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Organoids for personalized treatment of Cystic Fibrosis: Professional perspectives on the ethics and governance of organoid biobanking

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ABSTRACT

Background: Organoid technology is emerging rapidly as a valuable tool for precision medicine, particularly in the field of Cystic Fibrosis (CF). However, biobank storage and use of patient-derived organoids raises specific ethical and practical challenges that demand sound governance. We examined the perspectives of professionals affiliated with CF or organoids on the ethical aspects of organoid biobanking for CF precision medicine. By conducting this study parallel to the process of innovation and development of organoid biobanking, its findings are valuable for the design of responsible governance frameworks.

Methods: To identify relevant themes and attitudes we conducted 21 semi-structured qualitative interviews with professionals in the field of organoid technology, biobanking, or CF research and care.

Results: We identified three key challenges, as well as the suggestions of professionals on how to address them: (1) The challenges associated with commercial involvement, trust, and ownership, (2) Navigating the blurring boundary between research and clinical care, (3) Appropriate approaches to the informed consent procedure.

Conclusion: Sound governance of organoid biobanks aimed at precision medicine requires coming to terms with the fact that its stakeholders no longer belong to separate domains. Responsible governance should be aimed at finding a sound, context-sensitive balance between integration of ongoing co-operation and mutual consideration of interests, and maintaining a feasible and sustainable research climate.

1. Background

Organoids are 3D cell structures cultivated in vitro that function on a basic level like actual organs. They are characterized by their ability to self-organize, consist of multiple cell types, and can be grown indefinitely [1]. Organoids are emerging as valuable tools in biomedical research, including drug development, disease modeling, and ultimately even clinical transplantation [2–4]. Organoid technology is especially promising for precision medicine, which aims to increase cost-effectiveness and risk-benefit ratios of therapies by more precisely targeting therapies to individual patients [5,6]. This value has recently been demonstrated in Cystic Fibrosis (CF) research, by successfully screening drugs using intestinal organoids or 'mini-guts' for personalized targeting of treatment [7,8]. In 2015, the first person received treatment for CF on the basis of organoid drug screens [9]. The HIT-CF (acronym for ' (Drug) Hits for Cystic Fibrosis') project aims to follow-up on this breakthrough by expanding organoid-based drug screening to other CF patients in Europe[1].

Initiatives like HIT-CF are dependent on biobanks for the storage and distribution of organoids to researchers and commercial partners [10–12]. Crucially, however, the clinical application of organoid technology via biobanks raises specific ethical and practical challenges. First, organoids are living cell lines derived

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[1] See: https://www.hitcf.org/.

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from stem cells or tissue, and therefore they have ethical implications with regard to bodily integrity and identity, moral value, and responsible use [13–18]. Second, organoid biobanking aimed at therapeutics entails collaboration between different stakeholders with different interests. This raises additional ethical and practical challenges concerning informed consent, privacy, disclosure policies, commercial access, benefit-sharing, and involvement of participants [13,19–25].

In light of these challenges, sound governance structures are necessary to ensure responsible practice. While there is an extensive amount of academic work on biobank governance, little is known about which governance measures are appropriate for the specific context of precision medicine organoid biobanking. Providing an adequate answer to this question demands a deep understanding of the practical reality [26]. Our position as ethicists embedded within the multidisciplinary HIT-CF consortium provided a unique opportunity to examine the perspectives on the ethics and governance challenges of a diverse group of organoid biobanking and CF professionals, and explore potential solutions. To seize this opportunity, we conducted interviews to map the perspectives of professionals involved. These insights can be used to inform the design of responsible governance structures and ensure biobank longevity, especially in the context of precision medicine [27,28]. Moreover, empirical reflection on ethical issues associated with biomedical developments complements philosophical inquiry and stimulates responsible innovation, especially when it is carried out parallel to the development of a technology rather than 'end-of-pipeline' [29,30]. Prior empirical work by several co-authors of this paper has demonstrated the ethically complex ways in which people relate to the organoids cultivated from their cells [31]. Here, we present the results of our study of professionals' perspectives on the ethics and governance challenges of applying organoid technology for precision medicine (Box 1).

Box 1
KEY Points.

- Organoid technology is emerging rapidly as a valuable tool for CF precision medicine, raising specific ethical and practical challenges for governance
- Interviews with professionals were conducted to explore these challenges and potential solutions
- Responsible governance in precision medicine organoid biobanking should:
  1) Facilitate a balance between the strong interests of closely involved commercial stakeholders, and other interests
  2) Address the blurring boundary between research and clinical care by clearly delineating the duties and responsibilities of involved professionals, and
  3) Shift focus away from relying on initial one-off consent as an administrative tool, and rather emphasize ongoing communication and differentiation via tiered consent

Box 2
List of interview topics.

