UMC Utrecht

UPORT
Utrecht Platform for Organoid Technology

UPORT Cancer Biobank

Organoids as a resource for fundamental and applied cancer research

Sub-biobank title (up to 250 characters): UPORT Cancer Biobank, Organoids as a resource for fundamental and applied cancer research	
Sub-biobank acronym (up to 50 characters): UPORT Cancer	
Details of person with final responsibility and contact person	
Name responsible sub-biobank coordinator (= (medical) head of department) (surname, initials)):	Kranenburg, O.
Division (full name):	Imaging & Oncology
Department (full name):	Utrecht Platform for Organoid Technology
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Sponsor, if this is not UMC Utrecht:	N.A.
Grant provider (if applicable):	N.A.

Project goal: To create the UPORT Cancer Biobank, a 'living organoid biobank' for cancer research. Organoids can be derived from surgically resected tumor and surrounding normal tissues, or in some cases, from biopsies. Additional patient derived source material include urine, Pap smear and ascites.

The biobank will be complemented with:

- Paired blood samples which will be used to assess germline genetic variation in relation to the variants detected in the tumor.
- Cells from the microenvironment and from blood (e.g. fibroblasts, immune cells, endothelial cells, etc.) that can be used to generate more complex co-culture systems.
- Induced pluripotent stem cells (iPSCs) may be generated from the same material, allowing the further development of genetically matched high-end co-culture systems to study tissue-specific characteristics.

The biobank will be characterized in multiple ways with the aim to subclassify the organoids with specific features (genetic/drug sensitivity/clinical data):

- **DNA/RNA** sequencing. The organoids will be genetically characterized to identify for example driver gene alterations and to allow 'molecular subtyping'.
- **Protein** expression patterns.
- **Drug sensitivity**. The organoids will be used to assess their sensitivity/resistance to anti-cancer drugs in order to be able to classify organoids into subgroups.
- **Link to (clinical) data**. The organoids will be linked to medical data, retrieved from treatment records, scientific studies, general practitioners, other hospitals and cohort studies, including 'Prospectief Landelijk CRC cohort' (PLCRC), 'Nederlandse Kanker Registratie' (NKR) and the 'Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief' (PALGA).

The biobank, annotated with the above characteristics, will be used:

- **To optimize organoid culturing techniques** and protocols for e.g. expansion, differentiation and functional characterization of organoids from a large variety of tumor (sub-) types.
- **To establish a biobank catalogue** that facilitates access to organoids, encourages collaboration, reduces patient burden, and lowers research costs by providing an organized and accessible platform for available samples and data.
- **For future research projects.** This may involve collaborations with academic or commercial partners. Future research may entail in vitro and/or in vivo (animal) studies, e.g. to test the efficacy of novel treatment strategies.

Scientific background: Traditional frozen and paraffin-embedded tissue biobanks have proven to be extremely valuable resources for fundamental and applied cancer research. The combination of histopathological, genetic and clinical data has guided the development of many novel diagnostic tools and treatment strategies. However, such tissue biobanks cannot be used to empirically test novel hypotheses relating to tumor development or therapeutic vulnerabilities. Functional cancer research has so far largely relied on the use of immortalized (cancer) cell lines and animal models. However, *in vitro* immortalization of cell lines is accompanied by extensive genetic changes that allow cancer cells to adapt to the culturing conditions. This creates major and unwanted discrepancies between cancer cell line models and the tissues they are supposed to represent. About 10 years ago, a 3D culturing system was developed which allowed researchers to culture human adult stem cells from (tumor) tissues indefinitely as organoids, or 'mini-organs-in-a-dish' (1,2). Organoid cultures can be established with high efficiency from multiple healthy and diseased human tissues (3-14) whilst maintaining their phenotypic, functional and genetic properties.
The unprecedented faithful representation of the (tumor) tissue-of-origin by organoids opens many avenues for ***fundamental research into the (patho-)physiology of tumor development***, for ***drug discovery***, and for developing ***personalized medicine strategies*** (e.g.15-24).

The UMCU, the Hubrecht Institute, and the Prinses Maxima Centrum will apply organoid technology to culture organoids from tumor and healthy surrounding tissues, and/or from precursor lesions (e.g. adenomas) and/or from tissues at high risk of developing cancer (e.g. inflammatory lesions). This 'living biobank' can subsequently be applied in diverse areas of cancer research.
The envisioned UPORT Cancer Biobank, combined with genetic data and long-term patient follow-up, provides a unique resource for many aspects of biomedical cancer research and allows researchers to use UMCU patient tissues for the derivation of organoids. For the Hubrecht Institute, this is extensively described in the accompanying collaboration agreement and for the Prinses Maxima Centrum in a MTA.

Study population
Patients who are 16 years or older, mentally competent, treated in the UMC Utrecht and other collaborating hospitals like the Meander MC and Antoni van Leeuwenhoek and are diagnosed or suspected with cancer at any developmental stage. Patients are included if they undergo a surgical resection as part of their standard care/a clinical trial, or during an already scheduled appointment in the hospital, an (extra) biopsy can be taken. Patients are also included if urine, Pap smear or ascites fluid can be collected when this is relevant for the tumor type, even when no tissue is collected.

BIOBANK PROTOCOL SIGNATURE PAGE

1. The undersigned, who is the **responsible coordinator** for this **sub-biobank**, declares that:
   - he/she has taken note of UMC Utrecht's biobank regulations ("Kaderreglement Biobanken UMC Utrecht") and will follow this biobank protocol and these UMC Utrecht's biobank regulations;
   - he/she will inform the other parties with responsibility for this biobank protocol about any adjustments to this protocol in connection with questions from the committee and will obtain their approval for these adjustments. Note: If so, this biobank protocol will not need to be re-signed when resubmitted. It is advisable to keep a fully signed version of the final approved protocol in the biobank file.

Name	Signature	Date
Responsible sub-biobank coordinator Prof. Dr. O. Kranenburg Prof Translational Tumor Biology Chair UPORT Head LTO		13-06-2025

2. *Signature on behalf of division management*

The management of the imaging and oncology Division hereby declares that:

- they approve of the management of this sub-biobank within the division;
- the entire management team agrees with this approval;
- arrangements have been made about the set-up of this sub-biobank with the management teams of any other institutions/divisions participating in or supporting this sub-biobank.

Place: Utrecht Date: June 2nd 2021

Manager:

Name: Prof. Dr. Hendrikse Signature: 

CONTENTS

LIST OF ACRONYMS AND RELEVANT DEFINITIONS

DPA	Data Protection Authority of the Netherlands
GDPR	General Data Protection Regulation
BC	Broad Consent
CBB	UMC Utrecht Central Biobank
ICF	Informed Consent Form
EB	Executive Board
TCBio	Biobank Research Ethics Committee: independent committee set up by the Executive Board that reviews biobank protocols and the use of the materials for specific research questions.
UPORT	Utrecht Platform for Organoid Technology

1 INTRODUCTION AND RATIONALE

Immortalized cell lines and animal models are routinely used in biomedical cancer research in order to increase our understanding of tumor development and progression, and for drug discovery. Although these traditional models have contributed immensely to our understanding of tumorigenesis, they are not suitable for the development of personalized medicine. During cell line establishment, (tumor) cells undergo major genetic alterations as they adapt to the culture conditions. Following the highly selective culture establishment process, successfully adapted cells no longer form a faithful representation of the original (tumor) tissue. As a result, cell-line-based drug discovery programs have had disappointingly little success in the oncology domain.

Organoid technology is a new method of tissue culturing that was developed in the lab of Hans Clevers at the Hubrecht Institute and overcomes the limitations that are associated with cell line establishment. The technology is based on insight into the biology of adult stem cells and allows researchers to culture a diverse array of human (tumor) tissues in a dish without the selection process that is associated with traditional cell line establishment. Living organoid biobanks form a faithful representation of the heterogeneity of the disease (e.g. a specific cancer type) and, when coupled to genetic tissue/organoid analyses and to real-world data from patient cohorts, uniquely allow the development of strategies for personalized medicine.

The UPORT-CANCER biobank – We propose to create a 'living organoid biobank' derived from tumor and paired healthy tissues from various organs. Organoids may be derived from surgically resected tumor and surrounding normal tissues, or in some cases, from biopsies. Other patient derived source material included are urine, Pap smear and ascites. In addition, the tissues/organoids will be genetically characterized (DNA/RNA). Paired blood samples will be used to assess germline genetic variation in relation to the variants detected in the tumor. Cells from the microenvironment (e.g. fibroblasts, immune cells, endothelial cells etc.) may be used to generate more complex co-culture systems. Furthermore, induced pluripotent stem cells (iPS) may be generated from the same material, allowing the further development of genetically matched high-end co-culture systems.

Biobank characterization – The biobank will be characterized in multiple ways. First, the organoids will be genetically characterized (DNA/RNA sequencing) to identify driver gene alterations and allow molecular subtyping. Genetic analyses will be performed with the sole purpose of organoid classification without a specific research question. Genetic analyses that are needed to answer specific research questions (e.g. relating to genetic heterogeneity, sub-clonal dynamics, clone selection during therapy, etc.) will require a release protocol. Second the organoids will be subjected to drug screens, which will allow classification of the organoid collection according to drug sensitivities without an *a priori* research question. These activities will be restricted to standard-of-care drugs only. A release protocol will be required for testing novel (combination) treatments in the context of hypothesis-driven research. Third, the organoid biobank will be linked to medical data, thus providing a rich clinical annotation of the organoid collections.

