TAMPERE UNIVERSITY OF TECHNOLOGY

CYNTHIA FROMMELT

# BIOBANKING AND SUPPORT FOR PERSONALIZED MEDICINE: A MODEL FOR SUCCESS?

Master of Science Thesis

Examiner: Professor Ilkka Korhonen
Examiner and topic approved by the
Faculty Council of Natural Sciences
on 05.03.2014

# ABSTRACT

TAMPERE UNIVERSITY OF TECHNOLOGY
Master's Degree Programme in Biomedical Engineering
**FROMMELT, CYNTHIA: Biobanking and support for personalized medicine: A model for success?**
Master of Science Thesis, 55 pages
June 2014
Major: Medical Informatics
Examiner: Professor Ilkka Korhonen
Keywords: biobank, biobanking, missing elements, personalized medicine, triangle model

Personalized medicine is the natural evolution of medicine. More specific descriptions of diseases and more precise characterization of patients are said to make it possible to administer better treatment.

In this process towards more effective personalized medicine, biobanking could play a crucial role. It could allow for storing a large number of high quality biosamples linked to personal and medical data of the sample donor. The stored material can be retrieved and used in research to detect actionable defining molecular characteristics to classify patients in subgroups for certain diseases. Once proven in a clinical setting, these molecular characteristics can be used to enable more effective targeted prevention, diagnosis, and therapy.

The triangle model which is proposed in this thesis shall provide a guideline for biobanking and research to better support personalized medicine. It consists of three components – public, biobank, and research component – each with its respective subcomponents.

Parts of the triangle model have been discussed in recent literature but some key issues have not been addressed yet. These missing points are extracted in this work and include: 1) the availability of a complete governance plan, 2) proper standards for documentation and tracking of samples for quality control, 3) the use of electronic forms, and 4) proper standards for reporting in scientific journals.

A guideline as provided by the triangle model would be useful for biobanking to become a model for success for the support of personalized medicine. However, due to the relevance of the topic, new findings and developments are made continuously. Therefore, only time will tell if biobanking and research do indeed support personalized medicine.

# PREFACE

This Master thesis was performed in collaboration with the Institute of Biosciences and Medical Technology (BioMediTech) and the Department of Signal Processing at the Tampere University of Technology.

I would like to thank my supervisors Dr. Reija Autio and Professor G. Steven Bova for their time and guidance. Thanks to their valuable inputs for the formation of the thought experiment to this thesis I was able to expand my knowledge and enjoy this adventure of research.

I am very grateful to my mom, Olivia Frommelt, for her support during my years of study and for dealing with bureaucracy and finances so that I could concentrate fully on my studies. Thank you for all the help and encouragement along the way. Without you I would for sure not be where I am today.
I'm also thankful to my siblings, my brother Lenard Frommelt and my sister Lara Frommelt, for just being there. Growing up as the oldest of us three definitely taught me a lot for life. Thanks!

Furthermore, I would like to thank my friends for the great times we shared – my "Russian Family" (Lisa, Sasha, and Varya), the MEB group (Alex, Defne, Javier, Lukas, Marlitt, and Paul), and everyone else I met along my way. I'm utterly thankful to you all for the serious and not so serious conversations, the laughter, the stress and study times, and the often needed coffee breaks.

A special thank you goes to Johannes for sacrificing his free time to proofread this work. Thank you for your support, love and care, and for always being there for me, even though you were far away. Your kind words, your humor, and your patience have often served as a recharging source during the research and writing process of this thesis.

Tampere, 11.04.2014

Cynthia Frommelt

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ABN | Australasian Biospecimen Network |
| AIDS | Acquired ImmunoDeficiency Syndrome |
| BBMRI | Biobanking and Biomolecular Resources Research Infrastructure |
| BRISQ | Biospecimen Reporting for Improved Study Quality |
| CAP | College of American Pathologists |
| CLIA | Clinical Laboratory Improvement Amendments |
| ERIC | European Research Infrastructure Consortium |
| IARC | International Agency for Research on Cancer |
| IRB | Institutional Review Board |
| ISBER | International Society for Biological and Environmental Repositories |
| NCI | National Cancer Institute |
| OECD | Organisation for Economic Co-operation and Development |
| P3G | Public Population Project in Genetics |
| RAND | RAND Science and Technology |
| REC | Research Ethics Committee |
| SOPs | Standard Operating Procedures |
| SPIDIA | Standardization and improvement of generic Pre-analytical tools and procedures for In-vitro DIAgnostics |
| SPREC | Sample PREanalytical Code |
| TLCO | Total Life Cycle Cost of Ownership |
| TUKIJA | National Committee on Medical Research Ethics |
| VALVIRA | National Supervisory Authority for Welfare and Health |
| XML | eXtensible Markup Language |

# 1. INTRODUCTION

The vision of developing personalized medicine, a medicine where therapy and medication is based on an individual's unique characteristics in reacting to a disease, is fueled by the increasing knowledge about the molecular basis of disease and health status [1]. This molecular information can be used to highlight differences among patients with the same disease and can be used to predict a patient's response to therapy. Administering drugs and therapy only in cases where patients will actually benefit from them will save money in health care and save the other patients the stress of unnecessary treatment [2].

Personalized medicine and the research to improve personalized medicine are dependent on availability of high quality and well annotated human biosamples [1]. These samples can theoretically be provided by biobanks. Many thereof have been established in recent years [3]. The principle of biobanking includes the collection, processing, and storage of human biosamples and their related personal and medical information [1]. To realize the promise of personalized medicine, biobanking has to be done following standards to safeguard sample quality.

To my knowledge, there exists no structure or model which covers all aspects of biobanking and research that are needed to support personalized medicine. However, due to the demand for interoperability of biobanks, and the development of biobank networks to share data and collaborate in research, the need for a common guideline structure arises.

The aim of this thesis is to develop a model which shows the necessary steps needed in biobanking and research to support the development of efficient personalized medicine. The individual components of the model are identified and parts that have not been addressed so far or need improvement for the model to be usable as a guideline in practice are uncovered.

This thesis is structured as follows. Chapter 2 provides the necessary background information on personalized medicine, biobanking, and how both parts are connected. The main focus is on the triangle model, which is introduced in Chapter 3, listing its components and explaining each of them. Following this is the discussion of parts of the model which are missing from prior reports in the literature and of the situation in Finland in Chapter 4. Chapter 5 summarizes the work shortly and presents future prospects of biobanking and the triangle model.

# 2. BACKGROUND

To fully understand the model presented in Chapter 3, it is important to have some background knowledge. Therefore, I provide basic information on personalized medicine, biobanks, and biobanking in this section.

However, this section does not only include definitions of the most important terms. I also present information on the relevance of personalized medicine, biobanking, and biobanks in the literature. I describe important subcomponents of personalized medicine, the idealized biobanking process, and types and networks of biobanks before connecting biobanking with personalized medicine.

## 2.1 Personalized medicine

There are multiple definitions of the term "personalized medicine" [4–10] but most agree that through it, the right treatment is administered to the right person at the right time [8]. This is a very general motto for personalized medicine and in fact it also describes generally well-practiced medicine [6]. A more detailed description on the definition of personalized medicine is given in the report of the US President's Council of Advisors on Science and Technology (PCAST) in September 2008, where personalized medicine is stated to refer to the tailoring of medical treatment specific to the individual characteristics of each patient [2]. It is further described as the ability to classify individuals into subpopulations, which have different susceptibility to a certain disease or respond differently to a specific treatment rather than creating unique drugs or medical devices for an individual patient. Through this classification, those that will not benefit from the treatment will be spared from expenses and side effects while the preventive or therapeutic interventions can be concentrated on those that will benefit.

According to the PCAST report, personalized medicine is the natural evolution of medicine. Through more specific descriptions of diseases as well as precise characterization of the patients it will be possible to administer better treatments [6]. For precise characterization and classification in subgroups of the population, personalized medicine uses information about the patients' genomes as well as their environment and family history [10].

### 2.1.1 Personalized medicine in the literature

Having the patients' genomes as one of the parts needed to characterize them better, it is not surprising that the enthusiasm about personalized medicine followed after decades of research and the clinical translation in human genetics [10]. However, medicine has always been personalized in some way. Doctors have long taken their patients' environment, medical history, and family medical history into account when making treatment decisions [8].

The first paper mentioning the term "personalized medicine" was published in 1971 [11]. Another one followed in 1990 [12], however there were no further publications on that term until 1999 [13]. As it can be seen in Figure 2.1, from 1999 on, more and more papers regarding personalized medicine were published.

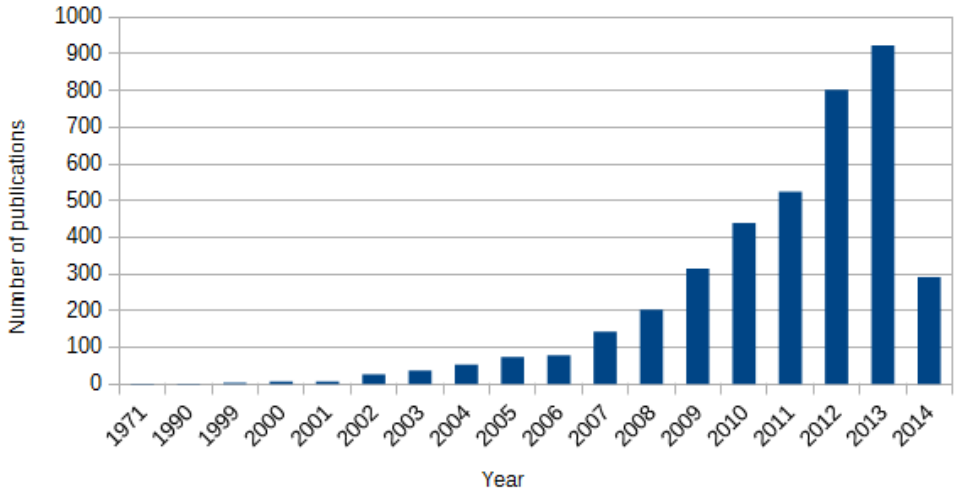


Figure 2.1: Academic publications per year on the term "personalized medicine" in the PubMed database. (Data of 08.03.2014)

The Human Genome Project was completed in 2003 [14] and provides information on the human genomic sequence and on the sequence variations [15]. With this information, the interest in personalized medicine increased and with it the research in genomic medicine as well as in pharmacogenetics. However, the general interest in this topic was not only sparked due to the promise of improved patient care and disease prevention but also due to its potential to have a positive impact on health care cost and medical product development [2].

### 2.1.2 Personalized genomics

While it is not the only component of personalized medicine, personalized genomics plays a vital role in its development because genetic profiling is an important method

used to classify individuals into subgroups [10]. Natural variations found in the human genome can influence each individual's risk for a certain disease [4]. The most important impact of these variations is how they affect the metabolism of an individual or tumor development. According to the behavior of the metabolism of an individual, the subtype of the disease can be determined. This knowledge can help physicians to select individual treatments and dosing of drugs leading to practical personalized medicine [4, 8].

To classify the subtype of a disease it is important to analyze certain biomarkers [4]. A biomarker is defined as any substance or biological structure in the human body that can be measured and may influence, predict, or explain the occurrence or outcome of a disease [16]. Because of their characteristics, biomarkers are gaining importance for personalized medicine in applications such as diagnosis, prognosis, and selection of target therapies. Mature genomic technologies and decreasing costs of genomic sequencing are helping in generating a flood of biomarkers and companies offering biomarker services [5]. A good way to improve medicine and progress towards personalized medicine is to improve the technology and techniques to detect biomarkers in a way that a physician can check a patient's genome in an easy, fast, and cheap way prior to prescribing a particular drug or treatment [4].

### 2.1.3 Personalized cancer medicine

Personalized medicine is becoming a viable option in oncology through enabling more personalized cancer treatment. This application of personalized medicine in oncology is often referred to as personalized cancer medicine. [5]

Oncologists have long understood that individual patients with cancer have different clinical presentation, prognosis, tumor response, and tolerance to treatment. However, only with the recent progress in research and the understanding of the variation in the human genome, scientists and clinicians have started to understand the heterogeneity of cancer. This knowledge has moved the field of cancer therapeutics in new directions. These directions include developing therapies that aim to break molecular pathways in tumors responsible for cell growth and survival, creating a molecular profile of tumors to have a better chance to assess prognosis and likelihood of benefit from treatment, developing single- or multigene expression signatures of response or resistance to certain drug treatments, and developing immunological approaches specific to an individual tumor such as vaccine therapies. [17]

The individual gene expression profile can be used together with a statistically defined algorithm to determine a recurrence score which will show if the patient is likely to benefit from additional accompanying therapy. Patients with low recurrence scores, giving them good prognosis, can be spared unnecessary therapy and the health care system can save the cost for the treatment. [6]

As cancer biology research continues and genome profiling activities advance, more will be known about cancer and tumors and more drug targets will be revealed. Personalized cancer care is becoming reality in clinical assessment and management of patients. These two factors fuel the expectation to improve treatment efficacy through better defined targets, reduce toxicity through individual drug dosage, and minimize cost through avoiding redundant therapy. [17]

### 2.1.4 Drug administration

Another big opportunity for the growth of personalized medicine is the development of drugs. Long did researchers believe that there is no progress in personalized drug development because large pharmaceutical companies were not interested. They had their blockbuster model where one drug has to fit for everyone and research for individual metabolisms was not part of the plan. Only with the technological advances that simplified and cheapened genomic research, and increased the availability of biomarkers, pharmaceutical companies became interested. [5]

Personalized medicine is especially important when looking at the standard drug treatments. There are big variations depending on the different diseases treated, however, between 30% and 70% of the patients will not respond to a given drug treatment [6]. While many different factors could in fact influence the drug response, it seems highly probable that individual drug metabolism rates and natural variations in the disease characteristics are also contributing. Therefore, the development of personalized drug treatment will make drug use safer because an accidental overdose due to metabolism differences is prevented [9].

