

7. Meet the professor (https://www.uu.nl/en/organisation/meet-the-professor)
(focus areas *Heart Failure* and *High Risk*)
To decrease the distance between university and society, professors at Utrecht University, UMC Utrecht and Wilhelmina Child Hospital yearly visit elementary schools in Utrecht (groups 6, 7 and 8; 9-12 years of age) to be questioned by the children on all kinds of topics (work, hobbies, university). Professors of *Circulatory Health* are regularly participating in these sessions, e.g.:

- In 2022: D.E. Grobbee, A.W. Hoes, H.M. den Ruijter, J.P.G. Sluijter.
- In 2023: D.E. Grobbee, A.W. Hoes, H.M. den Ruijter, J.P.G. Sluijter, K. Kaasjager, R. Schiffelers.
- In 2024: H.M. den Ruijter, J.P.G. Sluijter, F.H. Rutten.

8. Betweter Festival
(focus areas Heart Failure and High Risk)
The Betweter Festival is organized by Utrecht University. During the Betweter Festival artists, researchers and visitors meet each other to discuss the big questions of today and the world of tomorrow. In 2021 H.M. den Ruijter (Is there music in the rhythm of your heart) and in 2024 Y.T. van der Schouw (Does the food industry makes us ill?), principal investigators of *Circulatory Health*, participated in this event.

9. University Museum Utrecht
(focus area *Heart Failure*)
In the University Museum Utrecht, the public can explore and engage with research from Utrecht University, from the past to the present. In one of the rooms, you can get acquainted with (medical) technology used in the study of the human body. *Circulatory Health* contributed to the museum by providing knowledge of the heart-lung machine, a machine that during an operation can take over heart function. In an interactive session the public can build their own heart-lung machine and test its function.

10. Development of the Innovation Funnel for Valuable AI in Healthcare
(overarching focus areas)
At the request of the Ministry of Health, Welfare & Sports, one of our principal investigators (S. Haitjema) was involved as product owner in an action team for the development of the tool Valuable AI. This tool has been embraced, further developed and implemented over the past five years by all UMC's, the Dutch AI Coalition (NLAIC), investors and many peripheral houses.

# Strategic Program Infection & Immunity

Self-evaluation report 2019-2024

# Strategic Program Infection & Immunity

## 1 - Mission, governance, and main research topics

### Research strategy

The incidence of immune-mediated inflammatory diseases (IMIDs) and infections caused by microorganisms resistant to current therapies is increasing, necessitating a coordinated multidisciplinary scientific and healthcare response. At the same time, harnessing the immune system is emerging as a powerful therapeutic approach for preventing and treating infections, immune disorders, and cancer. These research themes are integrated into the strategic program Infection & Immunity (I&I) (Figure 1).

Infectious diseases and antimicrobial resistance are rising worldwide. With a decline in newly developed antimicrobials over the last decades, untreatable bacterial infections have become a realistic scenario in many parts of the world. At I&I, we study infection biology and pathology and model infectious diseases to develop effective public health interventions, enable early detection, predict disease spread, and guide treatment strategies like vaccination. We also contribute to collecting real-world trial data, developing new clinical trial methods, and establishing a European clinical trial network to better evaluate new antimicrobial agents and immune therapies for infectious diseases. This helps guide new (and non-antibiotic) treatment protocols, shape public health policies, and foster the development of next-generation therapeutics, significantly improving the global response to infectious disease outbreaks and pandemic preparedness.

IMIDs encompass over 30 chronic diseases affecting virtually every organ. About 5-7% of the population suffers from an IMID, making these diseases a significant healthcare problem. Some IMIDs are iatrogenic or infectious, but most have an unknown etiology. At 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 elderly. Integrated studies of the immune system will allow for the classification of patients based on the underlying mechanisms for IMIDs. Optimal treatment of patients with diseases resulting from failing or derailed immunity and/or infection requires a shift from a typically “organ-driven” to a personalized “immune activation pattern-driven” approach.

Furthermore, we leverage our knowledge to harness the immune system in the prevention and treatment of inflammation, infection, and cancer. By combining our fundamental knowledge of immunology with clinical expertise, we design and study novel immune-mediated therapies, including vaccines, biologicals and cell-based therapies. To accelerate clinical implementation, our scientists collaborate with industrial partners, such as biotech and pharmaceutical companies, or develop their discoveries through spin-off companies, maximizing clinical impact of early discoveries.

The program aims to contribute to solutions for these diseases with large societal impact, focusing on tertiary patient care, strong research facilities, strong connections in the region and beyond, continuous response to new developments, and an effective talent policy.

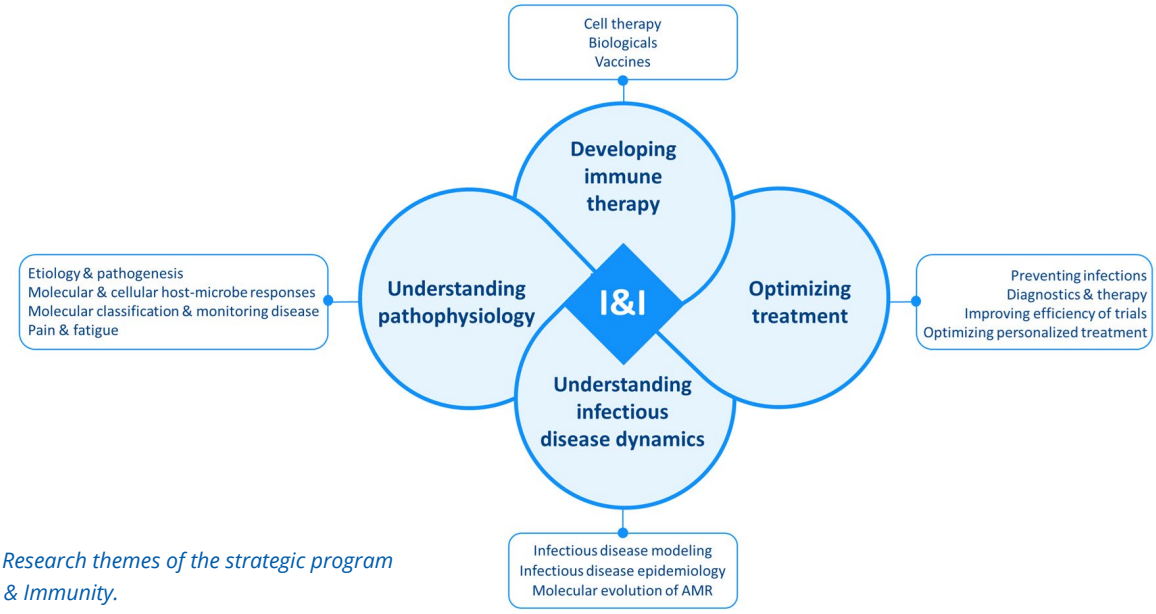



*Figure 1. Research themes of the strategic program Infection & Immunity.*

## Mission

The strategic program I&I aims to be a national and international leader in advancing and sharing knowledge and innovation on inflammatory and infectious diseases, and immune-mediated therapy. Our goal is to improve treatment for patients, especially those with complex infections, immune disorders, or cancer. Through close collaboration between our clinicians and researchers, we deliver high-quality care and cutting-edge research, involving patients where possible. We are committed to nurturing the next generation of experts by training talented individuals in this field.

## Governance

The strategic program I&I collaborates with eight divisions within UMC Utrecht. The research activities are primarily conducted by three major departments: the Center for Translational Immunology (CTI) and Medical Microbiology (MMB) within the division of Laboratories, Pharmacy and Biomedical Genetics, and the Epidemiology of Infectious Diseases (EpiID) at the Julius Center. These departments work closely with clinical research groups across the divisions of Pediatrics, Internal Medicine & Dermatology, Heart & Lungs, Images & Oncology, and Anesthesiology, Intensive Care & Emergency Medicine. The program brings together more than 600 researchers across 57 research groups. Our academic team includes 44 full professors, around 40 associate professors, 155 assistant professors, 70 postdoctoral researchers, and 250 PhD students.

Leadership of the program is provided by a Management team, which includes a Daily Board – consisting of chair Marc Bonten, Linde Meyaard, Annelies Verbon, program manager Jovanka Bestebroer – alongside representatives from the participating divisions. From July 2025, Linde Meyaard will be the chair of Strategic Program I&I. For details on the program's governance, please refer to Figure 2.

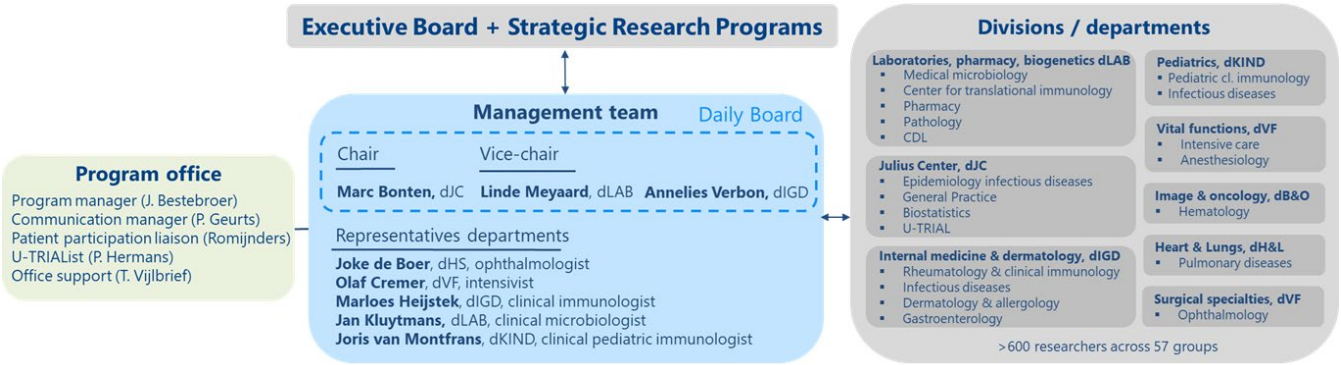



*Figure 2. Governance of the strategic program Infection & Immunity.*

## 2 - Concise reflection on the program-specific recommendations from the previous evaluation

During the previous SEP evaluation in 2019, the I&I program was reviewed as strong and vibrant with great societal as well as biomedical importance. Based on previous I&I-specific committee recommendations, we developed a strategy for future I&I technologies and facilities. Core facilities for the three largest research departments have been crucial, and we supported them over the past years. Significant efforts have established robust core facilities at the Center for Translational Immunology (CTI) - Central Flow Facility, Central Facility Imaging, Utrecht Monoclonal Antibody Facility, Computational Immunology Core - providing technical and logistic support to all research groups. Medical Microbiology (MMB) invested in a new microbiome lab and a bioinformatics group and quickly realized a Biosafety Level-3 laboratory for SARS-CoV-2 work in 2020. Epidemiology of Infectious Diseases focused on innovative biostatistics and research methodologies. We co-founded Ecraid, a large European network for clinical research in infectious diseases (with our clinical trial network activities now part of Ecraid foundation, with Marc Bonten as CEO) (EpiID), and coordinated several COVID-19 research programs during the pandemic (2020-2023). Ten clinical scientists with dedicated research time were appointed within I&I, enhancing the connection between research and clinic.

To foster international collaborations, also beyond Europe, we identified globally focused projects (2019-2020) to explore opportunities and experiences with non-European funding agencies. We organized PI meetings to discuss international collaboration opportunities, although these efforts were hindered by the COVID-19 pandemic. Additionally, we discussed grant scouting and writing support with two I&I-dedicated grants advisors from the Research Support Office (2019-2024). While our European collaborations remain strong, more efforts are needed to strengthen links with other continents.

## 3 - Main research accomplishments in the period 2019-2024

**Advancing epidemiological research: modelling disease transmission and pandemic preparedness**
Two months after the previous SEP (November 2019) the world was confronted with the COVID-19 pandemic. Many I&I research groups immediately shifted focus to address new research questions to inform policy makers and physicians. The Epidemiology of Infectious Diseases research theme (Prof. Marc Bonten, Dr. Martin Bootsma, Prof. Patricia Bruijning-Verhagen, Prof. Kretzschmar, Dr. Ganna Rozhnova, Dr. Roderick Venekamp, Prof. Janneke van de Wijgert) conducted epidemiological and mathematical modeling studies to characterize disease transmission across various settings and evaluate the impact of control interventions.

In recent years, our work has included COVID-19 vaccination and treatment trials, as well as epidemiological studies (e.g. characterizing transmission of respiratory pathogens, including SARS-CoV-2, within households, schools, and hospitals; effectiveness of digital contact-tracing), evaluation of SARS-CoV-2 rapid diagnostic tests, and mathematical modelling to support evidence-based policymaking. During the COVID-19 pandemic, team members contributed to the national Outbreak Management Team and advisory committees for the Ministries of Health and Education.

Our input informed key policies, including implementation of the “corona melder” contact-tracing app, the “corona passport”, and mitigation and testing policies in educational settings. Findings from our studies were shared with policymakers (Outbreak Management Team, ministries) and gained international recognition, featuring in reports by the European Centre for Disease Prevention and Control (ECDC) and World Health Organization (WHO).

More recently, we have secured multiple research grants (e.g., from ZonMw and Ministry of Education) to intensify our research on pandemic preparedness and Post-COVID. Our epidemiological projects explore transmission routes in classrooms, the development of pathogen-agnostic SIR models for schools, novel syndromic school-surveillance tools, and novel statistical methods to quantify in-school transmission. Modeling projects focus on understanding the spread of respiratory infections in and between schools, the impact of contact clustering on contact tracing, the interaction between social networks and epidemic spread, and the use of mobility data for epidemic modelling. (Key output highlighted in appendix A: Kretzschmar et al. 2020; Rozhnova et al. 2021; Wynants et al. 2020)

### Driving innovation in platform trials for infectious diseases

For the past decade, the Clinical Trials in Infectious Diseases group has led advancements in trial innovation. In 2014, the Randomized Embedded Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP) started, using a Bayesian adaptive platform methodology to deliver rapid, robust results in future pandemics. This global trial pivoted at the start of the COVID-19 pandemic and has delivered 14 practice-changing results, immediately incorporated into national (SWAB-FMS guideline for COVID-19) and international guidelines (WHO Therapeutics and COVID-19: Living Guideline). The trial has gained global recognition and media attention such as Parool, Nature, Chemistry World, UK's *Science Media Centre and JAMA podcast "Conversations with Dr. Bauchner*". To date, it has tested 66 interventions across 18 domains, involving nearly 300 sites worldwide to perform over 24,000 randomizations. Prof. Marc Bonten and Dr. Lennie Derde were among the initiating research team, and Dr. Lennie Derde chaired the International Trial Steering Committee from 2021-2023. Also, during the pandemic, UMC Utrecht initiated and participated in four randomized trials evaluating the efficacy of BCG-vaccination to protect against COVID-19 infection through inducing trained immunity. The REMAP-CAP trial methodology inspired others, which led to the *Staphylococcus aureus* Bacteremia Network Adaptive Platform (SNAP) trial, a global collaboration evaluating five interventions across three domains, which reached its first platform trigger in 2024. UMC Utrecht (Prof. Marc Bonten, Dr. Marjolein Hensgens, Dr. Miquel Ekkelenkamp) and Ecraid are leading the SNAP trial in Europe. Furthermore, UMC Utrecht investigators (Prof. Marc Bonten, Dr. Alike van der Velden, Dr. Roderick Venekamp) are co-leading an international adaptive platform trial evaluating treatments for Acute Respiratory Infections in Primary Care (ECRAID-PRIME). Finally, Prof. Janneke van de Wijgert is leading the RECLAIM trial, an adaptive platform trial testing multiple treatments in patients with Post-COVID syndrome.