The biobank can be used for future research within the UMC Utrecht with or without other academic and commercial partners. A well-annotated catalog of the extensively characterized organoids will provide an organized and accessible platform for efficient design of future research projects.

In case novel technologies become available that are considered useful for organoid classification purposes, we will submit an amendment to this protocol, for evaluation by the TcBio. Envisioned future use of the biobank – Organoids are amenable to genetic modification (e.g. through CRISPR/CAS technology), imaging, *in vitro* high-throughput drug screening, etc., which allows them to be used in a wide range of cancer research applications. Future research projects may entail (but are not limited to) studies aimed at developing novel treatment strategies and/or studies aimed at unravelling the mechanisms of cancer initiation and metastatic progression. Such projects may include *in vitro* experiments, as well as *in vivo* experiments using organoid-initiated (metastatic) cancer models. In addition, organoids can be used to study the interactions between tumor tissue and surrounding normal tissue. This may also involve incorporation of cells from the microenvironment, and even microbiota. Normal tissue organoids can also be used to study physiological processes that lead to cancer initiation,

or as a platform for toxicity testing of novel therapies.
The biobank may also have value in validating organoid technology as a diagnostic tool for predicting response to therapy. Organoids can now be grown from very small amounts of tumor tissue (e.g. biopsies) and can be rapidly expanded and drug-screened within a period of 2-3 weeks. As such, organoids may hold value as a patient stratification tool.
The UPORT Cancer Biobank will be generated in close collaboration between the UMCU, the Hubrecht Institute and the Princes Maxima Centrum, according to the agreements accompanying this biobank protocol.

2 OBJECTIVE

Primary objective:
To create the UPORT Cancer Biobank, a 'living organoid biobank' for cancer research. Organoids can be derived from surgically resected tumor and surrounding normal tissues, or in some cases, from biopsies. Additional patient derived source material include urine, Pap smear and ascites.

Secondary objectives:
The biobank will be complemented with:

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- For future research projects. This may involve collaborations with academic or commercial partners. Future research may entail in vitro and/or in vivo (animal) studies, e.g. to test the efficacy of novel treatment strategies.

3 BIOBANK POPULATION

3.1 General description of the biobank population

A) Healthy donors and/or patients?

☐ healthy donors
Number: ……..
☑ patients
Number: 3000-4500

B) From which donor category will materials be collected (more than one answer possible)?

☑ aged 16 years or over and able to exercise their free will (capacitated)
☐ aged 16 years or over and unable to exercise their free will **(incapacitated, proceed to question C)**
☐ aged 12-15 years and able to give informed consent **(proceed to question D)**
☐ aged 12-15 years and unable to give informed consent (unable to exercise their free will, incapacitated) **(proceed to question C)**
☐ under 12 years of age **(proceed to question D)**

C) If a donor is unable to exercise his/her free will, which category does he/she belong to?

☐ people with a mental disability
☐ people with a psychiatric disorder
☐ people with a dementing disorder
☐ people with a reduced level of consciousness
☐ other, i.e. ……

D) (If applicable:) Why will the materials not be collected from subjects who are of age / capacitated i.e. able to make a reasonable judgement of their own interests with regards to the biobank?
……

E) Which type or types of disorders/conditions does the biobank concern (up to 3):

☐ heart disorders
☑ congenital, familial and genetic disorders
☐ disorders of the blood and lymphatic systems
☐ nervous system disorders
☐ eye disorders
☐ balance and ear disorders
☐ respiratory, thoracic and mediastinal disorders
☐ gastrointestinal tract disorders
☐ renal and urinary tract disorders

☐ skin and subcutaneous tissue disorders
☐ musculoskeletal and connective tissue disorders
☐ endocrine disorders
☐ nutritional and metabolic disorders
☐ infections and parasitic diseases
☐ injuries, intoxications and complications of procedures
☑ neoplasms (benign, malignant and unspecified, including cysts and polyps)
☐ surgical and medical procedures
☐ vascular disorders
☐ general disorders and administration site disorders
☐ pregnancy, perinatal period and puerperium
☐ social circumstances
☐ immune system disorders
☐ hepatobiliary disorders
☐ reproductive system and breast disorders
☐ mental disorders
☐ other, i.e.

3.2 Specific description of the biobank population

The biobank population consists of patients who are 16 years or older, mentally competent, treated in the UMC Utrecht or other collaborating hospitals like the Meander MC and Antoni van Leeuwenhoek and are diagnosed or suspected with a form of cancer, at any developmental stage. For the collection of patient material and data from other hospitals, an agreement between that hospital and the UMC Utrecht is needed before the collection can start. The patients are included:

- If they undergo a surgical resection as a part of their standard care or a clinical trial
- When during an already scheduled appointment in the hospital, an (extra) biopsy can be taken.
- If urine, Pap smear or ascites fluid can be collected when this is relevant for the tumor type, even when no tissue is collected.

A. Is this group of donors also involved (as far as you know) in ongoing research that is subject to the WMO or in an existing biobank of UMC Utrecht? ☑ yes ☐ no

If so, in what division/department?
Multiple departments/divisions within the UMC Utrecht

B. Is this biobank being set up in consultation with the division/department concerned? ☑ yes ☐ no

3.3 Inclusion criteria

To be eligible for inclusion in the biobank, the donor must meet all of the following criteria:

- The donor must be 16 years or older, mentally competent and connected to the UMC Utrecht and other collaborating hospitals like the Meander MC and Antoni van Leeuwenhoek.
- The donor must be diagnosed or suspected with a form of cancer, at any developmental stage.
- The donor must undergo (partial) resection, a biopsy procedure and/or when it is relevant for the tumor type of a patient, be willing to donate a biopsy, ascites fluid, a Pap smear or urine.
- From all of the above patient's blood can be withdrawn for the interests of the biobank mentioned

in 4.1.

3.4 Exclusion criteria

A potential donor who meets at least one of the following criteria will be excluded from participation in the biobank:

- Patients who are positive for HIV virus (in case this is directly noticed in the patient's medical dossier/history).
- Patients who do not speak Dutch and do not know someone who can translate.
- Patients who are mentally incompetent.
- Patients who were thought to possibly have cancer or a precursor of it, but who were found not to have cancer after diagnosis.
    - In some cases, the first sample taken from a patient may be cancerous and the second sample, taken at a different time point, may be cancer-free due to for example treatment. In these cases, the patient is not excluded from the biobank and the tissue and data do not need to be removed from the biobank.

3.5 Intended or expected number of donors

We expect to include 3000-4500 patients in 10 years.

4 METHODS

4.1 Biobank procedures involving the donor

A) Will the donors have to undergo additional invasive procedures (which are not part of the standard care) as part of their participation in the biobank?

☑ no. In this case, does it concern:

a) residual materials[1]? ☑ yes ☐ no

- Residual resection tissue: tumor and/or normal.
- When relevant for the tumor type: Residual urine, collected during surgery when the bladder is emptied via a catheter.
- Ascites, only collected in the context of standard care and/or a clinical trial.

b) withdrawal of extra blood during standard venepuncture as part of regular care?

☑ yes, 6 times, 30 ml/procedure

☐ no

☐ venepuncture …… times …… ml/procedure

☐ arterial puncture …… times …… ml/procedure

☐ intravenous injection …… times ……ml/procedure

☐ intra-arterial injection …… times ……ml/procedure

☐ subcutaneous injection …… times ……ml/procedure

☐ intramuscular injection …… times ……ml/procedure

☐ intra-articular or peri-articular injection …… times ……ml/procedure

☐ withdrawal of cerebrospinal fluid …. ... times …… ml/procedure

☐ endoscopy, type of endoscopy:
……times

☐ biopsy, type of biopsy:
…… …….. times

☐ catheterisation, type of catheterisation:
……. ……. times

☐ assessment involving radiation exposure, type of assessment:
……times….. mSv/procedure
……times……mSv/procedure
……times……mSv/procedure

☐ vaginal/rectal examination …….times

☑ other procedures, i.e. (describe according to severity and frequency):

1) An additional biopsy when a biopsy is already being performed in the context of standard care and/or a clinical trial. In addition, biopsies which are not part of standard clinical care can be taken, but only in case it can be obtained during an already scheduled appointment in the hospital, such as an outpatient visit or an endoscopy for another reason. The tissues need to be easily accessible and at low-risk sites, such as tumors/metastases in the skin, in the mucosal lining, abdominal wall, and superficial lymph nodes. No biopsies will be taken from lung tissue due to the higher risk of complications.

[1] Materials obtained as part of diagnostics and/or treatment that no longer need to be used for quality assurance and/or further individual diagnostics.

2) For cervical cancer, we ask permission to obtain an additional Pap smear during pelvic examinations undertaken in the context of standard care and/or a clinical trial. (note: no additional pelvic examination will be undertaken solely for this biobank)
3) When relevant for the tumor type, patients can be asked to donate urine. The patient will be asked to donate urine during an outpatient clinic visit that is needed for standard care and/or a clinical trial.

B) How much time will donors spend on their participation in the biobank (and any prior examinations)?

Time to be spent:
- Time primary introduction: +/- 2-5 minutes
- Time to read the patient information and sign the informed consent: depending on the patient.
- Time explanation of biobank by biobank coordinator: +/- 15 minutes average

Total amount of time for the individual donor: +/- 45 minutes

Since all the material is collected during an already planned procedure, this time is not included in the calculation. Only the time required to obtain informed consent has been taken into account.