## 2.2 Biobanking

In this thesis, a biobank is defined as a collection of human biological samples and their associated data, stored in an organized form for the purpose of research [18]. Included in the data stored with the samples are clinical information taken from the person's health record as well as personal, lifestyle, behavioral, environmental, socioeconomic, and demographic information [19]. Biobanking includes the process of collecting, processing, handling, storing, and eventually distributing and sharing of samples and their associated data with researchers accessing the biobank [20, 21].

The sample, often referred to as biospecimen, can be of a wide variety such as cells, tissue, blood, or DNA for example. The type of sample that is collected usually depends on the purpose of the collection. [19]

### 2.2.1 History of biobanking

The first time the term "biobank" appeared in the literature was 1996 [22], not even 20 years ago [23]. As seen in Figure 2.2, only about 10 years later the number of papers containing the terms biobank or biobanking increased significantly.

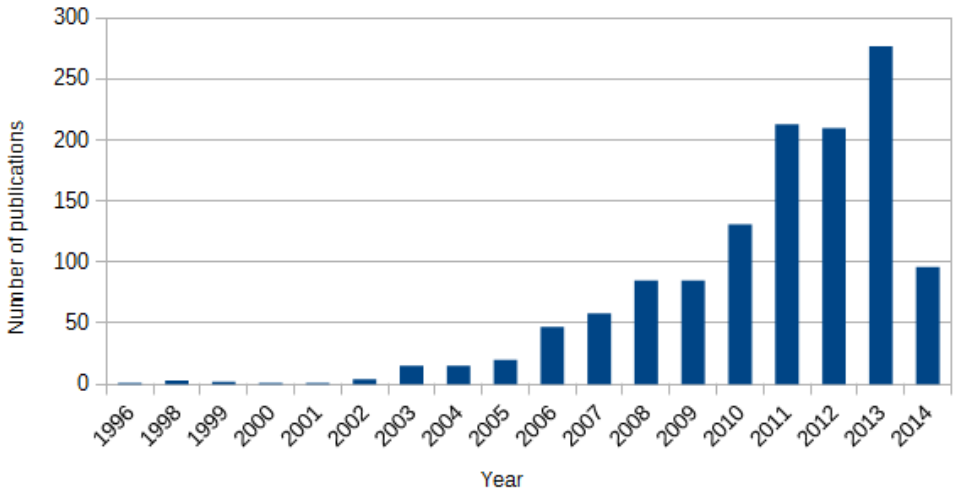


Figure 2.2: Academic publications per year on the terms biobank or biobanking in the PubMed database. (Data of 08.03.2014)

The process of storing human biological samples and associated clinical and research data, however, is not a recent development [24]. Collections of samples for research have been curated by researchers for more than a century. The first systematic collections of human cells and tissues began in the 19th century [25]. Those early biobanks, as they were developed in Europe for example during the 1930s had different purposes and operational mechanisms [26]. Only in the late 20th century were biobanks initiated that allow for coupling of the biological and genetic data with the general patient data [25]. The term biobank has come into use as the scale of such collections has vastly increased and the locus of organization has expanded to include individual research groups, entire institutions, and in many cases whole countries [27].

Two developments in life science encouraged the creation of "industrial size" biobanks currently in place and development. First, there have been methodological breakthroughs in molecular biology which offered new possibilities for medical research [26]. Especially in the understanding of genomic information and genetic mechanisms in diseases, it became important to be able to store large collections of samples together with the associated health data and clinical activities over time [28]. Second, developments in information and robotic technology, as well as

bioinformatics, have provided methods to collect and analyze large data and sample numbers [26].

### 2.2.2 Process of biobanking

The storage of samples and their associated information is only one part of the biobanking process. A simplified version of the most important steps of an idealized biobanking process and the interactions with the biobank can be seen in Figure 2.3.

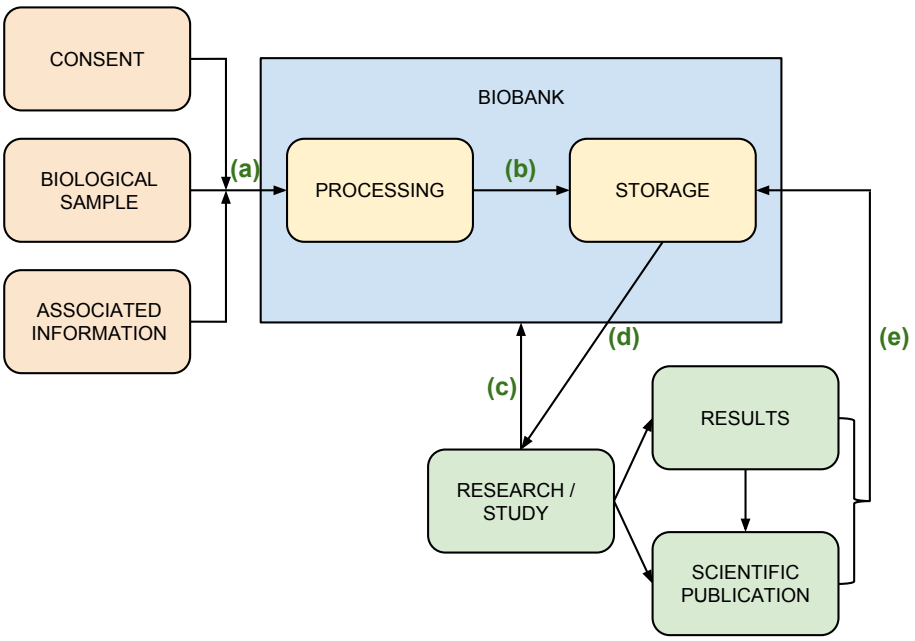


Figure 2.3: Systematic path of the biological sample and its relevant information. The biobanking process starts with the collection of the sample, associated information, and the consent (a). Then the samples and information are processed and stored (b) until needed. Researchers query the database of the biobank (c) and ask for samples that will be delivered to their laboratory (d). After concluding their research, the results and possible links to scientific journals are stored in the database (e).

Before samples can be stored, they have to be collected from the prospective sample donor, which can be a patient at the hospital or a volunteer. In some but not all instances, biobank collections are driven by researchers' needs for specific studies, and in many instances collections occur to support population-based research which often cannot be specified completely in advance. [29]

At the point of sample collection, an appropriate form of consent is required, depending on the type of study which is conducted [30]. Informed consent is seen as protecting the autonomy of the participants and allowing them to exercise their fundamental right to decide whether and how their donated samples and the associated data can be used in research. According to the Declaration of Helsinki, only

voluntary participants are allowed to enroll in medical research and they must be sufficiently informed about the research [29]. To assure this, the informed consent has to contain information about the aims and methods, any possible conflicts of interest, the funding sources, institutional affiliations of the researcher, the expected benefits and the potential risks or discomforts of the study, post-study provisions, and any other aspects of the study that might seem relevant. The participants have to be additionally informed about their right to refuse to take part or withdraw their consent at any time without giving a reason. The whole content of the informed consent has to be understood by the participants and signed to become valid.

Once the consent is given and the samples and information are collected, they are labeled with a unique identifier in the database and then transferred to the biobank which is depicted by (a) in Figure 2.3 [31]. This early labeling of samples should assure that there is no mix-up or accidental mislabeling later on. The labeling also makes it possible to disconnect personal information that is not relevant for research but necessary for possible later identification of the donor from the sample and health related information. Often, the collected samples are used to answer to research questions arising after the initial study, or certain tests could be rerun in the future with new technology or techniques [32]. To reduce the number of freeze-thaw cycles a sample is exposed to, it is divided into separate aliquots that are then labeled and frozen individually. Furthermore, depending on the purpose of the study, the aliquots are not necessarily just split up parts of the same material but they can also hold different material types, such as DNA or RNA, from the initial sample.

After processing, the samples are stored in a way appropriate for the sample material and the intended research purpose which is marked in Figure 2.3 by arrow (b). In most cases, the aliquots are stored in -80 °C freezers since only few biomolecules other than DNA preserve well at only -20 °C. Many of those -80 °C freezers in bigger biobanks are automated, so that the stored samples are not disturbed by temperature changes whenever the door is opened to retrieve a sample. An automated freezer works like a vending machine. The sample is selected from the outside, a mechanical arm then picks it up from the shelf and releases it in a hatch. [33]

No matter in what way the samples are stored, what processing they went through, or into how many aliquots a sample was divided, everything has to be documented and stored in the database of the biobank linked to the unique identifier of the collected sample. This information is important for sample tracking, quality assurance, and specimen availability for future research [32]. Researchers may query the database of the biobank through an interface shown in (c) in Figure 2.3 [34]. They can get additional information about a sample from their study, see if more aliquots of a certain kind are available, or request a sample for research.

The ordered sample is then retrieved from the storage, packed and sent to the research laboratory, marked by (d) in Figure 2.3, and again the documentation linked to the sample has to be updated.

The results are fed back to the biobank after the research was conducted. This is shown in Figure 2.3 by arrow (e). It is important since genetic and genomic research might reveal information and results of clinical relevance for an individual [35]. Although it is not common practice today, efforts are underway for participants in a study to be given an option to be informed about the general outcomes and results of the study [29]. To simplify a possible recontacting of those donors and help for future research, the results are linked to the original unique identifier in the database [24]. If the results of the study are to be published, also these scientific publications should be linked to the used samples. This will help to provide detailed information on the biospecimen and its processing, to make the published results comparable and the study repeatable [36].

### 2.2.3 Types of biobanks

Biobanks are often developed according to the research question at hand. This results in a variety of several different types of biobanks such as disease-oriented biobanks, population-based biobanks, tissue biobanks, biobanks for clinical trials, case-control biobanks, biomolecular resource centers that store antibodies, cell biobanks for cord blood or stem cells, and more [37]. However, many of these biobanks are similar in their structure and therefore two major formats of biobanks can be distinguished; population-based and disease-oriented biobanks, and all the other biobanks form subgroups to these categories [38].

#### Population-based biobanks

Population-based biobanks store biological samples and their associated data from consenting volunteers from a defined population. The collections are usually used for studies about common diseases in a population or the given risk factors for a disease. The main idea behind population-based biobanks is to screen the population and later on allow researchers to study the onset of a disease from the collected data over time. To achieve this goal, the typical sample types that are collected are blood and isolated DNA, together with primary information on data about the family history, lifestyle, demography, and environmental exposures. [38, 39]

It is possible to find biomarkers that are responsible for a disease already present in the healthy individual. This makes population-based biobanks an important tool for preventive medical programs. Furthermore, the observation of occurrence and progression of a certain disease in a specific population subgroup makes it interesting

for different researchers. However, establishing large population-based biobanks is expensive and challenging. [38]

Another issue is the continuous personal involvement of the participants. There need to be several follow-up collections as well as accurately updated health information. Without this information researchers are not able to make a valid prediction on possible biomarkers, drug response or efficacy. [38, 39]

#### Disease-oriented biobanks

By comparison, disease-oriented biobanks contain collections of tissue, cells, blood, or other body fluids of a variety of diseases and associated healthy controls. Together with the sample, biobanks of this type primarily store information from the health records of the participants. [18, 38, 39]

Disease-oriented biobanks can be very specifically focused on only one disease such as AIDS, diabetes, or any type of cancer or they can be focused on only one sample type such as tissue banks or cell banks. Such biobanks are usually connected directly to a hospital unit or research laboratory specializing in that field. [28]

The importance behind disease-oriented biobanks is that they offer a chance of comparing different stages of a disease from one participant. Furthermore, they allow researchers to compare a participant with a disease with healthy controls or to compare the forms of a disease for different patients at a certain stage with each other. By doing this on a molecular level researchers can make novel findings on the disease characteristics as well as identifying biomarkers and possible targets for drugs. [38, 39]

### 2.2.4 Networks of biobanks

Biobanks nowadays exist on every continent, including Antarctica [40]. Having samples in so many individual biobanks leads to a fractioning of the overall donated materials available [38]. This can be problematic, since large numbers of samples are needed for statistical significance of findings. Another issue is that if one biobank, even if it were a big institution itself, would have to collect all these samples, it would take years if not even decades to complete. Furthermore, for some studies several follow up collections of samples have to be made so that the actual research cannot start earlier than 10 to 15 years after starting the collection. Such a long collection interval can have negative influence on the results, since new scientific insights and changing techniques as well as the aging of the samples play an important part in the outcome of the study [20, 41].