These complex trials require specialized knowledge, particularly due to their adaptive nature. Our researchers bring expertise in (Bayesian) methodology, (bio)statistics, infectious diseases, critical care, legal and operational aspects, data management, quality control, finance, and project management. Our international networks and expertise make I&I a key asset to UMC Utrecht. (Key output: REMAP-CAP Investigators, 2020-2023)

### Unraveling infectious disease pathophysiology by dissecting molecular mechanisms of host-microbe interactions

The Department of Medical Microbiology has a strong track record in dissecting the molecular mechanisms of host-microbe interactions. By connecting over 20 partners within UMC Utrecht and across Utrecht Science Park, our newly established Microbiome Sequencing Facility contributed to over 15 publications in five years. The Molecular and Cellular Host-Microbiota Interactions group developed an innovative high-throughput, high-resolution technology to interrogate microbial IgA-coating. This open-access technology, led by Dr. Marcel de Zoete, is now applied to mechanistically study the role of intestinal microbiota in human health and disease. In collaboration with industry partners (GSK Vaccines, Genmab, argenx), the Bacterial Infections and Immunity group advanced the development of anti-bacterial immunotherapies by providing molecular understanding of the mechanisms by which antibody-complement interactions induce bacterial clearance. Prof. Suzan Rooijakkers was awarded both a Dutch Research Council (NWO) Vici and a European Research Council Consolidator grant. In collaboration with international academic partners, the Human Genetics of Host-Microbe Interactions group (Dr. András Spaan) identified human OTULIN haploinsufficiency as a previously unknown disorder underlying life-threatening bacterial infections in otherwise healthy individuals, with contributions from the international patient federation 5P- Society for patients with a chromosomal disorder. Dr. András Spaan received an NWO Vidi and a European Research Council Starting grant. (Key output: Cruz et al. 2021; Spaan et al. 2022)

### Unmasking tissue T-cells: differentiation, dynamics, and disease

While almost all T-cell research focuses on blood-derived cells, the Tissue Immunology group explores the 99% of human T-cells that reside in tissues. Supported by prestigious NWO Vici grants (Prof. Femke van Wijk and Prof. José Borghans) and an NWO Veni grant (Dr. Theo van den Broek), we have made several breakthrough discoveries. Contrary to common belief, our research has revealed that tissue-resident T-cells are not long-lived, and that they maintain immunological memory in a highly dynamic way. We have also demonstrated that distinct inflamed anatomical sites share dominant T-cell clones and functional traits. These clones expand with each disease relapse, appearing in both inflamed tissues and the circulation. Additionally, we have revealed that regulatory T-cells (Tregs) in tumors and inflamed tissues undergo similar functional imprinting, leading to highly differentiated and clonal Tregs. Together,

these findings are redefining our understanding of T-cell dynamics and unveil both opportunities and challenges in targeting T-cells in cancer and autoimmunity. Our work has gained significant international recognition, with invitations to present at over 15 international conferences and inclusion in the prestigious T Cell Connect Europe network and Quantitative T-cell Immunology and Immunotherapy (QuanTII) network (Horizon 2020). (Key output: Mijnheer et al. 2021; Baliu-Piqué et al. 2021)

**Leveraging real-world evidence: longitudinal cohorts and biorepositories driving translational research**
Several I&I research groups manage successful longitudinal cohorts and biorepositories driving scientific discoveries and sustained (inter)national collaborations. By systematically collecting high-quality real-world clinical data across diverse patient populations and treatment pathways, these registries enhance personalized therapy and enable pragmatic clinical trial enrollment. Biospecimens from these cohorts, stored at UMC Utrecht's central biobank, support numerous researcher-led and industry-sponsored studies. We highlight four cohorts. The BioDay registry (2018; Prof. Marjolein de Bruin-Weller) provides prospectively collected data and materials on atopic dermatitis, with over 2200 patients across 20 Dutch centers. Over 1000 Utrecht-based adult and pediatric patients also contribute to the BioBank Skin. The unique combination of a well-defined patient cohort and collected biomaterials enabled high-impact translational research (over 40 publications in five years). BioDay is expanding to include other chronic inflammatory skin diseases (prurigo nodularis, chronic urticaria, bullous pemphigoid). The MARS biorepository (2011; Prof. Olaf Cremer) contains daily plasma specimens from nearly 20,000 ICU patients with/at risk of sepsis, with prospective infection assessment. The PLUTO cohort (2020; Prof. Olaf Cremer) follows high-risk surgery patients, collecting infection screening, EEG, spirometry, blood sampling, and one-year follow-up data. Both have catalyzed (inter)national collaborations with academic and biotech partners in sepsis diagnosis, risk stratification, and subphenotyping, yielding over 100 publications. The ophthalmology cohorts (2017; Prof. Joke de Boer) collect clinical data, blood, and ocular fluid samples for uveitis, retinal, and corneal diseases. Unique cohorts include MHC-I associated uveitis (birdshot chorioretinopathy, HLA-B27 uveitis) and pediatric uveitis (juvenile idiopathic arthritis-associated, tubulointerstitial nephritis, and intermediate). Our research focuses on genetic predisposition and risk of developing uveitis. BioDay and MARS are FAIR-indexed in the European Health Research Data and Sample Catalogue. (Key output: Spekhorst et al. 2022)

**From bench to bedside: development of ARGX-117 to inhibit complement in multifocal motor neuropathy**
CTI investigators (led by Prof. em. Erik Hack) initiated the development of an anti-C2 antibody that blocks both the classical and lectin complement pathways. In collaboration with Prof. van der Pol (Neurology), this approach held promise for treating multifocal motor neuropathy (MMN), a rare disease where complement activation leads to nerve damage, impairing muscle function. Recognizing its therapeutic potential, the Antibody Therapy group, led by Prof. Jeanette Leusen, has an active collaboration with argenx to advance the development of this anti-C2 antibody, now called ARGX-117. We first described the mechanism of action in *Biologics and Immunotherapy* (2020). Our additional findings, described in *Neurology Neuroimmunology & Neuroinflammation* (2022), confirmed antibody's effectiveness in an MMN disease model developed at CTI. These studies laid the foundation for ARGX-117's clinical development as a promising treatment for complement-mediated diseases. In 2024, argenx reported encouraging results from the ARDA Phase II trial, showing positive outcomes for MMN patients treated with ARGX-117. A Phase III trial is planned for 2025. Dr. Krijgsman is leading efforts to analyze patient samples and further explore the role of complement in MMN. This collaboration between academia and industry underscores how basic research can drive clinical innovations, bringing MMN patients closer to a novel treatment option. (Key output: Budding et al. 2022; Van de Walle et al. 2021)

**Unlocking the therapeutic potential of inhibitory receptors in inflammation and cancer**
The Inhibitory Receptor Lab, led by Prof. Linde Meyaard and Dr. Michiel van der Vlist, is dedicated to harnessing the full potential of inhibitory receptors to cure inflammatory disease and cancer. It is one of the few labs worldwide that simultaneously explores the biology of these receptors in the context of health, cancer, and inflammation. Recently, our team made a full inventory of all potential inhibitory receptors (~440) encoded in the human genome, which in principle could all be targeted therapeutically. To enable target selection, we defined a functional categorization of inhibitory receptors in collaboration with theoretical biologist Prof. José Borghans. In a joint project with Prof. Niels Eijkelkamp, we identified an essential role for the inhibitory CD200Receptor in the resolution of inflammatory pain (see next accomplishment), now funded by an NWO ENW-M2 grant. The lab was also the first to identify collagens as ligands for the inhibitory receptor LAIR-1, followed by the identification of collagen-domain-containing proteins C1q, MBL and

SpD. Our collaborations with biotech companies NGM and NextCure have facilitated the translation of fundamental findings into clinical applications: LAIR-1 blocking therapeutics from both companies have entered in clinical trials for cancer. In ongoing studies, supported by KWF, we aim to determine which cancer types would benefit most from these therapies. Additionally, our lab is part of major research consortia, including a national initiative on myeloid cells targeting in cancer (supported by Oncode Institute, Dutch Cancer Society KWF and NWO ENW-XL) and the European REPRESSIT consortium (Horizon Europe EIC Pathfinder program) to design advanced therapeutics targeting LAIR-1. (Key output: Rumpret et al. 2020; Ramos et al. 2021)

**Decoding immune-neuron interactions for novel chronic pain therapies**

The Neuroimmunology of Pain group is dedicated to understanding chronic pain and developing new treatments, as millions in Europe suffer from chronic pain without effective treatments. We are a partner in the EU-funded consortium BonePain, now successfully funded for the third consecutive term. Additionally, we have collaborated in two European consortia alongside Oxford University, Karolinska Institute, Queen Mary University of London, and IBDML in Marseille. Our research has uncovered critical roles for immune cell-to-neuron communication in maintaining osteoarthritis pain and highlighted the essential function of macrophages in resolving inflammatory pain. These findings have been published open-access in leading journals, including Neuron, PNAS, JCI, and Cell Reports Medicine, and have garnered media attention from New Scientist, NRC newspaper, and BNR radio. Our work has led to three patents for novel pain therapies. These patents have been licensed to our spinoff company Synerkine Pharma, which has secured over €15 million in funding for the clinical development of cytokine fusion proteins for the treatment of chronic pain or are being utilized by pharmaceutical company argenx for a potential novel osteoarthritis pain therapy. We actively collaborate with pharmaceutical partners to develop new pain treatments, including therapies for diabetes-induced painful neuropathy. In partnership with a pain clinic, we conduct contract research to identify biological signatures of pain chronification for use in clinical trials. Our contributions to the field have been recognized through multiple keynote lectures and prestigious personal NWO Vici (Prof. Niels Eijkelkamp) and NWO Vidi and Veni (Dr. Hanneke Willemen) grants. (Key output: van der Vlist et al. 2022; Prado et al. 2021)

## 4 - Specific questions for the research committee

1. Are there notable gaps in our research program that we should consider investigating?
2. Which areas could benefit from increased collaboration between research and clinical practice?

# Appendix

## Appendix A - Key scientific outputs

This appendix showcases publications that support the narrative accomplishments outlined in the main section.

1. Kretzschmar, M. E., Rozhnova, G., Bootsma, M. C. J., van Boven, M., van de Wijgert, J. H. H. M., & Bonten, M. J. M. (2020). **Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study.** *The Lancet Public Health, 5*(8), e452-e459. https://doi.org/10.1016/S2468-2667(20)30157-2.
   Citations: 513, open access
   This modelling study identified key factors for successful contact tracing strategies. Minimizing testing delays had the greatest impact on reducing onward transmissions. Optimizing testing and tracing coverage and minimizing tracing delays, for instance with app-based technology, further improved contact tracing effectiveness, with the potential to prevent up to 80% of transmissions. The article gained significant attention from policy makers both in the Netherlands and internationally.

2. Rozhnova, G., van Dorp, C. H., Bruijning-Verhagen, P., Bootsma, M. C. J., van de Wijgert, J. H. H. M., Bonten, M. J. M., & Kretzschmar, M. E. (2021). **Model-based evaluation of school- and non-school-related measures to control the COVID-19 pandemic.** *Nature Communications, 12*(1), 1-11. Article 1614. https://doi.org/10.1038/s41467-021-21899-6.
   Citations: 50, open access
   This modelling study assessed the impact of school-based measures during the COVID-19 pandemic in the Netherlands using a transmission model fitted to seroprevalence and hospital admission data. Our finding showed that the impact of measures reducing school-based contacts depended on the remaining opportunities to reduce non-school-based contacts. The study attracted significant attention from national and international media, research networks and policy makers, informing COVID-19 policies nationally and internationally. Notably, the results were featured in ECDC guidelines on COVID-19 in children and school transmissions. This work led to invited lectures and strengthened international research collaborations and networks and contributed to securing European Commission funding.

3. Wynants, L., Van Calster, B., Collins, G. S., Riley, R. D., Heinze, G., Schuit, E., Bonten, M. M. J., Damen, J. A. A., Debray, T. P. A., De Vos, M., Dhiman, P., Haller, M. C., Harhay, M. O., Henckaerts, L., Lohmann, A., Jenniskens, K., Kreuzberger, N., Luijken, K., Ma, J., ... Van Smeden, M. (2020). **Prediction models for diagnosis and prognosis of covid-19: Systematic review and critical appraisal.** BMJ (Clinical research ed.), 369, 1-24. Article m1328. https://doi.org/10.1136/bmj.m1328.
   Citations: 2139, open access
   This study describes a living systematic review of diagnostic and prognostic prediction models and is also the first living review ever published in BMJ. It provides a relevant and accessible overview of existing prediction models, with the primary goal of helping users distinguish between high- and low-quality models (also see: www.covprecise.org/). The first article was first published in April 2020, and the fourth and final update was published in February 2021. This project was made possible through close collaboration with the Cochrane Prognosis Methods Group and an international partnership involving more than 40 prediction model experts.

4. REMAP-CAP Investigators. (2020). **Effect of Hydrocortisone on Mortality and Organ Support in Patients with Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial.** *JAMA - The Journal of The American Medical Association, 324*(13), 1317-1329. DOI. Citations: 621

REMAP-CAP Investigators. (2021). **Interleukin-6 receptor antagonists in critically ill patients with COVID-19.** *The New England journal of medicine, 384*(16), 1491-1502. DOI. Citations:1359

REMAP-CAP, ACTIV-4a, and ATTACC Investigators. (2021). **Therapeutic anticoagulation with heparin in critically ill patients with COVID-19.** *The New England journal of medicine, 385*(9), 777-789. DOI. Citations: 663

ATTACC, ACTIV-4a, and REMAP-CAP Investigators. (2021). **Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with COVID-19.** *The New England journal of medicine, 385*(8), 790-802. DOI. Citations: 618

REMAP-CAP Investigators. (2023). **Simvastatin in Critically Ill Patients with COVID-19.** *The New England journal of medicine, 389*(25), 2341-2354. DOI. Citations: 26

REMAP-CAP Investigators. (2023). **Long-term (180-Day) Outcomes in Critically Ill Patients With COVID-19 in the REMAP-CAP Randomized Clinical Trial**. *JAMA - The Journal of The American Medical Association, 329*(1), 39-51. DOI. Citations: 85

In REMAP-CAP, we have shown that Adaptive Platform Trials are a valuable and efficient tool to investigate new treatments for novel pandemic diseases. The methodology allows for fast integration of new potential therapies, avoids the need for (impossible) sample size estimations for new diseases, and allows for dropping ineffective therapies early. Since 2019, 14 platform conclusions have been delivered in ten publications in high-ranking clinical journals. The six examples referred here have delivered results on COVID-19 treatment with corticosteroids, IL-6 receptor antagonists, heparin (for moderately ill and severely ill patients, and simvastatin, as well as on long term outcomes, and were immediately incorporated into international guidelines. In all studies UMC Utrecht investigators are part of the REMAP-CAP investigators, and Dr. Lennie Derde was part of the writing team.