C) Will the donors be admitted to hospital in connection with their participation in the biobank, or will any hospital admission be extended?

☐ yes, their stay in hospital or in the institution will be extended in connection with their participation in the biobank
☐ yes, they will be admitted to hospital or to the institution for their participation in the biobank
☑ no

D) Describe the extent to which donors will be subjected to procedures or will be required to act in a certain way, such as cooperate with questionnaires, interviews or physical/mental assessments, deny themselves certain things, stick to a particular diet (for invasive procedures, see question A).

No specific lifestyle limitations are required for participation.

E) Will the donors be tested for certain disorders/conditions (e.g. HIV, pregnancy)?

☐ yes (explain), i.e. ……..
☑ no

F) Indicate which risks participation in the biobank carries for the donor.

The risks for patients participating in this biobank are negligible. We will use leftover material from resections, urine collected via catheter and ascites collected during standard care and/or clinical trial without introducing any additional risk. Urine collected through voluntary urine sampling during an outpatient clinic visit is also risk free. Blood is collected only during venepuncture for standard care and/or clinical trial, or if the patient has an IV.
If the patient is undergoing a biopsy procedure, we may request an extra biopsy that will be taken during standard care and/or clinical trial. However, we will not obtain lung biopsies for the biobank due to the higher risk of pneumothorax. In addition, biopsies which are not part of standard clinical care can be taken, but only in case it can be obtained during an already scheduled appointment in the hospital, such as an outpatient visit or an endoscopy for another reason. The tissues need to be easily accessible and at low-risk sites, such as tumors/metastases in the skin, in the mucosal lining, abdominal wall, and superficial lymph nodes.

An additional Pap smear will be obtained during pelvic examinations undertaken in the context of standard care and/or a clinical trial. (note: no additional pelvic examination will be undertaken solely for this biobank). In both cases, the same risks apply as for regular treatment. Mild discomfort may be experienced while taking the Pap smear.

G) Will participation in the biobank mean for the donor that the standard treatment or diagnostics can be deviated from or can be postponed?

☐ yes
☑ no
☐ not applicable

Ga) If so, what does the deviation or postponement entail, and why is it justifiable?

N.A.

H) Why do you consider the risks of collection to be minimal and why do you think the burden is in proportion to the purpose of the future research for which precisely this type of tissue or blood sample must be available?

The risk for the donor associated with their participation in this biobank is negligible (see point 4.1F). The organoids generated from these tissues can be used for research purposes as described in this protocol. Research activities that go beyond the under section 2 described objectives require a release protocol.

I) Additional information relating to the collection procedure:

N.A.

4.2 Withdrawal of individual donors from the biobank

Donors can terminate their participation in the biobank at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the biobank e.g. because the donor does not meet the inclusion criteria.
Donors receive a consent retraction form and the contact details of the biobank coordinator that allows them to retract their consent. Upon receipt of the consent retraction form, the biobank coordinator informs the relevant project partners of the receipt of the form. The patient can choose among the three options that are indicated in the consent retraction form. For more information, see also paragraph 7.2F
10.3 Appendix 3 - withdrawal form processing protocol; contains a step-by-step plan that is followed when a patient withdraws from the biobank.

4.2.1 Specific criteria for withdrawal (if applicable)

There are times where patients are expected to have cancer or a pre-stage of cancer. However, sometimes they appear not to have cancer or a pre-stage thereof after diagnosis. In these cases, the biobank coordinator will take the following steps:

- Inform the researcher that the material and associated data is not eligible for use in the biobank or research and needs to be destroyed. The researcher will be asked to confirm by email that all material and data has been destroyed.
- Informe the CBB and ask them to remove all stored materials and associated data that was collected from this patient for the UPORT Cancer biobank. For this, we use the document: *P-*

CBB16-F2---Vernietiging-van-materiaal-na-onterechte-inclusie. Information about the procedure can be found on https://zenya.umcutrecht.nl/Portal/#/document/2234a702-2655-4bf4-a720-3b9b4a13c893

- HiX: Withdraw the patient from the biobank by terminating his or her participation in HiX and noting that this termination is due to the fact that the patient no longer meets the inclusion criteria.
- Castor EDC: Note that the patient has been withdrawn from the biobank and why this has happened. In Castor EDC there is a special form for this. If this form is filled in, all information about previous sample collection, including data such as pretreatment, age and gender, becomes invisible. The information about the inclusion remains accessible.
- The key between the patient number and CastorID remains, but is moved within the key table to the list of patients whose IC has been withdrawn.
- We will collect the following information in our RFS, in a special folder for patients who have been withdrawn from the biobank. We will keep this information so that the documentation is complete:
    - Confirmation email from the researchers and Pathology Department.
    - The completed document *P-CBB16-F2---Vernietiging-van-materiaal-na-onterechte-inclusie*
    - The previously signed informed consent
    - If available: The stored Sample Information Sheet (SIS) of the previously collected material and/or the CDL blood/urine application form
- In the patient information folder, there is a paragraph included under *7. Duur van de deelname* explaining what happens if a patient ultimately does not meet the inclusion criteria. This paragraph indicates that, if it turns out that the patient does not have cancer or a pre-cancerous stage, the patient's consent will be terminated, and the already collected patient material and data will be destroyed. We will not explicitly inform the patient about this afterwards. This is because we want to avoid patient confusion when informing the patient that participation has been terminated due to diagnosis. After all, we do not want to put ourselves in the role of a doctor. There is also a small section included in the consent form.

In some cases, the first sample taken from a patient may be cancerous and the second sample, taken at a different time point, may be cancer-free, for example due to treatment. In these cases, the patient is not excluded from the biobank and the tissue and data do not need to be removed from the biobank.

4.3 Processing and storage of human biological materials

4.3.1 Processing procedures for human biological materials

Patient material is collected as specified under 4.1. After collection:

- The resected tissue, biopsy, Pap smear and/or ascites will be taken to pathology. From the resected material and ascites, the pathologist will decide if there is leftover patient material that will not be used for the patient's standard care and/or clinical trial. If so, they will try to take samples from this leftover material and place those in tubes with growth medium. In the case of a resection, they will try to collect tumor and normal tissue. The biopsy material and Pap smear is usually placed directly in a tube with growth medium and then taken to pathology. The samples will be registered and labelled with a pseudonymized code that is generated by the tissue facility's LMS system. The samples are then picked up by a UPORT biobank coordinator and taken to the responsible researcher. The material is always accompanied with a Sample Information Sheet (SIS). The SIS contains information about the sample, a limited amount of information about the donor, the pseudonymized code and a CastorID.
- Blood and/or urine samples go to the Central Diagnostic Laboratory (CDL). Depending on the project, the collected blood samples are either processed by the CDL and immediately stored in het CBB, or the samples are only registered at the CDL (i.e. given a pseudonymized code that is generated by the CDL's LMS system). The UPORT biobank coordinator ensures that this last group

of samples is delivered to the appropriate researcher, so they can be further processed for their research and the biobank. The urine samples will only be registered and labelled with a pseudonymized code before being delivered to the researcher. All the samples that are processed via the CDL will be accompanied by a CDL form that contains donor information and the pseudonymized code. Because of the donor information on the form, these forms remain with the biobank coordinators. Only the pseudonymized code will be handed to the researchers. The biobank coordinators will write this code on the SIS form that accompanies the tissue; however, if there is no tissue, no SIS form is made for the samples. The samples, along with the SIS form containing sample information, a limited amount of donor information, the pseudonymized code and a CastorID, is handled to the researchers.

Researchers that further process the samples can be from either:

- Hubrecht Institute (HI)
- Prinses Maxima centrum (PMC)
- UMCU
- External parties, via a release protocol

At the lab, the patient material will be generated into organoids and/or (stem) cell cultures by the researcher and directly used for research purposes, as described in this biobank protocol. For research purposes beyond the scope of this protocol, a release protocol is needed. Eventually, vials from each generated organoid and/or (stem) cell culture will be stored at the UMC Utrecht, HI or the CBB. These vials and the associated clinical database are available for future research. A well-annotated biobank catalog will provide an organized and accessible overview of the available samples and associated information.

A) Will any cells be amplified to immortal (stem) cells and cell lines?[2] ☑ yes ☐ no

4.3.2 Procedures for encoding and storage of personal and other data and human biological materials

General procedures: The UPORT biobank coordinators register new participants in the process of inclusion and tissue collection. To this end, UPORT collects informed consent forms and SIS, and maintains the key table. Limited characteristics and follow-up data are registered using Castor EDC. The information from Castor EDC is combined with data extracted from the electronic patient dossier (EPD) to create the UPORT clinical database. Upon request, data can be issued from this database to researchers, to combine the clinical data with experimental results.

Furthermore, patient data can be linked to various medical sources, including treatment records, scientific studies, data from general practitioners and other hospitals, cohort studies like the 'Prospectief Landelijk CRC cohort' (PLCRC), and national and European databases such as the 'Nederlandse Kanker Registratie' (NKR) and the 'Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief' (PALGA). This integration enables the creation of a clinical database that is as comprehensive and unbiased as possible.