Ownership
Ethical use of organoids
Benefit-sharing
Privacy
Commercial involvement
Consent
Findings
Patient participation
Governance

Box 3

(1) Commercial partnerships; fairness, trust, and ownership
(2) Blurring boundary between research and clinical care
(3) Informed consent

2. Methods

To study the perspectives of professionals, we used a qualitative, interview-based methodology. Approval for the study was given by the Research Ethics Committee of the University Medical Center Utrecht. 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 [32].

2.1. Data collection

Data were collected through semi-structured one-on-one interviews during the second half of 2018. Semi-structuring ensured that the most important topics were addressed in each interview, resulting in sufficient data breadth, while also allowing respondents to emphasize particular subjects of perceived relevance. Prior to interviewing, the research team compiled a topic list (Box 1 ,Box 2) for semi-structuring based on a literature survey of (1) the ethical aspects of organoids and (2) governance of biobanks. A total of 21 interviews were conducted by MAL, a doctoral researcher with a background in applied bioethics, formal interview training, and previous experience with qualitative research. Interviews lasted approximately 60 min, were conducted either face-to-face or via phone and, according to respondent preference, in either Dutch or English.

2.2. Sample

In order to be eligible to participate in this study, professional experience with organoid technology or biobanking was required. In particular, we focused on including academic researchers, clinicians, researchers and managerial staff at pharmaceutical companies or biobanks, and researchers and policymakers from CF patient organizations. Participants were recruited via the research team's professional network and the HIT-CF project. In order to maximize contrast, eligible participants outside of the consortium were also identified using snowball sampling. Moreover, we interviewed participants from a range of professional backgrounds and affiliations (see Table 1 for demographics). Lastly, considering the international focus of the HIT-CF project, we aimed to capture perspectives from several (Western) countries.

Participants were approached by MAL and provided with an information leaflet, which included the topic list. Prior to the interview, respondents were asked for their written consent to participate. Recruitment ended when additional interviews did not lead to the identification of relevant new themes (data saturation). All interviews were recorded and transcribed verbatim.

2.3. Data analysis

Data were analyzed using *thematic analysis* (TA), a methodology used to identify themes across data starting from an a priori list of relevant subjects to allow an initial broad categorization [33]. All transcripts were initially coded into sub-themes by MAL using NVivo 11 software. Parallel to this process, KRJ, SNB, and SEC also coded a number of interviews to compare findings and ensure inter-reliability of results. ALB checked a sample of interviews

Table 1
Respondent demographics.

Total number of respondents (n=21)	Working in Europe (n=13): *Netherlands(7), Belgium (4), Portugal (1), Spain (1)*	Working outside of Europe (n=8): *Israel (2), USA (6)*
Male (n = 11)	7	4
Female (n = 10)	7	3
Commercial affiliation (n = 7)	5	2
Profession		
Academic organoid researchers (n = 9)	6	3
Organoid biobank research staff (n = 1)	1	
Pharma research staff (n = 1)	1	
Patient advocacy affiliated (org.) research (n = 2)	1	1
Clinic (n = 3)	2	1
Organoid biobank management (n = 2)	2	
Pharma management (n = 2)		2
Policy (n = 1)		1

for code consistency. The analysis process was structured according to the constant comparative method [34], where data is systematically reviewed for supportive/conflicting evidence of emergent themes. The team then reflected on the analysis process, going back and forth between the data and the results to develop and revise themes and sub-themes. During this process, several codes emerged from the data set inductively and were added to the a priori coding list. To illustrate themes, representative quotations were chosen and translated into English where necessary.

3. Results

We identified three key themes in the perspectives of professionals on the ethics and governance challenges of organoid biobanking for precision medicine purposes (Box 3). Below we elaborate on respondents' accounts of these challenges and their suggested solutions.