5. Cruz, A. R., den Boer, M. A., Strasser, J., Zwarthoff, S. A., Beurskens, F. J., de Haas, C. J. C., Aerts, P. C., Wang, G., de Jong, R. N., Bagnoli, F., van Strijp, J. A. G., van Kessel, K. P. M., Schuurman, J., Preiner, J., Heck, A. J. R., & Rooijakkers, S. H. M. (2021). **Staphylococcal protein A inhibits complement activation by interfering with IgG hexamer formation.** *Proceedings of the National Academy of Sciences of the United States of America, 118*(7), 1-11. Article e2016772118. https://doi.org/10.1073/pnas.2016772118.
Citations: 70, open access

This study describes how Fc engineering of antibodies can be utilized to overcome bacterial immune escape. The work was performed in collaboration with GSK and currently other companies are applying this knowledge on host-microbe interactions from to enhance effectiveness of therapeutic antibodies in combating infectious diseases.

6. Spaan, A. N., Neehus, A. L., Laplantine, E., Staels, F., Ogishi, M., Seeleuthner, Y., Rapaport, F., Lacey, K. A., Van Nieuwenhove, E., Chrabieh, M., Hum, D., Migaud, M., Izmiryan, A., Lorenzo, L., Kochetkov, T., Heesterbeek, D. A. C., Bardoel, B. W., DuMont, A. L., Dobbs, K., ... Casanova, J. L. (2022). **Human OTULIN haploinsufficiency impairs cell-intrinsic immunity to staphylococcal a-toxin.** *Science, 376*(6599), Article eabm6380. https://doi.org/10.1126/science.abm6380.
Citations: 36

This work showcases the analytical and experimental strategy developed to integrate human genetics and host-microbe interactions studies. It describes the discovery of a single-gene inborn error of immunity that selectively predisposes to the detrimental effects of a major staphylococcal toxin, demonstrating that the study of inborn errors of immunity can serve as a compass for the clarification of human-specific host-microbe interactions.

7. Mijnheer, G., Lutter, L., Mokry, M., van der Wal, M., Scholman, R., Fleskens, V., Pandit, A., Tao, W., Wekking, M., Vervoort, S., Roberts, C., Petrelli, A., Peeters, J. G. C., Knijff, M., de Roock, S., Vastert, S., Taams, L. S., van Loosdregt, J., & van Wijk, F. (2021). **Conserved human effector Treg cell transcriptomic and epigenetic signature in arthritic joint inflammation.** *Nature Communications, 12*(1), 1-16. Article 2710. https://doi.org/10.1038/s41467-021-22975-7.
Citations: 54, open access
Our group identified a distinct effector Treg (eTreg) cell profile in humans, revealing a conserved signature with core Treg markers (FOXP3, CTLA4, TIGIT) and effector genes (GITR, BLIMP-1, BATF). Vitamin D receptor regulates eTreg differentiation through epigenetic modifications. Interestingly, this profile strongly overlaps with tumor-infiltrating Tregs, highlighting inflammation-driven Treg programming and potential therapeutic targets in inflammatory and tumor settings.

8. Baliu Piqué, M., van Hoeven, V., Drylewicz, J., van der Wagen, L. E., Janssen, A., Otto, S. A., van Zelm, M. C., de Boer, R. J., Kuball, J. J., Borghans, J. A., & Tesselaar, K. (2021). **Cell-density independent increased lymphocyte production and loss rates post-autologous HSCT.** *eLife, 10*, Article e59775. https://doi.org/10.7554/eLife.59775.
Citations: 8, open access
In this study, we combined in vivo deuterium labeling and mathematical modelling to investigate why lymphocyte reconstitution occurs so slowly in individuals undergoing autologous hematopoietic stem cell transplantation (autoHSCT). Our findings revealed that the production rates of most T- and B-cell subsets in autoHSCT-patients were two to eight times higher than in healthy controls, but went hand in hand with three- to ninefold increased lymphocyte loss rates. These results indicate that the slow lymphocyte reconstitution rate typically seen in HSCT patients is not due to limited lymphocyte production, and that elevated lymphocyte loss rates occur even long after autoHSCT, when cell numbers have already normalized.

9. Spekhorst, L. S., Bakker, D., Drylewicz, J., Rispens, T., Loeff, F., Boesjes, C. M., Thijs, J., Romeijn, G. L. E., Loman, L., Schuttelaar, M.-L., van Wijk, F., de Graaf, M., & de Bruin-Weller, M. S. (2022). **Patient-centered dupilumab dosing regimen leads to successful dose reduction in persistently controlled atopic dermatitis.** *Allergy, 77*(11), 3398-3407. https://doi.org/10.1111/all.15439.
Citations: 33, open access
Using data from the multicenter BioDay registry, our team was the first to investigate dose reduction with dupilumab, the first biologic for atopic dermatitis. Reducing the dose (by extending the interval between injections) provides benefits for patients (fewer side effects, fewer injections) and society (cost savings). This paper presents the results of implementing the dose reduction protocol in Dutch hospitals. The dupilumab tapering protocol is now included in the national atopic dermatitis guidelines and implemented in Dutch hospitals.

10. Van der Vlist, M., Raoof, R., Willemen, H. L. D. M., Prado, J., Versteeg, S., Martin Gil, C., Vos, M., Lokhorst, R. E., Pasterkamp, R. J., Kojima, T., Karasuyama, H., Khoury-Hanold, W., Meyaard, L., & Eijkelkamp, N. (2022). **Macrophages transfer mitochondria to sensory neurons to resolve inflammatory pain.** *Neuron, 110*(4), 613-626. https://doi.org/10.1016/j.neuron.2021.11.020.
Citations: 108, open access
This study demonstrates the intricate collaboration between macrophages and neurons in resolving inflammatory pain. The paper attracted considerable attention, with The Scientist picking it up as a preprint. It also received a preview by Kerschensteiner & Misgeld on the issue of publication, a commentary for the International Association for the Study of Pain (IASP), and a radio interview on BNR. The article has garnered over 100 citations and led to invited lectures and industry collaborations.

11. Prado, J., Westerink, R. H. S., Popov-Celeketic, J., Steen-Louws, C., Pandit, A., Versteeg, S., van de Worp, W., Kanters, D. H. A. J., Reedquist, K. A., Koenderman, L., Hack, C. E., & Eijkelkamp, N. (2021). **Cytokine receptor clustering in sensory neurons with an engineered cytokine fusion protein triggers unique pain resolution pathways.** *Proceedings of the National Academy of Sciences of the United States of America, 118*(11), Article e2009647118. https://doi.org/10.1073/pnas.2009647118.
Citations: 27, open access
By combining the immune cytokines IL-4 and IL-10 into a single entity, we can enhance pain resolution pathways by inducing unique signaling in sensory neurons. This paper provides evidence that the immune system can be harnessed to trigger pain resolution. Along with our earlier work on IL-4-10 and new research on IL-4-13, this manuscript forms the basis for several patents (incl. WO2013070076A1, WO2020212598A1), and underpins the spin-off company Synerkine Pharma. This work has been instrumental for Synerkine Pharma in securing over 15 million to advance clinical development.

12. Budding, K., Johansen, L. E., Van de Walle, I., Dijkxhoorn, K., de Zeeuw, E., Bloemenkamp, L. M., Bos, J. W., Jansen, M. D., Curial, C. A. D., Silence, K., de Haard, H., Blanchetot, C., Van de Ven, L., Leusen, J. H. W., Pasterkamp, R. J., van den Berg, L. H., Hack, C. E., Boross, P., & van der Pol, W. L. (2022). **Anti-C2 Antibody ARGX-117 Inhibits Complement in a Disease Model for Multifocal Motor Neuropathy.** *Neurology® neuroimmunology & neuroinflammation, 9*(1), 1-11. Article e1107. https://doi.org/10.1212/NXI.0000000000001107.
Citations: 9, open access
This study explores the role of complement activation in multifocal motor neuropathy (MMN) pathology using an induced pluripotent stem cell (iPSC)-derived motor neuron model. It reveals that IgM antibodies from MMN patients bind to motor neurons, triggering complement activation through C3 and C4 fixation. The work demonstrates that ARGX-117, a monoclonal antibody targeting C2, effectively inhibits complement activation, showing its potential as a therapeutic strategy to reduce complement-mediated damage in MMN. These findings offer valuable insights into the role of complement in MMN and support the development of targeted interventions.

13. Van de Walle, I., Silence, K., Budding, K., Van de Ven, L., Dijkxhoorn, K., de Zeeuw, E., Yildiz, C., Gabriels, S., Percier, J.-M., Wildemann, J., Meeldijk, J., Simons, P. J., Boon, L., Cox, L., Holgate, R., Urbanus, R., Otten, H. G., Leusen, J. H. W., Blanchetot, C., ... Boross, P. (2021). **ARGX-117, a therapeutic complement inhibiting antibody targeting C2.** *Journal of Allergy and Clinical Immunology, 147*(4), 1420-1429.e7. https://doi.org/10.1016/j.jaci.2020.08.028.
Citations: 29, open access
This study describes ARGX-117, a humanized monoclonal antibody targeting complement C2 to inhibit classical and lectin pathway activation. By binding the Sushi-2 domain of C2, ARGX-117 prevents C3 proconvertase formation and complement-mediated tissue damage, without affecting the alternative pathway or antimicrobial activity. Its efficacy was validated in vitro and in cynomolgus monkeys.

14. Rumpret, M., Drylewicz, J., Ackermans, L. J. E., Borghans, J. A. M., Medzhitov, R., & Meyaard, L. (2020). **Functional categories of immune inhibitory receptors.** *Nature Reviews. Immunology, 20*(12), 771-780. https://doi.org/10.1038/s41577-020-0352-z.
Citations: 60
Using mathematical modelling a novel functional categorization of inhibitory receptors using mathematical modeling was introduced. The categorization and accompanying illustrations from this work have since become widely used by fellow scientists as introductory slides in presentations. Since its publication, the paper has been cited over 60 times, including by a science philosopher who incorporated it as a building block for a theory on immune recognition of microbial functions rather than structures (Greslehner, Studies in History and Philosophy of Science, 2020).

15. Ramos, M. I. P., Tian, L., de Ruiter, E. J., Song, C., Paucarmayta, A., Singh, A., Elshof, E., Vijver, S. V., Shaik, J., Bosiacki, J., Cusumano, Z., Jensen, C., Willumsen, N., Karsdal, M. A., Liu, L., Langermann, S., Willems, S., Flies, D., & Meyaard, L. (2021). **Cancer immunotherapy by NC410, a LAIR-2 Fc protein blocking human LAIR-collagen interaction.** *eLife, 10*, 1-29. Article e62927. https://doi.org/10.7554/eLife.62927.
Citations: 52, open access
Since 2017, we have collaborated with NextCure, who developed NC410, a protein designed to block immune suppression mediated by LAIR-1. Our research demonstrated that NC410 reduces tumor growth and enhances T-cell effector function in humanized tumor models. Currently, NC410 is in Phase II clinical trials.

16. Salgado, M., Gálvez, C., Nijhuis, M., Kwon, M., Cardozo-Ojeda, E. F., Badiola, J., Gorman, M. J., Huyveneers, L. E. P., Urrea, V., Bandera, A., Jensen, B.-E. O., Vandekerckhove, L., Jurado, M., Raj, K., Schulze zur Wiesch, J., Bailén, R., Eberhard, J. M., Nabergoj, M., Hütter, G., ... Martinez-Picado, J. ; IciStem Consortium (2024). **Dynamics of virological and immunological markers of HIV persistence after allogeneic haematopoietic stem-cell transplantation in the IciStem cohort: a prospective observational cohort study.** *The Lancet HIV, 11*(6), e389–e405. https://doi.org/10.1016/S2352-3018(24)00090-0.
Citations: 9
To date, allogeneic stem cell transplantation (allo-HSCT) is the only curative intervention for HIV. The IciStem project, which includes the largest cohort of people with HIV undergoing allo-HSCT (30 individuals), demonstrates that HIV reservoirs in blood and tissues are rapidly depleted after full donor chimerism, regardless of donor CCR5 genotype. This depletion is driven by an initial reservoir reduction during conditioning chemotherapy and subsequent allogeneic immunity from donor cells. HIV-specific antibodies decline more gradually, suggesting that loss of T-cell immune responses may serve as a more reliable marker of HIV eradication. These findings may guide future cure strategies and biomarker identification.

## Appendix B - Most important collaborations

A selection of important collaborations (outside UMC Utrecht) with both scientific and societal stakeholders:

**SPIRAL: collaborations advancing an equitable HIV cure in a changing global landscape**
Through the Knowledge and Innovation Covenant, the Translational Virology group leads the international, multidisciplinary SPIRAL, advancing HIV cure research with €6 million in funding from NWO, Aidsfonds, SMEs, and pharmaceutical industry. Prioritizing sub-Saharan Africa, where HIV burden is highest and treatment access fragile, SPIRAL unites experts from UMC Utrecht (Medical Microbiology, Epidemiology, Infectious Diseases groups), Utrecht University, Amsterdam UMC, Erasmus MC, VU, Maastricht University, and research institutes in Zambia, Uganda, and South Africa, alongside HIV advocacy groups and patients. Combining experts in virology, immunology, gene therapy, social sciences, modeling, and health economics, SPIRAL is committed to developing an ethical, equitable HIV cure.

**Centre for Animal-Free Biomedical Translation (CPBT): collaborating for animal-free biomedical innovations**
UMC Utrecht plays an extensive role in CPBT for valorizing and disseminating animal-free innovations. This public-private initiative aims to accelerate biomedical advancements to patients at lower costs and without animals. The center unites public partners UMC Utrecht, Utrecht University, Maastricht UMC and 13 private primarily SME partners. The Dutch National Growth Fund invests €124.5 million in this initiative. Our Neuroimmunology of Pain group is participating herein to develop and validate human sensory neuron cultures incorporating the immune system, offering an alternative to animal models. This will enable objective, high-capacity testing of novel pain reduction therapies, particularly for osteoarthritis and rheumatoid arthritis.