Additionally, a catalog containing pseudonymized data, such as patient demographics, oncology history, treatment history, treatment response, and pathological information, is used to provide an organized and accessible overview of the available samples and associated information. This approach facilitates research access, encourages collaboration, reduces patient burden, and lowers research costs by enabling the reuse of existing data and samples. All shared data will be fully pseudonymized to ensure privacy and data protection.

A)

[2] The donor must consent to this.

I) Will any personal or other data be encoded?

☑ yes
☐ no, because ……

If the personal or other data will be encoded, please answer the following question:

II) Does it concern:

☑ encoding whereby directly traceable data will be replaced with a random code.
☐ pseudonymisation, whereby directly traceable data will be encrypted to a pseudonym using an algorithm (possibly via engagement of a trusted third party).

III) How will this code be structured?

All patients will be assigned a CastorID, which consists of a prefix indicating the Castor project followed by a random four-digit code (i.e. Cx-xxxx). Additionally, patients will receive a separate code for the catalog, starting with a "U" followed by a random five-digit code (e.g., Uxxxxx).

IV) Who will have access to the key to this code?

The UPORT biobank coordinator and UPOD data manager.

- Name: *UPORT biobank coordinators*: Jorieke Salij, Anneta Brousali, Meyram Çil, Hülya Özturk, Naomi Remkes, Angelique Scantlebery; *UPOD data managers*: Jan-Hendrik Venhuizen and My Nguyen, and new colleagues in the role of biobank coordinator/data manager.
- Position: UPORT biobank coordinator and UPOD data manager.
- Treatment relationship with the patient: ☐ yes ☑ no
- Division/department: *UPORT biobank coordinators*: Imaging & Oncology; *UPOD data managers*: DLAB.

V) Where will the key or keys be stored?

On secure drives of UMCU. (In the L map > Data>afd. CGO_Biobank > 21.042 U-PORT). See also section 'VI) How will the key or keys be secured?'.

VI) Will there be an extra copy of the key? (for availability reasons)

Yes, all (research) data is stored on UMC Utrecht network drives from which backups are made automatically twice a day by the IT division (dIT).

VI) How will the key or keys be secured?

The UPORT team uses the secured Research Folder Structure on the secure drives of UMCU, ensuring that only authorized personnel can access the key table. Access is granted by the IT coordinator of the Imaging and Oncology division.

VII) Who will have access to the source documents and any other data that can be traced back to the person concerned?

UPORT biobank coordinators handle the management of the biobank and may need to access source documents and related data for operational purposes. UPOD data managers manage the data for UPORT and may access these documents for data management and oversight.

- Name: *UPORT biobank coordinators*: Jorieke Salij, Anneta Brousali, Meyram Çil, Hülya Özturk, Naomi Remkes, Angelique Scantlebery; *UPOD data managers*: Jan-Hendrik Venhuizen and My Nguyen, and new colleagues in the function of biobank coordinator/data manager.
- Position: UPORT biobank coordinator and UPOD data manager
- Treatment relationship with the patient: ☐ yes ☑ no
- Division/department: *UPORT biobank coordinators*: Imaging & Oncology; *UPOD data managers:* DLAB

VIII) Where will the directly traceable personal or other data be stored?

Directly traceable personal or other data is stored on the secure drives of UMC Utrecht. UPORT uses the secured Research Folder Structure on the secure drives of UMC Utrecht, that ensures that only authorized personnel have access to this data (see above).
The original, hard copy of these files will be stored in the locked UPORT office.

IX) Who will have access to the directly traceable personal or other data?

- Name: *UPORT biobank coordinators:* Jorieke Salij, Anneta Brousali, Meyram Çil, Hülya Özturk, Naomi Remkes, Angelique Scantlebery; *UPOD data managers:* Jan-Hendrik Venhuizen and My Nguyen, and new colleagues in the function of biobank coordinator/data manager.
- Position: UPORT biobank coordinator and UPOD data manager
- Treatment relationship with the patient: ☐ yes ☑ no
- Division/department: *UPORT biobank coordinators:* Imaging & Oncology; *UPOD data managers: DLAB*

X) Who will be the data owner?

☑UMC Utrecht

XI) How will the data be secured?

Directly traceable personal data: The UPORT team uses the secured Research Folder Structure on the secure drives of UMC Utrecht. This ensures that only authorized personnel has access to the key table. Access is granted by the IT coordinator of the Imaging and Oncology division. The original, hard copy of these files will be stored in the locked UPORT office.

Pseudonymized data: Data recorded in Castor EDC is pseudonymized and the access to this data is monitored by the UPOD data manager. Researchers can request additional pseudonymized medical data for specific research purposes under an approved release protocol from the TCBio. Once approved, the UPOD data manager handles these requests and provides access to the required data. The genetic and clinical data that are generated as part of the characterization of this organoid biobank can be coupled to the drug screen data of the same organoids and published without the need for a separate release protocol.

XII) For how long will the data be retained? <*Note: If the intention is to use data from HiX, these must be extracted from Hix in encoded form before the retention period of the HiX data has expired.*>

☑indefinitely
☐…… years.

B) Storage in the CBB is compulsory at UMC Utrecht. If the materials will not be stored in the CBB but externally, please answer the questions below:

The proposed biobank is a collaboration between the following parties:

1) UMCU, an academic hospital with experience in the use of organoid technology
2) Hubrecht Institute (HI), the research institute that developed organoid technology and is a leading expert in the further development of this technology.
3) Prinses Maxima Centrum (PMC), the group of Dr. Hugo Snippert, Prof. Dr. Hans Clevers, Dr. Peng, and other PIs.

The conditions for exchange of patient-derived tissues (UMCU > Hubrecht/PMC), biobanking the generated organoids and the subsequent use of these organoids under a TCBio-approved protocol are defined in a collaboration agreement signed by UMCU and Hubrecht and material transfer agreements between UMCU and PMC. See *10.2 appendix* for information about the status of the agreements. If an agreement is not finalized yet, the agreement is added as an amendment once it is complete.

I) How will the human biological materials be stored?

☑ with a code that is indirectly traceable to the subject (code list)
☐ in a form that cannot be traced back to the subject (pseudonymised)
☐ anonymously; please note that this option is not useful for a biobank.

II) How will this code be structured?

All biobank samples are provided by the tissue facility (tissue, Pap smear and ascites) or the CDL (blood and urine) with a pseudonymized code. This code is made up of a year followed by a consecutive number. The biobank coordinator ensures that the pseudonymized code is placed on the SIS form that accompanies the sample and is handled to the researcher.

III) Who will have access to the key to the code?

The biobank coordinator and data manager have access to the key to the code. Indirectly, the CBB has access when samples are stored in their biobank. Also, the tissue facility (tissue, Pap smear and ascites) and the CDL (blood and urine) have access to the key but are not involved in this part of the process.

- Name: *Uport biobank coordinators:* Jorieke Salij, Anneta Brousali, Meyram Çil, Hülya Özturk, Naomi Remkes, Angelique Scantlebery; *UPOD datamanagers*: Jan-Hendrik Venhuizen, My Nguyen and new colleagues in the function of biobank coordinator/data manager.
- Position: Biobank coordinator and data manager
- Treatment relationship with the patient: ☐ yes ☑ no
- Division/department: *Uport Biobank coordinators:* Imaging & Oncology; *UPOD datamanagers: DLAB*

IV) Where will the key or keys be stored?

On secure drives of UMC Utrecht. (In the L map > Data>afd. CGO_Biobank > 21.042 U-PORT).

V) Will there be an extra copy of the key? (for availability reasons)

All (research) data is stored on UMC Utrecht network drives from which backups are made automatically twice a day by the IT division (dIT). Also, the internal LMS system from the CBB, tissue facility and CDL (in case of collecting blood and/or urine) functions as an indirect copy.

VI) How will the key or keys be secured?

The UPORT team uses the the secured Research Folder Structure on the secure drives of UMCU. This ensures that only authorized personnel has access to the key table. Access is granted by the IT coordinator of the Imaging and Oncology division.

They tissue facility, CBB and CDL have their own system which is only accessible to their own staff.

VII) Who will have access to the materials?

UMCU, HI and PMC: see Collaboration agreement UPORT-UMCU-Hubrecht and the MTA's UMCU-PMC. Researchers who would like to use organoids for their own future research purposes, will have to present an approved release protocol in order to gain access to the organoids stored in the UPORT Cancer Biobank, via the procedure specified in section 6.

VIII) For how long will the materials be retained?

☑ indefinitely.
☐ …… years.

5 INCIDENT REPORTING

5.1 Reporting of data breaches

For incidents involving personal data, a statutory reporting duty applies (even if the personal data have been pseudonymised/encoded). For this reason, anyone who observes a data breach must report this to the Data Protection Officer immediately, using the reporting form via the ICT Portal on Connect.
A data breach is a technical or organisational security breach whereby personal data are accidentally or unlawfully destroyed, lost or modified, or are disclosed or rendered accessible without authorisation. In case of any doubts as to whether a data breach, the incident should still be reported. Incidents can be reported via the ICT Portal on Connect: Selfserviceportal (umcutrecht.nl)
As the project partner HI does not have access to the UMCU Connect working environment, they shall report data breaches to their own data protection officer and to the biobank coordinator at the UMCU, who will then forward this information, via the procedure described above, to the UMCU data protection officer.

