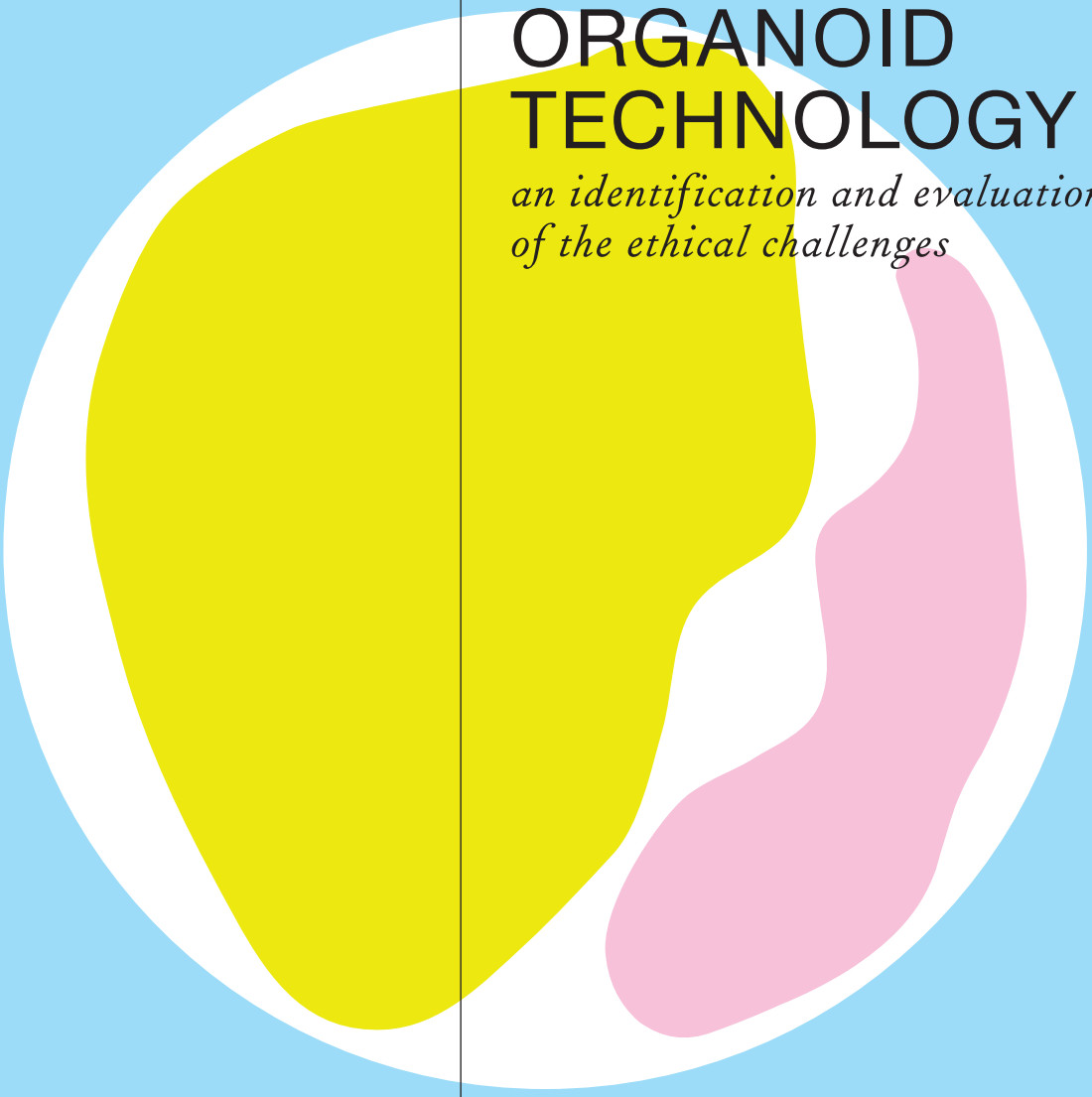
ORGANOID TECHNOLOGY

an identification and evaluation of the ethical challenges



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ORGANOID TECHNOLOGY: AN IDENTIFICATION AND EVALUATION OF THE ETHICAL CHALLENGES

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ORGANOID TECHNOLOGY:
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OF THE ETHICAL CHALLENGES

Organoid technologie:
een identificatie en evaluatie
van de ethische uitdagingen

(met een samenvatting in het Nederlands en in het Engels)

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CHAPTER 1

General introduction

CHAPTER 1

GENERAL INTRODUCTION

'Imagine… Imagine a living chunk of human cells in a petri dish, growing in a laboratory… This may seem far-fetched fiction, but in fact we are facing reality. Organoids can now be cultured out of pieces of human tissue. They are a tiny copy of the real-life human organ.'

(Quote from 'A Sculpture Like You and Me', Boers and Sijben 2017)[1]

INTRODUCING ORGANOID TECHNOLOGY

Recent advances in stem cell technology make it possible to culture three-dimensional human tissue structures in a dish that closely resemble the architecture and function of real-life organs.[2–4] These organoids, or mini-organs as they are called in popular language, are perceived as one of the most significant recent advancements in the stem cell field. Organoid technology elicits a hype in both academic and popular media.[2,5–7] Illustrative of this hype is the 2015 Nature headline 'The boom in mini stomachs, brains, breasts, kidneys and more'.[5] Organoid technology is regarded to be transformative, because it constitutes a revolutionary method to mimic human tissues in a dish and organoids thus form valuable tools for research and clinical care.[4,8–10] The technology promises to impact the entire biomedical innovation cycle with applications ranging from developmental studies to regenerative medicine, including fields that are subject to ongoing fierce ethical debate.[3] Organoid technology may give a new twist to these ethical debates and morally responsible innovation requires pro-active scrutiny of the ethical challenges. Therefore, this thesis identifies and evaluates the ethical challenges related to organoid technology.

Organoid technology: a revolutionary method to mimic human tissues in a dish

Organoid technology constitutes a revolutionary method to culture and mimic human tissues in vitro.[2,10] Earlier developments already made it possible to keep two-dimensional cell lines in long-term culture. Organoids, however, constitute a more faithful model of the development and (dys) function of human organs in the laboratory, because they self-organize into three-dimensional structures. The term organoid literally means 'resembling an organ'.[4,10]

An organoid can be defined as: '*an in vitro 3D cellular cluster derived exclusively from primary tissue, Embryonic Stem Cells (ESCs) or induced Pluripotent Stem Cells (iPSCs), capable of self-renewal and self-organization, and exhibiting similar organ functionality as the tissue of origin.*'[10]

Although the self-organizing capacities of human stem cells were known for a few decades in developmental biology, Toshi Sato and Hans Clevers only published the first paper on what we now define as organoids in 2009.[11] Their achievement of growing intestinal organoids from Lgr5+ mice stem cells signified a major breakthrough for the stem cell field. In 2011 the first publication on the cultivation of human organoids from intestine, oesophagus, and colon followed: the field of human organoid technology was born.[12] Since these first publications the field has tremendously advanced. The method developed by Sato and Clevers has been extended to other types of organs and parallel efforts have resulted in the ability to derive organoids from human pluripotent stem cells.[4,10]

The fact that organoids are capable of self-renewal implies that they can expand and be maintained in culture for long periods of time while they remain genetically stable.[13,14] This means that limited sources of human biomaterials, including tissues that are difficult to retrieve such as the human brain, can be expanded into virtually endless supplies of organoids. The ability to cryopreserve and store organoids in so-called living biobanks further facilitates long-term storage and distribution to multiple academic and industrial parties worldwide.[10,14–16]

Organoid technology promises to impact the entire biomedical innovation cycle

Organoids promise to impact the entire biomedical innovation cycle, because of their close representation of human tissues.[2,3,17] They can be used to study human development and disease and simultaneously they offer novel approaches to drug development, precision, and regenerative medicine (RM).[8,9] Gastruloids, for instance, enable the studying of early stages of human embryonic development in a dish.[2,10,18] Disease-specific organoids make it possible to model human hereditary and infectious diseases as well as cancer.[2,9,17] Brain organoids have, for instance, provided the first direct human evidence for a causal connection between the Zika virus and microcephaly.[19,20] Additionally, organoids offer alternative approaches to drug development. They can be used to identify promising novel therapeutics, to test drug-related toxicity (in liver, gut, or kidney organoids), and to stratify treatment strategies.[4,9,21] The use of organoids for drug development increases efficiency. Organoids can be plated in high-throughput platforms on which numerous novel drug candidates or combinations of existing drugs can be tested in short periods of time.

Patient-specific organoids can even be applied to develop personalized treatment approaches.[9,21,22] In the field of Cystic Fibrosis (CF), which is a severe hereditary disease, intestinal patient-specific organoids have already been used to adequately predict individual responses to drug treatment.[22–24] Furthermore, organoid technology may constitute a new generation of allogeneic and autologous cell-based therapies in the realm of RM.[17,25] Although organoid transplantation is currently in preclinical development a move towards the clinic is anticipated.[2,17,25] One area that would greatly benefit from these advances is the field of liver disease, where liver organoid transplantation would provide a less invasive and readily available 'off-the-shelf' alternative for liver transplantation.[13,26,27] The design and launch of first-in-human trials will constitute an important step towards clinical implementation.

Given the significant scientific and clinical promises, the hype and hope vested in organoid technology by professionals, patients, and the wider public is understandable.[2] However, hype and hope have to be tempered by realistic expectations. Although organoid technology offers a beautiful model for human organs, there are still various hurdles that need to be overcome to improve their scientific and clinical qualities.[2,10] For example, more standardization of organoid cultures is necessary for reliable drug development, precision medicine and regenerative medicine applications.[10] Furthermore, current culture media (Matrigel) are derived from mouse tumours which makes them unsuitable for human application.[25]

WHY IS ORGANOID TECHNOLOGY ETHICALLY CHALLENGING?

Organoid technology thus constitutes a revolutionary way of culturing human tissues in a dish that opens unprecedented avenues for science and health care. The organoid revolution, however, goes hand in hand with ethical challenges that urge pro-active scrutiny as the field advances.[3,28]

First, in organoid technology different biotechnological developments converge, among which fields that are subject to ongoing ethical debate. Examples include the creation of human pluripotent stem cell lines, genomics, chimera research, as well as biobanking and big data analytics. Together with these biotechnological developments the related ethical questions regarding, for example, the moral status of human tissues, biobank consent, and conditions for biobank governance, converge in organoid technology.[3,28–30] In examining how organoid technology affects

these debates, it should be scrutinized whether organoids have unique or special characteristics from a moral point of view. At least in popular media they have been framed as more 'tangible' and closer to real-life organs and tissues than other types of human tissues or tissue products.[5] Additionally, organoids can grow and expand limitlessly– some subtypes can even be immortalized– and organoids can model sensitive organs such as the human brain.[10,31] This raises questions of the ontological and moral status of organoids and the ways in which donors relate to organoids derived from their tissue.

Second, organoid technology is situated in an increasingly *commercialized* and *globalized* biotechnological field.[32–35] Financial resources coming from private parties are deemed necessary to sustain academic research endeavors and biobanks as public funding is limited. Collaboration with industry is regarded indispensable in bringing novel treatments from 'bench to bedside' and the biotechnological field is increasingly positioned as a source of economic value.[33,36] This results in an increasing pressure to commercialize stem cell technologies, that is, to turn research into marketable products or services.[33] An example is the establishment of human stem cell lines as either therapeutic solutions or research products.[34,37,38] The same holds for organoid technology where commercial interests are growing. This is illustrated by the growing number of patents, the establishment of commercially oriented biobanks (e.g. Organome), and the uptake of organoid technology by the biotechnological and pharmaceutical industry.[39–41] The commercialization of human tissues and related products, however, is ethically contentious and known to raise issues of public trust.[32,34,42–44] A profit-motive may conflict with the perceived moral worth of human bodily material, and commercialization could raise concerns of reciprocity, solidarity, and ownership.[32,44–46] Therefore, commercialization of organoid technology, and related human tissue products, requires careful ethical evaluation to balance the potential fruits with the concerns. The growing globalization of the stem cell field further convolutes this balancing act.[47] There is a rise of repositories that facilitate global distribution of human data and biological materials and similarly there is an increasing number of large international research consortia.[48] The fact that organoid technology is situated in a global market, in which the values and interests of multiple stakeholders have to be balanced, raises the question how the exchange of organoids (and related human tissue products) can be shaped in morally sound ways.

Third, the clinical translation of organoid transplantation in the field of regenerative medicine raises ethical challenges.[3] First-in-human organoid trials will constitute an essential step in bringing organoid transplantation from the bench to the bedside. However, these trials will be so-called

complex translational trials in which several invasive intervention and study procedures are combined.[49] They are paired with specific research ethics challenges regarding informed consent, risk-benefit evaluation, participant selection, and trial design that need pro-active scrutiny.[50,51]

Now that the organoid field advances at tremendous speed and creates a hype in science and popular media, the ethical challenges need attention to stimulate morally responsible innovation.[2,5] Therefore, it is necessary to set an ethical research agenda, and to carefully evaluate the ethical challenges related to organoid technology.

AIMS AND SCOPE OF THIS THESIS

Central aim

The aim of this thesis is to identify and evaluate the ethical challenges related to organoid technology.

Sub-questions

I. What are the key ethical challenges related to the donation, storage, and use of organoids?
II. How can we conceptualize and evaluate the moral status and the exchange of organoids?
III. Which moral conditions should be formulated for the exchange of organoids and related human tissue products?
IV. How can we ethically evaluate first-in-human organoid transplantation?

APPROACH

Ethical parallel research

In this thesis I conduct ethical parallel research. Ethical parallel research is an approach in which ethicists identify and evaluate the ethical challenges associated with a novel biomedical technology not end-of-pipeline but parallel or even pro-active as the field develops.[52,53] The advantage of this method is that it prevents ethical reflection becoming 'too little too late'. If ethicists are involved from the early start, the outcomes of ethical evaluation can be translated into morally sound design and governance of novel technologies.

Ethical parallel research is only possible when ethicists are embedded in the environment in which a novel technology is developed.[53] Knowledge of the specificities of the technology and the ethical hurdles encountered in practice are indispensable for sound identification and evaluation of the relevant ethical challenges.[53] Therefore, ethicists need to collaborate with the parties involved in the development and implementation of a novel technology, including (bio)medical professionals, patients and other groups in society. In this way science, technology, ethics, society and politics 'co-produce', rather than the traditional view where they have clearly demarcated roles. In co-production the different stakeholders work together to generate new knowledge and technology together for optimal alignment of output and needs.[54]

My affiliation with the UMC Utrecht created a perfect environment to work as an embedded ethicist in organoid technology. Utrecht is the home-base for the laboratory of Hans Clevers, one of the founders of organoid technology, and of a living biobank that consists of a growing collection of organoids from patients with various forms of cancer and CF.[14–16] In Utrecht, several research groups are making significant advancements in the scientific research as well as translational applications of organoids.[13,17,25,55] This provided me with the unique opportunity to regularly engage with several researchers and physicians that are at the forefront of developing and applying organoid technology. Additionally, I collaborated with two patient organizations: the Dutch Cystic Fibrosis Foundation (NCFS) and the Dutch Association for Metabolic Diseases (VKS). In both the fields of CF and inherited metabolic diseases, organoid technology promises to open avenues for disease modelling, precision, and regenerative medicine.[9,24,25,56]

Empirical research

The perspective of participants on organoid technology is explored by means of a qualitative interview study in close collaboration with the Dutch Cystic Fibrosis Foundation (NCFS) and the researchers and clinicians that are developing organoid technology in the realm of CF research and care. In 23 semi-structured interviews with 14 Dutch adult patients with CF and 12 parents of young CF patients we examine their opinions, experiences, and attitudes regarding organoid technology. A more in-depth description of the qualitative interview study can be found in Chapter 3.

Moral reasoning

I have used Wide Reflective Equilibrium (RE) as a method for moral reasoning. RE refers to both the process and the result of moral reasoning.[57–59] The reasoning process in RE can be characterized as 'going back and forth' between beliefs stemming from practice (morally relevant facts and moral intuitions) and from theory (principles and background theory).[58] The thinker attempts to achieve a state of RE in which moral intuitions, principles, and relevant background theories are moulded into a coherent moral view. From the perspective of RE, ethical reasoning is analogous to methods in science: we continuously test, modify, and refine hypotheses through experimental thinking.[60]

Wide RE allows for the integration of different types of (empirical and theoretical) input. Among the sources for moral reflection used in this thesis are the qualitative interview study mentioned above and the project entitled 'A Sculpture Like You and Me'. In this project fine artist Rosa Sijben and I examine the ambiguous nature of objects and the interchangeable roles of persons and things in a complementary performance and publication (See Chapter 4). The principles and background theories that I incorporate stem from various disciplines. Bio-ethics has become a field of scholarly enquiry in which it is widely accepted to analyse ethical issues from diverse ethical perspectives, using arguments derived from several ethical approaches including utilitarianism, deontology, contract-based approaches, ethics of care, virtue ethics, etc.[61] In addition to these 'traditional ethical approaches' I have included insights from the social sciences (e.g. Science and Technology Studies/ STS), (post)phenomenology, law, and feminist theory. This is necessary, because in 'traditional ethical approaches', the (meaning of the) human body is insufficiently conceptualized. Therefore, contemporary bioethical theory falls short in conceptualizing and evaluating the moral status and exchange of human bodily material in general, and organoids in particular.[62]

STRUCTURE OF THIS THESIS

The thesis is divided into four parts that each correspond with one of the four research questions.

Part I: Identifying the ethical challenges related to the donation, storage, and use of organoids

In Part I, I identify the key ethical challenges related to the donation, storage, and use of organoids. In **Chapter 2**, I set the ethical research agenda for organoid technology through a synthesis of the academic literature on ethical challenges in analogous fields (e.g. biobanking, genomics, stem cell research). In **Chapter 3**, I provide a first thematic exploration of the patient perspective on organoid technology. I do so by means of a qualitative interview that examines the experiences, opinions, and attitudes of Dutch adult patients with Cystic Fibrosis (CF) and parents of young patients with CF with regard to organoid technology.

Part II: Conceptualizing and evaluating the moral status and the exchange of organoids

In Part II, I conceptualize and evaluate the moral status and the (increasingly commercialized) exchange of organoids. In **Chapter 4**, I argue how the project 'A Sculpture Like You and Me', a collaboration with fine artist Rosa Sijben, has had an invaluable contribution to examining the moral value of organoids. In **Chapter 5**, I examine the moral status of organoids through an integration of insights from the social sciences, phenomenology, and the art project. I propose to recognize organoids as hybrids that relate to persons, things, bodies, technology, nature and commodities in ambiguous ways. Subsequently, I deconstruct the exchange of organoids by using the notion of 'disentanglement' and lay bare the ethical challenges that follow from the commercialized exchange of organoids. Finally, I propose a 'consent for governance' model to deal with these challenges.

Part III: Formulating conditions for the exchange of organoids and related human tissue products

In Part III, I formulate moral conditions for the exchange of organoids and related human tissue products. In **Chapter 6**, I propose to understand broad consent as consent for governance in the context of biobanking. I give a general outline for such a consent procedure. In **Chapter 7**, I further elaborate on a consent for governance model for responsible innovation in organoid technology and related biotechnological advances. Consent for governance implies that the ethical emphasis for justifying the use of human tissues

shifts from the initial consent procedure to ongoing governance obligations. I propose some first ingredients for the fulfillment of these governance obligations. In **Chapter 8**, I examine a specific governance obligation in the realm of genomics (as Next-Generation-Sequencing techniques are routinely applied in the stem cell and organoid field): the return of genetic information to family members of deceased patients.

Part IV: Ethical evaluation of first-in-human organoid transplantation

In Part IV, I evaluate first-in-human organoid transplantation. In **Chapter 9,** I examine whether it would be ethically acceptable to include children in a first-in-human liver organoid transplantation trial. In **Chapter 10**, I show how a novel approach towards the assessment of estimated efficacy in humans contributes to systematic, transparent, and non-arbitrary decision-making regarding risks and benefits in first-in-human trials.

Chapter 11 presents a general discussion of the main findings in this thesis. After a discussion of the answers to the four research questions, I propose a shift towards value-sensitive governance of complex exchanges of organoids and related human tissue products. Subsequently, I reflect on the potential contribution of an active engagement of bioethicists with the arts to the moral reflection on novel biotechnologies.

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Part I

Identifying the ethical challenges related to the donation, storage, and use of organoids

CHAPTER 2

Organoid biobanking: identifying the ethics. Organoids revive old and raise new ethical challenges for basic research and therapeutic use

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ABSTRACT

Recent developments in stem cell research and genomics have made it possible to grow mini-organs, so-called organoids, in culture. Organoids are self-assembling three-dimensional structures that closely resemble the architecture and function of real organs and are seen as one of the most significant developments in stem cell research with a wide range of applications in research and in the clinic. However, the relevant ethics for organoid technology have not been sufficiently addressed. First, the moral and legal status of organoids deserve further exploration. Second, organoid biobanking calls for the development of adequate consent procedures in both research and clinical applications. Third, the concept of mixed models in biobanking of organoids requires distinct governance structures. Fourth, we anticipate ethical challenges related to clinical translation. Further interdisciplinary discussion is required to stimulate morally responsible innovation.

INTRODUCTION

Organoids can be grown from several types of stem cells, including induced pluripotent stem cells (iPSCs), human embryonic stem cells (hESCs), and adult stem cells for a wide variety of organs including gut, kidney, pancreas, liver, brain, and retina, among others (see Appendix for suggestions for further reading). These mini-organs can be stored in biobanks and used for fundamental research, precision medicine, and regenerative medicine.[1,2] Cerebral organoids can be used to understand brain development, and mini-guts can serve as a personalized drug testing tool for cystic fibrosis (CF).[2,3] Mini-livers could form a complement to current organ transplantation to restore liver function of patients with metabolic liver disease.[2]

Stem cell research, and the use of embryonic stem cells in particular, has raised a fierce ethical debate, which mainly revolved around the moral status of embryos.[4] iPSCs provided an alternative to bypass moral concerns about the destruction of embryos, but, as it turned out, they raised other ethical challenges such as consent, ownership, commercialization, intellectual property rights, and safety; the debate on these topics is ever ongoing. The technological convergence of big data, genomics, stem cell technologies and biobanking, combined with increasing globalization and the growth of biotechnology, makes it particularly challenging to formulate harmonized ethical guidance. As organoid biobanking is growing rapidly, it should be scrutinized whether and to what extent organoids give new twists to the ethical challenges in stem cell research and analogous fields. Here, we identify key ethical challenges related to the donation, storage and use of organoids.

MORAL AND LEGAL STATUS

Similar to stem cells and stem cell lines, the first key question would address the legal and moral status of an organoid: what kind of entity is an organoid, who owns it and what can, and cannot be done with it? Answers to these questions could draw on the continuing debate about the legal and moral status of the human body and its parts.[4,5] Central to this debate is whether we own our bodily material, and whether it may be exchanged as a commodity. This is a complicated question, because human tissue is neither a person nor a thing.[5]

Traditionally, people donating organs or tissues have personal rights in their body parts, such as rights of control and informed consent.[5] It is

often argued that these rights should be limited though, so donors should not have property rights in their biological material, nor should they have the right to sell it. This is mainly based on notions of human dignity and on principles of non-commercialization of the human body.[4,5] Other parties, however, can establish a form of property rights in bodily material, namely if they transform it into intellectual property (IP) through an innovative step.[4,5] Consequently, a paradoxical situation could arise, in which individuals have no further rights to downstream use once they have donated the tissue, whereas researchers or companies can make profit out of their IP.[5] This, in combination with the increasing density of the IP landscape, requires us to consider how IP can best be constructed to maximize innovation, while protecting the rights and dignity of the donor.[4,5] This question remains a topic of debate in the stem cell field, and becomes increasingly important for organoid technology.

First, commercial interest in organoid technology is rising rapidly. Organoids are an exciting and cutting-edge tool for drug development and precision medicine, and are therefore very attractive for biotech and pharmaceutical companies. Galapagos has already entered a license agreement for the use of organoid technology for preclinical drug research in CF and inflammatory bowel disease. Organome pursues mass-production of brain organoids for research. Furthermore, if organoid transplantation enters a clinical stage, off-the-shelf organoids will be needed.

Second, organoids have a genetic and functional link to the donor, and they are complex entities associated with different categories of biological material, such as tissue samples, cell lines and whole organs. It is important to examine the moral status of organoids, and the ways in which organoids are related or refer to donors, because this can influence the ethical evaluation of the justifiable level of commercialization of organoid biobanking.

Waldby & Mitchell show compellingly that the context of donation, the type of tissue, and the subsequent use or transformation, highly influence the value that donors may put on their bodily material.[4] Organoids that are grown out of intestinal biopsies of patients with CF, for instance, could have direct individual benefit as personalized drug-testing tool.[3] If liver organoids are grown out of iPSCs from a healthy donor, this direct clinical relevance is less likely to occur. Furthermore, the tissue and the subsequent use of the organoids, may be more or less sensitive.[6] For instance, cerebral organoids could be particularly sensitive, as these models may reveal personalized cognitive features. In terms of applications, commercial use, gene therapy, and clinical transplantation could be more sensitive than basic research. It would require empirical studies to gauge the perspective of donors and their attitude towards commercial use and distribution of organoids.

CONSENT

A second set of ethical challenges relates to whether, and what kind of, consent is required. The use of human tissue for research purposes has so far been justified by either obtaining the donor's consent or by de-identification of the sample.[7] The potential harm related to (residual) tissue donation is mainly related to information and privacy. Consent is therefore usually not required if the tissue is de-identified, because these harms are not likely to realize. However, there is a dispute whether de-identification does indeed justify research on human tissue and whether it guarantees privacy.[7] Notwithstanding, complete de-identification is not desirable for organoid technology, because it will greatly decrease the scientific and clinical value. If removing the identity of the donor is not an option, consent is a requirement.

The emergence of biobanking, stem cell banking and genomics have already challenged more traditional notions of specific consent, in particular as it is impossible to know the scope and direction of future research in advance.[7] Organoid biobanking, as a convergence of these technological developments, encompasses these consent challenges. Whereas a thick opt-out (i.e. 'an opt-out procedure *with* the fulfillment of the following conditions: (1) awareness is raised about the opt-out procedure (2) adequate information is provided (3) a genuine possibility to object is presented and objections are adequately registered') is often considered sufficient for traditional biobanks with residual tissue,[6] this would not suffice for organoid technology, because of the potential sensitive uses. Several solutions for an appropriate opt-in procedure have been proposed, including broad consent, tiered consent and dynamic consent.[6,7]

Apart from the need for evaluating the appropriate consent procedure, emphasis on the consent paradigm alone may not be sufficient moral justification for using human tissue for organoid technology. Is consent able to fulfill all moral requirements brought forward by the characteristics of organoid technology, or will it become, as some called it in analogous fields, an overstretched and eroded concept?[5] It is therefore worthwhile to explore what could justify the storage, distribution, and use of organoids in addition to the requirement of consent.

BIOBANK GOVERNANCE

The storage of organoids will serve the combined goals of future research and clinical purposes. This mixed model of biobanking brings along a distinct set of ethical challenges.

First, the traditional research infrastructure of biobanking may be unsuitable when organoid technology moves towards the clinic. Biobank storage for research purposes has the main goal of generating scientific knowledge, whereas for a clinical biobank the interests of patients take precedence. This requires distinct ethical oversight. Moreover, if organoid technology is implemented in precision medicine, a suitable infrastructure is needed with the capacity for clinical validation of results, and for responsibly returning results to patients. In addition, data storage and linkage should be tailored to the clinical needs of patients, while safeguarding their privacy. Furthermore, if organoids are used for clinical transplantation, it requires off-the-shelf organoids of clinical-grade quality, which have to comply with current good manufacturing practices (cGMPs) in order to ensure safe clinical use.

Second, the clinical relevance of organoid technology further accentuates the discussion on public or private models of biobanks.[4] Organoids could be distributed globally, and research on organoids may lead to a complex patenting landscape, similar to that of iPSCs. Both public and private stakeholders may well be interested in organoid technology, which urges us to examine which proportion between both parties is ethically desirable. Whereas the establishment of public-private biobanking models may accelerate translational research for the eventual benefit of patients, it also requires considerations of benefit, data sharing and the maintenance of trust.

CLINICAL TRANSLATION

A fourth set of ethical challenges concerns the clinical use of organoids. A first point relates to precision medicine and translating the response of organoids in the laboratory to drugs towards the clinical needs of a patient. Although the organoid model closely mimics the *dys*function of the original organ, it does not account for an entire body, or for the broader context of the patient. It could therefore be challenging to clinically validate the *in vitro* response to drugs, especially in patients with rare diseases.[3]

The application of organoids in precision medicine will be at the margin of research and care, and new models are needed that enable integration of both. One avenue worthwhile to explore could be the implementation of 'n-of-1' trials: single-patient randomized controlled trials with multiple crossovers.[8] Nonetheless, such a design may bring along ethical challenges such as the appropriate framework of ethical review, cost-effectiveness, data sharing and consent.

A second ethical point regards the reimbursement of drugs. Although reimbursement policies vary per country, personalized drug testing in organoids may challenge prevailing practices, which depend on evidence of safety and efficacy from large-scale clinical trials. Testing drugs in organoids generates data on effectiveness in individual patients or in smaller groups, which is a novel type of evidence.

An example of this potential conflict in reimbursement policies is the use of organoids within precision medicine to treat patients with CF. This is a life-shortening hereditary disease in which thick and sticky secretions from various glands lead to gastro-intestinal and pulmonary complications. It is caused by ~2000 mutations in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene, and the large majority of mutations are rare.[3] For decades, treatment has been mainly symptomatic, but drugs that target mutation-specific defects of the CFTR protein are now being developed. Kalydeco, which costs around US$275.000 per patient per year, has been approved for a select subset of CF patients (~5-6%) that express so-called gating mutations.[3,9]

In the Netherlands, Kalydeco has been tested using a functional CFTR assay on gut organoids of CF patients whose mutations fall outside of this approved scope.[3] If the treatment is effective, improved CFTR function causes ion and fluid transport into the organoid lumen that can be quantitated by measuring organoid swelling, which is completely CFTR-dependent.[3] Although a subset of patients turned out to be drug responders, they were not eligible for reimbursement. After negotiations among physicians, scientists, the government and the National Health Care Institute, three subjects now receive treatment and are reimbursed. Further discussion about reimbursement of drugs based on organoid data is ongoing. Similar challenges may occur in other applications, such as targeted therapy in oncology. Therefore, pro-active scrutiny and potential adaptation of current practices is needed.

Another important promising application of organoids is transplantation, for example in treating liver disease. Although experiments are currently in a preclinical stage, the first clinical use in humans should be anticipated. At least three types of ethical challenges have been identified when setting

up complex translational trials, which are 'first-in-human trials involving several invasive interventional and study procedures'.[10]

First, early human studies are ethically challenging because the required evidence to predict risk and benefit in humans is lacking. The assessment of risks and uncertainties is especially vital in complex translational trials.[10] A first-in-human (FIH) organoid trial will require extensive attention to reduce risks and uncertainties, to maximize the scientific and social value and to assess whether making the leap from bench to bedside is justified.

Second, choosing the most appropriate study population – that is both ethically suitable, and sufficient to answer the research question – is challenging, even more so when first use would be a paediatric trial for children with inherited metabolic disease.

Third, there are questions concerning the right study design with the right choice of outcomes and comparators. Traditionally, a FIH trial is a safety study, but there are debates whether outcome measures should not also take efficacy into account in order to maximize benefit.

CONCLUDING REMARKS

Organoid biobanking is a promising and exciting new field with considerable potential for scientific research, precision medicine and regenerative medicine. We identified four interrelated ethical challenges for research and clinical use. Although these are not new, organoid biobanking is a complex technology in which several ethical discussions converge. The moral evaluation of this rapidly growing field requires an integration of these diverse topics, rather than an isolated assessment of either challenge. If the ethical challenges are only scrutinized separately, chances are that what may seem a solution to one question, could conflict with other areas. An essential question is therefore how we can integrate the different domains.

It is vital to involve all the different stakeholders in the debate on the development of adaptive governance structures. This includes the active and substantial participation of donors. A first step would be to investigate the perspectives, opinions and attitudes of patients and (potential) donors towards organoid technology. In addition, it is important to develop novel notions of benefit-sharing[11], especially in light of the increasing commercialization and globalization of organoid biobanking. The idea of benefit-sharing is twofold. It encompasses specific benefits to individual participants or to participant groups, such as feedback of results or access to treatments, for their efforts and contribution and embraces the generation of benefit for society at large.[11] After all, the rationale of the public good,

or social value, is frequently put forward as a moral justification for the use and exchange of human tissue. This rationale should not be taken for granted within organoid biobanking. It calls for further reflection, particularly because organoid technology crosses several boundaries between seemingly opposing categories, such as the public versus the private, and clinical versus research. Responsible advancement and implementation of organoid biobanking requires an optimization of its potential for clinical, scientific and social value, while respecting and fostering the rights and interests of participants.

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APPENDIX: SUGGESTIONS FOR FURTHER READING

Organoid technology

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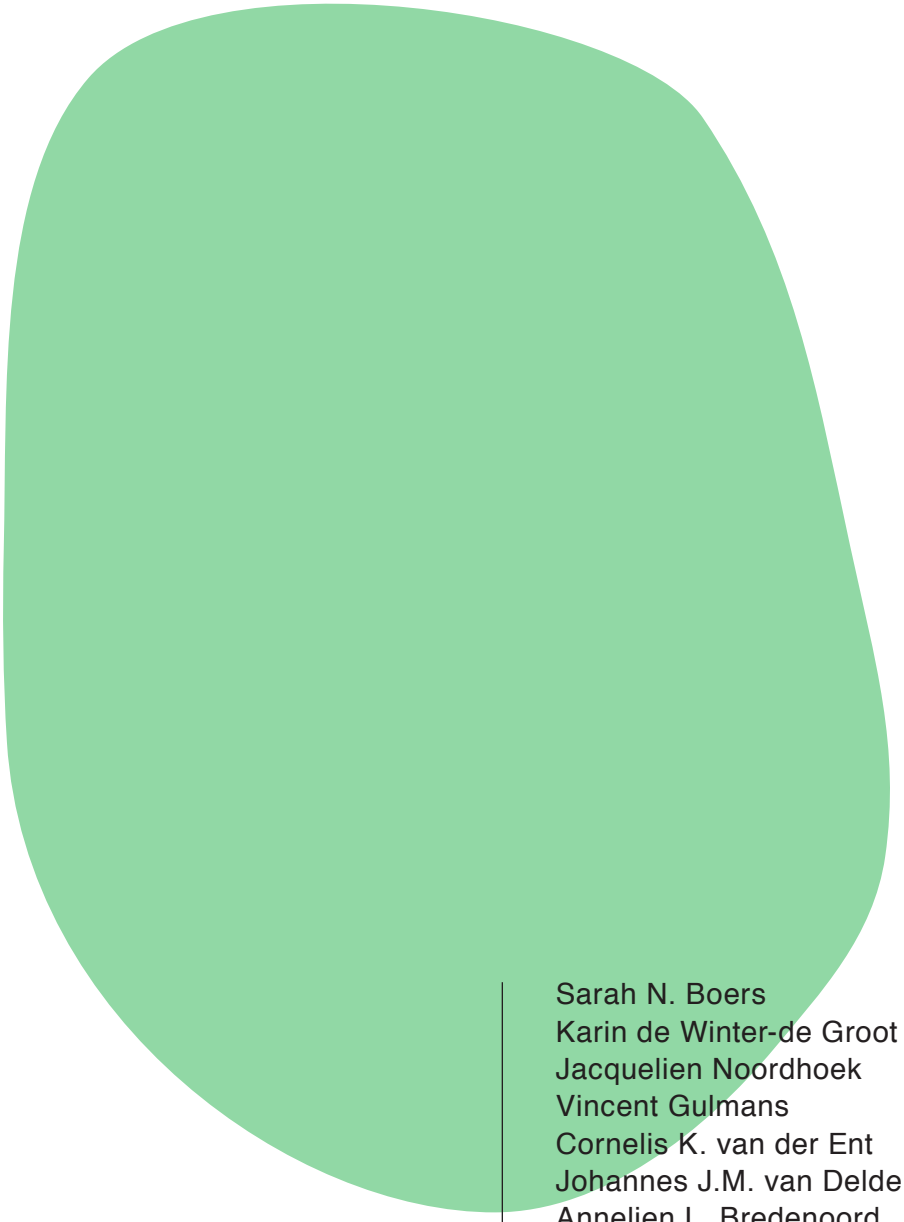
CHAPTER 3

Mini-guts is a dish: perspectives of adult Cystic Fibrosis (CF) patients and parents of young CF patients on organoid technology



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ABSTRACT

Background: Organoid technology enables the cultivation of human tissues in a dish. Its precision medicine potential could revolutionize the Cystic Fibrosis (CF) field. We provide a first thematic exploration of the patient perspective on organoid technology to set the further research agenda, which is necessary for responsible development of this ethically challenging technology.
Methods: 23 semi-structured qualitative interviews with 14 Dutch adult CF patients and 12 parents of young CF patients to examine their experiences, opinions, and attitudes regarding organoid technology.
Results: Four themes emerged: (1) Respondents express a close as well as a distant relationship to organoids; (2) the open-endedness of organoid technology sparks hopes and concerns; (3) commercial use evokes cautiousness. (4) Respondents mention the importance of sound consent procedures, long-term patient engagement, responsible stewardship, and stringent conditions for commercial use.
Conclusions: The precision medicine potential of organoid technology can only be realized if the patient perspective is taken adequately into account.

INTRODUCTION

Organoids are three-dimensional cell structures that can be cultured out of human pluripotent and adult stem or progenitor cells.[1] They closely recapitulate the architecture and function of real-life human tissues and they can be applied in fields ranging from disease modelling to drug development and regenerative medicine.[1,2] Organoids can be stored in so-called living biobanks, which enables widespread use of the technology.[3–5]

Organoid technology could potentially revolutionize Cystic Fibrosis (CF) research and care as it offers a strikingly accurate and personalized model for disease.[6–10] The development of novel drugs for patients with CF, particularly for those with rare mutations, is challenging, because small sub-groups make it impossible to conduct classical trials. The intestinal organoids, derived from rectal biopsy material of patients, constitute a novel model for stratified drug development and for the prediction of individualized drug response, as they are genetically and functionally similar to patients.[9,11] Although organoid technology has been predominantly applied in the research setting, the technology starts to impact the clinical care of patients with CF.[6] The technology promises to have a far-reaching impact on the lives of patients with CF, particularly on the lives of those with rare mutations (Appendix 1).[6–8]

Now that organoid technology promises to thoroughly change the CF field, what do patients with CF actually think of this revolutionary technology? Earlier we showed that organoid biobanking comes with ethical challenges related among other things to the moral and legal status of organoids, consent, commercialization, return of results and governance.[4,5] These challenges are not necessarily new, but form a convergence of existing debates on the ethical aspects of genomics, biobanking, big data, and other stem cell technologies.[4,5]

In related fields, such as the derivation and use of induced Pluripotent Stem Cells (iPSCs), ethical debate and empirical research on the attitudes of participants has already led to policy recommendations.[12–17] Although some common ground has been established, such as the need for patient consent, debates on the above mentioned questions are still unsettled. What is more, organoid technology is a novel type of stem cell technology that may give a new twist to ethical debates.[4,5] In this paper, we aim to provide a first thematic exploration of the patient perspective on organoid technology in order to set the further research agenda. We aimed to recruit respondents for whom organoid technology could be or could become of relevance, that is, adult patients with CF and parents of young patients with CF, to

examine their experiences, opinions, and attitudes with regard to organoid technology.