One solution to the problem is data sharing and working together of several biobanks, forming biobank networks. A survey published in 2010 [42] shows that

biobanking already is a highly networked activity both in Europe and worldwide. Especially in Europe there is a strong collaboration between biobanks, shown by the result of almost 90% of biobanks interacting with at least one other group. Already more than 50% of European biobanks share international data and samples regularly, and one third of them have formed permanent partnerships with other local, national, or international biobanks. [43]

This cooperation of biobanks leads to an increase in statistical power and sample size [28]. Especially smaller biobanks can increase their power by joining together in networks to conduct research studies. Another advantage of biobank networks is that the probability of sample usage increases. There are many samples and associated data collected that are stored but never used [44]. This is often due to only few people knowing about those samples. By working together in a network and providing a searchable catalog of all the samples in the biobanks of the network, researchers will easier find fitting samples for their research.

However, biobank networking also brings up some challenges that need to be overcome. In these new global networks, biobanks are the nodes on the information flow between institutions and researchers that make data and sample storage, organization, and reconfiguration for different research projects possible [45]. To achieve this seamless interaction between biobanks, it is important that some harmonization for their procedures for collecting and storing data and samples exists [20]. Only by harmonizing standards and following general ethical and legal rules, samples from different biobanks in the network render comparable and are usable in the same study. This interoperability leads to a more efficient structure to pool, analyze, and share biological samples. It will allow the scientific community to gain access to samples of comparable quality and more complex amounts of information.

One of the largest biobanking networks in Europe is the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), which is funded by the European Commission. Its goal is to provide comprehensive collections of biological samples from Europeans, linked with continuously updated data on health, lifestyle, and environmental influences of the sample donors. Through the creation of a single centralized infrastructure, it will increase the scientific excellence and research efficiency in Europe, ensure competitiveness of European research, and attract investments from outside of Europe. The BBMRI will consist of biomolecular resources and biobanks of different formats as well as harmonized standards to simplify data and sample exchange. Since the end of the preparation phase in early 2011, BBMRI has evolved into a consortium of 54 members and over 225 associated organizations from over 30 countries. [46]

## 2.3 Biobanking in personalized medicine

The evolution towards personalized medicine largely depends on the availability of research data. Its promise of customized treatment for each individual is seen to enhance patient care and reduce treatment costs by focusing on personal genetic data [47]. As described in Chapter 2.1, one of the important factors for success of personalized medicine is biomarker research. The search for biomarkers bridges multiple disease areas, clinical specialties, and drug development. Yet, it is dependent on large numbers of high quality samples [48].

Biobanks are the tools to be used to provide the required large collections of samples linked to sample related information as well as personal and medical information on the sample donor [46, 47]. Furthermore, biobanks also enable linking clinical outcomes to stored specimen, allowing clinical personal a much broader assessment of the genetic variations across a range of conditions [49]. Therefore, researchers believe that biobanks can play an important role in the development of personalized medicine by providing reliable samples and information [28, 39].

# 3. TRIANGLE MODEL

As previously mentioned, biobanking could be essential for the development of successful personalized medicine. Based on literature review I have created the triangle model shown in Figure 3.1. It presents the components to be considered when developing biobanking as support for personalized medicine. It displays a triangle around biobanking, research, and personalized medicine together with its three support components.

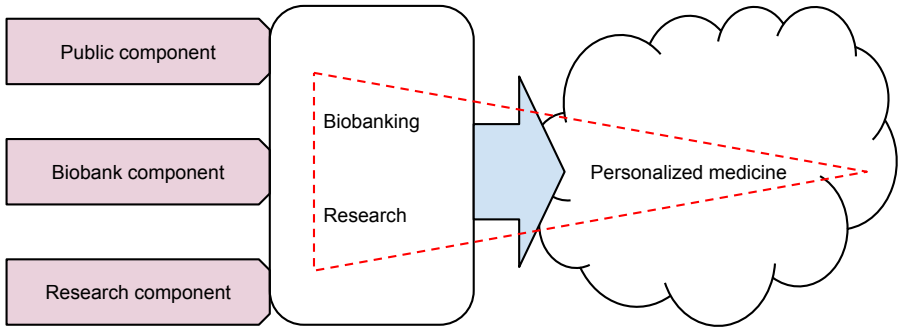


Figure 3.1: Triangle model – depicting the three driving components that ensure biobanking and research are leading to personalized medicine.

The presented three support components in the model are the public, biobank, and research component. They form the driving force for biobanking and research to lead to personalized medicine. In the following sections, the parts of these three components are evaluated separately in context of supportive biobanking. For each section, first the literature information if available and then my own view about each section is presented.

## 3.1 Public component

The public component is a very important component of the triangle model because a biobank could not exist without samples. These samples need to be voluntarily donated by the public to lay the foundation of a biobank and start the process of biobanking. However, the public does not only play a role in the beginning of the

biobanking process, as its support is also important for further success of biobanks.

As it can be seen in Figure 3.2, the public component of the triangle model consists of two parts, the sample provision and consent. It mainly concerns the prospective participants in biobanking studies and other sample donors.

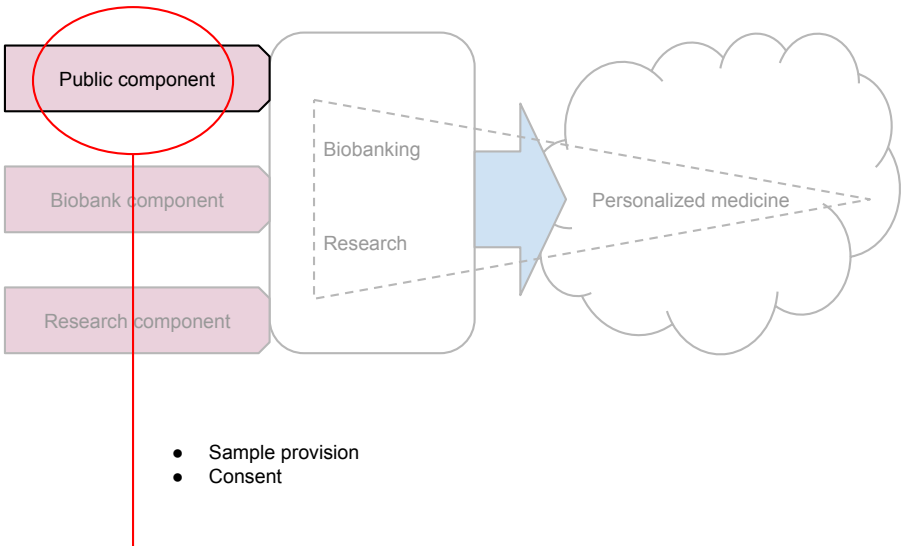


Figure 3.2: Triangle model: detailed view of the public component with its parts.

### 3.1.1 Sample provision

Sample provision indicates the donation of biosamples together with the corresponding personal and health related information. Here I discuss two issues that should be taken into account when talking about sample provision: 1) public education about biobanking, and 2) making donation as easy as possible for the participants. The advantage of education can be seen on the number of volunteers and the time the donation will take as visualized in Figure 3.3.

#### Education about biobanks

To conduct research that is in support of personalized medicine, large numbers of samples with great diversity are required to be stored accessibly in biobanks [39]. Many different participants are needed and can most easily be recruited by educating the public about the necessity of biobank collections [47]. Education of the public and promotion of biobanks is important for the initial success of biobanking, according to a study by Georg Gaskell and Herbert Gottweis based on the 2010 Eurobarometer on biotechnology [50]. It shows that people are more likely to join biobanking research if they are aware of its existence and importance. Few people

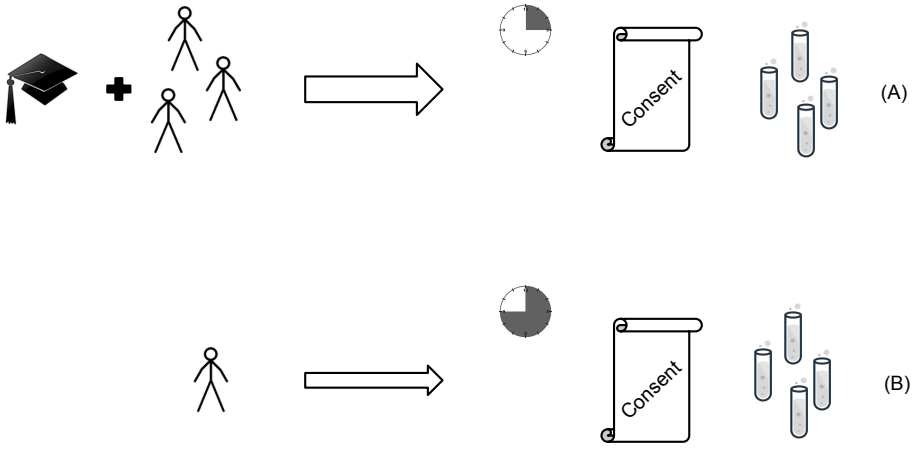


Figure 3.3: Sample provision: In case of good public education, more people will participate and the consent provision will take little time (A). If there is no or little public education, few people will participate and providing consent will take a long time (B).

allow for their samples to be kept in biobanks because there is little education on the topic and the public fears that the stored information could be used against the donor in the future [47]. In case of patient groups, however, it shows that they want to support biobanking research. Some patients' organizations even run and/or finance their own biobanks [25]. Public trust and confidence in biobanking are the most important points for the success of biobanking [39]. Not only information about the purpose of the biobank and its operation but also about the resulting social benefits should be provided. This information can be shared in seminars, workshops, surveys, interviews, genuine discussions among community members, health center meetings, social network forums on the internet, as well as in other media sources. Another option to educate the public is to arrange meetings with previous donors to bring the discussion to a more personal level [39,47]. In finding a way how to approach the public, it is also important to learn from their doubts and fears [50].

Following this, I assume that people who know about the long-term benefits of biobanking will be more likely to participate in biobanking studies and donate samples and information. Furthermore, teaching about biobanking will prevent the spreading of fear through wrong or misunderstood information.

One way to bring biobanking closer to the public is, as suggested, through information sessions which are conducted by professionals in this field and previous donors who can describe their experiences and why they decided to take part in a study. This would give potential participants a chance to ask questions and talk

about their concerns with people that have personal experience. Such sessions can be especially suitable for population-based biobanking studies because they can easily be coupled with the process of recruiting participants. For disease-oriented biobanking studies a good way would be to directly involve physicians. They can hand out information to patients and explain the advantages of research involving biobanks in their special case.

Overall, I believe that patients who have a certain disease donate samples more probably because they hope that this kind of research can find a better cure and therapy. They understand the benefits of biobanking research and the resulting personalized medicine and are more easily convinced to take part. In case of the general population it can be more difficult as they are not directly affected and for them possible risks weigh more than imminent benefits.

**Uncomplicated donation**

To get as many voluntary participants as possible it is important to make sample and information donation as easy as possible. In my opinion, there are two different approaches for simple sample and information donation.

In one case, the prospective participant is a patient already admitted at a hospital. This is often the situation for disease-oriented biobanks such as tissue banks that collect cancer tissue from a removed tumor. Having the participant already at the hospital has the advantage that the patient can stay at the same place for sample donation. Hospital staff can collect the removed tissue or other samples as they would do other hospital routines. The disadvantage is that the donation of samples is only a byproduct to the actual treatment and the patient has enough own worries in that situation. I think, even though most patients are willing to donate samples for biobanking research, if approached at the wrong time or in the wrong way they might feel exploited and disagree to sample donation.

The other case is that volunteers have to come to either the biobank directly or a designated physician for the collection. The advantage of this kind of sample collection is that it is precisely done as wanted because it is the main focus of the collection process. Additionally, if the donation is done at the biobank itself the sample does not have to be shipped but can be stored or processed right away. The disadvantage is that healthy volunteers have to come to certain sample collection points. This requires personal effort. In my opinion, this is the greatest disadvantage of sample donations and is one of the reasons why people might choose not to participate.

However, there is not just the biological sample that needs to be collected. Participants also have to provide personal and medical information needed for research.

Filling out questionnaires can take time and can be bothersome for the participant. Likewise can no connections between research results and medical history be made if not all details are asked for in the questionnaire. Especially patients with a long medical history do not want to write everything down, something might be forgotten, or an issue that does not seem important at that point could eventually be the key to solving a research question. To reduce the error potential and save time and trouble for the participants, I think that, whenever available, the person's medical record should be directly connected with the sample information stored in the biobank's database.