6 USE OF BIOBANK MATERIALS FOR SPECIFIC RESEARCH QUESTIONS

The UPORT Cancer Biobank, a 'living' biobank, is generated on the basis of specific projects. In this way, it deviates from a biobank of frozen and fixed (non-living) tissues, as is specified in the Biobank regulations. The reason for this is as follows: In order to generate living biobanks, patient material must be cultured into organoids directly upon collection. This is an expensive, time-consuming process requiring a lot of expertise. While UPORT provides the patient material and data, the researchers generate the actual organoid biobanks. If a researcher's project proposal complies with the UPORT-Cancer protocol, no additional release protocol is needed. This includes biobank (organoid) generation and characterization, resulting in richly annotated, well-defined organoid collections (see also 2.

Objective). The aim of setting up this well-characterized biobank of living cells is so that future experiments will benefit from the collected data.

Before the human biological materials, the associated clinical data, and any other data from this biobank can be used for specific research questions outside the research aims described under section 2 *Objective* in this protocol, approval must first be obtained from the TCBio. For this purpose, investigators must submit a release protocol to the TCBio, making use of the most recent version of the release protocol template, which can be downloaded from the TCBio's website. They must follow the submission instructions on the TCBio's website. Among other things, the committee will review the scientific value of the research proposal and assess whether the use of the materials will be in keeping with the donor's control rights. For example, the use of the materials must be covered by the scope of the broad consent given. For the release of materials, the responsible biobank coordinator must also give his/her approval, by co-signing the release protocol.
At the end of a specific research project, human biological material that is left over will always be returned to the UPORT Cancer Biobank or will be destroyed.

7 ETHICAL CONSIDERATIONS

7.1 Applicable regulations

This biobank will be set up and managed in accordance with UMC Utrecht's biobank regulations, as adopted by the Executive Board of UMC Utrecht in June 2013.

7.2 Recruitment and consent

The responsible biobank coordinator must ensure that broad consent is obtained and that the consent form is signed. The person obtaining consent must ensure that the donor and/or his/her representative possesses the information referred to in Article 4, under h, of UMC Utrecht's biobank regulations, and has received specific verbal and written/digital information on the release, retention, use and destruction of human biological materials, including information on the burden and risks associated with the collection of human biological materials. The donor and/or his/her representative may revoke broad consent at any time after granting it. This revoking of consent only applies to future research involving the collected human biological materials and the associated data.
The responsible biobank coordinator must also ensure that a paper or digital record exists for each donor, in which any consent and revocation forms are retained.

Within the UMCU, one or multiple person(s) is/are identified to fulfill the role of biobank coordinator. These persons have no treatment relationship with the patient.
If the biobank coordinator is a physician, a potential donor could be under the impression that the level of care that he/she will receive is dependent on his/her participation. Therefore, the biobank coordinator may not be a physician.
If the biobank coordinator is a researcher aiming to work with organoids generated from the potential donor, there is the risk that the biobank coordinator might put undue pressure on the patient. Ideally, the biobank coordinator should not be a researcher aiming to work with the organoids. However, if no suitable person can be found, this situation may occur. In such events the researcher must be clearly instructed not to put any pressure on the potential donor and that in this capacity he/she is merely there to inform the patient about the option to participate. Ideally, the biobank coordinator should receive training from another biobank coordinator.

A) How will the donors be recruited, and who (investigator, treating physician, other person) will inform the donor or his/her legal representative and ask for their consent?

Step 1: Paper and Electronic consent noted in protocol

Following the step-by-step guide in the "Guidelines for Electronic Consent for Participation in Medical-Scientific Research," dated August 22, 2022, from the CCMO guidelines, we will explain how the donors are recruited, informed, and asked for paper or electronic consent.

Step 2: Adequate description of the consent procedure

Depending on the project, the biobank coordinator selects eligible patients to participate in the biobank either through the electronic patient record (HiX) or by receiving potential participants via email from the involved physician or nurse. The coordinator then ensures that the patients who meet the inclusion criteria receive the biobank information on paper during an outpatient clinic visit, by post/email, or digitally via the online platform ValidSign. This information consists of a patient information folder (PIF), an informed consent form, a consent retraction form, and in case of the paper version, a return envelope. All documents have the same version number, so that it is clear that they belong together. Digital receipt of the information is only offered when it is suitable for the patient. It is important that the patient is digitally literate and understands that electronic consent is a valid form for receiving patient consent. In addition, it also depends on the patient's preference on how to receive the biobank information. The patient will be able to read the biobank information on paper or digitally at home and

discuss it with relatives. If a patient would like to switch from the digital route to the paper route or vice versa at a later time, they can always contact UPORT. An employee will then ensure that the correct information is available to the patient.

The biobank coordinator will contact the patient to verbally provide additional information (hereinafter referred to as verbal information) about the biobank and answer any questions that may arise after reading the information. This applies to all patients, regardless of whether they received the information on paper or digitally. . It was deliberately chosen not to provide the verbal information when the patient hears about the UPORT Cancer Biobank for the first time via the nurse/physician. At that moment the patient is often in the hospital for his/her own treatment. This is a day full of physician appointments and examinations. Our experience is that patients have enough on their minds and at the end of the day they would like to go home. If we visit the patient at such a time to provide the verbal information, there is a chance that they will sign more quickly without really understanding and reading the information thoroughly. There is also a chance that they may be more prone to decline. In both scenarios, this is not always because they are not interested, but simply because they are already overwhelmed with information. In our opinion, providing information about participation in the biobank a few days later, is less stressful and gives patients the opportunity to make a well-considered decision. Unless the patient wishes otherwise, we will therefore approach the patient at a different moment.
In most of the cases verbal information is given by telephone. However, when there is limited time and the patient is already hospitalized, the coordinator will stop by at the nursing ward. This exception is only made when the patient can confirm that it is not overwhelming for them and there is sufficient time for the patient to consider their participation. The coordinator will ensure that the patient understands the intentions and procedure of the biobank. This will allow potential donors to make an informed and thoughtful decision regarding their participation. In addition, the patient will be informed of the possibility of withdrawing consent at any time without giving a reason. We have drawn up a document that describes the steps we go through when we approach a patient for a verbal explanation of the biobank. The document is attached to this protocol as an appendix (*See appendix 10.1)*.
Based on the patient's response during the conversation, we assess whether the information has been understood correctly. For example, if a patient actively asks questions or refers to information from the patient information folder, this likely indicates that they have read and understood the document. On the other hand, if a patient responds briefly or vaguely—such as only saying "yes" or "okay" without asking questions—it may suggest that they have not read the information or did not fully understand it. In such cases, we take extra time to highlight the most important points from the information letter and ask more frequently whether the patient has understood the information just discussed.
Although we make every effort to convey the information clearly and to monitor whether the patient truly understands it, we cannot entirely prevent situations where patients give consent without fully realizing what they are consenting to. Sometimes, a patient may indicate that they wish to participate but do not want to read the information or receive an explanation.
If we receive a signed consent form from a patient with whom we have had contact, and there are indications that the information may not have been fully understood despite our efforts, we will still process the consent form. Ultimately, we cannot determine whether a patient chooses to submit their consent.
If it becomes clear during contact with the patient that it is to mentally overwhelming, there is for example a language barrier after all, or there is hesitance to participate but the patient does not mention this himself or herself, we proactively discuss the option of declining participation.
If the patient decides to give consent, they can sign the consent form either on paper or digitally. This is usually done remotely. The paper version can then be returned by post, using the enclosed return envelope. When the biobank coordinator has received the signed form by mail, he/she will also sign the consent form and return a copy to the patient for his/her own administration. The original form is stored in the hospital and a digital copy is added to the secured research folder.

In this biobank, we offer patients the option to give their consent digital via the online platform ValidSign. This method is approved by the UMC Utrecht for obtaining electronic Consent (eConsent). Through ValidSign, participants can read, complete, and download the information folder, informed consent form, and retraction form. These online documents are identical to the paper versions we provide.

ValidSign is a secure and approved way of obtaining consent, with no additional risks compared to paper-based consent. To verify patient identity, two-factor authentication is used, requiring both an email address and an SMS code. Once the participant has signed the consent form, the signature becomes part of the document, ensuring it cannot be altered. When the eConsent has been signed by both the patient and the biobank coordinator, the coordinator can download a summary with the time and date of signing the eConsent and the IP address.

The biobank coordinators receive a notification when the patient has signed, which includes an email with the patient's signed consent form in ValidSign. The coordinator verifies the form and signs it as well. The form is then archived in the research folder structure, where it can only be accessed by the biobank coordinators and data managers from UPORT. The patient automatically receives a copy of this completed eConsent form via email, which can be downloaded or printed for their own records. This email also includes the Patient Information Form (PIF) and a retraction form in PDF format. If the patient wishes to withdraw their consent in the future, they can complete this retraction form via mail. If they would like to withdraw their consent digitally, they can contact UPORT for a digital version of the retraction form via ValidSign. For the logistics of signing the retraction form, see the logistics described above, about singing the consent form.

Important to know: Giving digital consent via ValidSign is an option. The patient can always indicate that they still want to receive the information on paper and give consent this way. It is also always possible to change from the paper route to the digital route if the patient wishes so.

In ValidSign, only the biobank coordinators and data managers of UPORT have access and can see the associated personal data of the patient. When the data and well-being of the patient is checked by an external party (for example a monitor or inspection), they will also have access to the data in ValidSign. This is based on legal regulations. The IT provider does not have access to this data, except for what is strictly necessary for the execution of their work as stated in the contract with the UMC Utrecht.