3.1. Theme 1: commercial partnerships: fairness, trust, and ownership

Organoid biobanking for precision medicine involves close cooperation with commercial parties, such as pharmaceutical companies. Many professionals considered these partnerships crucial for making biobank research financially viable (quotation 1 in Table 2). Projects such as HIT-CF were seen as particularly valuable, because all involved stakeholders held the same goal: personalized targeting of CF treatment (quotation 2 in Table 2). Despite supporting close industry involvement, many respondents did express uneasiness with companies generating 'excessive' profits from patients with urgent health needs (quotation 3 in Table 2). While some considered this a fairness issue, others were concerned that it may be detrimental to biobank participants' trust and affect their willingness to provide their organoids (quotation 4 in Table 2). Cultural factors, political stability, the trustworthiness of national governments and institutions, and the extent to which research and industry are intertwined were seen as contributing factors to this concern (quotation 5 in Table 2). However, sharing monetary benefits with individual biobank participants was not supported, arguing that scientific progress is possible by virtue of a collection of different tissues (quotation 6 in Table 2), and that financial incentives may lead to a biased collection.

Reflecting on the close involvement of companies, respondents often raised the topic of sample ownership. Many professionals stressed the importance of specifying ownership, because organoids are living cell lines with enormous commercial value that have a unique genetic and functional link to the person providing the tissue. However, further exploration during interviews revealed its complexity. A common rhetoric, for example, was that biobank participants should be the 'ultimate owners' of their organoids, and have the 'final say.' (quotation 7 in Table 2). But respondents experienced difficulty defining what this would entail in practice, such as in case of genetically modified organoids (quotation 8 in Table 1). In addition, there was considerable variation between professionals' perspectives on the degree of ownership that sample providers should be given. For example, while some professionals considered it a fundamental aspect of ownership that biobank participants should be asked permission for continued storage and use of their organoids after death, others argued that this would be disproportionate to the minimal risks and burdens of organoid biobanking (quotation 9 in Table 2).

3.2. Suggestions for governing commercial access, trust, and ownership

Transparent, continuous communication with biobank participants was suggested as a way to alleviate potential worries about the close collaboration with industry (quotation 10 in Table 2). There was also wide support for biobanks as publicly-owned institutions that aim to reinvest (a part of) profits back into research projects to increase trust and fairness (quotation 11 in Table 2). Most professionals supported the idea of temporary (i.e. until withdrawal by the participant) ownership of organoids by the biobank to ensure feasibility (quotation 12 in Table 2).

In addition, some stressed the importance of balancing commercial incentives with other stakeholders' interests to maintain trust and fairness, such as multi-stakeholder involvement in biobank management. Several professionals also considered it important to give participants a voice in governance, particularly for patient-centered biobanks such as in HIT-CF, where those providing the organoids have urgent health needs (quotation 13 in Table 2). However, others emphasized the difficulty of organizing meaningful representation (quotation 14 in Table 2) and concerns that such measures could hamper research.

3.3. Theme 2: blurring boundary between research and clinical care

Organoid biobanking for precision medicine purposes involves close collaboration between academia, biobanks, industry, and clinical care. Many professionals viewed the convergence of these traditionally distinct domains as a source of challenges. For instance, there were different perspectives on the extent to which the clinical duties towards patients also apply to academic professionals or companies. Professionals were aware that organoid research is a vast source of potentially relevant information, particularly for those suffering from CF. Yet opinions differed on whether the duty exists to report these back to patient-participants, and if so, under which conditions (quotation 15 in Table 2). Some researchers argued that this responsibility should not extend to researchers because it would pose an unreasonable barrier to scientific progress

Table 2
List of supporting quotations.