### 3.1.2 Consent

According to Paragraph 32 of the Declaration of Helsinki, informed consent must be obtained for the collection, storage, and/or reuse of material and data for biobanking research [29]. Informed consent documents grant participants' wish to know what their samples are used for and protect their rights [1]. However, they also limit biobanking research because the participants have to be informed about the concept of biobanking, the purpose of the respective research project, and how its results may affect them in the future before collecting any sample or information [20].

Many biobanks have instead decided to use the form of "broad consent" which allows for future research by not defining in which research project the sample will be used to avoid the limitations of informed consent [28]. According to various studies conducted in 2012, there are no clear preferences between broad and informed consent in research participants [51]. Within the biobanking community there is strong support for broad consent, and most population-based biobanks in Europe are using a broad consent model [52]. However, there are further specifications to the reuse of samples with a broad consent such that any previously undefined research has to be appropriately supervised by an institutional review board (IRB) or a research ethics committee (REC) [47]. This would be in line with the Declaration of Helsinki that states in the second part of paragraph 32 that for situations where acquisition of consent is impossible or impracticable, research may be conducted after consideration and approval from a research ethics committee [29].

Furthermore, there is also the possibility to use "tiered consent" which gives participants a number of options on the consent form to govern the future use of their donated samples and information which participants can select according to their preferences [28, 51]. Another proposed model is "dynamic consent" which gives participants the possibility to give consent over a long period of time [37]. In the dynamic consent model participants give informed consent to one study when the samples are collected and receive a web account where information on the use of their sample is available. Through this platform researchers can ask for additional

informed consent for future studies along the way and donors can agree if interested. The mentioned types of consent are compared in Table 3.1.

Table 3.1: Comparison of the various consent types: informed consent, broad consent, tiered consent and dynamic consent.

| | **informed** | **broad** | **tiered** | **dynamic** |
|---|---|---|---|---|
| Information on research study | X | - | - | X |
| Information on area of sample use | - | X | X | - |
| Future use of samples | - | X | X | X |
| Allows sample sharing | - | X | X | X |
| Constant involvement of donor | - | - | - | X |
| Research type chosen by donor | - | - | X | - |
| Right to revoke consent | X | X | X | X |

Another problem with consent is linked to the sharing of samples. The breadth of donor consent is a critical determinant of the interoperability of biobanks [43]. There is an imminent need for an international guideline to facilitate data exchange [53]. A bridged consent for the use of a sample in more than one research laboratory cannot be achieved if informed consent is a requirement.

Giving consent to the use of information and sample in research is in my opinion a crucial element of the biobanking process because it protects the legal rights of the donors and allows the storage and use of their samples. However, there are several important aspects that need to be discussed such as the understandability of the consent and which are the detailed information it is supposed to hold.

It is necessary for the participants to read and understand the consent form before signing it to attest their voluntary participation. To ensure the understanding of the form, a consultant should be available for any questions. Another possibility is a short documentary about the biobanking process and the research. This should also explain what will happen to the donated biosamples and the corresponding personal and health information. It can also address some fears of donors about their rights and the protection of their privacy and information. To find out about the most widespread fears, it can be useful to make surveys and directly ask people about their reasons, if they choose not to participate.

Another point is the right of participants to know what they are participating in. It is important that donors know what their samples are used for, even though this also brings about the unique problem for biobanking research of informed versus broad consent. The true potential of biobanks is that they can hold the collection of many donors with different health backgrounds. As research progresses, these samples are becoming useful for follow up studies or other research which has not

been considered at the time of collection. For those cases it is not possible to describe the precise study or research plan in the consent form. Therefore, it should be possible to give some wider idea of what the usage of samples will be to not limit the options of biobanking research. Even having a wide original scope and allowing donors to then limit the scope if they do not agree, will still provide more possibilities for research than getting consent for only one study. Another way to deal with the reuse of samples would be to recontact participants. This is however often difficult because people move away, die, or they just do not want to be contacted again. The dynamic consent model could solve parts of this issue by providing a web interface for participants through which they can be connected. However, I think this model can only work if participants want to be involved with research because it requires their further involvement.

In my opinion, broad consent – or at least wider consent than informed consent for only one study – is the path of choice for biobanking research. Another option is to let participants choose a dynamic consent approach and agree to give consent continuously. For biobanking research to support personalized medicine, it is important to reuse the sample and recontacting participants will be bothersome for both parties, the researcher and the participants. Furthermore, I think it is important to share data with other research institutes and access samples from other biobanks, wherefore a wider form of consent is needed. However, there need not be a problem with the interoperability of biobanks if they have different consent conditions. As long as the content of the consent is stored with the biobanked sample, it is straightforward to only access samples that can be used for certain research.

## 3.2 Biobank component

The second component of the triangle model is the biobank component. It contains the parts of the model that are directly applicable to the biobank itself and mostly concern how the biobank is run and what precautions are taken to avoid its failure.

As it can be seen in Figure 3.4 the biobank component of the triangle model consists of five parts: standards implementation, quality control, coordinated governance and regulations, dynamic creation and destruction, and economic analysis.

### 3.2.1 Standards implementation

Due to the importance of human biospecimen for personalized medicine they have to be collected and processed based on certain standards to guarantee quality and annotation with the correct patient-related and sample-specific information [1]. To ensure this, biobanks need to adopt and implement best practices which include policies and standard operating procedures (SOPs) [36].

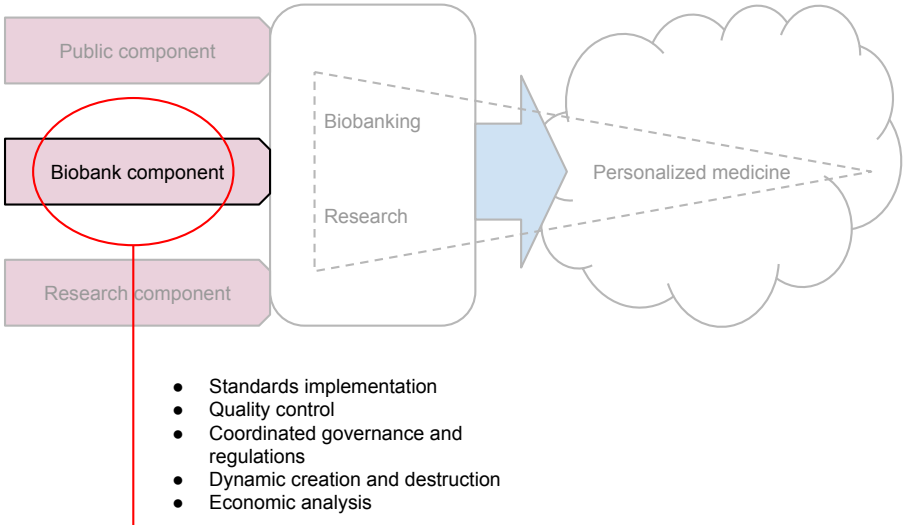


Figure 3.4: Triangle model: detailed view of the biobank component with its parts.

A number of different organizations have proposed best practice guidelines for biospecimen repositories over the past 15 years [36, 54]. A summary of the provided information from the Australasian Biospecimen Network (ABN) [55], International Agency for Research on Cancer (IARC) [56], International Society for Biological and Environmental Repositories (ISBER) [57], National Cancer Institute (NCI) [58], Organisation for Economic Co-operation and Development (OECD) [59], and RAND Science and Technology (RAND) [60] is shown in Table 3.2. In addition to guidelines about biospecimen handling such as collection, processing, and storage, also broader issues such as ethical, legal, and social aspects, and regulatory requirements as well as data and quality management are mentioned [54]. These best practice guidelines shall ensure the level of quality for the samples in the biobank. Furthermore, the use of best practice guidelines will lead to an economic benefit in the long run.

The guidelines proposed in [55–60] are mostly only suggestions or state some minimum criteria that can be followed because some biospecimen management steps are governed by national/federal, regional, and local regulations which have priority over the proposed best practice guidelines [57]. The newest and most complete set of guidelines is given by ISBER. Their 2012 version is the third edition after the first in 2005 and the second in 2008. Hence, ISBER has invested 7 years of revision in the current document, which explains the variety of information available. However, ISBER is not specialized on human biospecimen repositories or biobanks but provides best practice guidelines for general repositories used for the collection, storage, retrieval, and distribution of biological materials for research. There is a variety of biobanks with specific differences so that each will have to set up their own guide-

lines individually [41]. However, not many biobanks publish their own standards which they apply based on the provided guidelines. The variety of procedures used in different biobanks poses a significant problem if they want to collaborate with each other [20].

Table 3.2: Recommendations for biosample repositories collecting human biospecimen. Inspired by [61]. M = is mentioned / GL = guideline or protocol to follow is proposed / * = sample type dependent.

| | **RAND** | **IARC** | **OECD** | **ABN** | **NCI** | **ISBER** |
|---|---|---|---|---|---|---|
| Publication date | 2003 | 2007 | 2007 | 2009 | 2011 | 2012 |
| Funding / Sustainability | M | M | GL | - | GL | GL |
| Facility | - | - | GL | - | M | GL |
| Equipment | - | M | GL | - | GL | GL |
| Staff training | M | M | GL | - | GL | GL |
| Biosafety | - | GL | GL | - | GL | GL |
| Consent | GL | M | M | GL | GL | GL |
| Intellectual property | GL | M | M | - | GL | M |
| Privacy protection | GL | - | M | M | GL | GL |
| Sample Collection and Processing | GL | GL* | M | GL* | GL | GL* |
| Sample Storage | GL | GL* | GL | GL* | GL | GL |
| Transportation / Shipping | GL | GL* | - | GL | GL | GL |
| Traceability / Labeling | M | GL | M | M | GL | GL |
| Quality Control | GL | GL | M | GL* | GL | GL |
| Clinical Data Management | - | - | - | GL | GL | GL |
| Personal Data Management | - | - | M | - | - | GL |
| Sample-related Data Management | M | GL | GL | - | M | GL |
| Database | M | M | M | GL | GL | M |
| Access Right | GL | GL | M | GL | GL | GL |
| International Exchange | - | GL | - | M | - | M |

Since existing biobanks already have their own practices specific to their biobank, it would not make sense to demand complete uniformity among biobanks for collaboration [37]. Therefore, harmonization is used as a more flexible approach to ensure the effective interchange of valid information and samples. While standard-

ization would require the exact same protocols and SOPs to be used by all biobanks which is only necessary in case the processes need to be identical, harmonization is context-specific and relates to the compatibility of methodologies and approaches to facilitate cooperation between biobanks [24]. The harmonization of best practice policy guidelines and agreement on SOPs for laboratory procedures is important due to the necessity of collaborations between biobanks to improve biobanking research for personalized medicine [28, 36, 52]. However, there are not many organizations and networks which are successfully sharing common harmonized protocols [20].

The BBMRI is an international biobanking network with the goal to better coordinate biospecimen access and research activities across Europe [62]. They are coordinating their plans with those already in place proposed by the Public Population Project in Genetics (P3G), the OECD, and the IARC. The P3G has done a lot of work on collecting biobanking tools which are available in the toolkit on their website [63]. The BBMRI Legal WIKI provides a collection of common minimum standards that need to be followed by any member no matter what other laws, standards and guidelines they have in place [64]. Those standards focus on ethical principles, regulation of use, and accessibility of the biobank and its samples. A schematic image of the different levels of proposed standards is displayed in Figure 3.5. The BBMRI Legal WIKI also provides several templates for European biobanking research for the standard personal data processing security agreement, material transfer policy and agreement, data access policy and agreement, and biobank feedback policy [65]. Furthermore, documentation about past and present EU biobanking projects is available as well as templates for national biobanking research or national data processing notification requirements, and templates for biobanking research with non EU countries. Many of these templates are not yet filled and unfortunately there are no references on the use of any of the provided templates.

Standards are important in biobanking to ensure that each process step is done in a predefined way. However, it is not enough for standards to merely exist, they also have to be applied for each processing step and linked to the processed sample.