Step 3: suitable for the research

For this biobank, the option to give consent remotely by signing the digital consent form, is appropriate because the risks for patients participating in this biobank are negligible and it makes the consent process more successful and less time-consuming than via mail. Our experience is that mail is not always delivered on time. As a result, patients receive the patient information much later, which means they have limited time to read it and therefore sometimes refrain from participating. In addition, the signed informed consent sometimes arrives to late at the UPORT office, despite the patient having sent it in time. If we receive the inform consent form after for example the operation date, this means we are not allowed to collect material. We also see that patients often have a lot on their minds when we approach them for the biobank. The patients are willing to contribute but forget to post the consent form or forget to take it with them to the hospital. This results in the unnecessary inability to include willing patients and/or collect material for the biobank. By using eConsent, it will be easier to reach these patients, and it will save time compared to obtaining the consent form via mail. It also will accelerate the logistical process of including the patient when there is limited time between first contact with the patient and their treatment at the hospital. At last, there are also patients who indicate that they prefer to receive all information digitally. Therefore, there is also a need to have the option to give digital informed consent.

Because the storage of material in the UPORT Cancer Biobank is for an indefinite period, the signed consent forms must also be stored for an indefinite period. The use of eConsent ensures that this storage can take place digitally. The minimizes the change of information being lost, as there is always a backup (see section 4.3.2 A VIII). In addition, if necessary, digitally searching through the large amount of consent forms is also much easier than searching through physical folders and digital storage also takes up less space than physical storage.

Step 4: Reliability, confidentiality sufficiently ensured

All information about ValidSign for the provision of information and the granting of consent, and explanation of its use, complies with the applicable laws and regulations, such as the WMO, AVG, UAVG and other laws and regulations. There are no risks associated with the use of ValidSign and it has been approved by the UMC Utrecht as a safe method for obtaining consent. For more information, refer to:

- https://zenya.umcutrecht.nl/Portal/#/QC/FQ-46-45, see normering en veiligheid
- https://www.validsign.eu/nl/privacy/
- https://www.validsign.eu/nl/wetgeving-elektronische-handtekening/

How the identity of the patients participating in the UPORT Cancer Biobank is guaranteed can be found in step 2 above.

Step 5: Other requirements

When a patient chooses the digital route, he/she will receive the information about the UPORT Cancer Biobank digitally. However, there is always the possibility to switch to the paper route or vice versa. See also step 2.

For both, the paper and the digital route, the biobank coordinator contact the patient to provide verbal information and answer any questions. This enables potential donors to make a well-considered and well-thought-out decision about their participation. See also step 2.

B) Are any donors dependent in any way on the investigator or the party recruiting the participants?

☐ yes
☑ no

B.b) Why will human biological materials be collected from these particular donors, and how will the donors' interests be protected?

Advances in clinical science require tissue samples of patients with malignant disease, or precursor lesions thereof. The risk associated with biobank participation is negligible as material will only be collected during planned procedures in the context of standard care and/or clinical trial. Furthermore, patient data will only be provided in a pseudonymized manner to ensure researchers will not be able to ascertain the identity of the patients.
The decision not to participate or to retract initial consent does not have any negative influence on current or future treatment. It will not have any negative consequences for the care and attention the patient receives at the UMCU.

C) How much time to reflect will the donors or their legal representatives have when deciding on participation?

One day, when procedures are planned on short notice, otherwise, at least two days.

D) Can the donors be approached again during their participation in the biobank (for instance for further testing or follow-up)?

☑ yes
☐ no

E) Will the donors be asked to consent to this during the consent process for this biobank?

☐ yes
☑ no

F) Can donors revoke their consent for participation, and how will this be recorded?

Donors will receive a consent retraction form, along with the patient information folder and informed consent form. The consent retraction form can be sent to the address of the UPORT Biobank in the UMCU. If permission is withdrawn, this means that no new material will be collected for the UPORT Cancer Biobank. In addition, the (former) donor can choose one of the following options:

1. The material already collected for the UPORT Cancer Biobank will remain available for scientific research as specified in the consent form. In addition, new medical data can be collected to link to material that has already been collected.
2. The material already collected for the UPORT Cancer Biobank will remain available for scientific research as specified in the consent form. No new medical data or material is collected.
3. All material collected from the patient for the UPORT Cancer Biobank will be destroyed, except for material that has already been approved for use in a specific scientific study. If measurements have already been taken with that material, those data will also still be used.

7.3 Findings

If the donor and/or his/her representative grants broad consent, the donor will be told that he/she will be informed of any findings that may result from the actual use of the human biological materials and that may be important to the donor. If the donor and/or his/her legal representative does not wish to be informed, the human biological materials cannot be included in the biobank.

Findings based on the biobank materials that provide information about serious conditions that may be clinically relevant to the donor and/or his/her relatives will be reported to the TCBio. The committee will assess all relevant information and will decide, together with the medical head of the department who is responsible for the sub-biobank, whether or not the donor will be informed. Feedback to the donor will be given via the treating physician. If a patient does not wish to be informed about such findings, it is not possible for the patient to participate

7.4 Resistance by incapacitated adults (if applicable)

N.A.

7.5 Compensation (if applicable)

N.A.

8 ADMINISTRATIVE ASPECTS AND PUBLICATION

8.1 Amendments

Amendments are changes to the management of the biobank after the TCBio has issued a positive opinion before the start of the biobank. All amendments must be submitted to the TCBio for review.

Non-substantial amendments will not be submitted to the TCBio for review but will be recorded and included in the biobank file by the responsible biobank coordinator.

8.2 Disclosure and publication of results

Investigators will make results of research for which materials from this biobank have been used available in the public domain. Investigators are responsible for the completeness and accuracy of the publications. Investigators must adhere to the accepted guidelines for ethically sound result reporting.

Publications on research for which materials from this biobank have been used will be sent to the TCBio within 1 year after the end of the study in which the material has been used.

9 REFERENCES

1. Sato, T., Vries, R., Snippert, H., van de Wetering, M., Barker, N., Stange, D., van Es, J., Abo, A., Kujala, P., Peters, P., and Clevers, H. Single lgr5 gut stem cells build crypt-villus structures in vitro without a stromal niche. **Nature** 459 :262-265 (2009)
2. Sato, T., Clevers, H.. Growing self-organizing mini-guts from a single intestinal stem cell: mechanism and applications. Review **Science** 340: 1190-1194 (2013)
3. Barker, N., Huch, M., Kujala, P., van de Wetering, M., Snippert, H.J., van Es, J.H., Sato, T., Stange, D.E., Begthel, H., van den Born, M., Danenberg, E., van den Brink, S., Korving, J., Abo, A., Peters, P.J., Wright, N., Poulsom, R., Clevers, H. Lgr5(+ve) stem cells drive self-renewal in the stomach and build long-lived gastric units *in vitro*. **Cell Stem Cell** 6: 25-36 (2010)
4. Huch, M., Dorrell, C., Boj, S.F., van Es, J.H., van de Wetering, M., Li, V.S.W., Hamer, K., Sasaki, N., Finegold, M.J., Haft, A., Grompe, M., Clevers, H. In vitro expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration. **Nature** 494: 247-250 (2013)
5. Karthaus, W.R., Iaquinta, P.J., Drost, J., Gracanin, A., van Boxtel, R., Wongvipat, J., Dowling, C.M., Gao, D., Begthel, H., Sachs, N., Vries, R.G., Cuppen, E., Chen, Y., Sawyers, C.L., Clevers, H.C. Identification of Multipotent Luminal Progenitor Cells in Human Prostate Organoid Cultures. **Cell.** 159:163-175 (2014)
6. Huch, M., Gehart, H., van Boxtel, R., Hamer, K., Blokzijl, F., Verstegen, M., Ellis, E., van Wenum, M., Fuchs, S., de Ligt, J., van de Wetering, M., Sasaki, N., Boers, S., Kemperman, H., de Jonge, J. IJzermans, J., Niewenhuis, E., Hoekstra, R., Strom, S., Vries, R., van der Laan, L., Cuppen, E., Clevers, H. Long-term culture of genome-stable bipotent stem cells from adult human liver. **Cell** 160: 299-312 (2015)
7. Hu H, Gehart H, Artegiani B, LÖpez-Iglesias C, Dekkers F, Basak O, van Es J, Chuva de Sousa Lopes SM, Begthel H, Korving J, van den Born M, Zou C, Quirk C, Chiriboga L, Rice CM, Ma S, Rios A, Peters PJ, de Jong YP, Clevers H. Long-Term Expansion of Functional Mouse and Human Hepatocytes as 3D Organoids. **Cell.** 175(6):1591-1606 (2018)
8. van de Wetering, M., Francies, H.E., Francis, J.M., Bounova, G., Iorio, F., Pronk, A., van Houdt, W., van Gorp, J., Taylor-Weiner, A., Kester, L., McLaren-Douglas, A., Blokker, J., Jaksani, S., Bartfeld, S., Volckman, R., van Sluis, P., Li, V.S.W., Seepo, S., Sekhar Pedamallu, C., Cibulskis, C., Carter, S.L., McKenna, A., Lawrence, M.S., Lichtenstein, L., Stewart, C., Koster, J., Versteeg, R., van Oudenaarden, A., Saez-Rodriguez, J., Vries, R.G.J., Getz, G., Wessels, L., Stratton, M.R., McDermott, U., Meyerson, M., Garnett, M.J., Clevers, H. Prospective derivation of a 'Living Organoid Biobank' of colorectal cancer patients. **Cell** 161: 933-945 (2015)
9. Sachs N., de Ligt J., Kopper O., Gogola E., Bounova G., Weeber F., Balgobind AV., Wind K., Gracanin A.,Begthel H., Korving J., van Boxtel R., Duarte AA., Lelieveld D., van Hoeck A., Ernst RF., Blokzijl F., Nijman IJ., Hoogstraat M., van de Ven M., Egan DA., Zinzalla V., Moll J., Boj SF., Voest EE., Wessels L., van Diest PJ., Rottenberg S., Vries RGJ., Cuppen E., Clevers H. A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity. **Cell** 172(1-2):373-386.(2018)
10. Kopper O, de Witte CJ, Lõhmussaar K, Valle-Inclan JE, Hami N, Kester L, Balgobind AV, Korving J, Proost N, Begthel H, van Wijk LM, Revilla SA, Theeuwsen R, van de Ven M, van Roosmalen MJ, Ponsioen B, Ho VWH, Neel BG, Bosse T, Gaarenstroom KN, Vrieling H, Vreeswijk MPG, van Diest PJ, Witteveen PO, Jonges T, Bos JL, van Oudenaarden A, Zweemer RP, Snippert HJG, Kloosterman WP, Clevers H. An organoid platform for ovarian cancer captures intra- and interpatient heterogeneity. **Nat Med.** 25(5):838-849 (2019)
11. Organoid models of gastrointestinal cancers in basic and translational research. Lau HCH, Kranenburg O, Xiao H, Yu J.Lau HCH, et al. Among authors: kranenburg o. **Nat Rev Gastroenterol Hepatol**. 2020 Apr;17(4):203-222.
12. Mouse and human urothelial cancer organoids: A tool for bladder cancer research. Mullenders J, de Jongh E, Brousali A, Roosen M, Blom JPA, Begthel H, Korving J, Jonges T, Kranenburg O, Meijer R, Clevers HC.Mullenders J, et al.. Proc Natl Acad Sci U S A. 2019 Mar 5;116(10):4567-4574

