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SPOTLIGHT

Responsible use of organoids in precision medicine: the need for active participant involvement

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ABSTRACT

Organoids are three-dimensional multicellular structures grown *in vitro* from stem cells and which recapitulate some organ function. They are derivatives of living tissue that can be stored in biobanks for a multitude of research purposes. Biobank research on organoids derived from patients is highly promising for precision medicine, which aims to target treatment to individual patients. The dominant approach for protecting the interests of biobank participants emphasizes broad consent in combination with privacy protection and *ex ante* (predictive) ethics review. In this paradigm, participants are positioned as passive donors; however, organoid biobanking for precision medicine purposes raises challenges that we believe cannot be adequately addressed without more ongoing involvement of patient-participants. In this Spotlight, we argue why a shift from passive donation towards more active involvement is particularly crucial for biobank research on organoids aimed at precision medicine, and suggest some approaches appropriate to this context.

KEY WORDS: Stem cells, Organoids, Biobanking, Ethics, Precision medicine, Involvement, Governance

Introduction

Research on human tissues is quickly on the rise, especially with the rapid development of complex tissues such as organoids. Organoids are three-dimensional multicellular structures derived from stem cells, cultivated to self-organize into differentiated functional cell types spatially organized in a manner similar to an organ, and that are able to perform at least some organ function (Lancaster and Knoblich, 2014; Huch and Koo, 2015). Because of their characteristics, organoids have enormous potential for drug development and precision medicine, which aims to increase cost-effectiveness and risk-benefit ratios of therapies by more precisely targeting therapies to individual patients (Hewitt, 2011; Kinkorová, 2016). To illustrate, biobank research on patient-derived organoids has already led to successful personalized treatment of cystic fibrosis (Noordhoek et al., 2016; Saini, 2016).

In order to facilitate such research, organoids are cultivated from patient-derived stem cells and stored in tissue repositories called 'biobanks'. Biobanks facilitate multidisciplinary research aimed at a variety of purposes such as drug screening, drug development and disease modelling, as well as enabling large-scale data sharing and analysis. In biobanking, the traditional way of protecting the interests of participants is by relying on a one-off consent procedure, combined with measures to protect privacy and *ex ante* ethics review. However, organoid biobanking raises specific ethical and practical challenges related to the consent procedure, commercial access and commodification, privacy and ownership (Boers et al., 2016; Bredenoord et al., 2017; Munsie et al., 2017). In this Spotlight, we argue that these challenges call for a shift in focus from the paradigm of passive donation towards more active forms of participant involvement, and suggest some potential ways forward.

Limitations of the current approach in biobank-based research

At present, the dominant approach in biobank-based research can be considered a 'consent or anonymize' paradigm, in which consent for sample storage and use is viewed as a requirement only if samples are not, or cannot, be fully anonymized. In addition, emphasis is placed on measures to protect privacy and *ex ante* ethics review (Solbakk et al., 2009; Mostert et al., 2016). Broad consent is frequently defended as an appropriate model in the consent or anonymize-paradigm. Broad consent seeks permission for the use of stored samples for a broad range of research purposes, the specific details of which are unknown at the time of consent. Broad consent is valuable for biobank research, because demanding specific consent for each new potential use would significantly hamper research and make the use of stored samples unattractive – if not infeasible. Although broad consent is unable to provide specific details to participants, we believe it is coherent with the notion of an informed and voluntary decision (Sheehan, 2011). Broad consent therefore strikes an elegant balance, by allowing future (re-)distribution of samples without the burden of re-contacting participants every time a sample is requested.

However, this focus on either obtaining broad consent or on full anonymization of samples is being increasingly criticized for its inability to adequately protect participants' interests (Mostert et al., 2016). For example, there is no harmonization regarding appropriate measures to protect privacy in data- and sample-based research (Knoppers et al., 2007; Zika et al., 2011; Kaye et al., 2018). In addition, whether anonymity is actually possible is being increasingly questioned because of advances in genomics and data-driven research (Lowrance and Collins, 2007; Laurie, 2011; Freeman Cook and Hoas, 2013; Kasperbauer et al., 2018). These concerns are especially relevant in the domain of rare diseases such as cystic fibrosis, because of the small number of patients. Moreover, in contrast to the common assumption that anonymity is the most important interest of biobank participants, full de-identification of samples may in fact be at odds with the needs of patients, as it rules out the possibility of diagnostics or return of results (Eriksson and Helgesson, 2005), as well as denying biobank participants any degree of control over their tissue (Gottweis and Lauss, 2010; Boers and Bredenoord, 2018).

