Universiteit Utrecht

Ethical Analysis of the Living Biobank

Master Thesis Applied Ethics

Student: R.H.P. Wouters

Student number: 3531643

Supervisor: dr. A.L. Bredenoord

Second reader: dr. L.L.E. Bolt

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Table of contents

Chapter 1: Introduction

Recently, in 2013, the Hubrecht Institute and the University Medical Centre Utrecht founded The HUB Foundation for Organoid Technology. This foundation has initiated the building of the Living Biobank. This Living Biobank stores mini-organs grown out of stem cells obtained primarily by oncological surgery (The HUB foundation, 2013). The development of these so-called organoids is a promising biomedical technological with a wide scope of (future) applications.

In this thesis, I will focus on the ethical dimensions of the Living Biobank. A lot of issues arising from the use of already established biobanks have been subject to ethical inquiry during the last several years. This led to the identification of the relevant ethical pitfalls and, as a result, ethical frameworks are designed to guide research institutes and ethics committees (Bauer et al., 2004). However, because the organoid technology that underlies the foundation of the Living Biobank was discovered only very recently, these specific developments are fresh and untouched in the field of ethics. This thesis provides an initial ethical framework for the Living Biobank. This is done by identifying the characteristics of the Living Biobank and applying these characteristics to the ethical dimensions that have been discussed in ethical literature for existing biobanks.

The second chapter of this thesis clarifies the technical aspects of the Living Biobank in order to get a clear picture of what is discussed. The following chapters are considered with ethical issues of the Living Biobank, divided in three stages of biobank research: inclusion of participants and their tissue (chapter 3), storage and usage of the organoids (chapter 4), and the disclosure of findings to participants (chapter 5). The division is based on biobank research as a circle: it starts with the participants donating their tissue, than moves to the activities of the research institution and finally there is feedback of the results that brings the circle back to the participants. This subdivision is merely considered a useful model to analyse different stages of the research, I do not claim that this is the only subdivision possible. Chapter 6 deals with ethical issues that play a role in all three phases. Chapter 7 is concerned with ethical difficulties that arise in the pediatric branch of the Living Biobank.

The ethical analysis in this thesis is a case-study of the Living Biobank as the first organoid biobank established. Similar biobanks might be established in the (near) future. Naturally, the issues mentioned and arguments used in this thesis can also be used for the ethical assessment of future organoid biobanks, as long as these biobanks have similar characteristics as the Living Biobank. Besides, the ethical evaluation must be regarded the beginning of ethical inquiry and debate on this subject. Further research is definitely needed and this thesis mentions several suggestions for further inquiry.

Chapter 2: The Living Biobank: an introduction

What is a biobank?

In this thesis, a broad definition of biobanks given by Giesbertz and colleagues (2012) will be used: "a collection of human biological samples stored for medical-scientific research purposes, usually linked to phenotypic data" (p.4). According to this description, a collection of biological material that is not linked to particular phenotypic information cannot be a biobank. This is true because the scientific potential of a biobank depends highly on the information that is matched with it (Greely, 2007).

What is the Living Biobank?

As I already mentioned in the introductory chapter of this thesis, the Living Biobank is based on a research technology that was developed only very recently: the organoid technology. Organoids are chunks of cells that resemble the architecture and function of real-life human tissues. Moreover, "organoids proved to be both genetically and phenotypically stable during prolonged periods of cell culture and are amenable to all standard experimental manipulations" (The HUB foundation, 2013). The organoids are grown from the biological material of patients suffering from cancer (different types) or cystic fibrosis. The organoids are stored in the Living Biobank primarily for research purposes. They will be used for fundamental biomedical research as well as experiments aimed at discovering new drugs. Moreover, organoids in the biobank will be used for drug-testing within the framework of personalised medicine (Sato & Clevers, 2013). The latter applications entail that drugs are tested on organoids in order to choose the preferable treatment for individual patients (Cancer Genomics Centre, n.d; Verhaegh et al., 2014). The scope of the Living Biobank is not limited to oncological studies, also cystic fibrosis is now subject of organoid research and these organoids will be stored in the biobank as well. The latter research uses children as research participants (Schwank et al., 2013; UMC Utrecht, 2013). The time period that these organoids are stored is indefinite and can be virtually infinite. [1]The Living Biobank is also a genetic biobank in the sense that genetic sequencing is used to analyse the organoids (Utrecht Life Sciences, 2014).

[1] This information is derived from conversations the author had with the managing director of the HUB biobank and from the research protocol. This protocol was sent to the author confidentially. Readers may contact the author about this information, although no documents can be provided without explicit permission of the research institution.

Application of the organoid technology for transplantation purposes is likely to be one of the possibilities in the near future (Sato et al., 2011; Sato & Clevers, 2013). The latter use of the organoid technique is not part of the Living Biobank, as this requires different quality standards of organoid production and treatment. Therefore use of the organoids for transplantation purposes will not be discussed in this thesis (that is devoted to the Living Biobank).

Underlying technique

There are two recently discovered techniques that make the creation of organoids possible: the isolation of stem cells in human tissue and the development of a culture where these stem cells can expand by proliferation and differentiation to stable tissue structures (Sato et al., 2011). The identification of intestinal stem cells was possible due to the discovery of Lgr5. The discovery of Lgr5 (a so-called marker gene) has first been reported in 2007 and, although the role of stem cells has been studied for a long time, this was the first time that stem cells could be distinguished from other cells. The expression of this Lgr5 gene marks stem cells in various human tissues and cancers. (Buske et al., 2012; The HUB foundation, 2013; Barker et al., 2007). The process of isolation works as follows. Both tumorous and healthy tissue is obtained by tumour surgery and endoscopic biopsies. Other types of tissue than the tissue of interest are stripped from the samples and afterwards they are fragmented, washed and cooled. As a next step the part of the tissue that contains the stem cells is isolated, for example intestinal crypts (part of the bowel tissue where the intestinal stem cells are situated). Next these structures are dissociated into single cells, creating a mixture of different types of cells. Finally, the stem cells are isolated by technique called Fluorescence Assisted Cell Sorting (FACS) and placed on a culture medium. (Sato et al., 2009; Sate et al., 2011; Sato & Clevers, 2013).

As indicated above, the other requirement for growing organoids is a culture where stem cells expand to mini organs that resemble in vivo tissue. Inside the human body, stem cells are situated in a so-called stem cell niche of other cells types that supports the proliferation and differentiation of these stem cells into tissue structures (Sato & Clevers, 2013). In a culture where single stem cells are placed, this niche is absent, obviously. I will use the example of intestinal tissue here to illustrate the process of substituting the function of such a niche. In the intestinal crypts, Paneth cells support the maintenance of stem cells and their

expansion to intestinal villus domains (Sato & Clevers, 2013). For this reason, in the laboratory several substances are added to substitute the function of an in-vivo stem cell niche. These substances include R-spondin to maintain the stem cells, since otherwise the lifespan of an organoid would be limited to only a few days. This is the case because the intestinal villi are characterised by a rapid cycle of self-renewal. Enterocytes on top of the villi die as part of a natural process so stem cells in the crypts of the villi are indispensable to replenish these cells by differentiation and proliferation into new enterocytes and other intestinal cells. Without R-spondin, the stem cells differentiate into other cell types and lose their ability of indefinite proliferation and differentiation. Other constituents of the organoid-growing culture are epidermal growth factor, Noggin and Wnt3a. Finally, nicotamide, Alk inhibitor and p38 inhibitor are added for long-term stability (Sato et al., 2009; Sate et al., 2011). Under these conditions, mini organs can be produced that "retain hallmarks of the in vivo epithelium"(Sato & Clevers, 2013, p. 1190). In other words organoids resemble tissue that is found inside the human body. This can be done both for healthy and for cancer tissue (Sato et al., 2011). Figure 1 shows both a schematic drawing and a picture of the development of an intestinal organoid (Sato & Clevers, 2013, p. 1191).

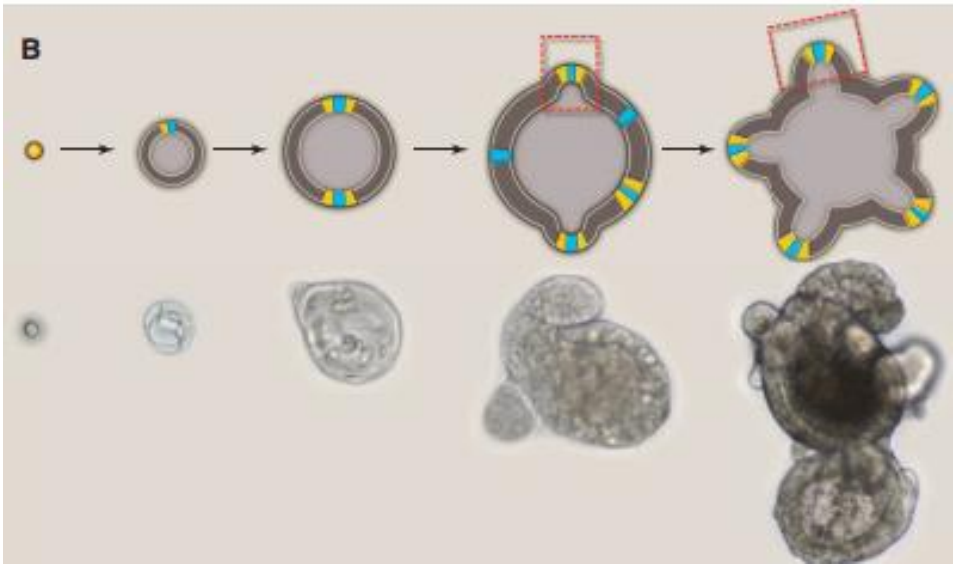

Figure 1 (Sato & Clevers, 2013, p. 1191).

