**Patient-derived Organoids in Precision Oncology
– Towards a Science *of* and *for* the Individual?**

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Abstract
An interesting question for philosophy of science is how the "personal" gets constituted, scientifically as well as socially, through new technologies and practices in personalized medicine. A novel approach to better account for patient variation is to develop so-called *tumor organoids* based on tumor samples from individual cancer patients. Given their ability to recapitulate tumor heterogeneity, patient-derived models have been highlighted as breaking way for a "science of the individual" or a "one patient paradigm" in medicine. But to what extent is it possible – and desirable – for *in vitro* models to become "substitutes" for patients or patient types? To explore such questions, we combine philosophical and ethnographic analysis of laboratory research and clinical research practice. We analyze how epistemic uncertainties about the evidential status of organoids relate to ontological uncertainties about the nature of cancer itself, and document challenges of determining what level of variation is scientifically and clinically meaningful in personalized medicine. Moreover, we show how epistemic and ethical implications intersect when tumor organoids are attempted used for patient-specific drug screening. In this context, researchers and clinicians become stretched between the hopes of patients and epistemic uncertainty.

Keywords: Personalized medicine; Precision oncology; Tumor organoids; Tumor heterogeneity; Patient-derived models

1. Introduction
Personalized medicine raises interesting philosophical questions about what counts as good translational models and appropriate evidence in a context where disease categories become hyper-stratified. We focus here on precision oncology, a field which is promoted as the most advanced domain within personalized or precision medicine (Plutynski, this volume)[3]. In this context, personalized models are currently developed as an attempt to account for the genetic heterogeneity of individual patient's tumors. This chapter focuses on so-called tumor organoids, i.e., 3D cultures developed from tumor samples of individual patients. We explore how the translational potential of organoids is viewed and negotiated in laboratory research and clinical practice, and discuss how epistemic uncertainties concerning the representational status of organoids intersect with ethical considerations about patient care.

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[3] We use the terms precision medicine and personalized medicine interchangeably to refer to the attempt to stratify and individualize modeling and treatment recommendations to individuals or finer-grained disease groups though the use of new molecular and computational techniques (such as genomics).

Organoids have a complex conceptual and experimental history (Drost and Clevers 2018; Simian and Bissell 2017). Developmental biologists have for decades emphasized the potentials of 3D cell cultures for capturing how spatial conditions influence cell differentiation and cell reprogramming, including tumor development (e.g., Bissell et al. 1987; Barcellos-Hoff et al. 1989). Research on organoids recently gained momentum with new approaches in stem cell research, exploring also the potential of organoids to develop lab-grown miniature versions of human organs such as guts and neural structures (Sato et al. 2009; Eiraku et al. 2011; Lancaster et al. 2013). In this chapter, we focus on organoids as models that aim to recapitulate *genetic heterogeneity* of patient tumors and hence to allow for *patient-specific drug screening* (Huang et al. 2015; Ooft et al. 2019; Sachs et al. 2018).

Patient-derived models potentially reshape how we think about science and medicine. The emphasis on patient variation in personalized medicine calls for reconsideration of the merits and necessity of the long-standing trust in numbers and standardization procedures in clinical trials (Lillie et al. 2011; Green et al. 2019). *Nature* recently endowed organoids as the "Method of the Year" (Nature Editorial 2018), and some have suggested that patient-derived models in personalized medicine will revolutionize the study of cancer and other diseases (e.g., Akkerman and Defize 2017). Organoids derived from patient tumors have been suggested to represent a kind of "disease in a dish", because one can directly intervene on malfunctioning tissues (Shen 2018). Philosopher Giovanni Boniolo even suggests that tumor organoids, qua their material embodiment of patient diversity, pave the way for a "science of the individual":

> Since the Aristotelian discussion of the architectonic of knowledge, it has been accepted almost as a platitude that there is no science of the individual. […] Whenever you study the primary cancer cells of a given patient, you are also studying tumor heterogeneity, that is, something at the universal level. But you are also studying the particular disease of that particular patient, that is, you are also studying the individual. […] Put in a different way, within the field of tumor heterogeneity we have the possibility of doing science of the individual, since the tumor cancer cell population actually is an individual (patient) *in vitro*. (Boniolo 2017, p. 29)[4].

Similarly, organoid biobanks refer to their resources as "a patient in the lab" (Hubrect Organoid Technology 2020), and organoids combined with patient-derived xenografts (PDX, or personalized mouse models) have been described as giving way for a "one-patient paradigm" in medicine (Malaney et al. 2014). Questions about the translational potential of patient-derived models are thus intimately connected to questions about how the "personal" gets constituted in personalized medicine. Important questions include whether it is possible and desirable for *in vitro* models to become "substitutes" for patients or patient types (cf. Svendsen 2018).

Organoids are philosophically intriguing because they blur the boundaries between human patient and experimental model. The quote by Boniolo above seems to suggest that tumor organoids establish a relation of *metonymy*, i.e., a part-whole relation of sameness between a 3D culture and the tumor of a specific patient. Similar to how we often take a picture of a face to represent a whole person, organoids come close to the vision of experimenting directly on a part of the patient in the lab. However, the idea of patients *in vitro* is complicated by ontological and epistemic instability of cancer itself. Whereas representation of heterogeneity is highlighted as a virtue of organoids, it is unclear which level of variation is necessary or useful to represent in experimental models. Heterogeneity of tumors does not "bottom out" at the level of cancer subtypes or even at the level of

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[4] It is beyond the scope of our paper to discuss the notion of a "science of the individual" in Aristotle's writings and later scholarly work (see e.g., Foucault 1973 [1963]). Similarly, we cannot go into the discussion whether medicine should be understood as a science or an art, and whether such a dichotomy is fruitful (see Solomon 2015). Or primary focus is to explore the implications of attempts to develop more "individualized" models to account for the shortcomings of standardized procedures.

individual patients. Rather, tumors of individual patients consist of *spatially* and *temporally* heterogeneous cell populations – what is often referred to as *intratumor heterogeneity* (Bertolaso 2016; Plutynski 2018). Intratumor heterogeneity is a major challenge in clinical practice, as there can be heterogeneity across metastases from the same primary tumor. This problem also challenges the stability of personalized models, as it is unclear to what extent tumor samples can account for biologically relevant features of whole patient tumors.