Theme	Quotations
Commercial access, trust, and ownership	1. *"[…] but at the end of course the companies make money from that of course. But as patient and as doctor, you want to have as many drugs in the market as possible. And that as many patients can be...can have access to a treatment as possible. And if the organoids can be instrumental there, so I support the idea of also commercial parties having access to organoids and to biobanks."* 2. *"We try to give the best treatment, […] and if we can do beautiful scientific things with the material, then I don't really see the objection to that. Not even when it's done commercially.."* 3. *"If the patient's organoids were directly and exclusively involved in drug development, then the patient should benefit from the financial benefit that the company that developed the drug or the body that stores the biobank, if they receive royalties I think the patient should receive it also. […] I feel a little bit uncomfortable that people will make money out of the desire of patients to receive therapy."* 4. *"And what people often indicate is that huge profits are being generated with their material, I know that people find this difficult. If you don't clearly explain what will happen to their tissues, then it could be that people say: no, I won't do it. Then you lose other possibilities for scientific research, for developing new treatment."* 5. *"I mean...some of the questions you're asking earlier about even just like access or you being able to get drugs, I think depending on people's understanding of their current countries' rules and regulations, access to healthcare, insurance status, things like that. Their understanding of their local kind of state versus what other countries are like, I think can really change the way that they answer things."* 6. *"But in general, in my view it is the group that contributes, it is not the individual. Particularly in the context of biobanks. It is purely the fact that you have a collection that allows you to create a model, and not the individual. Precisely the fact that you have 100, 200, 500 patients gives you the power to discover something. That is why I don't think these things should be returned individually."* 7. *"I don't know. So I mean, the patient, for me is the final owner, […] maybe like renting a house, you remain the owner, but you allow somebody else to live there under certain conditions. But I think the ultimate owners should remain the patient because they should have at any moment the right to withdraw the consent.."* 8. *"Suppose that we can use CRISPR technology.. […] Who is the owner of these organoids? Who gets right of say over modified tissues, or even modifications of modifications?"* 9. *"I just think from a feasibility perspective, I think it's just not...it's just too complicated. It's too expensive to keep that. So that expense alone probably makes it a no go. And if you're really going to keep it, keep that level, then you have to keep all that information and then if someone does come out and say 'I want to withdraw consent' then you have to go and you have to pull that sample. […] I think that if ethics committees allow you not to give that as an option, […] then I would say that that's the way to go."*
Suggestions to address	10. *"I think it's a question of educating, of talking to, analyzing things. And communication to explain things properly. Because at the end, maybe people just say 'oh there is someone who really makes, is becoming rich thanks to me'. And yeah maybe there are people becoming rich, but there are also people that give opportunities to many other people. So not only see the big CEO who eventually for the big pharma who is becoming rich thanks to that, but [also] how you [as a patient] can benefit from that."* 11. *"So you have to think about it from a, are we doing it for development, for clinical care and/or for payment of it. […] Is the purpose of the biobank to help with coverage later to help develop more evidence to support that because the evidentiary standard is different or is it for current and future drug development for CF or for something else?"* 12. *"That's a hard one.. I personally think that if the cells go into a bio-repository, I would think that the bio-repository should be the owner, but […] it's almost that they're doing a transfer of ownership to the bio-repository until they withdraw the ownership."* 13. *"I think it gives them […] a feel that their voice is being heard. […] Also, it gives them a way to be informed about where the process is. Because really I don't see it since the patients are not going to be known in general to the industry."* 14. *"Well, as in there are efforts to include patients in things and they run up against some challenges. […] how do you engage them because they are so different from everyone else on the board, right? Like, do you only just care for them to be there and/or are there ways to specifically elicit their feedback? And that takes a lot of energy and preparation on both sides."*
Blurring boundary between research and clinical care	15. *"Say that you are doing a trial, and […] a predisposition is found that may be relevant for the patient and his or her family, and then an interesting ethical dilemma emerges: should I share this information? But the whole point of anonymization was that the patient is not harmed or burdened through sharing tissue. You could argue then: that's not a burden, but a benefit, […] but who judges which is the case?"* 16. *"I don't think you should put that on the organoid research, that expectation. [The role of the researcher] is to advance knowledge in a broader scientific context."* 17. *"But you know, of course there are examples where […] they're looking for a mutation in a gene and they have these DNA samples and then somehow because they did it a little bit different, they found a mutation in a different gene that causes Alzheimer's or Huntington's. […] I think you're supposed to tell the patient."* 18. *"So I received this message: 'there is a 27 year old girl who has no treatment options left, […] can you help her?' So there is someone […] who thinks: I've provided my mini-guts and it is taking pretty long before I get any results. […] That is difficult; we are an academic lab and you just try to make the best of it."* 19. *"One risk […] is, let's say, you find this drug doesn't work on this sample and then somehow the insurance companies realize that, okay, well it's not going to help this patient. We're not going to pay for it, where in fact, you know, you're dealing with a cell in a culture dish and you might want to try it to see how the patient reacts on the drug."*
Suggestions to address	20. *"…they [the patients] may be patients who are strong enough to get the results like that, or they may be patients who don't want to know."*
Informed consent as the ethical backbone	21. *"How to let the person decide how far they would want their samples... like what they would want done to their samples. […]I don't want to say a not informed population because it's a very well informed population. But if scientists can't picture it, can a patient? Do they know what's out there? So I'm not actually sure how you would even deal with the consent."* 22. *"Maybe you should use an informed consent [with] menu A, B, C, and that you can say: menu A, go do it. Menu B, [additional governance measures]. Menu C, come back [for re-consent] […] Yes, that's great, but who is going to pay for that?"*
Suggestions to address	23. *"The moment that you involve commercial parties, it must be very clear what one is consenting to, [for example] allowing organoids to be used by pharmaceutical companies. I know people have issues with that. And under what conditions this is allowed, you should explain further."*

(quotation 16 in Table 2); others emphasized that, since the ultimate goal is to improve the health of patients, researchers should also play their part (quotation 17 in Table 2).