Advantages of the organoid technique

For research purposes, there are several advantages to the use of organoids over the currently used cell lines. First, cell lines are obtained from cancer tissue that is grown in an in-vitro culture that goes through a process of culture crisis. The cell lines are able to endure in the in-vitro culture only after adaptation to the artificial environment. This adaptation entails transformation, resulting in cell lines that is not perfectly similar to cancer cells in vivo (Borell, 2010; Sato et al., 2011). In organoids, no such crisis or transformation occurs (Sato et al., 2011). Second, organoids have a tissue structure that resembles the in-vivo situation. This allows for experiments where not only the cells but also the tissue is important (Sato & Clevers, 2013). Third, the genetic diversity of cancers that are clinically similar is enormous. Despite efforts to sequence the genome of several types of cancer, only the top of the iceberg has been identified. The result is a gap between these intensive research efforts and the associated clinical progression (Ledford, 2010). Because organoids that are stored in the Living Biobank are not based on common cell lines but derived from cancer and healthy cells of individuals patients, these technique is likely to close this gap. Experimental drugs can be tested on cancer organoids that are genetically identical to the tumour of the individual patient (Sato & Clevers 2013). Currently, this is not only possible for intestinal tissue, but also for other types of human tissue including the liver, stomach, oesophagus and pancreas (Huch et al., 2013a; Huch et al., 2013b; Barker et al., 2010).

Chapter 3: Inclusion of participants

Informed consent

Informed consent is considered one of the cornerstones in biomedical ethics in general. Also with regard to biobanks, (informed) consent is acknowledged as one of the key ethical requirements. Although it is uncontroversial that informed consent is a relevant topic, the content of such consent is fiercely debated (Budimir et al., 2011). Informed consent protects research participants and is rooted in the respect for persons and their autonomy (Beauchamp and Childress, 2013). This raises the question what the concept of autonomy entails. I do not have enough space in this thesis to discuss that philosophical question extensively. However, in research ethics in general it is broadly acknowledged that autonomy is not only about freedom of choice but also entails that "the research is consistent with their [research subjects, author] values, interests, and preferences" (Emanuel, 2000, p. 2706). Informed consent serves as a safeguard for this personal autonomy of the research subjects. Moreover, it is a means to protect participants, as they have to be informed adequately about the risks. Although the specific requirements of an adequate informed consent are controversial, there seems to be consensus on the core elements of informed consent. In the field of research ethics these elements include: (1) an agent has to be competent to make the decision to participate as a research subject, (2) that decision is made voluntarily, (3) an adequate amount of information has to be provided, (4) the subject understands that information and (5) the agents consents with the participation (Beauchamp and Childress, 2013).

Two different applications

Two fundamentally different applications of the Living Biobank have to be distinguished here: fundamental research on the organoids, for example in a study about how the cells in the human intestine interact with each other, and clinical biobank research that directly applies to individual patients. An example of the latter is that several drugs are tested on a tumor-organoid and a healthy-organoid of an individual patient in order to find out which drug is most effective in reducing the tumor while causing less harm to the healthy tissue. These uses of the Living Biobank are distinct in the sense that they put the participant in a different position. In the first case, the participant abandons tissue for the sole purpose of scientific research. This can be stated clearly in the informed consent form, and thereby the

participant is essentially a benevolent contributor to the development of biomedical science. However, in the latter, the participant does not stop being a patient after signing the informed consent form. On the contrary, from there on she participates in a clinical research project where she primarily fulfils the role of patient. The outcomes of these kind of studies will be formulated in terms of her and other patients' physical well-being. Therefore, organoids are not only sophisticated biobank samples but also a diagnostic test. If used for this purpose, they should be regarded as such in an ethical evaluation.

The Living Biobank used for diagnostic research

The difference between the donor and patient role is important for several reasons. First, the level of risk associated with the research is different. When the participant is only a donor, the risk of participating in the Living Biobank will not involve direct physical harm (Eriksson and Helgesson, 2005). However, physical harm can actually occur if the biobank is used for clinical studies in which the participant is still a patient. In this case, the outcome of the research has direct implications for the patient's therapy. This is illustrated by the example of cancer therapy. A certain drug might be more successful than its alternatives when tested on the organoids, but this nor guarantees a higher success rate nor is it a warrant for safe therapy when applied in the bodies of living patients. Needless to say, a patient's body consists of more than a collection of organoids. At least there is no conceptual reason to assume that such harms cannot occur. Empirical research might show that medicines that are safely tested on several types of organoids are safe to use in clinical practice. However, until that proof is given, caution is needed. The second reason why the role of the tissue-abandoning donor is different from the participating patient is the so-called therapeutic misconception. This misconception entails that while the study is designed to yield knowledge that contributes to medical science, a participant conceives it as a tool that is likely to benefit her health condition directly (Beauchamp & Childress, 2013). In this case, the patient mistakenly thinks that the biobank research is part of the therapeutic scheme rather than a scientific exploration of a potentially beneficial diagnostic and therapeutic tool. Especially when results on potentially life-threatening diseases are returned to the participant, as discussed in chapter 5, a therapeutic misconception looms for all types of biobank research.

Biobanks and informed consent

When it comes to biobank ethics, the question of what an adequate informed consent entails is particularly difficult to answer. Biobank institutions regularly do not know what research projects will be performed in the future. Without knowledge of those future applications, it is impossible to inform participants in the way a traditional conception of informed consent seems to require. Therefore, participants cannot give a so-called specific informed consent for all the research done with their samples (Greely, 2007). Moreover, as future research is still unknown at the moment a person is asked to participate, the risks related to these applications are also unknown. This observation is relevant for the moral acceptability of biobanks, because participants are exposed to unknown risks (these risks are discussed in chapter 6). It also raises questions with regard to informed consent because disclosure of possible risks is a viable aspect of the information requirement (Allen & McNamara, 2011) and therefore important within the framework of respect for autonomy. The requirement of a so-called specific informed consent could be maintained if participants are asked to re-consent with every single research application of the biobank. Yet, this seems an implausible solution to the problem, as it is inconvenient and very time-consuming both for the researchers and for the participants. Moreover, this precondition becomes challenging when participants die (Budimir et al., 2011).

An alternative to specific consent: broad consent

Generally speaking, the alternative to specific consent is broad consent. Broad consent is a comprehensive concept that comprises all variations on informed consent that allow for provision of information on a more abstract level than specific research projects. This includes general consent and tiered consent (Haga & Beskow, 2008). Sheenan (2011) points out that broad consent can be justified because autonomy, the foundation of informed consent, is respected. He asserts that giving broad consent may limit an agent's freedom of choice in the future, but this does not necessarily imply a limitation of one's autonomy. Autonomous decisions are commonly made without specific knowledge of future consequences, for example when someone asks another person to order her meal. Yet this is not regarded an infringement of the person's autonomy: it is simply a result of an autonomous choice. Helgesson (2012) argues that people participating in biobank research have different views on what information is relevant to them. Some people may find general

information sufficient to give their informed consent for participation. Moreover, people can make the autonomous decision to allow an ethics committee to assess risks of future research projects. Many authors seems to agree that broad consent is justifiable if certain conditions are met. These conditions include a right to withdraw from the biobank and supervision of the biobank by a review board (Budimir et al., 2011; Knoppers et al., 2012). Since specific consent is not feasible and broad consent is not necessarily an infringement on the participant's autonomy, I conclude that the Living Biobank can use a broad consent procedure when including new participants into the biobank research. However, a broad consent cannot entirely rule out the possibility that the organoids, cultured from a participant's sample, will be used for research purposes that? the participant would not specifically consent to (despite efforts of the biobank to avoid this). Acknowledging this is an essential part of the broad consent procedure so that the participant can take this into account when deciding to participate.

Tiered consent

A variation of broad consent is tiered consent. Tiered consent means that multiple options for consent are presented to envisioned research participants. People do not have to agree to a standard form, instead they can choose between several clusters of research applications. This approach is defended as autonomy enhancing. Yet it might also be unnecessary and over demanding, since informed consent is based on autonomy as a negative right (i.e. the right not to be included in a research without appropriate consent). Tiered consent may enhance a person's autonomy, yet it does not follow that biobanks have a duty to offer these choices (Haga & Beskow, 2008). So it would be praiseworthy if the Living Biobank provides the service of a tiered consent rather than merely a broad consent procedure, yet this cannot be considered a moral obligation.