**Oncode Accelerator: collaborating for development of cancer immune therapy**
Oncode Accelerator is a Dutch initiative that fosters public-private collaborations to accelerate the development of innovative cancer therapies. The National Growth Fund invested €325 million in this initiative. By uniting leading researchers, biotech companies, and healthcare providers, the program supports collaborative research in cancer, focusing on translating basic science into effective treatments, with the aim of improving patient outcomes and advancing the fight against cancer. UMC Utrecht plays a key role in this effort, with I&I researchers Prof. Jeanette Leusen leading the biologics workstream for antibody-based therapeutics and Prof. Jürgen Kuball contributing to the development of cell and gene therapy.

**European Clinical Research Alliance of Infectious Diseases (Ecraid): building collaborative networks for infectious disease research**
UMC Utrecht was instrumental in the establishment of Ecraid, a European clinical research network for infectious diseases. Ecraid aims to accelerate the evaluation of new therapies and vaccines through a pan-European 'warm-base' network of hospitals, clinical laboratories, and primary care sites. Ecraid is currently (March 2025) active in 16 studies with 450 study sites in 24 countries. The foundation unites academic, industry, and clinical partners to address emerging infections, ensure a rapid response to infectious disease threats, and support the development of critical health interventions. Prof. Marc Bonten has been CEO since its launch in 2022, with UMC Utrecht as a key partner.

**Netherlands Center for One Health (NCOH): One Health collaborations for infectious diseases**
UMC Utrecht is founding partner of the NCOH alongside eight Dutch academic institutes. Together, we aim for an integrated One Health approach to tackle the global risk of infectious diseases. The NCOH fosters collaborations across human, animal, and environmental health sectors with policymakers and industry. Our Epidemiology of Infectious Diseases and Medical Microbiology researchers contribute to these collaborations providing insights into emerging infectious diseases and antimicrobial resistance. Prof. Marc Bonten served as Scientific Director of the Antimicrobial Resistance research theme from 2016-2024.

**argenx: partnership in developing immune-mediated inflammatory diseases therapies**
argenx is a Belgian antibody engineering company focused on developing therapeutics for immune-mediated inflammatory diseases (IMIDs). Their model brings antibody expertise to academic scientists to advance immunology breakthroughs into differentiated medicines for IMID patients. argenx has research agreements with five I&I groups (profs. Jeanette Leusen, Linde Meyaard, Suzan Rooijakkers, Niels Eijkelkamp, and André Knulst), funding research

while co-developing novel drugs. Projects are at various technology readiness levels (TLRs), varying from early target discovery to Phase III clinical trials. The increasing number of contracts reflects mutual trust, and UMC Utrecht and argenx started discussions to streamline collaborations with aligned agreements on budgeting and legal aspects of contracts.

### Valorization at work: UMC Utrecht spin-off TigaTx brings antibody to the clinic

Several spin-off companies have emerged from I&I research, contributing to the valorization of our work, including Gadeta, Synerkine Pharma, and TigaTx. TigaTx B.V. started in 2018 as a UMC Utrecht spin-off, with Utrecht Holdings (the knowledge transfer office of UMC Utrecht) and Prof. Jeanette Leusen as the scientific founder. After a successful Seed Investment round, the company moved to Boston as TigaTx Inc in 2023 and received over €35 million in funding in 2024. TigaTx continues Prof. Leusen's work on novel IgA-based technology, leveraging engineered monomeric IgA antibodies to activate neutrophils for cancer treatment. In parallel, TigaTx will expand the engineered IgA technology to develop dimeric IgA for the treatment of infectious diseases.

### Collaboration Infectious Diseases: collaborating with patient representatives

Founded in 2024 (Prof. Annelies Verbon), the Samenwerking Infectieziekten initiative unites clinicians, researchers, patient federations, and healthcare funds to raise awareness of infectious diseases, develop monitoring infrastructure for hospital infections, and advance research. Funding from multiple foundations facilitated public awareness programs (e.g. workshops for policymakers) and outreach initiatives (e.g. Vaccination Coalition Day). Several research projects actively involve patients (e.g. a bacteriophage project by Dr. Marjolein Hensgens and Dr. Pieter-Jan Haas). Partnerships with organizations such as the Dutch Sepsis Coalition, the Influenza Foundation, and the Dutch General Patient Federation highlight the collaboration's impact, strengthening ties between healthcare professionals and patients to improve infectious disease prevention and treatment.

## Appendix C - Grants and prizes

A selection of individual and collaborative grants and awards:

### Individual grants

- NWO (Dutch Research Council) Talent Program grants: 5 'Vici' grants for senior researchers, €1.5 million each for Prof. José Borghans (CTI, 2020), Prof. Nina van Sorge (MMB, left UMCU 2020), Prof. Femke van Wijk (CTI, 2021), Prof. Suzan Rooijakkers (MMB, 2022), and Prof. Niels Eijkelkamp (CTI, 2022); 3 'Vidi' grants for mid-career researchers up to 8 years after PhD, €800.000 each for Prof. Patricia Bruijning-Verhagen (EpiID, 2020), Dr. András Spaan (MMB, 2023), and Dr. Hanneke Willemen (CTI, 2024); and 3 'Veni' grants for early-career researchers up to 3 years after PhD, €280.000 each for Dr. Hanneke Willemen (CTI, 2019), Dr. Theo van den Broek (CTI, 2023), and Dr. Daniëlle Krijgsman (2024).
- European Research Council grants: Consolidator grant for Prof. Suzan Rooijakkers (MMB, 2020) and Starting grant for Dr. András Spaan (MMB, 2021).

### National awards and prizes

- Prof. Marc Bonten (EpiID) was selected as member of the Royal Netherlands Academy of Arts and Sciences (KNAW) in 2021. KNAW membership is awarded based on scientific and scholarly achievement.
- Prof. Femke van Wijk (CTI) received the NWO Athena Award for outstanding female role models in beta sciences in 2023.
- Several researchers received awards from their scientific societies in recognition of their contributions. E.g. Prof. Marc Bonten received the Dutch Working Party on Antibiotic Policy (SWAB) Award for lifetime achievement for important contributions to antimicrobial stewardship and infectious diseases in 2023, Prof. Linde Meyaard (CTI) the Van Loghem Career Award 2023 in recognition of outstanding work by the Dutch Society for Immunology (NVVI), and Dr. Stefan Nierkens (CTI) the Joos Kerckhaert Award 2022 for an outstanding accomplishment in the field by the Dutch Medical Immunology group (CMI-NVVI).

### Large national collaborative grants

I&I is involved in two large projects funded by the Dutch National Growth Fund, the Centre for Animal-Free Biomedical Translation (CPBT) and Oncode Accelerator, as detailed in I&I Appendix B. External collaborations.

### Large international collaborative grants

- UMC Utrecht (in the I&I field) has been, or still is, the academic lead of the following IMI/IMI2-projects: COMBACTE-NET (building a pan-European clinical trial and laboratory network, performing clinical studies with innovative treatments for Gram-positive infections; 2012-2025), COMBACTE-CARE (performing clinical studies with innovative treatments for carbapenem-resistant Enterobacterales; 2014-2024), COMBACTE-MAGNET (building a pan-European epidemiology network, performing clinical studies with innovative treatments for antibiotic-resistant Gram-negative infections; 2015-2023), COMBACTE-CDI (assessing the burden of *Clostridioides difficile* infections in Europe; 2018-2022), VITAL (assessing the role of immunosenescence in infectious diseases and vaccine response in the ageing population; 2019-2024), COVID-RED (remote early detection of SARS-CoV-2; 2019-2024), PrIMAVeRA (quantifying the potential role of antibodies and vaccines on antimicrobial resistance; 2021-2026), and PROMISE (preparing for RSV immunization and surveillance in Europe; 2021-2024). Participant in NECESSITY (new clinical endpoints in primary Sjögren's syndrome; 2019-2025) and VALUE-Dx (value of diagnostics to combat antimicrobial resistance; 2019-2024).
- UMC Utrecht (in the I&I field) has been the coordinator of the following HORIZON projects: ECRAID-PLAN (establishing a business plan for the European clinical research alliance on infectious diseases; 2018-2020), ECRAID-BASE (building the European clinical research alliance on infectious diseases; 2021-2026), ECRAID-PRIME (adaptive platform trial for COVID-19 therapeutics in primary care; 2021-2026), and CLARITY (causative link between RSV and chronic lung diseases; 2023-2028), and partner in: PREPARE (preparing the scientific response capacity to future large-scale outbreaks; 2014-2021), RECOVER (multiple clinical studies for COVID-19; 2021-2023), VACCELERATE (building a pan-European network for COVID-19 vaccine trials; 2021-2024), MPX-RESPONSE (establishing a clinical trial for treatment of monkeypox infections; 2022-2026), and RECODID (reconciliation of cohort data in infectious diseases; 2019-2023).

## Appendix D - Key outputs or activities aimed at a professional of wider audience

### Policy advice, contributions to guidelines, and public engagement regarding COVID-19 pandemic

During the COVID-19 pandemic, four of our researchers – Prof. Marc Bonten, Dr. Pauline Ellerbroek, Prof. Jan Kluytmans, and Prof. Annelies Verbon – were part of the Dutch Outbreak Management Team. They and other researchers (such as Prof. Patricia Bruijning-Verhagen, Prof. Janneke van de Wijgert, Dr. Anne Wensing, Dr. Martin Bootsma) also participated in other advisory committees for the Ministries of Health and Education. Our research and insights informed key policies, including contact tracing, testing, prevention, and treatment. Our findings were featured not only in Dutch reports (10Jun21, 1Jul21, 13Aug21, 7Sep21, 17Jan22) but also in reports from the ECDC (report) and WHO. UMC Utrecht is the European lead of the global platform trial REMAP-CAP, which contributed to improved patient care for acute COVID-19 worldwide (see Appendix A key output: REMAP-CAP investigators 2020-2023). UMC Utrecht experts frequently appeared in national media, providing expert analysis on television, radio, and in print; they were featured almost daily on platforms such as *NOS Journaal, Op1, 1Vandaag, Jinek, WNL op Zondag, Jeugdjournaal, Nieuwsuur, and BNR*. UMC Utrecht also hosted two live TV shows providing updates on recent developments and in-depth background information for the general public, inlucding the Op1 Corona-special on Nov 15, 2021. On May 26, 2023, we organized "Looking Back at Corona" (recording), a well-attended public event where our scientists, doctors, and science journalist Maarten Keulemans (de Volkskrant) reflected on the pandemic's course and impact.

### Scientific contributions that changed guidelines for inflammatory and infectious diseases

- Gastroenterology: A predictive model for colitis-associated colorectal carcinoma was included in the British guidelines and will be incorporated in Dutch guidelines in 2025. (Prof. Bas Oldenburg)
- Translational atopic dermatitis: Tapering studies with dupilumab demonstrated feasibility, safety and cost reductions, and these regimens have now been widely adopted. (Prof. Marjolein de Bruin, Prof. Femke van Wijk)
- Juvenile dermatomyositis: Biomarkers were validated and are now used in routine diagnostics and since 2024 included in national guidelines. (Prof. Annet van Royen, Dr. Marc Jansen, Prof. Femke van Wijk)
- Vaccines: characterization of vaccine responses in preterm infants (Rouers et al., JAMA 2020) lead to an adapted immunization schedule implemented in 2022. (Prof. Patricia Bruining-Verhagen, Prof. Lieke Sanders)
- Vaccines: The RIVAR study on rotavirus vaccination in vulnerable infant populations (van Dongen et al. Pediatrics 2021), lead to a positive evaluation of the Dutch Health Counsel for rotavirus vaccination in 2020, prompting the Ministry of Health to incorporate it into the Dutch Immunization Program in 2024. (Prof. Patricia Bruijning-Verhagen, Prof. Marc Bonten)
- Q fever: UMC Utrecht hosts the national database for chronic Q fever infections and contributed to the diagnostic Q fever guidelines of the RIVM. (Dr. Jan Jelrik Oosterheert)
- Food allergies: Research conducted by TNO and UMC Utrecht on the sensitivity of individuals with food allergies and their eating habits formed the basis for scientific recommendations that have resulted in international adoption of improved allergen information on food labels. (Prof. Geert Houben)

### Patient engagement on inflammatory and infectious diseases

Strategic Program I&I actively engages with patients through various initiatives. The 'Patient Event on Rare Immune Deficiencies' (Nov 23, 2023) welcomed 150 patients with immune disorders and their families for expert talks and workshops. The 'Rheumatology & Clinical Immunology Patient Day' (Apr 20, 2024) to learn about recent advances in the treatment, diagnostics, and research of autoinflammatory diseases attracted 300 attendees, featuring presentations, interactive demos, and patient society discussion (video highlighting research).

### Public engagement and science communication

Over the past six years, I&I researchers have shared their work with the public, including children, through various television programs. Highlights include *Klokhuis* special on antimicrobial resistance by Dr. András Spaan (Apr 18, 2023) and on juvenile idiopathic arthritis by Dr. Bas Vastert (Apr 30, 2020), inflammatory diseases feature on colitis ulcerosa on *Dokters van Morgen* by Prof. Bas Oldenburg (Dec 9, 2020), a segment on HIV cure using stem cell transplantation *Briljante Breinen* by Dr. Monique Nijhuis and Dr. Anne Wensing (Aug 20, 2023), an item on prevention of herpes zoster in *Radar* by Dr. Mienke Rijsdijk (Nov 18, 2024). Our scientists annually contribute to Utrecht's Betweter Festival, a major arts & science event drawing 3,000 visitors, where they shared research on e.g., chronic pain (Dr. Hanneke Willemen, Dr. Mienke Rijsdijk), microplastics (Dr. Nienke Vrisekoop), and the microbiome (Dr. Marcel de Zoete). These initiatives foster dialogue between researchers, patients, and the broader public.

### Associate professor lectures

As part of our 'Recognition & Rewards' initiatives, the strategic program hosts lecture series for newly appointed I&I associate professors, offering them a platform to present their research to internal and external audiences.

### Twenty-year anniversary master's program I&I

The biomedical master's program Infection & Immunity celebrated its 20th anniversary (Nov 20, 2022) with 150 attendees, including alumni from the inaugural class of 2002. Program director Prof. Jos van Strijp and coordinator Dr. Kristin Denzer reflected on key milestones, while alumni and staff reconnected. Many former students now contribute as supervisors and work in academia or biotech companies. The event was a great success, marking this milestone while strengthening the I&I network.

