Research Article

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Personalized Medicine

Mini-gut feelings: perspectives of people with cystic fibrosis on the ethics and governance of organoid biobanking

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Aim: Organoid technology has enormous potential for precision medicine, such as has recently been demonstrated in the field of cystic fibrosis. However, storage and use of organoids has been associated with ethical challenges and there is currently a lack of harmony in regulation and guidelines to govern the rapid emergence of 'organoid medicine'. Developing sound governance demands incorporation of the perspectives of patients as key stakeholders. **Materials & methods:** We conducted 17 semi-structured interviews with people with cystic fibrosis to explore their perspectives on the ethics and governance of organoid biobanking. **Results:** We identified three themes: prioritization of research and trust, ambivalent views on commercial involvement and transparency and control. **Conclusion:** Our study offers important insights for ethically robust governance of 'organoid medicine'.

Lay abstract: Organoids are living tissues that can be grown in a lab out of stem cells, which can replicate some features of actual organs in the body. They can be used to study diseases or develop drugs, but also to test the effectiveness of therapy for a specific patient (which is called precision medicine). Organoid technology is promising for the treatment of cystic fibrosis. At the same, storing and using organoids raises ethical and practical challenges. In order to ensure that the interests of those who provide the cells are respected, we interviewed people with cystic fibrosis. Their motivation to participate in organoid research was high, but at the same time they wanted to know how their organoids are used. In addition, while they did not feel the need to be directly involved in decisions about how their tissue is used, they valued ongoing communication from biobanks about its activities.

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Organoids are 3D multicellular structures that can be grown *in vitro*, and which recapitulate organ function. The technology is currently rapidly emerging in biomedicine due to its enormous potential for precision medicine, which aims to target therapies to individual patients. As such, organoids have the potential to improve treatment effectiveness, reduce costs and decrease the risk of harm compared with *in vivo* therapeutic research [1,2]. The potential was confirmed in 2015, when the first person with cystic fibrosis (CF) was successfully treated with a drug of which individual effectiveness was demonstrated *in vitro* prior to administration using organoid technology [3,4]. Because CF involves a genetic mutation expressed in every cell and also strongly affects the gut of patients, intestinal organoids or 'mini-guts' grown from stem cells in rectal tissue were shown to be an adequate model to test the effectiveness of drugs for specific individuals [5]. Moreover, since procuring adult stem cells requires a biopsy of specific organ tissue, growing intestinal organoids is much less invasive for patients than growing organoids from the lungs. The 'mini-guts' were screened in assays to measure swelling in the organoid in response to many

Box 1. The HIT-CF project

The HIT-CF project, funded through the EU's Horizon 2020 program, aims to provide better treatment and better lives for people with cystic fibrosis (CF) and rare mutations. To achieve this, drug candidates of several pharmaceutical companies affiliated with the project will first be tested in the laboratory on patient-derived mini-intestines (gut-organoids). Based on the reaction in these organoid screens, subgroups of patients will be invited to participate in clinical trials with one of the drug candidates. The project entails setting up an organoid biobank for this purpose, as well as to facilitate broader, nontherapeutic organoid research which will require a separate consent from patient-participants. One of the overall goals of the project is to examine the ethics and governance aspects of innovation by conducting parallel ethics research. To this end, the 'Ethics and Governance' work package team based at the University Medical Center in Utrecht (The Netherlands) conducted this interview study to take into account the needs, opinions and preferences of CF patients and other stakeholders [29].

different specific (CF) drugs over a short period of time [6,7]. Since then, many people with CF have received individually-targeted effective therapy using organoids [8].

The application of organoid technology in the field of CF entails the cultivation of (stem) cells from patients into organoids and storing them in tissue repositories often called 'living biobanks'. In general, biobanks are aimed at distributing biospecimens to public and frequently also private parties to facilitate multidisciplinary tissue research and large-scale data-sharing and analysis. Ideally, biobanks aim for long-term storage of samples to maximize potential for research. Academic work on biobanking has identified an extensive variety of ethically challenging topics, yet organoid biobanks shed a novel light on these challenges and present unique ethical complexities. For example, rapid developments in organoid technology have already led to the successful cultivation of many different kinds of organoids, such as stomach, liver, intestine, lung, kidney, and more recently brain organoids, and gastruloids or embryoids [9–11]. These developments have sparked discussion about how organoids relate to bodily integrity and the identity of the tissue provider, the moral status of such living complex tissue structures, and ethically acceptable and responsible use [12–21]. Furthermore, applying organoid technology for precision medicine purposes blurs the distinction between industry, research, and clinical care. This challenges current regulatory systems and guidelines, in which the distribution of duties, responsibilities and oversight are viewed as belonging to separate domains [22–24].