Opt-in versus opt-out

Another discussion on informed consent with regard to biobanks is whether the default decision is either participation or non-participation. These considerations are often rejected in the field of clinical research, but they are widely discussed when it comes to biobank ethics. This issue is especially relevant to biobanks collecting residual samples (Knoppers et al., 2012). Traditionally, research ethics is focussed on the protection of autonomy, and informed consent is fostered as a way to protect it. Yet, in recent years values such is

solidarity and reciprocity have become more prominent in the field of research ethics (Hansson, 2009; Knoppers & Chadwick, 2005). These developments have consequences for the role of informed consent in the inclusion of samples in biobanks (Cambon-Thomsen, 2004). Reciprocity may require that people, using medical care and thereby profiting from biomedical research, have a moral duty to play a role in the development of medicine. Solidarity is important because scientific progression depends, to a certain extent, on the participation of entire groups. Refusing to participate could undermine this progression (Knoppers & Chadwick, 2005; Giesbertz et al., 2012).

Some authors in favour of participation as the default decision have argued for an opt-out policy. Giesbertz and colleagues (2012) have defined and opt-out procedure as "a procedure where inaction is treated as a signal of consent"(p. 4). When it comes to biobanks, this means that material is included in the biobank unless the envisioned participant explicitly rejects. This procedure does not abandon the underlying values of informed consent because people are both adequately informed about their options and free to withdraw. Therefore, they argue, autonomy is respected and values like reciprocity and solidarity are promoted. An opt-out policy is likely to be more effective than a traditional opt-in procedure in the sense that more samples will be obtained.

The Living Biobank: a plea for an opt-in procedure

At first sight, the Living Biobank would be perfectly eligible for the opt-out procedure. The samples in the Living Biobank are collected by surgery that had to be performed anyway. In that sense, the Living Biobank uses strictly residual tissue to create organoids for scientific research. Moreover, experiments done with organoids do not affect the integrity of the human body directly. A damaged organoid does not have direct implications for the health of a participant. I think that the Living Biobank is not strictly different from standard biobanks in this sense. Also for this new type of biobank, the risks will typically be lower than clinical research as the actual research is done outside the human body (Eriksson & Helgesson, 2005).

However, I think more caution is appropriate with regard to the Living Biobank. Two important differences between the Living Biobank and the convential types of biobanks are that the organoids in the Living Biobank can be used for an even larger scope of possible

applications and that these organoids are virtually immortal in the sense that they can be proliferated again and again (The HUB foundation, 2013). Today, researchers can easily gain access to the donor's genome using the technique of whole-genome sequencing. So all the problems associated with obtaining specific informed consent for genetic biobanks are equally applicable to the Living Biobank. But on top of that, there are a lot more possibilities. The development of new drugs alone represents a huge variety of research possibilities. One can think of the development of certain drugs to which some (or most) people would not want to contribute. Consider, for example, the hypothetical and extreme situation that a drug against homosexuality could be developed. Giesbertz and colleagues (2012) already recognize the need for an opt-in procedure when "controversial and/ or high-impact techniques are involved"(p. 4). I conclude here that the Living Biobank actually is such a controversial technique as it is impossible to predict what kind of research will be performed many years from now. In the future, moral norms might prevail in society that are irreconcilable with the values we hold today. Hence, even a solid ethical review procedure cannot guarantee that future research will be consistent with the participant's values. Therefore, an opt-out procedure is not a morally justifiable option for the Living Biobank.

Chapter 4: Storage and use of organoids

4.1 Privacy

There are several reasons why people might worry about privacy with regard to biobanks. Some people fear that disclosure of their medical information leads to discrimination, for example by insurance companies. Also, participants may be concerned about stigmatization when sensitive information from their medical history is revealed to other persons. Other people care about privacy simply for its own sake: they do not want other people to know things about them while that people are not entitled to receive this information. (Greely, 2007; Haga & Beskow, 2008).

There are basically three common strategies to protect the privacy of participants in a biobank. The safest strategy is to use anonymous samples. In this case, samples and data cannot be traced back to the participants because no personal information is stored at all. The scientific value of a biobank is likely to decrease dramatically when this type of information is absent, as biobank research typically combines samples and phenotypic information to yield scientific results (Hansson, 2009). Another option is to anonymize the samples. This entails the destruction of information that can be used to identify the participant. However, there is substantial doubt whether this is a real option, since data from the biobank combined with information that is publically accessible (for example on the internet) can often be used to find out who is the donor of the sample. Moreover, it can be argued that that anonymisation is unethical, since the benefits are limited while the costs can be high. The benefit is limited because it adds little to the protection of privacy. The costs, in contrast, are high because both contacting the participants and withdrawal is impossible. On top of that, the scientific value of the biobank will decrease (Greely, 2007). The third option is to codify personal information that could be traced back to the participant (Hansson, 2009). The key to this code is not kept by the researcher that processes the data. This alternative is favourable also for the Living Biobank, since the participants privacy is protected while the scientific value of the data remains intact.

4.2 Ownership, commercialisation and status of organoids

The Council of Europe, in a recommendation on research on biological material, seems to reject the commercialisation of tissues stored in a biobank. They state, in article 7:

"biological materials should not, as such, give rise to financial gains" (Council of Europe, 2006). Although this appears to be a clear statement, the description "as such" is vague and it is without any doubt that there are indeed commercialisation aspects to biobanking. Cambon-Thomsen and colleagues (2007) have pointed at the increasing interrelatedness of private and public funding of research projects. Biobank research is not an exception here. The sensitivity of this commercialisation when it comes to biobanks depends on the very nature of those banks, collections of human tissues. All these tissues where once part of a human body and belonged to a person. This gives rise to a number of complexities and sensitivities, and this is not different for the organoid biobank. In this paragraph, the question whether a biobank should be permitted to sell the organoids is addressed. Two opposing sides of the debate will be discussed here. Ultimately, a middle ground will be proposed as ethical guideline for the Living Biobank.

The Moore case and the traditional view on the human body

The question who owns human tissue once it is removed from a person's body has been asked compellingly in the late 1980s in a law case in the United States known as Moore versus Regents of the University of California. The controversy was about cell lines obtained from tissue of a patient suffering from leukaemia. After the surgery, the tissue of patient Moore was used to produce cell lines while he did not know anything about it so obviously he did not provide informed consent for this production nor for any of the research applications. When Moore found this out, he sued the physician and the university the doctor worked for, demanding a share in the profits that where made with the cell lines. The Supreme Court of California ruled that, although the physician was wrong in using the tissue without consent of the patient, Moore could not justifiably claim a share of the financial benefits because he could not consider the tissues his property (Haga & Beskow, 2008; Capps, 2014). This conclusion sounds not so surprising, since also blood donors (to give an example) cannot claim property rights over their serum once abandoned. The complexity, however, becomes clear when thinking of tissue that is still situated inside the human body. There is wide consensus in society that a person "owns" her own body, yet people are not allowed to sell their organs. Of course, arguments are given that contradict this norm, but the vast majority of people would morally rejects such practices. This touches upon an apparent paradox: on the one hand people are the owner of their body, while on the other

hand they cannot regard it as property with all the rights that we usually attribute to owners of certain possessions (Alta Charo, 2006).

The notion that one "owns" her own body is intuitively appealing, yet this paradox shows that the content of this ownership concept is not entirely clear. So some further analysis is needed her. The dominant view that a human body, or parts of it, cannot be owned rest upon the Kantian notion that a human body cannot be a subject and an object (that can be possessed) at the same time. A person is definitely a subject that can own something, therefore cannot be owned itself and thus parts of the body cannot be possessed either (Dickenson, 2006). This normative notion that a body cannot be possessed is rooted deeply in our moral thinking, as becomes clear when thinking of the organ trade, a practice fiercely rejected by many scholars as well as the public. This uneasiness is also reflected by the above mentioned statement of the Council of Europe. Donna Dickenson points out that in European countries such as the Netherlands and France the body is a "res extra commercium", a thing that cannot be sold, while tissue that has been removed voluntarily is considered abandoned: "res derelictae" (Dickenson, 2006, p. 52). She mentions that traditionally, this res derelictae is also a "res nullius", a thing that is nobodies property (Dickenson, 2002, p. 57). According to this traditional view on the human body, commercialization is considered immoral, as it is a first step towards instrumentalisation of human beings. Some people that adhere to this traditional view might even consider commercialisation of human tissue the first step on a slippery slope towards slavery.

Yet the philosophical appeal of such slippery slope arguments is rather weak. These arguments can only succeed logically if there is either (1) no conceptual difference between the two ends of the alleged slope so that there are no moral reasons left to embrace one side while rejecting the other or (2) no boundary (for example a legal boundary) in place that prevents the descending from the upper side to the feared bottom (McGleenan, 1995). Yet there is in fact a clear conceptual distinction between the commercialisation of organoids and the exploitation of human beings. Organoids are made out of human stem cells and resemble in-vivo human tissue, but they lack an wide variety of properties that humans have. There is also sufficient legal and social barriers in place to, for example, prevent people from selling organs if organoids can be sold (amongst other reasons because organoids are made of residual tissue from surgery performed for other reasons than to harvest organoid

material). These kinds of slippery slope arguments could also have a rhetorical strength by linking the proposal, in this case the sale of organoids, to atrocities of the past such as slavery (to given an extreme example). Yet there is no precedent or empirical research that could support those kinds of claims (McGleenan, 1995). Yet the researchers should be aware that the nightmares of the past make people more cautious in this controversial debate, although no argumentative support can be gained from such analogies.