# Strategic Program Regenerative Medicine & Stem Cells

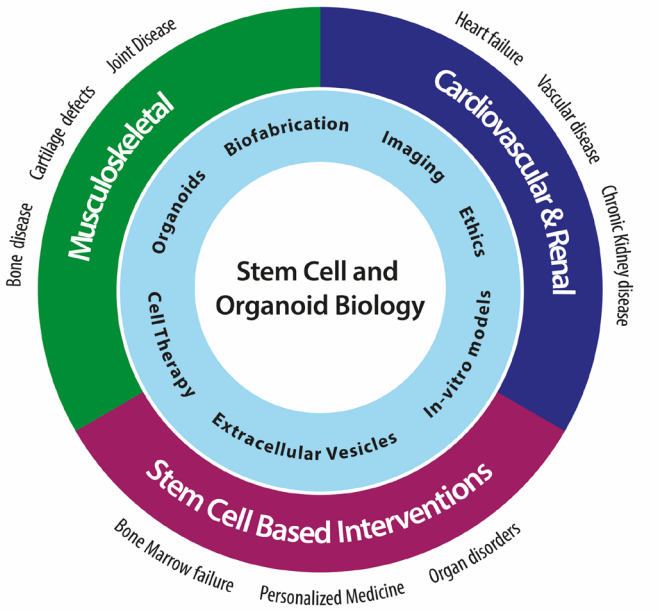
Self-evaluation report 2019-2024

# Strategic Program Regenerative Medicine & Stem Cells

## 1 - Mission, governance, and main research topics

Regenerative Medicine & Stem Cells (RM&SC) is one of six strategic programs at UMC Utrecht and is an integral part of the Regenerative Medicine thematic community within Utrecht University's Strategic Theme Life Sciences. At RM&SC, we see regenerative medicine as an emerging interdisciplinary field that bridges research and clinical applications. Our focus is on repairing, replacing, or regenerating cells, tissues, and organs to restore function impaired by congenital defects, disease, trauma, or aging.

The Regenerative Medicine Center Utrecht (RMCU), located within the Hubrecht Institute, serves as the physical research hub of the UMC Utrecht RM&SC community and is designed to optimize regenerative medicine research at Utrecht Science Park. At RMCU, approximately 350 researchers from UMC Utrecht, Utrecht University's Faculty of Veterinary Medicine and Faculty of Science, and the Hubrecht Institute collaborate in a single location, sharing state-of-the-art equipment and facilities. The center fosters daily interactions between fundamental and translational scientists, engineers, and clinicians, encouraging creativity and cross-pollination of knowledge across disciplines and institutions. This multidisciplinary environment is essential for integrating the broad range of expertise required to drive innovation in regenerative medicine, ultimately accelerating the development of new treatments for patients in need.




RM&SC activities are prioritized around three patient-oriented themes (see figure 1):
(1) musculoskeletal tissue regeneration
(2) cardiovascular and renal regeneration
(3) stem cell-based interventions

These patient-oriented themes are connected through supporting technologies, disciplines and infrastructures such as organoids, biofabrication, in vitro models, biomaterials, cell therapy, extracellular vesicles, imaging, and ethics. We also recognize a central role for innovative, fundamental research in stem cells and organoid biology as an important driver for future RM applications.

*Figuur 1. Thematic organization of RM&SC.*

RM&SC's research efforts are closely integrated with clinical care at UMC Utrecht, ensuring a direct link between scientific innovation and patient needs. Our goal is to identify areas where regenerative medicine applications can make a meaningful impact, assess how these innovations align with current clinical standards, and establish qualified teams to implement patient-focused interventions (e.g. investigator-initiated and industry-sponsored clinical trials) and to create translational research support infrastructures (e.g. stem cell biobanks, data registries, disease modeling infrastructures, biofabrication, ATMP facilities, etc.). Direct connections to patient care are embedded in areas such as spinal and maxillofacial surgery, joint preservation, advanced heart and kidney failure, and rare diseases. This comprehensive bench-to-bedside approach enables RM&SC to translate fundamental discoveries into societal impact—not only in therapeutic applications for human and animal patients, but also within the ethical and regulatory domains.

### Our Vision

To improve our understanding of stem cell biology, to develop innovative technologies, and to translate our findings into novel regenerative therapies.

### Our Mission

- To bring novel regenerative treatments for patients to standard clinical care.
- To provide a center of excellence for biomedical, technological, and stem cell-based research.
- To attract, train, and educate the next generation of investigators and caregivers to develop and implement regenerative therapies.
- To incorporate societal perspectives through active connections to patients (societies) and relevant stakeholders.
- To actively foster (international) collaboration with academia, government, and industry.

### Composition of RM&SC

The RM&SC strategic program aims to foster alignment and synergy among researchers from eight different UMC Utrecht divisions. Researchers are appointed at these divisions, and the divisions maintain responsibility for oversight, management and finances of their respective research activities and researchers and also enable connections to different themes.

Currently, the RM&SC program includes approximately 45 Principal Investigators (25 full professors, 11 associate professors, and 9 clinical researchers), 60 Investigators (assistant professors, postdoctoral researchers, and clinicians), as well as 110 PhD students and 30 technicians.

Leadership and management of the RM&SC is organized at different levels (see figure 2). It consists of the RM&SC (Kernteam) Executive Committee (RM&SC strategy-focused) which consists of seven senior members from participating divisions who represent the themes and main clinical areas. The executive committee is backed by support staff (program manager, coordinators on communications, education and funding, impact officer, and Trial & Innovation lead). The RMSC scientific board focuses on the management of the RMCU research center (technology infrastructures, logistics around finance and persons). Various community structures are also organized: a post-doc society (RUPS), a PhD council, technician meetings, and a student association (ReBio). Our educational activities encompass courses for BSc/MSc/PhD students, an RM PhD program, two master's programs, and three summer schools aimed at attracting, inspiring and training (inter)national talent. In addition, we have increased our efforts to engage the public, including children.

| | RM&SC Executive Committee Jeffrey Beekman | RM&SC Support team Solange Cleutjens | Representations & meeting |
|---|---|---|---|
| Research & Facilities | Jeffrey Beekman<br>Jos Malda | Joost Fledderus<br>Maaike Welling<br>Tse-Hsiang Chen | RMCU scientfic board meeting<br>(head) technician meeting |
| Education & Talent | Debby Gawlitta<br>Joost Sluijter | Koen Braat | RUPS (post-doc society), UMCU Young Academy PhD-council<br>ReBio (students association) |
| Valorization & Care | Moyo Kruijt<br>Linda van Laake<br>Sabine Fuchs | Erik van Tilborg<br>Joost van Duijn (ICAT)<br>Thomas Boelens (UTrial) | Biweekly valorization meeting (RMU, ICAT, ROM)<br>Periodic consultation UMCU divisions, departments |
| Outreach | Jeffrey Beekman<br>Jos Malda | Veerle Hoeve<br>Shanna Mesland<br>Ria Matthijssen | Biweekly S&W meeting (MarCom direction)<br>HelpdeskRM expert meetings |

*Figure 2 - Roles of RM&SC executive committee and support staff*
*NB: During 2019-2024 Marianne Verhaar was the RM&SC chair. Jeffrey Beekman took over this role in January 2025. During 2019-2024 Ria Matthijssen was the RM&SC program manager. Solange Cleutjens took over this role in July 2025.*

## 2 - Concise reflection on program-specific recommendations from the previous evaluation

The committee valued the RM&SC program as extremely relevant, with clear evidence for world-leading research. The two most important recommendations and response to those by RM&SC are summarized here:

*Recommendation 1*
**The committee emphasized the need for a long-term strategy (5–10 years) to strengthen RM&SC's internal and external positioning.**
In response, RM&SC developed the UMC Utrecht accelerator 'Biofabrication and Disease Modeling', which outlines critical valorization steps focused on discovery, prediction, and intervention. This strategic framework has helped to guide RM&SC's funding priorities, enabling the establishment of large-scale, long-term research infrastructures. UMC Utrecht has invested in the construction of three additional clean rooms of the GMP cell therapy facility. Additionally, public funding (seed & sector money) was applied in the context of disease modeling (iPSC) and genetic interventions, and external grants such as Summit (DRIVE-RM, €37.5M) and NWO Large Scale Research Infrastructure (LSRI) (hDMT INFRA, €13.5M) were obtained to prioritize stem cell research across the Netherlands. Another LSRI on gene therapy applications awaits approval. Large, 10 years public-private growth fund initiatives were granted in the context of ATMP development (ICAT, €85M) and animal-free biomedical translation (CPBT, €124.5M). These grants aim to build self-sustaining preclinical and clinical valorization infrastructures for RM applications in the coming 5-10 years.

*Recommendation 2*
**The committee also observed that the incentive and infrastructure for valorization was not sufficient:**
Regarding incentives, limited success was achieved in implementing the advice 'UMC Utrecht should enforce 5% equity limitation in spin-out companies only for clinical staff running clinical trials and allow a larger equity holding to be allocated to non-clinical research staff, where appropriate'. Direct financial benefit for inventors may still be further developed to increase the incentive for valorization. Improvements have been made around the definition of academic research use of organoid technology with companies, and the use of organoid biobanks. Since the beginning of 2025, an in-house impact officer has been associated with the RM&SC program, further aiming to stimulate impact and communicate between researchers and UMC Holding. This might help to better recognize and valorize business opportunities within RM&SC. Local and national initiatives are ongoing to further harmonize and improve the organization, support structures, policies, and culture of valorization. Timelines for legal support for contracts can be highly variable and can frustrate the setup of contracts with partners.

## 3 - Main research accomplishments in the period 2019-2024

### MUSCULOSKELETAL REGENERATION

#### Joint preservation

Innovative solutions for knee joint preservation is a goal for Roel Custers and team (Orthopedics). One example is the IMPACT study for symptomatic knee cartilage defects; a one-step cell therapy using autologous chondrocytes and allogeneic MSCs. This therapy was originally developed in the RMU lab, and moved from preclinical studies to first-in-human and a soon-to-conclude phase III trial comparing it to standard care, with plans for broader implementation. In collaboration with Daniel Saris (Mayo Clinic), the approach has expanded to hip and shoulder indications. Two additional first-in-human trials (ACTIVE and AXOS) are underway, with a third (JOINT) in preparation. A knee register was initiated and now includes over 3,500 patients.
For young patients with end-stage osteoarthritis, a joint distraction treatment has been developed by the rheumatology (Simon Mastbergen) and the orthopedic department. The CE-marked KneeReviver, commercialized through UMC Utrecht spinoff ArthroSave (nominated 1 of 10 academic startup competition of the ministry VWS), is in a large multicenter trial aimed at implementation (GODIVA n=1200) and is supported by ZonMw.

#### Bone and intervertebral disc regeneration

Ceramic bone graft substitutes have been improved from a scaffold to support stem cells towards stand-alone bioactive implants. Moyo Kruyt (Orthopedic department) and team were the first to demonstrate non-inferiority of these advanced microporous ceramics and demonstrated superiority of these regenerative bone substitutes in multicenter randomized clinical trials four years later. Debby Gawlitta (Maxillofacial department) investigates, in collaboration with Twente University, patented nanoparticle technologies to improve efficacy of living tissue implants or bone autografts after implantation (ZonMw Open, Health Holland). Further, this team was the first in the world to show that endochondral bone regeneration works in large animals. Activities now focus on upscaling and standardizing this patented methodology via the NWO OTP grant XLbone.
At the orthopedic department, dynamic implants were developed that can completely regenerate the scoliotic spine as shown in several preclinical studies. The patented Spring Distraction System™ (SDS), that is valorized by the spin off company Cresco spine BV, is currently used in a prospective clinical trial for almost all growing patients with severe scoliosis who are referred to UMC Utrecht for dynamic treatment. In house-developed 3D printed devices are investigated for several indications to preserve the joint congruity. Several spin-off companies (Presurgeo, Replasia, Amotio, Preimure) have emerged from this by Harrie Weinans, Ralph Sakkers, Bart van der Wal, and Saber Amin Yavari. The 3D laboratory established within UMC Utrecht plays an important role in advancing these medical innovations.

#### Biofabrication

We are using 3D printing technology and living cells to create functional tissues for transplantation and as miniaturized models of health and disease. The head of the facility, Jos Malda, focuses on the implementation of these techniques particularly for the regeneration of musculoskeletal tissues. His team is, for example, developing layered plugs of cartilage and bone for the treatment of joint damage. Results show that these implants integrate with the surrounding tissue and can provide long-term mechanically stable neo-tissue in large animals. Jos Malda's frontrunner position is evident from his awards (TERMIS-EU Mid-Career Award (2021), the ISBF Senior Investigator Award (2021), the Bertus Rahn Award (2021) and the excellence in Translational Science Award Journal of Orthopaedic Research (2022). He received an ERC Advanced Grant (2024) of €2.5M (largest individual grant in Europe) to understand how cartilage tissue can be used for regenerative treatments.
Riccardo Levato and his team are working on ultra-fast volumetric 3D bioprinting technique. Their publication in Advanced Materials (2019) was the first report of volumetric bioprinting. The manuscript ranked in the top 1% ever tracked by Altmetric and was featured in Scientific American and in Dutch newspapers such as 'Financieel Dagblad'. In 2022, they were the first to demonstrate light-based printing of organoids, by showing that the function of liver organoids can be maximized in volumetrically printed constructs, with controlled architecture. Riccardo Levato holds an ERC Starting Grant (2020, €1.87M), which was featured in a report from the EU Commission. Three of their inventions, a new gelatin for embedded printing, a hybrid supramolecular hydrogel for bioprinting and tissue culture, and a new volumetric printing system are patent-pending. Riccardo Levato also coordinates an EU Innovation Council-funded project on bioprinting and has received several awards (ESB Jean Leray 2021, TERMIS Robert Brown 2022, ISBF mid-career 2023).

## CARDIOVASCULAR AND RENAL REGENERATION

### Cardiovascular

The cardiology department aims to develop both cellular and gene-therapy approaches for different cardiovascular patients, whereas advanced disease models are developed to understand disease progression. While gene therapy via viral vectors for e.g. phospholamban is being developed within different programs (NWO-OTP-HARVEY, ZonMw PSIDER, H2020 GEREMY) and has already resulted in a clinical trial (GenePHIT), the use of natural extracellular vesicle-based nanoparticles for drug delivery is explored as an alternative strategy. They patented VINCI, obtained a NWO valorization Veni Grant to validate the active loading of drugs in EVs for disease treatment, and obtained an ERC Starting and Consolidator Grants to understand the use of nanoparticles and cargo transfer of these EVs.

In Joost Sluijter's group a heart patch is developed: a scaffold with living, contracting cardiac cells that is placed on the outside of the injured heart muscle. In the H2020-funded project BRAVE, these cardiac patches demonstrated successful integration and improved performance in pigs. In collaboration with Linda van Laake and Repairon, a Health Holland grant is used to test a similar approach in advanced heart failure patients. Further developments in cardiomyocyte generation, patch design, including vascularization and optimized alignment and preservation technologies are being developed. Also, direct injection of cardiomyocyte-based micro-tissue into the diseased myocardium is being compared to the patch application via the H2020 TECHNOBEAT and HEAL programs.