Moreover, the view of personalized medicine as a departure from procedures of standardization is complicated by its epistemic dependency on and contributions to population science (Hoeyer 2019). Organoids are clinically useful only insofar as they allow for inferences about features and drug targets concerning cancer subtypes that go beyond individual variation. Hence, organoid research presents insights into how material embodiment of patient variation also depends on and co-produces new relations of inference between patient-specific biology and shared molecular markers, i.e., between the individual patient and the collective (data populations of extant and future patients). The issue of interest is therefore not whether organoids adequately represent the patient tumor per se, but to explore what is considered the right level of abstraction of models for clinical purposes. We show how challenges of reaching a balance between variation and standardization are tied to social and ethical implications in translational contexts.

Our philosophical analysis is informed by a literature study of published scientific material on organoids as well as insights from ethnographic work. As part of a research project on personalized medicine in the Danish welfare state, we have followed the development of initiatives to implement personalized medicine in the Danish health care system. Through interactions with researchers and clinicians, we have explored how personalized medicine at the same time is shaped as a wide-ranging political priority (e.g., through the establishment of a National Genome Centre) and as a concrete practice that materializes in different laboratory and clinical settings. Specifically, we have followed a preclinical project where organoids are used to guide decisions on experimental cancer treatments in a phase I clinic, based on genetic and kinase profiling. In this context, we (together and separately) have participated in daily clinical practice and tumor board meetings, and have conducted interviews with researchers, oncologists, and patients. Moreover, we have interviewed researchers in the US working on patient-derived organoids for research purposes.

Our analysis shows that although organoids and other patient-derived models are sometimes framed as a technique that allows for direct inferences of patient-specific drug response, their status as preclinical and research models is complicated by various uncertainties and practical challenges. At present, organoids can be interpreted as future-oriented epistemic objects (Rheinberger 1997). This implies that open-ended questions about their evidential status are intimately connected to uncertainties about the nature of cancer itself, and about how much variation models in personalized medicine can and should embody.

2. What's so Special About Organoids?

Anti-tumor drug screening on human cancer cells began in the 1970s. From the late 1980s, standardized cancer cell lines have been developed for 2D studies and testing in murine models, following guidelines of the US National Cancer Institute. While standardized cell cultures have the advantage of allowing for comparison of drug screening results, critics have pointed to the translational challenge that very few candidate drugs make it further than phase III Studies (Kamb 2005; Feng et al. 2013). The translational gap is often seen as resulting in part from the failure of cancer models to account for patient-specific variation, as well as from the limitations of especially 2D cultures (or 2D monolayers) to recapitulate structural context of tumors. Tumor organoids are hoped to account for both limitations by embedding tumor cells of individual patients in a 3D matrix that mimics microenvironmental features, such as the chemical and physical structure of the extracellular matrix (Xu et al. 2018; Shen 2018). Organoids also have the advantage of being less

resource-demanding compared to murine *in vivo* models. Thus, they can be seen as a kind of intermediate model that in time may allow for faster and finer-grained drug screening (Yang et al. 2018).

Cancer has from the beginning been a major topic in organoid research, but the potential of organoids received renewed attention in recent years with the emphasis in personalized medicine to account for *genetic variation* as a predictor of drug response (Dancey et al. 2012; Kaushik et al. 2018). Meritxell Huch and colleagues demonstrated that organoids based on liver cancer tumors preserve tissue structure and gene expression patterns seen in patients, and that certain expression patterns correlate with poor prognosis (Broutier et al. 2017; see also Vlachogiannis et al. 2018). Several studies have documented the capacity of organoids to predict drug response in individual patients, which opens for the possibility of patient-specific drug screening (Huang et al. 2015; Ooft et al. 2019). In this context, a comparison of organoids grown from tumors and normal tissue can help establish which drugs primarily target cancer cells without harming normal cells.

Organoids raise intriguing questions about the implications of patient-derived models, and what evidence means in a context where each patient's cancer is considered unique. The ability of organoids to account for patient heterogeneity is typically seen as a positive feature. However, there are trade-offs between the variability of the experimental system and the reproducibility of experimental results, especially if cancer tumors are also *internally* heterogeneous (Huch et al. 2017). Moreover, organoids lack important elements of the natural environment of cancer tumors, such as blood vessels, immune cells, and other stromal components that are known to influence tumors beyond the tumor microenvironment (Laplane et al. 2019). It is therefore currently unclear to what extent organoids present an alternative to traditional cancer models, and what level of variation researchers should aim for, if the aim is to infer molecular action mechanisms or drug targets (Lang 2019). Developing models for personalized medicine is thus not about maximum fine-graining. Rather, it is about finding the right "resolution" or "level of variation" to provide meaningful evidence-based results for research and clinical practice (Reardon 2017).

In the following, we draw on insights from ethnographic studies to analyze how researchers and clinicians manage variation and uncertainty in two different contexts (a research laboratory and a phase I cancer clinic). We highlight that epistemic aspects concerning the evidential status of organoids are intimately related to social and ethical implications of the use of organoids in preclinical and clinical practice.