MATERIALS AND METHODS

We performed a qualitative interview study to identify relevant themes with regard to organoid technology as perceived by patients with CF and parents of young patients with CF.[18]

Sample

We aimed to collect a wide range of experiences and viewpoints from Dutch patients for whom organoid technology could be or could become of relevance. When we conducted our qualitative interview study, particularly adult patients with CF and young patients detected in the newborn screening were eligible for participation in organoid research. Therefore, we chose to recruit adult patients with CF and parents of young patients with CF (preferably < 5 years of age), that had participated in organoid research or not (Appendix 1).

Adult patients with CF and parents of young patients with CF were first approached via repeated calls on the website and on other types of social media of the Dutch Cystic Fibrosis Foundation (NCFS). Since mainly adult patients responded to these calls, we additionally recruited parents of young patients via treating physicians in the Wilhelmina Children's Hospital (WKZ).

In total, we conducted 23 interviews with 26 respondents: 14 adult patients and 12 parents of young patients with CF (Table 1 and 2). Since organoid technology was emerging in the CF field, for those respondents that had participated in organoid research the processes around retrieval of rectal biopsy material, consent, the research project, and long-term storage of organoids varied (Table 1 and 2, Appendix 1). The time span between their variable experiences (Table 1 and 2), including consent, and the interview varied between roughly a couple of months and two years. Due to poor recall of their experiences, we could not calculate exact time spans.

Data collection

The interviewer, SNB, conducted the interviews between June 2015 and February 2016. The interviews were held in Dutch, they lasted between 50 and 80 minutes, and took place at the University Medical Center (UMC) Utrecht or at the respondent's home. SNB used a semi-structured topic list to guide the interviews, which was based on literature, pilot interviews, and comments from the NCFS patients' research advisory board (Appendix 2).

The topics evolved following information that was obtained from completed interviews. The REC of the UMC Utrecht assessed that the study was exempt from formal review. Patients and parents provided oral informed consent for their participation.

Data analysis

The interviews were audiotaped, transcribed verbatim, and stored coded. In our data analysis we focused on identifying broad themes. We applied the constant comparative method, which means that data analysis is an iterative process in which we go back and forth to develop codes, concepts, and, lastly more interpretative themes.[18] SNB coded the full transcripts by labelling units of texts that referred to one or more topics, using NVivo 10 software.[19] The codes were developed into higher-order concepts and themes. Reliability was ensured by continuous discussion of the codes and themes during team meetings. Representative quotations were chosen to illustrate the themes and translated into English.

Patients (n=14)	**Participated in organoid research (n=5)[a]**	**Did not participate in organoid research (n=9)[b]**
Gender		
Male	3	7
Female	2	2
Age (years)		
18-30	1	2
30-50	2	3
>50	2	4
Education		
Primary, lower secondary general, or lower vocational	0	0
Higher secondary general or intermediate vocational	1	3
Higher vocational or university	4	6
Treating Hospital		
University Medical Center, Utrecht	1	5
Erasmus Medical Center, Rotterdam	0	1
Haga Hospital, The Hague	4	3

TABLE 1. CHARACTERISTICS OF ADULT PATIENTS

[a] The participation of adult patients in organoid research was variable in terms of the processes around retrieval of the rectal biopsy material, consent, use, and long-term storage of the gut organoids (Appendix 1). 3 patients participated in a specific organoid research project and had given biobank consent. 2 patients could not recall the context of their participation in organoid research.

Parents (n=12)[a]	**Whose child participated in organoid research (n=10)[b]**	**Whose child did not participate in organoid research (n=3)[c, d]**
Gender		
Male	6	1
Female	4	2
Age (years)		
30-40	8	3
40-50	2	0
Education		
Primary, lower secondary general, or lower vocational	0	0
Higher secondary general or intermediate vocational	4	0
Higher vocational or university	6	3
Children (n=10)	**Participated in organoid research (n=8)[b]**	**Did not participate in organoid research (n=2)[d]**
Age (years)		
2-3	2	1
3-4	3	0
4-5	1	0
>5	2	1
Treating Hospital		
Wilhelmina Children's Hospital, Utrecht	7	0
Sophia Children's Hospital, Rotterdam	1	1
Radboud Medical Center, Nijmegen	0	1

TABLE 2. CHARACTERISTICS OF PARENTS AND THEIR CHILDREN

[a] 6 interviews were conducted with either the father or the mother of the child, 3 interviews were conducted with both parents.

[b] The participation of young patients in organoid research was variable in terms of the processes around retrieval of the rectal biopsy material, consent, use, and long-term storage of the gut organoids (Appendix 1). Parents of 6 children had provided biobank consent, of whom 1 child had participated in a specific organoid research project. 5 children participated in the monitoring program (Appendix 1). Parents of 2 children could not recall the context of their participation in organoid research.

[c] These 3 parents consisted of the mother and father of one child that had not (yet) participated in organoid research and one mother of 2 children, one of whom did participate and one of whom did not participate in organoid research. Therefore the number of parents do not add up.

RESULTS

We identified four interrelated themes concerning different aspects of organoid technology that resonated among all our respondents.

Theme one: an ambiguous relationship to organoids

Most respondents see organoids as both closely *and* distantly related to them. Only a couple of respondents express a predominantly close *or* distant relationship. Respondents mention several characteristics of organoid technology that influence their thinking about organoids as closely or distantly related (Table 3).

First, respondents address the two-sidedness of the material nature of organoids. On the one hand, they reason that organoids are immortalized human cells grown out of bodily material that share unique characteristics with the donor. Therefore, most respondents regard organoids as living human materials (quotation 1 in Table 4). Some even regard organoids as living fragments of themselves. On the other hand, immortalization of organoids enables broad distribution and use, which creates a literal distance between patients and organoids. Moreover, respondents argue that organoids are just intestinal cells that have no thoughts or feelings (quotation 2 in Table 4).

Second, some respondents mention that the type of application influences their perceived relationship. The use of organoids as a personalized drug testing tool contributes to a sense of closeness. In this case organoids become an extension of the patient's body in the laboratory and testing results influence a patient's well-being (quotation 3 in Table 4). A close relationship is perceived by some if they strongly identify with the use of organoids or if, on the contrary, applications conflict with personal values (see Theme two). The use of organoids in an anonymous fashion for noncontroversial broad research purposes, however, feels as impersonal, as some say (quotation 4 in Table 4).

Third, respondents with strong motives for donation, whether personal or altruistic, mostly express a closer perceived relationship to organoids.

Fourth, imagination and language play a role in the perceived relationship to organoids. Some respondents vividly imagine organoids as organ-like structures in a dish. This image is strengthened by the term mini-gut that is sometimes used popularly (quotation 5 in Table 4). Others acknowledge that they would perceive a closer relationship to organoids if bigger organ-like structures were created.

In sum, respondents perceive an ambiguous relation to organoids and they each negotiate the ambiguity of the above-mentioned characteristics in their own way (quotation 6 in Table 4).

Theme two: hopes and concerns related to the open-endedness of organoid technology

The immortalization of organoids and biobank storage combined with a broad consent procedure (Appendices 1, 3 and 4) create certain degrees of open-endedness. All respondents express hopes and concerns related to the open-endedness of organoid technology.

Hopes related to open-endedness

Most respondents share the impression that organoid technology could revolutionize CF drug research, which could ultimately lead to *personalized* treatment. This hope for personalized treatment is their main motivation to donate the organoids to a biobank. Some respondents (would) predominantly donate for the good of future patients, whereas others (would) donate in the hope of benefitting personally. Some respondents, mainly those that had not participated in organoid research or respondents for whom the purposes of future use remain somewhat unclear, have relatively high hopes for personal benefits (quotation 8 in Table 4). Others have more moderate expectations (quotation 9 in Table 4).

Concerns related to open-endedness

Concerns mainly revolve around the uncertainty of respondents concerning whether their organoids will be used in their best interests and according to their values. Although a couple of respondents have found some reassurance in the broad consent process (Appendices 1, 3 and 4), most share the following concerns.

Some respondents mention the possibility that their organoids and related personal information are not being handled respectfully. Moreover, respondents mention that the open-endedness hampers a sense of contribution and identification with the aims for which their organoids are used. Most respondents wish to stay away from unworthy, trivial or unethical applications, such as growing whole organs, reproductive cloning, and purely for-profit use (quotation 10 in Table 4). This would clash with their values. Others explicitly formulate the type of research they wish to contribute to, notably CF research and care. Additionally, some respondents are uncertain as to whether their organoids will be used in ways that could positively impact their future care. Others are actively interested in organoid research and would like to get the opportunity to better comprehend the technology and its meaning for CF (quotation 11 in Table 4). Most parents

wish to be able to justify and explain the storage and use of organoids to their child.

Theme three: cautiousness towards commercial use of organoids

Most respondents, including those who have given biobank consent, struggle with commercial use, for instance, by pharmaceutical or biotech companies. Some respondents, including a parent that had consented to biobank storage, even categorically reject the use of organoids by commercial parties (quotation 12 in Table 4). Others accept that we live in a society in which drug development is predominantly market-driven (quotation 13 in Table 4).

The motives that respondents give for their cautiousness seem to reflect a distrust of commercial parties. First, most respondents fear that commercial parties will not act in the best interest of patients and society. Second, the profit motive is deemed unfair or even unjust (quotation 14 in Table 4). Making money out of severely ill patients is considered to be potentially exploitative and for-profit research may result in exorbitant prices of novel drugs. Third, respondents fear a lack of oversight of the use of organoids. Fourth, some fear negative consequences of commercial use, including the sharing of sensitive information with improper stakeholders (e.g. insurance companies), or perceived unethical applications.

Theme four: dealing with ambiguity

From the previous three themes it follows that respondents have ambiguous attitudes towards organoid technology: (1) they experience a close as well as a distant relationship to organoids, (2) open-endedness of organoid technology strengthens hopes and concerns, and (3) although commercial use is deemed necessary for drug development, it evokes cautiousness. Respondents come up with different ways to deal with their variable values, interests, hopes, and concerns.

First, respondents acknowledge the importance of initial biobank consent. Respondents that have given broad biobank consent mention a couple of aspects that they experienced to be reassuring. One parent mentions that the information provided in the consent conversation helped to have realistic hopes (quotation 15 in Table 4). Other respondents mention the written information that, for instance, addressed the installment of ethical oversight, the protection of privacy, and the return of clinically useful results (Appendices 3 and 4). Still, most respondents would ideally wish to restrict the scope of initial consent, although most of them had consented or would consent to the broad terms (quotation 16 in Table 4). Some would prefer to

donate to CF research exclusively or to limit the sharing of their organoids. Others would like to exclude certain sensitive uses.

Second, initial consent is generally considered to be insufficient. It should, according to the respondents, be coupled with long-term engagement of participants and responsible stewardship, which includes ethical oversight, privacy protection, transparency, and the fostering of trust (quotation 17 in Table 4). Minimally, respondents share the idea that participants should be informed about major changes in governance or use and about clinically useful results. In addition, most respondents would like access to collective information concerning planned, ongoing, and finalized projects. Some respondents would ideally have access to personal information on the use of their organoids (quotation 18 in Table 4). Some only wish to be asked to re-consent to sensitive applications, whereas others wish to be asked to re-consent to each new research project. Overall, if organoids are used by commercial parties, respondents put forward more stringent conditions for long-term engagement and stewardship, including an emphasis on reciprocity (quotation 19 in Table 4).

	Characteristics contributing to a closer perceived relationship	Characteristics contributing to a more distant perceived relationship
1.	**Material nature of organoids**	
	Organoids relate to the human body - Grown out of human material - Unique and personal characteristics ▪ Same genetic make-up ▪ Same biological function - Related to bodily integrity Living human bodily material - Organoids are immortalized - Organoids are 3D	Immortalization enables widespread distribution and use of organoids Organoids are just cells - Organoids have no feelings or thoughts - Intestinal tissue is not sensitive - Organoid donors have no physical connection to the organoids Organoids constitute a technology - created by researchers
2.	**Use of organoids**	
	Use of organoids can impact personal wellbeing - Improved treatment through personalized diagnosis and drug testing - Use can have negative impact (e.g. a breach of confidentiality) Use of organoids can impact personal values - Use of organoids can be a positive expression of personal values - Sensitive applications, e.g. reproductive cloning, growing whole organs and commercial use can conflict with personal values Use while coupled to personal information	Broad use for research is impersonal - Research only impacts future patients - Noncontroversial applications do not affect a person's values Only others can use organoids Anonymous use
3.	**Intention for (hypothetical) donation**	
	Strong motivation for and identification with donation Strong ideas about worthy use of organoids	Weak motivation for donation (e.g. 'not hindering research') Weak ideas about worthy use
4.	**Imagination and language**	
	The term 'mini-guts' Strong imagination of mini-guts in a dish Growing bigger organs or combining organ systems	The term 'organoids' No imagination of organoids: very abstract Merely growing tiny organoids

TABLE 3. CHARACTERISTICS OF ORGANOID TECHNOLOGY THAT INFLUENCE THE PERCEIVED RELATIONSHIP OF RESPONDENTS TO ORGANOIDS IN 4 DIFFERENT CATEGORIES

[a] The same respondent could mention characteristics of organoid technology that contribute to a closer perceived relationship and characteristics that contribute to a more distant perceived relationship.

	Quotation of Respondent
An ambiguous relationship to organoids	1.Parent-6:*'Yes these are after all living cells and they do something, they have a function. On the screen they show that with the right medication they can grow from small to large, however small that is, so they are alive.'*
	2.Patient-3: '*Yes, well, it is so abstract and such a tiny piece of tissue that I don't see anything wrong with it. You spread even more tissue around through blood and urine samples and hair that falls out everywhere.*'
	3.Patient-11: '*…so risk free…a part of myself, or a clone of myself that you can experiment on risk free…and from that you hope to get a better quality of life.*'
	4.Patient-4: '*If it is immediately used for research in a more generalized target group and used in large numbers, then yes it seems less personal to me, then it suddenly becomes a very different matter.*'
	5.Patient-10: '*In a manner of speaking, yes, mini-gut gives you the idea that you are really talking about an intestine, even if it is only a centimeter in size.*'
	6.Parent-2: '*It is in fact a part of him, so it is…everything that it is, is also him, so it is important that a link remains between him and the mini-gut, precisely because they could find something that could benefit him too, but it is not a part of him anymore; the way I see it they are real pieces of (son's name).*'
The hopes and concerns related to the open-endedness of organoid technology	7.Parent-7: '*Yes that is actually quite strange, something living outside your body, that's really out there, we're sitting here in Brabant and a piece of (son's name) is sitting in Utrecht or wherever it's being kept, I don't know…if you think about it it's quite strange.'*
	8.Parent-6: '*Because for us it is real, I feel that the mini-guts are the future for (name), that everything really depends on whether they can, well, if they can cure, or if we can turn CF into a chronic disease instead of a deadly disease.*'
	9.Parent-8: '*Well, in addition to the broader research I expect…that something will come of it for him, that they can do something with it. And preferably he would get a sort of tag for possible follow-up research.*'
	10.Patient-4: '*But maybe the creation of organs or very different purposes that have nothing to do with my disease or other diseases, and so more commercial purposes, then it becomes a more complicated story.*'
	11.Parent-1*: 'Yes it's just that you want to be kept up to date, we are very aware that you probably get a lot of information that you can't do anything with yourself, but you still want to follow it, you want to stay informed.'*

	Quotation of Respondent
Cautiousness towards commercial use of organoids	12.Parent-9: '*No, not with my child, I think. No, if I think about it, the hospital is fine, but something commercial, no. No, that makes me uncomfortable, I think*.'
	13.Parent-4: '*If I read something like Galapagos…that they are working on CF and they bought a license to use organoids, then I think yes, alright, we're going that much faster*.'
	14.Patient-2: '*Think of the pharmaceutical industry profiting from it, and it's also a piece of you. And once they start earning so much money that way, it doesn't feel so great*.'
Dealing with ambiguity	15.Parent-8: '*You have to keep in mind that it will take 10, 15, maybe 20 years before there are any real results. So we are very cautious not to get our hopes up*.'
	16.Parent-1: '…*if they say no then you don't get any research in the area of CF, then probably you will say yes*.'
	17.Parent-2: '…*there must be somebody, a committee or something that can manage it well, good ownership. That I have the feeling that my body parts, or my personal information, are safe there. There has to be a sort of trust in that biobank that it will be handled well*.'
	18.Parents-6: (mother) '*Yes but I can also imagine, look, lab technicians keep everything on the basis of the unique number assigned to the organoid, so you would think that it would be quite simple to seal certain information…*' (father) '*With your DigiD (*Dutch government digital identification code)'… (mother) '*Or with your personal organoid code*.'
	19.Patient-7: '*I would find it logical that there would be some sort of compensation for the use of that material, in terms of pharmaceuticals, in the form of expedited access to drugs or something*.'

TABLE 4. QUOTATIONS FROM RESPONDENTS

DISCUSSION

This is the as far as we know first study exploring the patient perspective on organoid technology. The four themes that emerge in our qualitative interview study give an impression of the experiences, attitudes, and opinions of Dutch adult patients with CF and parents of young patients with CF with regard to organoid technology. Although our respondents are generally supportive of organoid technology, the first three themes show that they have an ambivalent attitude. Respondents (1) experience a close as well as a distant relationship to organoids, (2) the open-endedness of organoid technology strengthens hopes and concerns: organoid technology is seen as a potential game changer in the treatment of CF; however, respondents express concerns about whether the organoids will be used in their best interests and according to their values; and (3) although commercial use is deemed necessary for drug development, it evokes cautiousness. In the fourth theme respondents come up with several ways to deal with their variable values, interests, hopes, and concerns. They mention the importance of a sound consent procedure, long-term engagement of patients, responsible stewardship, and stringent conditions for commercial use.

This first exploratory study gives an impression of the relevant themes to set the further research agenda, even though further research is necessary to identify differences among subgroups.

Understanding the interests of Dutch adult patients with CF and parents of young patients with CF

Like iPSCs, organoids should not be seen as a morally neutral alternative to embryonic stem cells [4,5,12]. Contrary to human embryos, intestinal organoids do not raise questions about *intrinsic* moral value. Nevertheless, organoids, particularly those derived from adult stem or progenitor cells, are genetically and functionally identical to the donor.[11] Therefore, donors may have a legitimate interest in managing conditions for derivation, storage, and use.[4,5] Our findings inform what the interests of donors, in this case Dutch patients with CF and parents of young patients with CF, might be.

In the first theme respondents reflect on their relationship to organoids. How can we relate their views to the moral value of organoids?[4,5] More specifically, could we regard organoids as sensitive tissue and could they give rise to sensitive applications?[12,20] This is relevant, because donors generally have more autonomy-based rights over sensitive tissues and applications and ethical oversight is more stringent.[12,16,20] Respondents do not regard the rectal biopsy material itself as sensitive. Rather, it is the

transformation of the biopsy into a three-dimensional immortalized cell line that is genetically and functionally similar to the donor that is considered meaningful, and to some extent as sensitive. What distinguishes organoids from other immortalized cell lines is their three-dimensional structure. Some respondents do find that this feature contributes to their idea of a close relationship to organoids.

Apart from the creation of organoids itself, organoids can be used in possibly sensitive ways that are partially unforeseen. In iPSC research some types of applications have been marked as potentially sensitive, such as certain basic research procedures (e.g. large-scale genomic sequencing), transplantation into humans, and for-profit use.[12,13,15] All of these apply to organoid technology and our respondents add to this the creation of bigger organ systems. Despite these and other concerns, respondents are generally supportive of organoid technology, which is in line with other empirical studies on the attitudes of patients towards biobanking and iPSC research.[13,21,22] For our respondents the hope for personal benefit may have been a somewhat stronger motive to (hypothetically) donate organoids. Patients with CF are not mere donors of bodily materials, they are simultaneously potential end-users of organoid technology. Therefore, their interests could differ from other types of tissue donors. The fear that organoids may not be used in ways that can positively impact their healthcare indicates this personal interest.

In the third theme, respondents reflect on an area of application that raises specific concerns: commercial use of organoids. Commercial use of human samples is known to be a sensitive topic among patients, donors, and the wider public.[13,23–25] Our respondents particularly fear that their organoids might be used for developing CF drugs that will be exorbitantly priced, which may impede access to these novel therapies. This fear is not unfounded given the high prices of the latest generation of CF drugs.[26]

Embedding patient perspectives in practice and policy

How should the practice and policy of organoid technology be shaped together with CF patients and their parents? In the fourth theme, respondents express that their interests and concerns could best be taken care of through sound initial consent procedures, long-term engagement, responsible stewardship, and stringent conditions for commercial use.

Donor consent for the collection, storage and use of human samples is generally recognized as an important means of protecting a donor's interests.[27,28] Explicit donor consent for the derivation and use of iPSCs is deemed indispensable and we propose extending this prerequisite to organoids.[4,5,12,13,15,16] Furthermore, several of our findings contribute to the

idea that the initial consent procedure has its limitations. Initial consent was deemed insufficient by most of our respondents to manage their hopes and concerns, a perspective that is reflected in other work on the storage and use of human samples.[12,15,29] Besides, many respondents had flawed recall of the consent procedure, a well-known phenomenon in biomedical research in general and stem cell research in particular.[30]

Therefore, we contend that initial consent should be coupled with long-term engagement of participants and responsible stewardship. For iPSC research it has already been argued that donors should be re-contacted to solicit re-consent for innovative, potentially sensitive applications, for the return of individual results, and to seek re-consent from paediatric participants once they reach an adult age.[12,15,31] We would like to add that at minimum participants should be informed about relevant collective information and major changes in governance.[32] Participatory medicine initiatives around the globe, however, show that patients can be involved more actively.[33,34] The incremental levels of involvement range from informing patients, to consultation, an advisory role, partnership, and ultimately a project in which patients have a leading role.[34,35] The desirable level of involvement is case and context dependent. A higher level of involvement may be necessary if a disease-specific biobank is set up in which participants are both donors and potential end-users, such as the CF organoid biobank, or if organoids are used for sensitive aims. The CF field in the Netherlands already sets the stage for close collaboration among patient organizations, researchers, and physicians.[35]

Furthermore, public-private partnerships are needed to translate the scientific fruits of organoid technology to marketable drugs for patients with CF, as is acknowledged by our respondents. In general, for the commercial use of organoids to be ethically responsible and widely supported by patients and the public, models are needed that balance potential merits with concerns.[5] In these models, reciprocity is key.[36] For the field of CF, the ultimate goal of applying organoid technology is the realization of precision medicine. To reach this goal, pro-active negotiation of pricing is prerequisite, particularly in light of recent difficulties with reimbursement of lumacaftor/ivacaftor, a promising CF drug, in the Netherlands.[37]

Limitations

First, whereas the heterogeneity of our sample allowed us to collect a wide range of viewpoints it also has limitations, particularly because the sub-groups are represented by small numbers. We, for instance, interviewed more adult male patients with CF than female patients, the experience of our respondents with organoid research was variable, and most of the parents we interviewed had a young child that had participated in organoid research.

Parents without experience in organoid research were underrepresented. In this first qualitative study, however, it was not our aim to provide in-depth insight into differences among sub-groups, nor to generalize the views of our respondents to the entire population of patients with CF.

Second, due to low response rates to the open calls, we additionally recruited parents via treating physicians in the WKZ, where most children are exposed to organoid technology. The WKZ professionals have a positive overall attitude towards organoid technology, which may have influenced parents. Nevertheless, parents voiced concerns equally.

Third, it is likely that patients and parents interested in new developments in the CF field responded most readily to the open advertisements. This could influence their level of knowledge and their desire for pro-active involvement in organoid technology. The educational level of our respondents was above average and consequently they may well have been more informed and articulate.

Fourth, the timing and process of interviewing may have influenced the views of respondents. Although most respondents were primarily positive regarding organoid technology at the beginning of the interview, they gradually started to voice concerns. Those that had participated in organoid research admitted that for them it was their first opportunity to thoroughly reflect on certain sensitive topics. It remains a question whether these concerns will fade away over time.

Fifth, patients with CF constitute a distinct group. They have a direct health interest in organoid technology and they are known for their pro-active attitude in their care and in research.[38]

The limitations of our explorative study clearly show the need for further future research. In order to analyze differences among sub-groups of patients with CF and to generalize findings to the entire population further empirical research is needed in which qualitative and quantitative approaches are combined and more diverse groups (in terms of e.g. educational level, disease severity, ethnicity, nationality) are included. Moreover, further empirical research should shed light on the perspective of other types of donors and organoids.

CONCLUDING REMARKS

Sound governance of organoid technology in CF research and care requires considerations of consent, long-term engagement of adult patients and parents of young patients, responsible stewardship, and responsible models for commercial use. Organoid technology holds a promise for personalized therapy in CF; however, this can only be realized if the perspective of the person in question, that is, the patient, is taken adequately into account.

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APPENDIX 1: BACKGROUND ON ORGANOID TECHNOLOGY AND CF IN THE NETHERLANDS

Recently, novel drugs have been developed that target the underlying cause of Cystic Fibrosis (CF): specific defects in the cystic fibrosis transmembrane conductance regulator (CFTR) protein that are caused by different mutations in the *CFTR* gene.[7,8,10,39] Nonetheless, the majority of patients with CF still have unmet needs for better medical treatments. Beekman and colleagues, working in the University Medical Centre (UMC) Utrecht, the Netherlands, have demonstrated that it is possible to derive patient-specific organoids from rectal biopsies of patients. These intestinal organoids comprise an accurate disease model, and a functional CFTR assay allows for novel approaches to drug development as well as predicting personalized drug response.[6,8] The CFTR assay works as follows. If a treatment is effective, improved CFTR functions causes ion and fluid transport into the lumen of organoids that can be quantified by measuring organoid swelling.[9]

Context of the generation of organoids

The UMC Utrecht, including the Wilhelmina Children's Hospital (WKZ), started to collect rectal biopsy material for the derivation of intestinal organoids in 2011. The respondents in our study would have had experience with organoid technology from 2011-2016. During this time organoid technology was rapidly emerging. The UMC Utrecht was the only Dutch institution offering facilities for the generation of gut organoids. However, collaboration with several of the six other CF centres, particularly with The Hague (Haga Hospital) and Rotterdam (Erasmus Medical Center), increased rapidly. Patients with CF could be approached for a rectal biopsy procedure and subsequent cultivation of organoids in several different contexts. We give the most common examples, without being exhaustive.

First, the majority of rectal samples were obtained during standard CF care where rectal biopsies are used for intestinal current measurements (ICM) with the aim of testing residual function of the CFTR protein. This procedure was frequently performed within the context of the Australian Respiratory Early Surveillance Team (AREST) protocol. In UMC Utrecht and Erasmus MC the AREST protocol aimed to standardize the follow-up of children aged 0-5 years. At age 1 and 5 a bronchoscopy and bronchoalveolar lavage under general anesthesia are combined with a rectal suction biopsy for ICM. After Research Ethics Committee (REC/IRB) approval many parents

of these children were asked to consent to the generation of gut organoids out of the rectal biopsy material left over after ICM. The gut organoids were used for different types of exploratory studies.

Second, patient consent for the generation of organoids was sought in the context of several small-scale research projects that aimed to validate the CFTR assay and its capacity for personalized drug testing.[39] Patients only underwent a rectal biopsy procedure if no residual rectal sample was available.

Third, organoids could be generated for personalized drug testing aims after patient consent. An example is the off-label testing of ivacaftor, a novel CF drug, on the gut organoids of patients with rare mutations and a deteriorating clinical condition.[8]

During the consent procedures information on the cultivation of organoids and the specific use of organoids is provided to patients or parents.

Biobank storage and consent

In 2014 the Hubrecht Organoid Technology (HUB), a not-for-profit organization affiliated with the UMC Utrecht, was founded and established a so-called living biobank.[40] The living biobank aims to culture and collect organoids from patients with various diseases including cancer and CF. The HUB provides access to organoids to both academic and for-profit parties with objectives ranging from basic research to drug development. Consent for biobank storage entails an explicit broad consent procedure. Broad consent can be defined as 'consent for an unspecified range of future research subject to a few content and/or process restrictions'.[41] Patients with CF (or their parents) receive oral and written information from research nurses working in the UMC Utrecht. The written information addresses, among other things, that the cells can be used for broad biomedical research purposes, can be shared with other parties, including commercial parties, and that patients cannot share in any potentially yielded profits (Appendices 3 and 4). Biobank consent is sought simultaneously with consent for the generation of organoids, or re-consent is sought from patients whose organoids have already been used in another context. A patient's refusal of biobank consent results in destruction of the organoids. Only patients treated or biopsied in the UMC Utrecht are eligible for biobank storage, due to local REC approval.

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APPENDIX 2: INTERVIEW TOPIC LIST

Research question: What are the opinions, attitudes, and experiences of patients with Cystic Fibrosis and their parents with regard to organoid technology?

Topics

- Experience with organoid technology
- Motives for participation in organoid technology
- Attitude towards biobank storage of organoids
    - Immortality of organoids
    - Scope of future use
    - Data and sample sharing
    - Privacy
- Attitude towards control rights
- Attitude towards ownership of organoids
- Attitude towards commercialization of organoids
- Attitude towards applications of organoids
- Attitude towards return or results (i.e. individual and collective)
- Perceived relationship to organoids
- What kind of entities are organoids

APPENDIX 3 AND 4: EXAMPLES OF HUB INFORMATION LETTER AND CONSENT FORM FOR PATIENTS WITH CF AND PARENTS OF CHILDREN WITH CF

These appendices can be accessed online at:

https://ars.els-cdn.com/content/image/1-s2.0-S1569199318300274-mmc3.pdf
https://ars.els-cdn.com/content/image/1-s2.0-S1569199318300274-mmc4.pdf

Part II

Conceptualizing and evaluating the moral status and the exchange of organoids

CHAPTER 4

A Sculpture Like You and Me: examining the ambiguity of organoids

Sarah N. Boers

Based on:

Sarah N. Boers and Rosa Sijben. A Sculpture Like You and Me. *Self-published*. 2017

Sarah N. Boers. Sculpting body parts: How the arts contribute to ethical reflection. Blogs *Journal of Medical Ethics*. 26 October 2018

INTRODUCTION

Recent advances in stem cell technology enable the cultivation of three-dimensional human tissues in a dish called organoids, referred to in popular media as 'mini-organs'.[1] Organoid technology constitutes only one example of the numerous ways in which human tissues can be utilized to create complex human tissue products. Organoids promise a wide variety of scientific and clinical applications, ranging from disease modelling to precision and regenerative medicine, because of their close representation of human tissues.[2] These developments are paired with increasing commercial interests. Growing commercialization can contribute to translating scientific promises of organoid technology from the bench to the bedside. However, commercialization of human tissues that serve as the source for growing organoids, is ethically contentious.[3]

Traditional bioethical literature gives two opposing answers to the question how the commercialization of human tissues should be evaluated from an ethical point of view. The 'gift paradigm' holds that a profit motive is irreconcilable with the donation and use of human tissues. The 'market paradigm' alternatively frames human tissues as commodities.[3,4]

The following can help to understand these opposing views. Our thinking about what we can(not) commercialize is underlined by a deeply rooted division between *persons* and *things,* or in other words *subjects* and *objects.* Whereas we can own and sell things, we cannot own nor sell people. Human tissue and related products, however, fall between two stools. To avoid the grey area, the gift paradigm categorizes human tissues as *'subjects'* and the market paradigm as *'objects'.*[4,5]

These categories, however, neglect the *ambiguity* of organoids. On the one hand, organoids relate to the category of subjects, because they are generated from human tissues and bear close resemblance to the genetic make-up and the (dys)function of the body of the donor. On the other hand, organoids relate to the category of objects, because organoid technology is a patented technology that bears economic worth.

To be able to adequately evaluate the commercialization of organoid technology, it is necessary to take a step back and examine the moral value of organoids in light of this ambiguity.

A SCULPTURE LIKE YOU AND ME

To properly wrap my head (and body) around the ambiguity of organoids I entered a collaboration with 'the arts'. Together with fine artist Rosa Sijben I worked on a project that we titled 'A Sculpture Like You and Me' (Appendix). In a complementary performance and publication we investigate the ambiguous nature of objects and the interchangeable role of persons and things. The performance premiered at De Appel Arts Centre in Amsterdam in June 2016 and the publication was released in February 2017 at Art Rotterdam, both in the Netherlands.[6]

A Sculpture Like You and Me – a complementary performance and publication

In the performance I act as an ethicist and I hold a monologue on the moral value and commercialization of organoids. In a square space Sijben and I perform together with several of Sijben's sculptures and the people in the audience (Image 1). The performance begins as follows:

'Imagine… Imagine a living chunk of human cells in a petri dish, growing in a laboratory… This may seem far-fetched fiction, but in fact we are facing reality. Organoids can now be cultured out of pieces of human tissue. They are a tiny copy of the real-life human organ.'

During my monologue, Sijben interrupts me regularly and directs me to repeat certain phrases while moving through the space or while holding or moving objects. Likewise, she directs the audience to move and to exchange objects. As such a choreography of the audience, Sijben, Sijben's sculptures, and myself arises.

IMAGE 1 PERFORMANCE 'A SCULPTURE LIKE YOU AND ME', PHOTO IRIS VAN VLIET

In the publication, the script of the performance is coupled with images of the performance sculptures and pictures of daily objects that served as an inspiration for the sculptures. It invites the reader to examine the ambiguity of organoids and the objects.

A Sculpture Like You and Me- a sensory and creative way of reflecting on the moral value of organoids

Throughout this project my moral reflection transformed from an *individual, formal, and mental* experiment to a *free, creative, sensory, and external* ethics lab in dialogue with different interrogators.
I could think freely, creatively, and leave existing frameworks, because both Sijben and I moved out of our respective disciplines to meet in a newly created hybrid space between science and art.[7]

We had weekly creative 'labs' in which we experimented with the ambiguity of organoids in dialogue with Sijben's work (her sculptures, performances, installations) and images of daily objects from her archive. We visualized our associations on the wall of Sijben's studio (Image 2). Among others, we explored the subjecthood of objects and the objecthood of subjects. Organoids are strange entities. They are pieces of technology that are created by people in a lab that can be used to develop drugs.

Simultaneously, they constitute a living part of a person from whose cells they were derived, *while living apart from that person.* Similarly, in one of Sijben's performances a member of the audience wondered '*Isn't talking to a performer like touching a sculpture?*'. This quote sheds a specific light on the objecthood of performers. Furthermore, we examined the factors, such as physical location and application, that influence the meaning of organoids, daily objects, and Sijben's works of art. For instance, when organoids are used as a personalized drug testing tool in a patient's treating hospital, they constitute a representation of that patient. Alternatively, when they are used for drug development in a distant commercial lab they are approached as commercial biotechnological artefacts. Likewise, one of Sijben's works 'Baustelle' consists of an installation of building materials that is 'exhibited' in a museum and at a construction site.[8] In the museum, it is regarded as a work of art, whereas at the construction site the materials are construction instruments.

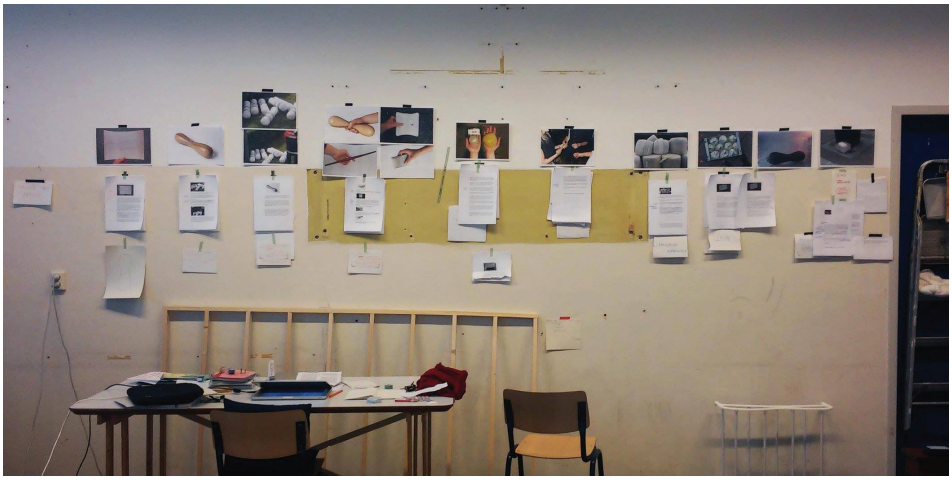

IMAGE 2 AN IMPRESSION OF THE WEEKLY LABS IN SIJBEN'S STUDIO, PHOTO ROSA SIJBEN

Parallel to 'A Sculpture Like You and Me' I was working on a paper in which I conceptualize and evaluate the moral value and commercialization of organoids (see Chapter 5). In this paper, I integrate insights from, among others, phenomenology and Science and Technology Studies (STS).[4,9,10]

During our weekly labs I experimented with insights from these theoretical approaches. In the performance my moral reflection becomes *'embodied'* by Sijben, myself, the sculptures, and the audience.

I have a *lived experience* of abstract philosophical concepts, such as the idea stemming from phenomenology that you both *are* and *have* your body, and the notion of hybridity.[4,10–12] Hybrids are entities that challenge existing categories and that are neither human nor non-human.[4,12] For example, I am both an actor and a sculpture that forms a part of an art installation. Round clay-like objects are moved through the performance space. When I hold them packed in a box and talk about treating organoids as commodities, I feel like a market woman selling goods (Image 3). At a later moment, I talk about how organoids could be seen as tiny parts of the human body that circulate the world. Simultaneously, the audience is asked to exchange the clay objects with their neighbours. Now they feel as intimate parts of their bodies (Image 4). Their meaning changes in a network of human and non-human actors. My spoken text constantly enters new relations with the objects and people from the audience.