In 2021 the first total artificial heart was implanted at the UMC Utrecht as the first and only center in the Netherlands based on its comprehensive clinical and research setting in the field of organ-replacing therapies. In the same year, the first ex vivo perfused heart following a DCD heart donation was transplanted at UMC Utrecht. On a national level, DCD heart transplantation has led to a doubling in the total number of annual heart transplants, while perfusion systems are still further improved via the RegMed XB Cardiovascular Moonshot.
The unique availability of explanted heart tissue at our center was instrumental in setting up an ex vivo living myocardial slices culture system. Almost all patients undergoing left ventricular assist device implantation or heart transplantation are included in the UNRAVEL biobank.

### Kidney regeneration

At the Department of Nephrology, research by Marianne Verhaar focuses on developing vascular and renal regenerative therapies for patients with cardiovascular and chronic kidney disease. A recent breakthrough from her team is the successful generation of organoids derived from adult kidney tissue and cells isolated from human urine (Nature Biotechnology). These adult-derived human kidney organoids or tubuloids introduce a novel technology for modelling kidney diseases. Furthermore, they work on multi-organ on chip models, e.g. a combined kidney-liver-lung model to study the effects and distribution of vesicle-based therapies and a kidney-heart model to study cardiorenal interactions. Additionally, tubuloids provide a valuable resource for generating transplantable kidney tissue and advancing bioartificial kidney development. Her group also focuses on in situ tissue engineering techniques, specifically targeting vascular grafts for haemodialysis access. She has a strong track record leading (inter)national programs and interdisciplinary collaborations. In 2024, the DRIVE-RM consortium, led by Marianne Verhaar, was awarded €37.5M, under the prestigious NWO SUMMIT program. Furthermore, she was recently appointed as Distinguished Faculty Professor; a new honorary role that acknowledges clinically active professors with an outstanding track record.

Karin Gerritsen's research focuses on novel and sustainable kidney replacement therapies, including miniature home-treatment systems (portable, wearable, and implantable (bio)artificial kidney) and green dialysis (design of 'the world's greenest dialysis department' to be realized at UMC Utrecht in five years – EU KitNewCare project). Her team and partners successfully developed prototypes for both portable haemodialysis and portable peritoneal dialysis which have both been tested for the first time in humans in 2024. Karin leads a €37M Growth Fund NXTGEN HIGHTECH project 'Artificial Organs' and realized a dedicated test lab (Artificial Kidney Innovation Lab) to ensure fast translation from bench to bedside. Additionally, she leads the (inter)national interdisciplinary collaborative projects BAKtotheFUTURE, KIDNEW, CORDIAL, REDESIGN_PD and UKID. Karin's research is conducted in close collaboration with the Dutch Kidney Foundation and aligns with the 'Roadmap towards development of novel renal replacement therapies'.

## STEM CELL BASED INTERVENTIONS

### Stem cell therapy for newborns with brain damage

Cora Nijboer and her team are developing a stem cell therapy for newborns with brain damage after a cerebral infarction. The clinical study, recently completed and published in The Lancet Neurology, indicates that mesenchymal stem cells can be safely administered to newborns via nasal drops, and is further being clinically developed (Zorginstituut and ZonMw, €5M). Cora Nijboer also received a ZonMw Vici grant (2024).

### Rare diseases

The main goal of Sabine Fuchs and her group is developing therapies for patients with rare diseases for whom there are currently no treatments. They prepare to use allogenic and gene-corrected autologous organoids for first-in-human liver organoid transplantations. In parallel, they develop a systemic in vivo gene correction program, first targeting the liver (ERC Starting Grant, ERC PoC, KNAW Ammodo), but now also focusing on other organs like the bone marrow, the eye, and the brain (ZonMwW Vici). To enable this, the group has generated a biobank with more than 300 organoid lines of patients with metabolic diseases. The NANOSPRESSO project funded by the Dutch Research Agenda (NWA) focuses on the delivery of the gene correction therapies using advanced microfluidic technology. The project enables hospitals to produce customized nanomedicines locally, providing advanced personalized treatments for patients with rare diseases. To prepare for in vivo gene correction therapies, Sabine Fuchs is PI of the first-in-human Moderna Phase I / II MMA mRNA trial to treat patients with metabolic diseases with mRNA encoding the deficient metabolic enzyme, encapsulated in lipid nanoparticles. This lays the basis for treatment of patients with mRNA encoding the gene editors to correct the genetic root cause of their disease. Her group also developed a new human liver culture model and co-founded the start-up HELLO R&D to valorize the model.

### Prediction models

Jeffrey Beekman's team aims to develop patient-derived, stem cell-based models for drug development and personalized medicine. He mostly focuses on the use of adult stem cells for modeling genetic diseases such as Cystic Fibrosis (CF). In the last five years, his work led to broadly applicable culture and assay technologies and further demonstrated individual predictability of organoid measurements for CF disease progression, large scale drug repurposing efforts leading to unique treatment combinations, and showed robustness and scalability of organoid-based assays for personalized medicine application at the European level. The organoid test is now part of Dutch CF treatment guidelines for inconclusive diagnosis and the UMC Utrecht provides a service for worldwide physicians to characterize CFTR function and response to CFTR modulators for individuals with rare CF. Qualification procedures for the organoid test are ongoing and led to a support letter and qualification advice from EMA. Recognition is also reflected in a recent request to contribute to a special report in Cell as well as his involvement in large (inter)national infrastructure grants focusing on further development of stem cell based infrastructures for research (biobanks, assay automation and AI) (hDMT-INFRA, Center for Animal-free Biomedical Translation). He has co-founded FAIR Therapeutics, a clinical-stage company that is developing CFTR modulators in organoid-selected individuals (phase 2b study).

### Ethics and society

Researchers within RMU provide input from an ethics perspective to increase societal awareness and opportunities for future translation of research results in a responsible manner. The Intimate Implants project won several prizes and enabled a social dialogue on science, technology and innovation within the context of regenerative implants. Health Technology Assessments showed an improved cost-effectiveness analysis of a first academic ATMP developed in Europe, leading to routine care and accessibility of treatment for patients in the Netherlands. Commissioned by ZonMw and FAST, researchers from Utrecht drew up a report to map the bottlenecks in ATMP regulation and admission and suggest solutions to them. Another way to involve patients and the general public in the RM developments are public campaigns (new kidneys 2021), public evening 'the hospital of the future' about living cells as medicine (2024), and HelpdeskRM. This interactive website offers reliable information in clear and accessible Dutch, tailored to questions from the public.

## 4 - Specific questions for the research committee

1. Space at RMCU is getting limited due to growth of successful research groups. This leads to complications at the workplace (limited growth possibilities, safety, enthusiasm). How can we expand across different locations, while remaining a community when activities become fragmented in space?
2. What tools can we use to maximize international visibility of RMU as an integrated community?
3. How can we increase the incentive for valorization?

# Appendix

## Appendix A - Key scientific outputs

### Musculoskeletal

1. Korpershoek, J. V., Vonk, L. A., Kester, E. C., Creemers, L. B., De Windt, T. S., Kip, M. M. A., Saris, D. B. F., & Custers, R. J. H. (2020). **Efficacy of one-stage cartilage repair using allogeneic mesenchymal stromal cells and autologous chondron transplantation (IMPACT) compared to nonsurgical treatment for focal articular cartilage lesions of the knee: study protocol for a crossover randomized controlled trial.** *Trials, 21*(1). https://doi.org/10.1186/s13063-020-04771-8
   Citations: 14, open access
   IMPACT is successfully executed in a first-in-human investigator-driven phase I/II clinical trial in 35 patients. The purpose of this study is to compare the efficacy of IMPACT to nonsurgical treatment for the treatment of large (2-8 cm2) articular cartilage defects in the knee. This study is designed to evaluate the efficacy of IMPACT compared to nonsurgical care. Additionally, safety of IMPACT will be assessed in 30 to 60 patients. Lastly, this study will evaluate the cost-effectiveness of IMPACT compared to nonsurgical care.

2. Stempels, H. W., Lehr, A. M., Delawi, D., Hoebink, E. A., Wiljouw, I. A., Kempen, D. H., Van Susante, J. L., & Kruyt, M. C. (2024). **Efficacy of biphasic calcium phosphate ceramic with a Needle-Shaped surface topography versus autograft in instrumented posterolateral spinal fusion.** *Spine, 49*(19), 1323–1331. https://doi.org/10.1097/brs.0000000000005075
   Citations: 2, open access
   Since the beginning of spinal surgery, patient's own bone has been used for transplantation, for example when the vertebrae are fused together to treat back pain. But the resulting fusion is not optimal, partially because these transplanted bone pieces quickly die and dissolve. As a result, the body has insufficient time to form new bone at the site of transplantation. This study shows that special grains of artificial bone may be a better option.

3. Li, Y., Jahr, H., Pavanram, P., Bobbert, F., Puggi, U., Zhang, X., Pouran, B., Leeflang, M., Weinans, H., Zhou, J., & Zadpoor, A. (2019). **Additively manufactured functionally graded biodegradable porous iron.** *Acta Biomaterialia, 96*, 646–661. https://doi.org/10.1016/j.actbio.2019.07.013
   Citations: 153, open access
   Here, we present the first report on 3D-printed functionally graded biodegradable porous metallic biomaterials. Our results suggest that topological design in general, and functional gradients in particular can be used as an important tool for adjusting the biodegradation behavior of AM porous metallic biomaterials. The biodegradation rate and mass transport properties of AM porous iron can be increased while maintaining the bone-mimicking mechanical properties of these biomaterials.

4. De Ruijter, M., Diloksumpan, P., Dokter, I., Brommer, H., Smit, I. H., Levato, R., Van Weeren, P. R., Castilho, M., & Malda, J. (2023). **Orthotopic equine study confirms the pivotal importance of structural reinforcement over the pre-culture of cartilage implants.** *Bioengineering & Translational Medicine, 9*(1). https://doi.org/10.1002/btm2.10614
   Citations: 6, open access
   We report that the use of a converged bioprinted, osteochondral implant, based on a gelatin methacryloyl cartilage phase, reinforced with precisely patterned melt electrowritten polycaprolactone micrometer-scale fibers in a zonal fashion, inspired by native collagen architecture, can provide long-term mechanically stable neo-tissue in an orthotopic large animal model. Our findings underscore the hypothesis that mechanical stability is more determining for the successful survival of the implant than the presence of cells and pre-cultured extracellular matrix. This observation is of great translational importance and highlights the aptness of advanced 3D (bio) fabrication technologies for functional tissue restoration in the harsh articular joint mechanical environment.

5. Bernal, P. N., Delrot, P., Loterie, D., Li, Y., Malda, J., Moser, C., & Levato, R. (2019). **Volumetric Bioprinting of Complex Living-Tissue Constructs within Seconds.** *Advanced Materials, 31*(42). https://doi.org/10.1002/adma.201904209
Citations: 411, open access
World-first report of Volumetric Bioprinting, the fastest printing technology, able to produce cm3-sized tissue constructs in less than 15 seconds. The manuscript ranked in the first 1% ever tracked by Altmetric and was featured in Scientific American, Engadget, Het Financieel Dagblad among other newspapers and media outlets.

6. Bernal, P. N., Bouwmeester, M., Madrid-Wolff, J., Falandt, M., Florczak, S., Rodriguez, N. G., Li, Y., Größbacher, G., Samsom, R., Van Wolferen, M., Van Der Laan, L. J. W., Delrot, P., Loterie, D., Malda, J., Moser, C., Spee, B., & Levato, R. (2022). **Volumetric bioprinting of organoids and optically tuned hydrogels to build Liver-Like metabolic biofactories**. *Advanced Materials, 34*(15). https://doi.org/10.1002/adma.202110054
Citations: 171, open access
First demonstration of light-based printing of organoids. We showed that the function of liver organoids can be maximized in volumetrically printed constructs, due to the mild, stress-free rapid printing, and that printed architectures allow to control liver functions. The work was featured in the Dutch magazine De Ingenieur, and is being included in a Dutch high school textbook.

### Kidney and Heart

7. Buikema, J. W., Lee, S., Goodyer, W. R., Maas, R. G., Chirikian, O., Li, G., Miao, Y., Paige, S. L., Lee, D., Wu, H., Paik, D. T., Rhee, S., Tian, L., Galdos, F. X., Puluca, N., Beyersdorf, B., Hu, J., Beck, A., Venkamatran, S., . . . Wu, S. M. (2020). **WNT activation and reduced Cell-Cell contact synergistically induce massive expansion of functional human IPSC-Derived cardiomyocytes.** *Cell Stem Cell, 27*(1), *50-63.e5*. https://doi.org/10.1016/j.stem.2020.06.001
Citations: 138
Deriving a large number of hiPSC-cardiomyocytes would be beneficial for large-scale tissue engineering and drug screening applications. We show that GSK-3β inhibition combined with removal of cell-cell contact enables massive expansion of hiPSC-cardiomyocytes with comparable function to non-expanded cells.

8. Schutgens, F., Rookmaaker, M. B., Margaritis, T., Rios, A., Ammerlaan, C., Jansen, J., Gijzen, L., Vormann, M., Vonk, A., Viveen, M., Yengej, F. Y., Derakhshan, S., De Winter-De Groot, K. M., Artegiani, B., Van Boxtel, R., Cuppen, E., Hendrickx, A. P. A., Van Den Heuvel-Eibrink, M. M., Heitzer, E., . . . Clevers, H. (2019). **Tubuloids derived from human adult kidney and urine for personalized disease modeling.** *Nature Biotechnology, 37*(3), 303–313. https://doi.org/10.1038/s41587-019-0048-8
Citations: 324, open access
Adult stem cell-derived organoids are three-dimensional epithelial structures that recapitulate fundamental aspects of their organ of origin. We describe conditions for the long-term growth of primary kidney tubular epithelial organoids, or 'tubuloids'. The cultures are established from human and mouse kidney tissue and can be expanded for at least 20 passages (>six months) while retaining a normal number of chromosomes. In addition, cultures can be established from human urine.

9. Yengej, F. a. Y., Jansen, J., Ammerlaan, C. M. E., Dilmen, E., Casellas, C. P., Masereeuw, R., Hoenderop, J. G., Smeets, B., Rookmaaker, M. B., Verhaar, M. C., & Clevers, H. (2023). **Tubuloid culture enables long-term expansion of functional human kidney tubule epithelium from iPSC-derived organoids.** *Proceedings of the National Academy of Sciences, 120*(6). https://doi.org/10.1073/pnas.2216836120
Citations: 15, open access
Here, we apply recently developed tubuloid protocols to purify and propagate kidney epithelium from iPSC-derived organoids. The resulting 'iPSC organoid-derived (iPSCod)' tubuloids can be exponentially expanded for at least 2.5 month, while retaining expression of important tubular transporters and segment-specific markers. This approach allows for selective propagation of the mature tubular epithelium, as immature cells, stroma, and undesirable off-target cells rapidly disappeared. iPSCod tubuloids provide easy apical access, which enabled functional evaluation and demonstration of essential secretion and electrolyte reabsorption processes.