3. Organoids as Disease Models and Living Biobanks

Realization of the research potential of organoids requires infrastructures that facilitate sharing of knowledge (cancer genomics) and material resources (tissue samples). Initiatives are currently taken to establish so-called *living biobanks* consisting of cryopreserved organoids, i.e., frozen but viable tissue cultures that can be (re)used as a resource for research and drug screening. The aim of such biobanks is to provide viable specimens representing tumor heterogeneity for research and drug screening, as well as protocols for method development (Sachs et al. 2018). One prominent example is the Hubrecht Organoid Technology (HUB)[5], established in 2013, but living biobanks are being established in many places throughout the world as way to establish closer collaborations between universities and cancer clinics.

One of the sites for our analysis is a US-based lab aiming to develop a living biobank, initially of breast cancer organoids, as a resource for translational preclinical studies. In this context, organoids are based on excess tissue material from breast cancer surgeries at a hospital they collaborate with. A goal stated in the institute's annual report, as well as in interviews with the researchers, is to develop organoids as intermediate models that display important model virtues of both standardized cell lines and mouse models. The same institute also has mouse models, and the two experimental

systems are perceived as having complementary benefits and limitations. Patient-derived xenografts are highlighted as providing an *in vivo* context for tumors, while organoids have other benefits in being less expensive and labor intensive to grow. Organoids also allow for dealing with obstacles resulting from the species barrier of mouse models. One example is estrogen receptor positive breast cancer, which requires estrogen supplement in mice. So far, the growth rate they have achieved with this cancer type in organoids is 80%, compared to only 10% in mice.

A key aspect of organoids emphasized in interviews is the aim of expressing the clinical heterogeneity of breast cancers. Because organoids embody the genetic and morphological heterogeneity of patient tumors, a panel of organoids is seen as an alternative to standardized (cell-line based) mouse models in clinical trials:

> Now in the lab, traditionally, what we'd do in a mouse experiment is to get 20 mice with the exact same tumor and then look to see if they respond or not. When, really, we should have mice of 20 different types of that tumor to really, really recapitulate what's happening in the clinical setting, right? With organoids you can look at these subgroups of disease and have a true representation of the heterogeneity and then ask questions about drug screening and about gene expression and response (PI of an organoid research project).

Organoids are here seen as better translational models because they allow for testing on more subtypes of cancer. This has intriguing implications for how we think about evidence in personalized medicine. The researchers hope that the FDA and other drug regulatory agencies in the future will accept drug testing based on a different test design, where testing on a panel of organoids can supplement and partly replace standardized animal experiments.

Using organoids, however, does not mean that every possible aspect of the model is attempted to be "personalized". To grow organoids for biobanking, many labs follow a standardized protocol, such as one developed by Hans Clevers' group at the Hubrecht Institute, Utrecht, where organoids are grown in a standardized 3D-matrix. A basement membrane functions as a more biologically realistic scaffold in which also the biomechanical tension of cancer tissues is mimicked. The gel is generated from mice tumors and mimics the tumor microenvironment by having a similar chemical and physical structure of the extracellular matrix. However, patient variation concerning stiffness of the surrounding tissues is currently not accounted for via organoids. This may be seen as a limitation of organoids as personalized models, since tissue stiffness can vary between different cancer types and patients, and also influence cancer development, metastasis, and drug response (Green, 2021). Yet, standardized protocols and procedures are required to minimize the complexity of the experimental tasks and to generate comparable results[6]. Hence, the most useful "resolution of variation" is therefore not necessarily the one that maximally mimics all aspects of variation among patients.

Mäel Montévil (this volume) contends that it is misleading to oppose evidence-based medicine and personalized medicine with reference to the often-mentioned dichotomy between a one-size-fits-all approach and one accounting for heterogeneous populations. Rather, he argues, the practices are better distinguished by different ways of addressing an inescapable compromise between specificity and generality as model virtues. This description fits well with what we see in the context of oncology, where tumor heterogeneity is often presented as both a virtue and a vice. The uniqueness of specific cancers is what motivates the field and continuously opens for new treatment options. Yet, as more genetic variants are uncovered in cancer genomics, the more researchers are confronted with additional layers of complexity, such as the vast heterogeneity of mutations between and *within* tumors (de Bruin et al. 2014; Kerr et al. 2019). The aim to embrace

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[6] Our interviewees mentioned potentials for also personalizing biophysical cues in the future but highlighted that there at present are more serious uncertainties to address first, and that there is a limit to how many variables can be meaningfully handled at present.

heterogeneity thus often results in the challenge of how to deal with the 'curse of dimensionality' resulting from the ever-expanding list of factors influencing tumor development and the associated expansion of treatment options (Plutynski, this volume).

As a researcher working with organoids in the lab noted, a patient-specific tumor is itself thought of as a heterogenous group of cells, rather than as a stable entity with clear boundaries. The spatial and temporal diversity of tumors not only has theoretical implications for the strength of inferences made but also comes with practical implications for model development. Because cancer tissue is a scarce resource, the development of organoids for living biobanks requires procedures for organoid expansion called *in vitro* passaging. Tumor cells are taken from patients (via biopsied or surgical material) and grown in 3D wells until they reach a certain density and size. Smaller clumps of the primary organoid are then taken out and grown in separate wells to expand the material and to get more test specimens. This procedure requires that the essential biological features of tumors remain stable through passaging. The researchers sometimes refer to the cell population dynamics in tumors as self-organizing "social capacities", which raises interesting questions about how far tumors can be fragmented and still retain their identity. The issue of tumor identity is not just a philosophical or theoretical problem, but also of practical concern in procedures of tumor fragmentation and passaging:

> When you have grown up organoids and you want to break them apart and plate them for an experiment, you don't digest them down to individual single cells. You should leave them as small clumps to then regrow and keep that heterogeneity. Right? But then when you see cells in multiple wells, you're getting different sized clumps in different wells. Your error bars are always pretty big. (PI of an organoid research project).