Considering the current rapid emergence of living biobanks aimed at precision medicine and its unique ethical challenges, there is an urgency to reflect on adequate models of governance. And since patients are a key stakeholder, incorporating their perspectives in the process of setting up governance is crucial to ensure that the technology develops responsibly, and that governance is ethically sound [25–28]. In a previous study conducted by some of the authors of this paper, the complexity of the relationship between people with CF and their organoids was demonstrated. They were seen both as common cell lines that did not invoke a special connection, and simultaneously as 'living fragments of the self' due to their 3D structure and the existence of both a genetic and functional link to the tissue provider. In addition, commercial access to organoids and the uncertainty around potential future uses of organoids were topics of concern [25]. This study, part of the HIT-CF project (see Box 1) [29], aims to build further on these findings, by gaining a deeper understanding of how patient-participants perceive the ethical and governance challenges of organoid biobanking. To explore their perspectives, we conducted semi-structured interviews. Our findings provide insights for designing responsible, ethically sound governance of organoid biobanks in precision medicine that respects the needs, values and preferences of patient-participants.

Materials & methods

We used a qualitative interview design to explore the needs, preferences and opinions of people with CF regarding the ethics and governance of organoid biobanks aimed at precision medicine. The Research Ethics Committee of the University Medical Center Utrecht evaluated this study as being exempt for full ethics review. The description of our methodology and presentation of our findings were structured according to the guidelines specified by the COREQ-method of reporting qualitative research [30].

Data collection

Data were collected through in-depth one-to-one interviews. Interviews were conducted throughout the second half of 2018 by Lensink (doctoral researcher with a background in applied bioethics), who had previous experience with qualitative research as well as prior training in interviewing skills. The interviews were semi-structured via

Box 2. List of interview topics

Ownership
Moral status of organoids
Benefit-sharing
Privacy
Commercialization
Consent
Findings
Patient involvement
Governance

the topic list shown in Box 2. A semi-structured interview guide ensured that the most important topics would be addressed resulting in sufficient breadth of data, while also providing space for respondents to emphasize particular subjects according to their perceived relevance. To select relevant topics for structuring the interviews, Lensink built on earlier work from the research group and conducted a nonsystematic literature study in PubMed and Google Scholar of prior academic work on the ethics of organoid technology and biobanking and the challenges in biobanking governance [12,15,25,26,31–33]. Eligible articles were selected and screened by Lensink and checked for relevance in close collaboration with Boers, Jongsma and Bredenoord. During interviews respondents were encouraged to freely share their thoughts and perspectives on the ethics and governance of organoid biobanking more broadly, as well as being asked to reflect on what would be important for ensuring responsible practice. In total, Lensink conducted 17 interviews lasting between 60 and 90 min, which were conducted either face-to-face or via phone and in Dutch or English, according to respondents' preferences.

Sample

The aim of our study was to gain a deeper understanding of the experiences, perspectives and opinions of participants in organoid biobanking aimed at precision medicine. We chose to focus on biobank participants (or, in case of very young people with CF, parents of patients) rather than the broader public, because the implications and risks of providing stem cells to a biobank are significantly more poignant for the patients that the tissue is derived from. By extension, their stakes in responsible governance of organoid biobanking are substantially higher, since they are directly affected by how the field is governed and by potential treatments developed out of 'their' donated tissues. We recruited respondents from several countries to capture a variety of cultural backgrounds across Europe. Recruitment was conducted via clinicians involved in the HIT-CF project (see Box 1), of which this study is a part. People with CF who wanted to participate in the organoid biobank were required to travel to the University Medical Center Utrecht for the biopsy. Clinical staff would ask patients after the procedure or during other clinical visits whether they were willing to participate in our study. Additionally, we also recruited via CF patient organizations in different countries across Europe, which brought our study under the attention of patients using digital communication channels. Potential respondents who had indicated their interests to participate in our study were instructed to contact Lensink, who provided participants with an information leaflet and a list of interview topics for preparation. Prior to the interview, respondents were asked for their written consent to participate. In case of the latter, respondents were asked to fill in and send back the consent form at least a week in advance. Eligible participants were also identified using snowball sampling, in other words, through recommendations by previous participants. Recruitment ended when saturation was reached, in other words, when no new significant data was encountered. The demographics of the respondents are shown in Table 1. All interviews were recorded and transcribed verbatim.

Data analysis

Data were analyzed according to the methodology of thematic analysis. Thematic analysis is an appropriate methodology to identify themes and patterns that extend across all data [34]. All transcripts were initially coded by Lensink using NVivo 11 software. Analysis of data started from an a priori list of codes based on the interview topic list, to allow an initial broad categorization. In addition, several codes emerged from the dataset inductively during the coding process and were subsequently added to the coding list. The analysis process was structured according to the constant comparative method [35]. This entails that data were systematically reviewed for supportive/conflicting evidence for emergent themes. More specifically, Lensink's coding process was used as a first step toward categorizing

Table 1. Respondent demographics.