Arguments in favour of granting property rights to the biobank

On the other side of this debate, however, one could argue that although cell lines or organoids originate from human tissue, these research tools are modified and treated in such a way that a new entity has been created. To understand this line of reasoning with regard to organoids, it is crucial to notice that these entities are not merely abandoned cells, but chunks of cells derived from donated material. The tissue that was removed from the patient is isolated, processed, and manipulated in a culture. Comparable with research cell lines, they are "human-made research tools" (Mathews et al., 2011, p. 726). This observation suggest that the biobank has some rights with regard to the organoids, because effort is put in. This argumentation invokes another normative principle that is rooted deeply in our moral understanding: property rights emerge from work put into an object by a person. A person's labour is what entitles her to regard something as property. This notion is often traced back to, or is at least formulated by, John Lock (Ohashi, 2013). According to the this line of reasoning, the patient that (voluntarily) abandoned the tissue cannot claim that the organoid is still her tissue. The stem cells obtained from surgically removed tissue would not have grown to organoids without the interference of the biobank researchers. Thus, the biobank can claim certain property rights regarding the organoids.

Benjamin Capps (2013) provides an argument against the traditional and intuitive view that the human body cannot be owned since a person cannot be owned. When physical injury is inflicted on a human person, people feel shocked and indignant. Yet the same reaction does not occur when human tissue outside the body is damaged. This example shows that in many situations, removed parts of the human body are not considered fragments of a person anymore. So the traditional view mentioned above may be intuitively appealing, but after closer evaluation it does not make out a strong case.

What does this mean for the commercial applications of organoids? Since these organoids cannot merely be considered parts of a human body, but are also distinct entities that exists partly because of human intervention, it follows that organoids might not be a complete *res extra commercium* in accordance with a Kantian view on the human body. It might also imply that organoids are not entirely *res nullius*. The biobank could claim some property rights over the organoids, since the employees of the biobank have produced them with their efforts. There is an analogy here with genetic research. The European Society of Human Genetics (2003) has agreed that once genetic samples (that belong to the participant) have been processed to research data, it is owned by the researchers. They add "It follows that intellectual property would be of the researcher but with due consideration for benefit sharing" (p. 908).

An argument for restraint regarding commercialisation

Yet there are reasons to show some restraint with regard to complete commercialization of organoids. An organoid has the same genetic blueprint as the patient, and resembles the in vivo tissue of the patient closely. This is of course the strength of the organoid technology, but it also implies that the organoid belongs to the patient in some way. This points towards a shortcoming of the traditional person-object distinction that I have addressed briefly. The organoids, like cell lines, do not fit well within this traditional dichotomy because on the one hand they originate from human bodies while on the other hand they are artificially produced research materials. Mathews and colleagues (2011) have already pointed towards the ambiguous position of cell lines. Unlike persons, those cell lines can be used as instrumental tools for medical research, yet "Recent cases make it clear that what happens to human research materials, especially "immortalized cell lines, " can be deeply meaningful to those from whom the materials have come" (p. 726).

A middle ground

When it comes to establishing a policy for commercialization, the observation that organoids emerge from the efforts of the biobank have to be reconciled with the notion that the organoids also have a special relationship with the donors of the initial stem cells. Lenk and Beier (2012) offer an approach to commercialisation issues with regard to human tissue in general that could be useful for organoids as well. They distinguish four different levels of commercialisation: (1) no commercialisation, (2) commercial use based on the donor's

preference, (3) financial transition of tissue on the bases of fixed prices as compensation for past efforts and (4) full possibilities for financial gain. Why the second scenario is included is not entirely clear: from the perspective that informed consent is vital to protect the participants and warrant autonomy, it is surprising that the authors present this as a distinct level of commercialisation instead of a prerequisite for level three and four. When evaluating the third and fourth option, the third option could be a sound solution for the problem addressed above, i.e. that we are looking for a middle ground between absolute property rights for the biobank and complete control by the participants. This acknowledges the special relationship of the organoids with the donor of the original tissue as well as the efforts and investments made by the biobank.

Yet there is another important aspect to this discussion that makes option three appealing. The organoids can contribute not only to the health of the patients that donate tissue to the biobank, but also to medical science in general. The research that is performed on organoids may contribute to the public health of entire populations (Cambon-Thomsen, 2007). This notion is important when considering the possibilities for commercialisation and needs to be balanced with other consideration that are mentioned here. Moreover, as formulated strikingly by Alto Charo (2006): “bodies and tissues may also be viewed as part of a common heritage, to be used for the collective good if such use does not unduly infringe on our liberties” (p. 1519). These perspectives introduce society as a party in the commercialisation debate. If organoids that are derived from human tissues are considered as public goods, at least to some extent, this is an argument in favour of choosing a compromise between complete privatisation and radical conservatism. Lenk and Beier’s (2012) third level of commercialisation provides such a middle ground: this scenario allows for compensation for processing costs between parties when tissues, in this case organoids, are transferred. This compensation could promote the scientific progression made with organoid research because optimal allocation of the organoids between research parties can take place. At the same time, private parties will be more likely to invest in biobanks and organoids when they know the costs of their investments will be compensated. Finally, the public good will be supported by this scenario as organoids remain available to public research institutions (such as universities), i.e. the organoids will not disappear in the private circuit.

Another, related, question is whether organoids can be patented. This concerns not the technique of producing organoids, but the organoids themselves. This question has neither been answered for cell lines, but is an important issue in the field of commercialisation that has to be addressed (Isasi & Knoppers, 2011). This is a follow-up question that becomes relevant once the question whether commercialisation can be ethically justified is answered. Moreover, this question also entails some legal and policy-related aspects. This is why it is recommended to discuss this particular patent issue in the following years both from a legal and from an ethical point of view.

The organoid as entity worth protecting as such

Until know, this chapter has only addressed the value of organoids related to the participant, the biobank, and society. However, organoids are living structures, as the name Living Biobank suggests. Unlike the human material that is discussed in the literature on biobanks, organoids consist of living cells that proliferate and differentiate and cannot survive outside a suitable environment. Formulated this way, one could suspect a parallel with embryos. This raises the question whether organoids have a moral status as such, as adherents of some philosophical and religious movements claim with regard to human embryos. This question addresses the intrinsic value of an organoid. This has to be distinguished from the relational value that is attributed to organoids as artifacts derived from tissue that belonged to a person. Intrinsic value, though, is a philosophically very complex notion. There is no room in this thesis to discuss this issue extensively. It is important, however, to notice that the moral status of humans is often defended with an appeal to rationality as the essential property that constitutes a human's intrinsic value. Some people have defended the intrinsic value of embryo's with the argument that embryos are potential bearers of this rationality (Baertschi & Mauron, 2008). Although there is a similarity between embryos and organoids in the sense that it are chunks of human cells, organoids do not have that potentiality. No claims are made here on the status of embryos and the normative implications of this debate. What is asserted here, however, is that one cannot translate arguments used in the embryo debate to organoids. People who are deeply opposed to embryonic research do not necessarily have to be worried about organoid research. For the goal of this thesis, it is sufficient to conclude that the value ascribed to humans and sometimes to embryos cannot be ascribed to organoids.

Beauchamp and Childress (2013) mention other properties in addition to rationality (or cognition, as they put it) that have been defended as ground for moral status: to have human properties, to be a moral agent or to be a sentient being. Organoids are certainly not sentient beings and are unable to make moral decisions. Yet an organoid cultivated from human stem cells unquestionably has human properties, such as human DNA. However, there are convincing reasons to reject this theory of moral status. First, it is odd to base this status solely on biological properties as this would imply that (imaginary) creatures that think, act, and feel like human beings but are biologically distinct cannot have moral status. Second, the line between biologically human and non-human is rather arbitrary as becomes clear when thinking of human-animal chimeras, that are already used in scientific research (Beauchamp and Childress, 2013). Of course, one can deliberate extensively on the moral status of cell lines and organoids and this is certainly an interesting subject for future research. But for now, there are no obvious reasons to reject commercialisation or other controversial applications of the organoid bank with an appeal to the intrinsic value of the organoids.

Chapter 5: Feedback of results

5.1 Feedback of aggregate results

Two subjects have to be distinguished here: feedback on aggregate results and individual results. The first is rather uncontroversial. The Living Biobank can keep its participants updated by giving information on aggregate results, for example by communicating the results of a study directly to participants in understandable language (supplementary to publication in scientific journals). In doing so, research groups show respect for the participants, by demonstrating the merits of their contribution. Moreover, it provides participants with a basis on which they can built their decision to withdraw or not-withdraw from the biobank. Furthermore, this feedback on aggregate results contributes to the public trust (Haga and Beskow, 2008).