13. Driehuis E, van Hoeck A, Moore K, Kolders S, Francies HE, Gulersonmez MC, Stigter ECA, Burgering B, Geurts V, Gracanin A, Bounova G, Morsink FH, Vries R, Boj S, van Es J, Offerhaus GJA, Kranenburg O, Garnett MJ, Wessels L, Cuppen E, Brosens LAA, Clevers H.Driehuis E, o. Proc Natl Acad Sci U S A. 2019 Dec 9;116(52):26580-90.
14. Schwank, G., Koo, B.K., Sasselli, V., Dekkers, J.F., Heo, I., Demircan, T., Sasaki, N., Boymans, S., Cuppen, E., van der Ent, C.K., Nieuwenhuis, E.E., Beekman, J.M., Clevers, H. Functional Repair of CFTR by CRISPR/Cas9 in Intestinal Stem Cell Organoids of Cystic Fibrosis Patients. **Cell Stem Cell** 13: 653-658 (2013)
15. Drost, J., van Jaarsveld, R.H., Ponsioen, B., Zimberlin, C., van Boxtel, R., Buijs, A.,Sachs, N., Overmeer, R.M., Offerhaus, G.J., Begthel, H. Korving, J., van de Wetering, M., Schwank, G. Logtenberg, M., Cuppen, E., Snippert, H.J., Medema, J.P., Kops, G. J. P. L., Clevers, H. Sequential cancer mutations in cultured human intestinal stem cells. **Nature** 521: 43-47 (2015)
16. Clevers, H. Modeling development and disease with organoids **Cell** 165:1586-1597 (2016)
17. Drost, J., van Boxtel, R., Blokzijl, F., Mizutani, T., Sasaki, N., Sasselli, V., de Ligt, J., Behjati, S., Grolleman, J.E., van Wezel, T., Nik-Zainal, S., Kuiper, R.P., Cuppen, E., and Clevers, H. Use of CRISPR-modified human stem cell organoids to study the origin of mutational signatures in cancer. **Science** 10.1126/science.aao3130 (2017)
18. Roerink S., Sasaki N., Lee-Six H., Young M., Alexandrov L., Behjati S., Mitchell T., Grossmann S., Lightfoot H., Egan D., Pronk A., Smakman N., van Gorp J., Anderson E., Gamble S., Alder C., van de Wetering M., Campbell P., Stratton M. & Clevers H. Intra-tumour diversification in colorectal cancer at the single-cell level. **Nature** 556(7702):457-462 (2018)
19. Tuveson D, Clevers H Cancer modeling meets human organoid technology. **Science.** 364(6444):952-955 (2019)
20. Heo I, Dutta D, Schaefer DA, Iakobachvili N, Artegiani B, Sachs N, Boonekamp KE, Bowden G, Hendrickx APA, Willems RJL, Peters PJ, Riggs MW, O'Connor R, Clevers H. Modelling Cryptosporidium infection in human small intestinal and lung organoids. **Nat Microbiol.** (7):814-823 (2018)
21. Survival of patients with deficient mismatch repair metastatic colorectal cancer in the pre-immunotherapy era. Wensink GE, Elferink MAG, May AM, Mol L, Hamers PAH, Bakker SD, Creemers GJ, de Groot JWB, de Klerk GJ, Haberkorn BCM, Haringhuizen AW, Hoekstra R, Hunting JCB, Kerver ED, Mathijssen-van Stein D, Polée MB, Pruijt JFM, Quarles van Ufford-Mannesse P, Radema S, Rietbroek RC, Simkens LHJ, Tanis BC, Ten Bokkel Huinink D, Tjin-A-Ton MLR, Tromp-van Driel CS, Troost MM, van de Wouw AJ, van den Berkmortel FWPJ, van der Pas AJM, van der Velden AMT, van Dijk MA, van Dodewaard-de Jong JM, van Druten EB, van Voorthuizen T, Jan Veldhuis G, Verheul HMW, Vestjens HJHMJ, Vincent J, Kranenburg OW, Punt CJA, Vink GR, Roodhart JML, Koopman M.Wensink GE, et al. **Br J Cancer**. 2021 Jan;124(2):399-406.
22. Ongoing chromosomal instability and karyotype evolution in human colorectal cancer organoids. Bolhaqueiro ACF, Ponsioen B, Bakker B, Klaasen SJ, Kucukkose E, van Jaarsveld RH, Vivié J, Verlaan-Klink I, Hami N, Spierings DCJ, Sasaki N, Dutta D, Boj SF, Vries RGJ, Lansdorp PM, van de Wetering M, van Oudenaarden A, Clevers H, Kranenburg O, Foijer F, Snippert HJG, Kops GJPL.Bolhaqueiro ACF, et al. Among authors: kranenburg o. **Nat Genet.** 2019 May;51(5):824-834.
24. Differential anti-tumour effects of MTH1 inhibitors in patient-derived 3D colorectal cancer cultures. van der Waals LM, Laoukili J, Jongen JMJ, Raats DA, Borel Rinkes IHM, Kranenburg O.van der Waals LM, et al. **Sci Rep.** 2019 Jan 28;9(1):819.

10 APPENDIX

10.1 Appendix 1 - Protocol contact patiënt

Opening gesprek

1. Uitleg wie je bent en waarom je belt
2. Controleer of je de juiste persoon aan de telefoon hebt.
3. Vraag of je gelegen belt
   - Nee→ Vraag of er een ander moment is dat je kan terugbellen.
4. Vraag of ze de informatie al hebben gelezen
   - Helemaal geen interesse in deelname → Bedankt voor de tijd en rond het gesprek af.
   - Wel interesse in deelname maar geen interesse in de uitleg: Benoem dan duidelijk dat als er toch nog vragen zijn de patiënt altijd contact met ons kan opnemen.
   - Wel interesse maar de informatie nog niet gelezen→ Bespreek twee opties:
     - De patiënt leest de informatie eerst graag zelf. Plan samen met de patiënt een moment dat je terugbelt voor uitleg, vragen en het bespreken van eventuele deelname. Bedank de patiënt en rond het gesprek af.
     - De patiënt wil liever al uitleg ontvangen over de biobank. In dit geval kan je bespreken dat je de uitleg nu geeft en op een later moment ook nog terugbelt om aanvullende vragen en eventuele deelname te bespreken. → Ga door naar 4
   - Interesse en informatie gelezen → Vraag of er nog vragen zijn over de tekst. Beantwoord deze indien mogelijk. *Als je het antwoord niet weet, geef aan dat je het zult uitzoeken en de patiënt daarover terugbelt.* → Ga door naar 4.
5. Vraag of het goed is om de belangrijkste punten nog kort door te nemen:
   - Nee → Vraag of je op een ander moment kan terugbellen→ rond het gesprek af.
   - Ja→ Ga naar 6.
6. Geef aan dat het niet mogelijk is om alle details uit de informatie te bespreken, maar dat de belangrijkste punten nu worden benoemd:
   - **Wat is een biobank?**
   - **Wat zijn organoïden?** Leg uit dat de cellen van de patiënt voor altijd bewaard worden, dat deze cellen in principe eeuwig kunnen blijven functioneren en dat ze ook na overlijden gebruikt kunnen worden voor onderzoek.
   - **Welk onderzoek** kan er gedaan worden met het materiaal uit de biobank?
   - Het **type materiaal** dat bij de patiënt verzameld kan worden. Belangrijk te benoemen:
     - De biobank wordt gebruikt voor onderzoek naar meerdere kankersoorten.
     - Niet alle onderdelen van de toestemmingsverklaring zijn op dit moment per se van toepassing op de situatie van de patiënt.
     - Deze onderdelen kunnen in de toekomst wél van toepassing worden als de situatie verandert.
     - Door te tekenen, geeft de patiënt toestemming voor alle genoemde punten. M.U.V. de Ja/Nee-vragen
     - Leg de nadruk op de materialen die voor de patiënt zijn situatie van toepassing zijn. (Operatie, bioptafname, urine, bloed, uitstrijkje, ascites).
   - **Toestemming geven:** Leg uit hoe een patiënt toestemming kan geven om deel te nemen aan de biobank.