Characteristic	Dutch (n = 9)	Non-Dutch (n = 8): Sweden (1), UK (2), Slovakia (1), Hungary (1), Austria (2), Germany (1)
Sex:		
– Male (n = 10)	6	4
– Female (n = 7)	3	4
Age:		
– 18–28	1	2
– 28-38	3	1
– 38-48	1	5
– 48-58	4	
Patient or parent of child with CF:		
– Patient (n = 13)	8	5
– Parent of child with CF (n = 4)	1	3
Organoid in biobank (or parent of):		
– Yes (n = 10)	8	2
– No (n = 7)	1	6

Total number of respondents (n = 17).
CF: Cystic fibrosis.

the data in themes. Parallel to this process, Jongsma and Boers cross-coded a number of interviews to compare and align findings and ensure inter-researcher reliability of results. Bredenoord checked a sample of interviews to ensure consistency in codes. The team discussed the analysis process, going back and forth between the data and the results to develop and revise themes and subthemes, while also ensuring agreement about the results. Alongside this evaluative process, data were further analyzed and abstracted by Lensink to develop overarching themes and subthemes and frequently discussed within the research team. Representative quotations were chosen to illustrate themes and were translated into English where necessary. Gulmans, head of research at the Dutch Cystic Fibrosis Foundation, provided his expertise for the topic list and during the drafting phase of the manuscript to ensure coherence of findings from the clinical and scientific perspective.

Results

Prioritization of research & high levels of trust

All respondents unanimously showed a highly supportive attitude toward the use of organoids for research. Many expressed their enthusiasm about undergoing a biopsy and having their organoid stored in a biobank for research, even beyond death (quotation 1 in Table 2). Two central considerations underpinned this positive attitude, both of which relate to the fact that respondents were (parents of) persons with CF. First, respondents indicated that their routine experience with clinicians and medical research led to the expectation that professionals working in the field of CF would act in the best interests of patients. Second, patients emphasized their personal stake in organoid biobanking. Their stake consisted of a personal dependency on innovative research for health improvement and of a more generally perceived importance of research for generating knowledge about CF disease and of developing drugs. Although some expressed hope for personal therapeutic benefit, others in fact described the wish to contribute to the advancement of CF medicine or sometimes medicine as a whole as the main reason for providing their organoid to a biobank (quotation 2 in Table 2).

In line with this perspective, respondents often reported the desire that their organoids will be applied in ways that ensure maximum potential for biomedical research. Many stated that wasteful use (i.e., not obviously contributing to biomedical knowledge) of the organoids they provided would upset them (quotation 3 in Table 2). Moreover, respondents valued organoid biobanking aimed at precision medicine because of its potential to reduce the notoriously high costs of CF drugs through more efficient targeting of treatment. Furthermore, they valued the organoid test as a more objective measure of drug effectiveness compared with the well-intended but sometimes inaccurate clinical judgment of doctors (quotation 4 in Table 2). Interviewees acknowledged certain concerns, worries and risks, but accepted these as a necessary aspect of contributing to the advancement of CF research for the 'greater good' (quotation 5 in Table 2). This tendency to prioritize research facilitation over other considerations was observed when discussing the close involvement of commercial parties and in respondents' views on measures to protect privacy and to ensure ethical use of tissue. These were seen as valuable and sometimes necessary considerations, but many respondents were concerned about the risk of such measures hampering research progress

Table 2. Supporting quotations.