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Indeed, patients have voiced their concerns about this (Pakhale et al., 2014; Boers et al., 2018).

In addition, although we concur that broad consent is valuable for biobank research and is not problematic per se, the current emphasis on a one-off consent and privacy protection positions patient-participants as passive donors. This approach does not adequately address the challenges associated with biobank research on patient-derived organoids, nor does it sufficiently take into account the interests of patient-participants, because it does not facilitate ongoing involvement around the use of their tissue.

Why active involvement is particularly important for precision medicine research on organoids

Support for closer involvement of participants in biomedical research initially emerged as a means to increase the quality and value of clinical trials, and to facilitate efficient translation from bench to bedside by working with citizens or patients, rather than simply subjecting them to research (Ocloo and Matthews, 2016). In biobank research, this emphasis on more active forms of involvement rather than passive donation is similarly on the rise, as a way to collaborate on setting up research and governing data, to share ideas and perspectives on data and tissue use, and to improve the governance of research biobanks (Gottweis, 2008). We believe that there are a number of reasons why more involvement is important for biobank research on organoids for precision medicine purposes.

First, the specific characteristics of future research are unknown at the time of consent. At the same time, organoid technology is developing rapidly, which has already led to the successful cultivation of many different kinds of organoids, such as stomach, liver, intestine, lung, kidney, and more recently also brain organoids, as well as gastruloids or embryoids that provide *in vitro* models of the early embryo (Aach et al., 2017; Huch et al., 2017; Schutgens and Clevers, 2020). These developments have raised questions about bodily integrity and identity, and what is considered ethically acceptable use (Boers et al., 2016, 2019; Bredenoord et al., 2017; Munsie et al., 2017; Boers and Bredenoord, 2018). Moreover, embryoids or gastruloids have led to discussion about whether, and to what extent, they might have moral status (Sutton, 1995; Munsie et al., 2017; Appleby and Bredenoord, 2018). Some of these applications, such as embryoids, genetic modification, chimaera research (Rowe and Daley, 2019) or brain emulation (Serruya, 2017; Trujillo et al., 2019), have already sparked public and political controversy. In fact, empirical research has demonstrated that participants in organoid biobank research experience different relationships and attribute relational value to their organoids (Boers et al., 2018). Biobank participants therefore have legitimate interests in continuous, downstream involvement around the use of their tissue (Bagley et al., 2017; Bredenoord et al., 2017; Huch et al., 2017), and participants in genomic biobanks have voiced their support for such measures (Wendler and Emanuel, 2002; Murphy et al., 2009).

Second, organoids have enormous economic value, meaning there are strong commercial interests involved (Bartfeld and Clevers, 2017; Bredenoord et al., 2017; Boers et al., 2019). The application of organoids in precision medicine brings together different stakeholders with potentially conflicting interests (Caulfield et al., 2014). Commercial parties have strong incentives to prioritize the most profitable research, but these choices will not necessarily be aligned with patients' most urgent health needs, or with academic interests. This raises the complex question of how to fairly distribute benefits. Benefits here should not be understood in a strict monetary sense, such as a share of the profits. Rather, by benefits we mean contributions to the general well-being of individuals (Hugo Ethics Committee, 2000), for example via post-trial access to drugs. Our point is not that biobank participants deserve compensation in general for their provision of tissue (Allen et al., 2018). However, contrary to healthy participants, patients depend on the activities of precision medicine organoid biobanks for treatment. To view their decision to participate as a voluntary, non-reciprocal donation would therefore be inappropriate. In our view, generating profits using tissues derived from patients is ethically contentious, if it is done without adequately taking into account their perspective on how these organoids are stored and used.