- **Vrijwillige deelname:** Benadruk dat deelname vrijwillig is. Wie niet wil meedoen, hoeft niets te doen.
- **Duur van deelname:** De deelname blijft geldig totdat de patiënt het intrekkingsformulier opstuurt. Dit houdt in dat:
    - Toekomstige materiaalverzameling: Zolang iemand deelneemt, mag bij toekomstige ziekenhuisbezoeken opnieuw materiaal worden verzameld (bijvoorbeeld bij een nieuwe operatie of biopt). Dus onderdelen die nu niet van toepassing zijn, kunnen dat in de toekomst wél worden bij veranderende medische situaties. Voornamelijk bij patiënten die nu voor operatie gaan is het nuttig om te noemen dat we, wanneer hij/zij in de toekomst voor een bioptafname gaat, we een extra biopt mogen afnemen.
    - Bijzondere situatie: Als een patiënt eerder toestemming gaf vanwege darmkanker en later blaaskanker krijgt, wordt altijd eerst contact opgenomen voordat nieuw materiaal voor dat andere type kanker wordt verzameld.
- **Toestemming intrekken:** Uitleg over hoe een patiënt zich kan uitschrijven via het intrekkingsformulier, dat thuis bewaard kan worden tot gebruik.
- **Codering van materiaal:** Bespreek dat al het verzamelde materiaal gecodeerd wordt om de privacy te beschermen.
- **Terugkoppeling bij belangrijke bevindingen:** Als er tijdens onderzoek iets belangrijks wordt gevonden dat specifiek relevant is voor de patiënt, wordt dit gemeld.
- **Internationale samenwerking:** Licht toe dat er mogelijk samengewerkt wordt met buitenlandse bedrijven. Benoem de gevolgen voor de privacy bij samenwerkingen met bedrijven buiten de EU.
- **Ja/Nee-vragen:** Bespreek de twee specifieke Ja/Nee-keuzes op het toestemmingsformulier, waarbij patiënten zelf mogen beslissen.

7. Bespreek of er na deze informatie nog **vragen** zijn.
8. **Herhaal hoe de patiënt toestemming kan geven** voor de UPORT Cancer Biobank en dat het belangrijk is dat we de toestemming binnen hebben voordat de behandeling plaats vindt.
9. **Opvolging bij ontbrekende toestemming:** Vraag of het goed is dat we de patiënt kort voor de behandeling bellen als de toestemming nog niet is ontvangen, om te verduidelijken of de patiënt alsnog afziet van deelname, of dat de toestemming onderweg is, of per ongeluk vergeten is in te sturen.
10. **Kopie van toestemming:** Geef aan dat de patiënt een kopie van de toestemming ontvangt zodra deze door beide partijen (de patiënt en de biobank) is ondertekend.
11. **Vragen of onduidelijkheden:** Vraag opnieuw of alles duidelijk is en vermeld dat de patiënt altijd contact met ons kan opnemen via e-mail of telefoon als er later nog vragen zijn.
12. Bedankt de patiënt voor zijn/haar tijd.

10.2 Appendix 2 - Overview agreements

UMC Utrecht - Hubrecht Institute:

- Type of agreement: Collaboration agreement
- Name document: 20231106-CONO001767-CRA_UPORT TCbio_UMCU-Hubrecht_FINAL_FE
- Status: Active

UMC Utrecht – Princes Maxima Center/Peng

- Type of agreement: Material Transfer Agreement
- Name document:
    - MTA: K3. Maxima - MTA - organoids uport - fully signed
    - Amendment to MTA: K3. 20250926 - Maxima - amendment 1 to MTA - organoids uport Peng - UMCU - CONO008445 FE
- Status: Active

UMC Utrecht - Princes Maxima Center/Snippert

- Type of agreement: Material Transfer Agreement
- Name documents:
    - MTA: 20250324 - CONO003937 - Maxima - MTA - organoids uport Snippert - PMC_partly signed UMCU
    - Amendment to MTA: 20250704 - CONO007732 - Maxima - amendment 1 to MTA - organoids uport Snippert - FE
- Status: Active

UMC Utrecht – Princes Maxima Center/van de Wetering (Seok)

- Type of agreement: Material Transfer Agreement
- Name document: K3. MTA PMC(Seok) and UMCU (organoids UPORT) - 20250814 FE
- Status: Active

UMC Utrecht – Meander Medical Center:

- Type of agreement: Biobank Site Agreement
- Name document:
    - MTA: 20250430 - Meander - Biobank Site MTA - UPORT_clean final version_signedUMCU
    - Approval TWO Meander: TWO 24-028 Goedkeuringsbrief niet-WMO Meander MC
- Status: Active

*In progress: The agreement has not yet been finalized. As soon as it is completed, it will be submitted as an amendment to this protocol.

**Active: The agreement is finalized, signed en approved by all parties involved.

10.3 Appendix 3 - withdrawal form processing protocol

Options on the withdrawn form:

1. Mijn lichaamsmateriaal en medische gegevens, die al verzameld zijn in de UPORT Cancer Biobank, blijven wel beschikbaar voor wetenschappelijk onderzoek zoals vastgelegd in het toestemmingsformulier. Alle informatie blijft ook zichtbaar in de biobankcatalogus. Daarnaast mogen er wel nieuwe medische gegevens van mij verzameld worden om te koppelen aan het lichaamsmateriaal en de medische gegevens die al eerder van mij verzameld zijn. Er wordt geen nieuw lichaamsmateriaal van mij verzameld.
2. Mijn lichaamsmateriaal en medische gegevens die al verzameld zijn in de UPORT Cancer Biobank blijven wel beschikbaar voor wetenschappelijk onderzoek zoals vastgelegd in het toestemmingsformulier. Alle informatie blijft ook zichtbaar in de biobankcatalogus. Er wordt van mij geen nieuw lichaamsmateriaal of medische gegevens verzameld.
3. Mijn lichaamsmateriaal en medische gegevens die in de UPORT Cancer Biobank aanwezig zijn worden vernietigd. Er wordt van mij geen nieuw lichaamsmateriaal en medische gegevens meer verzameld. Alle informatie wordt verwijderd uit de biobankcatalogus.

Protocol for processing a withdrawal form:

- Inform the researcher that the patient has withdrawn his/her consent and which of the 3 withdrawal options the patient has chosen. The researcher will be asked to confirm by email that they received the email and when applicable, to confirm that all material and data has been destroyed.
- Informe the CBB and ask to remove all stored materials and associated data that was collected of this patient for the UPORT Cancer biobank. For this we use the document: *P-CBB16-F2---Vernietiging-van-materiaal-na-onterechte-inclusie.* Information about the procedure can be found on https://zenya.umcutrecht.nl/Portal/#/document/2234a702-2655-4bf4-a720-3b9b4a13c893
    - In case the patient choses option 1 or 2 from the withdrawal form, this step does not need to be done.
- HiX: Withdrawal the patient from the biobank by terminating their participation in HiX and noting that this termination is because the patient no longer meets the inclusion criteria.
- Castor EDC: Note that the patient has been withdrawn from the biobank and why this has happened. In Castor EDC there is a special form for this. If this form is filled in, and option 1 or 2 from the withdrawal from are chosen, all information about previous sample collection, including data such as pretreatment, age and gender, stays visible. When option 3 is chosen, it becomes invisible. The information about the inclusion always remains accessible.
- The key between the patient number and CastorID remains but is moved within the key table to the list of patients whose IC has been withdrawn.
- We will collect the following information in our RFS, in a special folder with contains a subfolder for every patient who has withdrawn from the biobank. We will keep this information so that the documentation is complete:
    - Confirmation email from the researchers and Pathology Department.
    - The completed document *P-CBB16-F2---Vernietiging-van-materiaal-na-onterechte-inclusie*
        - Only in case the material needs to be destroyed.
    - The previously signed informed consent
    - If available: The stored Sample Information Sheet (SIS) of the previously collected material and/or the CDL blood/urine application form
- In the patient information folder, there is a paragraph included under *7. Duur van de deelname* explaining what happens if a patient ultimately does not meet the inclusion criteria. This paragraph

indicates that, if it turns out that the patient does not have cancer or a pre-cancerous stage, the patient's consent will be terminated, and already collected patient material and data will be destroyed. We will not explicitly inform the patient about this afterwards. This because we want to avoid patient confusion when informing the patient that participation has been terminated due to diagnosis. After all, we do not want to put ourselves in the role of a doctor. There is also a small section included in the consent form.