Theme	Respondents' quotations
Prioritization of research and high levels of trust	1. "I hope that in the future, this disease can be cured. And for this it is necessary to do research. And that is precisely why I want to provide these cells. And I wouldn't mind at all if they were used after I die, because it is great that you can indirectly still help people after you die." 2. "I think you're helping all of humanity with that. Individually I probably won't benefit much from the organoid, because the disease has already progressed so much. [...] But with the organoids, if I can help other people with CF who have not been born yet, then that is really something." 3. "I don't mind at all, as long as [broader use] is made useful, as long as they don't say 'we're doing a test' and then use it for something else. Or that first year students are told: 'here we have some organoids, it doesn't matter what happens, just throw something on there and see what happens'. I think that would be a huge waste." 4. "And I think, with these mini-guts, everything you get has been proven in the lab on a piece of yourself. If you ignore that, compared with the many things that doctors or sometimes claiming, then I think you're not acting right." 5. "I think that forms specifying that you are always the owner of your DNA, that's nice that they write that down, but after a while that is obviously no longer the case. That is difficult, but I had already counted this in [...] A sort of necessary sacrifice for the greater good, so to speak." 6. "I mean the governance and legislation around this kind of development and science slows everything down which is hugely frustrating when you have a life limiting condition. So, in a way I want to say just get on with it, get on with the science, help those people that are suffering and you know, work that out later but on the other hand I realize that this is very new, it is somewhat controversial [...], you need that sort of governance in place before you sort of go too far." 7. "I don't know how many research is being done on one [organoid]? There is overlap, and [communicating] would be crazy in the sense of administration, and also from the perspective of research it would be too burdensome. I'll just read it in a publication, if you're still interested." 8. "Maybe I have enough faith that it will be used properly. [...] Say that I want my tissue to be removed from the biobank, that this really happens, that I will be listened to. And that there are regular checks that they will be properly stored and used." 9. "Well, I believe this research is expanded [internationally]. [...] If you talk about certain cultures, and you're talking about ethics, then I think that you should stay away from those countries with this kind of research until it is completely secure."
Ambivalent views on close commercial involvement	10. "I still feel partly connected to these cells over there and just want to know what happens to them. And in a way I think, while they remain over there, who knows what they will be used for in 40–50 years when we do reach the cloning phase?" 11. "As long as they use [organoids] to repair errors, fine. But don't go and use them to enhance humans. Of course you improve a person with CF with it, but you don't make him better than a normal person. I think that is where the boundary of good governance and ethics lies." 12. "With the big pharmaceutical companies, I get that they need to have the money to reinvest in science and further development and so it's really important that they do make a profit on one hand but I think there is a huge piece of work to do with working with governments and coming up with affordable pricing that enables them to further their research but also make drugs available to patients who need them, at the right time." 13. "[Companies] are everywhere, so and I think it's not always bad, because the research needs money. So and it depends on the reason, yeah, and they can tell you everything. Yeah, it's our world, so you have to trust and if you don't, and if you know, if you don't want that anything commercial is going on you have to go and live in hole. Without internet, without mobile phone, without anything." 14. "But if there's money involved I don't feel that if someone gets, if someone makes money on my organoid it's OK as far as I can benefit from the drugs. The only thing that matters is drug development and actually speeding up drug development."
Conditions for responsible organoid biobanking in (CF) precision medicine: transparency and control	15. "If you would only include [some information] of a successful study where they were able to use the results, that would already make consenting [to participate] so much more trustworthy." 16. "I reckon that's more the medical side of things and the scientist side of things, you know. The practitioner side [...]. I don't see why that bit would need to be anything to do with the patient." 17. "I think that [patients] should be involved also and informed, they could be also negotiating with both parties, the researchers, and the private companies [...] Because at the end they will give the access to the researchers and this would protect the owners or the donors." 18. "The owner could give their consent to give the authorization to do whatever we did for good. But at the beginning the donor is the owner. [...] if it's part of your body, then who else could be the owner?" 19. "I have offered it knowingly, so I don't completely see myself as its owner anymore. That is strange, with DNA. [...] Emotionally you are the owner because you know there is something of you there, but pragmatically speaking I know I am not [...] and the longer it is there, the bigger this distance will become." 20. "Because if you simply assume the good nature of people then I think you are not doing it right. It only works by virtue of good management." 21. "The possibility to withdraw, it's just the last straw to have some sort of say in what happens. Like if things go, if I get pissed off. I can take my organoid, it just feels more reassuring to know that you can withdraw and not that I can think of any situation where I would do it. I just think it's a way to give more power to the patients that, who would usually don't feel that they have enough power." 22. "Medical research alone is so broadly formulated that it could include many other things. And then I don't know exactly what. And then I would get stronger doubts [about participation]. I would still do it, but I can imagine there are patients who think this is terrible." 23. "[Scientists] know that if you've got a certain gene mutation Orkambi will help you, but it's whether you can get it or not. But I suppose if you know that you're more likely to have a better quality of life with that drug, you're going to petition to get that licensed, aren't you? You are going to push for that. But if you knew nothing about it, how does anyone ever, you know, move forward?" 24. "It is too black and white to say I want to know or not, because this depends on what it is and whether something can be done about it. It could mean that you could anticipate something in the future. But if it doesn't provide such an opportunity, then I don't really know what would be the benefit of hearing about such things."

CF: Cystic fibrosis.

(quotation 6 in Table 2). In fact, some argued that maximizing the potential of organoid research justified a sacrifice in terms of protection against commercial exploitation, privacy or being kept informed about research applications (quotation 7 in Table 2).

Many patients considered the informed consent procedure to be a formality, stressing their trust in clinicians and researchers to use their organoids responsibly. Respondents often stated that they would have provided their consent regardless of the specific content of the consent form. When discussing their view on risks associated with participation, most referred to the trustworthiness of European institutional oversight, and the assumption that

ethical standards would be followed (quotation 8 in Table 2). Some highlighted country to country variability in terms of ethical standards (quotation 9 in Table 2).

Ambivalent views on close commercial involvement

Underneath this dominant attitude that organoid research and the advancement of biomedical knowledge should be prioritized, a number of concerns about organoid biobanking were present in respondents' accounts. For example, some respondents were cautious about the uncertainty regarding future technological applications and possibilities and referred to sensitive topics such as cloning, transplantation, or human enhancement (quotation 10 and 11 in Table 2). Most concerns, however, were associated with close commercial involvement in organoid biobanking. Some concerns were explicitly attributed to the negative reputation of pharmaceutical companies regarding drug pricing and access (quotation 12 in Table 2). Respondents referred to the controversy around the excessive pricing of CF treatment. Many respondents admitted feeling uncomfortable with the close involvement of commercial parties in organoid biobanking and were critical about excessive profit generation. However, this was often dismissed or downplayed with optimism and pragmatism. Respondents were aware that drug development is expensive and viewed collaboration with pharmaceutical companies as a necessity for successful precision medicine research (quotation 13 in Table 2).