5.2 Feedback of individual results

Yet feedback of individual results is the subject of a fierce international debate in ethical literature. As in many studies in the field of medicine, research using the Living Biobank can yield information that may be important for participants. This may concern incidental findings as well as results that where foreseen in the design of the study. The research may, for example, reveal a disease the participant is not yet aware off. Knowledge of these latent diseases could be important for therapeutic reasons, for example if the affection is treatable only in an early stage. Moreover, such information could have a tremendous influence on the decisions people make in life. Since the Living Biobank combines functional analysis of the organoids with genetic sequencing data, research on organoids could reveal at least a wide variety of genetically inherited diseases. There is no reason, however, to assume that this issue is limited to genetics, as organoid research might also reveal diseases that have an adaptive or multifactorial aetiology. This chapter discusses what the duties of the Living Biobank are when such incidental findings occur.

Respect for persons and beneficence

Both advocates in favour and against individual feedback have invoked the principle of respect for persons . On the one hand, respect for persons requires to treat participants as autonomous agents. According to this argument, return of results would give people information that they want, that recognizes their contribution, that gives them more

information about themselves, and that improves their opportunities for self-determination (Ossorio, 2006). On the other hand, following Clayton and Ross (2006), respect for persons can be regarded a protection and not an entitlement to information that participants can claim. Proponents of feedback also invoke the principle of beneficence: it can be used as an argument in favour of disclosure because the information concerned may be beneficial for the participants' health or quality of life. Moreover, such information can be vital for crucial decisions in life (Haga and Beskow, 2008), for example reproductive decisions.

Disclosure of results as duty to rescue

Many authors have suggested that disclosure of information can be a moral duty of the researcher if the results are life-saving. This is often considered an application of the duty to rescue another person whenever possible (Isasi et al., 2012). A duty to rescue, however, is a morally complex notion. A duty to rescue is a positive duty, since it obliges an agent to act rather than simply refrain from certain harmful actions. The problem here is that this positive duty is open-ended. A duty to rescue could require that people all over the world give up all their daily activities as long as there are people in need that they can rescue. Yet these kinds of arguments are not applicable here, since a duty to rescue applies to cases where a third person witnesses the need of someone else. However, a researcher is a second person rather than a third person when it comes to the feedback of potentially life-saving results. This means she has even a stronger moral obligation to save the participant by disclosing the results (Greely, 2007). This moral obligation to provide care that goes beyond good research practices, like confidentiality, certainly applies to the Living Biobank as well. The biobank acquires unique knowledge about the participant's biological composition linked to phenotypical information. Acknowledging this special relationship between the participant and the biobank comes with certain moral obligations. This has been referred to as ancillary care, a duty of the researcher following from the role of a professional who has the privilege to access tissue obtained from the participant's body and to acquire private knowledge of the patient (Richardson, 2008; Miller et al., 2008; Wolf et al., 2012).The professional aspect is important here. Researchers or research institutions such as the Living Biobank are not in a therapeutic relationship with the participants, yet they do have a relationship as professional and layman. The institution has knowledge the

participant does not have, and the participant entrusted the biobank with this information by handing over her own tissue.

Difficulties in determining the nature of the feedback

The content of the researcher's obligation, however, is still vague. In order to avoid open-ended duties that would overwhelm the researchers' capacity, criteria have to be formulated to decide what information has to be returned to the participant. Here a lot of complexities arise that have been mentioned in the ethical literature on biobanks. These complexities have to be taken into account when establishing a framework for feedback on research findings. A question with regard to the feedback of results is whether investigators are able to actually translate this results to clinically significant figures, since scientific results are often presented as odd ratios measured in large cohorts (Hansson, 2009). Greely (2007) acknowledges this problem, and lists several more: how informed should the investigator be, what about relatives (when it comes to genetic information), for how long is there an obligation to inform, who bears the costs, and is there a right not to know? Moreover: what should be the threshold for returning the results, based on seriousness, confidence, penetrance and possible interventions? Especially when it comes to genetic research, counselling is of major importance in the feedback of results. Special skills are needed to return these results. Several authors have stressed that misinterpretations of this type of results is more susceptible to harm because treatment or prevention is not available and it also affects relatives (Cambon-Thomsen et al., 2007; Hansson 2009). Finally, it has been put forward that the value of the information cannot be determined by the investigator because the impact of the results also depends on the participant(Dressler & Juengst, 2006).

Emerging consensus

Although the mentioned difficulties hinder the determination of a universal ethical standard for feedback, this does not exclude situations where the importance of results for individual participants is so obvious that there actually is a duty to communicate these results. The old comparison with bald and non-bald men can be applied here: a threshold for baldness cannot be established, yet there is a clear distinction between completely bald men and men with a hairy coiffure. Similarly, it does not follow from the observation that some situations are controversial with regard to the question whether the researcher should communicate results or not that there are indeed findings that should be communicated to the participant.

There seems to be an emerging consensus in literature on criteria that certainly imply a duty to disclose results. These criteria establish, one might say, a minimal baseline for feedback. These criteria include that the concerned condition is potentially life-threatening to the participant or (in case of genetic information) her offspring and that the information is scientifically valid and reliable (Wolf et al., 2012).

The specific nature of the Living Biobank and feedback of results

The Living Biobank is different from other biobanks in the sense that living samples are stored that can be used during a virtually infinite period of time. This could be morally problematic, as stated in the informed consent chapter, because the future research potential of the organoids is cannot be predicted. In 30 years from now, scientific progression will almost certainly provide a whole new spectrum of research possibilities, not only in the field of genetics ,but also in cell biology in general . The implications of this progression for the amount of life-saving information that could be acquired are likely to be extensive but cannot possibly be overseen. One could argue that it is over-demanding to ask researchers to actively seek communication with participants over an almost infinite period of time. It can be made clear to envisioned participants that the specific nature of the Living Biobank requires that this feedback does not take place for years and years to come. This is important not only to avoid over-demanding moral claims on researchers, but also to protect participants from a consent procedure that they cannot possibly oversee. Broad consent, as defended in the informed consent chapter, is a justifiable alternative to specific consent. Yet the scope of possibilities of the Living Biobank is so extensive that giving broad consent with regard to the return of all potentially life-saving information in the future would approximate a blanket consent.

The need for a restriction clause

It does not follow, however, that the Living Biobank can pull away entirely from the ethical consensus that is mentioned above. That the scope of the Living Biobank is extensive does not mean that parts of its possibilities do not resemble the possibilities of existing biobanks, for example those storing genetic samples. There is no reason why the rationale that justifies feedback in genetic research would not apply to the Living Biobank, as far as similar applications are concerned. So I propose the following strategy for the Living Biobank: participants will be informed about the possibility to receive feedback on results that meet

the criteria mentioned above: life-saving to participants or offspring and scientifically valid. In addition to this criteria, there is the prerequisite that this feedback lies within the range of the current possibilities in (genetic) research. I would like to introduce an restriction clause here as part of the informed consent procedure. The initial informed consent can be seen as a contract that expires under certain conditions. If there are revolutionary developments in the kind of results that the Living Biobank research could produce, the contract expires. In this case, an ethics committee has to decide whether feedback is still feasible and desirable. If not, the obligation of the biobank to disclose essential results expires. If it is, the biobank should re-contact the participants, inform them about the new possibilities and ask for consent again.

Therapeutic misconception

Another difficulty here concerns, again, the pitfall of a creating a therapeutic misconception (Bredenoord et al., 2011). An envisioned participant may be tempted to participate when she learns that it could result in knowledge crucial to her health. Yet it is by no means certain that participation in the Living Biobank will yield such results. The researchers of the Living Biobank have to be aware of this pitfall, and should minimise this risk by informing the participant in the informed consent procedure that although there may be incidental findings that will be disclosed to the participant, this is not the purpose of biobank research.

Routine screening on genetic disorders

Some experts have argued in favour of a duty for the biobank that goes much further than an ethical obligation to communicate crucial results that are found incidentally. The American College of Medical Genetics and Genomics (Green et al., 2013) has published a recommendation that states that laboratories ought to perform a routine screening on a long list of genetic disorders. Although this specific statement is pointed towards a clinical context, the line between clinical genetic sequencing and genome sequencing done for research purposes is thin. Such a routine screening would be an undesirable practice in case of the Living Biobank, and thus must be rejected. Routine screening for genetic disorders is not available on demand in the Netherlands. As a result, envisioned participants could be tempted to participate in the biobank research to acquire access to such a screening. The Living Biobank, however, is not a screening programme but a biobank for scientific research. Participants should participate because they wish to contribute to the biomedical sciences,

not because they want to know about possible inherited diseases. Likewise, the biobank cannot be expected to provide this kind of services for an increasing number of genetically identified diseases over an extended time period with their limited resources in terms of personnel and money. The point here is that such a procedure surpasses the initial goals of the biobank. Crucial results that are either incidental or foreseen are the direct result of the research that is performed deliberately to answer research questions. These results are linked directly or indirectly to the goals of the study, as they arise from the research that is the biobank's core business. Screening routinely on common genetic disorders is neither the biobank's core business nor an incidental by-product of it. Therefore a duty to provide these services can be considered an over-demanding obligation for the researchers and an improper incentive for envisioned participants.