Because of the current publicity around organoid technology – particularly in the field of CF – several professionals worried about being increasingly confronted with patients and clinical issues in their work, without having the necessary clinical expertise to adequately deal with such situations (quotation 18 in Table 2). In addition to the *whether* unsolicited research results should be reported back to the clinic, there were also concerns about *how* this information should be communicated to patient-participants. Moreover, some professionals worried about causing unrealistically positive expectations about receiving treatment by informing patient-participants about the results of drug screens, especially since reimbursement policies differ between countries involved in the HIT-CF project (quotation 19 in Table 2). Because of the heterogeneity of national policies and regulations around permissible stem cell applications, harmonization of quality standards, privacy protection, and defining ownership were seen as additional challenges for international projects operating at the intersection of organoid technology and clinical care.

3.4. Suggestions for addressing challenges raised by the blurring distinction between research and care

The development of adequate cross-border governance, such as ethics oversight bodies and standard operating procedures, were seen as crucial to address the challenges raised by regulatory differences between countries. For example, professionals stressed the value of clear criteria to guide decisions about whether and when to disclose research results back to patients. Some argued that patient-participants should be asked during the consent procedure if and in what circumstances they would like to be informed (quotation 20 in Table 2). When asked which criteria should be used to formulate these questions, professionals responded with uncertainty. That said, there was consensus that disclosure of information generated using organoids derived from patients demands prior consultation with the treating physician.

3.5. Theme 3: the place and purpose of the consent procedure in precision medicine organoid biobanking

The consent procedure was the most extensively discussed topic during interviews. It was unanimously considered a central element in the governance of organoid biobanks, for which professionals put forward several arguments. First, some respondents emphasized that organoids have certain ethically sensitive features that underline the importance of obtaining a well-informed, voluntary decision to participate. Second, informed consent was considered important, because organoid biobanking is both aimed at therapeutic and non-therapeutic, commercial purposes and so participation does not necessarily lead to direct clinical benefits for patients (quotation 21 in Table 2). In connection to this, respondents often stressed the importance of providing clear and complete information on these subjects during the consent procedure. Lastly, professionals valued the consent form as a sort of contract that specifies the terms and conditions of participation and the ways in which the organoids may be used. This was seen as a crucial governance tool to ensure that researchers and industry are able to do their work without the risk of getting into conflicts with patients.

3.6. Professionals' suggestions for governing the consent procedure

Many professionals supported the idea of more continuous approaches to the consent procedure rather than a one-off signature, thereby allowing participants to respond to new and possibly ethically controversial applications or commercial partnerships. A 'tiered' approach to consent in organoid biobanking was therefore often brought up, which allows participants to differentiate some of the terms of their participation, for example by being able to refuse commercial, non-therapeutic use of their organoids, to express their preferences concerning the disclosure of unsolicited research findings, or whether their organoid should be destroyed after death. Some even suggested exploring the possibility of using a more dynamic, digital consent model, in which participants can make real-time adjustments. This was also seen as a way to more closely involve participants and maintain or increase their trust (quotation 22 in Table 2).

However, a common concern was that the use of a more continuous, elaborate consent procedure implies an investment of time and resources that may significantly hamper research. Several respondents viewed such consequences to be disproportional to the minimal risks associated with organoid biobank participation (quotation 23 in Table 2). Broad consent (i.e. consent to a broad range of research purposes) was therefore often seen as the most effective way to create a feasible balance between respecting the autonomy of patients, and maintaining a viable, financially sustainable research environment.