10. Ramada, D. L., De Vries, J., Vollenbroek, J., Noor, N., Ter Beek, O., Mihăilă, S. M., Wieringa, F., Masereeuw, R., Gerritsen, K., & Stamatialis, D. (2023). **Portable, wearable and implantable artificial kidney systems: needs, opportunities and challenges.** *Nature Reviews Nephrology, 19*(8), 481–490. https://doi.org/10.1038/s41581-023-00726-9
Citations: 40
Haemodialysis is life sustaining but expensive, provides limited removal of uraemic solutes, is associated with poor patient quality of life and has a large carbon footprint. Innovative dialysis technologies such as portable, wearable and implantable artificial kidney systems are being developed with the aim of addressing these issues and improving patient care. An important challenge for these technologies is the need for continuous regeneration of a small volume of dialysate. To achieve more complete therapy and provide important biological functions, novel membranes could be combined with bioartificial kidneys, which consist of artificial membranes combined with kidney cells. Implementation of these systems will require robust cell sourcing; cell culture facilities annexed to dialysis centers, large-scale, low-cost production, and quality control measures. These challenges are not trivial, and global initiatives involving all relevant stakeholders, including academics, industrialists, medical professionals, and patients with kidney disease, are required to achieve important technological breakthroughs.

### Stem cell-based interventions

11. Baak, L. M., Wagenaar, N., Van Der Aa, N. E., Groenendaal, F., Dudink, J., Tataranno, M. L., Mahamuud, U., Verhage, C. H., Eijsermans, R. M. J. C., Smit, L. S., Jellema, R. K., De Haan, T. R., Ter Horst, H. J., De Boode, W. P., Steggerda, S. J., Prins, H., De Haar, C. G., De Vries, L. S., Van Bel, F., . . . Benders, M. J. N. L. (2022). **Feasibility and safety of intranasally administered mesenchymal stromal cells after perinatal arterial ischaemic stroke in the Netherlands (PASSIoN): a first-in-human, open-label intervention study**. *The Lancet Neurology, 21*(6), 528–536. https://doi.org/10.1016/s1474-4422(22)00117-x
Citations: 67
This first-in-human study demonstrates that intranasal bone marrow-derived MSC administration in neonates after PAIS is feasible and no serious adverse events were observed in patients followed up until three months of age.

12. Schene, I. F., Joore, I. P., Oka, R., Mokry, M., Van Vugt, A. H. M., Van Boxtel, R., Van Der Doef, H. P. J., Van Der Laan, L. J. W., Verstegen, M. M. A., Van Hasselt, P. M., Nieuwenhuis, E. E. S., & Fuchs, S. A. (2020). **Prime editing for functional repair in patient-derived disease models.** *Nature Communications, 11*(1). https://doi.org/10.1038/s41467-020-19136-7
Citations: 149, open access
Prime editing is a recent genome editing technology using fusion proteins of Cas9-nickase and reverse transcriptase, that holds promise to correct the vast majority of genetic defects. Here, we develop prime editing for primary adult stem cells grown in organoid culture models. Prime editing is as efficient in 3D grown organoids as in 2D grown cell lines and offers greater precision than Cas9-mediated homology directed repair (HDR). Base editing remains more reliable than prime editing but is restricted to a subgroup of pathogenic mutations. Whole-genome sequencing of four prime-edited clonal organoid lines reveals absence of genome-wide off-target effects underscoring therapeutic potential of this versatile and precise gene editing strategy.

13. Sachs, N., Papaspyropoulos, A., Ommen, D. D. Z., Heo, I., Böttinger, L., Klay, D., Weeber, F., Huelsz-Prince, G., Iakobachvili, N., Amatngalim, G. D., De Ligt, J., Van Hoeck, A., Proost, N., Viveen, M. C., Lyubimova, A., Teeven, L., Derakhshan, S., Korving, J., Begthel, H., Clevers, H. (2019). **Long-term expanding human airway organoids for disease modeling.** *The EMBO Journal, 38*(4). https://doi.org/10.15252/embj.2018100300
Citations: 666, open access
Here, we describe a method to establish long-term-expanding human airway organoids from broncho-alveolar resections or lavage material. Organoids established from lung cancer resections and metastasis biopsies retain tumor histopathology as well as cancer gene mutations and are amenable to drug screening. We conclude that human airway organoids represent versatile models for the in vitro study of hereditary, malignant, and infectious pulmonary disease.

14. Muilwijk, D., De Poel, E., Van Mourik, P., Suen, S. W., Vonk, A. M., Brunsveld, J. E., Kruisselbrink, E., Oppelaar, H., Hagemeijer, M. C., Berkers, G., De Winter-De Groot, K. M., Heida-Michel, S., Jans, S. R., Van Panhuis, H., Van Der Eerden, M. M., Van Der Meer, R., Roukema, J., Dompeling, E., Weersink, E. J., Beekman, J. M. (2022). **Forskolin-induced organoid swelling is associated with long-term cystic fibrosis disease progression.** *European Respiratory Journal, 60*(2), 2100508. https://doi.org/10.1183/13993003.00508-2021
Citations: 45, open access
Large cohort of >170 organoids showing that organoids associate with long-term disease severity indicators in CF. This allows the degree of swelling to be interpreted in the context of CF disease severity, which has led to the inclusion of the CF swelling test in the care guideline for CF and was part of a data package leading to an EMA qualification advice.

15. Geurts, M. H., De Poel, E., Amatngalim, G. D., Oka, R., Meijers, F. M., Kruisselbrink, E., Van Mourik, P., Berkers, G., De Winter-De Groot, K. M., Michel, S., Muilwijk, D., Aalbers, B. L., Mullenders, J., Boj, S. F., Suen, S. W., Brunsveld, J. E., Janssens, H. M., Mall, M. A., Graeber, S. Y., . . . Clevers, H. (2020). **CRISPR-Based Adenine Editors Correct nonsense mutations in a cystic fibrosis organoid biobank.** *Cell Stem Cell, 26*(4), 503-510.e7. https://doi.org/10.1016/j.stem.2020.01.019
Citations: 159, open access
A newer type of CRISPR, called base editing, can repair a mutation without cutting into the DNA, but by directly altering the DNA enzymatically. Utrecht researchers have built a biobank of more than 600 patient tissues and showed for the first time that base editing was possible in human cells to cure a disease at the DNA level.

16. Marsee, A., Roos, F. J., Verstegen, M. M., Gehart, H., De Koning, E., Lemaigre, F., Forbes, S. J., Peng, W. C., Huch, M., Takebe, T., Vallier, L., Clevers, H., Van Der Laan, L. J., Spee, B., Marsee, A., Roos, F., Verstegen, M., Clevers, H., Vallier, L., Hendriks, D. (2021). **Building consensus on definition and nomenclature of hepatic, pancreatic, and biliary organoids.** *Cell Stem Cell, 28*(5), 816–832. https://doi.org/10.1016/j.stem.2021.04.005
Citations: 200, open access
Hepatic, pancreatic, and biliary (HPB) organoids are powerful tools for studying development, disease, and regeneration. As organoid research expands, the need for clear definitions and nomenclature describing these systems also grows. To facilitate scientific communication and consistent interpretation, we revisit the concept of an organoid and introduce an intuitive classification system and nomenclature for describing these 3D structures through the consensus of experts in the field. To promote the standardization and validation of HPB organoids, we propose guidelines for establishing, characterizing, and benchmarking future systems.

## Appendix B - Most important collaborations

### Regenerative Medicine Utrecht (RMU)

One thing is certain: the RM community is proud of their unique Utrecht ecosystem and the impact they have on the field of regenerative medicine in the region and beyond. This pride is noticeable in every aspect of our work, from the day-to-day realities of research to the interdisciplinary collaboration that allows us to continue innovation in this exciting field. There is a unique collaboration at the Utrecht Science Park between RM researchers from the faculties of Medicine (UMC Utrecht), Hubrecht Institute, Veterinary Medicine and science faculty University Utrecht (UU). And a large part (>350) of the RM researchers are working together under one roof.

### RegMed XB

RegMed XB brings together leading RM scientists at Dutch (Utrecht, Leiden, Eindhoven, Maastricht) and Belgian (Leuven) universities and institutes and a range of companies in so-called 'Moonshots': long-term visions of breakthroughs for patients, translated into research roadmaps with specific short-term milestones. Each is championed by a Health Foundation and their related patient organizations, putting patient impact at the heart of RegMedXB. Utrecht plays an important role in this collaboration, which is evident from the fact that four out of five moonshots are led by UMC Utrecht PIs: Cardiovascular (Pieter Doevendans), Kidney (Marianne Verhaar), Osteoarthritis (Keita Ito), and Eye (Mor Dickman).

### hDMT INFRA StemCells

hDMT INFRA StemCells is a joint initiative of the UMC Utrecht, Rotterdam, and Leiden in affiliation with hDMT, funded by a grant of almost €13.5M from the National Roadmap Large-Scale Research Infrastructure of the Netherlands Organization for Scientific Research (NWO). Within the project, researchers will collaborate closely to develop a unique new class of human models that leverage the advantages of both adult stem cells and induced pluripotent stem cells. During the project, hDMT will establish the 'Central Hub' and four Service Centers of Expertise, located at each of the partner institutions, will make their expertise available for the entire Dutch research community.

### RESCUE CO-Fund

Together the UMC Utrecht (coordinator), the University Utrecht, and the Hubrecht Institute offer 30 PhD positions on REgenerative Medicine & Stem Cells in UtrEcht. All positions are fully funded for four years and are located in the Regenerative Medicine Centre Utrecht, the Netherlands, within the H2020 MSCA-COFUND project RESCUE. 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 organizations, creating a new generation of research experts, empowering them to take leading positions in the field of Regenerative Medicine world-wide. The PhD students' experiences from these past years (2019-2023) have been collected in a booklet. In it, they share a brief summary of their research, reflect on their time as PhD students, and give advice to both other (future) PhD students and supervisors.

### Orgestra

Orgestra is an EU-funded MSCA Joint Doctoral network that trains thirteen doctoral candidates in developing personalized disease models using stem cell-derived organoids for rare diseases, including the lung and kidney diseases, Cystic Fibrosis and cystinosis. This four-year project funded by the European Committee is made up of fourteen partners from seven European countries providing international, intersectoral, and interdisciplinary training that brings together molecular biologists, engineers, pharmacologists, clinicians, epidemiologists, ethicists, and patient representatives to give each of our doctoral candidates a unique, joint-doctoral training experience complemented by a rich network training program. The project started January 2024 and will end in December 2027.

### Eindhoven-Wageningen-Utrecht University-UMC Utrecht Alliance (EWUU)

Eindhoven University of Technology, Wageningen University & Research, Utrecht University, and UMC Utrecht together cover a broad range of fields in scientific research. By cooperating and bringing together different areas of expertise, the four partners enhance the joint impact of their research. The focus in the cooperation is on the social challenges in the fields of health, energy, food and sustainability. RM&SC is initiator and actively involved in the Living Technologies program.

## Appendix C - Grants and prizes

### Collaborative grants/awards

**NWO SUMMIT - DRIVE-RM**

In 2024 the DRIVE-RM consortium, led by Professor of Experimental Nephrology Marianne Verhaar, has been awarded €37.5M under the prestigious NWO SUMMIT program. The SUMMIT grant recognizes world-class collaborations, while further strengthening these partnerships. The DRIVE-RM collaboration involves UMC Utrecht, Utrecht University, Eindhoven University of Technology, Maastricht University, and the Hubrecht Institute, focusing on smart materials that assist the body in healing. Within Utrecht University, the faculties of Medicine, Veterinary Medicine, and Science are involved.

**NGF - Innovation Center for Advanced Therapies (ICAT)**

In the first round (2021) of the Dutch National Growth Fund (NGF), €56M were awarded for the construction, equipment and staffing of the RegMed XB Pilot Factory. With five specialized pilot lines in different regions, the Pilot Factory offers access to the entire regenerative chain: development and production of stem cells, mini-organs, tissues and smart (bio)materials. Innovation Center for Advanced Therapies (ICAT) is the microtissue pilot line is located in Utrecht and integrates 3 facilities; a biofabrication pilot facility, a GMP simulation facility, and a GMP production facility, enabling the development, optimization, and standardization of complex manufacturing processes of engineered immune cells and (patient specific) microtissues

**NGF - Centre for Animal-Free Biomedical Translation (CPBT)**

In the third round (2024), the Dutch National Growth Fund (NGF) invested €124.5M in transition to animal-free biomedical innovation. Initially, it will focus on ALS, cystic fibrosis, osteoarthritis/rheumatic diseases and asthma/COPD. The CPBT will implement the developed methods, tools, and expertise together with researchers and companies. The new center will also offer education, training, advice, and support to enhance the acceptance and use of animal-free biomedical innovations. The CPBT is an initiative of Utrecht University, UMC Utrecht, HU University of Applied Sciences Utrecht, and the National Institute for Public Health and the Environment (RIVM). The initiation, preparation, coordination, and implementation of it are being led by researchers from RMU.

**KNAW Ammodo Science Award - Omnes Pro Uno**

In 2022, the Omnes Pro Uno (OPU) consortium led by Sabine Fuchs was one of the two winners of the Ammodo Science Award for groundbreaking research. This bi-annual award (€1.2M) offers excellent scientists space to develop new work and contributes to the visibility of their work. OPU's mission is to cure patients with a genetic disease by detecting and correcting errors in DNA before irreversible damage occurs in the body. The five highly talented researchers (Sabine Fuchs, Hans Clevers, Edward Nieuwenhuis, Ruben van Boxtel, and Annelien Bredenoord) have the expertise to optimize the gene editing techniques that are currently being developed at a rapid pace, and to apply them in a safe and responsible manner. Sabine Fuchs also received an ERC Starting Grant (2022), ERC Proof of Concept (2024), and a ZonMw Vici grant (2024).

**Horizon Europe 'Health' - Bio-printing of living cells for regenerative medicine**

In five out of six awarded projects of this EU call, UMC Utrecht is involved. In the micro2MACRO project of Jos Malda, the focus is on directing the development of cells after printing. By including nutrients and signal molecules in the print, cells are boosted to become functional tissue more quickly. Harrie Weinans' aim is to bioprint in a patient, during a laparoscopic knee operation to repair cartilage, a printed version of the IMPACT treatment developed in Utrecht. Laetitia de Kort and Petra de Graaf are focusing on printing a piece of the urethra in the STRONG-UR project. Mor Dickman's aim is to bring a solution to the shortage of cornea donors. The goal of the KeratOprinter project is a bioprinted cornea that mimics the entire structure and function of the human cornea. This underlines the importance of RMU for Europe, and the potential of bioprinting for patients.