Although close collaboration with industry was seen as key for realizing the potential of organoid research, many felt uneasy about excessive profit generation. Excessive company profits using tissue provided by people with CF was seen as unfair, because patients are dependent on research for treatment. Some raised concerns that the organoids from patients with ultra-rare mutations would be neglected in research, because the small patient cohort would provide little financial incentive for pharma investment. Moreover, several respondents highlighted that companies are only able to generate profits by virtue of the patients providing the organoids. Financial profit generation by companies from organoid research was not considered problematic *per se*, but many respondents expressed unease with excessive industry profits, for example through prohibitive drug pricing. Many respondents supported the idea of reinvesting profits back into CF research, or using it to pay for post-trial access to drugs. However, in spite of these concerns, involvement of commercial parties was not seen as problematic but rather as necessary in the process of drug development (quotation 14 in Table 2).

Conditions for responsible organoid biobanking in (CF) precision medicine: transparency & control

Although all respondents were willing provide their organoids to the biobank, many stressed the importance of transparency from biobanks about how organoids are being applied and by whom. This was associated with the desire to have some degree of control over the terms of their participation, for example, by being informed about the results of research conducted with their material, or about the arrangements made between the biobank and its commercial partners regarding profits and drug pricing (quotation 15 in Table 2). Particularly ongoing communication from biobanks was considered important to facilitate a sense of patient control, and interviewees also reported that it may increase their willingness to participate in organoid research. Some respondents suggested the use of a digital platform to facilitate more continuous updates and engagement with biobank participants.

Respondents were hesitant about their direct participation in governance of biobanks. While a few expressed enthusiasm about being able to further contribute to research by offering their personal accounts, the majority of interviewees were reluctant about this. Some stated, for example, that biobank governance should be left to experts (quotation 16 in Table 2). Representation of the patient community as a stakeholder, however, was supported by many respondents as an effective way to communicate and negotiate interests, manage expectations, or to increase trust in the biobank (quotation 17 in Table 2). Some respondents argued that the biobank should play an active role in negotiating drug prices and fair access to treatment, to ensure that the benefits of organoid research are shared in a mutually acceptable way.

When asked about the topic of organoid sample 'ownership', many respondents felt that they remained the 'owner' of the organoid, based on the fact that it was once a part of their body or that it contained their DNA (quotation 18 in Table 2). Others considered their provision of a tissue sample to imply a transfer of ownership. One respondent felt a conflict between the perceived feeling of being the owner of the organoid, and the 'pragmatic' situation whereby it would effectively be owned by other parties (quotation 19 in Table 2). It was often stressed that the biobank should be publicly rather than privately owned, because of concerns about potential commercial exploitation and access to treatment. It was suggested that the biobank should act as the steward or custodian of the organoids to ensure responsible use (quotation 20 in Table 2). Moreover, respondents valued the right to withdraw

organoids from the biobank to prevent future use, since having the ability to use withdrawal as leverage acts as a form of control or empowerment (quotation 21 in Table 2).

The consent procedure was also seen as a way to exert a degree of control. In spite of the high levels of trust mentioned earlier, respondents supported the idea of being able to differentiate certain preferences and conditions about the terms of participation via the consent procedure. This could be used to address concerns about use of organoids when a donor dies, whether and which research findings should be disclosed to participants and specifying the context of organoid use (quotation 22 in Table 2). However, this was balanced by the concern that the information provided in a tiered approach to consent may be too much or complex, posing a barrier to understanding. Close alignment of the content of the consent form with the needs of participants was seen as a way to help alleviate any concerns around potential sensitive future applications of the technology, and the fact that commercial parties may have access to donated organoids.

At last, respondents reflected extensively on approaches to the disclosure of research findings generated through the use of their organoids. For example, the importance of always communicating results about potentially effective treatment back to patients was stressed, regardless of whether the treatment is accessible or not (e.g., due to potentially differing national reimbursement policies). This was seen as a way to offer some hope and perspective on research progress (quotation 23 in Table 2). Full disclosure of any (incidentally) generated information, however, was seen as potentially overwhelming to some people. Tiered consent was also seen as a way to accommodate the variety of individual values and preferences. It was suggested to use certain criterion to determine whether information would be disclosed, such as the accuracy of a finding or whether it is clinically actionable (quotation 24 in Table 2). But again, respondents were also worried that the necessary investment of time and resources of such a personal disclosure policy may hamper research.

Discussion

This study was conducted as part of the HIT-CF project aimed at setting up a stakeholder-informed, ethically sound governance framework for a cross-country CF-focused organoid biobank. It builds upon earlier work studying the perspectives of people with CF on the ethical aspects of organoid technology, while deepening our understanding of the practical implications of using organoids in the context of precision medicine.

Maximizing research value: to what extent?