4. Discussion

There is ample academic literature available on biobanking, precision medicine and stem cell technology, which echoes the global rise of biobank-based research, and the move towards precision medicine [5]. These trends are particularly well known within the field of CF, where characteristics of individual patients are especially crucial for optimal treatment [35]. It has even been called 'a model system' for precision medicine, due to the development of CFTR-modulator drugs (e.g. ivacaftor) that can be targeted to individual patients through in vitro pre-testing of cells stored in biobanks [36]. However, the broad scope of much of the academic work on the ethical and practical challenges of biobanking has led to quite general results, with little insights into the complexities and details that exist within a specialized field [26]. As the subtitle of prior work by two of the co-authors of this study indicates, organoid biobanking 'revives old and raises new ethical challenges' [13]. In our analysis, we therefore focused on identifying aspects specific to the storage and use of organoids derived from patients within a therapeutic context, either because they are novel, or because the unique characteristics of the context make these insights particularly relevant for responsible governance. A deeper understanding of these topics is crucial for responsible advancement of the field, especially considering that many of these topics are still heavily debated due to the lack of harmony between regulations on human tissue research, precision medicine and biobanking [37–39]. This is obvious from the EU's 2019 evaluation of the European BTC (blood, cells and tissue) directives (2002/98/EC & 2004/23/EC).[2] The report concluded, for example, that 'many of the detailed and prescriptive safety and quality requirements are no longer adequate to address fully the challenges associated with rapid technological, scientific and epidemiological developments', that 'key oversight principles are not sufficiently robust', and that 'some citizen groups, such as donors and offspring are not adequately protected'. In what follows, we discuss our findings in terms of their relevance for setting up responsible governance tailored to the specific characteristics of organoid biobanking for precision medicine.

[2] European Commission (2019). Evaluation of the EU blood and tissues and cells legislation. Consulted on September 2, 2020 at: https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/swd_2019_376_en.pdf.

4.1. Close commercial involvement, trust and balancing interests

Much recent literature on biobanking has focused on the importance of closer involvement or engagement of biobank participants. The idea is that treating participants more like 'partners' rather than as passive tissue 'donors' makes biobank governance more ethically responsible and fair, particularly in the context of living cell lines derived from patients stem cells [27,60–65]. Our results suggest that professionals are to some extent supportive of these considerations. For example, some argued for ongoing communication with participants about aggregated research results; maintaining their trust was considered a crucial factor for the success of organoid biobanking, for which ongoing communication was seen as an effective approach. There is empirical evidence that more continuous provision of information to participants is also supported by tissue providers, particularly in the form of aggregated research results [26,66]. Some of the professionals in our study pointed out the challenge of deciding what is the most appropriate approach in terms of *which* information should be communicated, as well as how frequently and via which channels. People with CF have voiced their desire to be informed about 'major changes in governance and use', as well as to be kept in the loop about the biobank's past, current, and future research projects [31]. This also provides some degree of downstream control, for example by facilitating an informed decision to enforce the right to withdraw consent.

Trust was a central theme in our study's findings. Professionals anticipated that participants may harbor concerns about privacy, commercial access to cell lines and (excessive) profit generation, which could potentially affect their trust. Although they may be right in this assumption [62,67], people with CF have reported highly trusting attitudes towards organoid biobanking [31]. Interestingly, several respondents viewed these concerns as grounded, in the sense that there are actual risks that deserve consideration. In order to prevent exploitation of the trusting attitudes of biobank participants towards other stakeholders, it is therefore particularly important to set up governance that is in line with their interests and expectations [68].

Although a unilateral communication policy will surely be beneficial to this end, it questionable whether this is ethically sufficient. In fact, adequate protection of the interests of biobank participants rather calls for trustworthy institutions [69], which requires more than just a willingness from biobanks to provide information to participants. Prior work suggests that biobank participants need more than simply the initial one-directional communication during the consent procedure to call a biobank trustworthy [70]. Since biobanking takes place in a wider context of 'innovation politics', trustworthiness rather requires governance frameworks that facilitate a fair balance between market forces, academic incentives, and other interests [71]. This is particularly relevant in the context of complex living tissues such as organoids, which people ascribe different levels of moral value and ownership to [26,31,40]. Participatory governance arrangements could facilitate a more fair balance between these interests [15,25,31]. Several approaches to biobank governance such as the *surrogacy*-model, the *charitable trust*-model, or the *adaptive governance*-model, stress that continuous, bi-directional communication and involvement of participants are necessary to ensure that biobanks can act as a responsible custodian of stored samples, for example via representation in oversight bodies, or via ways of incorporating changing values due to unknown future scenarios [72–75]. This may be especially effective in the field of CF, where the community is known for being generally very well-informed, and advocacy groups are highly professionally organized. While respect for autonomy and for the interests of biobank participants remain core aspects of responsible biobanking, we contend that these notions are fully compatible with decisions that involve the acceptance of a certain level of risk and uncertainty. People make these kind of decisions all the time, and there is no a priori reason to question their autonomy in these situations. We contend therefore that a governance framework that appeals to the solidarity between biobank participants and researchers, in the sense of being both willing to accept some of the costs and risks for the purposes of advancing medicine, is not necessarily problematic. This is especially relevant considering the discontentedness of researchers with the sometimes excessive burdens of administrative and logistical measures requirements [76–81]. Since drug developing and biobanking are expensive enterprises, especially for rare diseases like CF and cutting-edge technologies such as organoid biobanking [82], concerns sustainability and feasibility should be given due consideration [48,83].