The quote illustrates how optimization of passaging procedures requires exploration of how far a tumor can be broken down before the cell population patterns seen in the original tumor are lost (or at least differentiated in the new organoids). Thus, the relation of metonymy between tumor and organoid cannot be grounded at the lowest scale of analysis (e.g., in genetic signatures of individual cells). The phenomenon of interest literally disappears at the lowest scale, because cancer is a cell population phenomenon. In this sense, the individual patient's tumor gets destabilized through experimental procedures. A related concern is whether tumor biopsies can capture the relevant features of the whole tumor, as biopsy samples from different spatial sites in a tumor are likely to have different proportions of mutations. A researcher figuratively described a biopsy sample as a "look through the keyhole", where they only get to see and intervene on some aspects of the tumor. This presents a severe challenge for drug screening, as highlighted in the following quote:

> You know, let's say you get a biopsy, and it looks HER2-negative, so you don't give the patient HER2-therapy. Yet actually, if you look to the whole tumor, maybe some of it or a lot of it would have been HER2 positive. (PI of an organoid research project).

A related challenge is that tumors display plastic behaviors that change over time, in patients as well as in the 3D matrices. For instance, a post.doc explained how fibroblast cells are present (and clearly visible) in the first organoid culture from patient tumors but disappear over time and through multiple passages[7]. This makes organoids a research resource that is available only within certain time windows. While cryopreservation is an efficient strategy to deal with the temporal challenge, the evolvability of organoids adds to the complexity of the model system (Green et al. 2021). Researchers must balance tradeoffs between maximally accounting for patient-specific features and developing tractable methods that allow for comparison across cases. Similarly, they must balance

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[7] He clarified that this is probably due to the lack of growth factors for stromal components in the Matrigel, and that it is currently unclear what this means for the capacities to draw inferences from later passages to patients.

the aims of ensuring model validity and that of developing material resources for biobanking. Tradeoffs between these arise when there is uncertainty about whether the cultures are "contaminated" with normal (non-cancer) cells and there is limited organoid material to perform a validation analysis. Cancer cells are typically conceptually distinguished from normal cells based on their tendency to grow more aggressively, e.g., by replicating infinitely and resisting apoptosis (Hanahan and Weinberg 2011). In the context of the lab, however, cancer cells often grow slowly, and studies of the histology of tumor tissue (microscopy) do not always give clear answers to whether the culture only contains cancer cells, or also normal cells. In such cases, genome sequencing to test for occurrence of cancer-related mutations may be needed to validate the model. But this procedure also faces practical constraints:

> With sequencing technologies and things like this we are able to [determine whether it is cancer], but this also takes a lot of resources. Organoids divide and proliferate and expand. But still, you start with a tiny bit of material, and even if you expand them tenfold, you still got a really small amount of material. And now you want to sequence it to characterize it, but the only value of characterizing it is if you're then going to use it for something else. So, then you sequence it, but then you also need enough to drug screen, and then if you publish it, someone else is going to want some. How we can manage this is challenging. (PI of an organoid research project).

The quote illustrates that the need for validation analysis must be weighed against the importance of other epistemic aims. The ideal of organoids as living biobanks highlights the role of organoids as collaborative and commercial commodities for reuse across different institutions and borders. But since organoids have to be grown from patient tissue and may change over time, they present a resource that is limited and exhaustible.

The challenges brought up in this section highlight that organoids at present by no means constitute straightforward and stable representations or "substitutes" of individual patient tumors. As research tools with open-ended features and applications, organoids may be seen as what Rheinberger (1997) termed epistemic objects, i.e., as research entities with unstable features that productively generate new research questions alongside their role as models in knowledge production. Importantly, the instability of organoids in this context is tied to uncertainties about the nature and stability of cancer itself, and about how much variation models in personalized medicine can and should embody. The following section explores how these and related uncertainties play out, when organoids are used as preclinical models in a translational cancer project. In this context, organoids speed up the traditional translational process by making new or off-label treatments available to patients, but they also introduce new complexities in the cancer clinic.

4. Organoids for Patient-specific Drug Screening

As mentioned in the introduction, organoids are currently promoted as translational models that enable patient-specific drug screening. Developing organoids for this purpose is the aim of a preclinical research program for cancer precision medicine in Denmark that we have followed. In this project, scientists in a biotech center at a university and clinical researchers in a phase 1 unit at one of the main hospitals collaborate closely to identify effective treatment options for metastatic cancer patients that have exhausted all standard treatment options. Organoids are hoped to provide

patient-specific evidence on whether a potential targeted treatment[8] could be effective for incurable cancer patients[9].

The ideal diagnostic pipeline in the preclinical project can be summarized as follows. When a patient has consented to take part in the project, biopsies of metastatic tissue will be scheduled and a lab team member collects the tissue samples at the hospital immediately after biopsies have been performed. The tissue samples are then analyzed and cultivated in several ways. Through a combination of kinase profiling and DNA and RNA sequencing, the researchers seek to identify potentially effective drugs (kinase inhibitors). This takes two tissue samples and the analyses take 4-6 weeks. In parallel, a third tissue sample is cultivated *in vitro* in a 3D organoid cell culture. If the organoids grow, they can serve as the basis for patient-specific drug screens, which is ideally established within about 5 weeks. In practice, however, the translational path is far bumpier.