Chapter 6: Ethical considerations for all three stages

6.1 Governance and oversight

Independent review is important because researchers have multiple interests when it comes to their projects. This variety of interests may conflict, and an independent review procedure serves to avoid negative effects of that conflict (Emanuel, 2000). This applies not only to the minimisation of harm, but to all ethical values that are at stake in the field of biomedical research. Amongst other things, this includes the scientific value of the study. Another function of review committees is to ensure social accountability. As Emanuel (2011) formulates strikingly: "clinical research imposes risks on participants for the benefit of society. Independent review of a study's compliance with ethical requirements assures members of society that people who enroll in trials will be treated ethically" (p.2706). Ethics review committees play a vital role in safeguarding the values and requirement that are discussed throughout this thesis.

It is important to notice that biobank research requires an ongoing role for the ethics review committees involved. New research projects that use an existing biobank have to be submitted to an ethics review committee for ethical approval (Knoppers et al., 2012). This is especially important because broad consent forms are used to obtain informed consent (Greely, 2007; Hansson 2009). The Living Biobank has a characteristic that articulates the importance of ethical oversight: the organoids are actually living mini-organs that can be used for a lot more purposes than, for example, biopsy materials on formaldehyde. This is challenging for ethics committees as guardians of public trust and ethical behaviour.

In the Netherlands, a legal framework for biobanks is still absent. In June 2012, the Dutch minister of health announced to the parliament that an expected bill would not be submitted anytime soon (Schippers, 2012). Also on the European level, such a legislation is lacking. The already mentioned recommendation of the Council of Europe is not binding for all EU member states (Haga & Beskow, 2008). This is a serious omission, since especially genetic samples and data are being shared across countries in and outside Europe. The legislation differs significantly between states (or is even absent), making the need for a European framework even more urgent (Kaye, 2006). While such a framework is still absent, restraint is needed with regard to exchange of organoids as well as data derived from them.

In absence of governance by legal means, a committee is needed to assess the proposals for exchange of organoids and data. As this exchange may occur both nationally and internationally, specific knowledge on international research collaboration is needed here. This expertise is not necessarily represented in current biomedical ethics committees (Knoppers et al., 2012), so people with this particular expertise have to be added to the committee or a separate review board has to be established.

6.2 Balancing risks and benefits

An import task of ethics review committees is to weigh possible risks and benefits in order to judge whether the proposed research can be approved. As already mentioned, biobank studies differ from clinical research studies in the sense that biobank research is done outside the human body and thus cannot affect the actual health of the participant directly (by damaging structures inside the body). It does not follow, however, that biobank research cannot cause any risk. Several important risks have already been mentioned in previous chapters: risks associated with feedback on research results, psychological harm due to research the participant finds inconsistent with her own values, and the risk of violation of the participant's privacy. In addition, there are safety issues that have to be taken into account: measures have to be taken to ensure safe collection, storage and processing of the organoid material (Isasi & Knoppers, 2011). It is the researcher's responsibility to convince the ethics committee that these safety risks will be minimised or otherwise acknowledged. Exhaustion of the samples is an issue that has been mentioned with regard to existing biobanks (Eriksson & Helgesson, 2005), but this is not likely to be a relevant issue for the Living Biobank. If the researchers comply with the relevant safety rules, the organoids can be preserved and proliferated virtually without limits. However, stigmatisation and discrimination due to the research performed may actually occur (Haga & Beskow, 2008). Discrimination can lead to the infliction of economic harm, for example when sensitive information about the participant's health is passed-on to an insurance company (Eriksson & Helgesson, 2005). This could be a matter of privacy measures, but the extent of this risk also depends on the specific legal context of the concerned biobank. Further legal research is needed to evaluate the extent of this particular kind of risk. Ethics committees have to evaluate this risk in light of the specific legal and political context.

The risk of stigmatisation and discrimination is relevant, not only on the level of individual participants, but may also affect entire groups. This risk is especially important with regard to genetic research (Cambon-Thomsen et al., 2007). This is relevant when tissue is collected for the Living Biobank from participants belonging to one specific minority group. This does not seem to be the case in the current applications of the biobank since no particular minorities are addressed. However, specific studies may reveal genetic information that has consequences for entire families or entire groups in society. Moreover, it is possible that tissue will be stored into the biobank to investigate diseases that are more prevalent in certain groups. These group-related risks are not as obvious as direct physical harm. This makes them more susceptible to be overlooked or trivialised. Hence these issues deserve special attention of ethics committees.

An important advantage of the Living Biobank is that it gives rise to new research possibilities in the field of drug testing. The first time that new drug are administered to humans is an ethically precarious point in the development of new medicines. These so-called phase 1 trials are morally controversial since the risks are typically unknown. (Anderson & Kimmelman, 2014). If the Living Biobank succeeds, it might bring about that certain phase 1 trials can become less hazardous because the drugs that are administered are already tested on living human tissue. In that case, the risks for participants in first-in-human trials can be significantly lower. This is a relevant consideration for ethics committees when evaluating proposals for new biobanks such as the Living Biobank or proposals for new studies using the organoids in these biobanks. It can cause a shift in the risk-benefit analysis that ethics committees make when they have to decide on the ethical acceptability of a proposed project. The risk of a biobank research proposal should not only be weighed against the direct benefits of the envisioned results, but also against the associated diminishing of risks in in-human studies.

6.3 Public trust

The success of a biobank, as for scientific research in general, depends highly on public trust. Moreover, a violation of public trust by biobanks will affect the reputation and interest of biomedical research in general. A decline of the public trust may result in a huge difficulty in the recruitment of participants as well as a massive withdrawal from the biobank (Hansson, 2009). The latter would undermine the scientific value of the Living Biobank because in that

scenario there will be less organoids available for future research. Obviously, when public trust is damaged, this could result in legal boundaries that rule out much of the activity in the field of biobanks or biomedical research in general since politicians will feel the need for governmental intervention. How the public trust is warranted is not only one of the considerations that should be evaluated by an ethics committee, the very existence of such an ethics committee is also important at this point. A well-organised and reliable oversight can contribute vastly to the public trust.

6. 4 Collaborative partnership

Collaborative partnership has been described by Emanuel and colleagues (2011) as a principle that "recognizes that the community in which research is conducted should collaborate in the research endeavor" (p. 125). This principle recognizes subjects of the research as actual participants. This has been noticed as a trend in research, and applies not only to individual participants, but also towards the community or the public (Cambon-Thomsen et al., 2007). However, there is no consensus in literature on the question who should be involved and to what extent (Hansson, 2009). It is proposed that the Living Biobank involves the particular patient groups and patient associations that represent patients suffering from the diseases that are being researched by the Living Biobank. When the scope of patients included in the Living Biobank expands, more people or groups have to be involved.

Chapter 7: Issues concerning the pediatric branch of the Living Biobank

Biobanks that store samples obtained from children face some specific ethical difficulties, additional to the ethical dimensions that have been identified for biobank research using adult participants. These specific ethical questions arise in every cluster of ethical issues that has been mentioned in the previous chapter: inclusion of participants, storage and use of samples and return of results. The Living Biobank involves pediatric research explicitly, focussing not only on cancer research but also studying the pediatric disease cystic fibrosis (The HUB Foundation, 2013). This chapter addresses specific issues with regard to pediatric applications of the Living Biobank. The division in clusters mentioned above will also be used in this chapter.

7.1 Inclusion of participants

As stated before, informed consent as warrant for autonomous participation is one of the corner stones of contemporary research ethics. However, this practice cannot simply be translated to pediatric research. Since children are considered (at least to some extent) incapable of making autonomous decisions, they cannot give a full informed consent. They are not competent of making such decision and especially younger children are not able to understand the necessary information presented to them. For obvious reasons though, it would be undesirable to rule out all the pediatric research for that reason. The common strategy to solve this problem entails that a surrogate decision maker, often the parents, must give informed consent while the child gives assent. This practice is articulated by the declaration of Helsinki: “When a potential research subject who is deemed incapable to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected” (WMA, 2013). There is much consensus that a child cannot be included in a study in case of dissent, although it is not always completely clear what behaviour should be interpreted as such. When it comes to assent however, there is substantial disagreement about the very nature of this concept. Two ways of interpreting assent have been identified (Giesbertz et al., 2014): assent as a reflection of adult informed consent (i.e. grounded in the principle of respect for autonomy) and assent as a warrant for

engagement. Giesbertz and colleagues (2014) argue in favour of the latter. They put forward that when children are considered incompetent, they cannot make autonomous decision and therefore cannot give an informed consent at all. Instead, they defend assent on the ground of engagement. There are several reasons why assent is important from the perspective of engagement. First, it empowers children as participants of the study (as opposed to merely research subjects). Second, assents promotes the development of a child because an assent procedure contributes to the moral uprising of a child. Third, assent supports the communication between a researcher and the child. These considerations are all relevant with regard to the assent procedure developed by the Living Biobank. An ethically sound procedure should focus on these subjects and promote its underlying values rather than merely requiring a child to nod yes or no to a question which implications cannot possibly be overseen by the minor participant.