4.2. Navigating the blurring distinction between clinical care and research

Organoid biobanking aimed at the treatment of patients further blurs the distinction between clinical care and tissue research [53]. It is precisely the convergence of these two domains that makes clinical biobanking so promising for precision medicine [5]. However, we also observed uncertainty among professionals about dealing with situations that demand clinical expertise, such as how to approach the disclosure of findings. The current popularity of organoids was seen as potentially beneficial to people's willingness to provide their organoids for research, but professionals were also concerned about the high level of expectation among patients. Precision medicine organoid research has been previously associated with therapeutic misconception [2], and there is empirical evidence that people with CF indeed have high hopes for organoid technology to deliver on the promise of personalized treatment [31].

The application of tissue derived from patients with urgent health needs in laboratory research raises the question whether and how the duties and responsibilities of clinicians towards patients transfer over to biobanks and researchers [54]. Our study shows that professionals perspectives differ regarding which responsibilities towards patients apply to non-clinical researchers and biobanks, or to what extent. However, while this indicates the need for guidelines, current regulatory frameworks do not provide an adequate answer to these challenges [37,38,55–58]. In addition to the challenges taken from the 2019 EU evaluation described above, the BBMRI European biobanking research infrastructure has stated already in 2012 that patient-driven biobanks 'must develop clear policies' to this end.[3] A report by Zika et al. (2010) from the EC's Joint Research Center on biobanking challenges in Europe also signals the challenges that are raised by using patient-derived tissue in a research context, the lack of regulatory harmony, and the 'extremely' varying ways in which different countries interpret and implement guidelines in this regard [59]. Without proper guidelines for navigating biobank-based research on the intersection with clinical care, researchers may either become unduly burdened with clinical obligations, or there may be too little attention for the interests of patients [54]. Addressing the lack of guidelines and harmonization is therefore crucial, particularly considering the rise of precision medicine biobanks and organoid technology, and the concerns that our study indicates still exist in the field.

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4.3. Consent: more than an administrative tool

Similar to other empirical studies on biobanking, we observed a strong fixation among professionals on the topic of consent [26,40]. Within the context of precision medicine biobanking with patient-derived organoids, we found almost unanimous support for a consent procedure in which patient-participants are able to differentiate some of the terms of their participation. Some valued such a 'tiered' approach to consent for its ability to negotiate and mitigate potential conflict between biobank participants and other involved stakeholders. In addition, many professionals considered this an effective way to increase participants' trust in the biobank and its partners. It was also seen as a way to offer patient-participants some space to act on their personal values and preferences, which suggests that professionals acknowledge the importance of interests among biobank participants that go beyond a simple yes or no decision to provide cells. Empirical evidence suggests that biobank participants support tiered consent for similar reasons [41,42].

The tendency of professionals to view the consent procedure mainly in terms of its instrumental value highlights an important and persistent issue in biobanking more generally, namely that informed consent seems to be increasingly relied on as an administrative measure to anticipate conflict. While the consent procedure is likely very effective in this regard, excessive fixation only on this aspect is also ethically problematic, because it is potentially detrimental to the broader goal of protecting the autonomy or interests of research participants [43]. In fact, Waldby and Mitchell (2006) have argued that it is precisely the consent procedure which constitutes the 'disentanglement' between tissue and the person that gives the material its value for research [16,44].