IMAGE 3 PERFORMANCE 'A SCULPTURE LIKE YOU AND ME', PHOTO IRIS VAN VLIET

A Sculpture Like You and Me- organoids as hybrids

Reflecting on the question '*What is the moral value of organoids?',* I gained invaluable insights from the project 'A Sculpture Like You and Me'. It allowed me to experiment with the subject- and object-like values of organoids in a playful and associative way. This experiment, in concert with the theoretical work performed in Chapter 5, has brought me to conclude that, rather than trying to categorize organoids, we should embrace their ambiguity. The term 'hybrid' perfectly captures the ambiguity of organoids. Hybrids are entities that precede categorization and that are neither human nor non-human.[4,12] Organoids are such hybrids, because they ambiguously relate to persons and their bodies as well as to technologies and markets (see Chapter 5). The subject- and object-like values of organoids are intimately interwoven. Organoids are valuable instruments for science and clinical care, because they closely represent the persons behind the tissues (see Chapter 5). Furthermore, the project has allowed me to experiment with the network of human and non-human actors in which organoids come into being and in which their meaning is shaped.

To conclude with the final passage of 'A Sculpture Like You and Me':

'There is a book, a book that says: bodies are fluid. They are not bound entities that stand on a one-to-one relation with a person of human dignity. Bodily material is even more ambivalent. The material is ambiguously related to persons, bodies, technology, and nature. This perfectly resembles with the state of organoids: they are hybrids. The tissue and the human invention are an integral entity: the one cannot do without the other. Organoids inhabit a grey area, a wetland between person and thing: sometimes more human, sometimes more technology. Sometimes a gift, sometimes a commodity. But no single characteristic can ever be fully excluded, our bodily aspects can get to the background, but will always remain.'

IMAGE 4 PERFORMANCE ‘A SCULPTURE LIKE YOU AND ME’, PHOTO IRIS VAN VLIET

ACKNOWLEDGMENTS

I am very grateful for the collaboration with Rosa Sijben with whom I made ‘A Sculpture Like You and Me’. I gratefully thank Lotte Schröder for the graphic design of the publication ‘A Sculpture Like You and Me’ and the graphic design of this chapter, the chapter headings, and the cover of the thesis. I thank Iris van Vliet for the use of her photos made at the Appel Arts Centre in Amsterdam June 2016. I gratefully acknowledge the feedback on this Chapter by Hans van Delden.

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APPENDIX: AN IMPRESSION OF ‘A SCULPTURE LIKE YOU AND ME’

IMAGE 5 ‘A SCULPTURE LIKE YOU AND ME’- THE PUBLICATION

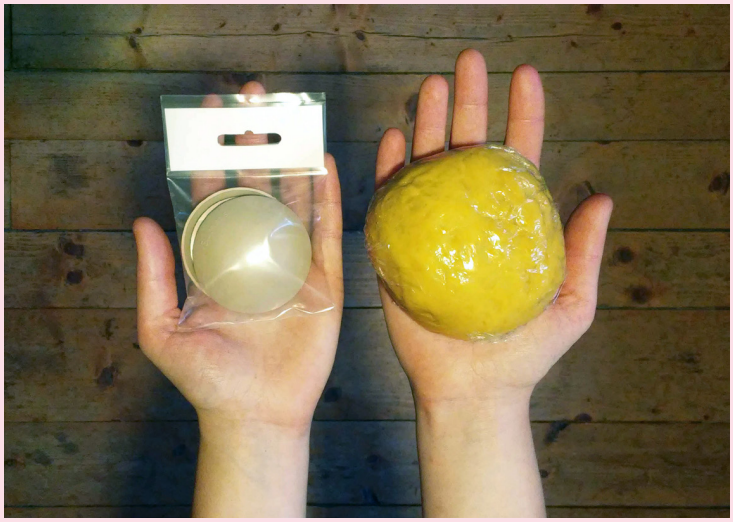
In what follows I invite the reader to form an impression of 'A Sculpture Like You and Me'.

A two-minute trailer of the performance as performed at the Appel Art Centre Amsterdam in June 2016 can be viewed on the website of Rosa Sijben: http://www.rosasijben.nl/a-sculpture-like-you-and-me/.

The publication is limited to 200 editions. A virtual impression of the publication in its entirety can be found on Sijben's website: http://www.rosasijben.nl/a-sculpture-like-you-and-me-the-publication/. In the following section I provide an excerpt of page 8-13 of the publication.

Well, we can endorse some of these arguments, can't we? Indeed our body is a special thing. So maybe that also holds for its *fragments 3*?

(Hier een lange break waarbij ik echt ontspan, denk aan *andere dingen*[C], bier, terrasjes etc.)



3

Market advocates say: certainly a patient can sell her organoids. If we own anything, it must be our bodies, right? If we want to sell our organoids, why should someone prohibit that? They should be exchanged via the market.

One moment. Could you [to a member of the audience] please help me to lift *this D* and hand it to Sarah?
[Lifts box and hands it to Sarah]
Could you [to Sarah] repeat from 'If we own anything' and continue?

If we own anything, it must be our bodies, right? If we want to sell our organoids, why should someone prohibit that? They should be exchanged via the market.

After all, market systems can perfectly manage the supply and demand of everything, including organoids, so why hinder such a well-oiled machine? Besides, commercial parties can bring about innovation, *like drugs and transplantation devices 4*. They are efficient, they have capital, and they can bring products from the bench to the market. Profit-making is an absolute prerequisite, otherwise companies are not at all interested in developing a product.

Moreover, it is a fair transaction: a patient provides material for growing organoids, gets paid, and transfers the property to another party. That party can process and transform it, and profit from their efforts.

So, we could see organoids as perfect commodities.

E

[to Sarah]
We'll put it down now.
Thanks.

[Starts moving the *white objects E* back and forth]

I wonder, if we fully excluded commercial parties would we ever get new drugs? And isn't it unfair not to include the patient in the transaction? But then, to regard organoids as full commodities, such as pills or tables, does seem counterintuitive. Could making financial gain out of organoids lead to treating the entire patient as a commodity?
–repeats–

I wonder, if we fully excluded commercial parties would we ever get new drugs? And isn't it unfair not to include the patient in the transaction? But then, to regard organoids as full commodities, such as pills or bicycles, does seem counterintuitive. Could making financial gain out of organoids lead to treating the entire patient as a commodity?

[Squats down, ready to drop the shuttle]

Things get even more complicated when we observe the ways in which organoid exchange actually happens in the real world. Organoids are usually not exchanged as either gift or commodity; they transform from one into the other.

[DROPS *it F*]

F

Let me explain with an example:

CF patients who have gut organoids grown for personalised drug testing can donate organoids to a biobank out of personal or altruistic motives. They thereby give broad consent for unknown future use. Subsequently, researchers can patent organoids, which gives them the legal right to own and sell them. The patent makes organoids ready to enter the market…
They move from gift to commodity status.

My question is:
How can an organoid go from a person to a thing?

Could you please stand *here G*, repeat that last sentence and continue?

How can an organoid go from a person to a thing?

People are human subjects: they have culture, and can enter relations. Subjects have rights, such as autonomy. A thing is a passive object that we can observe or put to our use. Objects are pieces of technology. They can be owned, and sold if they have *exchange value H+I*.

On the donor side, the tissue is seen as part of the person. You have autonomy over your body, but you do not have property rights in it. If some tissue comes loose from your body, then it is considered waste, something you no longer need. In legal terms this is referred to as an abandoned thing, or no-one's thing. The tissue enters a state of no-one's land.

INDEX

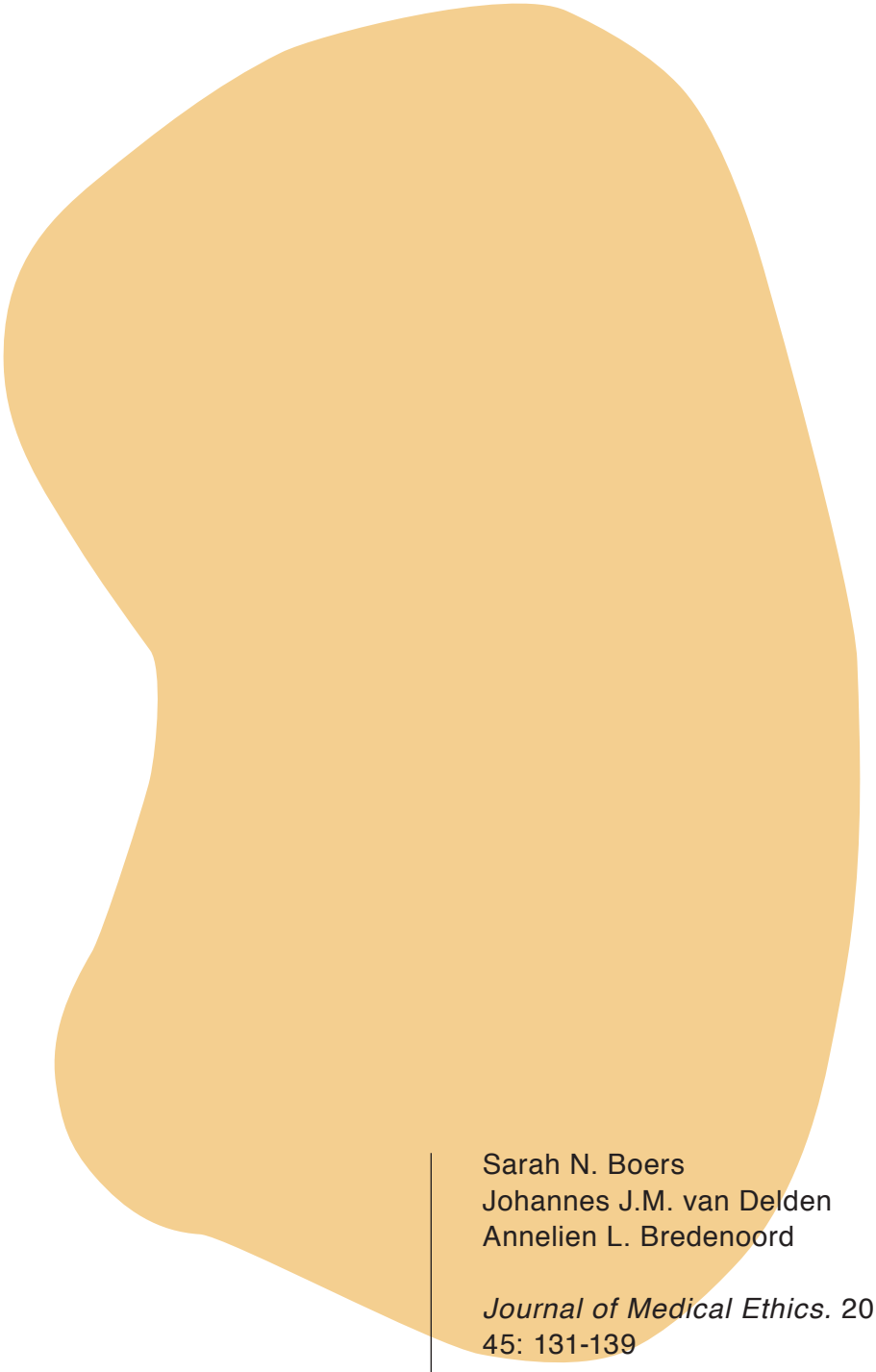
1. Fridges and chairs, Italy 2014
2. Boxing ring, Italy 2014
3. Door stoppers and dough, Switzerland 2015
4. Ten salad heads in a box, Amsterdam 2015
5. Folded piece of carpet in a bicycle crate, Amsterdam 2016

A. Untitled sculpture, 2016, part of the performance, PVC canvas, 5 x 5 m
B. Untitled sculptures, 2016, part of the performance, hardened fabric and two chairs, 60 x 150 cm
C. Untitled sculptures, 2016, part of the performance, cardboard, 5 pieces of 80 x 57 x 120 cm
D. Untitled sculptures, 2016, part of the performance, MDF, 77 x 52 x 14 cm, plaster and plasticine in plastic, 10 pieces of 20 x 20 x 8 cm
E. Untitled sculptures, 2016, part of the performance, insulation foam, 10 pieces of 70 x 30 x 25 cm
F. Untitled sculpture, 2016, part of the performance, painted metal, 112 x 102 x 10 cm
G. Untitled sculptures, 2016, part of the performance, painted wood, 2 pieces of 100 x 20 x 20 cm
H. Sarah Boers, 1988, part of the performance, 174 cm (incl. heels)
I. Rosa Sijben, 1988, part of the performance, 174 cm
J. Untitled sculptures, 2016, part of the performance, plaster and plasticine in plastic, 10 pieces of 20 x 20 x 8 cm
K. Screenshot of documentation of *A Sculpture Like You and Me* at de Appel arts centre, Amsterdam, 19 June 2016

All photos by Rosa Sijben

CHAPTER 5

Organoids as hybrids: ethical implications for the exchange of human tissues



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Johannes J.M. van Delden
Annelien L. Bredenoord

Journal of Medical Ethics. 2019;
45: 131-139

ABSTRACT

Recent developments in biotechnology allow for the generation of increasingly complex products out of human tissues, for example, human stem cell lines, synthetic embryo-like structures, and organoids. These developments are coupled with growing commercial interests. Although commercialization can spark the scientific and clinical promises, profit-making out of human tissues is ethically contentious and known to raise public concern. The traditional bioethical frames of gift versus market are inapt to capture the resulting practical and ethical complexities. Therefore, we propose an alternative approach to identify, evaluate, and deal with the ethical challenges that are raised by the increasing commercialization of the exchange of sophisticated human tissue products. We use organoid technology, a cutting-edge stem cell technology that enables the cultivation of 'mini-organs' in a dish, as an example. First, we examine the moral value of organoids and recognize them as hybrids that relate to persons and their bodies as well as to technologies and markets in ambiguous ways. Second, we show that commercialization of organoids is legitimized by a detachment of the instrumental and commercial value of organoids from their associations with persons and their bodies. This detachment is enacted in steps of disentanglement, among which consent and commodification. Third, we contend that far-reaching disentanglement is ethically challenging. (1) Societal interests could be put under pressure, because the rationale for commercializing organoid technology, that is, to stimulate biomedical innovation for the good of society, may not be fulfilled. (2) The interests of donors are made subordinate to those of third parties and the relational moral value of organoids may be insufficiently recognized. Fourth, we propose a 'consent for governance' model that contributes to responsible innovation and clinical translation in this exciting field.

INTRODUCTION

In recent years biotechnological developments enable the processing of human bodily materials into increasingly complex tissue products. Examples include the creation of human stem cell lines, synthetic embryo-like structures, and organoids.[1–3] These developments promise to deeply impact science and clinical care, because they allow for a closer examination of human development and disease as well as offer approaches towards precision and regenerative medicine.[1–3]

These promises are coupled with an increasing commercialization of the exchange of human tissues.[4,5] With exchange we refer to the transformation of human tissues into complex products, and their transfer, storage, distribution, and use. Examples include the growing patents in human tissue products, the establishment of commercial biobanks, and the use of tissue sources and their products by commercial parties, such as the pharmaceutical industry.[5–8] Commercialization can spark the clinical and scientific promises of the biotech field. Collaboration with private parties may, for example, be needed to transform scientific knowledge into marketable medical products. Nevertheless, profit-making out of human tissues is ethically contentious and it is known to raise public concern.[5,9] This raises the question of how to deal with the growing commercialization of human tissue exchange.

Current bioethics approaches rely on gift versus market thinking. Whereas the gift paradigm frames the exchange of human tissues as altruistic donations to the public good, the market paradigm conceptualizes human tissues as marketable products that can be exchanged for profit.[10,11] We contend that these dichotomous modes of thinking are inapt to capture the practical and ethical complexities of the field.

In this paper, we therefore propose an alternative approach that allows for a richer identification, evaluation of, and dealing with the ethical challenges that are raised by the increasingly commercialized exchange of human tissues and their products. Our approach integrates insights from ethics, the social sciences, phenomenology, and science and technology studies (STS). We use organoid technology (Table 1), a cutting-edge stem cell technology that allows for the cultivation of 'mini-organs' in a dish, as an example of increasingly sophisticated human tissue products.[3] After an examination of the moral value of organoids, we deconstruct their exchange, identify the ethical challenges that are raised, and propose ways to deal with those challenges. To support and illustrate our analysis, we use a scenario of organoid exchange in the field of Cystic Fibrosis (CF) research and care.

In this field organoid technology is already fulfilling its precision medicine promises and commercialization leads to an intricate web of values and interests (Appendix).[12 1]

BACKGROUND ON ORGANOID TECHNOLOGY

Organoid technology makes it possible to grow three-dimensional human tissue structures in a dish out of human pluripotent or adult stem or progenitor cells (Table 1).[3] Organoids can already be established for a wide variety of organs, among which, liver, brain, intestine, and retina. If organoids are grown out of adult stem or progenitor cells, researchers can isolate these stem cells from human tissues, such as liver or rectal biopsy material. After isolation, the stem cells are put in a petri dish, containing a culture medium with the right growth factors, and the cells start to grow, expand, and self-organize into organ-like three-dimensional structures.[13] These structures look like tiny blobs underneath a microscope, and they closely resemble the architecture and function of real-life human organs.[3,13]

Organoids are perceived to be one of the most promising recent developments in stem cell research as they can impact the entire biomedical innovation cycle, with applications ranging from studying human development and disease, to drug development, precision and regenerative medicine.[14–18] Brain organoids give insight into human cognitive development and diseases, such as a closer understanding of the relation between Zika virus and microcephaly.[19] Disease-specific organoids serve as personalized drug testing tools.[20] A striking example is the field of Cystic Fibrosis (CF), a severe hereditary disease with predominantly lung and intestinal problems, where gut organoids of patients with CF predict individual drug response to existing and novel therapeutics, in a dish (Appendix).[20,21] Organoids could alter the drug development pipeline, since they enable large-scale testing of novel therapeutics.[14] Although clinical transplantation of organoids is still in a preclinical phase, regenerative medicine applications are foreseen in the future.[16] The potential to immortalize certain types of organoids and to store them in so-called living biobanks, further increases their promise:

1 The scenario is inspired by our qualitative study that examines the perspective of patients with CF on organoid technology12 and by our current collaboration with CF clinicians, researchers, companies, and CF patient organizations in a European project called HIT CF Europe that aims to evaluate efficacy and safety of three drug candidates in patients with CF and rare mutations, preselected by their intestinal organoids in the laboratory (https://www.hitcf.org/).

it enables distribution to and usage by multiple public and private parties worldwide.[14,17,22] Commercial interests in the field are growing.[6,8,23]

Elsewhere, we have identified and discussed the overall ethical challenges that are raised by organoid technology.[14,17] Here, we use organoid technology as an exemplary case for complex human tissue products and specifically analyze the ethical challenges that are raised by the growing commercialization of organoid exchange.

Adult Stem Cells	Are undifferentiated cells found in differentiated adult tissue that can renew themselves and differentiate to yield all specialized cell types of the tissue from which they originated.
Cystic Fibrosis	Is a rare and severe hereditary disease that is characterized by thick and sticky mucus leading to predominantly pulmonary and gastro-intestinal complications.
Gastruloids	Constitute a certain type of organoids that are cultured out of human Pluripotent Stem Cells and that recapitulate early stages of embryonic development.
Human Embryonic Stem Cells (hESCs)	Are primitive undifferentiated cells from the human embryo that have the potential to become any of a wide variety of specialized cell types.
Induced Pluripotent Stem Cells (iPSCs)	Are human body cells that have been reprogrammed to behave like embryonic stem cells, that is, to be able to differentiate into cells that could regenerate and repair many different kinds of damaged or diseased tissues.
Organoids	The term organoid means 'resembling an organ'. Organoids are defined by three characteristics. The cells arrange themselves in vitro into 3D organization that is characteristic for the organ in vivo, the resulting structure consists of multiple cells found in that particular organ, and the cells execute at least some of the functions that they normally carry out in that organ.
Human Pluripotent Stem Cells (hPSCs)	Are human cells that are unspecialized and capable of renewing themselves. They can specialize into different cell types of the human body. hPSCs can be either hESCs or iPSCs.
Stem Cells	Are cells that have the ability to divide indefinitely in culture and give rise to specialized cells.

TABLE 1. GLOSSARY

CHAPTER 5

EXCHANGE OF ORGANOIDS: QUESTIONING THE TWO DICHOTOMIES

Gift versus Market

Bioethical debates on exchange of human bodily material are frequently framed in terms of gift versus market.[10,11] Although many variants and combinations of both paradigms exist (e.g. in bioethics, law, anthropology), each side of the divide comes with characteristic perspectives on bodily exchange.[4,10,11,24] For the sake of this paper we will broadly outline both paradigms, in order to sketch the opposing views.

The gift paradigm broadly embraces the idea that individuals donate their bodily material as a gift to science or medicine, out of altruistic motives. The subsequent exchange takes place in the public domain.[10,11,25] The market paradigm embraces an opposing view: individuals have property rights in their bodily material and some authors argue that these property rights should include the right to sell.[10] In this case, human bodily materials are framed as commodities, that can be 'traded' and used in the private domain.[10]

The gift paradigm has long been the dominant paradigm in laws and regulations on the exchange and use of bodily material.[10,24,26] Generally, a non-commercialization principle is defended and enshrined in several national and international guidelines and recommendations. This means that the use of bodily material should not, as such, give rise to commercial gain.[26] Nonetheless, the market paradigm has its proponents as well, particularly in the debate on living organ donation.[27,28] The premise is that a monetary incentive would diminish the profound organ shortage.

Despite their different stances on norms for bodily exchange, generally both the gift and market paradigm frame human tissues as a solid substance, and gift and market systems as separate spheres. They focus on one type of transfer at one point in time, mostly the transfer of human tissues from donor to recipient, and on the (un)desirability of the commercialization of that transfer. This, while human tissues can be endlessly transformed and exchanged; gift and market systems are heavily intertwined; the value of human tissues encompasses more than being either a gift or a commodity; and commercialization knows many forms.[4,10,11,24,29] Even though there has been an ongoing refinement and nuancing of both paradigms over the years, still the oppositional frames are inapt to capture the practical and ethical complexities of the current biotechnological developments. A first step forward is to question one of the conceptual underpinnings of gift versus market thinking.

Subjects versus Objects?

In ethical and legal discourses on what can(not) be commercialized usually a divide is made between subjects and objects.[10,24,30] Subjects, or persons, have intrinsic moral value and therefore they should not be owned nor sold. Objects, or things, have an instrumental value. Objects can be owned and sold if they have exchange value.

A reason to keep a strict separation between the realm of subjects and objects, is to prevent persons, including their bodies, from being regarded as commodities. As long as body and person coincide, the rationale of keeping the person separate from the market sphere may also hold for the body. Nevertheless, once tissue becomes detached from the body and thus in a way from the person, it enters a grey area.[10,31]

The gift and market paradigm have an opposite response to this greyness. Within the gift paradigm bodily material is conceptualized as belonging to the subject-side of the divide: potential tissue donors only have personality rights in their bodily material and it is argued that bodily material should not give rise to commercial gain.[4,10,31] In the market paradigm bodily material is framed as an object, that can be owned and sold if it has exchange value – a full commodity.[10]

This conceptualization of human bodily materials as either subject or object is problematic in evaluating the commercialization of organoid technology, because the categorization of organoids as either subjects or objects partially black-boxes their (moral) value. The gift paradigm focuses on the personality rights that potential donors have over their bodily material, such as autonomy and privacy rights. The market paradigm emphasizes the instrumental and commercial value of human bodily materials. However, the value of human bodily materials is more pluralistic than a simple divide between subject or object and gift or commodity, as human tissues also relate to bodily experiences, integrity, and identity, among others.[10,24,29,32] Therefore, rather than trying to categorize organoids as subjects or objects beforehand, we will show the 'subject- and 'object-like' values that organoids could have (Table 2). The CF scenario serves as a narrative illustration of the potential different values of organoids (Appendix).

Organoids have subject-like values

Currently the subtypes of organoids that raise questions of *intrinsic* moral value receive most attention in the bio-ethical literature and popular media.[33–38] Organoids made out of human embryonic stem cells (hESCs) as well as so-called 'gastruloids' (Table 1) relate to the fierce ethical debates on the use of embryos for research.[33] Gastruloids are cultured out of human PSCs (either hESCs or iPSCs) and they closely recapitulate early stages

of human development in a dish, including markers of primitive streak formation.[33] This raises questions about the acceptability of 'creating life in a dish' and the extent of maturation of gastruloids that is allowed.[33,35] Related to questions about 'creating life in a dish' is the culturing of brain or cerebral organoids.[33,34] Current cerebral organoids are far away from being cognitive and sensory functioning entities. However, what if future research can overcome the challenges and researchers can create cerebral organoids that have certain sensory in- and output?[33,34,38] Additionally, in the future, several types of organoids could be combined with other types of (animal) tissues and techniques (e.g. bio-printing) to grow more complex organ-systems.[33,35]

Less attention has been paid to the *relational* moral value of organoids, that is, the ways in which they refer to and are meaningful to persons.[4,39] This, while all subtypes of organoids, including seemingly 'harmless' types such as gut or liver organoids, have some form of relational moral value.

First, organoids could relate to the bodily integrity of donors and recipients.[40] Organoids are self-organizing three-dimensional entities in a dish that are genetically related to donors and that represent the (dys) functioning of their bodies.[3] Some subtypes are immortalized, which means that they can grow and expand limitlessly. Organoids challenge the boundary of what does and does not form part of a human body. Particularly, if organoids are employed to grow complex organ systems, for example through bioengineering techniques, this boundary becomes blurred.[35] If clinical transplantation of organoids proves to be safe and effective, organoids can become an integral part of the recipient's body. This recipient could be either the donor (i.e. autologous transplantation) or another patient (i.e. allogeneic transplantation).

Second, organoids could relate to the personal identity and values of donors. Svenaeus argues that human tissues, which he coins 'sobjects', associate with personal identity, although in variable levels.[32] He introduces the concept of strong-identity-bearing sobjects (SIBS) with concomitant criteria to discern bodily material that has closer ties to a person's identity.[32] Organoids could at least meet two of his criteria, namely that they can be (1) 'expressive of her (the person's) perceived personality in a world shared with others' and (2) 'made use of in ways that express the specific genetic setup of the sobject'.[32] The second criterion in fact applies to all human tissues. For organoids the chances that the genetic setup of donors will be revealed are considerable, because genomic sequencing techniques in which the entire genome is screened are routinely applied in the stem cell field.[41] These may generate unsolicited findings, such as an increased risk of hereditary diseases. In certain patient-derived organoids the genetic mutations causative of the conditions that donors bear are specifically

targeted in both scientific and clinical applications. Examples include CF (Appendix) and cancer research.[16] Regarding the first criterion, organoids could form a literal and symbolic representation of the donors and their bodies in the laboratory. If organoids are used at the intersection of research and clinical care, for example, in precision medicine, the results yielded in the lab may influence the diagnosis, prognosis, or treatment possibilities of donors.[16,17,20] Consequently, the ways in which donors give meaning to their disease may be reshaped (Appendix).[12] Both scientific and clinical applications of organoids may alter the meaning of disease entities. Research on cerebral organoids of psychiatric patients may, for instance, emphasize the neurobiological origin of psychiatric diseases.[42] Moreover, organoids can function as a stand-in for the values and beliefs of individuals. Through donation of tissue for the generation and subsequent biobank storage of organoids, donors could create meaning by contributing to scientific and clinical aims that they find meaningful.[12,17,22] Participants could delegate their participation to 'their' organoids, instead of participating directly in research.[12] This ties in with the work of Waldby and Mitchell on blood donation, in which they describe the donation of blood as a form of embodied altruism.[4] Alternatively, donors may disapprove of certain, partially unforeseen, sensitive applications of organoids, such as chimera research or commercial use.[12,41]

Third, organoids relate to the privacy of donors, because they are genetically similar and frequently coupled with personal information. In this era of genomics and big data analytics the traceability of donors is generally increased.[43] Certain types of organoids could be extra privacy-sensitive. Examples include patient-derived organoids (e.g. from adult stem cells, progenitors, or iPSCs) of patients with rare, hereditary conditions (e.g. CF or metabolic diseases) or of patients with diseases susceptible to stigma, such as psychiatric disorders.[21,42]

Fourth, because of their promise for clinical care in both precision and regenerative medicine organoids can impact the wellbeing of donors and other patients.[17] If organoids are used for personalized drug testing, they can directly inform clinical treatment.[16,20] Precision medicine applications of organoids are most advanced in the field of CF (Appendix), however, initiatives in cancer research and cerebral organoids are progressing.[12,16,20,21,44,45] In addition to these informational benefits, the use of organoids can generate informational harms such as the yield of unsolicited findings or privacy concerns.[43] In the case of future organoid transplantation, organoids can have short and long term effects on the wellbeing of the recipient, being either the donor or another patient, both in terms of clinical improvement and safety risks.[16,17] In sum, the creation of organoids means that 'ordinary' tissue can be transformed into entities

that could raise questions of intrinsic moral value and that are meaningful to (groups of) donors and patients in several ways. Although all subtypes of organoids bear some form of relational moral value, their relations to bodily integrity, personal identity, privacy, and wellbeing will differ. Donors could, for instance, perceive closer ties if organoids are patient-derived, privacy-sensitive, donated within care relations, used controversially, if 'intimate organs' are modelled (e.g. the brain), or if they strongly identify with the applications of organoids.[12] Further empirical research on the perspective of donors and patients should shed light on the relevant differences.[12] Despite these differences, donors could generally use their organoids to contribute to ends they find meaningful. On the other hand, the use and distribution of organoids constitutes a privacy risk, the creation of organoids could be regarded as sensitive by some, and organoids can give rise to sensitive applications. Therefore, donors may have legitimate interests in managing the banking and subsequent use of their organoids.

Organoids have object-like values

First, organoids constitute biotechnological artefacts.[46] An artefact can be defined as an object made by a person; biotechnology entails the usage of living things in industrial processes. For the establishment of organoids human cells are used by researchers or lab assistants, to create mini-organs in a dish. These in vitro artefacts can be stored in so-called living biobanks, multiplied and distributed to a variety of stakeholders worldwide.[6,16,22]

Second, organoids constitute a technology. Here, we understand technology as a process. In this process science, technology, ethics and society 'co-produce' each other [47]. This means that organoids are co-created in a complex network of human and non-human actors. Individuals have to donate human cells within the context of health care institutions. The self-organizing capacities of these human cells form a key characteristic of organoids.[3] The work of researchers has to be facilitated by academic or private institutions and sound infrastructures and funding sources are needed for organoid banking to be sustainable. Ethical guidance, policy, and politics have a profound impact on organoid technology.[29]

Third, organoids can serve as instruments to achieve scientific, clinical, or commercial aims.[14,16] Their unique capacity to represent the function and dysfunction of the human body means that organoids can be used to model human development and diseases as well as to test and even form novel treatment strategies. Gastruloids, for instance, recapitulate the early phases of human development and tumour organoids constitute a model for disease or a platform for drug development.[16,22] Researchers can put hundreds of tumor organoids in plates filled with tiny petri dishes and test numerous novel drug candidates in short periods of time. In the realm of

regenerative medicine, organoids could be developed as advanced therapy medicinal products (ATMPs). Moreover, organoids can serve as a starting point for multiple transformations, such as 3D bio printing.[35]

Fourth, because of their scientific and clinical promise the commercial value of organoids is rapidly increasing. A rising number of patents in inventions related to organoids are being issued.[23] Patents are increasingly licensed to pharmaceutical companies worldwide. They use organoids for drug development purposes.[8] Moreover, organoids could be commercially banked and distributed.[6] If transplantation is effective, organoids could become commercially available as ATMPs.

EXCHANGE OF ORGANOIDS: AN ALTERNATIVE APPROACH

Organoids as hybrids

As we have shown above, organoids have both subject- and object-like values. Therefore, rather than trying to categorize organoids as subjects *or* objects, we propose to recognize organoids as hybrids.

The term hybrid perfectly captures the ambiguity of organoids. In the social sciences literature, hybrids are seen as entities that precede categorization, and that challenge existing categories.[10,30] Hybrids are neither human nor non-human.[10,30] We recognize organoids as hybrids that relate to the categories of persons, things, bodies, technology, nature and commodities in ambiguous ways. It is the technological transformation of human biological material into organoids that establishes novel intrinsic and relational as well as instrumental and commercial value.

To recognize organoids as hybrids means that organoids do not have a fixed ontological status or moral value. Rather, the value and meaning of organoids is changeable.[48] It implicates that the value of organoids comes into being and changes in a network of both human and non-human actors, such as institutions, donors, researchers, policy makers etc. We explicitly do not draw on the ways in which the term hybrid is used in biology, that is, to refer to the combination of two different species through reproduction.

Other words have been used to capture entities that ambiguously relate to persons and their bodies, such as 'ubjects'[10], 'sobjects'[32], and 'bio-objects'.[49,50] Nevertheless, we choose to use the term hybrids, because it adequately captures the broad variety of meanings of organoids, including their inherent technological nature, and it emphasizes the importance of a network for organoids to acquire meaning.

The notion of hybrids ties in with a broader world view in which a categorical division between subjects and objects is rejected and in which existing categories are not taken for granted.[10,30] To recognize organoids as hybrids serves as a starting point for further ethical analysis of the increasingly commercialized exchange of organoids.

Disentangling organoids

Present-day biomedical innovation in general and the stem cell field in particular is inherently interwoven with economic interests. The stem cell field has the potential to yield health and financial benefits. Simultaneously, financial resources coming from industry are necessary to bring novel treatments from 'bench to bedside', as public funding is limited.[5,10] This results in an increasing pressure to commercialize stem cell technologies, that is, to turn research into marketable products or services.[5] The same applies to organoid technology. These developments are in sharp contrast with the still dominant gift paradigm in bioethical discourses on and regulations of 'donation' of human bodily materials. The ethical mandate is that human tissues, should not, *as such,* give rise to financial gain.[26] This mandate is informed by an adherence to subject versus object and gift versus market thinking. The meanings associated with persons and their bodies, including human tissues, are thought to be irreconcilable with a profit-motive.[10,24] Since human bodily materials are used as a source for the generation of organoids, this leads to tension.

Here we deconstruct a way of negotiating this tension that we believe is dominant in current discourses on and practices of exchange in the stem cell field. To approach and understand this negotiation we draw on the way in which Waldby and Mitchell use the notions of 'entanglement' and 'disentanglement', that were introduced by Michel Callon in his study on the technologies of the market.[4,51] Callon describes the exchange of whole organs as very 'entangled' as they are profoundly involved in kinship, mortality, bodily relations, and immunological relations.[4,51] The circulation of money forms the direct opposite and is 'disentangled': money has pure exchange value, and it circulates freely and anonymously.[4,51] What makes human stem cell lines distinct from the exchange of whole organs is that they have the potential for a disentangled circulation, almost like the circulation of money. To achieve such a flexible circulation, however, steps have to be taken to 'disentangle' stem cell lines, that is, to cut ties to the original tissue provider, and to the intrinsic and/or relational moral value of the human tissue sources and products.[4,51]

Like other types of human stem cell lines, organoids have a potential for such disentangled circulation. Organoid biobanks, as other tissue banks, play a crucial role in making organoids available to the research community

through steps of disentanglement, while simultaneously respecting the rights and interests of donors and society.[4] We show what the processes of organoid disentanglement could be and how we can ethically evaluate the ways in which a flexible circulation is enabled (Table 2). For the sake of the analysis we divide the processes of disentanglement in separate steps, although we are aware that these steps could occur disorderly, simultaneously or reversely. We use the case of the application of gut organoids in CF research and care as an example of organoid exchange.[12,20,21] The scenario illustrates the negotiation of the values of and the interests that are vested in organoid technology and the different actors that are involved in exchanging organoids (Appendix).

First, to create and store organoids, rectal-biopsy material of patients with CF has to be harvested.[21] This could be residual tissue left-over in the course of diagnosis and treatment or material that is obtained for certain research or care purposes.[12,16] Patients donate rectal-biopsy material in the context of long-lasting care relations, and in the hope for new treatment.[12,20,44] Patients have to provide consent to biobank storage for future use. The type of biobank consent influences the level of disentanglement. If patients were to give specific consent for a certain study this would disentangle the organoids less than broad consent for biomedical purposes.[52]

A second step is the technological transformation of rectal biopsy material into the gut organoids.[13,46] Gut organoids can be regarded three-dimensional immortalized cell lines, as they can grow and expand limitlessly.[13] This step plays a double role. On the one hand, a biotechnological artefact is established. On the other hand, it is the technological transformation of intestinal tissue into organoids, being immortal and relatively tangible, that creates value, meaning and proximity to patients.[12]

A third step of disentanglement is to cut ties between the organoids and personal and medical information, transforming the organoids into anonymous artefacts. The type of anonymization affects the degree of disentanglement. Organoids could either be completely anonymized, which means that the identification of the patient is irreversibly prevented (with the caveat that in this era of genomics and big data anonymization can never be fully guaranteed), or pseudonymized, that is, single or two-way coding, in which case patients are still traceable.[43]

A fourth way of disentangling organoids is through commodification processes.[29] The technological transformation of rectal biopsy material into organoids can be seen as an invention. This invention, if sufficiently novel, is patentable, and can therefore endow parties other than the patient with property rights.[29] This is a first step into making organoids ready to enter the market. The commodification of organoids can vary. The closer organoids come to complete commodities, the more disentangled they become.

Storage of organoids in a non-profit bank with academic researchers as patent holders, coupled with strict ethical oversight for use and access, would detach organoids less than commercial banking, with a for-profit organization as patent holder, and widespread commercial use.[53]

This aligns with a fifth manner of disentanglement which is the mode of organoid distribution. Organoids could for example be stored and used within one institution, only permitting access to its own researchers and collaborators. This is in fact the way in which most hospital tissue banks were traditionally set up. A next step could be to outsource storage and distribution to an affiliated non-profit organization, such as the Hubrecht Organoid Technology (HUB) foundation in the Netherlands.[54] This enables wider distribution, because the HUB provides access to national and international commercial parties, although still on a limited scale. If organoids were to be distributed through a world-wide repository, this would further increase detachment.[40]

Step 1: Tissue donation and consent	The donation of human biological material for the generation of organoids and consent for the generation, biobank storage, and use of organoids.
Step 2: Technological transformation	The generation of organoids out of the human biological material (e.g. adult stem or progenitor cells, iPSCs, hESCs). The technological transformation can be seen as a patentable intervention.
Step 3: Anonymization	The pseudonymization or complete de-identification of organoids.
Step 4: Commodification	The different mechanisms to commodify organoids, such as the establishment of Intellectual Property Rights (IPRs), price setting for access, and use by commercial parties (e.g. pharmaceutical companies).
Step 5: Distribution	The national or international distribution of organoids to academic and for-profit parties.

TABLE 2. DISENTANGLEMENT OF ORGANOIDS

Evaluating disentanglement of organoids

How can we understand and evaluate the negotiation of the different values and interests pertaining to organoid technology through processes of disentanglement?

