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

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/medethics-2018-104846).

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Received 12 March 2018
Revised 27 September 2018
Accepted 1 October 2018

To cite: Boers SN, van Delden JJM, Bredenoord AL. *J Med Ethics* Epub ahead of print: [please include Day Month Year]. doi:10.1136/medethics-2018-104846

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 commercialisation 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 commercialisation 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 recognise them as hybrids that relate to persons and their bodies as well as to technologies and markets in ambiguous ways. Second, we show that commercialisation of organoids is legitimised 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 commercialising 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 recognised. 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 commercialisation 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] Commercialisation 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 commercialisation 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 conceptualises 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 commercialised exchange of human tissues and their products. Our approach integrates insights from ethics, the social sciences, phenomenology, and science and technology studies. 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 commercialisation leads to an intricate web of values and interests (online supplementary file 1).[12i]

[i] The scenario is inspired by our qualitative study that examines the perspective of patients with CF on organoid technology[12] and by our current collaboration with CF clinicians, researchers, companies and CF patient organisations 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/).

Table 1 Glossary

Adult stem cells	Are undifferentiated cells found in differentiated adult tissue that can renew themselves and differentiate to yield all specialised cell types of the tissue from which they originated.
Cystic fibrosis	Is a rare and severe hereditary disease that is characterised by thick and sticky mucus leading to predominantly pulmonary and gastrointestinal 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 specialised 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 three-dimensional organisation 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 unspecialised and capable of renewing themselves. They can specialise 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 specialised cells.

BACKGROUND ON ORGANOID TECHNOLOGY

Organoid technology makes it possible to grow three-dimensional (3D) 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-organise into organ-like 3D 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 personalised drug testing tools.[20] A striking example is the field of 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 (online supplementary file 1).[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 immortalise certain types of organoids and to store them in so-called 'Living Biobanks' further increases their promise: 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 analyse the ethical challenges that are raised by the growing commercialisation of organoid exchange.

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 (eg, 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-commercialisation 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 commercialisation 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 commercialisation 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 commercialised, 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 conceptualised 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 conceptualisation of human bodily materials as either subject or object is problematic in evaluating the commercialisation of organoid technology, because the categorisation 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 emphasises 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 categorise organoids as subjects or objects beforehand, we will show the 'subject-like and 'object-like' values that organoids could have. The CF scenario serves as a narrative illustration of the potential different values of organoids (online supplementary file 1).

Organoids have subject-like values

Currently, the subtypes of organoids that raise questions of *intrinsic* moral value receive most attention in the bioethical 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 pluripotent stem cells (either hESCs or induced pluripotent stem cells (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 input and output?[33 34 38] Additionally, in the future, several types of organoids could be combined with other types of (animal) tissues and techniques (eg, bioprinting) 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-organising 3D entities in a dish that are genetically related to donors and that represent the (dys)functioning of their bodies.[3] Some subtypes are immortalised, 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 (ie, autologous transplantation) or another patient (ie, 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 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 set-up of the sobject'.[32] The second criterion in fact applies to all human tissues. For organoids the chances that the genetic set-up 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 (online supplementary file 1) 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 laboratory 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 (online supplementary file 1).[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, emphasise 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 (eg, from adult stem cells, progenitors or iPSCs) of patients with rare, hereditary conditions (eg, 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 well-being of donors and other patients.[17] If organoids are used for personalised drug testing, they can directly inform clinical treatment.[16 20] Precision medicine applications of organoids are most advanced in the field of CF (online supplementary file 1); 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-term and long-term effects on the well-being 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 well-being 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 (eg, 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 laboratory 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 healthcare institutions. The self-organising 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 tumour 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 bioprinting.[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-like and object-like values. Therefore, rather than trying to categorise organoids as subjects *or* objects, we propose to recognise organoids as hybrids.

The term hybrid perfectly captures the ambiguity of organoids. In the social sciences literature, hybrids are seen as entities that precede categorisation and that challenge existing categories.[10 30] Hybrids are neither human nor non-human.[10 30] We recognise 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 recognise 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 and so on. 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 emphasises 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 recognise organoids as hybrids serves as a starting point for further ethical analysis of the increasingly commercialised 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 commercialise 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 (online supplementary file 1).