They have to be used for the collection of samples, medical, and personal information as well as for the consent. Different sets of standards need to be available, depending on the sample type and the form of consent used. Furthermore, specific standards should be used for every step along the way of processing that a sample is going through. The implemented standards for these steps depend on the sample type, the processing goal, and devices and expertise available. In addition to that, the processing of the personal information needs to be standardized. Standards should be used to decide how personal information is secured, stored, and protected

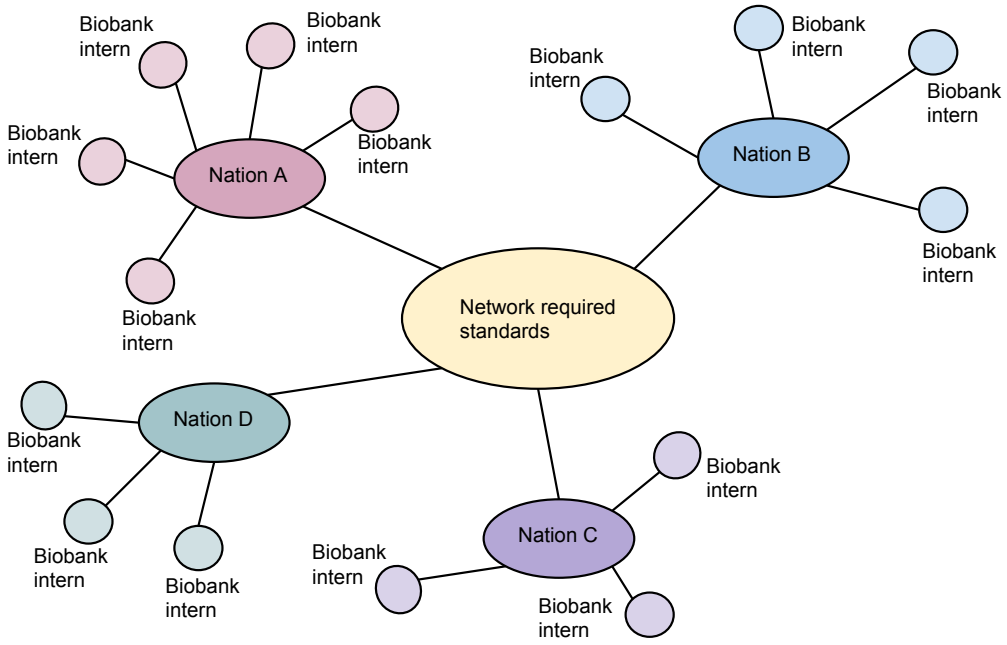


Figure 3.5: The standard hierarchy biobanks are facing when they want to interact in a network. A biobank in a certain nation needs to implement its own internal standards, national laws and regulations, and minimum standards proposed by the network when joining a network.

as well as who will have access to this information. Further standards that are important determine the access rights and conditions to the database of the biobank and the minimum data set of information on the stored samples that researchers can access. There seem to be already several proposed standards that can be followed if a biobank chooses to do so. But still most biobanks seem to implement their own standards or change the proposed guidelines to fit for the purpose of their biobank. This does not pose a problem, as in most cases, harmonization is more important for cooperation than the standardization of procedures. However, one problem is that only few biobanks have their best practice standards accessible. Providing them to the public would make their work more transparent and could increase the public's trust.

In my opinion, standard implementation becomes especially important when considering the cooperation with other biobanks. In that case it is important to know the standards of the respective other biobank to see if the samples are comparable or of sufficient quality for the intended research. More harmonization guidelines are required to ensure the interoperability of biobanks. These guidelines should propose a way to evaluate various dissimilar standards for different biobanks to know if their samples are comparable.

### 3.2.2 Quality control

High-quality human biospecimen are important for personalized medicine [1, 39]. The quality of the specimen is directly proportional to the richness of the associated data profile and the confidence of researchers in the completeness and validity of the information [1]. For biobanks the quality of their stored specimen is a key factor in their success [20, 36]. However, studies from 2011 show that there are not enough samples of sufficient quality available [33, 36, 52].

To increase the number of high quality human biospecimen stored in biobanks, quality control and quality management processes are adopted to enforce and test quality standard usage [25, 43]. Proper documentation of any processing step that could influence the sample quality is important since the interoperability between biobanks requires not only high-quality but especially known quality specimen [51]. Four levels of quality applicable to biobanks have been suggested in 2005 [32]:

- training and certification of biobank staff and assignment of responsibilities,
- instrument maintenance,
- property control of processed materials, and
- long-term control of stored samples.

#### Biobank personnel and equipment

Since being able to assure high quality biospecimen is important for the biobank, it is necessary to train all personnel involved in handling the sample during the collection, processing, annotation, storage and distribution step [25]. Apart from regular training also certification for staff and the relationship between different personnel types need to be defined [25, 36]. Each staff member should be trained according to the skills needed for their job and should receive training whenever new technology becomes available or new practices are introduced [31]. Figure 3.6 shows the influence on sample quality that the personnel and equipment have during any process of sample handling.

Furthermore, also the internal laboratory and its specially trained staff need to be certified to guarantee high-quality samples in the biobank. One approach is SPIDIA (Standardization and improvement of generic Pre-analytical tools and procedures for In-vitro DIAgnostics), an initiative launched in Europe to develop standardization and improvement of pre-analytical procedures for in-vitro diagnostics [66]. In the SPIDIA pilot study, molecular diagnostics laboratories are isolating nucleic acids from standard blood and plasma samples [36, 62]. The isolated nucleic acids are then analyzed in centralized facilities and their quality assessed. Laboratories with

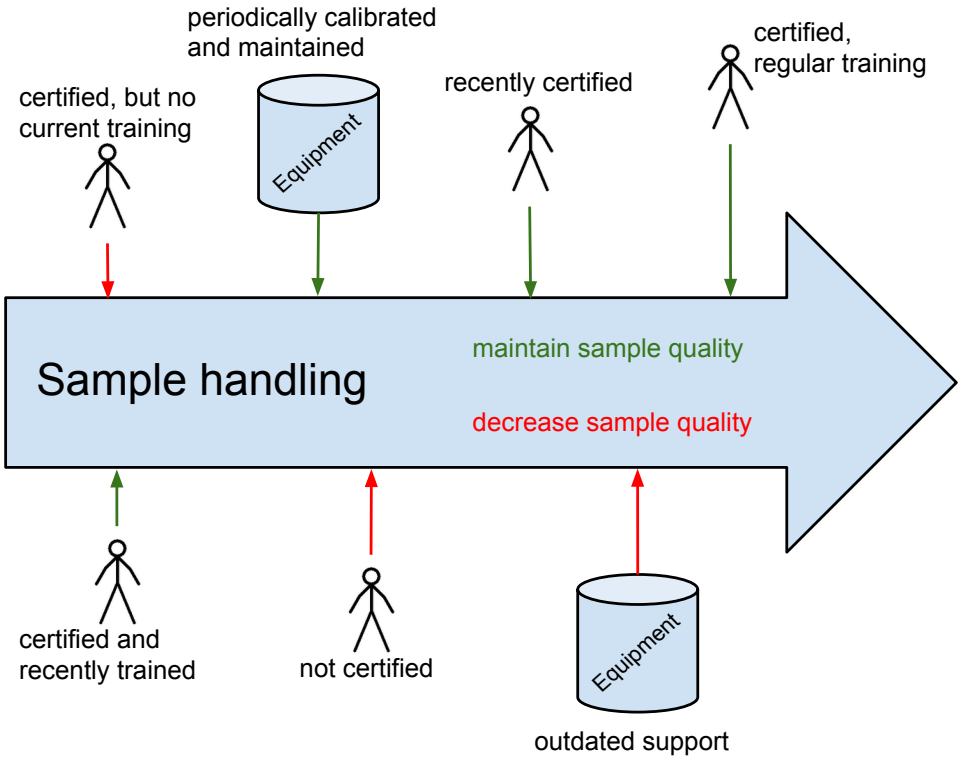


Figure 3.6: Influence of qualified or not qualified personnel and properly maintained equipment or equipment with outdated support on the sample quality.

poor pre-analytical performance are guided on how to improve the reliability of their procedures and are invited to participate in SPIDIA training courses [62]. To directly support enhanced patient care for personalized medicine, the internal biobank laboratory can get for example Clinical Laboratory Improvement Amendments (CLIA) Certification and College of American Pathologists (CAP) Accreditation [67]. This does not only enable the use of the banked samples for clinical patient management but also increases the confidence of patients and physicians in the biobank [68].

Technology can help to ensure biospecimen quality, and there are many examples in biobanks such as reliable freezers with monitoring and alarm systems, automation, or various laboratory devices [36]. However, all this equipment needs up-to-date instructions for use and maintenance as well as appropriate personnel to use it [31]. All equipment needs to be maintained and calibrated regularly and service records are to be kept by the quality manager.

Every person who handles a sample needs to be trained and all equipment need to work as intended to minimize unpredictable and undocumented influence on the sample that could lower its quality. Biobank staff need to be aware of the importance

that sample quality has on future research and the resulting influence on personalized medicine. Therefore, staff members have to avoid mistakes and document the procedures along the way of the biobanked sample. The likelihood of mistakes can be reduced through periodic training and staff members can earn certificates on proper treatment of samples. Having certified people working in the biobank will increase the trust in the biobank and through this its value.

However, for cases where biobank staff can be substituted through automation processes, this can be used to increase the processing quality. Automation will decrease the treatment variability that is natural with human work and lead to more comparable samples. However, the downside of automation is that it requires regular maintenance and calibration. If the device is not set up properly, an error could spread fast through the samples before it is detected.

**Pre-analytical variation**

Research results often depend on situations arising prior to sample usage [31]. These are called pre-analytical variations. There are two parts to the pre-analytical phase: the pre-acquisition phase and the acquisition phase [41]. The pre-acquisition phase is the time, when the sample is not yet under supervision and control of biobank personnel, while during the acquisition phase it already is. Circumstances that need to be considered during the pre-acquisition phase include for example the treatment the donor was given prior to the collection of the sample, such as drug treatments with antibiotics, anticoagulants, or anesthetics. In the acquisition phase the lag time – the time between removal of the specimen from the body until it is frozen – and other sample processing steps are important [20]. While it is known that even small pre-analytical variation can significantly influence the downstream results, it is difficult to minimize these variations [20,43]. To ensure interoperability regardless of these variations, it is needed to monitor and document the pre-analytical phase [43]. To facilitate the recording of such information the Sample PREanalytical Code (SPREC) has been developed [36].

The SPREC can be applied to primary samples and their simple derivatives from either solid tissues or fluids. Primary samples are samples that are directly collected from the donor and simple derivatives are samples that are prepared through a simple laboratory manipulation such as centrifugation of fluids or cutting of solid tissue samples. Complex derivatives are samples for which preparation multiple steps or chemical substances, such as nucleic acids, proteins, cultured cells, and others are used. Complex derivatives, however, are not covered by SPREC. Furthermore, there are no elements about freeze-thaw cycles or storage procedures included in the SPREC because the code is already applied during the processing and labeling

procedure. The code consists of seven elements which correspond to pre-analytical variables as seen in Table 3.3. [69]

Table 3.3: SPREC for fluids (fluid biospecimen – supernatants and/or fluid-derived cells) and solid tissues (or tissue-derived cytologic biospecimen) [69].

| | **fluids** | **solid tissue** |
|---|---|---|
| First code element | type of sample | type of sample |
| Second code element | type of primary container | type of collection |
| Third code element | precentrifugation | warm ischemia time |
| Fourth code element | centrifugation | cold ischemia time |
| Fifth code element | second centrifugation | fixation type |
| Sixth code element | postcentrifugation | fixation time |
| Seventh code element | storage condition | storage condition |

The SPREC gives important information about the pre-analytical variations that should be mentioned in the documentation of biospecimen. Whoever uses this sample will know exactly under what conditions the sample was collected. Nevertheless, there are some shortcomings of the SPREC. So far, the SPREC is not usable for complex derivatives of samples, even though it would be especially useful for processing nucleic acids to have proper documentation to estimate sample quality. The other problem with the SPREC is that it only takes the acquisition phase into account. Drug treatment that patient received prior to sample collection or any other habit that could influence sample quality are not recorded with SPREC.

### Quality control parameter

One way to deal with unknown sample quality is the definition of quality control parameters that can be used to compare and ensure certain quality. Since the quality of samples can only be specified in the context of their intended use, there are different quality control parameters for morphological, genomic, transcriptomic, or metabolomic analyses [38]. Relevant parameters for nucleic acids for example would be the total yield and the largest fragment length that can be extracted while the protein quality depends on sustained antigenicity, preservation of biological activity, and post-translational modifications. For this, the analysis of a variety of molecular components is important [36]. It can be performed by using biomarkers for sample quality.

A biomarker giving an on/off response can be used as quality indicator to determine the suitability of a sample for a certain research technique [41]. Ideal quality

control biomarkers should furthermore be ubiquitous and measurable with generally accessible methods [70]. Analyzing the response of such biomarkers can be used to see differences in pre-analytical sample handling and processing [43]. Additionally, they can also be used to reveal if samples were stored and handled as described during their lifetime [41]. For accurate results, biomarkers need to be found for any sample type and any derivative, and end product.

However, before being able to use biomarkers as quality control tools, it is necessary to identify the quality markers which reflect factors that affect the sample composition with sufficient accuracy and efficiency. After the identification of markers, quality consensus conferences involving stakeholders of national and international biobank collaborations have to decide which of them can be used for quality control. [43]

The usage of biomarkers as quality control tools for pre-analytical and storage conditions will improve the interoperability of biobanks [43]. Having known quality samples and testing methods for quality control enhances the comparability of studies and research results [70].

Knowing some factors that can be tested to ensure the quality of a sample for certain research techniques, will be a big help for researchers. If the quality relevant elements from the pre-analytical phase are properly documented, researchers can directly ask for samples with certain quality properties. This will save time and avoid unnecessary usage of samples and lead to high-quality research results. Elements related to storage and shipping conditions are usually not tested before the sample reaches the researcher. So a quick test for quality relevant factors to check the usability of the sample needs to be in place.