Our study's respondents were all willing to provide their organoids for research, and while they have a life-long medical condition, many expressed a strong desire to contribute to the advancement of biomedicine precisely because of being severely ill. When asked about the ethical aspects of organoid biobanking, their first response often emphasized the importance of ensuring that the medical or scientific potential of their organoids was fully realized. Interestingly, many respondents were aware that biobank participation may not necessarily yield any personal clinical benefits in their lifetime, while stating that this would have minimal effect on their inclination to participate. The importance that patient-participants attribute to maximizing the research value of organoids is understandable. First, CF is a life-long illness, and only recently advances in research made it possible to treat some of the basic problems in the secretory cells of a minority group, and with varying degrees of effectiveness [36–38]. For many people with CF, therefore, treatment options are still very limited, and they are dependent on the speed of scientific progress for their health. Second, exorbitant pricing of the few (orphan) CF drugs that have been granted market access has sparked public outrage [39–41]. Many of our respondents raised these subjects during interviews, which may explain why development of drugs is so important to them. Third, having CF means extensive involvement in hospital treatment and medical research, which has resulted in a relatively well-informed and trusting community. The high level of trust may explain the face that their desire to contribute to biomedical research trumps the specific ethical conditions under which this happens.

However, as the interviews progressed and more time was spent discussing the deeper implications of participating in organoid biobanking, we observed a number of parallels with our prior study of how people with CF perceive organoid technology [25]. First, there is a shared dynamic at play, in the sense that respondents initially stress their highly positive attitude toward organoid technology, accompanied by several underlying concerns which surfaced through more extensive reflection. Second, there is consistency in the specific topics that were considered challenging or raised concerns [25]. Respondents in our study stressed the importance of research and trusted that their organoids would be used responsibly. Yet significant amount of academic work has focused on the ethical challenges, risks, and burdens associated with both biobank participation and organoid technology, for example,

concerning privacy, commercialization, disclosure of research findings and the ethical sensitivities associated with (clinical) application of stem cell technologies [12,15,26,42–44]. People with a chronic illness may be particularly inclined to provide organoids to a biobank under conditions that maximize research value, and in doing so, sacrifice certain personal values. However, the willingness of patients to accept conditions that may be insufficient to adequately respect their interests should not be seen as an ethical justification of such conditions. On the contrary: one of the core values in research ethics holds that those who are in a vulnerable position (e.g., patients with urgent health needs) should be particularly protected against exploitation and harm, precisely because of their inclination to accept the risks of participating in research for their own benefit [45]. For example, it may be more convenient for biobanks to require patient-participants to agree with a policy of full or no disclosure of research findings. While patient-participants may be inclined to accept such terms for the reasons described earlier, it is also known that disclosure policies that have no regard for personal preferences and values can be severely burdensome or even harmful to participants [46–48]. People can have a strong desire to live their lives without the burden of knowing certain things about themselves that may not even be clinically beneficial or actionable; should they be forced to accept this risk in order to benefit from providing their organoids to a biobank? The willingness of patients to contribute to scientific progress, as well as their hope for personal benefit, particularly stresses the importance of having sound governance structures in place that respect patient trust and ensure a fair balance between the interests of all stakeholders.

The desire for ongoing communication & transparency

In spite of the motivation to contribute to organoid research and their trusting attitude toward biobanks, researchers and industry, patient-participants wanted to stay informed about how their organoids would be used. Our respondents strongly valued the provision of clear information, transparency and open communication, both about the terms and conditions of biobank participation, as well as the results of research activities. Many indicated that they would appreciate some sort of assurance or proof that their organoids were indeed used to make a meaningful contribution to science or medicine. In addition, many respondents felt that they had or at least should have, to some extent, ownership over the organoids derived from their cells. There were concerns that strong commercial interests and close industry involvement could incentivize research applications that may not be aligned with their interests and values, which has been observed in prior empirical work [25]. Respondents therefore expressed the desire to be reassured that their act of providing organoids is at least reciprocated through a commitment of biobanks and researchers to act with respect for their perspectives.

The importance of such broader 'nonwelfare interests' to biobank participants has been previously observed [49,50]. As Tomlinson argues, tissue providers have a right to 'informed donation', which in his view is an important aspect of ethically sound biobanking because it supports a broader notion of respecting the values of tissue providers [51]. The moral force of this argument is strengthened by the fact that our respondents' emphasis on openness and transparency partly stems from the desire to have some degree of control, at least in the sense of being able to monitor how organoids are being used. Prior work has already established the importance of ongoing communication and engagement with biobank participants [50,52,53]. Put differently, transparency about biobanking activities facilitates accountability between stakeholders. Prior empirical work has similarly demonstrated the importance of transparency, accountability and institutional trustworthiness for biobank participants, and the perceived value of ongoing communication with biobank participants to reach these goals [54].

These insights are relevant for the governance of organoid biobanking in precision medicine in two respects. First, while people with CF are highly trusting of professionals and institutions to apply the organoids responsibly, they also wish to be more continuously informed about how their tissue is being used, both out of curiosity, as well as having the desire for monitoring as a degree of control. This observation suggests that patient-participants do not experience their provision of tissue as unconditional or nonreciprocal, even though they may verbally stress that advancing research is most important. Since these are important considerations of a key stakeholder group, responsible governance means taking these interests seriously [55]. In fact, the moral duty to respect (nonwelfare) interests of (patient-)participants has led to the idea that they are entitled to ongoing provision of information from the biobank as derived from having a 'right to informed donation' [15,24,51]. Moreover, if a share of the profits is used to fund such measures, it can function as an elegant way of sharing benefits between stakeholders.