## Individual International Grants and recognition

- ERC Advanced Grant: Jos Malda (2024), Keita Ito (2021)
- ERC Starting Grant: Sabine Fuchs (2021), Riccardo Levato (2020)
- Jos Malda received the Excellence in Translational Science Award Journal of Orthopaedic Research (2022), a TERMIS-EU Mid-Career Award in 2021, the ISBF Senior Investigator Award 2021, the Bertus Rahn Award (2021). Moreover, Jos Malda featured in the prestigious Top 2% Scientists list every year since 2020, as recognized by the renowned Elsevier/Stanford University ranking, reaffirming his status as a leading figure in the fields of Engineering and Biomedical Engineering.
- Riccardo Levato won the Jean Leray award from the European Society for Biomaterials, the 2022 Robert Brown award from the Tissue Engineering and Regenerative Medicine International Society, and the 2023 Mid-career Investigator Award from the International Society for Biofabrication (ISBF).
- Jeffrey Beekman won the prestigious Prix Galien Research Award in 2019.
- Karin Gerritsen won the KidneyX Prize in 2021 award from the American Society of Nephrology (ASN) and the U.S. Department of Health and Human Services (HHS).

## Individual National Grants and recognition

- Vici: Cora Nijboer (2024), Sabine Fuchs (2024
- Vidi: Karin Jongsma (2023), Riccardo Levato (2023)
- Veni: Nazma Ilahibaks (2024), Mylene Jansen (2023)-, Renske ten Ham (2023)

## Appendix D - Key outputs or activities aimed at a professional of wider audience

### 3D technologies open up many avenues in healthcare

Healthcare focuses more and more on personalized approaches. Since every person is different, 3D technologies play an increasingly important role in analyzing and mapping each patient's unique needs. At UMC Utrecht, an innovative collaboration 3D Lab was established to develop advanced technology such as 3D printers, scanners, prosthetics, and implants to support both patients and doctors. The 3D-Lab develops these technologies forward with multiple applications. First of all, they utilize 3D scans and models to prepare for and guide surgery. Second, they use 3D technology to create the best fitting implants. And finally, the three-dimensional aspect helps to advance implants towards more regenerative, smart implants.

### National Service Center of Expertise

The Utrecht Platform for Organoid Technology (UPORT) support living tissue access or biobanked living stem cells. Several 'living biobanks' are already established such as airways (357), gut (630), kidney (18), metabolic diseases (>300), cancer (2037), and tissue and cells can be acquired for academic and commercial research. A searchable organoid catalog (often linked to clinical information) is available for researchers. If the desired material is not available, a request can be made to set up a protocol to obtain the right material and make it available for the research.

The UMC Utrecht AI lab for Living technologies is a hDMT INFRA StemCells service center of expertise for AI in the context of living cell technologies. They enable automation, data analysis, and modeling for impactful applications in biology and healthcare. The development and implementation of artificial intelligence for patient-derived living technologies in microscopy, bioprinting, and automation to accelerate the development of personalized and curative treatments. Through the HDMT platform, people can reach out to our UMC Utrecht services.

### European Reference Networks (ERNs)

The ERNs were established by the European Commission in 2017. Each ERN focuses on a cluster of rare conditions with common characteristics. Various ERNs have been set up within RM&SC: Skeletal malformations, congenital facial and dental defects, Osteochondritis Dissecans, Lung (Cystic Fibrosis), hereditary metabolic diseases, hereditary and congenital renal and urinary tract disorders.

### Patents

The following patents have been applied for and/or obtained:

- Karin Gerritsen: Ureum Sorbent Membrane (NeoKidney), PGA Sorbent (NeoKidney)
- Debby Gawlitta: Engineered Cartilage
- Jos Malda: Method and gel for bioprinting at micro scale
- Moyo Kruyt: Universal Sliding Bearing for Spine
- Harrie Weinans: Deformable Hip Cup
- Saber Amin Yavari: Bactericidal Coating (Preimure), Generic Hip Implants
- Riccardo Levato: Gelatins for Bio-Printing (Rousselot), Matrigel Alternative
- Joost Sluijter: VINCIs
- Sabine Fuchs: HELLOs
- Cora Nijboer: iSTOP-CP
- Laura Creemers: Celecoxib

### Start-ups

- Laura Creemers: Establishment of Epione Therapeutix, an SME dedicated to treat pain via intra-articular and intradiscal celecoxib-releasing microspheres in patients with osteoarthritis and chronic low back pain.
- Jeffrey Beekman cofounded FAIR Therapeutics with Kors van der Ent. Fair TX raised significant pre-series A funding to develop affordable CFTR modulators for CF in the context of organoid technology; currently FAIR is engaged in a phase 2b clinical trial.

- Sabine Fuchs, Indi Joore and Ibrahim Ardisasmita started HELLO-R&D based on a patent technology for culture of human liver cells to enable drug efficacy testing. They won the Ureka Mega Challenge, the animal free Venture Challenge, an Utrecht Holding and RegMedXB voucher and a BioTechBooster grant to start their company.
- Several spin-off companies (Cresco Spine, Presurgeo, Replasia, Amotio, Preimure) have emerged from by (Harrie Weinans, Ralph Sakkers, Saber Amin Yavari, Moyo Kruijt). Just like the 3D laboratory that was established within UMC Utrecht, working closely with surgeons to advance medical innovation.
- The KneeReviver is CE market and has a UMCU spinoff company: ArthroSave.

### HelpdeskRM

Regenerative Medicine Utrecht has taken the initiative to respond to the information needs of the public and launched the HelpdeskRM in 2022. On this Dutch-language website you can find questions and answers about RM, and visitors can also send in questions for answers by an expert. After steady growth in the first two years, the HelpdeskRM now attracts about 100-150 visitors per day. In addition, we are frequently present at events where the general public, both children and adults, (Weekend van de Wetenschap, expeditie NEXT) are introduced to science. In 2024, during the Utrecht Science week, a public evening Hospital of the Future, your own cells as medicine, was organized.

### Intimate Implants, dialogue on science, technology and innovation

The Rathenau Institute has awarded the Melanie Peters Prize 2024 to the developers of Intimate Implant (co-production by artistic designer Bertrand Burgers and bioethics researchers Anne-Floor de Kanter and Manon van Daal. The prize awarded to people who make an important contribution to the social dialogue on science, technology and innovation. Intimate Implant is a speculative art-based experience focused on an underexplored theme in science: the emotional relationship between humans and technology.

### Minister and members of parliament visits RMU

In April 2023 the Minister of Agriculture and several members of the House of Representatives visited the Regenerative Medicine Center Utrecht. In addition to the visit of some laboratories, a round table discussion took place with various stakeholders about how the institutions, such as the UMC Utrecht, are working to refine, reduce and replace the external link of animal testing, and what obstacles there are to animal-free innovation. During the round table discussion, the chair of knowledge organization ZonMw, Arfan Ikram, presented the Knowledge Agenda for the Transition to Animal-Free Innovation to the Minister. In it, the organization makes recommendations for accelerating the transition. Several RMU researchers contributed to this report.

### Lay Media and crowdfunding efforts

Metabolic Diseases: The annual end-of-year campaign of one of the largest radio stations in the Netherlands in 2024 was dedicated to children with metabolic diseases. During this 'Serious Request / Glazen Huis' action, money was collected (more than €12M) for research, but especially attention was drawn to these diseases. Also, a documentary was made in which Sabine Fuchs was followed for a year in her 'struggle' for solutions to cure these patients. Sabine was also a guest on some television talk shows.

Public campaign 'Nieuwe nieren': in 2021, a large-scale public campaign for new kidneys was held. Through a special website and social media, explanations were given in various ways about kidney diseases, the consequences for patients and current treatments. There was also a lot of attention for scientific research such as the portable artificial kidney, kidney organoids and models to better understand the functioning of the kidney. The campaign had nearly 225,000 views on social media and 2000 visitors on the website

Articles and interviews have also been published in national newspapers or broadcast on radio and television:
- Roel Custer (Volkskrant 2019, Algemeen Dagblad 2019, NRC 2024, BNR 2024, Een Vandaag 2024.
- Sabine Fuchs (Volkskrant 2024, Telegraaf 2022& 2024, Trouw 2022. Koffietijd 2022, Tijd voor Max 2021.
- BNRadio: Roel Custers, Marianne Verhaar, Jos Malda, Debby Gawlitta, Jeffrey Beekman.
- Several doctors and researchers (Moyo Kruyt, Sabine Fuchs, Jeffrey Beekman) were also featured in episodes of the 'Children's Hospital' which was broadcast on television and more than 800.000 attracts.

# SWOT analysis & strategy for the next six years

# SWOT analysis & strategy for the next six years

## 1 - Strengths, weaknesses, opportunities, and threats

### STRENGTHS

- Unique combination of public and private research institutions at Utrecht Science Park
- Strategic programs are involved in all central promotion decisions
- Strong research infrastructure with core facilities, including a 'living biobank' with organoids
- Strong research support, especially research funding as well as regulatory compliance in clinical research
- The link between patient care and research is structurally embedded in governance (e.g. dedicated clinical scientists and clinical faculty professors)
- Talent program and international onboarding program for researchers in all career phases, both highly appreciated
- High visibility and leadership for Open Science and Recognition & Rewards
- Major revision of UMC Utrecht governance will improve decision making and integrate financial and research-strategic responsibilities

### WEAKNESSES

- Fragmented support for 'valorization', specifically public-private collaboration and technology transfer
- Common practice to offer early- and mid-career researchers only temporary contracts conditional to external funding
- Floor space for research laboratories and personnel is limited
- Governance of 'Diversity, equality and inclusion' policies requires consolidation
- Much uncertainty and discussion due to upcoming governance transformation
- Position of so-called 'clinical scientists' with 0.4 FTE dedicated research time often remains precarious

### OPPORTUNITIES

- Improve collaboration with Princess Máxima Center for Pediatric Oncology
- Set up more clinical trials with commercial partners (supported by U-TRIAL)
- Expand on strategic collaboration with Wageningen University & Research (food and agriculture) and Technical University Eindhoven and Utrecht University (EWUU Alliance)
- National and international developments and funding for Data Infrastructure and Artificial Intelligence in health (research)
- Better use of knowledge generated in large national consortia like Oncode, Imagine, Center for Animal-free Biomedical Translational research
- Increase collaboration between university medical centers in the Netherlands, including shared research facilities and focusing of research topics

### THREATS

- Geopolitical instability threatens collaboration and knowledge exchange
- Privacy regulations and knowledge security policies increasingly interfere with health research and innovation
- National political climate leading to (further) budget cuts for academic research and teaching
- Deterioration of government-coordinated national healthcare governance, specifically with regional and national agreements between hospitals (IZA)

## 2 - Strategy for the next six years

For the next strategic period, based on the existing Connecting Worlds strategy, UMC Utrecht is changing its governance and broadly keeping the underlying research topics in place. We are exploring how to shape processes more intelligently and consistently, allowing us to innovate and improve faster while better responding to changes and societal demands. To continuously make progress in care, education, and research, we want to collaborate more effectively. In the current governance, with budget-responsible divisions that make decisions on their own, UMC Utrecht tends to operate too much like a collection of small independent hospitals.

Therefore, we will move from strategic programs, divisions, and directorates to Themes, Centers, and Services. Divisions will be transformed into Centers, which will closely collaborate with the Themes. As a result, the work of a Center will directly contribute to the goals of a Theme, and thus to the mission and vision of UMC Utrecht. The Centers are responsible for people, resources, and facilities.
The Themes encompass the key areas where, from UMC Utrecht, we provide care, conduct research, and innovate. Themes focus on 'what' we do and are goal oriented. In collaboration with other Themes, they ensure effective alignment of strategic and substantive choices. Themes determine which care, education, and research we provide. In short, the Themes provide direction, while the Centers make the execution possible. In addition, Services offer support, frameworks, information, and advice in this collaboration.
The combination of budget responsibility and strategic research leadership in Themes implies a fundamental change in UMC Utrecht's research governance, and it meets a long-term and recurring recommendation.
On January 1, 2027, we will start with the new organizational structure. It will take until January 1, 2028, to fully integrate the new structure and way of working. An overview of the new organizational structure is visualized in figure 1'.

**New governance UMC Utrecht**

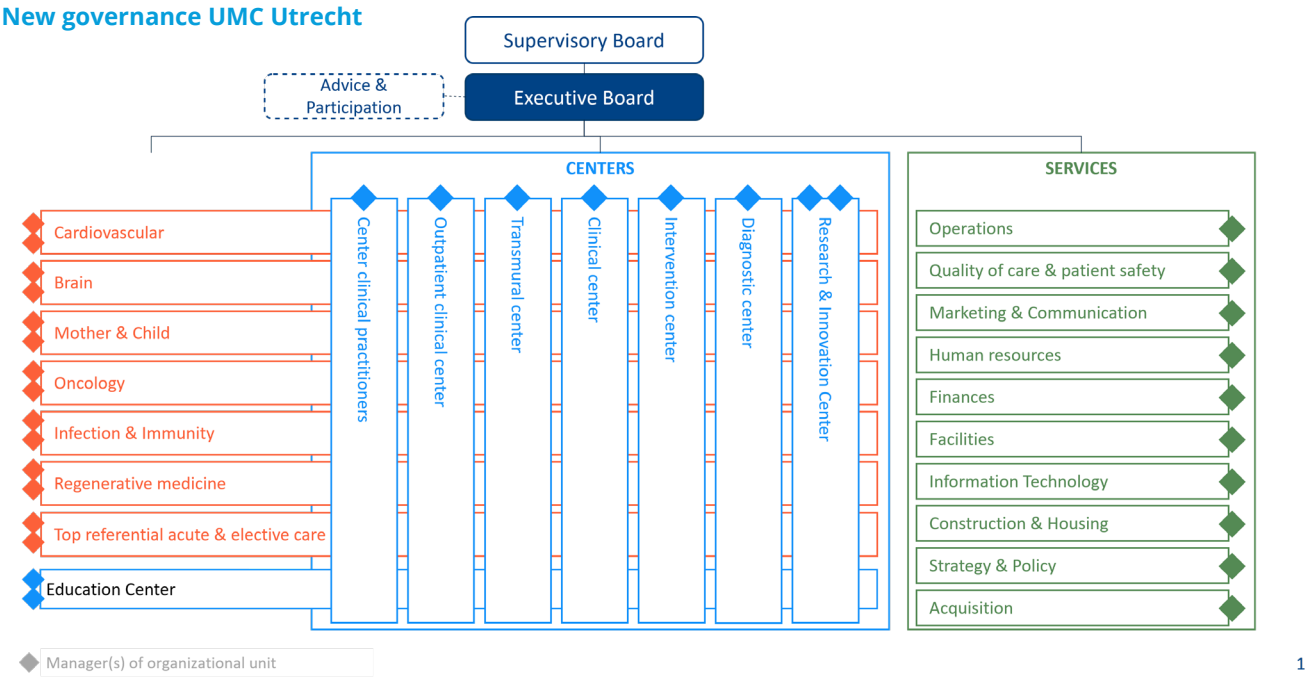



*Figure 1: New organizational structure of the UMC Utrecht from 2027 onwards.*

**Colophon**
This self-evaluation report is part of the 2025 SEP research evaluation of UMC Utrecht, covering the period 2019-2024.

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