Quality control biomarkers can be used to identify the influence of some factors to sample quality. They provide a good method to check for quality features in the sample. They can further be used for sample monitoring over time and in research to find the ideal storage condition for different sample types. I think quality control biomarkers will become especially useful if they are affordable and can be detected and evaluated with simple methods or tests in every laboratory.

### Documentation and tracking

Since sample quality is relative to the research question asked, a biobank might have multiple samples of different quality level [3]. This makes proper documentation essential because it permits the assessment of sample properties later on. The value of the samples in a biobank is therefore not only defined by their physical qualities but also by the abundance and quality of the associated data [20]. Recording and

tracking each known step in the biosample's lifetime is very important since incomplete or incorrect documented data could lead to low value samples and possibly influence study results. To avoid decreasing sample quality through incomplete documentation some crucial information needs to be recorded including treatments and outcome of each treatment, diagnosis, time of sampling, type of primary collection tube, delays, and temperatures of processing and storing the samples [20, 41].

Other important information that should be documented include any unexpected events along the biobanking process such as unforeseen temperature shifts during storage or transport [41]. Repeatedly during the lifetime of a sample, quality reviews should be performed to verify the integrity of the sample [34]. Furthermore, bar-code tracking should be used to ensure traceability of the sample collection and processing and reduce the error potential of tracking samples by hand [41].

By recording every step during a sample's lifetime, the processes possibly influencing the sample quality are also recorded. This can result in a huge amount of data. This data, however, should be manageable and accessible with proper recording in the database of the biobank. Especially when considering future research with new techniques, this information could potentially become important when new factors are identified that can influence sample quality and research results.

Researchers who are interested in ordering a sample, need to be able to search for the recorded factors that could influence sample quality. Furthermore, researchers should be able to track samples to find other samples from the same collection with the same or different properties. Good documentation simplifies database management, which in turn is important to have an accessible database that properly presents the sample collection. Well presented samples along with searchable variety of sample properties will increase the usage of the biobank.

### 3.2.3 Coordinated governance and regulations

The term regulation is often used interchangeable with governance in the context of biobanking. However, the scope of regulation is more narrow and applies only to the formal structures of law and legally constituted regulatory bodies [37, 45]. In case of biobanking, governance is understood to be an interaction network along the scientific/technological, the medical/health, the industrial/economic, the legal/ethical, and the social/political field [3, 25]. This means biobanking governance is concerned with all processes governing the biobanking structure. This includes the development of standardized protocols for different routine activities in the biobank such as data and sample handling, training of the personnel working at the biobank, and the development of a bioinformatics system for operating the biobank as well as for data management and data access for different stakeholders [25].

Another part handled in biobanking governance is to have biobanks tightly connected with the health care system in order to support personalized medicine. Therefore, clinicians and hospital administrations should be involved in the governance and financing of biobanks because they will benefit from the advantages personalized medicine will be able to offer. [68]

Biobanking projects tend to be expensive considering the high investments for setting up the biobank and high maintenance costs for facility, storage, and personnel [25]. Therefore, biobanking governance has to create solid business models for biobanks to ensure funding, operation, and utilization of the biobank. This issue is further discussed in Chapter 3.2.5.

Due to the undeniable link between biobanks and bodies, ethical issues are also part of biobanking governance which include consent, privacy, autonomy, and confidentiality features. Biobanking governance has to include RECs or IRBs which are responsible for approving the establishment of the biobank, as well as approving any research using samples and/or information from the biobank. [37, 71]

Furthermore, biobanking governance is supposed to communicate biobanking research openly and transparently and to establish a trusting relationship with the public. Through higher trust in governance, people will develop a more positive attitude towards biobanking and are more likely to support it. [19]

Biobanks should develop a governance plan which describes their oversight and structure, including the roles and responsibilities of parties involved in the biobanking processes [51]. The governance plan is needed for researchers, clinicians, and the public to know what the purpose of a sample collection is. Important elements that should be described in the governance plan are shown in Figure 3.7.

Especially in the times of cooperation between biobanks and data sharing, a good governance plan is important [37]. Without a plan and policies to follow human rights and data protection laws, a biobank cannot legally share data or samples in a network. However, the current structures of biobanking governance are not developed for networks and do not allow for the flow of samples and data at a global level [45]. Most governance systems are still based on national laws, creating boundaries on international use and interoperability with other biobanks. This creates problems since there is no unified governance system for samples and no harmonization for most of the national laws and regulations, except for the law of data protection [19]. To overcome the legal differences resulting from dissimilar national laws between European countries, the EU suggested to create a common legal framework for biobanking in 2009 [37]. As for March 2014, the BBMRI states that it will be implemented under the European Research Infrastructure Consortium (ERIC) [72]. BBMRI-ERIC foresees a headquarter in Austria which coordinates the interaction of the so called national hubs in several of the member states. Each of

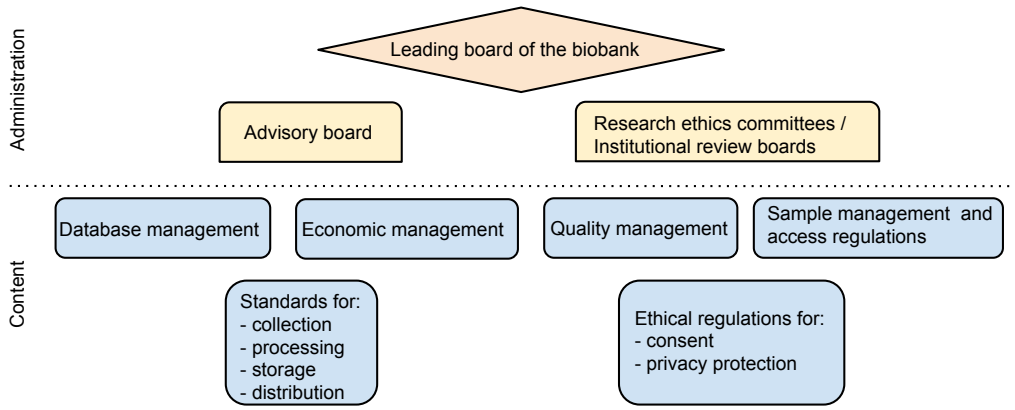


Figure 3.7: Elements of a governance plan. The governance plan needs to provide information on the leading board of the biobank as well as the advisory board and the REC and/or IRB that is in charge. The boards are made up of specialists in the scientific/technological, medical/health, industrial/economic, legal/ethical, and the social/political field. They are needed to ensure all aspects of this interdisciplinary structure. Furthermore, the governance plan has to present the database management, economic management, quality management, sample management, and access regulations. It also needs to list the standards used in the biobanking processes of collection, processing, storage, and distribution of samples, as well as the ethical regulations for consent and privacy protections.

these national hubs is also established under ERIC and its task is to link its national scientific community to BBMRI-ERIC. Through this collaboration under a common legal framework, BBMRI-ERIC is expected to increase the efficacy and excellence of biomedical research in Europe.

However, also on the level of individual biobanks there are suggestions of what has to be changed to get biobanking governance to the modern standard to efficiently support personalized medicine. The embedding of biobanks in clinical care is one of these changes needed. It is important for personalized medicine and will also ensure financial sustainability and attractiveness of biobanks for clinicians, researchers, and the industry. Furthermore, using e-governance solutions could improve many processes. One example is to use e-governance in case of interaction with participants for dynamic consent. Another one is the use of digital identifiers for biobanks that can then be used in publications and funding grants to reference the custodians. [37]

The governance structure is important because through it, the biobank presents itself. This is why I think it is important to have a good coordinated and transparent governance structure at hand with appropriate oversight bodies.

There needs to be a clear structure of the people in charge of the components of the biobank. This will increase the trust that the public has in a biobank because they can see who is behind the sample and data collection. Furthermore, they can

familiarize themselves with the regulations the biobank has in place that ensure their data and privacy protection. It would be good if funding institutions required a governance plan from the biobank before deciding to support them. Through this they can estimate the probability for success of the biobank and therefore determine the risk they run with an investment.

Another issue is that a lot of documents and forms for applications for research studies and others are still paper based. Even the oversight bodies are still working with paper documents that might have to be digitalized later to make it more easily accessible. However, time and resources could be saved by using for example electronic forms to fill research applications. A computer program could already pre-screen the application to make sure everything necessary is filled out and sort it according to its purpose. This will make it easier for researchers that will know right away if their application is complete and will be processed or if they missed something. Also the responsible people in the relevant oversight body will only get complete applications that concern their area of expertise.

### 3.2.4 Dynamic creation and destruction

Biobanking is not a finished invention but is a highly complex, interactive, and dynamic multi-disciplinary field of science [37]. Through progress in genomic research, technological advances, development of new laws more accurately adapted to biobanking research, as well as improved standards, guidelines and best practices, there is constant movement and evolution in biobanking governance [25]. Furthermore, the public's opinion on methods of research can change over time and differ between countries [3]. Each new proposal, development, or invention in one of the areas of biobanking will potentially affect the others, leaving the need for constant adjustment. Therefore, biobanks have to be designed, constructed, managed, and funded with flexibility, sustainability, and international interoperability [24].

Several aspects have to be taken into consideration to keep biobanks and biobanking research active and dynamic [24]. Interoperability of biobanks as already mentioned is important for a more robust, more efficient, and more flexible research structure, which helps to pool, share, and analyze information and biological samples between them [20]. To be able to cooperate with other biobanks there is a need for flexible guidelines which can be harmonized [37].

Due to the nature of biobanks and biobanking research, a dynamic and flexible structure is needed. A biobank is in my opinion doomed if it cannot adapt to changes since there will constantly be new developments as biobanking is – as described in this thesis – a relatively new venture.

However, allowing for change is not as easy as it might sound. A biobank is governed by its governance plan where the regulations and laws to be followed are listed. This plan is approved by oversight bodies that make sure that for example data and privacy protections are in place and that donors' rights are protected. Therefore, it is very important to try to consider future changes and leave the possibility to modify given structures in the governance plan and in the biobank's legal documents.

### 3.2.5 Economic analysis

Funding difficulties, changing market needs, and the need to create a fitting business model on which to achieve long-term sustainability, make financing one of the most challenging aspects regarding biobanks [20]. The main problem is the high costs for setting up a biobank and maintaining it [25]. One way to afford these costs is to get adequate funding for the biobank [36]. There is a need for long-term secure funding for establishing and maintaining biobanks and biobanking research [34]. To achieve this, there are several funding models that are used by biobanks such as the entrepreneurial model, the biosocial model, or the public model [3]. An overview over these three models is given in Figure 3.8 and they are explained in detail in the following.

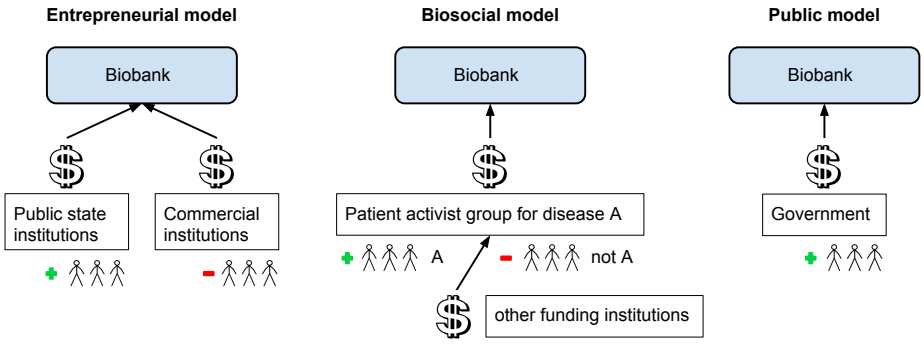


Figure 3.8: Comparison of the three funding models: entrepreneurial model, biosocial model, and public model. Displayed are the funding types for each model and which funding types get public support (+) and which get public opposition (−).

The entrepreneurial model is a collaboration between a commercially oriented organization and public state institutions [3]. Through the cooperation with public institutions it is hoped to catch the support of the people since public support is also needed for the sustainability of biobanks [25]. Biobanks that have commercially oriented funding often have the problem of little public support due to the commercialization of the stored tissues [73]. Participants may not support commercial research because it can lead to the undermining of the equality of biobank benefits

through the development of expensive therapies and diagnostic tests. Therefore, the entrepreneurial model has turned out to be more challenging than expected [3].

The biosocial model is promoted and funded by patient activist groups who are often creating and operating biobanks as well. It has proven to be a stable model for funding of biobanking research. However, since it is run by a specific patient activist group, research in their disease areas is favored. This can lead to a limitation of general biobanking research and an uneven distribution of samples. On the other hand, this model is important for the biological faith of citizens that are neglected in public health schemes because it can specifically represent that part of the population. The main problem of the biosocial model is that the funding patient activist groups themselves are dependent on financial donations. This leads to high uncertainty in this kind of financial support for biobanks. [3]

The most commonly used funding model for biobanks is the public model [1, 3]: biobanks are supported through taxpayers' money and non-profit funding organizations. It is often argued that due to the impact that personalized medicine will have on the health care sector, the government should fund biobanks and biobanking research [3]. Getting the government as main funder helps to shield projects from corporate influence [74]. However, one issue with this funding model is that its support depends on politics and can be lost if voters have no more confidence in the promise of personalized medicine and other important outcomes from biobanking research [3]. Overall, publicly funded projects are regarded trustworthy by the population, which is important for the support, especially for population-based biobanks [37]. The public model for funding also gives importance to data and sample sharing [43]. Publicly funded biobanks are widely seen as data and sample collections for the promotion of scientific research for the public good [24]. The resources funded by the public should be made accessible to as many researchers as possible to eventually maximize the benefits for society [45].