Second, ignoring the desire of patient-participants for open communication and transparency is likely to be detrimental to their level of trust regarding organoid biobanking, and in turn may affect their willingness to participate [50,51]. In fact, a qualitative study of Japanese biobank participants suggests that ongoing communication

is seen as an effective way of addressing the limitations of a one-off initial consent procedure in terms of providing participants with ethically sufficient information [56]. Adopting an adequate policy for ongoing, transparent communication with patient-participants as part of the governance framework may therefore also contribute to biobank longevity and research feasibility [57–59].

Context-sensitive governance: involvement & control

Although our respondents expressed a desire for some degree of control over their organoids, there was little support for active participation in governance (e.g., in ethics oversight or managerial decision-making). These findings align with prior empirical work studying biobank participants' perspectives [54]. Rather than having a say in decision-making, what seems to really matter to biobank participants is that their organoids contribute to scientific development in a responsible way. Interestingly, however, there is a substantial amount of academic work that stresses the importance of more actively involving participants in biobank governance [33,57,60–63]. Some approaches, such as the 'charitable trust'- or the 'wiki-governance'-model, specifically envision direct involvement of individual biobank participants, for example, to facilitate shared decision-making about the biobank's activities [64,65]. Our study results, however, show a possible asymmetry – at least in the field of CF – between this emphasis on involvement of individual (patient-)participants, and the actual preferences of the people those models aim to serve. On the other hand, particularly in the case of organoid biobanking aimed at the treatment of patients, it may be crucial to ensure that patients have a voice to negotiate their interests [66].

This leads to several insights for governance. First, which way of involving patient-participants is most appropriate depends on the purpose of the biobank in question, the characteristics of its stakeholders, and their specific interests and preferences. Moreover, people use different conceptualizations of 'control'. For example, while control via direct involvement in the management of biobanks could fit certain contexts, people with CF were rather interested in control via the ability to monitor what is going on, as well as control via the ability to withdraw. Which of these forms of control is most appropriate to facilitate via governance depends, too, on the context. People with CF valued protection of their interests without direct involvement adding to the already heavy burden of disease [67,68]. Rather than appealing to individual biobank participants, involvement of patient advocacy groups in biobank management and decision-making can help contribute to this goal, for example, in the process of setting fair research priorities in the face of economic incentives, or improving the position to negotiate (post-trial) access to treatment [69–71].

Second, it underlines the importance of distinguishing between individual and collective interests in terms of how these are incorporated in governance frameworks. There may be convincing reasons why one or the other is more appropriate for a specific context [72]. While there are certain individual interests of biobank participants that deserve respect (e.g., concerning the communication of research findings), it does not follow that this should necessarily be achieved via direct personal involvement at the managerial level of a biobank. But in order to respect other, more collective interests of the patient community, some form of representation at the level of biobank decision-making may be necessary, for example, by involving patient organizations.

Third, our findings further highlight the need to recalibrate the debate on ethically sound biobanking, which in our view suffers from a myopic focus on privacy and informed consent. Patient-participants are more concerned with how their tissues are being used than with the initial consent, or the privacy risks associated with the storage and use of their cells. It follows that it would be significantly more useful to shift emphasis to reflection on what ethically sound or responsible storage and use of complex, stem cell-derived living tissues such as organoids aimed at patient care means, and how responsible stewardship should be enshrined in governance frameworks. Several experts have already argued for a 'new pragmatism' in biobanking and complex tissue research ethics that is less individual-centered, and focused more on notions such as reciprocity, mutuality, co-operation, solidarity, stewardship, custodianship, oversight and consent for governance [54,55,73–76].

Strengths & limitations

The purpose of our study was to provide a deeper understanding of the ethical challenges associated with organoid biobanking in precision medicine. By conducting face-to-face interviews with people with CF who were also already familiar with this technological innovation, we were able to discuss highly complex subject matter in a way that allowed us to thoroughly examine the perspectives and experiences of one of the core stakeholder groups on a broad range of topics. We increased the breadth of our data by also including the perspective of parents bestowed with taking care of a child with CF. Importantly, we did not encounter any significant differences compared with the people that we interviewed who themselves have CF, which suggests broader support of our findings. A side effect

of this approach is that our respondents were predominantly supportive of organoid biobanking as a whole and may not be representative of the wider CF community, or other patient communities. Studying a broader sample for comparison would therefore be a valuable future step, both to increase representativeness, but also to gain insight into how governance can be improved to better meet the needs of the community as a whole. Nevertheless, we believe our choice of sample is justified since it represents the end users (i.e., organoid biobank participants) affected by the governance structures in place. Moreover, we interviewed people from different national and cultural backgrounds across Europe, which allowed us to capture a diversity of perspectives that reflects the scope of the HIT-CF project.