That being said, what constitutes fair distribution must also take into account the importance of financial sustainability. It is crucial to maintain an economically viable climate to attract industry investment in order to realize the most important goal of organoid biobanking in precision medicine: developing treatment. The ethical challenge here is to ensure that benefits are distributed fairly among all involved stakeholders (Caulfield et al., 2014; Mitchell et al., 2015; Boers et al., 2016; Munsie et al., 2017; Boers and Bredenoord, 2018). What fair compensation or distribution of benefits means, however, is subject to debate (Howard et al., 2011; Chalmers et al., 2015; Steinsbekk and Solberg, 2015). This discussion is highly complex from an ethical as well as a practical perspective, and an attempt to settle it is beyond the scope of this Spotlight. However, we believe that closer involvement of patient-participants can help facilitate fair deliberation between stakeholders.

Third, the combination of organoid biobank research and precision medicine blurs the traditional boundary between the domains of biomedical research and clinical care, which are subject to different rules and standards (https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html). Although doctors are legally charged with the responsibility to act in the best interests of their patients, the same obligations do not apply to researchers (Berkman et al., 2014). The convergence of research and care therefore raises the issue of to what extent the clinical duties doctors have towards patients extend to biobanks and researchers. Organoids can be a vast source of potentially clinically relevant information. However, what counts as clinically useful or in someone's best interests partly depends on the perspective of the individual, and researchers can only act in accordance with these preferences when these are known. Similar to the debate in genomics (Vos et al., 2017), we believe that biobank research on patient-derived organoids calls for a recalibration of researchers' duties around the protection of privacy, the disclosure of research findings, and data-sharing, for which we believe more active forms of involvement of patient-participants is useful (Berkman et al., 2014; Jarvik et al., 2014; Johnsson et al., 2014; Viberg et al., 2014).

Approaches to more active forms of participant involvement in biobanks

We have argued why involvement is important, which subsequently raises the question of how it can be done. An exhaustive assessment of all potentially appropriate approaches is beyond the scope of this article, but for the sake of demonstrating the merits of closer involvement, we provide some suggestions.

Biobank participants do not enrol in a specific trial; they enrol in an institution that performs certain activities, under certain terms and conditions that may change (Mongoven and Solomon, 2012). Broad consent is appropriate in this context because, contrary to specific consent, it entails a decision to permit unspecified tissue use under certain governance conditions to protect participants' interests (Boers et al., 2015; Boers and Bredenoord, 2018). The 'consent for governance' model aims to better align the consent procedure with

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this context, by emphasizing the creation of ongoing governance arrangements that are ethically sound, and by focusing on informing participants about (changes in) those arrangements. Without such information, it is not clear to us whether participants can make a well-considered decision to enforce their right to withdraw. In addition, the type of information provided during the consent procedure will most likely be easier to understand, which may help professionals overcome the challenge of ensuring that participants sufficiently grasp the terms of their consent (Lensink et al., 2019). The consent for governance model aims for responsible biobank research through establishing a more continuous relationship between biobank and participant (Gainotti et al., 2016).

Another promising model is 'dynamic consent' – a model of two-way communication between biobank participants and researchers through the use of digital interfaces, allowing patient-participants to be continuously engaged in the activities of the biobank, and share preferences around data-sharing and access, agenda-setting and return of results. The use of a digital interface allows for real-time adjustments, which addresses the limitations of a one-off consent, and facilitates researchers and biobanks in their ability to act in accordance with these preferences. Empirical research into the merits of dynamic consent shows that dynamic consent may potentially provide a solution to a number of research-related challenges experienced by professionals, such as facilitation of specific research tasks, improvement of recruitment and retention, and simplification of collecting and managing consents. In addition, dynamic consent could potentially reduce costs, because transferring (some) biobank activities to the digital domain may lead to greater operability across nations and organizations, as well as provide professionals with practical tools to address changes in legislation (Budin-Ljøsne et al., 2017).

Involvement of patient-participants by providing them with some form of representative power improves their position to negotiate collective interests with other stakeholders in biobank research. We do not contend that patient-participants should be given absolute decisional authority, but rather that they should be systematically included in deliberative processes. The appropriate approach depends on the specific context of biobank and research, but in complex tissue biobanking for precision medicine, examples could be managerial involvement of patient organizations, participation in advisory board meetings, or consultation rounds to assess decisions or results (https://www.bbmri.nl/sites/bbmri/files/guidelineeng_def_0.pdf). For organoid biobanks aimed at treating a specific disease, advocacy groups such as patient organizations can be appropriate parties to engage (www.bbmri-eric.eu/wp-content/uploads/2016/07/stakeholders-forum-report-a-step-closer-a4.pdf; Budin-Ljøsne and Harris, 2016). Patients have indicated their desire for some system of checks and balances to prevent concentration of power, and to facilitate negotiation between stakeholders to balance interests (Kraft et al., 2018).