Major translational bottlenecks are created by two serious issues also seen in the research context described in Section 3, namely limitations on the tissue material available and the slowness of cancer cell growth outside the human body. The challenge is here further complicated by the specific clinical context. Metastatic cancer tissue is often difficult to access and can only be collected through core needle biopsies. Common complications of the procedure are pain and discomfort, while rare but serious complications include infections, bleeding, and organ damage. When deciding whether or not to take additional biopsies, clinicians must therefore balance the risks of biopsy procedures against potential benefits of a drug screen that could open a door to a potentially beneficial treatment (see also, Kerr et al. 2019). Whether the patient will benefit from the procedures is, however, not clear due to uncertainty about the status of organoids as substitutes for patients in a clinical trial. As we shall see below, this creates new ethical dilemmas for clinicians.

For researchers working on culturing organoids in lab, the scarcity of tissue material (a few needle biopsies) makes it very challenging to grow the *in vitro* models within a clinically meaningful time-window[10]. Also in this context, researchers have to prioritize different epistemic and practical aims. The priorities are explicitly highlighted in team meetings through common procedures to follow during laboratory practices. The first priority is to grow and maintain organoids for patients that could potentially benefit from drug screens. If a cancer patient who has donated cancer tissue dies, the researchers will cryopreserve the organoids for later use and instead prioritize the lab resources to grow organoids for patients who could still benefit from a drug screen. Prioritization of laboratory resources is here particularly important to ensure that there is sufficient organoid material to run a drug screen of multiple treatment options. In this context, organoids take on a role as patient substitutes that undergo different parallel treatments. However, also in this context, the role of organoids as *in vitro* models of patient tumors gets de-stabilized through uncertainties about the relation between organoid and tumor.

Researchers (biomedical as well as clinical) in the translational project sometimes talk about the organoids as individual patients that recapitulate key features of patient tumors. For instance, a researcher in the lab explained that "there is a patient in each plate" (plates for culturing organoids), and metaphorically referred to the fridge-like incubators for organoids (37°C) as a "hospital" hosting patients. But when asked about the identity and stability of the organoids, researchers often express uncertainties about how stable the organoids are, whether the biopsy samples only contain

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[8] The majority of the drugs are targeted treatments approved for other cancer types (say, breast cancer), but here given "off-label" to patients with a different type of cancer (say, pancreatic cancer), because the molecular analysis and drug screen suggest a potential match and benefit.

[9] To be included in experimental treatment protocols, patients must have i) exhausted treatment options (or are expected to exhaust standard treatment options shortly), ii) a performance status of 0-1, iii) a life expectancy of at least 3 months, iv) normal organ function, v) measurable disease, and vi) metastatic tissue accessible for biopsy.

[10] Initially, the aim was to also grow tumors inside the body of a mouse (or a PDX) to also allow for *in vivo* drug validation. Because of practical difficulties, this part of the project was put on hold and we here focus primarily on the use of organoids.

tumor cells or also normal cells, and whether biopsies taken several months ago are still representative of specific patient tumors, if the patient's tumor has since progressed and possibly developed new genetic alterations. Similar to what we described in Section 3, resources spent to ensure the validity of the model trade off with those needed for practical uses of organoids:

> It is a bit of a dilemma whether one should drug screen without knowing whether they are cancer cells or if you should do a DNA analysis, and then risk that there are not enough cells to do a drug screen. (Interview with a post.doc in the preclinical research project).

The challenge that tissue samples become exhausted in the analytical and diagnostic process is particularly hard in clinical contexts where the available material amounts to a few biopsies (see also, Kerr et al. 2019, p. 229). Moreover, procedures to ensure model stability and optimize testing cultures must be evaluated against the time pressure to deliver test results to patients. Waiting longer to grow more organoid material for multiple drug screens must be balanced against the risk that the performance status of the patient declines, which can make the patient unable to receive the targeted treatments. Hence, even if "the right drug for the right patient" can be found, it may not be available "at the right time"[11].

As a result, the hopes and suffering of cancer patients move into preclinical research and manifest as a pressure to deliver reliable results within a clinically defined time frame. Researchers in this context become stretched between the practical challenges of growing organoids and the temporal constraints determined by the patients' progression status. This is illustrated in the following quote by a post.doc in the translational project, who has just been informed that a successful test result came too late for the patient to receive treatment:

> Oh. That is so sad! You see, it has been like that with a lot of [the organoids] I've had. When I've done the drug screen and sent it to the clinic, half of the patients [that I have made drug screens for] have died. Then I'm left thinking: could something have been done if I had been faster?

The researchers work hard to align the different temporalities of laboratory work and clinical practice but keeping pace with the clinical needs is a constant struggle. This greatly contrasts with how organoids are often presented in literature as rapid models for real-time drug screening. It takes tremendous work and care to grow the fragile cancer cells to a size where they allow for drug screens. Organoids must have optimal growth conditions, which involves changing the nutrient media twice a week as well as strict hygiene requirements to avoid contamination of the cultures. To manage the practical challenges of personalized models, options for standardization and simplification of some procedures are often considered. For instance, the organoids are also in this context "housed" in a standardized medium:

> Right now, we use the same medium for all [cancers], no matter whether it is breast cancer or colon cancer or whatever, and that is maybe not optimal, but on the other hand we would like a system that is "one-size-fits-all", so that it – for those running the program – doesn't get too complicated. (Postdoctoral researcher in the preclinical project).