Now what can be considered as an appropriate and satisfactory assent? The European Commission has published a guideline for assent in pediatric research in general that distinguishes three categories of children based on their age (Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC1 relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, 2008). On this scale, the level of assent is stratified along the lines of the child's age, reflecting an increase in competence and understanding of children while they grow up. In literature however, there seem to be a tendency towards an individual, tailor-made assent. In this view, the level of information that has to be provided and the required format of approval depends not on age alone but on an individual assessment of the child's emotional, psychological and cognitive capacities. This approach might provide an answer to the debated question whether assent should require the child's signature on a form, similar to informed consent. According to this line of reasoning, the individual development of the child determines the appropriate way of documenting the assent (Miller & Nelson, 2006; Samuel et al., 2008; Giesbertz et al., 2014). Yet individual development as a determinant for the level of assent faces some difficulties that are quite similar to objections concerning the so-called subjective standard for adult informed consent. Beauchamp and Childress (2013) state strikingly: "patient often do not know what information is relevant for their deliberations, and we cannot reasonably expect a doctor to do an exhaustive background and character analysis

of each patient to determine the relevant information" (p. 127). Likewise, the employees of the Living Biobank cannot be expected to assess perfectly the child's capacities to understand the information disclosed and the related capacity to translate this information into a deliberated assent. This is why there need to be some kind of standard based on the child's age or school level or other types of objective starting points. Otherwise the assent procedure will be too arbitrary, and in that case assent cannot promote and protect the values mentioned above. Nevertheless, an individual assessment of the child's capacities can be very useful for fine-tuning of the objectively determined standards.

Although protection from harm is a crucial element in research ethics in general, this subject is especially emphasized when it comes to research projects involving children. Ethics review boards are responsible for weighing the envisioned benefits and risks for every research project involving human subjects. In pediatric research, however, the risks are considered with more caution, as the participants are particularly vulnerable as a result of their limited competence and understanding. Therefore, additional to the requirement of parental informed consent, ethics review boards should take this vulnerability into account. It affects the level of risk that is deemed proportional to the envisioned benefits of a biobank. Moreover, the establishment of pediatric biobanks is ethically justified only if it is likely to yield results that cannot be achieved using adults. This is the so-called subsidiarity principle (Hens et al., 2013). This subsidiarity principle should be considered carefully also with regard to the inclusion of participants in the Living Biobank. A difference between organoids and the biological samples stored in more conventional biobanks is that organoids are made of stem cells. The HUB foundation should formulate clearly not only on what aspects pediatric organoids are necessary but also why this organoids cannot be produced out of adult stem cells. Relevant here is that many pediatric diseases are based on innate rather than adapted conditions so it is at least questionable on a theoretical level why stem cells of children have to be used instead of stem cells of adults suffering from pediatric diseases (such as cystic fibrosis). There might be good biomedical reasons to do so, but those reasons have to be provided by the researchers. Moreover, the subsidiarity principle is subject to proportionality considerations itself. There may be research that can be performed on adults, but yield better results if children are used. The research institution, for example the HUB foundation, should inform the ethics committee about this considerations. Ethics

committees can only make a deliberate and well-balanced decision once this information is on the table.

7.2 Storage and use

Once samples of children are stored into the biobank, they will often remain there for years. Throughout these years, a child grows up. It is very well possible that the attitude of the child towards the research changes or that the child disagrees with a decision its parents made at some earlier point in time. So a child might want to withdraw from the research at some point. As for research subjects in general, minor participants have the right to withdraw from a study without any costs (WMA, 2013). Although complete withdrawal might be infeasible because the samples can be analysed to data that is used in a way that cannot be reversed, there seems to be consensus that children have indeed such a right to withdraw from the biobank research (Holm, 2005; Ries, 2007; Samuel et al., 2008).

Another issue that arises during the time that the pediatric organoids are stored and used is whether a minor participant should be asked to re-consent when she reaches the age of legal competence. This is a different issue that withdrawal, as re-consent requires not only the right of the participant to contact the researcher and demand a withdrawal but also that the researcher contacts the participant and asks whether that person is still willing to participate. To the letter the word re-consent is not carefully chosen, although frequently used in literature. Since the child was not able to give consent at an earlier age, it will give consent for the first time. There seem to be a tendency among ethicists that (re-)consent is ethically desirable (Samuel et al., 2011; Hens et al., 2013), yet others have asserted that re-contact and a possibility to withdrawal is sufficient (Wilfond & Diekema, 2012). This point has to be considered carefully, as a duty to re-contact grown-up participants and ask for consent would imply a significant burden and responsibility for researchers and research institutions. This requirement can be logistically very difficult to meet since it entails that participants are contacted years after they abandoned the samples (Hens et al., 2013) Yet it can be contradicted by pointing out that it is the researcher's responsibility to keep her card-box updated (Samuel et al., 2011).

My argument here is basically an extrapolation of the argument Soren Holm (2005) uses to argue in favour of a right to withdrawal: "there is something wrong about making a decision

irreversible that could just as well be reversible at the point when the child reaches decisional competence" (p.22). He builds his argument on the right to an open future argument that has been drawn up by Joel Feinberg in the early 1990's. This argument comes down to the moral statement that it is wrong to limit the number of options children have in their future on the basis of their parents' (or other representatives) decisions unless it is necessary to limit this options, as children can develop distinct preferences and values (Feinberg, 1992; Holm, 2005). Since the Living Biobank covers a wide range of research possibilities, it is very well possible that this research does not fit in with the grown up's child individual values. This is a strong plea for a right to withdrawal for grown-up participants who have not been able to give consent earlier. But does it also imply a duty to actively seek contact and start a full informed consent procedure? Two things are worth noting here. First, in order to overcome the scenario that a legally competent child does not know that her biological samples are stored in the biobank, re-contact is a key component of a withdrawal as well as an informed consent procedure. A grown-up participant might have forgotten about the biobank contribution entirely, and especially when the inclusion took place at a very young age she might not be informed by her parents at all for whatever reason. So to make withdrawal an actual option, it is necessary that the researcher (re-)informs the participant. This counters much of the hesitance on the side of the researchers, since the logistical objections to re-consent as opposed to providing merely an option to withdraw are refuted by this observation. Note that there is an essential difference here with an option to withdraw for adults who have consented with their contribution to the biobank. In the latter case, knowledge of the biobank participation can be assumed to some extent, since legally and morally competent persons have given their informed consent. Although it is morally desirable that the research institution provides the contributors with recent updates on the research performed, the researcher might expect from the participant that she has not forgotten about the biobank at all (and otherwise this lies within the scope of the participant's own responsibility). However, children still incompetent of giving informed consent cannot be expected to remember and understand all this.

Even if logistical doubts to re-consent seem to be partly inappropriate, a researcher could still insist on adequately informing the participant and providing a possibility for withdrawal rather than seeking consent. One could argue that the possibility of withdrawal does not

close-off the options of the participants concerned. Once the grown-up participant finds her contribution to the Living Biobank inconsistent with her own values, nothing hinders the participant from withdrawing. Arguments used in the adult debate to argue in favour of an opt-out procedure could be used here as well: the research institute does not infringe in the grown-up participant's autonomy as all her options are still open. However, similar to analysis in the chapter about informed consent: the scope of the Living Biobank is too broad to be eligible for an opt-out procedure. This large number of applications and the extended time period that the organoids will be used make it very well possible that the research will indeed be inconsistent with the participant's values.

It is important to notice that the participant concerned has not given informed consent at an earlier point in time. Her parents have, and she gave some kind of assent (depending on her age), but this is substantially different than informed consent provided by the participant herself. Parental consent combined with the child's assent is not a full substitute for informed consent. It is the best option if informed consent is not feasible, but cannot provide an equal warrant that the research is in line with the participant's own values. The parental consent and assent combination has to be considered a temporary license to use the child's material as long as this young person cannot give informed consent herself. As soon as the child is competent of making an autonomous decision , this provisional license expires as the underlying reason to rely on the parental consent (i.e. that the child cannot make an autonomous decision while the tissue of the child is needed for important research) is no longer valid. For this reason, obtaining informed consent once the participant reaches a competent age can be considered a moral obligation of the Living Biobank. The default proposed here is withdrawal rather than participation. Yet, empirical research might provide an argument to shift this default. This kind of research might indicate that this informed consent condition results in a tremendous loss of participants, while a vast majority of these participants drop out due to indifference or passivity instead of conviction. In that case, principles of beneficence and reciprocity can justify a shift of the default towards continuation of participation. This is because the impairment of the research and its potential benefits would be extensive while the participants' autonomy is hardly promoted.