Table 2 Disentanglement of organoids

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 (eg, adult stem or progenitor cells, iPSCs, hESCs). The technological transformation can be seen as a patentable intervention.
Step 3: Anonymisation	The pseudonymisation or complete deidentification of organoids.
Step 4: Commodification	The different mechanisms to commodify organoids, such as the establishment of intellectual property rights, price setting for access and use by commercial parties (eg, pharmaceutical companies).
Step 5: Distribution	The national or international distribution of organoids to academic and for-profit parties.

hESCs, human embryonic stem cells; iPSCs, induced pluripotent stem cells.

First, to create and store organoids, rectal biopsy material of patients with CF has to be harvested.[21] This could be residual tissue leftover 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 3D immortalised 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 anonymisation affects the degree of disentanglement. Organoids could either be completely anonymised, which means that the identification of the patient is irreversibly prevented (with the caveat that in this era of genomics and big data anonymisation can never be fully guaranteed) or pseudonymised, 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 organisation 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 organisation, 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 worldwide repository, this would further increase detachment.[40]

Evaluating disentanglement of organoids

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

In the processes of disentanglement, different actors (eg, 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 anonymisation. 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 emphasised. Consent and anonymisation and the technological transformation of biological material into organoids play an important role in the legitimisation 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] Anonymisation, and particularly complete deidentification, further hampers the donors to exercise control, as they cannot even exercise their right to withdrawal.[55] Obtainment of consent and complete deidentification mean that the ethical standards for tissue donation are met, which at the same time grants third parties more flexibility regarding use, distribution and commercialisation of organoids. The technological transformation of the rectal biopsy material into organoids can be regarded as a patentable invention, and as such it further legitimises their framing as marketable products.[29 53] The patent owner, in our example, the HUB (online supplementary file 1) 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 deidentified, patented, stored for-profit and distributed via a global for-profit repository that grants access to international public as well as commercial parties 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,[57] we could speak of far-reaching disentanglement. We deem far-reaching disentanglement ethically problematic for two (inter-related) reasons. Societal interests could be put under pressure, because the rationale for commercialising 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 recognised.

First, commercialisation 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 commercialisation will eventually stimulate or hamper innovation.[58] What at least should be recognised 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 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 pricey 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. 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 (eg, 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 well-being 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

Table 3 Consent for governance

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, for example, 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, for example, 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.

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 European Union General Data Protection Regulation that demands data protection by design and data protection by default.[62] This means that the most appropriate privacy standards apply by default, for example, 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 prioritised 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 Evaluating disentanglement of organoids section), the role of commercialisation in biomedical innovation is not undisputed.[40 58] To adopt a more holistic approach to innovation, commercialisation 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 commercialisation 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, recognise and deal with potentially controversial use of organoids and keep oversight over commercial uses of organoids.

CONCLUDING REMARKS

The pressure to commercialise organoid technology and related stem cell technologies is increasing. This is in sharp contrast with the still dominant non-commercialisation 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 recognises 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 commercialised exchange of organoids (as an example of human bodily products). We propose to recognise organoids as hybrids that relate to persons, things, bodies, technology, nature and commodities in ambiguous ways. Organoids derive value and meaning from the inter-relatedness of subject-like 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 recognised when organoids are exchanged. Our proposed 'consent for governance' model contributes to the responsible shaping of the increasingly commercialised exchange of organoids. It offers ingredients (table 3) that help to fulfil the rationale for commercialisation 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 sociocultural circumstances) may require a distinct interpretation of the ingredients. For instance, participant engagement and benefit-sharing measures will be different for patients with CF who '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 versus market. This we feel is necessary to allow for responsible innovation and clinical translation in the increasingly commercialised biotechnological field.

Acknowledgements We thank our colleagues at the Department of Medical Humanities, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands, for their helpful feedback on earlier versions of the manuscript. We acknowledge our colleagues at the Department of Thematic Studies: Technology and Social Change, Linköping University, Sweden, for their constructive comments on an earlier version of the manuscript. We also thank Rosa Sijben for her contribution to the line of thought presented in the manuscript through the collaboration in the project 'A Sculpture Like You and Me'.

Contributors SNB drafted the first manuscript. SNB, JJMvD and ALB made substantial contribution to the manuscript and revised it critically. All authors have read and approved the final manuscript.

Funding We gratefully acknowledge financial support by the associate professor's stimulation grant, a personal grant awarded to ALB by the UMC Utrecht, The Netherlands.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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