In the processes of disentanglement different actors (e.g. researchers and oversight bodies) attempt to retain a separation between the value regimes attributed to subjects versus objects and gift versus market systems. The initial exchange of human tissue from patients to the biobank appears to take place within a gift discourse. The exchange is framed as a donation. Patients have personality rights in their tissue: they can exercise their autonomy by giving a type of consent and their privacy is protected by a form of anonymization. Through their donation they contribute to a public good: a non-profit biobank that aims to stimulate biomedical research. In subsequent exchanges of organoids there is a shift to a market discourse in which the object-like values of organoids are emphasized. Consent and anonymization and the technological transformation of biological material into organoids play an important role in the legitimization of this shift.[4,29] Effectively through consenting the donor gives up further rights to organoids, which includes the right to share in any commercial profit. As such, the procedure 'acts as a kind of surrogate property contract'.[4] Anonymization, and particularly complete de-identification, further hampers the donors to exercise control, as they cannot even exercise their right to withdrawal.[55] Obtainment of consent and complete de-identification mean that the ethical standards for tissue donation are met, which at the same time grants third parties more flexibility regarding use, distribution, and commercialization of organoids. The technological transformation of the rectal biopsy material into organoids can be regarded as a patentable invention, and as such it further legitimizes their framing as marketable products.[29,53] The patent owner, in our example the HUB (Appendix), has the right to grant or deny access to organoids and to determine price setting.[29,53] The organoids are disentangled from their associations with persons and their bodies and the related gift thinking, and as such they become ready 'to enter the market'.

When the instrumental and commercial value of organoids are detached from their relational moral value this may contribute to far-reaching disentanglement. An example of far-reaching disentanglement would be exchange practices in which donors give broad consent, and where organoids are completely de-identified, patented, stored for-profit and distributed via a global for-profit repository that grants access to international public as well as commercial parties (Table 3). This example is far from unlikely given the establishment of Organome, a Baltimore-based company, that aims to commercially distribute cerebral organoids

for research.[6,56] Even if the biobank or tissue repository itself is non-profit, such as the American Type Culture Collection (ATCC)[57], we could speak of far-reaching disentanglement. We deem far-reaching disentanglement ethically problematic for two (interrelated) reasons. Societal interests could be put under pressure, because the rationale for commercializing organoid technology, that is, to stimulate biomedical innovation for the good of society, may not be fulfilled. The interests of donors are made subordinate to those of third parties and the relational moral value of organoids may be insufficiently recognized.

First, commercialization of organoid technology does not unequivocally result in innovative therapies that have social value and that reach society in a just manner. There is an ongoing discussion on whether commercialization will eventually stimulate or hamper innovation.[58] What at least should be recognized is the double edged sword of intellectual property regimes, collaboration with industry, and industry initiated research.[5,53,58] For example, even though patents can stimulate innovation, the patent holders have an exclusive right.[53] This can lead to restricted use and limited access, disproportional profit-making, lack of transparency, and the impediment of dissemination of organoid technology and innovation.[4,24,53] Furthermore, use of organoids may have less scientific and clinical value if organoids are not coupled to patient data. Additionally, there is usually less oversight over use of organoids by commercial companies, because of business secrets. Lastly, monetary and non-monetary benefits following from organoid technology may be unjustly shared or distributed.[40] Initial banking and use of organoids is usually publicly funded while profits are mostly made by the private sector.[40] Drug development through usage of organoids may result in exorbitant prices and access to these novel pricy drugs may be hampered for certain groups of patients.[59]

Second, if all ties are cut, donors may have insufficient means to ensure that organoids are used in accordance with their personal identity and values. Diminished possibilities to control use of donated tissue may be relatively unproblematic if it concerns ordinary tissue that is used for uncontroversial aims. The establishment of organoids, however, can be regarded meaningful and potentially sensitive,[12,33,34,38] and organoids can be used in other potentially sensitive ways, such as chimera research or commercial use.[12,33,34,38] Svenaeus argues that if human tissues have close ties to personal identity, this may be irreconcilable with the material being part of a 'commercial biological machinery'.[32] In addition, donors lack the possibilities to positively identify with the aims for which organoids are used, or to continuously contribute to organoid banking and use (e.g. through providing updated personal information). Furthermore, far-reaching disentanglement may lead to inequality and lack of reciprocity.[40] Everyone

but the donor appears to have a financial interest in organoid technology. Although donors may not necessarily wish to share in direct financial benefits,[60] they equally lack the ability to share in non-monetary benefits, such as, the generated knowledge or clinical benefits on the shorter term. For precision medicine and regenerative medicine aims (especially autologous transplantation) coupling to patient data is indispensable. Furthermore, it is not ensured that donors/patients will gain access to novel therapies that are developed through usage of 'their' organoids (also depending on the health insurance system).[59] So relatedly, organoids cannot be used in ways that positively impact the wellbeing of donors.

In sum, disentanglement of organoids may appear to facilitate their transformation into valuable instruments for biomedical innovation. Contrarily, however, far-reaching disentanglement erodes both the instrumental and relational moral value of organoids. To stimulate biomedical innovation in organoid technology for the good of society and to foster the interests of donors, ongoing connections to donors, patients, and, society need to be established. In other words organoids need to be 're-entangled'.[4] Sound governance structures should be developed that make organoids available to the research and clinical community while giving shape to such ongoing connections.

Consent for governance

Here, we propose some necessary, but not exhaustive, ingredients for the development of ethically sound governance structures for organoid exchange. We propose a 'consent for governance' model, on which we elaborate in more depth elsewhere.[61] Consent for governance implies that the ethical justification for the exchange of organoids shifts from initial consent to continuous governance obligations, among which (1) privacy by design, (2) participant engagement, (3) benefit-sharing, and (4) ethical oversight (Table 3).[61] In the initial consent procedure donors are informed on the ways in which the governance obligations take shape in the organoid infrastructure to which they contribute.

Let us shortly elaborate on the governance obligations of our proposed 'consent for governance' model and on how these obligations contribute to ethically sound governance of organoid exchange.[61]

First, with privacy by design we refer to incorporating privacy measures in the entire infrastructure of organoid exchange, which is in line with the new EU GDPR that demands data protection by design and data protection by default.[62] This means that the most appropriate privacy standards apply by default, for instance, in coding samples, governance of IT, and data-sharing policies.[62] Privacy by design enhances the social value of organoid technology while the interests of donors can be protected. Tailored coupling

to personal data allows for the parallel use of organoids for scientific, clinical, and commercial aims. Simultaneously, the protection of the personal data of donors can be made proportionate to the application of organoids. For instance, if organoids are used by clinicians for precision medicine it is proportionate and even desirable to reveal the donor's identity. If organoids are used by commercial companies, however, coupling to basic phenotypical data will suffice and it is in the interest of the donor to remain anonymous. Furthermore, if a link to donors is upheld, they could continuously exercise control.[55]

Second, with participant engagement we mean that (groups of) donors or the wider public should be substantially engaged in the design and continuous adaptation of biobanking governance. Donors could either directly engage in the governance of organoid biobanking, or other models could be thought of, such as a deliberative or representative model. Engagement could range from informing participants to having participants in the lead.[63] Through participant engagement the interests of participants and the wider public can be taken into account, expert views are complemented, and reciprocity could be advanced.[63–65] Participant engagement may enhance the social value of organoid biobanking. For instance, projects could be prioritized that meet important health needs or address knowledge gaps and continuous contribution of participants to research or clinical projects could be facilitated.

Third, benefit-sharing encompasses the fair sharing of monetary and non-monetary benefits generated through organoid exchange among all parties involved, including donors, patients, and society.[40,66] As such, innovation in organoid technology is facilitated while the goods are distributed according to principles of justice and reciprocity. As noted before (see section 'Evaluating disentanglement of organoids'), the role of commercialization in biomedical innovation is not undisputed.[40,58] To adopt a more holistic approach to innovation commercialization strategies should be complemented with open science approaches.[58] Measures should be taken to share data, technologies, knowledge, and products generated in organoid exchange. Furthermore, the monetary and non-monetary goods ought to be justly distributed. For instance, if initial research is publicly funded while profits are yielded in the private sector, part of the profits could be reinvested in organoid research and infrastructures. Moreover, benefit-sharing measures should be taken to ensure reciprocity to donors.[65] Although donors mostly do not act with a profit-motive[60], non-monetary benefits could include the return of clinically useful results and granting access to novel therapies on grounds comparable to those supporting post-trial access to drugs. Additionally, benefit-sharing measures could take away part of the concerns that donors and the wider public have regarding

commercialization by accounting for just distributions.[60,67] As such, trust is increased, which may contribute to sustainable organoid biobanking and use.

Fourth, ethical oversight bodies should be incorporated in different stadia of organoid exchange. They can review the ways in which the above mentioned governance obligations are fulfilled. Furthermore, oversight bodies can function as an extra safeguard to ensure that the interests of all the different stakeholders, including donors and the wider public, are taken into account. They could, for instance, recognize and deal with potentially controversial use of organoids and keep oversight over commercial uses of organoids.

Consent procedure	In the initial consent procedure donors are informed on the ways in which the governance obligations take shape in the organoid infrastructure to which they contribute, e.g. the protection of their privacy, conditions for access to data and samples, regulations of property rights and commercial interests, and ethical oversight.
Ingredients for ongoing governance obligations	
1. Privacy by design	The incorporation of privacy measures in the entire infrastructure of organoid exchange. The most appropriate privacy standards apply by default, e.g. in coding samples, governance of IT, and data-sharing policies.
2. Participant engagement	The substantial engagement of (groups of) donors and/or the wider public in the design and continuous adaptation of biobank governance.
3. Benefit-sharing	The fair sharing of monetary and non-monetary benefits generated through organoid exchange among all parties involved, including donors, patients, and society.
4. Ethical oversight	The involvement of ethical oversight bodies in different stadia of organoid exchange.

TABLE 3. CONSENT FOR GOVERNANCE

CHAPTER 5

CONCLUDING REMARKS

The pressure to commercialize organoid technology and related stem cell technologies is increasing. This is in sharp contrast with the still dominant non-commercialization principle in human tissue exchange. Since human bodily materials are used as a source for the generation of organoids and other human tissue products, this leads to ethical challenges. There is an emerging body of literature that recognizes that these challenges cannot be solved when adhering to dichotomous modes of thinking of subjects versus objects and gift versus market systems.[10,11,50]

We contribute to this broader debate by proposing an alternative approach to identify, evaluate, and deal with the ethical challenges arising from the increasingly commercialized exchange of organoids (as an example of human bodily products). We propose to recognize organoids as hybrids that relate to persons, things, bodies, technology, nature and commodities in ambiguous ways. Organoids derive value and meaning from the interrelatedness of subject- and object-like values. It is the technological transformation of human biological material into organoids that establishes novel intrinsic and relational as well as instrumental and commercial value. This hybridity should be continuously recognized when organoids are exchanged. Our proposed 'consent for governance' model contributes to the responsible shaping of the increasingly commercialized exchange of organoids. It offers ingredients (Table 3) that help to fulfill the rationale for commercialization of organoid technology, that is, to stimulate biomedical innovation in organoid technology for the good of society. Simultaneously, the ingredients contribute to fostering the interests of donors and to the related adequate recognition of the relational moral value of organoids.

These ingredients, however, do not form a ready-made and one-size-fits-all recipe for ethically sound governance of organoid exchange. Different types of organoids and exchange regimes (including variable socio-cultural circumstances) may require a distinct interpretation of the ingredients. For instance, participant engagement and benefit-sharing measures will be different for patients with CF that 'donate' their organoids at the verge of research and care, than for healthy donors whose blood samples are transformed into iPSCs and gastruloids to model human development. In the former case, substantial engagement of participants as well as benefit-sharing measures aimed at individual donors may be needed. In the latter case, donors may be less interested in substantial engagement in the governance of 'their' organoids. It may be sufficient to put in place ethical oversight bodies that guard the moral value of gastruloids and that ensure a just societal distribution of benefits.

Further theoretical and empirical inquiry should shed light on the hybrid moral value specific to different types of organoids and other human bodily products. Equally, we call for further theoretical and practical elaboration of our consent for governance model and other models that evade the dichotomies of gift vs. market. This we feel is necessary to allow for responsible innovation and clinical translation in the increasingly commercialized biotechnological field.

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CHAPTER 5

APPENDIX: THE BANKING OF GUT ORGANOIDS OF PATIENTS WITH CYSTIC FIBROSIS (CF) FOR PRECISION MEDICINE

Background on organoid technology and Cystic Fibrosis

Cystic Fibrosis (CF) is a severe hereditary disease that leads to predominantly lung and intestinal problems and results in a limited life expectancy. Previously only symptomatic treatment was available. However, recently novel drugs have been developed that target the underlying cause of the disease: a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein that affects the ion channels of cells and is caused by ~2000 different mutations in the related CFTR gene.[20,44] Nevertheless, it remains hard to predict which patients benefit from these costly drugs and there are numerous patients with rare mutations still awaiting proper treatment options. Organoid technology can aid in developing treatment strategies for all patients with CF.[20]

Rectal biopsies of patients can be transformed into gut organoids in a dish. Because of their genetic and functional resemblance to the individual patient, they constitute a strikingly accurate and personalized model for disease. This allows for studying the disease mechanisms as well as personalized and large-scale drug testing and development with the use of a so-called swelling or CFTR assay. If a treatment is effective the improved function of the CFTR protein causes the transportation of ions and fluid into the lumen which results in swelling of the mini-gut. The CFTR assay was developed by Dutch researchers.[20,21]

Here, we will outline a hypothetical scenario of an 'organoid journey' to illustrate how rectal biopsies of patients with CF can be transformed into gut organoids, acquire different meanings and value, become of interest to multiple parties, and move through gift and market discourses. Although the scenario is fictitious, it reflects a potential real-world journey.[12]

Gut organoids: from patient to biobank

Jasper is a 25-year old Dutch patient with CF. Recently, despite symptomatic treatment such as physiotherapy exercises and antibiotics, his lung function is declining which affects his ability to study and exercise. During his periodical out-patient visit to the CF center his treating physician mentions the possibility to participate in a new study called the 'Rainbow project' in

which rectal biopsies of patients with rare mutations are used to generate mini-guts and test several existing and novel drugs.[68] If there is a positive response in the patient's mini-gut, the drug will be tested in the patient. Jasper is positive about participation, because this may open up new avenues for treatments.

During a follow-up conversation with the research nurse the details of the rectal biopsy procedure and the project are elaborated on and Jasper's consent is sought for participation. Simultaneously, the research nurse asks consent for storage in the Hubrecht Organoid Technology (HUB) biobank.[54] She explains that biobank storage enables longitudinal use of the mini-guts for CF research as well as drug testing and development. Jasper receives a detailed patient information letter on the conditions for biobank storage.[12] These include the notification that the biobank (a non-profit organization) may grant access to commercial parties. Donors cannot claim any ownership in nor share in any future financial benefits flowing from the products that these companies develop. Jasper decides to consent to biobank storage, even though he finds it uncomfortable that his mini-guts can be endlessly used by others without his knowledge and he is ambiguous about commercial use. However, he considers it to be a waste if his mini-guts are destroyed after closure of the Rainbow project and he trusts his physician.

After Jasper's consent his tissue is procured through a rectal biopsy procedure in his treating hospital. The specimen is coded and transported to the laboratory of the principal investigator of the Rainbow Project. A postdoctoral researcher isolates adult stem cells from the specimen and puts these into a petri dish containing the right culture medium. Within 7 days the stem cells start to grow and expand and self-organize into 3D intestinal structures: gut organoids. These gut organoids are stored in the freezer until the drug testing starts. A couple of months later the inclusion is complete and the researcher tests ~900 FDA approved drugs in high-throughput plates on the gut organoids of over 120 patients with CF. The research team aims to validate the organoid screening model and to repurpose existing drugs for treating CF patients with rare mutations.[68] Apart from these academic aims they schedule periodical meetings with the clinicians to discuss the findings that may be of clinical relevance in the course of the Rainbow Project. During the periodical out-patient visit Jasper asks for the results on his organoids. Unfortunately, no response to existing drugs has been found during the Rainbow Project. Nevertheless, Jasper is hopeful that drugs will be found for him in the future. After all, his mini-guts remain stored in the biobank.

Simultaneously, the HUB distributes CF organoids nationally and internationally. The HUB is a so-called living biobank that aims to culture, collect, store, and distribute organoids from patients with various diseases

including CF and cancer.[54] The HUB holds the intellectual property on organoid technology and distributes organoids to academic and commercial parties with objectives ranging from fundamental research to drug development. The CF organoids are for example used by academic parties to investigate disease mechanisms and gene-editing approaches. They are stripped from identifiers and transported to international companies (including overseas companies) to screen candidate drugs for CF.

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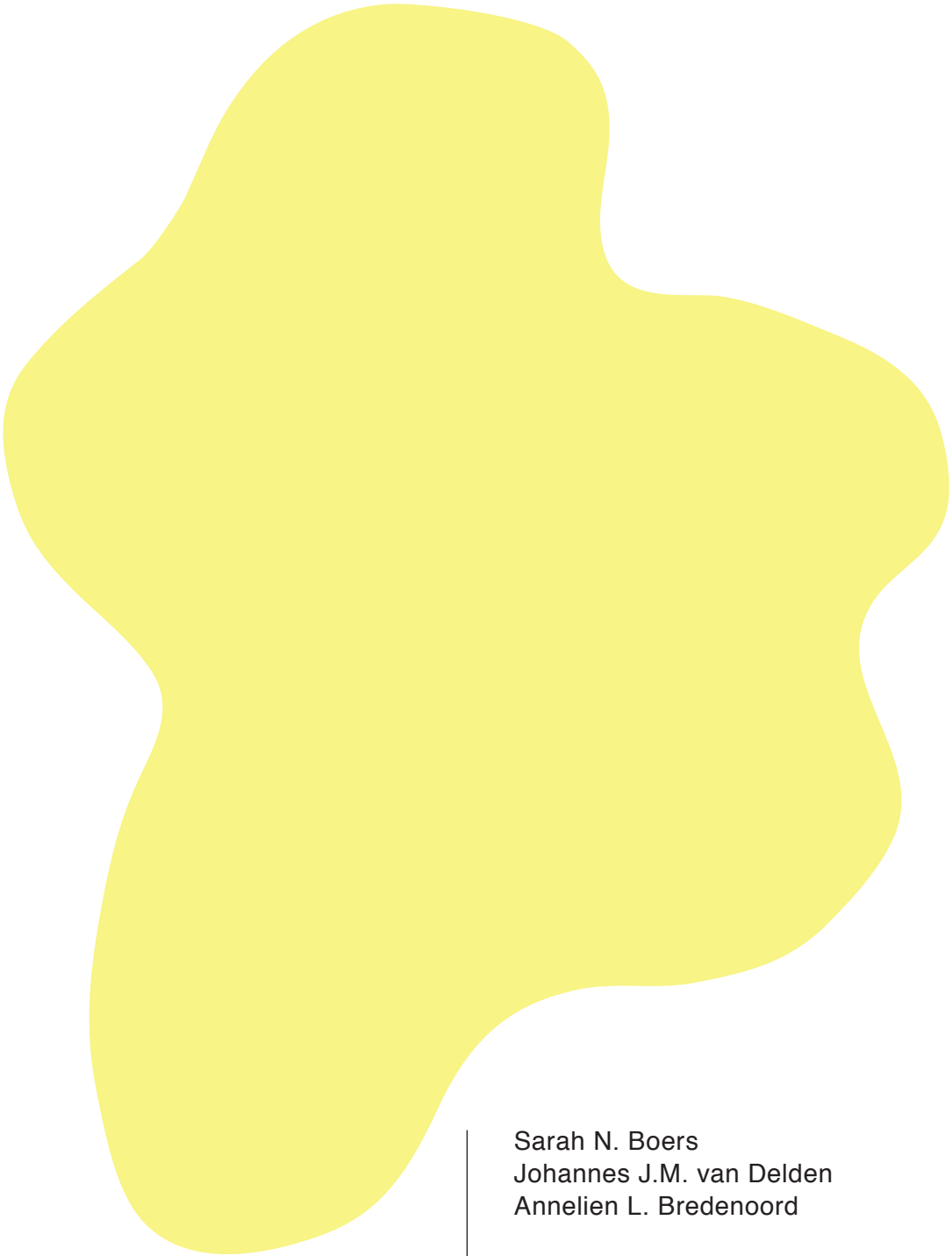
Part III

Formulating conditions for the exchange of organoids and related human tissue products

CHAPTER 6

Broad consent is consent for governance



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ABSTRACT

In the context of biobanking we propose to understand broad consent as consent for governance. Whereas it is impossible to inform donors about the specific study details, it is possible to inform them on the governance structure specific to the biobank. Consent for governance enables autonomous decision-making by informing donors on the governance structure of the biobank in question, together with its inherent risks and benefits. In addition, it allows for a discussion among stakeholders focused on the elements that are necessary for solid and adaptive governance. It thereby stresses that biobanking is a research enterprise aimed at promoting the health of the collective, rather than the individual. We emphasize that the engagement of participants as stakeholders in designing and continuously adapting governance procedures is a prerequisite, since broad consent for governance is based on transparency and trust.

BROAD CONSENT: FROM CONTENT TO CONTEXT

In recent years, novel types of consent have been proposed for research with biological samples, one of these being broad consent. The exact scope, justification, and definition of broad consent have been topics of ongoing debate. In their article, Grady and colleagues propose to define broad consent as 'consent for an unspecified range of future research subject to a few content and/or process restrictions'.[1] In doing so, they make a noteworthy departure from the conventional definition of broad consent, being 'permission for a broad range of research purposes that were not specified at the time of recruitment'[2] by adding that broad consent is paired with ongoing oversight of research.[1]

Nevertheless, their proposal seems to hinge on two ideas. On the one hand, they hold on to the traditional idea of informed consent by focusing on research content, namely that the individual should be informed on the type of research that will be conducted, together with the estimated risks and benefits.[2] On the other hand, they emphasize research context, such that donors should be informed on the ethical oversight procedures and the process restrictions. However, the latter is still secondary in their definition of broad consent.

Although we recognize the importance of both levels of information within consent (i.e. research content and context), we suggest shifting the focus even more toward context and understanding broad consent as consent for governance. This implies that the broad consent procedure is aimed at providing the donor with information on the governance structure of the biobank in question. Indispensable to this approach would be to design a solid and adaptive governance structure that protects the interests of the wide variety of stakeholders that are involved.[3]

ADVANTAGES OF BROAD CONSENT FOR GOVERNANCE

Some authors have criticized broad consent as merely being consent for governance.[4] We argue quite the contrary, namely, that understanding broad consent as consent for governance can lead to a meaningful perspective on consent within biobanking.

First, Grady and colleagues already mention some arguments that endorse our point of view. They state that empirical studies have shown that potential donors would want to indicate whether their samples can be used for research, but that the majority say that 'their willingness to [participate] is not affected by the specific details of the future research'.[1] This argument could indeed be put forward to support a shift from specific consent to broad consent for a wide scope of future use. However, it could also endorse a departure from a focus on research content, since apparently that is not what is most important to potential donors. In addition, Grady and colleagues refer to empirical studies showing that 'individuals are reassured that their interests will be protected when oversight mechanisms are in place to review proposed research'. Furthermore, they propose that the initial consent form should contain information about data and sample handling and on the ethical oversight processes.[1]

Second, although it is impossible to inform donors about the specific study details, it is possible to inform them on the governance structure specific to the biobank. This approach enables autonomous decision-making because it clearly displays what information can and what cannot be provided and foreseen. In addition, information on estimated risks and benefits is provided, albeit the risks inherent to the governance structure (e.g. data handling and sound ethical oversight), instead of to the specific study. A prerequisite would be the possibility for participants to receive up-to-date information on the conducted research and governance policies and the opportunity to withdraw.[5] As such, donors could act in accordance with their values and beliefs, particularly when it comes to sensitive or controversial research.[6]

Third, an emphasis on governance allows for attention and discussion on those issues that are essential within biobank research. Currently, there is much debate on the amount of information regarding possible future uses that a donor should receive. The dialogue among different stakeholders, however, should mainly be on the elements of a governance structure that is sustainable and able to adapt to changing circumstances,[3] while balancing a donor's interests with the interests of researchers and society.

Fourth, consent for governance stresses that a biobank is primarily aimed at conducting research that might promote the health of the public.[2] Developing a robust governance model could promote collective interests through the development of structures that enable data and sample sharing. Global collaboration could result in an efficient and effective use of time and resources.[4] Nevertheless, the rationale of the public good should not be taken for granted.[2] Therefore, research should be prioritized and only research with sufficient anticipated social value should be granted permission.

Fifth, we aim to encourage substantial engagement of participants in the design and continuous adaptation of governance procedures within biobanking.[3,4] Participants could, for instance, be involved in developing criteria for ethical assessment and oversight. After all, consent for governance is based on trust. This also poses a responsibility for researchers to handle samples and data in a morally responsible manner. An active governance model that engages participants can prevent broad consent from becoming a means that mainly protects researchers and institutions instead of donors.

BROAD CONSENT FOR GOVERNANCE: PROCEDURE

Here we suggest some ingredients to serve as a general outline for the consent procedure of broad consent for governance. We recommend that consent forms address that donors consent to a specific governance model because the future scope of research is unknown.

Ethical oversight

We agree with Grady and colleagues on their general proposal for ethical oversight. It should be clear what oversight body is put in place, what their conditions are for the use of samples, and which limitations to research uses are formulated.

Property rights and commercial interests

It should be clear who is in charge of the management of the biobank and whether the biobank is privately or publicly funded. In addition, the policy on property rights should be elucidated. This encompasses, among others, policies on intellectual property rights (IPRs), material transfer agreements (MTA) and on the property rights of the donor. Usually, donors are not granted any property rights; however this should be clarified in the broad consent form. Further collaboration with commercial parties should be disclosed.

Data and sample management

There should be definition of how data and samples are stored, whether and to which personal information samples are linked, and whether there is a central database or record that allows for data and sample sharing. It should be made explicit which parties have access, on what conditions and how

competition among researchers in cases of scarcity is settled. In addition, the policy on coding of personal information and the privacy safeguards that are put in place should be addressed. Furthermore, the mechanisms for quality control of the samples could be described. Moreover, it is important to address the duration of sample storage and the policies after the death of a donor.[7]

Communication with donors

The broad consent form should be clear on the communication policies toward donors. They should receive information on the disclosure of aggregate and individual research results. Furthermore, it ought to be clarified by which means donors remain informed of ongoing and novel research activities, how and whether they can withdraw, and whether re-consent can be sought. If the biobank aims at an active involvement of donors, this should also be explained.

Research content

Where possible, the aim of the biobank should be disclosed, for example, to distinguish between a population-based or a disease-specific biobank. In addition, if the use of innovative approaches is already foreseen, like whole-genome sequencing or stem-cell technology, this should be clearly addressed.

CONCLUDING REMARKS

In the context of biobanking we have proposed to understand broad consent as consent for governance. Whereas it is impossible to inform donors about the specific study details, it is possible to inform them on the governance structure specific to the biobank. Consent for governance enables autonomous decision-making by informing donors on the governance structure of the biobank in question, together with its inherent risks and benefits. In addition, it allows for a discussion among stakeholders focused on the elements that are necessary for solid and adaptive governance. It thereby stresses that biobanking is a research enterprise aimed at promoting the health of the collective, rather than the individual. We emphasize that the engagement of participants as stakeholders in designing and continuously adapting governance procedures is a prerequisite, since broad consent for governance is based on transparency and trust.

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CHAPTER 7

Consent for governance in the ethical use of organoids

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20: 647-645

CHAPTER 7

ABSTRACT

Current advances in biotechnology open unprecedented possibilities to transform human tissues into complex, valuable tissue products, such as organoids. Here, we propose consent for governance as a leading paradigm for the derivation, storage, and use of complex human tissue products to ensure adjustment to changing ethical requirements.

INTRODUCTION

Rapid progress in biotechnology means that the human body increasingly becomes a source for the creation of complex bodily products, such as immortalized stem cell lines, stem cell-derived gametes, and synthetic embryo-like structures.[1–3] One specific example is the possibility to culture human pluripotent and adult stem or progenitor cells into self-organizing three-dimensional tissue structures in vitro that closely resemble the architecture and function of real-life human tissues.[4] These so-called organoids are highly promising for a wide variety of scientific and clinical purposes, such as developmental biology, disease modelling, drug development, and precision and regenerative medicine.[5,6]

The possibility to create complex human tissue products, such as organoids, challenges the dominant approaches in research ethics, in which the use of human materials is justified by either obtaining a donor's consent or by anonymization of the material.[7] The creation of complex human tissue products means that new value is generated out of 'ordinary bodily material'. Human materials are transformed into biotechnological artefacts with considerable scientific, clinical, and, not unimportantly, commercial value.[8,9] Consequently, the tissue products become of interest to various parties, among them donors, patients, researchers, and companies. These complex products may subsequently acquire distinct types of moral value, particularly if they resemble human tissues for which research use is ethically controversial, such as human embryos.[10] The traditional 'consent or anonymize' approach is insufficient to manage the complex scheme of values and interests that pertain to complex human tissue products. Additionally, it does not fit the current scale and complexity of the increasingly commercialized human tissue and data infrastructures.

In this Commentary, we therefore propose consent for governance as leading paradigm for the derivation, storage, and use of complex human tissue products. We use organoids as the main example, as they are anticipated to impact the entire biomedical innovation cycle, ranging from basic research at the bench to precision medicine applications. Although organoids resemble other complex human tissues products in many ways, the public and commercial attention that organoids receive and the high expectations that are placed on this type of research make them an important showcase to discuss ethical use of complex human tissue products.[4,11]

CHAPTER 7

IN FAVOUR OF CONSENT FOR GOVERNANCE

The traditional approach for the ethical use of human (residual) tissue and data is the so-called 'consent or anonymize' paradigm, which implies that donor consent is not required if human materials or data are completely anonymized.[7] This approach has, however, been criticized as unfit for the current developments in biotechnology, which result in increasingly complex and sophisticated human tissue research and data analytics. First, the development of immortalized human stem cell lines, such as induced pluripotent stem cells, has already shown that, although tissue research may constitute minimal physical harm, donors may have interests in their tissue that include and go beyond privacy interests.[12] Second, in this era of big data research and high-throughput genomic sequencing, individuals who donate tissues or data are better identifiable than ever. This issue has led to the discussion whether 'anonymity' should be a category at all when deciding on how to obtain and use human tissue samples.[7] Hence, we propose that in stem cell research and in particular for organoid technology, we should no longer consent or anonymize, but rather ask for consent and provide some sort of privacy enhancing measures.[12–14]

A focus on research context when obtaining consent

Despite a broad consensus on the necessity of some types of donor consent, there is ongoing debate regarding the appropriate type of consent.[13,15,16] Although an in-depth review of the different proposed consent types is beyond the scope of this Commentary (see Text Box for consent models), most consent models differ in terms of the scope of future use that donors consent to, ranging from research limited to demarcated projects to an unspecified range of biomedical research purposes.[15,17–19] What these different consent types have in common is an emphasis on the content of future use; in other words, the type of research that will be conducted. Furthermore, the burden of moral justification for the use of human tissues usually lies in the initial consent procedure. We propose to shift the focus of the consent procedure from the content to the context of future use, and to shift the ethical emphasis from initial consent to ongoing governance obligations, so-called 'consent for governance'. Rather than consenting to an unspecified range of biomedical research purposes, we propose that donors should consent to contributing to an infrastructure that is subject

to certain governance conditions – the *context* of research.[19] This shift from content to context will be explained in 'Elements of consent for governance'.

Three developments in biotechnology underline our proposal. The first is a shift from small-scale human tissue research projects to large-scale, longitudinal, complex infrastructures that combine human data and tissues for use in various, unforeseen ways. Some sub-types of organoids can, for instance, be immortalized and stored in living biobanks,[20] coupled to data platforms, and distributed globally.[6,21] The second biotechnical development is the increased possibilities for transforming 'ordinary' human tissues into complex human tissue products that acquire new scientific, clinical, and moral values.[1–4,9,10,14] Intestinal organoids generated out of rectal biopsy material of patients with cystic fibrosis, for instance, can be of interest to researchers and companies as a disease model or platform for drug development.[6,22] Simultaneously, if applied in the realm of precision medicine, intestinal organoids – being genetically and functionally similar to the donor – can directly impact the personal care of patients with cystic fibrosis.[11] Intestinal organoids can also be experienced by donors as an entity with close ties to their personal identity and values.[23] Furthermore, they can give rise to future sensitive applications, such as chimaera research. Another example is the creation of brain organoids out of induced pluripotent stem cells generated from ordinary skin cells.[3,24,25] Although brain organoids are far from functioning human brains, they raise questions about the desirability of 'creating life in a dish', particularly if future possibilities for sensory input and output increase.[24] Third, the biotechnology field in general, and organoid technology in particular, also has tremendous commercial value.[8,9,26–28] Although commercialization has advantages for the field, as it increases overall investment and enhances the translation from basic research into clinical products that benefit patients and society, it is paired with ethical challenges and is known to raise public concerns.[8,29]

These three developments have implications for the ways in which we should ensure that the use of complex human tissues is ethically sound. To adequately balance the values and interests of donors and patients with those of researchers, companies and society as a whole, initial donor consent (although necessary) is not sufficient. Instead, governance measures should be installed that ensure the design of fair and ethical human data and tissue infrastructures. We will provide some examples of elements necessary for such fair infrastructures below. During the initial consent procedure, donors should be informed on the governance measures put in place, such that they can judge whether they consider the infrastructure to which they contribute to be sufficiently fair and in line with their values and interests. Consent for governance means that initial consent is conditional on the design of a

TEXT BOX: CONSENT MODELS

Specific consent
Donors or participants give consent for the use of materials for each specific future study and for every different type of research method or question that will be conducted with the obtained tissue.[13]

Tiered consent
Donors are given a set of choices and are allowed to choose among several options to give them greater control of the use of their biological samples and medical and genomic information. They could, for example, indicate that their samples may be used for all types of studies except those using human embryos or using whole genome sequencing methods.[18]

Dynamic consent
A personalized digital communication interface that facilitates long-term and two-way communication between participants and researchers. Dynamic consent can take specific forms. For example, it can entail a very concrete information and communication technology platform where donors can log in and communicate with researchers about research results, consent preferences and unsolicited findings, but is also a wider concept that stimulates participant engagement.[16]

Broad consent
Consent for an unspecified range of future research questions and methods with specified content and/or process restrictions. Broad consent is less explicit than specific consent (for example, consent for each use), but more narrow than open-ended permission without any limitations (for example, blanket consent).[15]

Blanket consent
Donors give consent to use their samples for future research with no limitations and without any restrictions. This means that all types of studies and research questions can be studied when this type of consent has been obtained.[15]

Opt-in
Explicit donor consent is solicited before samples can be used for scientific research.[30]

Opt-out
Donor consent is implied, unless the donor objects. This means that samples can be used for research unless donors have explicitly refused to use their biomaterials.[30]

governance structure that protects the long-term interests of the donors as well as the wide variety of other parties that are involved.

ELEMENTS OF CONSENT FOR GOVERNANCE

The following section outlines the type of information that should be included in the initial consent for governance procedure. In addition, we provide a non-exhaustive list of suggestions for ongoing governance measures that could be implemented to ensure that the long-term interests of donors are balanced with those of the various other parties involved.

Initial consent procedure

The initial consent procedure is broad, because donors do not consent to a specific research project. Our proposal for consent for governance, however, departs from common interpretations of broad consent that define it as giving permission for a wide range of biomedical research purposes that cannot be specified at the time of recruitment.[15,31] Rather than consenting to an unspecified range of biomedical research purposes, we propose that donors should consent to contributing to an infrastructure that is subject to certain governance conditions – the context of research.[19] Therefore, information should be provided about these governance conditions during the consent procedure, such as the management of data and samples, property rights and commercial interests, ongoing communication with donors, and ethical oversight.[19] If possible, information on foreseeable research projects or procedures should be provided, particularly if certain procedures are foreseen that are known to be sensitive, such as whole genome sequencing or chimaera research.[12]

Protection of privacy

A second element that should be considered and discussed when obtaining consent is the protection of donor privacy. We argue that complete de-identification of organoids is neither possible, as outlined previously, nor desirable.[14] Although complete de-identification was originally meant to protect the interests of donors, it seems to have transformed into a means to protect the interests of third parties, such as researchers and companies. Once third parties have ticked the boxes of consent and complete de-identification, they are granted more flexibility regarding distribution, use, and commercialization of human tissues. On the other hand, the donors

are effectively left without any measures to manage downstream use of their samples, as even withdrawal is hampered.[32] However, donors may have legitimate wishes to control the use of the organoids derived from their tissues,[23] for example, to change their preferences regarding the return of relevant research results or the types of studies conducted with their samples. In addition, complete de-identification makes organoids scientifically less useful, as it impedes the coupling of organoids with phenotypical data. Furthermore, for precision medicine applications of organoids that further affect the clinical care of patients, as is already the case for cystic fibrosis, a link between the samples and personal data has to remain.[6]

Therefore, rather than focusing on the type of sample anonymization, we propose a shift towards enshrining privacy measures in the entire sample and data infrastructure. This proposal would be in line with the new EU General Data Protection Regulation that demands data protection by design and data protection by default.[33] To comply with this regulation, researchers and research institutes would need to implement appropriate technical and organisational measures to ensure that, by default, only personal data that are necessary for each specific purpose are processed. The obligation applies to the amount of personal data collected, the extent of their processing, the period of their storage, and accessibility. In other words, researchers would take into account privacy and data protection at every step of the research enterprise. The most appropriate privacy standards would apply by default, for example in coding samples, governance of IT systems, and data-sharing policies.

Participant engagement

A third element concerns the engagement of donors and the wider public in the governance of organoid biobanks. There is a growing consensus that substantial engagement of these groups in the design and continuous adaption of biobanking governance structures is necessary for various reasons, such as epistemic (the expert view is incomplete), intrinsic (to foster reciprocity and donor interests in what happens with their tissues) and instrumental reasons (to strengthen public trust).[34,35] The desirable level of engagement depends on the case and context, and may range from informing patients about planned, ongoing, and finalized projects, to consultation, advisory roles, partnership or, ultimately, to a project in which patients have a leading role.[35] A higher level of engagement may be necessary if: commercial interests are prominent, the organoid biobank may yield clinical benefits for participants, organoids are used for controversial aims (for instance, chimaera research or commercial applications), or there

are potentially controversial types of organoids generated (for instance, brain organoids).