These considerations carry particularly weight when viewed in the context of storing and using patient-derived organoids in close collaboration with commercial stakeholders. First, in contrast to more conventional tissues such as blood or skin, the characteristics of organoids raise ethically sensitive questions concerning their moral status and bodily integrity [13,17], and potentially controversial uses such as chimaera research or 'brain emulation' [45,46]. This makes the lack of any downstream control over tissue use problematic for organoid biobanking, especially because organoids are living tissue that can be stored indefinitely, and the technology is developing at a rapid pace into novel applications. In other words, these uncertainties underline the issue whether initial consent for long-term storage can really be said to meet the criterion of being 'informed'. Second, patient-participants have a significant stake in how their organoids are being used, because they are dependent on these activities for the treatment of severe illness, which is at least part of their decision to participate. However, organoid biobanking aimed at precision medicine involves close collaboration with commercial entities with strong economic interests, which may not always be in line with those of patients [16]. Crucially, fixating on initial consent, whether with tiered approach or using broad consent, does not facilitate any downstream control over how organoids are being used, or allow participants to change their preferences in response to how the technology develops, which applications the organoids are being used for, or who is provided access to the cells [13,15,25]. An empirical study of the perspectives of people with CF indicates that they appreciate the consent procedure for being a source of realistic information and reassurance, but that they would appreciate being more continuously involved [31].

The consent procedure is and should remain a core element of any biobanking governance framework in order to ensure voluntary, well-informed participation. But there are additional interests at play within the context organoid biobanking aimed at precision medicine that we believe call for an emphasis shift in governance [25]. Several approaches have been proposed that envision such a shift, such as 'dynamic' consent or 'consent for governance' [15,47–50]. Although our study suggests that professionals have concerns about costs, many also acknowledged the value of such approaches by facilitating more continuous downstream alignment of the terms of participation with the values and preferences of tissue providers, stimulating ethically sound governance in accordance with the interests of patient-participants, and in turn also likely increasing trust [48,49]. Moreover, it may also address another challenge raised by both professionals in our study and well-known in biobanking literature, namely of ensuring that information is sufficiently understood by consenters [51]. In fact, this issue may be particularly poignant in the context of complex tissue biobanking, as empirical work by McCaughey et al. (2016) demonstrates that stem cell biobank participants generally have poor recall of the information provided to them during the consent procedure, especially about industry involvement and the fact that their living cell lines allow for indefinite storage and use [52]. Information about the ongoing governance obligations that are in place will likely be easier to grasp than specific details about possible research applications. Shifting focus to the research context in the consent procedure may therefore help professionals fulfill their duty of obtaining informed, voluntary consent [24].

4.4. Strengths and limitations

Due to the complex nature of the research subject, a high level of expertise around organoid technology and biobanking was required in order to be eligible to participate in our study. As mentioned, the fact that our team was situated in a large research consortium provided a unique opportunity to capture deep, highly specialized perspectives on the details and nuances of the practical reality of organoid biobanking in precision medicine. However, one side-effect of this approach is that our sample and findings predominantly represent European and US views. Additionally, some of our respondents were professionally engaged with patient organizations. It is possible that these respondents were more inclined to speak on behalf of patients and their interests. However, considering patients are a core stakeholder in organoid biobanking, we think these perspectives are particularly important for governance. Moreover, the accounts provided by our specific pool of CF-oriented professionals may not be representative of the broader community of professionals engaged in organoid biobanking for precision medicine purposes. However, as similar initiatives are in the rise, we see no reason why our insights into the practical and ethical challenges and potential solutions in this field cannot serve as a source of practical wisdom for the broader research community.

5. Concluding remarks

Researchers in the field of CF have shown that biobank-based research on complex living tissues is highly promising for personalized treatment of patients. The rise of these developments will lead to a further convergence of patients, researchers, clinicians, biobanks, and commercial parties. Moreover, they are happening in an era that increasingly emphasizes the importance of engaging stakeholders and the creation of participatory arrangements. While it is crucial to ensure a feasible, financially sustainable research climate for organoid biobanks, it does not follow that these goals may be pursued *at all costs* and under *any* conditions. Adequate governance of organoid biobanks aimed at precision medicine will require coming to terms with the needs and concerns of its multi-domain stakeholders, and embracing biobank participation as more than a passive and non-reciprocal enterprise. Designing responsible governance for this context rather starts from the awareness that it

takes place in an ecosystem the success and longevity of which depend on governance structures that facilitate ongoing co-operation and mutual consideration of interests.

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Declaration of Competing Interest

The authors declare no conflict of interests.

CRediT authorship contribution statement

Michael A. Lensink: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Project administration, Software, Writing - original draft, Writing - review & editing. **Sarah N. Boers:** Methodology, Formal analysis, Supervision, Writing - review & editing. **Karin R. Jongsma:** Methodology, Formal analysis, Supervision, Writing - review & editing. **Sarah E. Carter:** Formal analysis, Writing - review & editing. **Cornelis K. van der Ent:** Validation, Writing - review & editing. **Annelien L. Bredenoord:** Methodology, Supervision, Formal analysis, Writing - review & editing.

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