However, with the unsteady economic climate, it is often difficult to find potential investors for a project like a biobank [20]. This reluctance is mainly coming from the fact that there are not only start-up costs for the biobank facilities but running a biobank also requires a huge amount of investment with usually little returns [73,75]. To still find funding organizations there have to be proposals of cost recovery in the biobank's business model [25]. It is important for biobanks to create some kind of value that can be used for cost recovery [25]. One way is commercially by selling data by itself, licensing biospecimen or research services for research institutions, or offering collaboration to other biobanks [20, 34, 73]. Another often underestimated value is that of the samples that are stored in the biobank [34]. Rare samples or samples of very high quality have high value because they are more demanded than average quality samples that are available in large quantities. Therefore, having

the right samples according to the market need will attract more customers to the biobank, increasing its reputation and making it appealing to funding organizations to invest money.

In 2011, Vaught et al. presented an example for a sustainable business model for human tissue banks. They suggested that the main parts that need to be considered in the economic model for a biobank are 1) understanding the market need for the biobank type, and 2) effectively managing the value chain of the biobank. The five key factors in a biobank's value chain are the collection of samples, the processing of samples, their storage, their distribution, and the infrastructure and administration. With the help of these factors the Total Life Cycle Cost of Ownership (TLCO) model can be calculated. The purpose of the TLCO is to estimate all costs coming from owning, operating, and maintaining the biobank through-out its life time. A business model with this information is important for prospective funding institutions to see how the money will be spent and makes the financial aspect behind the biobank more transparent. [34]

It is important for biobanking projects that rely on funding to inform funders about their financial situation. At the start of the project there has to be a sustainable economic plan which includes the overall costs and the planned cost management. During the lifetime of the project regular financial reports have to be published to display transparency of the project. Therefore, the biobank needs to have a business model, where among other things, a cost estimation, the planned cost management, the frequency and content of financial reports, and a tool to easily report on finances periodically is determined. I think the value chain elements as suggested by Vaught et al. make up the main cost factors in the biobank and therefore are important elements for the TLCO. The TLCO is a reasonable way to show the cost estimates for operating and investment costs. Providing a TLCO in the business model will make a biobank's finances comparable and clearly state cost over time for possible funders.

Furthermore, the business model should state what kind of cost recovery mechanisms the biobank is using. While it is a good idea to not fully depend on funding organizations I think one problem is that especially the licensing of biosamples can be regarded as exploiting volunteers. One tries to make profit from something that was voluntarily donated to help solving research questions and improve treatments and drugs for the good of the public. Especially for publicly funded biobanks there should not be any profit made directly from samples or data that is stored. There are still other ways for cost recovery, for example by offering pre-processed samples such as extracted DNA or RNA from the sample, organizing trainings for research laboratory staff, or renting freezer space to other institutions.

## 3.3 Research component

The third and last component of the triangle model is the research component. As shown in Figure 3.9, it consists of two parts; the training and certification of research laboratories and the reporting of research results.

While biobank institutions can do their own research, most other sample collections have researchers and laboratories not directly linked to the collection that use the samples in their studies. To make the best out of all sample collections, researchers and laboratories should use them under high quality standards and provide feedback about their results.

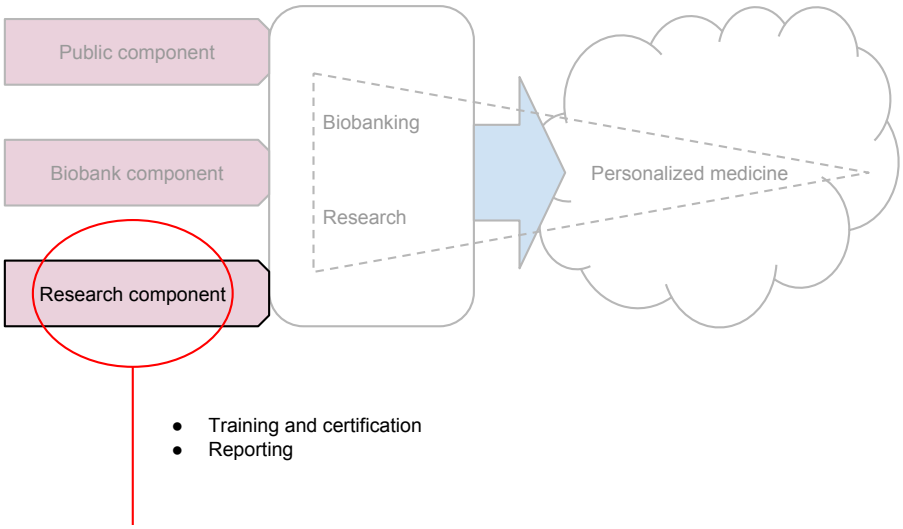


Figure 3.9: Triangle model: detailed view of the research component with its parts.

### 3.3.1 Training and certification

While training for biobanking staff and certification of biobank intern laboratories is important to assure high quality samples (as mentioned in Chapter 3.2.2), there are no training or certification requirements mentioned for researchers and their laboratories that want to conduct further research with biospecimen from a biobank. However, knowing about training and certification of a researcher or a laboratory that applies for the use of samples, can be helpful when deciding on the granting of access to the biobank. The only restriction for research laboratories that is mentioned in the literature, is that if they are not CLIA-certified, they cannot report patient test results or use banked samples for patient management [68]. The SPIDIA training can also be applied to researchers and laboratories that are using samples from a biobank to maintain the sample quality [66].

To have high quality results, the provided samples must be of high quality but also the laboratory that handles them must do high quality research. The quality of research can be estimated with training and certification documents provided by the research institution. In my opinion, there are two areas where certifications of a laboratory can be used to make decisions; when applying for the use of rare samples and when other researchers want to rely on stored previous research results. Biobanks should be conscious of the reputation that they will get through the publication of good research results from laboratories that have used the biobanks' provided samples. Therefore, biobanks want to make sure that researchers and laboratories that receive their samples have high standards and are certified and well trained to ensure high quality research and respective results.

When it comes to applying for the sample usage for research, researchers can give with the proposed research plan also the certification of their laboratory and their personal certification and trainings to show the biobank their capability of high quality research. Especially for rare and non-renewable samples there has to be a way for biobanks to prioritize who will get the sample wherefore such information on the laboratory and the researchers are important for decision making. How a biobank decides about the access regulations is as mentioned part of the governance plan. Furthermore, when publishing or sharing results, the information on certification and training of the researchers is an important criteria to evaluate trustworthiness and quality of the results.

### 3.3.2 Reporting

There are three different forms of reporting. The first one is sharing the information and individual results with the participant. The second one is sharing the research results with other researchers and the third one is publishing the study results in scientific publications. In Figure 3.10 the three result types and the way of reporting them are summarized while they are discussed in more depth in the following.

#### Results for individuals

The Declaration of Helsinki states that participants who donate samples have the right to know about the general outcome of the study their samples were used in [29]. However, there is no specific saying that they also have the right to receive information about individual results.

Biobanks often return individual results of diagnostic tests and biometrics conducted for the participation in a biobanking study. However, there is still a lot of controversy regarding the return of genetic or genomic results to participants. It is agreed that if individual results are going to be returned they need to be scientifically

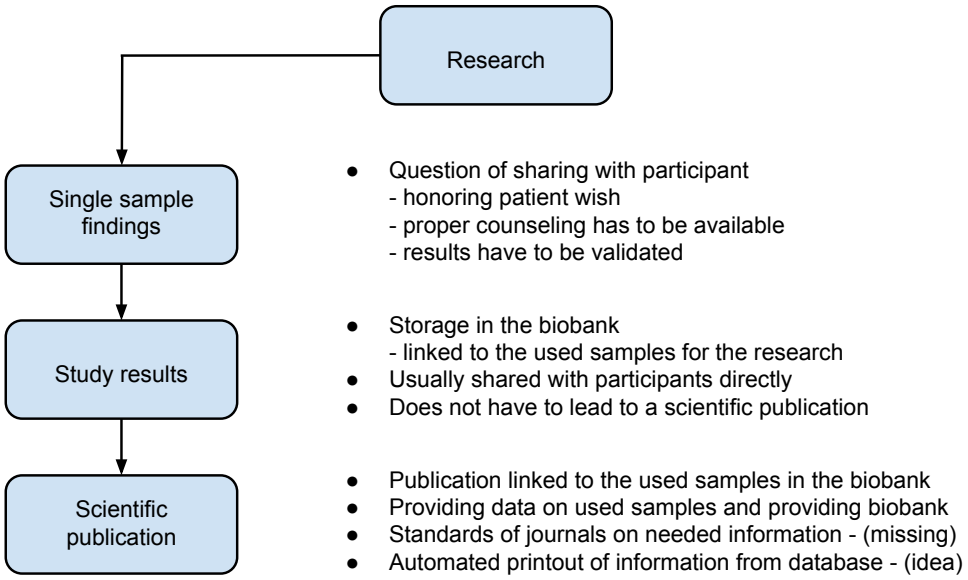


Figure 3.10: Summary of the different results that are encountered while conducting research and how the reporting on these results is discussed and proposed to be handled in the literature. First, one might make findings about single samples that could be shared with the donor. Then, after all the samples for a study have been investigated, the results of the study could be presented and further on these results could be published.

validated and the nature of the results need to be examined with regards to the risk for the individual to develop a condition, the severity of that condition, and available treatment options. The recommendation is to consider the risks and benefits as well as ensuring the validity of the data before the results are returned. [28]

Research shows that participants in general want to know their personal research results. A special problem occurs with genetic and genomic results because of the impact they might have on genetic relatives or on the health of a future child. This brings up the question for researchers if they are ethically responsible to return such results. This is especially difficult in cases where people do not want to know about their results: their right to not know has to be respected even though knowing and finding early treatment could improve their life expectancy for example. [35]

Other issues arise with the sharing of samples. It is unclear who is responsible for informing the participant about research results: is it the researcher who got the results or the one who originally collected the sample [28]? Another concern is the understanding of the meaning of the results [35]. A genetic counselor is needed to properly prepare a participant and inform them about results and their probable impact [76].

Since the donation of biosamples for research is done voluntarily, it is understandable that participants want to know about the results of the study or research their samples were used for. When talking about sharing individual results, however, it gets more complicated. It is highly possible that participants want to know if they have a risk for a certain disease and there should be some way to communicate such findings. However, informing participants about individual findings requires additional effort from the laboratories. If the research laboratories want to offer personal research results there should be a way for the participants to mark in the consent form if they want to be recontacted in case of any findings. This wish as it is marked should be respected in both ways, in case they want and in case they do not want any information.

**Results for researcher**

One problem of sharing genetics research results is the amount of work that is associated with it. Another one is the wish of every researcher to protect the current research and possible findings and publications from other laboratories. [52]

However, to avoid that researchers working with one sample have to redo certain tests over and over again, it would be useful to share results with each other. The database in a biobank is the ideal tool for result sharing. Any information related to the sample, sample handling, sample processing as well as results for certain tests and who conducted them can be stored. I believe that there are several advantages for research if previous research results are available.

Accessing these information allows researchers to use previously conducted tests and their results to shorten their own research duration. Alternatively, they can compare results they got in their laboratory with the ones that had been previously stored. This can be used to verify study results and it allows also to see how samples change over time and how this affects research results. Another advantage is that by storing also the information of the researcher and the laboratory that had performed the tests and recorded the results, researchers can easily get in touch with each other. This can help to understand the reasoning behind conducting research in a certain fashion, get additional information on the research, and even lead to new cooperations between researchers and laboratories.

**Scientific publications**

The information about research results of biobanking studies is generally made available in the form of publications in scientific journals [76]. One of the problems these

publications are facing is the recognition of the involved biobank [37]. While many journals require the acknowledgment of the data provider, it is left up to researchers who usually follow the norms of their field. A possible solution is to provide a unique identifier to each biobank which can be used to cite and acknowledge the use of these biobanks in publications and funding grants [37, 71].

Another problem is that it is not clear how much information on the used samples have to be provided when publishing research results. Biobanking experts say that researchers give little thought to sample quality and many do not include information about the obtaining, storing, or processing procedures in publications [33]. Having different or no information on these parts makes it difficult to compare studies [36]. There has to be a standardized way of data reporting and including in publications which journals should enforce [24, 33]. To address this problem the Biospecimen Reporting for Improved Study Quality (BRISQ) recommendations are introduced which apply to any study including biospecimen [77]. The BRISQ list consists of recommended data elements to report in journal publications which include general biospecimen information and factors that could influence the integrity, quality, and/or molecular composition of the biospecimen. The list is intended to help to report information on the handling of biospecimen in an accurate and standardized way. In addition, any formal certification or accreditation the laboratory was operating under should be reported. This list as first published in 2011 is the first step in defining general reporting recommendations and will evolve over time.