7.3 Return of results

The issue whether potentially important results should be communicated to participants is also more delicate in the case of biobanks using children's samples. Even if the issues that are identified for adults are solved, several questions remain unanswered when it comes to children. Parents give informed consent as representatives of their children to participate in the research. As mentioned earlier in this thesis, the question whether a person wants to receive information about the results can be included in the consent form. In many cases this strategy may be a satisfying solution for adult participants, but it faces a complexity in case of pediatric biobanks. The parents might refuse, for whatever reason, to know that their child has a severe condition. Moreover, it is very well possible that the parents want to be informed about their child's future health hazards, while the child regrets this knowledge once grown-up. Hens and colleagues (2013) argue, following the European Society of Human Genetics, that the onset of the condition is ethically relevant for the researcher's decision whether participant and parents should be informed. If it concerns an early-onset condition, the researcher has a moral obligation to communicate the results. If the information reveals an disease that has an adult-onset, the return of results should be postponed till the participant reach the age where it can make competent decisions herself (Hens et al., 2013; Borry et al., 2009). This position however is opposed by the already mentioned policy statement of the AMCG. The latter group asserts that the benefits of having knowledge of adult-onset diseases justify this sort of feedback (Green et al., 2013). There was ethical consensus that such results are not communicated until the grown-up child consents with feedback on these results, and the already mentioned right to an open future gives a good reason for that. The AMCG seems to deviate from the former consensus without giving a reason for that shift. Yet this shift would implicate that the future autonomy of the child will be jeopardised before this autonomy could even fully develop (Feinberg, 1992; Bredenoord, 2014). Bredenoord (2013) and colleagues call this an infringement of the "anticipatory autonomy right" (p.2). The biobank has a duty (at least prima facie) not to violate the child's negative right make her own autonomous decisions once she reached competent age (hence: anticipatory).

Currently, there is no consensus in literature on whether parents have the right to keep silent about the information, and what the related implications for the researcher entail

(Samuel et a., 2008; Samuel et al., 2011). This issue is even more complex than similar cases in clinical care where parents refuse essential therapy for their children. In the latter cases, a clinician can ask a judge to lift the parental authority in order to be able to provide crucial care. The biobank researchers, however, are not the persons who are responsible for providing this care. The results may reveal that a child has an early-onset and treatable condition, yet sharing this knowledge with the parents does not guarantee that there will be any action. So, in order to protect the child from potential harm, it may be required to inform not only the parents but also the child's general practitioner or paediatrician. This should be a sine qua non condition in the informed consent procedure. Parents either consent with feedback to parents and physician on results that reveal an early-onset and treatable disease or refrain from participation. This limitation of choice can be justified because the alternative is morally undesirable: the researcher has information that could save the life of a child but she is not allowed to share this information with the relevant persons. Besides, a sine qua non condition will not have a significant impact on the number of participants as there will not be many parents who refuse to know such life-saving information.

Chapter 8: Conclusion

The aim of this thesis was to develop an ethical framework for the Living Biobank. This biobank stores so-called organoids: chunks of living cells that resemble closely in-vivo human tissue, such as liver, pancreas and intestinal tissue. These organoids are being developed from stem cells obtained from residual tissue. The research done with these organoids includes fundamental biomedical research, disease-specific research and pharmacological studies. In this thesis several ethical issues have been identified for biobank research in general and the Living Biobank in specific. These issues can be classified into categories reflecting the different stages of biobank research: inclusion of participants, storage and use of the organoids, and the feedback of results. In addition there are ethical requirements that play a role in all these phases. Moreover, the pediatric branch of the Living Biobank (that stores organoids obtained from children's stem cells) encounters some specific ethical issues.

What stands out for all these categories is that the ethically relevant differences between the Living Biobank and traditional biobanks are based on the following properties of organoids. Organoids are (1) living tissues cultivated from participants' stem cells, (2) stored for a very long/ virtually infinite period of time and (3) can be used for a wide variety of known and unknown possibilities.

When it comes to the inclusion of participants and the collection of their stem cells from residual tissue, informed consent is a major issue. As specific consent is not a feasible for the Living Biobank because the future research applications are typically unknown, broad consent can be considered a justified alternative. The specific considerations for the Living Biobank implicate that this biobank is too controversial to justify an opt-out procedure. This debate is closely linked to the debate concerning the feedback of research results. It has been recommended in this thesis that foreseen and incidental results are returned to the participant if and only if the participant consented to that feedback. The research institution has a special moral obligation to provide this feedback on scientifically valid and reliable results, at least if these results are potentially life-saving. Since the scope of future research applications is very broad, re-evaluation of this obligation to feedback might be necessary if the nature of these results changes dramatically. It has been pointed out that it is over-demanding and undesirable to provide feedback on an extensive list of conditions, thereby

using the biobank more as a screening tool. Yet there might be a grey area of results that are vitally important, although not life-saving, for the participant. More ethical research has to be done to determine the specific content of the researcher's obligation with regard to the latter results. This issue is currently at the heart of the ethical debate on biobanks, and the outcomes of this debate are important for the Living Biobank as well.

With regard to the pediatric branch, it has been argued that a combination of parental informed consent and the child's assent is required when the child's tissue is included into the biobank. The assent is a tool for adequately engaging the child, not a replacement of informed consent as a warrant for an autonomous decision. Therefore, the child has to provide informed consent for participation when she reaches competent age. The nature of the assent procedure should be adjusted to the child's individual abilities. Yet some standard based on general development levels might be needed to avoid arbitrariness in this procedure. More research has to be done to define a useful and morally justifiable framework for the assent procedure. Regarding the feedback of results, it is stressed that only life-saving results on early-onset diseases should be communicated to parents and the child's physician. This is a sine qua non condition in the informed consent form that parents have to sign.

In general, structural governance and oversight is needed. This applies to biobank research in general, but the mentioned characteristics emphasize the importance of an equipped ethics committee that has the expertise to supervise the wide range of the biobank's activities. The absence of national and international legislation underlines the importance of solid oversight. Such an ethics committee should safeguard all the ethical considerations mentioned for the different stages. In addition, the committee should pay attention to the balance of risks and benefits, the involvement of participants as partners in research, and the preservation of public trust.

Concerning the storage and use of the organoids, the Living Biobank has to comply with privacy requirements that are similar to other types of biobanks. With regard to potential commercial applications of the organoids in the biobank, the mentioned properties point out that caution is needed. Participants may consider the organoids as parts of their body that live on ex-vivo. This relational value of organoids has to be taken seriously and respect for

the participants dictates that organoids cannot be submitted to unlimited commercialisation. Yet this does not exclude (financial) compensation for the use of organoids or derived data by third parties. Further, ethical research could provide more clarity on the organoids' relational or even intrinsic properties that make those organoids worth protecting. This requires a comprehensive analysis of theories on moral value and moral status and should provide an answer to the question what the normative implications of these theories are with regard to the commercialisation of organoids.

Empirical research may contribute to the debates addressed in this thesis for several reasons. This research could inform the ethical debate (Cornelis et al., 2014) by clarifying the interests of participants (and their parents). This can be valuable information because (inevitable) assumptions are made in this thesis regarding the participants' preferences. For example, empirical research might show that participants consider a broad consent as too nonconcrete or vague to make an autonomous decision. This has consequences for the ethical evaluation of broad consent applied to the Living Biobank. To give another example: qualitative or quantitative research could point out what feedback most participants prefer to receive.

A distinct application of the organoids made for storage in the Living Biobank is to use them as a clinical research tool. In this case, the organoids are used to determine the most effective therapy for the individual patient by testing the medicines on the organoids before in-vivo administration. Concerning this specific application, two specific issues have been mentioned in this thesis, i.e. that the researcher has to be apprehensive of a therapeutic misconception and that physical risks have to be taken into account. Yet more work is needed here to identify all the ethically relevant issues. This type of research is full-blown clinical research, and has to be evaluated within the broad framework of clinical research ethics.

The conclusion of this thesis is that the Living Biobank faces ethical challenges that have already identified for other types of biobanks, yet the specific nature of the organoid biobank stretches these issues further. Although this does not bring about a revolutionary shift in biobank ethics, the Living Biobank combines morally sensitive characteristics of previously established biobanks, such as genetic and cell-line biobanks. This concerns the

observation that organoids are living human mini-organs that are stored during an indefinite period of time and can be used for an numerous (and partly unkown) research applications. The Living Biobank and the underlying organoid technique is a promising development in contemporary biomedical research. Yet restraint and caution is needed regarding the different stages and applications of the Living Biobank because of the conjunction of ethical sensitivities.

Summary

The most important recommendations for the Living Biobank

Inclusion of participants

1. Use broad consent as an alternative to specific informed consent since the latter is not feasible due to the nature of the biobank.
2. Include participants using an opt-in procedure, since the wide scope of possibilities and the indefinite time period of the Living Biobank make it too controversial to use an opt-out procedure.

Storage and use

1. Protect the participant's privacy by coding personal information.
2. Do not sell the organoids, although compensating prior investments may be justified.
3. Although organoids are cultivated research tools, be aware that people might consider them as parts of their body.

Return of results

1. Communicate aggregate results to the participants in a way they can understand.
2. Give feedback on individual results if they are potentially life-saving to the participant or her offspring.
3. Include a restriction clause in the informed consent form that the feedback procedure will be reconsidered if diseases can be revealed that nor the researcher nor the participant could expect at the moment of inclusion.

Over-arching requirements

1. Organise structural oversight through an ethics committee that has the mandate to adequately safeguard all the relevant ethical requirements.
2. Make sure the ethics committee has the expertise to govern the national and international exchange of organoids and derived data.
3. Ensure public trust
4. Foster interaction between participants and researchers as partners in scientific research.

Pediatric branch

1. Adjust assent procedures for inclusion of children on development levels but use standards as a reference point.
2. Obtain informed consent once the child has grown-up to complement the previously obtained assent and parental consent.
3. Only give feedback on life-threatening diseases if it concerns early-onset conditions.

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