Benefit-sharing

Although increasing commercialization of the organoid field may bring about both scientific and clinical applications for organoids, it also challenges social justice.[36] One of these challenges is the risk of unequal distribution of benefits. Whereas donors and patients altruistically donate their tissues without any claim to profits, third parties such as researchers and companies may acquire property rights and yield profits.[36] Although the initial banking and use of organoids is frequently publicly funded, profits are often made by the private sector. In related fields, such as human genetic research, this apparent inequality has led to growing appeals to the concept of benefit-sharing, which entails the fair sharing of monetary and non-monetary benefits among all parties involved, including donors, patients, and society.[36–38] To ensure justice and reciprocity, the concept of benefit-sharing should be extended to organoid research and benefit-sharing measures should be enshrined in the governance of organoid infrastructures, such that public-private partnerships are shaped responsibly.

Here, we give some examples of benefit-sharing measures that can be implemented at the level of individual donors, groups of patients or donors, and at a societal level. First, benefit-sharing with donors and patients should include the return of individual results that are of clinical relevance. Second, if organoids are used for drug-testing purposes, pro-active measures (e.g. negotiation of reimbursement and fair pricing of drugs) could be taken to ensure that patients will have access to innovative therapies. Third, private profits could be reinvested into the public sector to build sustainable infrastructures for organoid storage, distribution, and use. Furthermore, efforts should be made to follow the increasing appeal by governments, science funders and universities to open science and make knowledge and data publicly available when yielded in projects that are (partially) publicly funded.[39] Lastly, the role of patents deserves consideration. Whereas patents can stimulate innovation, they can also lead to restricted use, disproportional profit making, lack of transparency, and the impediment of dissemination of organoid technology and its products.[40] To stimulate innovations in the organoid field that have social value, certain conditions for patenting could be formulated that contribute to ethical licensing.[41]

Ethical oversight

A final element is full clarity and transparency about the type of oversight body that is put in place. Rigorous review of organoid study protocols by a research ethics committee on submission to a biobank, combined with

access requests for organoids and/or data, privacy protection, participant engagement, benefit-sharing and ethical oversight, would add to the ethical and scientific quality of organoid research. Existing research ethics committees that assess the participation of human research participants and/or the procurement of human tissues in research may suffice for the assessment, as long as appropriate expertise is available to ensure that the committee is capable of evaluating the unique aspects of the science. Special attention could be paid to the type of organoid research and commercial arrangements. The International Society for Stem Cell Research provides template documents for consent forms that can be customized for organoid derivation and research.[42]

CONCLUDING REMARKS

Organoid technology exemplifies broader biotechnological advances that allow the generation of complex human tissue products that are derived, stored, and used within increasingly commercialized infrastructures. We propose that consent for governance should be obtained from tissue donors instead of more traditional consent models, to ensure that organoid research can thrive and reach its full potential in an environment in which the values and interests of all the parties involved are adequately balanced. Consent for governance entails an initial consent procedure that provides donors with information on governance and shifts the ethical emphasis from initial consent to ongoing governance obligations, which include protection of donor privacy, participant engagement, benefit-sharing, and ethical oversight. Our proposal of consent for governance is of relevance for all research fields in which complex human tissue products are used. More research is needed to further develop the elements of fair governance structures, which should include further inquiry into the preferences and interests of donors, patients, and the wider public.

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CHAPTER 8

Postmortem disculosure of genetic information to family members: active or passive?

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CHAPTER 8

ABSTRACT

Advances in next-generation DNA sequencing (NGS) now make it possible and affordable to sequence the entire genome of an individual. Routine clinical application is on the horizon. There is a consensus that some subsets of genetic information should be disclosed to patients, but disclosure to their relatives is less consensual. This issue becomes especially salient after a patient's death, when permission can no longer be sought. There has however been little debate on postmortem disclosure. We identify and explain the arguments in favour of and against disclosure of genetic information to the relatives of a deceased patient. We conclude that there are valid reasons to communicate some subsets of genetic information to family members after death, and we propose a passive postmortem disclosure policy.

DISCLOSURE DILEMMAS AFTER DEATH

Advances in next-generation DNA sequencing (NGS; see Glossary) have now made it both feasible and affordable to sequence the entire genome of an individual. Routine clinical application is on the horizon.[1–3] Sequencing the complete exome or indeed the whole genome of a patient generates an overwhelming amount of data, yielding both solicited and unsolicited findings. The unequalled quantity of data, and the wide variation of validated and non-validated, highly and poorly predictive and more or less probabilistic data, leads to ethical, legal and counseling challenges that surround the feedback of individual genetic information.[1,4–6]

There is now consensus that at least some subsets of genetic information should be disclosed to patients[1,4–6] (i.e. clinically relevant and actionable genetic aberrations), but communication to family members of genetic information about hereditary risk is less consensual. Individuals share a significant fraction of their genomic sequences (biological) relatives. At-risk family members may therefore have a legitimate interest in also receiving results, especially if genetic information is available which may have a bearing on their own health. Disclosure of genetic information to family members becomes especially salient when patients have passed away, and permission can no longer be sought.[6–10] In this paper we identify and explain the potential arguments in favour of and against postmortem disclosure to relatives of the deceased (Table 1). We examine whether genetic information should be disclosed, and argue in favour of a passive postmortem disclosure policy.

Arguments for disclosure	**Arguments against disclosure**
Beneficence	A relative's right not to know
The duty to warn relatives	Nonmaleficence
Fostering the autonomy of relatives	Respect for a deceased's wishes as expressed in life
The familial nature of the human genome	Respect for a deceased's (genetic) privacy and confidentiality
	Disclosure is not feasible

TABLE 1: ARGUMENTS FOR AND AGAINST POSTMORTEM DISCLOSURE TO RELATIVES

GLOSSARY

Beneficence: the duty to do good.
BRCA1/BRCA2: two genes regularly screened for inherited forms of breast/ovarian cancer. Both are tumor-suppressor genes, and mutations in both are associated with increased risk of these cancers.
Biological relatives: persons who, to a significant extent, have a shared genetic structure.
Disclosure: communication of genetic and/or genomic information to patients or family members of patients or deceased patients.
Exome: genetic information limited to the sequences of protein-coding genes in a genome. The protein-coding genes lie within exons, which constitute about 1% of the whole genome.
Genome: the entire set of genetic instructions found in a cell. In humans the genome consists of 23 pairs of chromosomes in the nucleus, as well as a small chromosome in the mitochondria. Taken together, these chromosomes contain approximately 3.1 billion bases of DNA sequence.
Multiple endocrine neoplasia syndrome type 2a (MEN2A): an autosomal dominant predisposition to tumours of thyroid C cells (medullary carcinoma), adrenal medulla (pheochromocytoma), and nodular hyperplasia of parathyroid glands.
Negative autonomy: an individual's right to make his/her own decisions without interference or coercion from others.
Next-generation sequencing (NGS): also known as high-throughput sequencing, NGS describes a number of modern sequencing techniques that sequence DNA and RNA much more quickly and cheaply than the formerly used Sanger sequencing.
Nonmalifecence: the prevention or avoidance of harm.
Positive autonomy: an individual's ability to take control of his/her own life and to be able to fulfill their own values and beliefs.
Postmortem disclosure: revealing genetic and/or genomic information to family members of deceased patients.
Privacy: an individual's personal autonomy that makes him/her master of all those facts about their own identity. A patient's right to privacy follows from respect for a patient's autonomy.
Solicited findings: genetic variants searched for in a clinical or research context.
Unsolicited findings: collaterally obtained byproducts outside the targeted scope.

ARGUMENTS IN FAVOUR OF POSTMORTEM DISCLOSURE

Beneficence

A first argument to support disclosure of genetic information to the family members of a deceased patients is the principle of beneficence.[4,8,11] Disclosure could promote the health or well-being of a relative if treatment or prevention for the hereditary condition is available.[7,8,12–15] Awareness of a *BRCA 1/2* mutation, for instance, could enable affected relatives to opt for prophylactic surgery to prevent development of breast cancer.[6] Furthermore, a genetic diagnosis could have psychological benefits, such as in understanding the origin of a particular disease that has a high frequency within the family (e.g. colon cancer).[15,16] However, the positive duty of beneficence towards relatives cannot be limitless, and must be demarcated.[17,18] One cannot expect physicians to promote the well-being of relatives of their deceased patients limitlessly because, for example, this would interfere with their primary tasks.

The duty to warn relatives

The second argument in favour of postmortem disclosure is the duty to warn. Some argue that physicians have a duty to warn family members of hereditary disease risk, provided that particular conditions are met: the clinician should take reasonable actions to disclose genetic information to relatives if that information encompass a condition potentially leading to serious, imminent and actual harm, and for which treatment or prevention is available.[19–21] Multiple endocrine neoplasia type 2a (MEN2a) is one such condition– prompt detection of thyroid cancer in individuals with this syndrome can lead to early treatment, whereas late detection frequently leads to incurable disease.[22]

It could be said that the duty to warn relatives surpasses a patient's death.[20,21] During life it is generally considered sufficient for a physician to encourage patients to inform their relatives of hereditary risks.[3,19] However, after their death this is no longer possible, and it could be argued that a clinician's moral obligation then becomes stronger, particularly if genomic data only become available after a patient's death.[8,23] Nonetheless, the duty of the physician to warn the relatives of the deceased is again not without qualification because confidentiality and feasibility must also be taken into consideration.[19,24]

Fostering the autonomy of relatives

Postmortem disclosure may foster the positive autonomy of family members, and this provides the third argument in favour of disclosure. Genetic information could facilitate the management of the health of relatives and of their children, may contribute to reproductive decision-making, and could influence the way they choose life projects or approach life planning.[4,25,26] Furthermore, they could derive existential meaning from knowledge on their genetic make-up.[27] Fostering autonomy through disclosure surpasses the mere promotion of well-being, because disclosure enables relatives to take (some) control of their lives.[17,28] Nevertheless, the extent to which physicians have a responsibility to promote the autonomy of the relatives of the deceased remains a point of contention. It may be unduly exigent to require a physician to promote the autonomy of a relative with whom no clinical relationship is present.

The familial nature of the human genome

The fourth argument in favour of postmortem disclosure regards the familial nature of the genome. Although human beings share 99,9% of their DNA, each person has a unique arrangement of 3 billion base pairs.[29] A significant fraction of that package is shared with first-degree relatives. This biogenetic kinship defines family by the sharing of genes. In some cases, blood samples from relatives may be necessary to diagnose patients at risk of genetic disease. Moreover, the specific medical diagnosis of a patients can have a profound health impact on close relatives.[29] The enrollment of an individual in NGS testing could even cause harm to relatives.[26,30]

In view of these considerations, some have argued that the sequence of the genome could be considered to be familial in nature. It has even been argued that DNA is 'shared property' with biological relatives.[12,31,32] As a consequence, it is argued that the biological relatives of the patient should be able to access the patient's genetic information so as to identify their own health risks or verify the existence of a genetic disease.[12,25,33]

However, regarding the genome as shared familial property brings some difficulties. First, it would require outlining the biogenetic family. What 'degree of relatedness' (i.e. first degree, second degree, etc.) would a person need to have with a family member to take part in the 'shared possession'? Second, viewing DNA as shared property would imply a need to request for consent from the wider family.[26] This would raise numerous ethical, counseling, and practical challenges, and might even bring participation in NGS testing into question. Third, the autonomy of the patient is challenged. To consider DNA as 'shared property' risks restricting the autonomous decision-making of the patients and perhaps also of his/her relatives.

Therefore, the genome should not be regarded as 'shared property', but nevertheless the familial dimension of DNA must be taken into account when considering postmortem disclosure.

ARGUMENTS AGAINST POSTMORTEM DISCLOSURE

A relative's right not to know

A first argument against postmortem disclosure is the potential violation of family members' right not to know.[34,35] Some people do not wish to be informed of their genetic status. For example, only 50-75% of first-degree female relatives of an index patient with a known *BRCA1/2* mutation want to be tested.[36–38] Although the right not to know is a contested matter, there are different conceptions of this right, including the autonomy-based approach and the privacy perspective.[34,35] The autonomy of a relative may be jeopardized if information is disclosed against a prior expressed wish to not be informed.[34,35] Even if family members are unaware of the availability of genetic information, unsolicited disclosure could still fail to respect their autonomy, because they were not given an opportunity to make an autonomous choice to not receive information. That is, they could not exercise their right not to know.[34] From a privacy point of view, unsolicited disclosure could violate a state of privacy (i.e. a state of ignorance).[35] As some have suggested, it is more appropriate to speak of an individual's interest in not knowing, rather than of a right.[35] A relative's interest in not knowing should be balanced with other concerns, such as the potential beneficial effects of disclosure.

Nonmaleficence

A second argument against postmortem disclosure is the principle of nonmaleficence. Disclosure could cause psychological, social, financial and existential harm to family members.[17,23,25,39,40] Although a majority of these harms only occur after the identification of a pathogenic mutation in a family member's own genome, they can nevertheless count as being dependent on disclosure. Even though these harmful consequences have been suggested many times, current empirical support is limited.[15,41,42] In addition, psychological harm is very dependent on the type of genetic information and the counseling procedure.[16] Denying disclosure, by contrast, could also have harmful consequences, especially if results are relevant to relatives to facilitate prevention or treatment.[25] In addition to possible

harmful consequences for relatives, harm could be said to be inflicted upon the deceased patient by breaching confidentiality through unconsented disclosure. However, as with autonomy, it is not possible to harm the deceased.[40] It is only possible to harm the memory of the person, and this can be a harmful consequence for the relatives who carry that memory.[25]

Physicians have a duty to avoid harm to patients. It could be argued that they have a similar moral obligation towards a deceased's relatives, particularly because family members had no opportunity to make an informed decision regarding genomic testing. However, denying disclosure because of uncertain harmful consequences could be considered unduly paternalistic and in conflict with the widely recognized 'right to know'.[11]

Respect for a deceased's wishes as expressed by life

A third argument to reject disclosure could relate to respect for the 'autonomy' of the deceased.[25] It is problematic to speak of a patient's autonomy after death, because autonomy requires capacity and competence. Nevertheless, one can argue that a physician should respect the prior expressed autonomous choices of the deceased.[25,43] The autonomy of a living patient would devalue if it became evident that the patient's wishes would not be respected after death. As a consequence people's trust in the confidentiality in health care might decrease. A patient could have various reasons not to disclose genetic information to family members, such as the protection of sensitive information, cultural norms, and timing concerns.[44] Furthermore, it is said that some personality rights surpass death, including respect for the expressed wishes (e.g. succession) and moral integrity of the deceased (e.g. reputation, dignity, privacy).[25] Postmortem disclosure of genetic information might jeopardize a professional's duty to respect the deceased's wishes. Nondisclosure, by contrast, could be in conflict with the interests of relatives. It is possible that health-related interests of living family members may sometimes outweigh the interests of deceased patients. In addition, disclosure could be in line with the deceased's expressed or unexpressed wishes. Unfortunately, in many cases the true nature of the deceased's wishes can no longer be ascertained.

Respect for a deceased's (genetic) privacy and confidentiality

Respect for the privacy of a deceased patient is a fourth argument for withholding communication of genomic information.[24] To respect individual privacy and to create a secure environment in the patient-physician relationship, confidentiality of genetic information is required. Communication of genetic information to relatives after death could involve

a breach of confidentiality, because permission for disclosure cannot be obtained. Postmortem disclosure without permission may even be in conflict with legislation (e.g. the US HIPAA Privacy Rule).[24] However, many argue that privacy and confidentiality should not be regarded as absolute values or rights. Especially in genetics, where the interests of family members may be at stake, breaching confidentiality should be possible under certain conditions.[25] However, there is no consensus on the conditions under which such confidentiality might be breached.[21,25,45]

In addition, when balancing respect for a deceased's (genetic) privacy against the interests of relatives, some argue that a different weight should be ascribed to privacy after death.[46] Indeed, an important value of respecting privacy lies in preventing harm that could result from misuse of information. One could question whether possibly inflicted harm could be as significant postmortem as it would be ante-mortem.[25]

Disclosure is not feasible

A fifth argument against postmortem disclosure is feasibility.[8,17] Indeed, many findings generated by NGS do not meet analytical and clinical validity.[1,17] Furthermore, the selection and validation of results is time-consuming and costly for both the laboratory and clinicians.[47] One could therefore question whether disclosing genetic information to relatives is appropriate, particularly when there is no consensus on what information should be returned to patients. It could also be questioned whether the physician ordering the tests (e.g. a paediatrician or cardiologist) is responsible for informing and counseling relatives, notably because he or she generally lacks the appropriate expertise to do so.[48] Moreover, because contact information may be lacking, and counseling is extensive, a duty to inform will impose an undue burden upon health-care professionals if they are required to contact, inform, and counsel at-risk relatives, and would also interfere with the primary duty: providing health care.[49,50]

Despite the above stated objections to postmortem disclosure, feasibility should not be regarded an absolute argument to justify withholding disclosure. The majority of the drawbacks regard practicalities, none of which are impossible to overcome.

CHAPTER 8

POSTMORTEM DISCLOSURE TO RELATIVES: ACTIVE OR PASSIVE DISCLOSURE?

We have discussed the pros and cons of postmortem feedback of genetic information to relatives. The principles of beneficence, the duty to warn and the familial nature of genetic information could all provide justification for postmortem disclosure. In addition, disclosure may have the favourable side-effect of fostering a relative's positive autonomy. Postmortem disclosure could however be in conflict with the deceased's privacy. Moreover, communication of genetic information could disregard the deceased's wishes, have harmful consequences for relatives, or violate a relative's interest in not knowing. Finally, postmortem disclosure may not always be feasible. When balancing these different types of arguments we conclude that there are strong justifications for postmortem disclosure. Potential objections are manifold, but as our discussion has shown, none of them supplies compelling fundamental reasons against postmortem disclosure. There are, however, important competing values that need to be taken into account. Therefore, a well-considered postmortem disclosure policy that offers an optimal balance between possible benefits and harms should be designed.

Active disclosure

A first option would be an active disclosure policy, where the family members of a deceased patient are actively approached and contacted concerning the provision of provide genetic information. The main argument for active disclosure would be the fulfillment of the duty to warn, because it offers the highest chance that at-risk relatives will be informed about potentially life-saving genetic information.[8,9,19,20] However, some serious drawbacks can be identified. First, a physician must have persuasive reasons to actively disclose genetic information to a deceased's relatives because this would mean a serious violation of confidentiality if permission to disclose was not given. Second, even in the case of a deceased's permission, there are boundaries to the physician's duty to do good towards relatives outside the scope of a clinical relationship. Active disclosure could pose a disproportionate burden on physicians and distract them from their primary tasks. Instead, more effort should be put into providing clear counseling on hereditary risk before death, as to support familial communication between patients and their family members and ideally to prevent the need for

postmortem disclosure. Third, the active approach of family members may violate their interest in not knowing, even in cases where a first contact only reveals that genetic information is available. Fourth, although potentially harmful consequences are uncertain, relatives deserve protection because they did not have an opportunity to make an informed decision with respect to genomic testing. We currently consider that active disclosure to the relatives of a deceased patient is too far-reaching.

Passive disclosure

A second option would be a passive disclosure policy, where family members are given access to genetic information at their explicit request. A passive disclosure policy offers some advantages over active disclosure. First, passive disclosure is more feasible, because the responsibility for contacting lies with the family of the deceased patient. Consequently, scarce resources and time can be used for appropriate care and genetic counseling of family members who are actively interested in receiving information. Second, passive disclosure offers greater respect for the privacy of the deceased. Third, it provides family members with the option of remaining in a state of ignorance.

The principle disadvantage of passive disclosure lies in the uncertainty of reaching all at-risk family members in the case of life saving data, making it difficult to respect the duty to warn.[9,20] However, it is questionable whether this drawback is of such weight that a general active disclosure policy should be chosen. After all, the duty to warn is based on the 'rule of rescue'– reasonable emergency assistance should be given when this can easily be given without neglecting other duties.[51] Passive disclosure constitutes 'disclosure that is given easily' by offering clinically actionable genomic information at the request of a relative. In addition, to fulfill a physician's duty to warn, it might be possible to develop a concomitant policy to cover exceptional circumstances.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The emergence of NGS techniques creates new moral duties, including those surrounding postmortem disclosure. Clinicians may have duties towards their patients' family members that continue after the death of the patient. We conclude that passive disclosure of genetic information currently offers an optimal balance between the potential benefits and harms of disclosure.

Therefore, we propose a passive postmortem disclosure policy that offers access to genetic information if the following conditions are met. First, before undergoing NGS patients should be counseled appropriately on the familial importance of genomic information and about possible postmortem disclosure to relatives. Second, an appropriate procedure for informing and counseling relatives should be agreed upon before implementing NGS. Third, there should be agreement on the selection of results, including those of immediate clinical significance that are eligible for postmortem disclosure to relatives. Fourth, although passive disclosure forms the default policy, active disclosure could be morally justifiable if, for example, a dominant, highly-penetrant genetic variant causative for a clinically-actionable, severe disease is present, provided that the required effort is reasonable, and counseling and consent are available.

It should be noted that our proposal of a passive postmortem disclosure policy could be construed as the moral minimum. It is, however, context-dependent, and will be subject to the rapidly changing field of genomics, meaning that further debate on active or passive disclosure is certainly needed. We acknowledge that in the future an active disclosure policy could become the ethically superior option; nevertheless, there are important sets of questions that must first be resolved (Text Box). In addition, societal awareness must be increased about NGS testing and its implications.

TEXT BOX: OUTSTANDING QUESTIONS

- Which clinically useful and actionable results should be returned to the family members of a deceased patient after his/her death?
- What genetic information could be defined as 'life-saving'?
- What would be an adequate counseling procedure for patients regarding postmortem disclosure?
- What would be an adequate counseling procedure for family members?
- How do the family members of a deceased patient perceive the beneficial effects and harmful consequences of postmortem disclosure?
- What national and international guidelines and legislation could be developed to design a concrete professional framework with respect to postmortem disclosure?
- How can the familial dimension of DNA gain more attention, and what broader influence does it have in genomics?
- How do the family members of a deceased patient perceive an active versus a passive disclosure policy? Under what conditions would they be willing to sacrifice their 'state of ignorance'?
- What would be the logistic, legal, and counseling requirements for a reorganization of health care that would provide a suitable environment for active disclosure?

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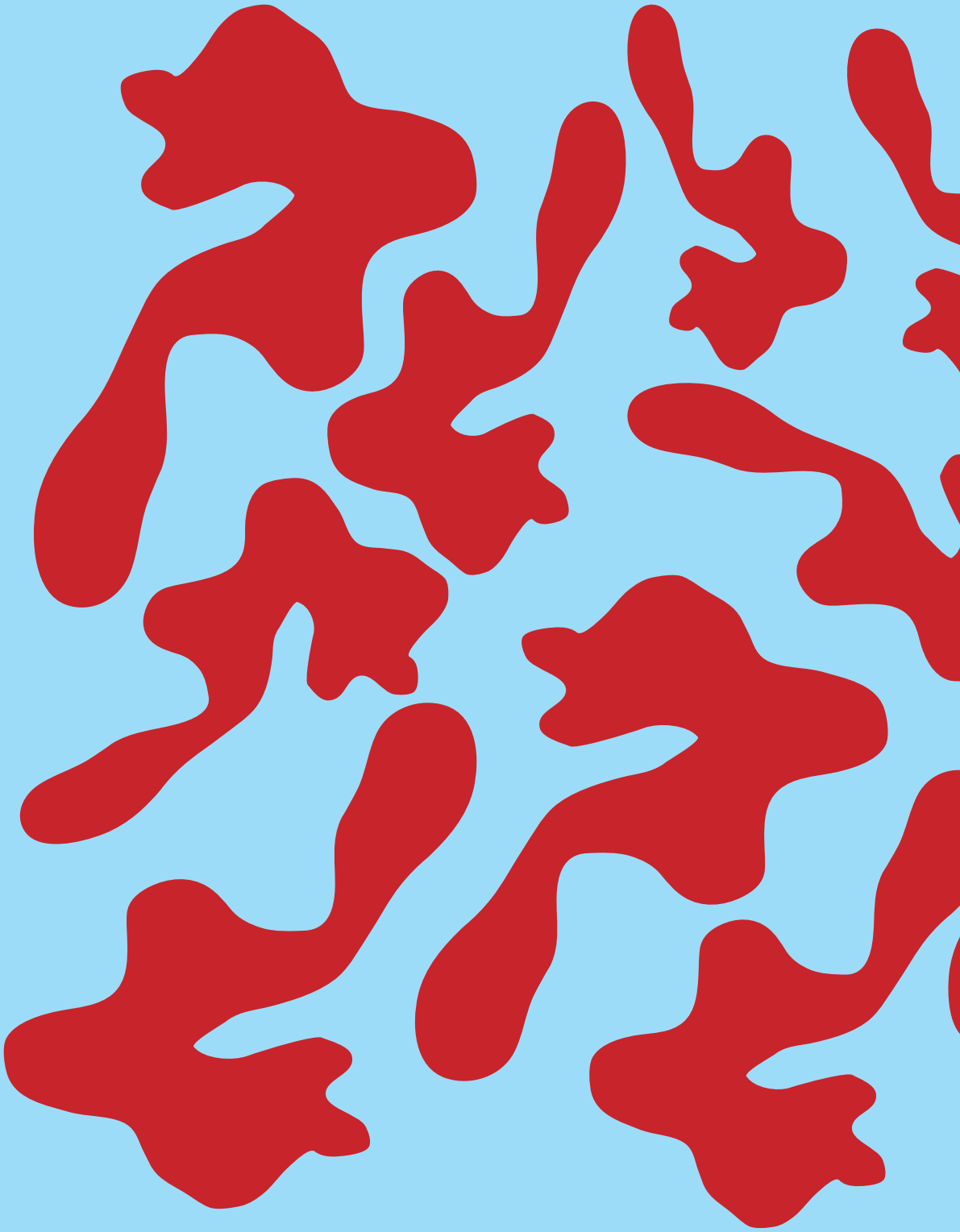
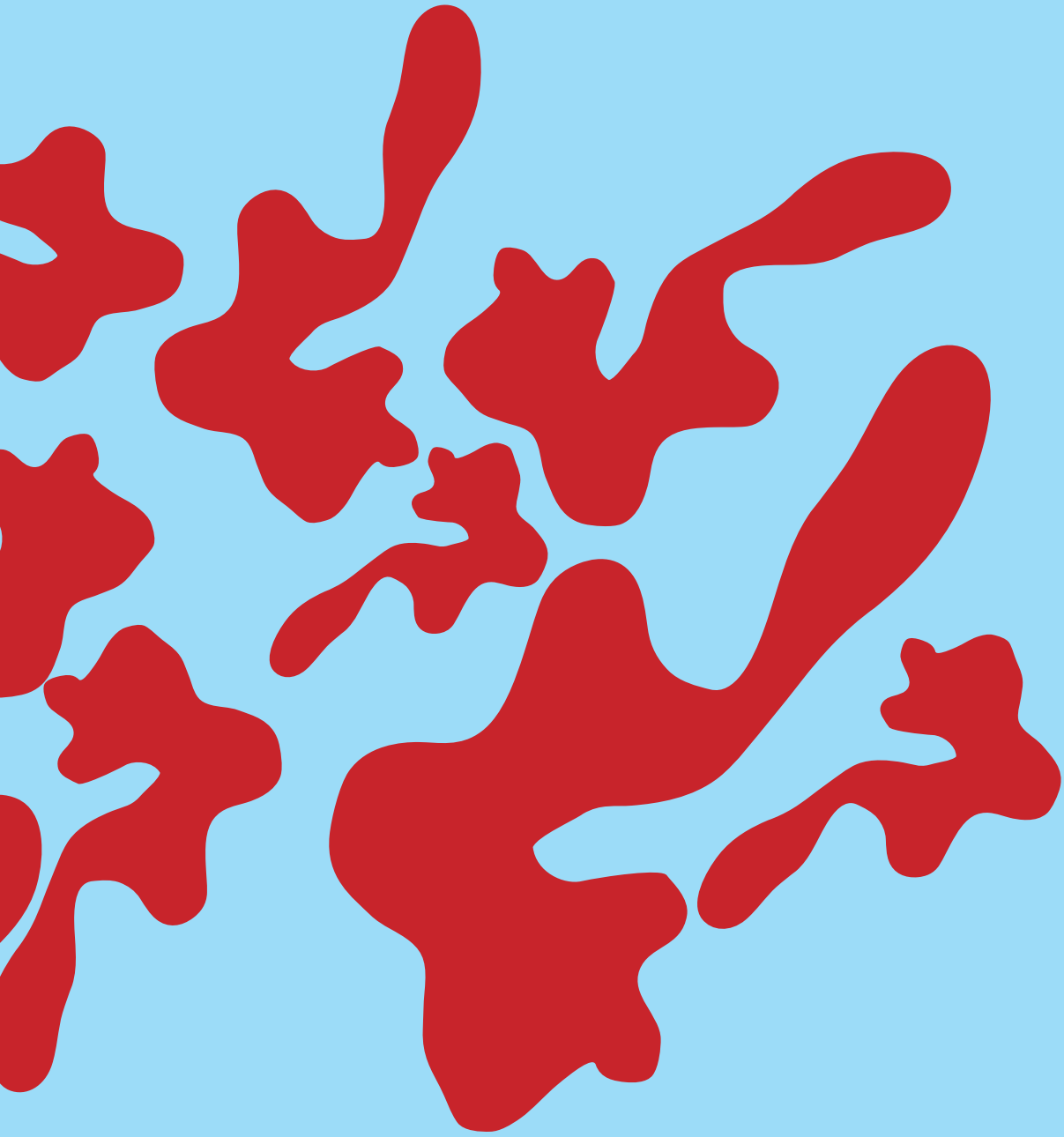
Part IV

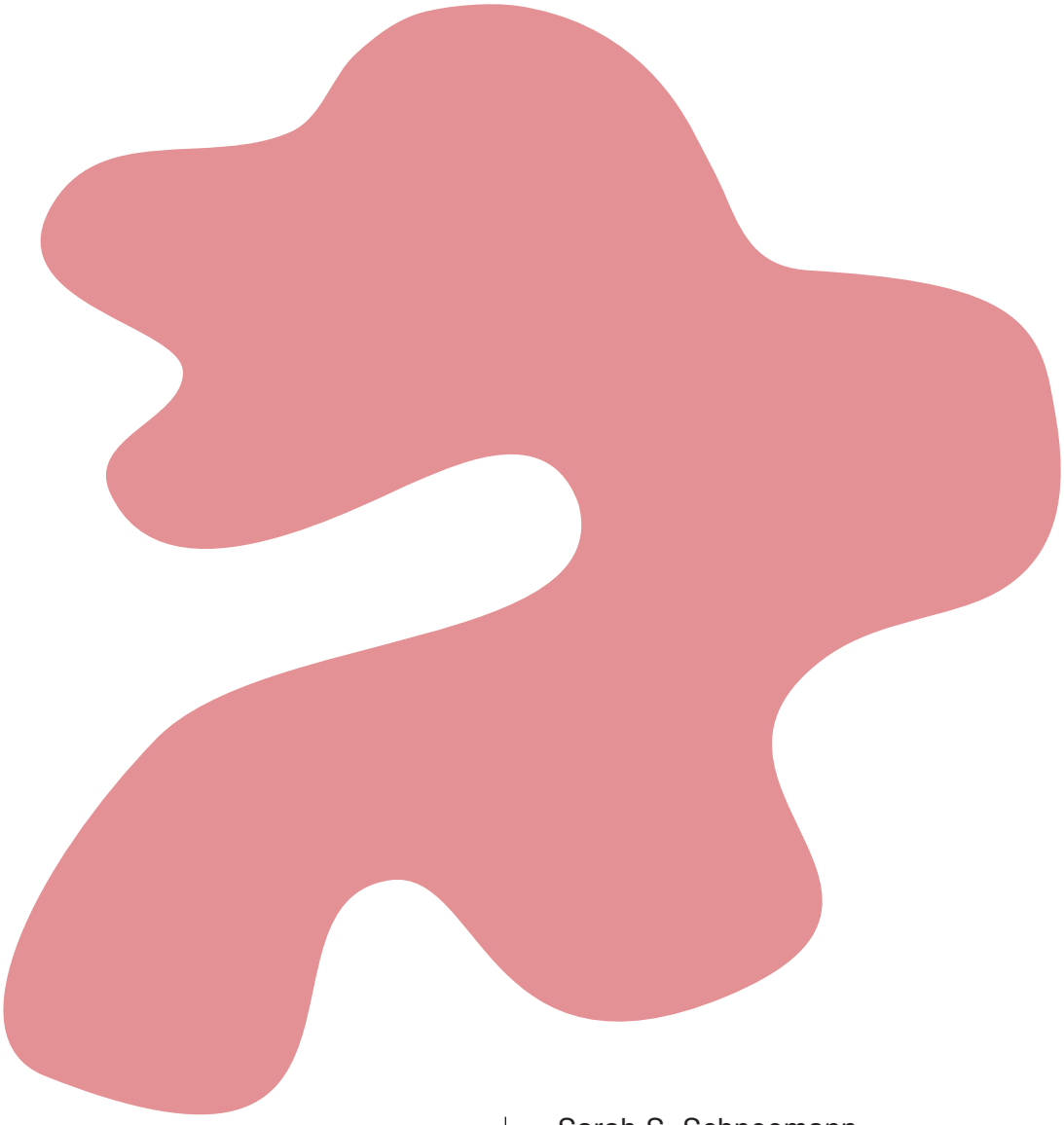


Ethical evaluation of first-in-human organoid transplantation



CHAPTER 9

Ethics of organoid transplantation: first-in-children?



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ABSTRACT

The recent possibility to generate liver organoids from adult stem cells opens avenues for patients with liver disease. First-in-human trials constitute an essential step in bringing liver organoid transplantation from the bench to the bedside. However, they are paired with significant ethical challenges. In this article, we examine the ethical acceptability of a first-in-children organoid trial. While we are aware of the delicate nature of this discussion, we propose to move from preclinical studies directly to children, if potential individual benefits are warranted after rigorous assessment of the preclinical evidence, provided that the following three conditions are met. 1) The risks are minimized, 2) the potential benefits outweigh the risks, and 3) attention is paid to valid informed consent and assent.

INTRODUCTION

Recent developments have made it possible to grow stem cells or organ progenitors into 'mini-organs' in culture, called organoids.[1,2] Organoids have been successfully generated for a variety of organs and offer a range of research and translational applications.[1,2] Organoids hold the promise to impact the entire innovation cycle in biomedical research, including fields that have been the subject of intense ethical debate.[3] Transplantation of liver organoids generated from Lgr5+ adult stem cells could revolutionize prospects for patients with liver disease.[4] For these patients, liver transplantation is still the ultimate treatment option. However, this major intervention is associated with serious complications. If successful, organoid transplantation would provide a less invasive alternative that makes it possible to break away from organ transplantation and the associated organ shortage.[5]

Current experiments are still in the preclinical stage and clinical safety and efficacy must be established before liver organoid transplantation can fulfill its potential.[4,6–9] Patients with metabolic liver diseases may constitute a particularly eligible group of participants for first-in-human liver organoid transplantation trials for both scientific and clinical reasons. They offer a clear-cut model and for most metabolic diseases recovery of only 10% of the deficient liver function is thought to be sufficient for correction of the clinical phenotype.[5]

The majority of metabolic liver diseases manifest in early childhood and intervention is particularly effective when performed at an early age, before irreversible damage has occurred.[5] This raises the question whether a first-in-children liver organoid trial would be justified. There are several additional arguments to be made to include children in a first trial. First, the nature and severity of disease often differ between children and adults. This emphasizes the need for obtaining results on safety and efficacy within the paediatric target population. Second, excluding children at this stage of research may cause a delay in providing potentially important benefits to seriously ill children. Moreover, in patients with a serious disease, the effect of an intervention may have a greater beneficial impact. Finally, paediatric livers might provide a more favourable microenvironment for engraftment, because cirrhotic changes of the liver that are thought to impair engraftment of organoids have not yet occurred.[5,10–13]

Including children in first-in-human trials, however, is ethically contentious.[14–19] Children are considered vulnerable, among others, because they are less (or not) capable to protect their own interests. Therefore, they deserve protection from harms associated with clinical trials (and these can

be considerable in early phase stem cell trials). However, overprotection of children could unnecessarily hamper the introduction of potentially beneficial treatments in paediatric care. Therefore, paradigms are shifting in favour of including children in clinical research. In this paper, we address whether it is ethically acceptable to include children in a first-in-human organoid trial, and if so, under what conditions.

THE ETHICS OF INCLUDING PAEDIATRIC PATIENTS

When defining whether it is acceptable to include children in research, ethical guidelines discriminate between interventions and procedures that do or do not have potential individual (or direct) benefits for participants (referred to by us as 'therapeutic' and 'non-therapeutic' interventions and procedures) (Appendix). Generally, therapeutic interventions are justified, other things being equal, in the case of a favourable risk-benefit balance. This means that the aggregate risks of the intervention are minimized and outweighed by the potential individual benefit and expected social value. Non-therapeutic interventions are justified, other things being equal, if the condition affects children only and/or if the necessary data cannot be gathered without their participation. Risks must be minimized and no more than minimal, and aggregate risks of the study should be justified by social value.[14] In some jurisdictions, a minor increase over minimal risk is deemed acceptable.[15] The stricter regulations for non-therapeutic interventions are subject to discussion and change. Thanks to the European Union (EU) Clinical Trials Regulation (No 536/2014), EU member states are currently expanding the possibilities for research with minors and incapacitated adults.[17] Liver organoid transplantation cannot be considered as an intervention that has (a minor increase over) minimal risk. Therefore, it is vital to examine whether organoid transplantation meets the conditions for therapeutic interventions.

ORGANOID TRANSPLANTATION: IS THERE A PROSPECT OF INDIVIDUAL BENEFIT?

Potential individual benefits to participants are defined as benefits arising from the intervention that is being studied.[20] Actual benefits, however, are simply unknown until the final evidence in human subjects is provided. The challenge lies in the preceding evaluation: when can individual benefits reasonably be expected?

It can be argued that a claim of potential benefit can only be made if there is sufficient warrant based on solid evidence.[21] This goes particularly for phase II/III trials where previous studies may offer credible evidence on safety and efficacy in humans. For first-in-human studies only preclinical in-vitro and animal evidence is available, which is known to poorly translate to humans, due to physiological and genetic differences. Additionally, generally accepted quality standards for designing and reporting preclinical studies are lacking.[22] Therefore, a therapeutic warrant is limited to rare cases.