We want to stress that meaningful representation of patient-participants implies providing them with at least a degree of leverage or control (Burton et al., 2008; O'Doherty and Burgess, 2009; Arnstein, 2019). Without any real commitment to be responsive to the input of patient-participants, such involvement would remain tokenistic (i.e. 'ticking the box'), which will do little to reduce the agency gap between stakeholders (Winickoff, 2007). A number of governance structures have been proposed to facilitate this, such as the wiki-governance model, the Every Participant is a PI (EPPI) model and the adaptive governance model (Hunter and Laurie, 2009; O'Doherty et al., 2011; Dove et al., 2012; Buyx et al., 2017). In any case, as complex tissue biobanking raises ethical challenges and patients have legitimate interests distinct from those of healthy participants, a 'social approach' in biobanking that focuses on transparency, openness, solidarity and reciprocity between stakeholders can be valuable (Vos et al., 2017).

The cost of transitioning

Although we contend that shifting from passive donation to more active forms of involvement is needed, such a transition is not without its own set of challenges. The most important, and in our view legitimate, concern is whether the cost of such measures will have a detrimental effect on biobank sustainability and on the professional freedom of tissue researchers (Forsberg et al., 2013; Williams et al., 2015). Although the measures we propose may eventually lead to a decrease in costs – and there is evidence that suggests this (Kondylakis et al., 2017) – setting up and maintaining such a digital infrastructure implies investment of resources and coordination. Moreover, such experimental approaches to consent and governance require new forms of collaboration with research ethics committees to reach agreement on required criteria and quality (Budin-Ljøsne et al., 2017). However, as these are also changes at a broader institutional or societal level, it should not be the sole responsibility of biobanks and researchers to bear its burdens. The currently almost unanimous operationalization of ethics review and privacy protection measures can serve as an analogy: these are a significant investment of time and resources, though nevertheless crucial, and the burden of their cost is not simply placed on those working with the tissue. Moreover, European policy has already adopted involvement as a core aspect of personalized medicine (Kinkorová, 2016).

In addition, we believe these concerns may overlook the benefits of involvement of patient-participants for biobanks and research. For example, there is evidence that closer involvement of participants is an important aspect of responsible biobank research and governance, and can contribute to accountability and trust (Gottweis and Lauss, 2010; Ocloo and Matthews, 2016). Such measures not only lead to more inclusive decision-making processes, but may also result in larger tissue collections (Tutton et al., 2004; Winickoff, 2007; Blasimme and Vayena, 2016; De Vries et al., 2016; Noordhoek et al., 2019). In addition, involvement may also improve the quality and efficacy of translation from the bench to the clinic (Kirwan et al., 2017; van der Scheer et al., 2017; Noordhoek et al., 2019), which may be especially valuable for organoids, considering their potential for precision medicine (Drost and Clevers, 2017). Biobanking is an expensive endeavour, and ensuring its sustainability is crucial. A shift towards more customized, virtual approaches to biobanking with a stronger emphasis on involvement is likely to improve sustainability (Chalmers et al., 2016).

Final remarks

Further research is necessary to assess which specific conceptualizations for the involvement of patient-participants will be most fitting in the context of complex tissue biobanks aimed at precision medicine (Levitt, 2011). In assessing this, it will be crucial to find an appropriate balance between meaningful involvement and a feasible research climate. Involving biobank participants in decisional processes and governance can increase fairness, but in particular situations or by using certain approaches, it may very well turn out to be practically unfeasible and pose an unjustified barrier to research. We do not contend that involving patient-participants should be maximized at all costs; feasibility considerations should be given due respect, for the sake of all stakeholders. It is also important from a moral perspective to minimize the barriers to

developing treatment. This is precisely why ensuring a responsible future for biobanking should be a priority, especially as many facets of society are currently undergoing changes in the wake of rapid biotechnological developments. Closer involvement of patient-participants can help reach these goals, and is therefore a morally important step towards safeguarding the longevity and sustainability of complex tissue biobanking.

Competing interests
The authors declare no competing or financial interests.

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