Concluding remarks

Our study provides us with a number of valuable insights for setting up responsible governance for the specific context of organoid biobanking in the field of CF. First, while many people with CF are highly trusting toward researchers and industry and have a strong desire to contribute to research, this does not mean that their provision of tissue should be seen as a nonreciprocal arrangement. Second, this reciprocity could be established by serious consideration of their desire to be more continuously informed about the ways in which their organoids are being applied. This satisfies both their desire that the act of providing tissue leads to a meaningful contribution, as well as their wish for some degree of control. Third, although people with CF seem reluctant about control in the form of direct influence as participants in the management or governance of the biobank, they valued a degree of control in the form of being able to monitor as well as being able to withdraw. Moreover, it may therefore be especially important to involve CF patient organizations in order to fill the representation gap. With the enormous potential of organoid technology for precision treatment, 'organoid medicine' initiatives quickly on the rise [77,78]. Since these developments not only challenge existing regulations and guidelines but also raise new challenges [12], the time is now to set up ethically robust governance that ensures responsible advances in the field that respects the needs and values of patients as key stakeholders.

Organoid technology is still emerging, yet already this innovation has resulted in breakthroughs in the path toward personalized medicine. In organoid technology, the fields of genetics, regenerative medicine, synthetic biology and tissue engineering already converge. As all of these fields are currently developing at a rapid pace, other types of more advanced complex (living) tissues will likely be developed in the near future, which will in turn also be increasingly valuable for precision medicine. We therefore face an era in medicine with an unprecedented focus on human tissue biobanking. Our study has demonstrated how the application of complex tissues in precision medicine raises challenges that are highly context-specific; they are dependent on the type of tissue, the aim of the biobank and its partners, the nature of the disease, the characteristics of participant community, etc. The rise of complex tissue biobanking for precision medicine – like organoid medicine – undeniably brings significant benefits for patients, and also poses novel ethical and practical challenges. The speed at which these developments are taking place is tremendous, but through sustained efforts in the future toward normative reflection and stakeholder involvement, we can ensure the creation of responsible governance frameworks that adequately respect the interests of all those involved.

Author contributions

MA Lensink contributed in methodology, recruitment, interviewing, data-analysis, writing and original draft preparation. SN Boers contributed in methodology, data-analysis, supervision, editing and reviewing. KR Jongsma contributed in methodology, data-analysis, supervision and reviewing. VAM Gulmans contributed in validation and reviewing. AL Bredenoord contributed in methodology, supervision, data-analysis, reviewing and editing.

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Ethical conduct of research

The Research Ethics Committee of the University Medical Center Utrecht evaluated this study as being exempt from full ethics review. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Summary points

- Organoid biobanking aimed at precision medicine raises ethical and practical challenges, but there is currently a lack of harmony in regulation and guidelines to govern the rapid emergence of 'organoid medicine'.
- The perspectives of patient-participants on these challenges are crucial to ensuring responsible development of the field.
- A total of 17 semi-structured interviews were conducted to explore patient-participants' needs, preferences and opinions on the ethics and governance of organoid biobanking.

Findings

- Three key themes were identified in the data:
  - The prioritization of research and trust.
  - Ambivalent views on commercial involvement.
  - Transparency and control.

Relevance

Maximizing research value: to what extent?

- Our study demonstrates that people with cystic fibrosis (CF) are highly inclined to provide their organoids to a biobank under conditions that maximize research value and therapeutic potential, and in doing so, sacrifice certain personal values. However, the willingness of patient-participants to accept conditions that may be insufficient to adequately respect their interests should not be seen as an ethical justification of such conditions. On the contrary: this rather stresses the importance of ethical safeguards.

The desire for ongoing communication & transparency

- In addition to being strongly motivated to provide their organoids, our respondents valued clear information, transparency, and open communication by the biobank. Based on their wish to make a meaningful contribution to research with their organoids and their concerns about commercial involvement, patient-participants desired a commitment of biobanks and researchers to act with respect for their perspectives.

Context-sensitive governance: involvement & control

- The specificity our respondents' accounts suggests that the most appropriate way of involving patient-participants in governance is dependent on the purpose of the biobank in question, the characteristics of its stakeholders and their specific interests and preferences. People with CF were specifically interested in control via the ability to monitor tissue use, as well as via the ability to withdraw.

Concluding remarks

- Our study provides us with a number of valuable insights for setting up responsible governance for organoid biobanking, both in the field of CF but also broader. First, while patient-participants in organoid biobanking are highly trusting toward researchers and industry and have a strong desire to contribute to research, this does not mean that their provision of tissue should be seen as a nonreciprocal arrangement. Second, such reciprocity could be established by serious consideration of their desire to be more continuously informed about the ways in which their organoids are being applied, both to respond to their desire that their organoids are used in a meaningful way, as well as to take seriously the wish for some degree of control. Third, although reluctant about direct involvement in the management or governance of the biobank, our study's participants valued the ability to monitor tissue use and research progress and the ability to withdraw, which is an important insight for participatory governance.

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