The current stage of preclinical evidence does not allow us to evaluate potential benefits of liver organoid transplantation.[4,6,8,23] Nevertheless, we argue that potential individual benefits may eventually be expected for two reasons. First, although organoids are novel, the route of administration, the target population, and the mechanism of action are similar to hepatocyte transplantation. Organoids have proven to differentiate into functional hepatocyte-like cells,[4] and studies using hepatocytes have proven to offer an effective therapy for liver disease, although for a limited period (up to 18 months).[10] The short-lived effects of hepatocyte transplantations might well relate to the limited lifespan of hepatocytes. Liver organoids, alternatively, are hypothesized to have the potential to engraft and proliferate long-term in vivo. The second reason to expect clinical benefit is because only 10% recovery of the deficient liver function is expected to correct the clinical phenotype in patients with metabolic diseases.[5]

These arguments are currently hypothetical, because preclinical evidence is not yet solid enough to estimate potential individual benefits. However, we deem it important to pro-actively conduct the ethical discussion on the inclusion of children while the organoid field advances. Eventually, careful evaluation of the preclinical evidence, right before a first-in-human trial is initiated, should point out whether individual benefits to participants can be warranted. This evaluation should include a careful and structured scrutiny of the validity and generalizability of preclinical animal studies to the

clinical setting.[24] Additionally, decision-makers should be aware that both participants and researchers might suffer from therapeutic mis-estimation: the overestimation of potential benefits and the underestimation of potential harms.[25] Ultimately, evaluators (e.g. Research Ethics Committees) should decide whether the evidence is convincing enough to warrant a claim of individual benefits to research participants.

PERFORMING A FIRST-IN-CHILDREN TRIAL IS ETHICALLY ACCEPTABLE IF FUTURE EVIDENCE WARRANTS POTENTIAL INDIVIDUAL BENEFITS

We only consider it ethically acceptable to perform a first-in-children organoid transplantation trial if future preclinical studies provide sufficient warrant for potential individual benefits. Furthermore, the below conditions for studying therapeutic interventions in children should be met (following the CIOMS guideline). The CIOMS guidelines prescribe that toxicity studies should be conducted in adults first.[14] Although a first trial will entail safety aspects, we argue that, if potential individual benefits can be reasonably foreseen, a first-in-human liver organoid transplantation trial will not concern a classic safety (or toxicity) study that should be performed in adults first.

Condition 1: Risks are minimized and outweighed by potential individual benefits

Risks associated with the research intervention, i.e. liver organoid transplantation, should be minimized and outweighed by potential individual benefits.[14] For research procedures that do not offer a prospect of individual benefits, such as biopsies and blood draws, the risks should be minimized and appropriate in relation to the anticipated social value.[14]

A first-in-human liver organoid trial will entail several risks, uncertainties, and unknown harms.[26] The above-mentioned evaluation and minimization of risks demands a careful mapping and characterization of the risk (and benefit) profile of the different research interventions and procedures.[14,27] Risks and uncertainties related to the transplantation of liver organoids (and the administration of immunosuppressive drugs) include those associated with injection of organoids to the portal vein, which may cause technical complications.[10] Risks associated with immunosuppressive regimens are

considered similar to hepatocyte and liver transplantation, which is the current standard of care.[11] Furthermore, in comparison to hepatocytes, organoids present additional sources of potential harm, because organoids are generated from stem cells and cultured in vitro in the presence of growth factors. This raises questions of the genetic stability of liver organoids. In the analogous field of induced pluripotent stem cells, genetic instability has raised concerns of malignant progression. However, adult stem cells have not undergone genetic reprogramming. They are not pluripotent but dedicated to produce cells only from their organ of origin. Most importantly, extensive genotyping of organoids that had been long-term clonally expanded in vitro has demonstrated remarkable maintenance of genetic stability.[4] The potential harms associated with organoids constitute uncertainties, rather than quantifiable risks, because the probability and magnitude of potential harms cannot be quantified based on preclinical studies.[26] In early phase trials, there is also the element of ignorance: it can be unknown whether there is any risk at all ('the unknown unknowns').[26]

To minimize risks, safety should be tested in robust preclinical studies. Additionally, (hepatocyte) transplantation experts should be involved in deliberating which trial design will minimize risks. Results from the first participant could be awaited before the next participant is included, and follow-up of participants should be intensive in terms of both frequency and length. Moreover, parents and patients may have valuable additional suggestions to reduce trial-associated burdens. Evaluators should decide whether the prospect of individual benefits outweigh the risks, uncertainties, and unknown harms associated with liver organoid transplantation and the administration of immunosuppressive drugs.

Condition 2: The aggregate risks are acceptable in light of potential individual benefits and social value

The aggregate risks should not exceed an upper limit of risk and should be acceptable in light of the potential individual benefits and the anticipated social value.[14]

Aggregate risks can be defined as the sum of all risks related to the interventions and procedures in the study. The aggregate risks include not only the above-mentioned risks related to organoid transplantation, but also the risks and burdens related to blood draws, imaging and a potential liver biopsy. When considering social value we refer to the nature and magnitude of improvement an intervention is expected to have on the wellbeing of future patients or society.[28] Although no standards exist for assessing social value, we anticipate that liver organoid transplantation can be assigned social value because of the severity of metabolic diseases, the risks and

limitations associated with liver and hepatocyte transplantations, and the potential implications for organoid transplantations for other indications.

Condition 3: Informed consent and valid assent

In paediatric research, informed consent consists of parental permission and children's assent (their voluntary agreement or refusal to participate). In order to minimize therapeutic misconception (which is the potential misunderstanding that the study has a therapeutic instead of a scientific aim) it should be stressed that a first trial has an investigational nature.[21] Children's assent should be personalized, that is, assent should be adjusted to the individual child (age, development).[29]

Which group of paediatric patients should be included?

Several models of participant selection have been distinguished (e.g. the healthy volunteer model, the suitable patient model, the oncology model, and recently the individual at risk model), and all models have their strengths and weaknesses.[30] In most first-in-human studies, the oncology model is used. It is argued that potential risks might be more acceptable in patients that are treatment refractory for standard treatments and potential benefits can be lifesaving for these patients. However, in the case of liver organoid transplantation, we do not consider this group ethically appropriate. Patients that are excluded from liver transplantation could be in such a poor clinical situation that they might not be able to benefit from liver organoid transplantation. We expect that the risk/benefit balance will be most favourable for patients with metabolic liver diseases that are on the waiting list for liver transplantation. This group is still able to benefit from liver organoid transplantation (provided that there is no irreversible damage in the liver). Furthermore, it only seems justified to include patients that will otherwise need immunosuppression for liver transplantation, because liver organoid transplantation is expected to require immunosuppressive therapy. One could at the same time question the ethical acceptability of exposing these patients that already face potential harms following from their disease, to the risks associated with the trial, or with the potential delay in performing a liver transplantation. However, patients with metabolic liver diseases generally receive a liver transplantation to overcome an enzyme deficiency, rather than to treat end-stage liver failure. Therefore, a slight delay in performing a liver transplantation may not be too problematic, because transplantation is usually less urgent. If liver organoid transplantation proves ineffective, liver transplantation can still be performed.

To eventually design a morally sound study, it is vital to give parents of patients (and when possible children themselves) a voice, and to identify

their perspectives on the risk/benefit balance, informed consent and assent, the selection of research participants, and the trial design.[14,31]

Implications for trial design

The current phasing paradigm of phase I-IV trials, and the division between therapeutic/nontherapeutic research and efficacy/toxicity trials may not be completely suitable for complex translational trials of new biopharmaceuticals, such as organoids.[28] We argue that a first-in-human organoid trial should be a combined safety and efficacy study. Individual benefits can only be reasonably expected if the trial design allows participants the chance of benefits. This means that they should be given an expected therapeutic dose and efficacy should be added as an endpoint in a first-in-human liver organoid trial. Additionally, a combined safety and efficacy study could prevent that promising interventions are discarded due to high-risk outcomes in safety studies before efficacy is tested.[28,32]

CONCLUDING REMARKS

The recent development of adult stem cell-derived liver organoids is exciting and opens avenues for patients with liver disease. However, the design of first-in-human trials presents significant ethical challenges.[3,33] In this article, we examine the ethical acceptability of a first-in-children organoid trial. While we are aware of the delicate nature of this discussion, we propose to move from preclinical studies directly to children, if potential individual benefits are warranted after structural and rigorous assessment of the preclinical evidence, provided that the following three conditions are met (in complement to the other requirements to make clinical research ethical).[34] 1) The risks related are minimized and outweighed by potential individual benefits, 2) the risks are outweighed by the potential benefits, and 3) attention is paid to valid informed consent and assent. If future preclinical studies do not warrant a reasonable prospect of potential individual benefits, it does not seem justified to include children. To allow research participants a prospect of individual benefits, a first-in-human liver organoid trial should be a combined safety and efficacy study. Our line of reasoning can be applied to other complex translational (stem)cell trials and innovative technologies.

In conclusion, the clinical introduction of new biopharmaceuticals, such as organoids, raises ethical and regulatory challenges that need proactive scrutiny. An interdisciplinary dialogue, involving not only scientists and clinicians, but also patients, policy makers, ethicists and the public is needed to stimulate responsible research and innovation in this field.

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APPENDIX: OVERVIEW OF THE RELEVANT REGULATIONS CONCERNING RESEARCH IN CHILDREN

Guideline	Type of intervention	Conditions
CIOMS[a] Ethical Guidelines, 2016[14]	Research interventions with potential individual benefit	Risks must be minimized and outweighed by the prospect of potential individual benefit.
	Research interventions without potential individual benefit	1. Should be performed in adults first, when conditions are targeted that affect adults as well as children and adolescents, unless the necessary data cannot be gathered without participation of children or adolescents. 2. Risks must be minimized and no more than minimal.
	Other relevant content	The agreement (assent) of the child or adolescent should be obtained in keeping with the child's or adolescent's capacity, after having been provided with adequate information about the research tailored to the child's or adolescent's level of maturity.
	Specific commentary on guideline	In rare cases (e.g. when a disease affects large numbers of people, including children and adolescents, the available treatment options are limited, and an investigational agent shows great promise), waiting for conclusive results from research in adults before initiating paediatric studies can significantly delay the acquisition of relevant data and development of beneficial interventions for children. The current guidelines do not require that research first be conducted in adults if the research includes interventions that hold out the prospect for individual benefit for children and adolescents. This prospect is sufficient to justify the risks associated with the interventions and procedures. Research must always be conducted in adults first when exploring the toxicity of new drugs.

Guideline	Type of intervention	Conditions
ISSCR[b] Guidelines for Stem Cell Research and Clinical Translation, 2016[15]	Research interventions with potential therapeutic benefit	Risks should be exceeded by the prospect of therapeutic benefit.
	Research interventions without potential therapeutic benefit	Risks should be limited to no greater than minor increase over minimal risk.
	Other relevant content	Clinical research should generally seek to enrol those who have a capacity to provide consent rather than those who are unable. Assent of the research subject should be obtained where possible. Researchers should validate safety and techniques in research subjects with advanced disease before testing their products in research subjects with more recent disease onset. There may be situations where, because of delivery or disease target, a cell product is not suitable for initial evaluation with advanced disease.
WMO[c], 1998/2017[16]	Research study with potential individual benefit	Risks and burdens must be outweighed by the prospect of potential individual benefit.
	Research study without potential individual benefit	1. The necessary data cannot be gathered without participation of children or adolescents. 2. Risks and burdens must be minimal in comparison to standard of care. If there is no existing standard of care, the risks and objections must be minimal in relation to the severity of the disease/ current treatment options for the specific patient group.
	Other relevant content	Research on minors is only allowed if: 1. The study is needed to confirm the results of research on individuals who have a capacity to provide consent. 2. This group stands to benefit from the research. In addition to parental informed consent, children between 12-16 years should provide written consent.

Guideline	Type of intervention	Conditions
EU Clinical Trials Regulation (No 536/2014), 2016[17]	Clinical trial with potential direct benefit	Risks and burdens must be outweighed by the prospect of a direct benefit.
	Research interventions without potential direct benefit	1. Should produce some benefit for the population represented by the minor concerned. 2. Risks and burdens must be minimal in comparison to the standard treatment of the minor's condition.
	Other relevant content	Research on minors is only allowed if: 1. The clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods. 2. The clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors. The minor must take part in the informed consent procedure in a way adapted to his or her age and mental maturity.

Guideline	Type of intervention	Conditions
WMA[d] Declaration of Helsinki, 2013[18]	Research with potential benefit	Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens of the research subjects.
	Research without potential benefit	1. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens of the research subjects. 2. It is intended to promote the health of the group represented by the minor. 3. It cannot instead be performed with persons capable of providing informed consent. 4. It entails only minimal risk and minimal burden.
	Other relevant content	Research on vulnerable groups is only justified if research is responsive to health needs or priorities of this group and it cannot be carried out in a non-vulnerable group. This group should stand to benefit from the knowledge, practices or interventions that result from the research. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
CoE[e] Convention on Human Rights and Biomedicine, 2005[19]	Research with potential direct benefit	Risks and burdens should be minimal.
	Research without potential direct benefit	1. Risks and burdens should be minimal. 2. It has the aim of contributing, through significant improvement in the scientific understanding of the individual's disease, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons the same age category/ with the same disease.
	Other relevant content	Research on children is only justified if research of comparable effectiveness cannot be carried out on individuals capable of giving consent. The opinion of a minor should be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity.

[a] Council for International Organizations and Medical Sciences, [b] International Society for Stem Cell Research, [c] Dutch Medical Research Involving Human Subjects Act, [d] World Medical Association, [e] Council of Europe. A division is made between therapeutic interventions (with potential individual benefit) and non-therapeutic interventions (without potential individual benefit). Only statements are shown that are considered relevant to this paper.

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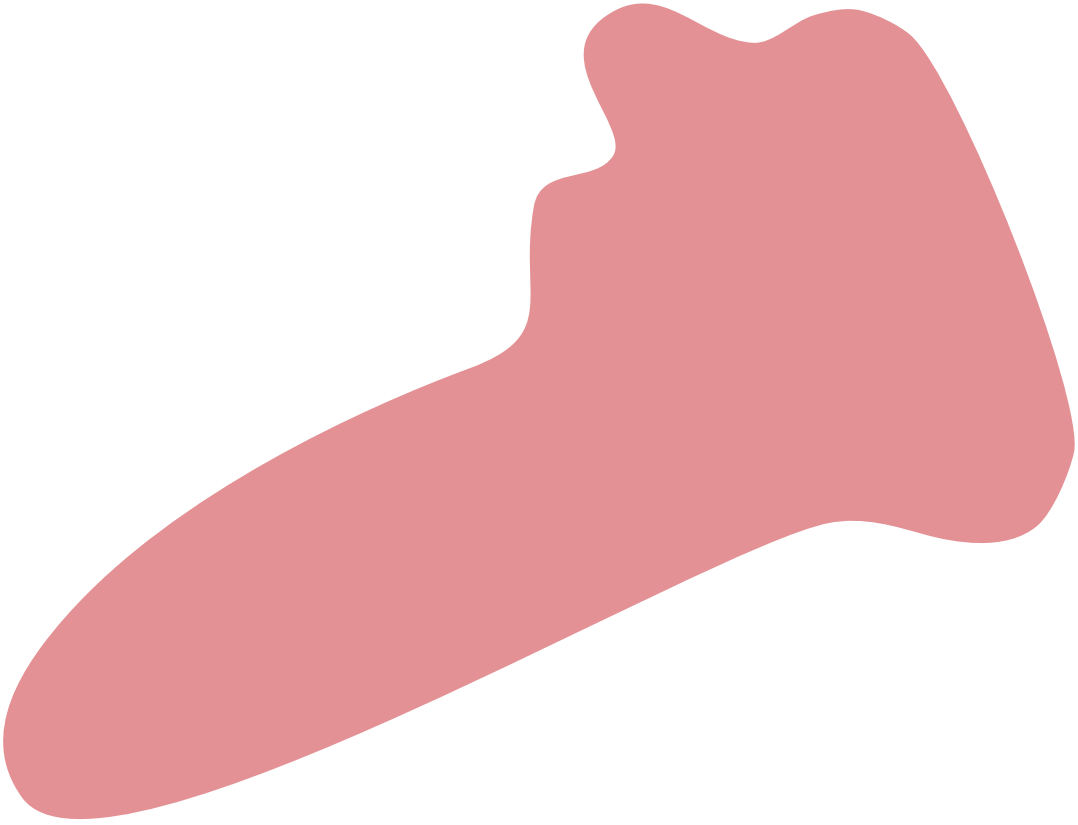
CHAPTER 10

Risk-benefit in first-in-human trials: how a novel approach to estimate efficacy in humans contributes to systematic and non-arbitrary decision-making



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ABSTRACT

First-in-human (FIH) trials are a key step in translating novel therapies from bench to bedside. They may, however, present considerable risks to participants that need to be justified by the anticipated benefits. Here, we contribute to systematic, transparent, and non-arbitrary decision-making regarding risks and benefits in the ethical review of FIH trials. We connect a novel approach to the systematic assessment of estimated efficacy, that integrates preclinical efficacy and reference class evidence contributes, to the four risk-benefit tasks: (1) benefit analysis, (2) risk-benefit evaluation, (3) benefit optimization, and (4) decision-making.

INTRODUCTION

Although first-in-human (FIH) trials are a key step in translating novel therapies from bench to bedside, they may present considerable risks to participants. Evaluators, such as members of Institutional Review Boards (IRBs) or Research Ethics Committees (RECs,) need to judge whether the condition of a favourable risk-benefit balance is met before FIH trials can be initiated. This judgment requires a systematic and non-arbitrary assessment of the available information to examine and characterize harms and benefits.[1,2]

Although the assessment of potential harms has received a fair amount of attention, formal ways to assess benefits in FIH trials are less developed.[1,3–6] We refer to trials as FIH, if an intervention is administered to humans for the first time after in vitro and in vivo preclinical testing.[7] In FIH trials, the evidence to support clinical benefits is limited to mechanistic and preclinical efficacy studies.[3,8] However, findings from non-human animal studies are difficult to generalize to humans. Additionally, the quality of design and reporting of preclinical animal studies is criticized, and the relation between preclinical efficacy and benefits in FIH trials is not self-evident.[3,9] Currently, evaluators have insufficient tools to judge the relevance of animal studies in predicting the effects in humans, and to reason how estimates of efficacy can feed into the assessment of benefits in FIH trials.[5,9]

Kimmelman (one of the co-authors on the present paper) and colleagues have previously attempted to partially address this gap by proposing a systematic approach to assess the estimated efficacy (or clinical promise) of novel interventions.[4,5] This approach encompasses a systematic evaluation of preclinical efficacy studies that is premised on basic rules of scientific inference. Such an approach formalizes the consideration not merely of the preclinical efficacy studies, but also of so-called reference class evidence.[4,5]

For evaluators to be able to appropriately apply this approach, it should be further elaborated how these distinct types of evidence can be integrated to estimate efficacy in humans, and how an appropriate reference class can be selected. Additionally, this previous work does not yet connect the assessment of efficacy to the estimation of benefit. In the present paper, we further develop the approach and set out to show how the outputs of the proposed analysis can be applied to the objective of deciding upon risks and benefits in ethical review. We use FIH application of organoids, a novel stem cell technology, to illustrate the selection and evaluation of reference class evidence.[10]

CHAPTER 10

AN APPROACH TO THE ASSESSMENT OF ESTIMATED EFFICACY

Estimating efficacy in humans

Estimated efficacy is roughly defined as the probability that efficacy is demonstrated after a small number of trials.[5] Although it would be the responsibility of investigators to perform an assessment of estimated efficacy in humans, evaluators need to be able to formulate their own independent judgments about benefits (and risks) in FIH trials.[11] Here, we explain how both preclinical efficacy and reference class evidence can be integrated to form judgments of estimated efficacy in humans. The following three determinants should be taken into account (Table 1).

(a) *How have similar treatments fared in clinical translation?* This is the so-called reference class evidence. This determinant relies on the premise that the prior probability of efficacy in humans is higher where similar agents have been frequently translated to target populations, and lower where those agents have generally failed.[5,12]

(b) *What is the probability that the treatment is effective in human beings, given the observed results in preclinical efficacy studies?* All else being equal, the larger the treatment effect in preclinical efficacy studies, the greater estimates of efficacy will be.[5,6]

(c) *What is the probability of observing preclinical efficacy results under (b)?* To answer this question, one should ask what the probability of observing the results under (b) would be, if the treatment is in fact ineffective. This determinant corresponds with the *validity* of preclinical efficacy studies. If validity is threatened, it is possible that the observed treatment effects cannot be attributed to the study intervention, and/or that treatment effects cannot be generalized from animals to the clinical population.[4,5]

These three determinants correspond in the following way. The reference class evidence sets a prior probability (a).[4,12] This prior probability (a) is multiplied with the probability of efficacy in humans based on treatment effects found in preclinical efficacy studies (b), and divided by the probability that those findings could have been observed if the study treatment is in fact ineffective (c). Together these three determinants result in estimates of efficacy in humans (it is outside the scope of this paper to theorize how estimated efficacy could be calculated based on these three determinants). To give an example: if (a) the reference class is low (thus similar treatments have been unsuccessful in clinical translation), the prior probability of estimated efficacy is low. This means that even if (b) the preclinical evidence shows large effects, and if (c) the preclinical studies

are valid, then estimations of efficacy in humans should be very modest. If, on the other hand, (a) the reference class has been relatively successful, (b) preclinical efficacy studies show large effects, and if (c) preclinical studies are valid, estimated efficacy could be substantial. However, if (c) the validity of preclinical efficacy studies is threatened, then the estimated efficacy in human beings will be lower.

To formulate values for the three determinants, systematic evaluation of reference class and preclinical efficacy evidence is necessary. Here, we address how such systematic evaluation could take form.[4,5] We particularly expand on the selection and evaluation of reference class evidence, because this constitutes a novel strategy towards estimating efficacy in humans.[5,12]

	Question	Evaluation
a	How have similar treatments fared in clinical translation?	Determination and evaluation of reference class evidence
b	What is the probability that the treatment is effective in human beings, given the observed results in preclinical efficacy studies?	Assessment of the nature and the magnitude of treatment effects through systematic assessment of all available and relevant preclinical efficacy studies
c	What is the probability of observing preclinical efficacy results under (b)?	Assessment of (b) considering an evaluation of three types of validity threats: internal, construct, and external validity

TABLE 1. THREE DETERMINANTS TO ESTIMATE EFFICACY IN HUMANS

TEXT BOX: FIRST-IN-HUMAN LIVER ORGANOID TRANSPLANTATION

Regenerative Medicine (RM) aims to develop therapies that enable self-repair of the human body.[13] Cell-based therapies, such as transplantation of human stem cells, constitute a significant contribution in this rapidly developing field. Recent advances have enabled the transition from three-dimensional cell cultures to three-dimensional human cell structures that closely recapitulate the function and architecture of real-life human tissues: organoids.[14] Organoids generated from adult stem cells are easy to expand in vitro while retaining genetic stability. With current methods, it is possible to establish organoids from a variety of epithelial organs. Organoids hold the promise to form a new generation of cell-based therapies.[15–17]

Although organoid transplantation is still in preclinical development, launch of clinical testing is expected in the near future.[10,18] The field of liver disease would greatly benefit from these rapidly progressing technological advances, because liver organoid transplantations could provide a less invasive and readily available 'off-the-shelf' alternative for liver transplantation.[19–22] A first-in-human (FIH) liver organoid transplantation trial would be a so-called complex translational trial in which several invasive interventional and study procedures are combined.[23] The interventional procedure would probably involve the injection of allogeneic liver organoids into the portal vein, followed by immunosuppressive treatment. This implies that inclusion of healthy volunteers is not justifiable. Healthy volunteers would be exposed to multiple and interlocking risks of harm, while they lack the ability to benefit from the study intervention. Instead, patient-participants from a potential target population could be included (e.g. patients with inherited metabolic disease, in whom clinical benefits would already be anticipated upon limited engraftment).[21] Thorough assessment of the anticipated benefits is indispensable to justify trial risks, especially as these diseases mostly manifest in early childhood.[24] Inclusion of children is only justified if direct benefits can be reasonably anticipated and if the overall benefits outweigh the risks (see Chapter 10).

Selection and evaluation of reference class evidence

To formulate a value for determinant (a) (Table 1), an appropriate reference class should be determined, and it should be assessed whether and to what extent clinical translation in this reference class has been successful.[5]

Selection of the appropriate reference class

To determine an appropriate reference class, investigators and evaluators should consider classes of treatment that are similar in terms of (1) the central causal premise that underlies the study intervention, (2) the disease entity that is studied, (3) the treatment regimen, and (4) the nature of preclinical evidence that supports clinical translation.[5,12]

If applied to liver organoid transplantation, hepatocyte transplantation could constitute an appropriate reference class, based on the abovementioned criteria. Liver organoids constitute a new member of the family of cell-based therapies for liver diseases, of which hepatocyte transplantation is currently the most established form.[21] First, the central causal premise is similar. Both hepatocyte and liver organoid transplantation aim to partially restore the liver function via allogeneic cell transplantation (~5-10% restoration of liver function is estimated to correct the clinical phenotypes of most inherited metabolic disease).[21,24] Second, the target population is similar: hepatocyte transplantation has, among others, been applied in patients with inherited metabolic diseases.[21] Third, the administration and treatment regimens are comparable. Hepatocytes are generally administered via the portal vein. This has proven to be safe and effective, and therefore, it is likely that organoids will be administered via the same route. Furthermore, similar immunosuppressive drugs may be given, because liver organoids, like hepatocytes, are expected to elicit an immune reaction. Fourth, comparable non-human animal models that represent human (metabolic) liver disease are used (e.g. Fah-knockout mice).[21,25–27]

In addition to examining the similarities, it should be judged to what extent there are differences between the reference class and the study intervention. These differences could impact the reasoning by analogy between efficacy in the reference class and the estimated efficacy of the study treatment.

The nature of the difference between liver organoid and hepatocyte transplantation lies in the *cell product* that is used. They differ in terms of the cell source, the culturing methods, and characteristics of the eventual cell product.[28] Liver organoids constitute a strategy to overcome the limited availability of donor livers that serve as the tissue source for clinical hepatocytes.[21,28] Organoid technology enables the expansion and long-term

culturing of small pieces of liver tissue into an unlimited supply of liver organoids that can be cryopreserved for future use.[20,22,25] The eventual cell product is different, because long-term culture and storage of liver organoids raises the question whether their (genetic) characteristics remain stable over time, even though genetic stability has proven remarkable in vitro.[22] Furthermore, liver organoids are generated from organ progenitor cells, and they do not yet contain fully mature hepatocytes in vitro. On the one hand, this may be beneficial. It is hypothesized that progenitor cells lead to long-term effects, because they will retain their stem cell regenerative potential after transplantation. However, liver organoids have to eventually mature into hepatocytes to fulfill all liver functions. This maturation process is currently being improved in vitro, and might further benefit from the hepatic environment after transplantation.[19,20]

Evaluation of the reference class evidence

To evaluate reference class evidence investigators and evaluators should assess (1) the nature and magnitude of the treatment effect, and (2) the 'robustness' of the evidence that supports the central causal premise.[5,12] The robustness of the evidence can be evaluated by considering the level of clinical evidence, and the correspondence between preclinical and clinical findings.

If applied to hepatocyte transplantation, (1) hepatocytes tend to generally establish a *short-term* improvement in the metabolic state and clinical condition of patients. Currently, hepatocyte transplantation is therefore employed to bridge the time to liver transplantation in children with life-threatening metabolic liver diseases.[2112] (2) Clinical studies are based on extensive preclinical animal studies that demonstrate metabolic improvement overall.[21] However, human clinical studies only rely on case series, which constitute a low level of evidence. This relates to the rareness and heterogeneity of inherited metabolic disease and the limited availability of human hepatocytes and applicability due to their short-term clinical effects, making it difficult to conduct large Randomized Controlled Trials.[21]

Evaluation of preclinical efficacy evidence

We briefly touch upon the main components of the assessment of preclinical efficacy evidence that has been described in more depth elsewhere.[5,29]

To formulate a value for determinant (b), the nature and the magnitude of treatment effects should be determined through systematic assessment of all available and relevant preclinical efficacy studies.[5,30] For instance, does the intervention impact primary outcomes, such as clinical improvement or increased survival, or does it only effect secondary outcomes? Regarding

the latter, one could ask to what extent symptoms are relieved and what the duration of the effect is.

To formulate a value for determinant (c), three types of validity threats should be evaluated: *internal, construct,* and *external* validity.[5,29,31] An animal study is internally valid, if the observed effect can be attributed to the study intervention. Internal validity can be threatened by different types of biases, among which selection or performance bias.[8] Evaluators should judge whether strategies to counter these biases, such as randomization and blinding, have been sufficiently employed.[5,8] *Construct validity* means that the animal model adequately corresponds with the target population in humans. Evaluators could, for instance, assess whether the animal models are similar in terms of the causal pathway, treatment regimen, and outcome measures, and whether 'state of the art' animal models have been used.[5,29] *External validity* means that the effects in animals uphold under varied test conditions. Thus, evaluators should ask whether efficacy studies have been replicated in more than one species, in different model settings, and in more than one laboratory.[5]

In addition to internal, construct, and external validity, evaluators should be aware of reporting or publication bias. Frequently, only positive results are published, which may lead to an overestimation of efficacy.[3,5]

CONNECTING ESTIMATED EFFICACY TO THE RISK-BENEFIT TASKS

Here, we connect the assessment of efficacy to the objective of deciding risk/benefit in ethical review. Decision-making regarding risks and benefits has to be systematic, transparent, and grounded in evidence.[1,2]

To increase systematization, we draw upon insights from decision-theory and divide the risk-benefit tasks into four steps: (1) risk-benefit analysis, (2) risk-benefit evaluation, (3) risk-benefit management, and (4) decision-making (Table 2).[11] Analysis and evaluation together constitute risk-benefit assessment. The responsibilities for the four different tasks are distributed among investigators/sponsors and evaluators. It is the primary responsibility of investigators/sponsors to perform risk-benefit analysis and evaluation and to report the overall assessment to evaluators (e.g. in an investigator brochure).[9,11] Evaluators (e.g. members of IRBs and RECs) should be able to form an independent judgment on the analysis and evaluation of risks and benefits. Subsequently, evaluators need to judge whether investigators need to implement measures to modify risks and benefits (i.e. risk-benefit

management). Finally, they need to decide whether benefits truly outweigh risks given all the information gathered in the previous steps.[11]

We particularly focus on the 'benefit-side' of the different tasks. At first glance, the assessment of estimated efficacy could especially contribute to the analysis of benefits (i.e. their systematic mapping and characterization). We thus elaborate in most depth on this task. However, we also argue how the approach formulated above contributes to evaluation, management, and decision-making.

(1) Risk-benefit analysis	The systematic use of information to map and characterize harms and benefits and to present this information in a systematic and comprehensive way.
(2) Risk-benefit evaluation	The attribution of weight to harms and benefits and the comparison of risks and benefits against given criteria to determine their significance.
(3) Risk-benefit management	The selection and implementation of measures to modify risks and benefits (ideally to minimize risks while maximizing benefits).
(4) Decision-making	The final discussion amongst evaluators (e.g. RECs) on whether benefits truly outweigh risks, given all the information provided are the risks of the trial ethically acceptable due to the merits of the probable benefits.

TABLE 2. RISK-BENEFIT TASKS

Task 1: Benefit analysis

Mapping benefits

To map benefits, we propose to divide clinical trial benefits into direct, inclusion, and aspirational benefits (Table 3).[6]

Although FIH trials that offer a prospect of direct benefits will constitute the exception to the rule, the possibility of direct benefits should not be excluded beforehand. Conversely, as is common to do, we exclude collateral benefits from further analysis.[6,32]

The category of aspirational benefits (or social value) remains underexplored. It is ambiguous, as it has many interpretations with variable objects and types of value.[32,33] Although it is outside the scope of this paper to provide a comprehensive account of (the assessment of) social value, for the sake of our argument, we propose to divide aspirational benefits into: (1) the anticipated social value of the *intervention*, (2) the progressive value, and (3) the translational value of a *trial* (Table 2).[31,33,34]

The anticipated social value of the intervention encompasses the value that an *intervention* could eventually have on the wellbeing of groups of patients and/or society (Table 3).[33,34] Although highly relevant, in the

stage of FIH trials this eventual effect lies in the distant future. Therefore, regulatory bodies (e.g. FDA) frequently judge the success of FIH trials on their ability to generate knowledge that promotes progression to later stages of research in which successful clinical translation becomes more likely. Kimmelman coins this type of knowledge value the 'progressive value' of a trial.[31] However, even if a FIH trial is well-designed, the progressive value of early phase studies may be limited. After all, novel interventions frequently fail to translate to later stages of research. Therefore, it is important to account for other types of knowledge value that FIH trials can generate.[31,32] FIH trials can produce knowledge that informs and motivates further preclinical testing ('reciprocal value'), that informs other related areas of research ('collateral value'), or that leads to modifications in the trial itself when repeated ('iterative value'). These three types of knowledge value together constitute the 'translational value' of a FIH trial.[31] Progressive and translational value do not necessarily constitute two entirely different types of knowledge value. Rather, translational value takes a broader perspective on the types of knowledge value that FIH trials can generate, even if findings are 'negative'. Furthermore, translational value corresponds with a non-linear view on clinical translation.[31]

Direct benefits	Benefits arising from receiving the intervention being studied to individual research participants.[6]
Aspirational benefits	Future benefits on an aggregate level
(1) Anticipated social value of the intervention	The nature and magnitude of the improvement the intervention is expected to have on the wellbeing of patients, individuals in society, or society.[33]
(2) Progressive value	The ability of a FIH trial to promote progression of the intervention to the next phases of research.[31]
(3) Translational value	The knowledge produced in a FIH trial that informs and motivates further preclinical testing ('reciprocal value'), that informs other related areas of research ('collateral value'), or that leads to modifications in the trial itself when repeated ('iterative value').[31]

TABLE 3. BENEFITS IN FIH TRIALS

Characterization of benefits

Direct benefits

To take direct benefits into account in justifying trial risks, there must be a *reasonable prospect* of direct benefits.[6] This means that there is no external standard or threshold for direct benefits. Rather, a claim of direct benefits should *be open to deliberation and discussion and it should be grounded in*

evidence, to the extent possible, on all three dimensions of direct benefits (i.e. the nature, magnitude, and likelihood).[6]

Overall, substantive estimates of efficacy form a *prerequisite* for a reasonable prospect of direct benefits. However, there is no threshold for direct benefits, nor is there a threshold for 'substantive estimates of efficacy'. Because the 'proof' for direct benefits lies particularly in a transparent reasoning process, it is worthwhile to show *how* the assessment of estimated efficacy grounds this reasoning process in evidence.

With regard to the *likelihood* of direct benefits, all else being equal, the higher the overall estimates of efficacy in humans, the more probable a prospect of direct benefits becomes. FIH trials that offer a prospect of direct benefit will form the exception to the rule. The reference class evidence can contribute to identifying these exceptions to the rule through reasoning by analogy, because it sheds light on the 'novelty' of study interventions. It may be challenging to warrant a claim of meaningful direct benefits by using preclinical efficacy studies only even if (b) treatment effects are large and (c) is low because validity threats are addressed properly.[31] However, if there is an (a) appropriate reference class in which there is robust evidence for the central causal premise of the study intervention, claims of direct benefits may be better supported. This reasoning by analogy can be applied to trials studying 'me-too' drugs, as well as to complex translational trials, such as organoid transplantations (that are modelled after hepatocyte transplantations).

Regarding the *nature* and *magnitude* of direct benefits, both (a) reference class and (b) treatment effects found in preclinical efficacy studies can provide valuable insights. Particularly if animal models are used that adequately model the clinical setting (c) (i.e. if threats to construct validity are adequately addressed), the *nature* and *magnitude* of treatment effects can be extrapolated to target population.[5] The reference class can further contribute to projecting treatment effects found in animal models to effects in the clinical population, particularly, if the reference class is based on similar preclinical models.

In analyzing a prospect of direct benefits other aspects have to be taken into consideration. Even despite substantive estimates of efficacy, FIH trials could still lack prospects of direct benefits, because the therapeutic window of the intervention is insufficiently known. Furthermore, trial design has to allow for direct benefits to all research participants.[31] For instance, participants have to be patients that are still able to benefit from the study treatment (e.g. that are not treatment refractory) and that all receive expected therapeutic doses. Additionally, for the assessment of direct benefits, the context, such as the standard of care and treatment alternatives, have to be taken into account.[6]

That being said, the burden of proof should lie with those that argue in favour of direct benefits in FIH trials. It is up to evaluators to decide whether claims of direct benefits are sufficiently warranted by preclinical and reference class evidence.

Aspirational benefits

Anticipated social value of the intervention

In characterizing the anticipated social value of an intervention, we draw upon the proposal by Habets and colleagues.[34] They argue that at least three steps should be followed.

First, the nature and magnitude of efficacy in humans must be critically assessed. Second, the anticipated clinical improvement in actual patients should be assessed, assuming that the intervention is efficacious. This means that it must be asked whether treatment effects are clinically meaningful, and that they must be weighed against factors that may hamper beneficial effects, such as adverse effects and ease of use. Third, the nature and magnitude of the anticipated improvement on the wellbeing of patients, individuals in society, and society has to be evaluated.[34] This assessment is contextual: the social value of the intervention is the expected improvement relative to other considerations, such as treatment alternatives, number of patients, and costs etc. Ultimately, determining what has social value constitutes a moral judgment.[33,34]

The assessment of estimated efficacy forms a systematic approach to the first step and, as such, it constitutes an essential part of the assessment of the anticipated social value. However, according to the approach of Habets and colleagues, substantive estimates of efficacy in humans are neither necessary, nor sufficient for an intervention to have social value. Not necessary, because the authors uncouple questions of likelihood from the evaluation of social value (even though it is debatable whether likelihood can be uncoupled from the anticipated social value). They ask what the anticipated social value would be, assuming that the intervention will be efficacious. For a positive estimation of efficacy, however, demonstration has to be *probable* after a small number of trials.[5] Not sufficient, because the other considerations that have to be assessed in step 2 and 3 of their approach have an important contribution to the eventual anticipated social value of an intervention.

Progressive value

To characterize progressive value, we argue that at least two elements should be evaluated: (1) whether there is a reasonable *probability* that an intervention could progress to the next stages of research, and

(2) whether the trial is *designed* such that the yielded results can contribute to progression to the next stage of research (typically Phase II).[31]

The assessment of estimated efficacy can contribute to the evaluation of both elements. (1) A study intervention only has the *potential* to progress to the next stages of clinical research if estimated efficacy in humans is substantial. Evaluators should judge whether they consider estimates of efficacy and the related potential to progress to be sufficient.

(2) FIH trials are frequently designed as Phase I studies that aim to yield information on safety, dose and schedule, and the mechanism of action in humans.[35] Typically, dose escalation schemes are employed to determine dose-response curves and the Maximum Tolerated Dose (MTD). Such a trial design is particularly fruitful, if there is a relatively small 'translational gap'. This means that, based on animal models and/or reference class, researchers can make reliable projections of mechanism of action and treatment effects in humans.[31] If, on the other hand, the translational gap is wider, small pilot or exploratory studies in humans may be needed to bridge the gap, and to ultimately stimulate progression to the next stages of research (see the section on translational value and benefit treatment) [31].