It is here striking that a practitioner within personalized medicine, a field explicitly defined as a departure from a "one size fits all" approach in medicine, stresses the need for standardized procedures to make laboratory work practically tractable. Another important aspect of standardization in this context is drug administration. To generate evidence for the protocolized

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[11] See also Plutynski (this volume) for a discussion of the commonly used slogan of precision oncology to provide "the right drug, at the right dose, for the right patient, at the right time".

treatment, drug doses and enrollment guidelines must be standardized. This raises important questions about how the personalization of some aspects of treatment often requires standardization of others. More generally, it also raises questions about what aspects of medicine are possible or most useful to "personalize", and for what purposes.

The instability of organoids has important implications for status of these as new "technologies of hope" (Koch and Høyer 2007), envisioned as translational models that provide a road to personalized medicine. Insights into challenges do, however, not automatically lead to revision of the near-future expectations to personalized medicine. As emphasized by Roger Strand (this volume), challenges and knowledge claims are representations of present realities, whereas personalized medicine presents a vision or imaginary of desired futures that are hoped to revise existing states of knowledge. In the exploratory space where new medical technologies are developed and implemented, uncertainty has "generative potential" in mobilizing further investment in and expansion of research domains (Timmermans et al. 2017). This is for instance highlighted in a publication in the journal *Cell*, emphasizing the genetic basic for cancer treatment decisions:

> Although the challenges of integrating genomic testing into cancer treatment decision making are wide-ranging and complex, there is a scientific and ethical imperative to realize the benefits of personalized cancer medicine, given the overwhelming burden of cancer and the unprecedented opportunities for advancements in outcomes for patients. (Dancey et al. 2012, p. 409).

Anticipation of future scientific advancements is not only an epistemic orientation toward the future, but is also an *ethical imperative* to inhabit states of uncertainty so as to improve future conditions for research and clinical practice (cf. Adams et al. 2007). In other words, evidence must be co-produced with procedures for implementation. In this sense, the ethical imperative to improve existing practices also comes with concerns about how to manage the current gap between the persistent uncertainties of and high expectations to the new technologies in contexts where patient care is the central concern (Kerr et al. 2019).

From interviews and interactions with patients and oncologists we have learned that organoids generate new hope for incurable cancer patients. The translational project on organoids open for new treatment options that could potentially prolong their life, and organoids present an intuitive and more "personalized" form of evidence. For oncologists, however, the possibility to attain new forms of evidence also entails a confrontation with new types of uncertainties – as well as new ethical responsibilities to inform patients about these to recalibrate their expectations. As expressed by an oncologist in the phase I unit:

> [The patients] sometimes ask, "How are the organoids doing? Does something happen?" Sometimes things do happen, and we conduct a drug screen, but it can also be that we get more confused about the result. Sometimes we get data that we don't really know what to do with. If we do not get any effect on the drug screen, then it is clear that we cannot use it. We can maybe use it when we get a signal, but it is perhaps not quite clear, and then the question is whether we should give a treatment, that may have side effects, and that blocks the patient from receiving another treatment. So again, it generates a lot of dilemmas (Oncologist in phase I unit).

A "signal" in this context means cell death, growth, or growth inhibition, but a decrease in organoid growth cannot straightforwardly be interpreted as treatment efficacy. There can be multiple reasons for why organoids grow slowly or die, and the strength of the signal can vary. Also the clinicians are therefore stretched between the patients' hopes and epistemic uncertainty. In the interview, the oncologist further emphasized that he views organoids as being quite low on the evidence scale, in

part because the lab results often are uncertain, and in part because they cannot rely on statistical results from many patients receiving specific genetically targeted drugs or off-label treatments. Such reflections also destabilize the idea of organoids as an alternative to standardized forms of evidence. At present, organoids are primarily seen as an additional tool that in a few cases may provide new treatment possibilities, and where the potential is still uncertain and future-oriented:

> I tell my patients that they should not expect to benefit from this. It is a method under development, and it is only something that can give a piece to the puzzle. It is not something that can stand alone. It cannot. So they have to see it as a bonus, and as a way to help research further. In 5 years, things probably look differently. So in this way it is really interesting from a scientific point of view. In the clinic it is not that interesting yet. But it will be, we think. And that is probably the expectation you have to have, so we don't talk up the method to patients either. (Oncologist in the phase I clinic).

The quote exemplifies how appeals to existing uncertainties are used to moderate patient expectations, while at the same time motivating the production of evidence for future needs (see also, Kerr et al. 2019).

Organoids at present fulfill purposes of cancer research and clinical practice in different ways. There are more immediate benefits of the results for research, as organoids are already helping researchers identify new genetic variants and pathways that can guide the understanding of cancer and suggest potential drug targets (Broutier et al. 2017)[12]. Clinical benefits at present comprise only a few cases, where patients respond well to new targeted treatments. The main clinical benefits are therefore envisioned to be realized in the future. Hence, the oncologist is concerned about the risk of installing unrealistic expectations in the hopeful cancer patients. This concern is not only relevant in the context of the phase I unit, but also for discussions about who will contribute to and benefit from personalized medicine more generally (Plutynski, this volume). To clarify this point further, the following section examines how personalized medicine not only focuses renewed attention to individual differences but also form new epistemic and ethical collectives.

5. Personalized Medicine from a Population Perspective

The emphasis on individual variation may give the impression that personalized medicine marks a departure from population science. However, realizing the potential of the new technologies requires heavy investments in population-based databases to integrate genomic data with other health data (Hoeyer 2019). Organoids may seem like the exception, since they physically represent individual tumor samples. Upon closer inspection, however, the use of organoids relies on results from population-based efforts and, as we shall show, also mobilize new collectives through data collection and biobanking.