Scientific articles are a way to become known in the community and to present yourself and your study results to the world. When reporting on research, however, not only the results are important but also the materials used.

When biobanks are involved, it is important to give them recognition by mentioning the biobank used and details about the sample. Since most of the information is stored in the database, one solution I suggest is the automatic creation of information files on the samples used. There need to be standards about what information should be reported and the database could then directly provide a collection of them. Ideally the researcher can download them in a table already formatted for a given form of publication that can then be just added as appendix for example. The BRISQ list can be a good starting point in deciding which information should be available in publications. By having a standard list of information about samples used in research for publications, it would help to make research more transparent and allow for studies and results to be comparable, repeatable, and verifiable.

# 4. DISCUSSION

The individual parts of the three components of the triangle model were discussed in the previous sections in comparison with my thought experiment that laid their foundation. In this section I focus on those parts that have not been mentioned in the revised literature or are not even developed.

Furthermore, I take a look at the situation in Finland. Finland has only recently implemented a new law on biobanks. Therefore, I want to discuss, how parts of the triangle model are used in the Finnish biobanking and health care system.

## 4.1 What is missing?

Much has been done in the area of biobanking to support personalized medicine. However, when working on the development of the triangle model, I came across some issues that are to the best of my knowledge still missing.

There are basically four parts that require attention. They are concerned with: the governance plan and its components, details in quality control management, the usage of information technology in biobanking, and the reporting mechanisms in scientific publications.

### 4.1.1 Governance plan

The governance plan for a biobank is essential for its transparency to the public, researchers, other biobanks in a biobanking network, and funding institutions. The governance plan is needed for funding institutions to know what they are funding, and for the public to know, who is in charge and what the participants' rights are when taking part in a biobanking study and donating samples. The governance plan should include in addition to information about the biobank's administration the following information:

- ethical regulations for consent type and privacy protection,
- sample management and access requirements to samples and data,
- standards and best practice guidelines that are used in the biobanking process,
- quality and database management, and
- economic management including a business model for the economic analysis.

However, the parts of the governance plans that are currently available focus only on the first two points about ethical and legal aspects of biobanking. It is true that they make up an important part to governance since they are the parts closest linked to laws and regulations. Yet, the other parts are just as important but are not featured in currently available governance plans.

Knowing the standards and best practice guidelines applied in a biobank and the included quality and database management plans help other biobanks and researchers to estimate the sample quality that they can expect from that biobank and the data security and safety. It ensures them that proper measures are taken to guarantee the quality of samples and corresponding data.

There have been suggestions for business models for the economic analysis of biobanks [3], however it is important to include financial models to the governance plan. This helps funding institutions in particular to understand where the money is used. In addition to that, a standardized financial analysis plan such as the TLCO model is required. It could render spendings of different biobanks comparable.

One important aspect of biobanks is the dynamic creation and destruction as stated in Chapter 3.2.4. Since the governance plan is the internal law the biobank has to follow, it is important that it allows for the flexibility that the biobank needs. The more precise the governance plan states its regulations, the more difficult it is for the biobank to maintain a certain flexibility and adapt to changes if there is no exception statement included. An exception statement allows to change regulations through the inclusion of RECs or IRBs in the governance plan which will ensure the observance of ethical and legal values.

### 4.1.2 Quality control

While the quality management plan is supposed to be listed as one of the best practice guidelines, there are more parts missing in current quality control. More quality control parameters, especially biomarkers for different sample types and for the use with different techniques need to be found. Furthermore, the proposed SPREC is so far not valid for the case of complex derivatives. This, however would be of importance: for example, nucleic acids are complex derivatives and play a significant role in genetics and genomic research as parts of personalized medicine. The SPREC code should be stored with each sample aliquot. However, the storage conditions and freeze-thaw cycles should be documented as well because they can influence sample quality, too.

Sample tracking is important for quality control but is mostly done by the biobank personnel. With the help of a barcode they can scan an item to recognize it, store the scanning time and place to track the sample during shipping, and whenever adding information to the sample's data in the database. The scanning of the

barcode prevents mix up errors of sample information through typos when having to copy the unique identifier for example. However, tracking also needs to be able for researchers directly through the interface they are using when accessing the biobank. For research it is sometimes important to repeat tests with an aliquot from the same sample that was stored under either the same or different conditions. Therefore, a way has to be provided to track the sample and find aliquots of either the same or a different processing batch.

Every information on sample handling, the SPREC, and tracking information have to be stored with the corresponding sample. Many steps need to be documented during the lifetime of a sample; however, so far the decision whether or not to document depends mostly on the people who handle the samples and the opinion, how important they think a certain step or condition is. Obviously, there are clear standards missing describing what information needs to be documented and stored with each sample. This is of importance to researchers so that they can query the database to find samples that have gone through certain steps in their processing, have specific characteristics, or are of well defined quality.

### 4.1.3 Using information technology

Storing data in large databases has become easier through recent advances in information technology. Biobank database systems allow not only for storing large amounts of text data, but also for adding electronic forms, reports, images, and other data types to a database entry.

This possibility calls for e-governance systems, which allow for electronic forms to be filled and submitted online on the web interface of the biobank. If available, there should be a direct link from the database to the electronic medical health record. To make this more secure and to prohibit access to personal or other restricted information, only certain fields from the record could be accessible. For the case that a researcher wants to access other fields, there could be an application form provided where the reason for such access could be stated, which is then verified by an ethics committee. Electronic consent forms could include educational movies to explain the procedure, and could even be signed through an electronic signature. Another idea is the provision of dynamic consent, where participants can access their sample's information through a web interface and give continuous consent for research. However, this requires further security considerations. While the web access for dynamic consent would be used from a private computer, the original consent form will still be filled at the institution where the sample is collected which will allow for higher data security.

### 4.1.4 Reporting in scientific publications

Scientific publications on research with biobanked samples require clear reporting guidelines that have to be enforced by journals. So far, this was mostly left up to the researcher and treated according to standards from their respective field.

A standard for the minimal set of information about a biosample is needed and has to be accepted by journals. As soon as this minimal set and possible extensions are defined, a standard based on the eXtensible Markup Language (XML) could be used. The biobank could then allow to retrieve the required information in this form. It could be attached to a publication in the appendix or as an additional information file.

Another issue is that it is general consent that publications should contain a reference to the biobank and the biosamples which were used. However, the used samples should also provide a link to the published article, so that researchers using a sample can see which types of studies have been done with the sample and where to read about them.

## 4.2 View on Finland

After this general approach, it is interesting to see how the triangle model can be used in the example of Finnish biobanks. The Finnish biobanking system has recently been changed through the Biobank Act (Act 688/2012) [78], which was approved on October 2, 2012 by the Finnish Parliament and came into force on September 1, 2013 [79]. According to Sirpa Soini, a legal adviser for the Finnish national biobank coordination and a member of the Governmental Expert Steering Group for the Implementation of the Biobanking Act, this is the first such law in Europe which is applied to all biobanks independent of their type and purpose [80]. Other biobank regulations are usually type specific, leading to different regulations in case of for example tissue banks, blood banks, population-based, or disease-oriented biobanks.

Finnish biobanks are also going to be part of the BBMRI network with BBMRI.fi as their national node. On March 10, 2014, Auria Biobank and THL Biobank have been registered in the national biobank registry of the National Supervisory Authority for Welfare and Health (VALVIRA), making them the first two official biobanks in Finland in accordance with the Biobank Act. [79]

Comparing the information available on the requirements for Finnish biobanks and their set up with the triangle model brings the following results:

- Information on biobanks in general and specifically on donor rights, consent, and data protection is available for the public. The topics, the public is most concerned about are explained in a short and easy understandable manner on the web page about biobanks in Finland in Finnish, English and Swedish. [81]

- The Biobank Act makes it possible to ask for consent for unspecified future research. This so called biobank-specific consent allows the inclusion of samples and data to several projects in one specified biobank infrastructure. However, participants have to be informed on the voluntary nature of participation, biobanking in general, potential risks, the reason for the collection and storage, as well as on their rights to cancel or limit their consent at any time. Furthermore, due to the strong link of samples and data to the biobank, participants need to be informed about the owner of the biobank and the biobank itself. [80]

- There is no information available on the specific governance of the Auria Biobank while information on the THL Biobank is only available in Finnish. However, BBMRI.fi states that biobanking activity is governed by five laws: the Biobank Law, the Law on the Medical use of Human Organs, Tissues and Cells, the Law on the Status and Rights of the Patient, the Medical Research Law, and the Personal Data Act. Furthermore, it states the National Supervisory Authority for Welfare and Health (VALVIRA), the National Committee on Medical Research Ethics (TUKIJA), and the applicable regional ethical committees as authorities to guide and monitor the biobanks. However, standards applied in the biobanking process, quality control mechanisms, or a business model for the financial analysis of the biobanks are not explicitly mentioned. [79, 81]

- The Biobank Act describes biobanks as shared research resources. Therefore, samples and data can be used for research if the intended use fits to the notified field of research activities of a biobank and is consistent with the provided consent. Only in a few cases, the restriction of delivery is justified, such as to safeguard intellectual property rights, privacy or primary research, for reasons related to research ethics, if the intended use is against a biobank's field of activity, and to preserve rare or limited collections for significant purposes. These access criteria apply to both, internal and external research, and must be transparent in the access policy. [80]

- According to the Biobank Act it is obligatory for the biobank to publish information on their banked samples, their use in research projects and the results of those projects. The goal is to have data accumulate in the biobank for other researchers' benefits. This would help to minimize analytical repetitions and present a common platform for research findings. [80]

This shows that Finland's biobanks already have a good structure to provide support for personalized medicine, while the same issues remain missing as for all biobanks. However, creating a network of same standard high quality biobanks is in my opinion a good approach taken in Finland. It will make the BBMRI.fi a high quality node in the BBMRI network and will allow high quality national interoperability of biobanks as well as international collaborations through the BBMRI network.

# 5. CONCLUSION

The motivation for this work was that to the best of my knowledge no scientific publications exist that present all aspects that would be necessary for biobanking and research to support the development of efficient personalized medicine. To fill this gap in the literature I created and presented the triangle model in this thesis.

The biggest problem I experienced during the writing process was the relevance of this topic. Continuously new articles are being published, biobanks are set up or fail, and there are many people with various opinions on what is good or bad practice. And even though there are many recent articles concerning biobanking and biobank research there are some processes in biobanks that have their information not published. Many times something that seemed to be missing was in fact already used in practice in some other biobanks.

The triangle model was created based on a thought experiment after extensive literature study. Every element of the model was presented, examined, and compared to published information to find the elements or parts of the elements which have not yet been developed or have not been regarded as important for biobanking and research to support personalized medicine. From the previous chapters it can be seen that there is indeed much information on most elements of the triangle model and I found mainly four points that are missing. These are:

- the availability of a complete and flexible governance plan since only ethical and legal aspects as well as access regulation are mentioned and corresponding information accessible,
- proper standards for documentation and tracking of samples for quality control,
- use of electronic forms, and
- proper standards for reporting in scientific journals.

This model and the results from the analysis to find elements that are still missing can be used as a base line for setting up a biobanking project in support of personalized medicine. The triangle model should stir up a discussion about the presented components and lead to a development of the missing parts. Then, it can be used as a guideline to support biobanking to lead to better personalized medicine.

When asked whether biobanking is a model for success for the support for personalized medicine, I would say that I believe biobanking can become a model for success but there is still work to be done. Especially for enhancing interoperability between biobanks as well as research institutions and clinics there is a lot of work in progress. The BBMRI is one big network in Europe that tries to provide a simplified way of sharing data and samples among different national biospecimen collections. However, the network is currently only in its establishing phase and only time will tell if it will fulfill its promise.

Another issue I found during the literature review was that most authors see a biobank as a standalone physical entity. This model of a biobank can potentially cause problems if it is not in any way connected to a clinical or research setting. There has to be a tight link between biobanking, research, and personalized medicine, and standalone biobanks tend to miss what is needed for interoperability in an interdisciplinary field. However, I do not believe those biobanks have to be a failure. Through employing clinicians and researchers in their advisory board, for example, a closer link to research and personalized medicine can be created. The triangle model presents important aspects to connect these fields. Therefore, following the guidelines of the triangle model could help biobanks to become a more successful support for personalized medicine.

The future of biobanks will depend on the usability of the stored information. If no one uses the collections for research, or if the public does not support such collections anymore, funding institutions will lose interest and biobanks might have to close. However, at the moment this field is still in the collection phase where new biobanks are established in almost every country. In a couple of years it will be seen how many of them are used and if biobanking and research really support personalized medicine.

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