Translational value

To characterize the translational value of FIH trials, it should be assessed whether there is a reasonable prospect of reciprocal, iterative, and collateral value.[31]

For FIH trials to have translational value, they should be hypothesis-driven. Preclinical and reference class evidence constitute the basis for the generation of hypotheses and the context for the subsequent interpretation of both positive and negative findings.[31] For instance, if a positive result in animals is followed by a negative result in humans, this can prompt further explorations of this difference (reciprocal value) and/ or modifications to the intervention to overcome translational hurdles (iterative value). Furthermore, the reference class helps researchers to put their findings in a broader context, and to communicate their findings to other areas of research (collateral value). Evaluators should judge whether investigators base their hypotheses on a solid assessment of preclinical and reference class evidence.

Task 2: Benefit evaluation

An extensive discussion of risk-benefit evaluation is outside the scope of this paper. However, we contend that investigators and evaluators should be explicit on the weight they ascribe to the different types of benefits (and harms).[11] The maximization of the prospect of direct benefits, for instance, may require an increase of dosage that increases risks of adverse events.

To enhance translational value, additional biopsies and blood draws may be necessary that can be risky and burdensome.[31] Progressive and translational value are not necessarily mutually exclusive. However, they may require a different trial design.[31] Therefore, it should be made explicit how a trade-off between different types of benefits and harms is made.

Task 3: Benefit management

Benefit management (sometimes referred to as benefit treatment) refers to measures that can be taken to modify and ideally to optimize benefits.[11] The assessment of estimated efficacy can contribute to the optimization of the prospect of direct benefits, progressive, and translational value in the following ways.

First, if direct benefits and/or the progressive value of a FIH trial are considered to be insufficient, this can be (partially) due to a lack of estimated efficacy. After all, substantial estimates of efficacy constitute a *prerequisite* for both types of benefits. If estimates of efficacy are deemed insufficient, this can be due to (a) a low prior (the reference class), (b) a lack of treatment effects in animal studies, and/or (c) threats to validity (Table 1). Whereas (a) is given, (b) and (c) constitute modifiable factors, to some extent. Evaluators should therefore ask whether and what type of additional animal testing could contribute to increases of estimated efficacy and to a reduction of the translational gap. If treatment effects are disappointing, investigators could be prompted to scrutinize alternative treatment strategies in animal studies (e.g. different dosage, mechanisms of delivery etc.). If *internal validity* is threatened, investigators could be advised to conduct additional animal studies in which measures to counter bias (e.g. randomization and blinding) are implemented.[36] In case of *construct validity* threats, investigators could conduct additional testing in animal models that more reliably correspond with the clinical setting (e.g. larger animal models).[5,29] However, sometimes more appropriate animal models are simply lacking. In these cases, it may be possible to conduct small pilot studies in patients.[31] If *external validity* is questioned, then animal studies could be repeated under different experimental circumstances.[5] If, alternatively, a lack of prospect direct benefits and/or progressive value is due to inadequate trial design, the assessment of estimated efficacy can offer clues for optimization of design. Particularly evidence generated in the reference class can provide insights on the type of patients that are most likely to benefit and on the expected therapeutic window. If the prospect of direct benefits and progressive value are considered to be insufficient, the optimization of translational value deserves even more attention.[31]

Second, the following measures can be taken to enhance the *translational value* of a FIH trial. If hypotheses are insufficiently supported by evidence,

investigators can be advised to gather and assess existing preclinical and reference class evidence more thoroughly, or to conduct additional preclinical testing. Furthermore, open *sharing* of the assessed preclinical and reference class evidence and of the data generated in and (tissue) samples collected during the trial (e.g. through data and tissue banking) can enhance the translational value.[31,32] Additionally, amendments to the trial design can spur the translational value. If the translational gap is relatively wide, small correlative studies in which various mechanisms of action are explored may be preferable. In these correlative studies patients rather than healthy volunteers should be included and molecular and physiological responses should be measured.[31] To monitor these outcomes it may be necessary to perform additional procedures such as biopsies and blood draws. For reciprocal and iterative value to materialize, the study interventions need to be flexible, the treatment and methods for treatment evaluation (including the measurement of target effects) need to be explicitly described, and potential follow-up experiments need to be anticipated.[31]

Task 4: Decision-making

Finally, evaluators have to decide whether benefits truly outweigh the risks, given the outcomes of the previous three steps.[11] If the assessment of efficacy is connected to the three risk-benefit tasks, decision-making processes become more systematic, transparent, and grounded in evidence.[1,2] This is valuable in itself, and it helps to better uncover the reasons for both agreements and disagreements within and across committees, as well as among evaluators and investigators/sponsors. More insight into diverging judgments contributes to resolving conflicts, to come to joined decisions, and to act upon differences (e.g. it can guide investigators in what additional evidence or argumentation is necessary to convince evaluators).

For instance, it could be that investigators come to a favourable risk-benefit balance, whereas the evaluators decide that the risks are unacceptable in relation to the benefits. There may be different reasons for this disagreement. For instance, (1) based on the reference class and preclinical evidence investigators could come to a different *probability* of efficacy than evaluators. (2) Alternatively, both parties could agree on the probability of efficacy, but they *appreciate* the probability differently. Investigators may deem 60% chance of efficacy enough to warrant claims of direct benefits, whereas evaluators deem this insufficient. (3) Or, although investigators and evaluators agree on the prospects of the different types of benefits, they attribute a different weight to different types of benefits and risks. These various causes for diverging judgments could elicit different courses of action. In example (1), investigators could come with additional argumentation to support *their* estimates of efficacy. In example (2),

investigators could try to increase estimates of efficacy through performing additional animal tests that examine alternative treatment strategies, and to address validity threats to increase estimates of efficacy. Or, they could provide additional argumentation for their claim that a 60% chance of efficacy is enough to warrant claims of direct benefits (e.g. because treatment alternatives are lacking). In example (3), the preclinical efficacy studies are beyond discussion.

CONCLUDING REMARKS

With this paper, we contribute to systematic, transparent, and non-arbitrary assessment decision-making regarding risks and benefits in the ethical review of FIH trials. We further develop and connect a novel approach to estimate efficacy in humans, in which estimates of efficacy are based on both reference class and preclinical efficacy evidence, to the four risk-benefit tasks (Table 2).[11] We clarify the selection and evaluation of reference class evidence, and use liver organoid transplantation as an exemplary case.

Because of these important contributions to decision-making in FIH trials, we deem the practical implementation of our approach to assessing estimated efficacy worthwhile. Here, we offer some first suggestions for practical implementation, and identify barriers that should be addressed.

First, the division of responsibilities should be appropriately articulated. We deem investigators/sponsors responsible for the assessment of estimated efficacy, the subsequent benefit analysis, and for composing a report. Based on this report, evaluators should be able to come to their own independent analysis and evaluation of benefits (and risks).

Second, guidance for the conduct of estimated efficacy assessment is necessary. A systematic review (SR) or meta-analysis should be conducted to systematically assess preclinical efficacy evidence.[9,30] The SYCRLE guidelines could be used as a guide to systematically gather preclinical evidence and to address threats to internal validity.[30] Additional tools are needed that standardize the assessment of threats to construct and external validity, as well as other types of bias (e.g. publication bias).[8,29] Moreover, the quality of conduct and reporting of animal studies should be improved.[3] Evaluators could, for instance, demand adherence to the ARRIVE guidelines.[33] A formal SR may not be needed for the evaluation of reference class evidence. However, investigators should give a general indication of the robustness of the reference class evidence, and of how the reference class was selected. Further methodological research (e.g. drawing on insights from forecasting analysis and Bayesian statistics) is

needed to scrutinize whether and how estimates of efficacy in humans can be calculated based on reference class and preclinical efficacy evidence.

Third, the report should entail a step-wise description of (1) the evaluation of reference class and preclinical efficacy evidence, (2) the final judgment on estimated efficacy, and (3) the mapping and characterization of benefits. It could be integrated with (and improve) investigator brochures.[9] The report should be understandable, objective, balanced, and concise rather than exhaustive, for evaluators to be able to come to independent risk-benefit judgments.[9] Researchers, policy makers, evaluators, and regulators should collectively formulate context-sensitive standards for the assessment and reporting of estimated efficacy, while taking into account aspects of feasibility.

Fourth, evaluators should have the appropriate expertise to judge whether they agree with the benefit analysis, and to propose measures to augment benefits (in consultation with investigators).[4] Such expertise may be lacking, particularly if complex translational trials are reviewed. Potential solutions may be additional training programs on the interpretation of estimated efficacy assessments, and/or the appointment of ad hoc committee members.

Ultimately, it is the shared duty of investigators and evaluators to substantiate the leap of faith from bench to bedside, and to optimize the value of FIH trials. We hope that our approach contributes to bridging the translational gap and to bringing promising treatments to patients in ethically sound ways.

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CHAPTER 11

General discussion

GENERAL DISCUSSION

This thesis aimed to identify and evaluate the ethical challenges related to organoid technology. This main aim was divided into four research questions:

I. What are the key ethical challenges related to the donation, storage, and use of organoids?
II. How can we conceptualize and evaluate the moral status and the exchange of organoids?
III. Which moral conditions should be formulated for the exchange of organoids and related human tissue products?
IV. How can we ethically evaluate first-in-human organoid transplantation?

The four parts of this thesis correspond with the four research questions. Here, I will answer the four research questions through a discussion of the main findings of each part. Next, I will propose a shift towards value-sensitive governance of complex exchanges of organoids and related human tissue products. Subsequently, I will reflect on the potential contribution of an active engagement of bioethicists with the arts to the moral reflection on novel biotechnologies.

DISCUSSING THE MAIN FINDINGS IN LIGHT OF THE FOUR RESEARCH QUESTIONS

Part I: Identifying the ethical challenges related to the donation, storage, and use of organoids

To set the agenda for ethics research we aimed to identify the ethical challenges associated with the donation, storage, and use of organoids (see Chapter 2 and 3).

First, we pointed out that the moral and legal status of organoids deserve further examination. Organoids constitute novel types of entities that closely represent the human body, that are relatively tangible and that bear a close functional and genetic link to donors.[1,2] Additionally, some types of organoids may model sensitive human bodily materials, such as the human brain

(cerebral organoids), or the human embryo (blastoids and gastruloids).[3–6] This raises questions regarding the moral value of organoids and the perceived relationship of donors to organoids derived from their bodily material. Answers to these questions may affect views on the adequate type of donor consent, ethical oversight, governance requirements, ownership, and the desirability of commercialization.[1,5] Therefore, we have explored the perspective of participants in organoid research and biobanking, namely patients with Cystic Fibrosis (CF) and parents of children with CF, on organoid technology in Chapter 3. Furthermore, we have conceptualized the moral value of organoids in Chapter 4 and 5.

Second, we argued that the storage of organoids in so-called living biobanks calls for the development of adequate consent procedures in both research and clinical applications. We deemed an opt-in required because of the potential sensitive future uses of organoids.[7] Since specific consent is regarded to be impracticable and undesirable in biobank research, we called for the consideration of alternative consent models.[8] In Chapter 5, 6 and 7, we have proposed 'consent for governance' as a leading consent paradigm for organoids and related human tissue products.

Third, we called for the development of adequate governance models for organoid biobanking. In establishing organoid biobanks both scientific and clinical aims and public and private domains are intertwined, which results in mixed models in biobanking.[9–12] Adequate governance is indispensable in balancing the long-term and potentially conflicting interests of the different stakeholders involved, among which, patients, participants, researchers, physicians, and commercial parties. Our proposed consent for governance model aims to respond to this challenge (see Chapter 5, 6 and 7).

Fourth, we anticipated ethical challenges related to the clinical translation of organoids. We have called for the development of new models of ethical oversight and reimbursement that enable the adequate integration of research and care in the precision medicine applications of organoids (see Chapter 2). In regenerative medicine, First-in-Human (FIH) trials will constitute a key step in translating organoid transplantation from the bench to the bedside. We argued that FIH organoid trials will be so-called complex translational trials that are coupled with ethical questions regarding risk-benefit, informed consent, participant selection, and trial design.[13,14] In Chapter 10 and 11 we have addressed participant selection and risk-benefit assessment.

Organoid technology is a complex field in which several ethical discussions converge, organoids raise specific questions of moral value, and organoid technology is situated in an increasingly commercialized and globalized landscape. Therefore, we argued that the abovementioned ethical

challenges, although they are not new, need reconsideration in the context of organoid technology.

Part II: Conceptualizing and evaluating the moral status and the exchange of organoids

We aimed to conceptualize and evaluate the moral status of organoids and their increasingly commercialized exchange.

We argued that the traditional bioethical frames of gift versus market are inapt to capture the practical and ethical complexities of the increasingly commercialized exchange of organoids. The 'gift paradigm' holds that a profit motive is irreconcilable with the donation and use of human tissues. The 'market paradigm' alternatively frames human tissues as commodities (see Chapter 5).[15,16] Both paradigms are underlined by a deeply rooted division between *subjects* and *objects*. Whereas we can own and sell things, we cannot own nor sell people. Human tissues and related products, however, fall between two stools.[15,17] To handle this grey area the gift paradigm categorizes human tissues as *'subjects'* and the market paradigm as *'objects'*. However, we argued that these categories black-box the moral value of organoids and overly simplify the intricacies of their commercialization.

Alternatively, we have examined what subject- and object-like values organoids have (see Chapter 4 and 5). We have proposed to recognize organoids as hybrids that relate to persons and their bodies as well as to technologies in ambiguous ways.[15,18] This hybridity is reflected in the perspective of participants on organoids. They perceive a close as well as a distant relationship to organoids (see Chapter 3). Some sub-types of organoids, such as cerebral organoids or gastruloids, raise questions of *intrinsic moral value*.[3–6,19] All types of organoids have some form of *relational moral value*, because they refer to and are meaningful for persons.[20] Organoids relate to the bodily integrity, personal values and identity, privacy, and wellbeing of donors. Simultaneously, organoids constitute technological artifacts that have instrumental and commercial value. The 'subject- and object-like' values of organoids are inseparable. It is the technological transformation of human tissue into organoids that generates potential intrinsic and relational moral value as well as instrumental and commercial value. Organoids do not have a fixed ontological status or moral value. Rather, the value and meaning of organoids comes into being and changes in a network of both human and non-human actors, such as institutions, donors, researchers, policy makers etc.

In this network of exchange the 'subject-like and object-like' values of organoids and the interests of the different stakeholders have to be considered. We have used the notion of 'disentanglement' to deconstruct

the ways in which commercialization and distribution of organoids is negotiated [20,21]. We have argued that commercialization of organoids is legitimized by a detachment of the instrumental and commercial value of organoids from their associations with persons and their bodies. This detachment is enacted in steps of *disentanglement*, among which measures that are traditionally employed to protect donors, namely consent and anonymization. Consent and anonymization together with commodification may lead to far-reaching disentanglement of organoids. We problematized far-reaching disentanglement because of two interrelated reasons. (1) Societal interests could be put under pressure, because the rationale for commercializing organoid technology, that is, to stimulate biomedical innovation for the good of society, may not be fulfilled. (2) The interests of donors are made subordinate to those of third parties and the relational moral value of organoids may be insufficiently recognized. A central ethical challenge is thus to enable (partial) commercialization of organoids to stimulate biomedical innovation in research *and* care, while adequately respecting the relational (and in some cases the intrinsic) moral value of organoids as well as the interests of patients, participants, and society. Our proposed 'consent for governance' model (see Part III) aims to contribute to meeting this challenge.

Part III: Formulating conditions for the exchange of organoids and related human tissue products

We aimed to formulate conditions for the exchange of organoids and related human tissue products.

We have proposed a 'consent for governance' model as a leading paradigm for organoid exchange (see Chapter 5-7). Consent for governance implies that the consent procedure is aimed at providing the donor with information on the governance structure of the biobank in question (e.g. information on property rights, data handling, ongoing communication with donors etc.). Furthermore, the ethical emphasis shifts from initial consent to continuous governance obligations, among which (1) privacy by design, (2) participant engagement, (3) benefit-sharing, and (4) ethical oversight.

Privacy by design encompasses the incorporation of privacy measures in the entire infrastructure of organoid exchange.[22] This means that the most appropriate privacy standards apply by default and that the amount of coupling to personal data should be tailored to the application of organoids. Participant engagement refers to the substantial engagement of (groups of) donors and the wider public in the design and continuous adaptation of governance. Benefit-sharing encompasses the fair sharing of monetary and non-monetary benefits generated through organoid exchange among all parties involved, including donors, patients, and society.[23–26] Ethical

oversight bodies should be incorporated in different stages of organoid exchange. We position organoid technology as exemplary for broader developments in the biotechnological field where human tissues can be increasingly transformed into complex human tissue products. Our consent for governance model extends to these other types of human tissue products (e.g. artificial gametes, synthetic embryo-like structures).[27–29] The interpretation and implementation of the formulated governance obligations should be case- and context dependent.

In Chapter 8, we have examined the interpretation of a specific form of participant engagement in the realm of genomics, that is, the return of genetic results to family members of participants (see Chapter 8). Next-Generation-Sequencing techniques are routinely applied in the stem cell (and organoid) field. The genetic information yielded with these techniques may be of relevance not only to participants but also to their family members.[30] This raises the question whether and how genetic information should be disclosed to relatives. This issue becomes especially salient after the death of participants, when they can no longer warn family members for hereditary risks and permission for disclosure can no longer be sought. We have identified and explained the arguments in favour of and against disclosure of genetic information to the relatives of the deceased. We proposed a passive postmortem disclosure policy for the communication of genetic information to family members.

Part IV: Ethical evaluation of first-in-human organoid transplantation

We aimed to evaluate FIH organoid transplantation. We have evaluated the ethical acceptability of including children in a FIH organoid transplantation trial (see Chapter 9). Patients with inherited metabolic liver disease constitute a likely target population for liver organoid transplantation, a field in which initiatives are advancing towards the clinic.[31–33] Inherited metabolic liver diseases mostly present in early infancy.[34] However, the inclusion of children in FIH trials is ethically contentious, among other reasons, because they are less (or not) capable to protect their own interests.[35] We have argued that a first-in-children trial would be justifiable, if direct benefits are warranted by preclinical and reference class evidence, provided that the following conditions are met: 1) the risks related to organoid transplantation are minimized and outweighed by the potential individual benefits, 2) the aggregate risks are acceptable in light of the potential individual benefits and social value, and 3) attention is paid to valid informed consent and assent.

In Chapter 10, we have contributed to systematic, transparent, and non-arbitrary decision-making regarding risks and benefits in the ethical review

of FIH trials. We connected a novel approach to the systematic assessment of estimated efficacy in humans, that bases estimates of efficacy on both preclinical efficacy and reference class evidence, to the four risk-benefit tasks.[36,37] We have used liver organoid transplantation as an example to illustrate the appropriate selection and evaluation of reference class evidence.

ORGANOID TECHNOLOGY: TOWARDS VALUE-SENSITIVE GOVERNANCE OF COMPLEX EXCHANGE OF ORGANOIDS AND RELATED HUMAN TISSUE PRODUCTS

Here, I will further reflect on our findings regarding the moral value and exchange of organoids and propose a shift towards value-sensitive governance of complex exchange of organoids and related human tissue products.

From a 'biobank model' towards 'complex exchange'

In Part I of this thesis, I have pointed towards the need to develop adequate governance models for the establishment of organoid biobanks. However, I contend that the 'biobank model' is not entirely apt to capture the ethical and practical complexities of the circulation of organoids (see Chapter 5). The banking of human tissues implies a unidirectional flow of one product, a human tissue sample, from (1) the initial collection to (2) the subsequent storage, and (3) use.[7,38] Additionally, it presupposes one central body or bank that coordinates the collection, storage of, and access to samples. However, the circulation of organoids does not follow such a pipeline structure, nor is there one central coordinating body. Rather, as I have argued in Chapter 5, organoids (and related human tissue products) move within a complex network of exchange in which human bodily materials can be continuously transformed, stored, distributed, and utilized in a disorderly fashion. In the remainder of the thesis I have, therefore, evaluated the complex *exchange* of organoids, and I have proposed a 'consent for governance' model to govern the exchange of organoids and related human tissue products.

The exchanges are particularly complex because (ordinary) human tissues can be transformed into hybrid tissue products that associate with multiple value regimes. These hybrid products can be exchanged in a global market while moving through the realms of both research and care (see Chapter 5). In Part II, I argued that we should focus on the following ethical challenge: *to enable (partial) commercialization of organoids to stimulate biomedical innovation in research and care, while adequately respecting the relational (and in some cases the intrinsic) moral value of organoids, as well as the interests of patients, participants, and society.*

From 'consent and anonymization' to 'consent for governance'

In Chapter 5 and 7, I have argued that the current emphasis on and interpretation of donor consent and the protection of privacy for the ethical use of human tissues is insufficient to meet the above-mentioned challenge.

Over the past couple of decades ethicists have made significant advancements in the development of consent procedures, mechanisms for the protection of privacy, and ethical oversight for the banking and scientific use of human tissues.[26,38–40] Although alternative models have been proposed [41–43], a frequently proposed consent model for the banking of human samples and data is broad consent.[8,44] Broad consent is generally interpreted as consent for an unspecified range of future research questions and methods (subject to specified content and/or process restrictions).[8] To protect the privacy of donors there has been an emphasis on cutting ties between tissue samples and personal information through anonymization or pseudonomyzation.[40] Although consent and anonymization may constitute important means to protect the interests of donors, they came to play a double role, because they *disentangle* tissue products from donors and their bodies (see Chapter 5 and 7). Once third parties have ticked the boxes of consent and anonymization, they are granted more flexibility regarding distribution, use, and commercialization. Donors, however, are effectively left without any measures to manage downstream use of their samples (see Chapter 7).[20,45,46]

I have proposed 'a consent for governance model' to better recognize the hybrid character of organoids and to maintain ongoing connections to patients, participants, and society when organoids are (commercially) exchanged (see Chapter 5, 6 and 7). In this model consent still plays an important role. However, both the *process* and the *role* of consent change. Rather than providing information on potential future uses, I have argued that the consent procedure should be aimed at providing the donor with information on the governance structure of the biobank in question (e.g. information on property rights, data handling, ongoing communication

with donors etc.). Furthermore, the ethical emphasis shifts from consent to ongoing governance obligations (see Chapter 5 and 7). While consent for governance still enables flexible use and distribution of organoids, simultaneously novel relationships to patients, participants, and society are established. Thus, through consent for governance organoids are not only *disentangled* but also *re-entangled.* [20] Although the protection of the privacy of donors constitutes one of the proposed ingredients for ongoing governance obligations, it is interpreted differently. In what I have called 'privacy by design' the most appropriate privacy standards apply by default (see Chapter 5 and 7). I have stressed that the coupling of personal data to samples should be proportionate to their use. Thus, rather than *detaching* organoids from personal information, links between organoids and donors can be maintained to enable downstream management of samples by donors, return of (clinically useful) results, and requests for new phenotypical information. The protection of privacy is complemented with the long-term engagement of participants, measures of benefit-sharing, and ethical oversight.

Towards value-sensitive governance of complex exchange

If I attribute such weight to *governance,* I should further elaborate on what I mean with the term. Particularly, because governance knows many different interpretations.[47–50]

Governance can be defined as '*the processes of interaction and decision-making among the different stakeholders that are involved in a collective problem that lead to the creation, reinforcement, or reproduction of social norms and institutions'.*[47] This sociological definition provides a useful perspective on the network of human and non-human actors in which the value of organoids comes into being and changes (see Chapter 5). The definition is descriptive, as it does not prescribe which modes of governance are preferable.[47] Although a purely descriptive take on governance may be useful for analyses of different types of governance in the social sciences, I wish to take a value-laden stance on governance, as I operate from within the field of bioethics. Therefore, I loosely combine the sociological definition with the concept of Value-Sensitive Design (VSD).[51] VSD is a theoretically grounded approach to the design of technology that accounts for human values in a principled and systematic manner throughout a design process. This is done through an iterative process of conceptual, empirical, and technological investigations. For instance, in designing an office environment guiding values could be the physical health, emotional wellbeing, and creativity of employees.[51] From empirical research in the field of psychology it is known that even a minimal interaction with nature

can relieve stress and reduce sickness. These guiding values and empirical insights can be accounted for in the design of office buildings, for example, through allowing for 'real views' of nature (e.g. large windows) or through technological representations of nature, such as plasma screens.[51] What I wish to adopt from the concept of VSD is the idea that *values* should be explicitly guiding the decision-making processes and the creation of norms in the exchange of organoids. Furthermore, it is useful to keep the idea of 'design' in mind when thinking about ways to reproduce and reinforce social norms.

I thus define value-sensitive governance as: '*the processes of interaction and decision-making among the different stakeholders that are involved in a collective problem that lead to the creation, reinforcement, or reproduction of social norms and institutions and that are explicitly informed by values.*'[47,51] I propose to move towards value-sensitive governance of complex exchanges of organoids and related human tissue products.

Here, I connect our proposed consent for governance model to the idea of value-sensitive governance. Following the proposed definition of value-sensitive governance, I formulate ways forward in thinking about (1) which values to include, (2) fair processes of decision-making, and (3) ways to reproduce and reinforce values. As such, I mean to provide ways to further deal with *the collective problem* of enabling (partial) commercialization of organoids and related products to stimulate biomedical innovation in research and care, while adequately respecting the relational (and in some cases the intrinsic) moral value of organoids as well as the interests of patients, participants, and society.

(1) Which values to include

If the processes of decision-making and the creation and reinforcement of norms are to be informed by values it is necessary to ask which values to include, which values should be guiding, how are values interpreted, how could different values conflict, and which trade-offs are to be made?[51]

As I argued previously, consent and anonymization have been dominant in justifying the use of human tissues for research. Both consent and anonymization are manifestations of autonomy-based interests.[45] I deem respect for the autonomy of donors of vital importance. After all, I have argued that consent for governance contributes to autonomous decision-making on behalf of the donor (see Chapter 6). However, as I have shown in this thesis and as other authors have argued before me, autonomy-based interests should be complemented with other values to responsibly guide the exchange of organoids and related human tissue products.[26,45,52,53]

I have pointed towards the importance of taking hybridity seriously throughout organoid exchange. The nature of this hybridity should be

examined for different human tissue products. What questions of intrinsic moral value do they raise, what is their relational moral value, and how do these values relate to their technological, instrumental, and commercial values? How could these values potentially conflict and how will conflicting values be negotiated?

Furthermore, in Chapter 5 I have argued that the rationale for commercialization, namely biomedical innovation for the good of society, should not be taken for granted. Rather, it should be addressed what scientific and clinical aims should be pursued. Through organoid exchange different types of value can be generated, for example, knowledge value, value for health care, and economic value. [20,49] It should be considered what types of endeavours are thought to generate value for society, or in other words, 'social value'.[45,54]

Moreover, in light of the increasing clinical applications of organoids and commercialization of the biotechnology field, notions of reciprocity, solidarity, and justice need to be reconsidered.[23,25,45,53,55,56] As I have argued in Chapter 5, reciprocity and justice can become compromised in the case of far-reaching disentanglement, among others, because everyone but the donor appears to have a financial interest. Donors may not necessarily want to or need to share in monetary benefits,[57] but particularly if the lines between research and care are blurring, participants should be able to reap the 'clinical fruits' of organoid exchange. The proposed ingredient of benefit-sharing can prove valuable in giving substance to solidarity, reciprocity and justice.[23–25,55,58]

(2) Processes of decision-making: engagement of participants, patients, and the wider public

A key question that deserves further attention is what can be regarded as *fair* processes of interaction and decision-making.[49] Fair processes are needed to balance the values and interests of different stakeholders and to come to shared norms for organoid exchange. In thinking about fair processes considerations of social, epistemic, and procedural justice require attention. Although it is outside the scope of this discussion to provide an account of fair processes, I do wish to point towards the need to engage patients, participants, and the wider public in iterations of value-sensitive governance. After all, they constitute important stakeholders. This is in line with the emergence of initiatives under the umbrella terms Public and Patient Involvement (PPI) and Participatory Medicine.[59,60] It should be further examined what the contribution of participants to value-sensitive governance could and should be, how such engagement could be shaped, and how participant leverage could be ensured.[59]

In my opinion, participants and the wider public could have important contributions to the identification and interpretation of guiding values. They can, for instance, contribute to exploring the intrinsic and relational moral value of the human tissue products. Additionally, they can contribute to discussions on what is regarded to have social value and to the prioritization of scientific and clinical projects.[61] Furthermore, ongoing engagement of participants is necessary for the reproduction of values. For instance, to put reciprocity in practice through the return of clinically useful results, a feedback loop to participants is necessary. The social value of research projects can be enhanced if participants can provide novel personal and clinical information. A central point of concern is patient leverage. How can it be ensured that the voice of participants and the wider public is not only heard, but that they can also exercise power?[60]

In shaping participant engagement there is not one superior model. Rather, different models of participant engagement and participant leverage deserve to be explored.[58,60,62] In doing so, form should follow function. In other words, participant engagement should not be some sort of decorative element to keep funders happy, and the adage 'the more the merrier' does not apply. Rather, it should be asked *who* should be engaged and *why* participants are engaged (e.g. to interpret values, to take part in decision-making, or to ensure reproduction or reinforcement of values)?[59]

(3) Reproduction and reinforcement: alternative models of innovation and ownership

Traditional means to reproduce and reinforce values and norms in the realm of biobanking are donor consent, privacy protection, and ethical oversight committees, as I have argued above.[45,58] All these models are of paramount importance and they constitute important ingredients of our consent for governance model. Nevertheless, now that the exchange of hybrid human tissue products is intricately interwoven with economic interests, possibilities to put values into practice via (alternative) models of innovation and ownership should be explored. I deem it particularly worthwhile to scrutinize models that adopt a holistic approach to biomedical innovation, that put benefit-sharing into practice, that steer desirable use of technology, and that contribute to a (fair) distribution of power among the different stakeholders.[20,53,58,63,64]

For instance, the role of patents could be reconsidered. Patents grant the patent-holder the right to provide and deny access to the patented technology and to determine the terms under which access is provided.[63,65,66] While these rights can be exercised to yield profit they can also be employed to steer desirable use or to prevent controversial applications through so-called ethical licensing.[63,65] This form of 'private governance' deserves

to be further explored in the context of organoid exchange. Additionally, patents could be used to maintain open access to organoid and related technologies. Open access could for instance be maintained via a 'Creative Commons' construction that resembles legal structures in the creative industry.[65] Furthermore, patent holders could establish pricing differences for access to organoids between academic and private parties. This could contribute to (re)distribution of benefits. Besides, profit yielded through licensing of organoid technology could be reinvested in endeavors that contribute to public and social benefits, such as the maintenance of a research infrastructure or the conduct of research projects that address unmet health needs.

Moreover, it is worthy to explore alternative models for the ownership of tissue and data collections (and the knowledge and technologies resulting from their use).[17,58,67,68] The charitable trust, for instance, has been proposed as a model to put benefit-sharing into practice and to give leverage to participants. In a charitable trust donors transfer their property rights to a trustee. The trustee has the rights and obligations to keep or use the property (the samples and/or data) for the benefit of a specified party, the beneficiary. The beneficiary could be a group of participants, patients, or the wider public. Participants could form part of the advisory board that governs the trust.[58,67]

Finally, the merits of different 'business models' for sustaining infrastructures of organoid exchange deserve to be examined (e.g. public-private partnerships).[49]

THE CONTRIBUTION OF THE ARTS TO THE MORAL REFLECTION ON NOVEL BIOTECHNOLOGIES

In Chapter 4, I show how the collaborative project 'A Sculpture Like You and Me' with fine artist Rosa Sijben has contributed to the moral reflection on the moral value and commercialization of organoids. Here, by drawing on this example, I would like to further reflect on what the active engagement of bioethicists with the arts could contribute to the moral reflection on novel biotechnologies.

Relationship between the arts and ethics of biotechnologies

Ethics and the arts have a longstanding relationship that takes multiple forms. Art is, for instance, seen as a way of examining the good life.[69] To quote Aristotle 'beauty produces data for ethics'.[70] Through art we can examine potential interpretations of personal virtues and meaningful relationships. Moreover, art is seen as a means to raise or examine ethical issues, for instance, through protest songs. Alternatively, art can be evaluated from a normative point of view. It is sometimes argued that if a work of art is morally flawed this influences its aesthetic value.[69,70] Furthermore, there is an emerging recognition that the engagement of works of art with novel biotechnologies can shed light on their ethical and societal implications.[69–71]

There are several ways in which artworks can engage with novel biotechnologies.[70,72] 'Bio-art', for instance, is a particular genre in which artists literally experiment with novel biotechnologies.[71,72] Artists use biomaterials such as tissues, blood, genes, or viruses as the canvas for their work and they employ scientific processes (e.g. tissue culture and bio-engineering) to produce their artworks.[71] Organoid technology has already inspired a work of bio-art. In the project entitled 'Et In Arcadia Ego' artist Charlotte Jarvis has collaborated with scientists to generate tumorous organoids from healthy cells harvested from her intestine.[73] In an exhibition and performance in which she displays the process of creating these tumorous organoids and her emotions during that process, she means to examine mortality and to create a dialogue with and about cancer. Another example in the field of genomics is the project 'Cellout.me' by Dutch artist Jeroen van Loon.[74] In this artwork Jeroen van Loon has offered his entire DNA for sale online during one year. As such, Van Loon questions what the value of a single human DNA profile is, and touches upon questions concerning authorship, intellectual property, and privacy.

Art is particularly apt to contribute to moral reflection on novel biotechnologies, because it allows for the exploration of different future scenarios and the augmentation of potential effects of technologies.[70] Through art one can experiment with the uncertainties and ambiguities inherent to novel biotechnologies. Art can provoke, make controversies insightful, and elicit emotional, sensory, and imaginative experiences.[70,71] As such, works of art can prompt moral reflection, lead to taking on fresh perspectives, and stimulate more profound thinking, particularly because the technological and ethical complexities can be made insightful. The recognition of the important role of the arts in the responsible development of biotechnological innovations is reflected by the increased demand for inclusion of 'the arts' or creative industry in different funding

bodies.[70] It has been emphasized that arts could play a role in engaging scientists, policy makers, and the wider public in moral reflection on novel biotechnologies.[70,71] Ethicists may be involved in initiating the collaboration with creative industry, in reflecting on artworks, or in reflecting on the moral views of others elicited by an art work.[70,75] Although this can indeed be very valuable, here I would like to take on the task of reflecting on how the active engagement of bioethicists *themselves* with the arts can contribute to *their own* moral reflection on novel biotechnologies.

'A Sculpture Like You and Me'- How the arts can complement Wide Reflective Equilibrium

The project 'A Sculpture Like You and Me' does not constitute a direct form of bio-art as I do not directly engage with organoid technology (as Jarvis does). Rather, Sijben and I examine the ethical implications of organoid technology through spoken and written text in *dialogue* with different audiences, objects, and imagery. Here, I would like to connect the ways in which 'A Sculpture Like You and Me' has enriched my moral reflection to the model of Wide Reflective Equilibrium (RE) that I introduced in Chapter 1. In Wide RE, the thinker attempts to be comprehensive and critical. To do so the set of initial moral intuitions should be broadened and the thinker should try to disrupt a narrow state of RE by considering background theories and alternatives to his or her moral theory.[75]

First, 'A Sculpture Like You and Me' broadened and deepened the initial input for RE, among which the moral intuitions and moral emotions as well as the perspective on morally relevant facts.[70,76] My engagement with the audiences and Sijben both during and after the performance allowed me to include their moral views, experiences, and emotions of the audience that the performance elicited. Furthermore, I could include the initial reactions of Sijben and her colleagues that I encountered during our weekly arts-ethics labs. And, perhaps most importantly, the weekly labs and the performance both deepened my own moral intuitions and emotions through sensory and emotional engagement with the subject: organoid technology. For instance, as I have described in Chapter 4, in the performance round clay-like objects are moved through the performance space. When I hold them packed in a box and talk about treating organoids as objects of sale, I have the experience of being a market woman that is selling goods. Alternatively, when I talk about the relation between organoids and the bodies of donors while the audience exchanges the clay objects with their neighbours, the objects (and the organoids) feel as intimate parts of their bodies. Sijben and I together reflected on the role of different factors, such as the physical location and application of organoids, that influence their meaning (see Chapter 4). For instance, when organoids are used as a personalized drug

testing tool in a patient's treating hospital, they constitute a representation of that patient. Alternatively, when they are used for drug development in a distant commercial lab they are approached as commercial biotechnological artefacts.

Second, 'A Sculpture Like You and Me' has allowed me to *disrupt* a narrow state of RE, which is mandatory to achieve a Wide RE.[75,76] Organoid exchange challenges a distinction of gifts vs. commodities and the underlying world view in which subjects and objects are separated (see Chapter 5). Sijben equally challenges this world view in her work: she examines the subjectivity of objects and the objectivity of subjects.[77] During our collaboration my world view was slowly tilting. Our joint investigation of the blurring lines between subjects and objects permeated my daily activities and shed a different light on my perception of, among others, the relationship between myself and my body, between men and women, and on (invisible) racism. Her work has prompted me to challenge subject/object distinctions in ethical discourse and has further stimulated me to examine theoretical perspectives that challenge these dichotomous modes of thinking, such as feminism, (post)phenomenology, and Science and Technology Studies.[15–18,78] Our collaboration helped me to better understand these background theories. For instance, the dialogue of these background theories with her work made them more insightful. The quote '*Isn't talking to a performer like touching a sculpture?'* beautifully illustrates the ways in which humans can be both subjects and objects at the same time. Finally, I had a lived experience of abstract concepts, such as hybridity and 'to have and to be a body' (stemming from phenomenology) during the performance.[15,18,78]

Third, 'A Sculpture Like You and Me' has had an invaluable contribution to the experimental process of RE, in my opinion the core activity of the reasoning process, that is, going back and forth between beliefs stemming from practice and theory to reach a coherent view.[76] During our weekly labs and the performance I could experiment with the relationship between concepts such as hybridity and organoids. What happens if we do not categorize as subjects or objects or gifts or commodities? What relationship do organoids have to persons and their bodies? How is this relationship mediated by their technological nature? How is their value negotiated and influenced when they are exchanged in a network of human and non-human actors? I have tried out different associations and possibilities during our weekly meetings and I have formalized these associations in the performance and the publication. This has allowed me to scrutinize the potential intrinsic and relational moral value of organoids as well as their technological, instrumental, and commercial value and to come to the insight that the value regimes are intertwined rather than separated (see

Chapter 5). This connects to the broader world view that a strict separation into subjects and objects cannot be upheld.[15]

In sum, active engagement with the arts in the project 'A Sculpture Like You and Me', has had an invaluable contribution to both the *process* and *outcome* of Wide RE. The project has broadened and deepened the initial input for RE, has allowed me to disrupt narrow RE, and has proven an invaluable experimental lab for the mutual adjustment of theory and practice. This is mainly because as I have argued in Chapter 4 my process of moral reflection transformed from an *individual, formal, and mental reasoning process* to a *free, creative, sensory, and external* experimental ethics lab in dialogue with different interrogators. I believe that other bioethicists, whether or not committed to RE as an approach, can also benefit from an active engagement with the arts when reflecting on novel biotechnologies. To quote Camus: 'if the world were clear art would not exist'.[79] Particularly in technologies that touch upon our notions of the human body and our person- and objecthood, I think that the lived experiences that can be evoked by the arts are of vital importance for bioethicists. Therefore, I recommend art to gain a more prominent place in ethical discourses on novel (bio) technologies. Some first steps are being taken already.[70,71,80–82] In the years to come it is worth exploring practical forms in which this can be implemented and to further examine the theoretical place of the arts in moral reflection on novel technologies.