The current use of organoids in research and clinical practice is highly focused on the identification of genetic biomarkers, e.g., of mutations or overexpressed genes, which may be suggestive of a cellular pathway to explore in research or a potential targeted drug for cancer therapy. These markers are established on the basis of a comparison of the individual's profiles to data on thousands of other individuals. The identification of molecular features or "biomarkers" characterizing the individual patient's tumor presupposes comparisons to reference classes and, hence, relationships of similarity in terms of shared biology. In the context of the translational project, clinicians rely on a bioinformatics analysis of the sequenced genome. Software filters based

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[12] In the context of the specific translational project, though, the need to prioritize laboratory resources for clinical purposes makes it difficult to develop publishable results. In an interview, the PI commented on how many researchers are not interested in doing translational research, because it involves many uncertainties and practical challenges. But she also highlighted that alignment of project goals is central for closing the translational gap between biomedical research and clinical practice.

on compiled cases help to identify potential clinically relevant targets. Yet, as we and others have observed during tumor board meetings, the actionability of identified genetic variants is often uncertain and depends on many factors such as the availability of open treatment protocols, the frequency of the variants, other test results, previously received treatments, and patient status, as well as the often changing evidence status of specific genetic variants (see also, Hey et al. 2019; Kerr et al. 2019). The evidence status of markers can change over time with the inclusion of more cases in the database, further exemplifying the relational characteristics of biomarkers (Timmermans et al. 2017). Hence, variation in personalized medicine is always relative to a specific scale of analysis, and defined in relation to specific epistemic purposes.

Practitioners must in this context navigate in a space where reliance on statistic evidence is very limited, and where treatment options are only open for patients fulfilling certain requirements (biomarkers and disease status, see note 9). The results from genetic testing and organoid drug screens for individual patients must be evaluated against highly limited knowledge about the efficacy of the drugs, which again must be contextualized according to the specific patient's situation. At the same time, current implementations are also conducted in order to develop better diagnostics and treatments for similar (future) patients:

> On the one hand we consider the utility value for the individual patient, but there is also the consideration that patients – who are in treatment either on the basis of drug screen or phase I trials – deliver utility for the general good. You also have to take this into consideration, and we also present the considerations to the patient. We have some that we treat "beyond progression", meaning that they still get drug in the phase I trial even if the disease is progressing – you can do that in some protocols. If it is written that this is acceptable, we have a conversation with the patient where we say "the cancer is progressing but you can be allowed to continue in the protocol, knowing that [the drugs] probably do not work so well on your illness, how do you feel about that?". And some say that "I really want that, because I keep delivering data for the experiment, and it gives meaning to my disease. […] For some, it makes sense to be able to deliver something to future patients" (Oncologist in phase I unit).

Notably, this way of ethically justifying a practice that may be of limited benefit of current patients *epistemically* presupposes that targeted treatments are not specific for individual patients, as results must be comparable to broader population types. The expectation of benefits for future patients is based on the hope that personalized medicine – with time – can compile enough cases for databases and biobanks to ease the translational paths for future patients with similar tumor characteristics. Recategorization of cancer into finer-grained subtypes co-produces new epistemic relations of (molecular) identity or similarity, and may also give rise to what Gibbon and Novas (2007) term *biosociality*. The term points to how the collective of data populations also have social and ethical implications. The willingness of oncologists and patients to contribute to the development of personalized medicine shows how personalized medicine does not represent an individualizing departure from reliance on the collective, epistemically as well as ethically[13]. Although much focus in personalized medicine is on the development of more individualized models, the vision for future living biobanks presupposes a coarse-grained mapping of variation that does not drill down the heterogeneity to the uniqueness of individual patients.

Precision oncology develops around the negotiation of the trade-off between emphasis on tumor heterogeneity of individuals and genetic similarity of coarser grained (although stratified) patient

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[13] Similar wishes to contribute to the development of cancer research for future patients with similar diseases is seen in a recent pilot project on patient-derived xenografts, where a patient says the following: "I understand there is no gain to me directly. But in a small way, maybe I can help grow our understanding of what makes triple-negative breast cancer what it is." (Wanner and Haskell 2014).

groups. But while not departing from statistical methods altogether, precision oncology does potentially change the nature of relations that connect different patients. As Montévil (this volume) highlights, measurement in medicine is conditioned upon procedures of symmetrization by which organisms are considered equivalent with respect to some specific selected features, while being non-equivalent with respect to others. In this context, traditional criteria of diagnosis and case comparison – such as cite of tumor origin, histology and stage of tumor – are being reframed in light of genetic technologies that categorize cancers and cancer patients in new ways. This can not only change how we conceptualize disease but also how health systems and clinical trials are organized (Green et al. 2019; Plutynski, this volume).

Large-scale cryopreservation of patient-derived models, biobanking, and sharing of data and research results exemplify how the contributions of individual patients can become scientific and social commodities of benefits to the collective of future patients. At the same time, national initiatives for collection of population-wide genomics data and integration of health records exemplify how the collective of large data populations is envisioned as a requirement for realizing personalized medicine for the individual patients. One example is the National Genome Centre in Denmark that has recently been launched to integrate genomic data and health data on the whole population. Within this context, establishment of personalized medicine is seen as something that requires the participation of the whole population. Initially, data will be stored from selected patient groups, and cancer patients are among the candidates to make up (some of) the 60.000 already financed whole genome sequences. The database is expected to create an invaluable source for research and personalized medicine in the future. At the same time, the envisioned implementation also raises concerns about how new procedures for genome sequencing of cancer patients will affect the patients' expectations:

> If it's just about putting data in the bank and looking at it later, then that's fine. But many will have the expectation that they upfront must have an in-depth explanation of exactly their gene profile and why they should have the standard treatment. Many will say: "I don't want the standard treatment, I need something that is special for me". Many have the expectation that if there is a skilled doctor who has looked at a genome profile, something that is better than standard treatment can be offered. But the vast majority should still get the standard treatment. (Oncologist in phase I unit).