CHAPTER 11

CONCLUDING REMARKS

The cutting-edge and transformative organoid technology promises to have a profound impact on fundamental research, drug development, personalized drug testing and regenerative medicine. Simultaneously, organoid technology is paired with ethical challenges that urge pro-active scrutiny to stimulate morally responsible innovation.[1,2] In this thesis I have identified and evaluated the ethical challenges associated with organoid technology. I have particularly evaluated the ethical challenges related to the (increasingly) commercialized exchange of organoids and to their clinical translation in the realm of Regenerative Medicine. Organoid technology presents a unique convergence of ethical challenges and may bear special features in terms of their moral value (the hybridity specific to organoids) and their scientific and clinical possibilities. Nevertheless, I have particularly positioned organoid technology as exemplary for the complex exchanges of human tissue products in present-day biotechnology. These complex exchanges urge us to reconsider current autonomy-based approaches in bioethics that take form in consent, privacy protection, and ethical oversight. Alternatively, I have proposed a consent for governance model as a leading paradigm. This model can be connected with a shift towards value-sensitive governance of complex exchanges of organoids and related human tissue products. To move towards value-sensitive governance and to stimulate morally responsible innovation in organoid technology, I deem interdisciplinary approaches, in which bioethicists play an important role, indispensable. Finally, in moving forward we should not be afraid of the ambiguities inherent to organoid technology, rather we should involve the arts.

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APPENDICES

SUMMARY

Organoid technology constitutes a revolutionary way to culture human tissues in a dish. Organoids are self-organizing three-dimensional cell structures that can be grown from human stem cells or progenitors. They closely resemble the architecture and function of real-life human tissues. This technology makes it possible to expand limited sources of human biomaterials into virtually endless supplies of organoids. Organoid technology opens unprecedented avenues for science and health care. Organoids can be used to study human development and disease and they simultaneously offer novel approaches to drug development, precision, and regenerative medicine. The ability to store organoids in so-called living biobanks facilitates long-term storage and distribution to multiple academic and industrial parties worldwide.

These significant promises are paired with ethical challenges. For instance, different biotechnological developments, such as biobanking and stem cell research, converge in organoid technology, together with the related ethical questions (e.g. questions regarding the moral status of human tissues, biobank consent and governance). In examining how organoid technology affects these debates, it should be scrutinized whether organoids have unique or special characteristics from a moral point of view. Furthermore, organoid technology is situated in a global market. This raises the question how the exchange of organoids (and related human tissue products) can be shaped in morally sound ways. In addition, the clinical translation of organoid transplantation, and particularly the design and launch of first-in-human (FIH) organoid trials, raises research ethics questions (e.g. informed consent, risk-benefit evaluation, and participant selection).

Now that the organoid field advances, the ethical challenges need pro-active scrutiny to stimulate morally responsible innovation. The main aim of this thesis is, therefore, to identify and evaluate the ethical challenges related to organoid technology. This main aim is divided into four research questions. (1) What are the key ethical challenges related to the donation, storage, and use of organoids? (2) How can we conceptualize and evaluate the moral status and the exchange of organoids? (3) Which moral conditions should be formulated for the exchange of organoids and related human tissue products? (4) How can we ethically evaluate first-in-human organoid transplantation? These four questions correspond with the four parts of this thesis.

Part I: Identifying the ethical challenges related to the donation, storage, and use of organoids

In **Chapter 2**, we identify four clusters of interrelated ethical challenges associated with the donation, storage, and use of organoids. This is done through a synthesis of the academic literature on ethical challenges in analogous fields (e.g. biobanking, genomics, stem cell research). First, the moral and legal status of organoids deserve further examination. Second, the storage of organoids in so-called living biobanks calls for the development of adequate consent procedures in both research and clinical applications. Third, adequate governance models for organoid biobanking should be developed. Fourth, the clinical translation of organoids in precision and regenerative medicine raises ethical challenges, including appropriate return of results, ethical oversight, participant selection, risk-benefit balance, and trial design. Although these challenges are not necessarily new, they need to be reconsidered in the context of organoid technology.

Chapter 3 provides a first thematic exploration of the patient perspective on organoid technology. We do this by means of a qualitative interview study in which we examine the experiences, opinions, and attitudes of Dutch adult patients with Cystic Fibrosis (CF) and parents of young patients with CF regarding organoid technology. In the field of CF, the precision medicine potential of organoid technology is starting to impact both research and care. In the Netherlands, a living biobank consisting of organoids of patients with CF is being built to further advance research and clinical applications. Patients with CF and parents of young patients thus constitute a suitable population to explore the perspective of participants on organoid technology. From our interview study it follows that although patients are generally supportive of organoid technology, they have an ambivalent attitude. This ambivalent attitude is reflected in the four themes that we establish: (1) respondents experience a close as well as a distant relationship to organoids, (2) the open-endedness of organoid technology strengthens hopes and concerns, and (3) although commercial use is deemed necessary for drug development, it evokes cautiousness. (4) To cope with this ambiguity they mention the importance of initial consent together with long-term engagement of participants, responsible stewardship, and responsible models for commercial use. In sum, organoid technology holds a promise for personalized therapy in CF. However, this can only be realized if the perspective of the person in question, that is, the patient, is taken adequately into account.

Part II: Conceptualizing and evaluating the moral status and the exchange of organoids

In **Chapter 4** and **5**, we argue that the traditional bioethical literature provides two opposing perspectives on the commercialization of human tissues. The 'gift paradigm' holds that a profit motive is irreconcilable with the donation and use of human tissues. The 'market paradigm' alternatively frames human tissues as commodities. These dichotomous paradigms are underlined by a division between *persons* and *things*, or *subjects* and *objects*. Whereas we can own and sell things, we cannot own nor sell people. Human tissue and related products, however, fall between two stools. To avoid the grey area, the gift paradigm categorizes human tissues as 'subjects' and the market paradigm as 'objects'. These categories, however, run the risk of partially black-boxing the moral value of organoids.

In **Chapter 4,** I describe how a collaboration with the arts in a project entitled 'A Sculpture Like You and Me' has contributed to examining the ambiguous moral value of organoids. 'A Scuplture Like You and Me' consists of a complementary performance and publication in which fine artist Rosa Sijben and I investigate the ambiguous nature of objects and the interchangeable role of persons and things. During the project my moral reflection transformed from an individual, formal, and mental experiment to a free, creative, sensory, and external ethics lab in dialogue with different interrogators. 'A Sculpture Like You and Me' allowed me to experiment with the subject- and object-like values of organoids in a playful and associative way.

In **Chapter 5**, we integrate insights from chapter 3 and 4 and perform the theoretical work necessary to conceptualize and evaluate the moral status and the increasingly commercialized exchange of organoids and related human tissue products. In examining the moral value of organoids, we show what 'subject- like' and 'object-like' values organoids could have. Regarding the former, all types of organoids have some form of relational moral value, because they refer to and are meaningful for persons. Organoids relate to the bodily integrity, personal values and identity, privacy, and wellbeing of donors. Some sub-types of organoids, such as cerebral organoids or gastruloids, raise questions of intrinsic moral value. Regarding the latter, organoids constitute technological artifacts that have instrumental and commercial value. The concept of hybridity perfectly captures this ambiguity. Hybrids are entities that precede categorization and are neither human nor non-human. We recognize organoids as hybrids that relate to persons, things, bodies, technology, nature and commodities in ambiguous ways. This hybridity implies that the 'subject- and object-like' values of organoids are intertwined and that the moral value or ontological status of organoids

is not static. It is the technological transformation of human tissue into organoids that generates novel relational (and potentially intrinsic) moral value as well as instrumental and commercial value. The value and meaning of organoids come into being and change in a network of both human and non-human actors, such as institutions, donors, researchers, policy makers etc. Next, we deconstruct the exchange of organoids by using the notion of 'disentanglement'. We argue that commercialization of organoids is legitimized by a detachment of the instrumental and commercial value of organoids from their associations with persons and their bodies. This detachment is enacted in processes of disentanglement, among which measures that are traditionally employed to protect donors, namely consent and anonymization. Consent and anonymization together with commodification may lead to far-reaching disentanglement of organoids, which is ethically problematic because of two interrelated reasons. (1) Societal interests could be put under pressure, because the rationale for commercializing organoid technology, that is, to stimulate biomedical innovation for the good of society, may not be fulfilled. (2) The interests of donors are made subordinate to those of third parties, and the relational moral value of organoids may be insufficiently recognized. Finally, we propose a 'consent for governance' model to deal with these challenges (see Chapter 7), and to establish ongoing connections to donors, patients, and, society when organoid are (commercially) exchanged. In other words, consent for governance contributes to the 're-entanglement' of organoids.

Part III: Formulating conditions for the exchange of organoids and related human tissue products

In **Chapter 6** we propose a reinterpretation of broad consent in the context of biobanking, namely, to understand broad consent as consent for governance. Broad consent is usually understood as consenting to a broad range of unspecified biomedical use. In broad consent for governance the emphasis shifts from this *content* of future use to the *context* of research, i.e. the governance structure that is put in place. Consent for governance enables autonomous decision-making by informing donors on the governance structure of the biobank in question (e.g. ethical oversight, property rights and commercial interests, and future communication with donors), together with its inherent risks and benefits. In addition, it stresses the need for the design of a solid and adaptive governance structure that protects the interests of the wide variety of stakeholders that are involved.

In **Chapter 7**, we further elaborate on a 'consent for governance' model in the context of organoid technology and related biotechnological advances. In consent for governance, the emphasis for the ethical justification of the exchange of human tissue products shifts from initial

consent to ongoing governance obligations, which include privacy by design, participant engagement, benefit-sharing, and ethical oversight. Privacy by design encompasses the incorporation of privacy measures in the entire infrastructure of organoid exchange. This means that the most appropriate privacy standards apply by default and that the amount of coupling to personal data should be tailored to the application of organoids. Participant engagement refers to the substantial engagement of (groups of) donors and the wider public in the design and continuous adaptation of governance. Benefit-sharing encompasses the fair sharing of monetary and non-monetary benefits generated through organoid exchange among all parties involved, including donors, patients, and society. Ethical oversight bodies should be incorporated in different stages of organoid exchange. Our proposal of consent for governance is of relevance for all research fields in which complex human tissue products are used. We call for more research to further develop the elements of fair governance structures, which should include further inquiry into the preferences and interests of donors, patients, and the wider public.

In **Chapter 8**, we examine a specific governance obligation in the realm of genomics, namely the return of genetic information to family members of deceased patients. Next-Generation-Sequencing techniques are routinely applied in the stem cell (and organoid) field. The genetic information yielded with these techniques may be of relevance not only to participants but also to their family members. This raises the question whether and how genetic information should be disclosed to relatives. This issue becomes especially salient after the death of participants, when they can no longer warn family members for hereditary risks and permission for disclosure can no longer be sought. We identify and explain the arguments in favour of and against disclosure of genetic information to the relatives of the deceased. We propose a passive postmortem disclosure policy for the communication of genetic information to family members. A passive disclosure policy means that family members are given access to genetic information at their explicit request. We position a passive postmortem disclosure policy as the moral minimum. We acknowledge that an active disclosure policy can be the ethically superior option in some cases and could become the ethically superior default option in the future. However, there are important sets of questions that must first be resolved.

Part IV: Ethical evaluation of first-in-human organoid transplantation

In **Chapter 9**, we examine whether it would be ethically acceptable to include children in a first-in-human (FIH) liver organoid transplantation trial. Although organoid transplantation is still in preclinical development,

launch of clinical testing is expected in the near future. The field of liver disease would greatly benefit from these rapidly progressing technological advances. Liver organoid transplantations could provide a less invasive and readily available 'off-the-shelf' alternative for liver transplantation. Patients with inherited metabolic liver disease constitute a potential group of research participants for a FIH trial. Inherited metabolic liver diseases mostly present in early childhood and intervention is thought to be most effective at young age. This raises the question whether inclusion of children in a FIH trial is ethically justifiable. We argue that the inclusion of children in a FIH liver organoid trial is ethically acceptable, if potential individual benefits are warranted after rigorous assessment of the preclinical evidence, provided that the following three conditions are met. (1) The risks are minimized, (2) the potential benefits outweigh the risks, and (3) attention is paid to valid informed consent and assent.

In **Chapter 10**, we contribute to systematic, transparent, and non-arbitrary decision-making regarding risks and benefits in the ethical review of first-in-human trials. In FIH trials, the evidence to support clinical benefits is limited to preclinical efficacy studies. Currently, evaluators have insufficient tools to translate findings from preclinical animal studies to estimates of benefits in humans and to ultimately inform risk-benefit evaluation. We fill this gap by further developing a novel approach that bases estimates of efficacy on a systematic assessment of both preclinical efficacy and reference class evidence. We use organoid technology as an example to illustrate the selection and evaluation of reference class evidence. Next, we set out to show how the assessment of estimated efficacy makes the four risk-benefit tasks, being (1) benefit analysis, (2) risk-benefit evaluation, (3) benefit optimization, and (4) decision-making, more systematic, transparent, and grounded in evidence. We conclude by offering some first suggestions for practical implementation of our approach and identify barriers that should be addressed.

Chapter 11 presents a general discussion of the main findings in this thesis. After a discussion of the answers to the four research questions, I reflect on the governance of the complex exchanges of organoids and related human tissue products. In this thesis I stress the importance of appropriate governance in our proposed 'consent for governance' model. In this discussion I further elaborate on what I mean with governance. I propose to speak of value-sensitive governance, which I define as: *'the processes of interaction and decision-making among the different stakeholders that are involved in a collective problem that lead to the creation, reinforcement, or reproduction of social norms and institutions and that are explicitly informed by values.'* Following the proposed definition of value-sensitive

governance, I formulate ways forward in thinking about (1) which values to include, (2) fair processes of decision-making, and (3) ways to reproduce and reinforce values. (1) Guiding values and principles should include the hybrid moral value of organoids as well as social value, reciprocity, solidarity, and justice. (2) Fair processes of decision-making require the engagement of participants, patients, and the wider public. (3) Now that exchange of hybrid human tissue products is intricately interwoven with economic interests, possibilities to put values into practice via (alternative) models of innovation and ownership should be explored. Finally, I reflect on how an active engagement of bioethicists with the arts can contribute to the moral reflection on novel biotechnologies. I argue that 'A Sculpture Like You and Me' (Chapter 4) has contributed to both the *process* and *outcome* of Wide Reflection Equilibrium (RE). I contend that other bioethicists, whether or not committed to RE as an approach, can also benefit from an active engagement with the arts. The arts can particularly contribute to making sense of the ambiguities inherent to novel biotechnologies in creative ways.

SAMENVATTING

Recente ontwikkelingen in de stamceltechnologie maken het mogelijk om menselijk weefsel op een baanbrekende manier in vitro te kweken tot organoids. Deze organoids, ook wel mini-orgaantjes genoemd, zijn drie-dimensionale celstructuren die qua bouw en functie sterk lijken op menselijke organen. Met organoid technologie kan uit kleine hoeveelheden menselijk weefsel een oneindige hoeveelheid organoids gekweekt worden. Deze organoids zijn veelbelovend voor zowel wetenschappelijke als klinische toepassingen. Zo is bijvoorbeeld in vitro onderzoek naar ziektes zoals kanker mogelijk, en kunnen organoids bijdragen aan het testen van medicijnen op maat en de ontwikkeling van nieuwe medicijnen. De verwachting is zelfs organoid transplantatie dat in de toekomst aangewend kan worden om beschadigde organen te herstellen. Organoids kunnen lange tijd worden opgeslagen in zogenaamde 'levende biobanken' en daarvandaan over de hele wereld verspreid worden naar zowel academische als commerciële partijen (zoals de farmaceutische industrie).

Deze beloftes gaan gepaard met ethische uitdagingen. In organoid technologie komen verschillende technologische ontwikkelingen en de daaraan gerelateerde ethische uitdagingen samen. Te denken valt aan ethische discussies rondom de adequate toestemming van donoren voor en de governance van de langdurige biobankopslag van menselijk weefsel. De vraag is of organoids vanuit moreel oogpunt speciale karakteristieken hebben die maken dat we op een andere manier tegen deze discussies aan moeten kijken. Daarnaast kunnen organoids in de context van een wereldwijde markt verspreid en gebruikt worden. Dit roept de vraag op hoe de uitwisseling van organoids op een moreel verantwoorde manier vormgegeven kan worden. Ook de eerste klinische testen van organoid transplantatie in zogeheten 'first-in-human' (FIH) trials roepen ethische vragen op over onder andere adequate toestemming en het afwegen van risico's en baten. Om op een moreel verantwoorde manier te innoveren is aandacht voor deze ethische uitdagingen nodig.

Dit proefschrift heeft daarom tot doel om de ethische uitdagingen rondom organoid technologie te identificeren en te evalueren. Dit hoofddoel is onderverdeeld in vier onderzoeksvragen. (1) Wat zijn de belangrijkste ethische uitdagingen omtrent de donatie, opslag en het gebruik van organoids? (2) Hoe kunnen we de morele status en uitwisseling van organoids conceptualiseren en evalueren? (3) Welke morele voorwaarden moeten geformuleerd worden voor de uitwisseling van organoids en daaraan gerelateerde menselijke weefselproducten? (4) Hoe kunnen we first-in-human organoid transplantatie trials evalueren vanuit een moreel

oogpunt? Deze vier vragen corresponderen met de vier delen van het proefschrift.

Deel I: Een identificatie en evaluatie van de ethische uitdagingen omtrent de donatie, opslag en het gebruik van organoids

In **Hoofdstuk 2** identificeren we vier clusters van ethische uitdagingen gerelateerd aan de donatie, opslag en het gebruik van organoids. We doen dit door de academische literatuur over de ethische discussies gerelateerd aan verwante technologische ontwikkelingen binnen onder andere de genetica, het stamcel onderzoek en biobanken, samen te brengen en toe te passen op organoid technologie. Allereerst stellen we dat de morele en juridische status van organoids verder onderzoek behoeven. Ten tweede vraagt de opslag van organoids in levende biobanken om de ontwikkeling van adequate toestemmingsprocedures. Ten derde moeten er adequate modellen voor de governance van organoid biobanken ontwikkeld worden. Ten vierde roept de klinische vertaalslag van organoids naar het testen van medicijnen op maat (ook wel gepersonaliseerde geneeskunde) en naar organoid transplantatie ethische vragen op die verder onderzoek behoeven. Voorbeelden zijn het adequaat terugkoppelen van resultaten naar patiënten, ethische toetsing, het selecteren van onderzoek deelnemers en het evalueren van risico's en baten. Hoewel deze ethische uitdagingen niet nieuw zijn, is het belangrijk om er in de context van organoid technologie opnieuw over na te denken.

Hoofdstuk 3 biedt een eerste thematische exploratie van het perspectief van patiënten ten aanzien van organoid technologie. Middels een kwalitatieve interview studie onderzoeken we de ervaringen, meningen en houdingen van Nederlandse volwassen patiënten met taaislijmziekte (ook wel cystic fibrosis of CF genoemd) en ouders van jonge patiënten aangaande organoid technologie. Bij patiënten met CF is het testen van medicijnen op maat met organoids al volop in ontwikkeling. In Nederland wordt tevens een 'levende biobank' met organoids van CF patiënten opgezet om onderzoek en medicijnontwikkeling verder mogelijk te maken. Uit de vier thema's die we identificeren in onze interviewstudie blijkt dat, hoewel patiënten met CF over het algemeen positief zijn ten aanzien van organoid technologie, ze ook een ambivalente houding hebben. (1) Ten aanzien van de relatie tussen de organoids en de respondenten, zien respondenten zichzelf als nauw verbonden met hun organoids. Tegelijkertijd zien ze de organoids als iets dat ver van hen af staat. (2) Het feit dat biobank opslag leidt tot een 'open toekomst' (open-endedness) leidt bij respondenten tot zowel hoop als zorgen. (3) Commercieel gebruik wordt noodzakelijk geacht voor het ontwikkelen van medicijnen, maar roept ook zorgen op. (4) Respondenten

noemen verschillende manieren om met deze dubbelzinnigheden om te gaan. Ze benadrukken het belang van toestemming, blijvende betrokkenheid van deelnemers, verantwoordelijk beheer van de opslag en het gebruik van organoids en verantwoorde modellen voor commercieel gebruik. Concluderend, organoid technologie kan therapie op maat voor patiënten met CF mogelijk maken. Echter, dit kan alleen op een verantwoorde manier gedaan worden als het patiënten perspectief op een adequate manier meegenomen wordt.

Deel II: Conceptualisatie en evaluatie van de morele status en uitwisseling van organoids

In **Hoofdstuk 4** en **5** stellen we dat de 'traditionele' bio-ethiek literatuur twee tegenstelde perspectieven biedt op de vraag hoe de commercialisering van menselijk weefsel beschouwd moet worden. Het 'gift paradigma' stelt dat een winstmotief niet verenigbaar is met de donatie en het gebruik van menselijke weefsels. Het 'markt paradigma' stelt dat menselijke weefsels beschouwd kunnen worden als handelswaar. Deze tegenovergestelde zienswijzen zijn onderbouwd door een tweedeling in *mensen* versus *dingen,* of *subjecten* versus *objecten*. Hoewel we eigenaar kunnen zijn van 'dingen' en deze ook kunnen verkopen, kunnen we geen eigenaar zijn van mensen. Het lastige is dat menselijk weefsel en daaraan gerelateerde producten tussen wal en schip vallen. Om dit grijze gebied te omzeilen, wordt menselijk weefsel binnen het gift paradigma gecategoriseerd als mens, en binnen het markt paradigma als ding. Echter, deze beide categorieën knellen, waardoor het niet goed mogelijk is om de morele waarde van organoids met open vizier te onderzoeken.

In **Hoofdstuk 4** beschrijf ik hoe een samenwerking met beeldend kunstenaar Rosa Sijben binnen het project 'A Sculpture Like You and Me' heeft bijgedragen aan het onderzoeken van de ambigue morele waarde van organoids. 'A Sculpture Like You and Me' bestaat uit een complementaire performance en publicatie waarin Sijben en ik de ambigue aard van objecten en de uitwisselbare rol van mensen en dingen onderzoeken. Door dit project transformeerde mijn morele reflectie van een individueel en formeel gedachtenexperiment naar een vrij, creatief, zintuiglijk en extern 'ethics lab', in dialoog met verschillende mensen en objecten. 'A Sculpture Like You and Me' bood me een speelse en associatieve proeftuin om te experimenteren met de subject- en object-achtige waarden van organoids.

In **Hoofdstuk 5** integreren we inzichten uit Hoofdstuk 3 en 4 en voeren we het theoretische werk uit dat nodig is om de morele status en de toenemend commerciële uitwisseling van organoids (en gelijksoortige menselijke weefselproducten) te conceptualiseren en evalueren. Eerst laten we zien dat organoids zowel subject- als object-achtige waarden

hebben. Wat betreft hun subject-achtige waarden: alle organoids hebben een vorm van relationele morele waarde. Ze verwijzen naar donoren en zijn betekenisvol voor donoren en patiënten. Organoids zijn gerelateerd aan de lichamelijke integriteit, persoonlijke waarden en identiteit, privacy en het welzijn van donoren. Daarnaast roepen sommige sub-types van organoids, zoals brein organoids, de vraag op of ze intrinsieke morele waarde zouden kunnen verwerven. Wat betreft de object-achtige waarden: organoids zijn technologische artefacten die een instrumentele en commerciële waarde hebben. Daarna stellen we dat het idee van hybriditeit mooi aansluit bij deze ambiguïteit. In de sociaalwetenschappelijke literatuur worden hybriden gezien als entiteiten die voorafgaan aan categorisatie en die zowel menselijk als niet-menselijk zijn. Wij herkennen organoids als hybriden die op een ambigue manier gerelateerd zijn aan zowel personen en hun lichamen als aan technologie en markten. De subject- en object-achtige waarden van organoids zijn nauw met elkaar verweven en de morele waarde van organoids is niet statisch. Het is de technologische transformatie van menselijk weefsel naar organoids die maakt dat er nieuwe relationele (en mogelijk intrinsieke) morele waarde alsmede instrumentele en commerciële waarde ontstaat. De waarde en betekenis van organoids komen tot stand in een netwerk van zowel menselijke als niet-menselijke actoren, zoals instituten (onderzoekslaboratoria, ziekenhuizen), donoren, onderzoekers en beleidsmakers. Vervolgens deconstrueren we de uitwisseling van organoids door gebruik te maken van het begrip ‘disentanglement’ (loskoppelen). Er is een toenemende druk om organoids (en verwante weefselproducten) te commercialiseren, met als rationale het stimuleren van biomedische innovatie in het belang van de maatschappij. Wij stellen dat de commercialsering van organoids wordt gelegitimeerd door de instrumentele en commerciële waarde van organoids los te koppelen van hun associaties met mensen en hun lichamen. Deze loskoppeling komt tot stand middels processen van ‘disentanglement’, waaronder mechanismen die traditioneel juist ingezet worden om de belangen van donoren te beschermen, zoals toestemming en anonimisatie van weefsel. Vooral verregaande ‘disentanglement’ (ofwel commercialisering) van organoids is ethisch problematisch. (1) Maatschappelijke belangen kunnen onder druk komen te staan. In het geval van verregaande ‘disentanglement’ zijn er mogelijk onvoldoende waarborgen om ervoor te zorgen dat commercialisering biomedische innovatie in het belang van de maatschappij stimuleert. (2) De belangen van donoren worden ondergeschikt gemaakt aan die van derden. Daarnaast wordt de relationele morele waarde van organoids onvoldoende (h)erkend. Tot slot stellen we een ‘consent for governance’ (ofwel ‘toestemming voor governance’) model voor om blijvende connecties

met donoren, patiënten en de maatschappij te waarborgen wanneer organoids uitgewisseld worden.

Deel III: Voorwaarden voor de uitwisseling van organoids en verwante menselijke weefselproducten

In de context van biobank onderzoek is zogeheten brede toestemming (of broad consent) een model dat vaak verdedigd wordt als een gepaste vorm van toestemming. Brede toestemming wordt gewoonlijk gedefinieerd als toestemming voor een brede range aan toekomstige biomedische toepassingen.

In **Hoofdstuk 6** stellen wij voor om brede toestemming op een andere manier te interpreteren en wel als brede toestemming voor governance, ofwel 'broad consent for governance'. Dit betekent dat de nadruk in de initiële toestemmingsprocedure verschuift van de *inhoud* van toekomstig gebruik naar de *context* van toekomstig gebruik, te weten de governance structuur van de biobank. Deze vorm van brede toestemming maakt autonome besluitvorming ten aanzien van de risico's en baten mogelijk. In biobank onderzoek liggen de risico's en baten immers vooral besloten in de governance structuur van de biobank. Bijvoorbeeld, hoe is de bescherming van privacy, de ethische toetsing, de omgang met eigendomsrechten en commercieel gebruik geregeld? Daarnaast legt 'broad consent for governance' de nadruk op het ontwerpen van een solide en adaptief governance model waarin de belangen van de verschillende belanghebbenden (bijv. patiënten, donoren, onderzoekers, commerciële partijen) worden meegewogen.

In **Hoofdstuk 7** gaan we verder in op het 'consent for governance' model in de context van organoid en aanverwante technologieën. We benadrukken dat 'consent for governance' inhoudt dat de nadruk van de rechtvaardiging voor het gebruik van menselijke weefselproducten verschuift van de initiële toestemmingsprocedure naar blijvende governance verplichtingen. Wij suggereren ingrediënten voor deze governance verplichtingen, waaronder 'privacy by design', betrokkenheid van deelnemers, 'benefit-sharing' en ethische toetsing. Privacy by design houdt in dat de mechanismen om privacy te beschermen ingebed zijn in de hele infrastructuur. Daarnaast moet de mate van koppeling tussen organoids en persoonlijk gegevens aangepast worden aan de toepassing van organoids (bijvoorbeeld gepersonaliseerde geneeskunde versus commercieel gebruik). Betrokkenheid betekent dat deelnemers op een substantiële manier betrokken moeten zijn bij het ontwerpen en de aanpassing van governance structuren. Benefit-sharing verwijst naar het eerlijk (ver)delen van zowel de geldelijke als niet-geldelijke baten die gegenereerd worden tijdens de uitwisseling van organoids onder

de verschillende partijen die betrokken zijn (waaronder donoren, patiënten en de maatschappij in bredere zin). Ethische toetsingsorganen moeten ingebed worden in de verschillende stadia van het uitwisselen van organoids. Ons 'consent for governance' model is relevant voor alle onderzoeksvelden waar complexe menselijke weefselproducten gebruikt worden. De ingrediënten moeten verder uitgewerkt worden voor deze verschillende contexten. Dit vraagt om verder onderzoek naar de voorkeuren en belangen van donoren, patiënten en het publiek in bredere zin.

In **Hoofdstuk 8** onderzoeken we een specifieke governance verplichting op het gebied van 'genomics' (grootschalig onderzoek van het menselijk genoom), namelijk het terugkoppelen van genetische informatie naar familieleden van overleden patiënten. Next-Generation-Sequencing technieken (technieken die het aflezen van het hele menselijke genoom mogelijk maken) worden tegenwoordig routinematige toegepast in stamcelonderzoek. De genetische informatie die hiermee gegenereerd wordt kan relevant zijn voor zowel deelnemers als hun familieleden. Dit roept de vraag op óf en hoe genetische informatie teruggekoppeld moet worden aan familieleden. Deze vraag wordt vooral prangend wanneer deelnemers overlijden. In dit geval kunnen zij familieleden niet meer zelf op de hoogte stellen van mogelijke erfelijke risico's en kunnen zij niet meer om toestemming gevraagd worden voor terugkoppeling door professionals. Wij onderzoeken mogelijke argumenten voor en tegen het terugkoppelen van genetische informatie aan de familieleden van overleden deelnemers. We stellen dat een 'passive postmortem disclosure policy' op dit moment de beste balans biedt tussen voor- en tegen argumenten. Dit betekent dat familieleden toegang krijgen tot genetische informatie van een overleden deelnemer als zij hier expliciet om vragen. Een dergelijk beleid is wat ons betreft het morele minimum. Het kan zijn dat een actievere vorm van terugkoppeling in sommige gevallen de voorkeur geniet, bijvoorbeeld als er een bevinding is die belangrijke klinische consequenties heeft. In de toekomst kan een actieve terugkoppeling van genetische informatie zelfs de voorkeursoptie worden. Echter eerst zijn er nog belangrijke vragen die beantwoord moeten worden.

Deel IV: Ethische evaluatie van first-in-human organoid transplantatie

In **Hoofdstuk 9** onderzoeken we of het ethisch acceptabel zou zijn om kinderen te includeren in een first-in-human (FIH) lever organoid transplantatie studie. Hoewel de ontwikkeling van organoid transplantatie nog in een preklinisch stadium is, moeten de eerste klinische testen geanticipeerd worden. Patiënten met leverziekten zouden mogelijk veel baat kunnen hebben bij het transplanteren van lever organoids, als alternatief voor levertransplantatie.

Lever organoid transplantatie is waarschijnlijk minder invasief en kan een oplossing bieden voor het tekort aan donorlevers. Patiënten met erfelijke metabole aandoeningen zijn mogelijke deelnemers voor een FIH lever organoid transplantatie studie. Deze ziekten beginnen vaak al op jonge leeftijd en de gedachte is dat een interventie het meest effectief is als er nog geen irreversibele schade is opgetreden. Dit roept de vraag op of het includeren van kinderen ethisch acceptabel is. Wij beargumenteren dat de inclusie van kinderen in een FIH lever organoid trial ethisch acceptabel is, als mogelijke individuele baten geborgd worden door rigoureuze beoordeling van preklinisch bewijs. Daarnaast moet aan de volgende drie voorwaarden voldaan worden: (1) de risico's zijn geminimaliseerd, (2) de potentiële baten wegen op tegen de risico's, en (3) er wordt aandacht besteed aan valide geïnformeerde toestemming en instemming.

In **Hoofdstuk 10** dragen we bij aan systematische, transparante en niet-arbitraire besluitvorming ten aanzien van risico's en baten in de ethische toetsing van first-in-human studies. In FIH studies is het bewijs voor klinische baten beperkt tot preklinisch onderzoek. Momenteel hebben besluitvormers onvoldoende handvatten om het bewijs uit preklinische effectiviteitsstudies te vertalen naar de inschatting van baten en de uiteindelijk afweging van risico's en baten in FIH studies. Om deze lacune te dichten werken we een nieuwe benadering uit die handvatten geeft om een inschatting te maken van klinisch effectiviteit op basis van zowel preklinische studies als bewijs uit een referentie klasse. We gebruiken organoid technologie ter illustratie van het selecteren en beoordelen van referentieklasse bewijs. Vervolgens laten we zien hoe de inschatting van klinische effectiviteit gekoppeld kan worden aan de risico-baten evaluatie en zo de (1) baten analyse, (2) risico-baten evaluatie, (3) optimalisatie van baten en (4) de besluitvorming systematisch en transparant maakt. Tot slot formuleren we suggesties voor de praktische implementatie van onze benadering en identificeren we mogelijke belemmeringen die geadresseerd moeten worden.

Hoofdstuk 11 biedt een algemene discussie van de hoofdbevindingen van dit proefschrift. Na een bespreking van de antwoorden op de vier onderzoeksvragen, reflecteer ik op de governance van de uitwisseling van complexe menselijke weefselproducten, zoals organoids. In het proefschrift benadruk ik het belang van governance in het 'consent for governance' model. In de discussie geef ik verdere invulling aan het begrip 'governnace'. Ik stel voor om te spreken van 'value-sensitive governance', hetgeen ik als volgt definieer: *'de processen van interactie en besluitvorming tussen verschillende belanghebbenden die betrokken zijn bij een collectief probleem, die leiden tot de creatie, versterking, of reproductie van sociale normen en instituten en die expliciet geleid worden door waarden'.*

Ik formuleer ‘ways forward’ voor het nadenken over (1) welke waarden leidend moeten zijn, (2) eerlijke processen van besluitvorming en (3) manieren om waarden te reproduceren en te versterken. (1) Leidende waarden en principes moeten de hybride morele waarde van organoids bevatten alsmede ‘social value’, wederkerigheid, solidariteit en rechtvaardigheid. (2) Eerlijke processen van besluitvorming vragen om de betrokkenheid van deelnemers, patiënten en het publiek in bredere zin. (3) Alternatieve modellen van innovatie en eigenaarschap moeten onderzocht worden nu de uitwisseling van hybride menselijke weefselproducten nauw verweven is met economische belangen. Vervolgens reflecteer ik op de mogelijke bijdrage van een actieve samenwerking van bio-ethici met de kunsten aan de morele reflectie op nieuwe biotechnologieën. Ik beargumenteer dat ‘A Sculpture Like You and Me’ (Hoofdstuk 4) heeft bijgedragen aan zowel het proces als de uitkomst van een wijd Reflectief Evenwicht (RE) (dit is een benadering voor morele reflectie). Ik stel dat andere bio-ethici, of ze nu wel of niet RE als benadering gebruiken, baat kunnen hebben bij een samenwerking met de kunsten. De kunsten kunnen een creatieve manier bieden om het hoofd te bieden aan de ambiguïteit die inherent is aan nieuwe vormen van biotechnologie.

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CURRICULUM VITAE

Sarah Nelina Boers was born on 5 May 1988 in Rotterdam, the Netherlands. In 2006 she graduated 'cum laude' from secondary school 'Gymnasium Celeanum' in Zwolle. In 2006, she started to study Medicine at Utrecht University. During her bachelor she participated in an elective course in interdisciplinary ethics. She combined her master's programme in Medicine with several courses from the bachelor programme of Spanish language and culture. She put her Spanish in practice during an internship in social medicine at the 'centro de salud', Quiquijana, Peru. Her scientific internship at the Julius Center for Health Sciences and Primary Care, University Medical Centre (UMC) Utrecht, under the supervision of prof. dr. Annelien Bredenoord, formed the starting point for her further career in bio-ethics. She obtained her medical master's degree in 2014. During her time as a student, Sarah worked as a student-assistant in medical education and research and was a board and committee member of Dekoor Close Harmony, a semi-professional and award winning student's choir, and of USAC, the student's Alpine Association.

In October 2014, Sarah started as a PhD Candidate at the Julius Center for Health Sciences and Primary Care, UMC Utrecht. Her PhD project focused on the ethics of organoid technology. She was supervised by prof. dr. Annelien Bredenoord and prof. dr. Hans van Delden. She participated in the PhD programme 'Regenerative Medicine' at the Graduate School of Life Sciences (GSLS) and took additional courses in bioethics and philosophy of technology at the Dutch Research School of Philosophy and the University of Twente. From 2015-2016 she participated in the Arts/ Science Academy Honours Programme for young artists and scientists organized by the Royal Netherlands Academy of Arts and Sciences. Together with fine artist Rosa Sijben, she created the performance and publication entitled 'A Sculpture Like You and Me', for which they support from the Mondriaan Fund. In 2017, she was a visiting researcher at the Department of Thematic Studies at Linköping University Sweden and at the Biomedical Ethics Unit, McGill University, Montreal, Canada. For the latter she obtained funding from Foundation de Drie Lichten, Jo Kolk Study Fund, Girard de Mielet van Coehoorn Foundation, and the KNAW Ter Meulen Fund. She taught ethics and medical humanities in various undergraduate, graduate, and postgraduate courses at the faculty of Medicine and Biomedical Sciences, the GSLS, and the Vocational Training for General Practice.

Since November 2018 Sarah works as an assistant professor at the department of Medical Humanities of the UMC Utrecht, on a project entitled HIT CF-Europe. Together with prof. dr. Annelien Bredenoord she obtained

funding by the European Union's Horizon 2020 research and innovation programme for the work package 'Organoid biobanking for precision medicine: ethics and governance'. Within this work package she (co-) supervises a PhD Candidate. Her research focus extends to the ethics of eHealth and digitalization in primary care. She combines her academic work with a position as physician at Me-Doc. Via this organization she works in Careyn Maria-Oord, a health care centre for elderly care in Vinkeveen.

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