The quote highlights the difficult challenge of communicating to cancer patients that the benefits of personalized medicine is at present only for a relatively small patient group with rare variants and poor response to standard treatment (see also, Prasad 2016; Marquart et al. 2018). The reality in clinical practice is thus often very different from the picture painted of personalized medicine in politically authorized reports and communication material, where a vision of tailor-made solutions to all patients are promoted while the effects of standardized treatments are downgraded (Hoeyer 2019). Hope based on unfounded hype can create unrealistic expectations among patients and can negatively affect science and medicine when promises are not realized. Pioneers in organoid research have similarly expressed concerns about overpromising in their field and have emphasized the need for a slower pace to realize the potential of organoids (Huch et al. 2017). These worries add to concerns about the consequences of fast tracking of drug approval for targeted cancer therapies, including waste of resources and potential harm to patients (Plutynski, this volume). Aside from the issue of pace of implementation and realization, the quote above raises an important question about whether "personalization" is a useful regulatory ideal for medicine or cancer treatment in general. As highlighted by Anya Plutynski (this volume), precision oncology has so far primarily been successful in cases where the cancers are relatively simple (from a molecular perspective), and it is unclear whether "low-hanging fruits" can also be found among more complex cases. While tumor heterogeneity is what motivated precision oncology in the first place, the

realization of precision medicine through organoid biobanking is conditioned upon the potential to reduce the dimensionality of variation to a manageable number of genetic variations with associated treatment options. Ultimately, creating substitutes for patients, and patient types, hinges upon the ability to *control variation*, i.e., to represent the clinically relevant kind and level of heterogeneity in models for drug testing.

6. Concluding Remarks

Patient variation at the same time motivates and challenges precision oncology. Tumor organoids exemplify the aim to recapitulate the heterogeneity of tumors through personalized models developed from individual patients. As a kind of material substitute for patients, organoids call for rethinking models and evidence standards in translational medicine, as well as the relation between experimental model and human target. But whereas precision oncology is often presented as the very anti-thesis of a one-size-fits-all approach, it may not be productive to view the field as developing towards a science *of* and *for* the individual. Despite being directly derived from the patient's tumor, our cases show how organoids by no means straightforwardly represent the individual patient's tumor, and how that is also not always intended as the aim of patient-derived models.

Organoid research illustrates the difficult challenge of managing and representing variation at different levels: between cancer types, between patients with different tumors, and even within the individual patient's tumor. Hence, patient-derived models, perhaps surprisingly, destabilizes the very notion of individual patients and patient tumors as unique and homogenous entities with clear boundaries. Important epistemic uncertainties include the extent to which biopsies only present a "look through the keyhole" of a spatially diverse tumor with different cell populations. Similarly, the experimental task to find the optimal size and density of tumor fragments for *in vitro* passaging raises intriguing questions about the extent to which the self-organizing capacities and ontological identity of tumors can be recapitulated in growing tumor fragments. Moreover, whereas organoids are often considered as "personalized models", the anticipation of future benefits via biobanking is epistemically dependent on the ability to connect test results of extant patients to future patients with similar molecular profiles. Thus, patient-derived models representing the individual patient also rely on and co-produce a vision of biosocial relations among larger collectives.

As a result, the most useful resolution of variation is not necessarily the one that maximally mimics the heterogeneity of the individual patient or patient tumor. Our analysis shows that the challenge of balancing standardization and variation still remains in personalized medicine. We see this epistemically in the ways in which the use of patient-derived models and biomarker analysis is dependent on standardized procedures and population science. And we see this ethically in how experimental treatment of individual patients are expected to primarily benefit future patients when enough cases have been collected to allow for inference of evidence of treatment effects. The latter also shows that realization of personalized medicine for the individual relies on the establishment of new collectives based on shared molecular characteristics. The individual *me* of patients and patient-derived organoids is dependent on the collective *we* of data and tissue donors. At the same time, the collective *we* of future patients are dependent on present procedures to develop models for patient-specific drug screening.

New sources of evidence in personalized medicine come with new uncertainties and ethical responsibilities to inform patients about these. Developing patient-specific organoids can potentially open a translational path for new treatments for incurable cancer patients, but the approach also involves risks associated with biopsy procedures and uncertainties about test results and treatment benefits. Moreover, time constraints for growing organoids present severe challenges for the aim to deliver the right drug for the right patient *at the right time*. Facilitation of medical innovation

alongside considerations about patient care can be challenging to achieve in practice. Researchers and clinicians are therefore often stretched between epistemic uncertainties and patient expectations, and between the potential benefits for the individual and future patients.

In summary, tumor organoids do not straightforwardly represent a shift from the collective to the individual. They can be seen as new technology-mediated ways of "inscribing the population in the individual and of letting individuals contribute in new ways to the population" (Hoeyer 2019). Organoids represent both these aspects. They are experimental models that embody important features characteristic of specific patients' cancers, but they do so through reliance on population science. At the same time, patient-derived organoids are at present not only developed for the sake of extant patients. Tumor organoids exemplify how individual cancer patients contribute to future populations through relations of biosociality, i.e., by generating "living biobanks" as forward-looking resources for precision oncology.

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