Biobanks and the Public.
Governing Biomedical Research Resources in Europe.

A Report from the BBMRI Project

Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)

BIOBANKS AND THE PUBLIC

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This report provides a summary of the research undertaken by the *Working Group on Ethical, Legal, and Social Issues (ELSI)* of the *Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)* project, a major effort funded by the European Commission and aimed at coordinating biomedical resource collections in Europe. The explicit goal of the ELSI sub-project was to provide guidance and advice on the governance of biobanks and biomolecular resource collections. The material presented in the following is based on empirical research—in the form of numerous "focus group" interviews—as well as a series of meetings and discussions of the experts participating in the BBMRI/ELSI effort. As such, what follows represents perhaps the most comprehensive collection of materials related to the political and social governance of biobanks and biomolecular resource collections in Europe today. This summary guide was written for a very broad audience, including government officials, medical researchers or biobank practitioners, corporate managers, journalists, representatives of NGOs, and members of the informed public. In itself, this report reflects the main conclusion of our research: In order to be successful in the long term, *biobanks must engage with the public.*

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1. Introduction

Over the past two decades, the explosion in biomedical research since the 1950s, together with important technical advances in high-throughput analysis, has resulted in the creation of an increasing number of facilities for the long-term storage of human cell and tissue samples for research. Despite significant differences in approach, purpose, scale, and scope, these facilities are now collectively known as "biomolecular resource collections" or simply "biobanks".

When "biobanks" were first reported in the European science press almost 15 years ago, they were greeted with a healthy dose of scepticism and, on occasion, with outright fear. At least to some, the proposal by the Icelandic biotechnology firm deCODE to build an exhaustive database of genetic linkages between all Icelanders raised fears of a new kind of "big brother", with access to our family history and genetic make-up and funded by US American venture capitalists.

Since then, much has changed. For example, large biobank projects throughout the world are now aiming at sequencing the entire genome of tens of thousands of individuals. At about the time deCODE started its endeavour, the private company Celera Genomics raised around US$300 million to assemble the first full sequence of a single human genome, while a parallel public-sector project spent probably billions of US$ on the same task. Over the past years, the cost of genome sequencing has dropped considerably and, if we are to believe the announcements from a number of companies developing new sequencing equipment, in only a few years the cost of sequencing the entire genome of a person will cost less then a few hundred US$.

But, while inexpensive genome sequencing may well be a necessary prerequisite for a new area of genome-informed, personalized medical care, cheap sequencing alone is far from sufficient when it comes to extracting real medical benefits from genome research. Thus, apart from a few singular cases, for many years to come the main beneficiaries of inexpensive genome sequencing will not be patients—but, rather, biomedical scientists.

In this new world of clinical genomics, where the entire genomes of tens of thousands of individuals will be readily available, the role and importance of biobanks—which link physiological samples to medical and biomedical information, such as whole genome sequence data—will become ever more important. But, future biobanks are no longer simply organizations that collect, and store, peripheral blood samples, and then make them available to scientists and, in this fashion, limit the potential risks—ranging from a breach of confidentiality to the violation of a informed consent agreement—that an investigator faces when dealing with human-derived materials or genetic information.

Rather, we believe biobanks will increasingly turn into strong and trusted partners of both medical scientists and the public—and, especially, the invisible community of biobank "donors" or "participants". * In this report we advocate a novel approach toward biobank governance; an approach where biobanks are no more simply service institutions for the scientific community, but *active, and reliable partners of both the scientific community and the public in the pursuit of genomic medicine.*

* Note that, in the case of scientific research there is, strictly speaking, no "donation" to a different patient. Thus, it has been argued that biobank donors should be more appropriately termed "source persons". In what follows we will continue to use the more common term "donor" or "participant" when referring to individuals who have provided blood or tissue samples, or medical information, to biobanks.

1. From Pathology Collections to "Biobanks"

Collections of paraffin embedded tissue samples, built up since the late 18th century by many pathology institutes across Europe, are the predecessors of today's biobanks.

Materials derived from human bodies have been collected at many sites, and with a variety of purposes, for many decades and, in some cases, even centuries. Pathology institutes started to systematically collect, and store, tissue samples at least since the beginning of the 19th century. Since then, sites that collect human materials have multiplied tremendously. Today, there exist many different types of organizations collecting a wide variety of human cells and tissues, and for numerous purposes, ranging from diagnostics to law enforcement.

Pathological institutes at university hospitals have collected tissue samples for pathological analysis and further research for over two hundred years. While the collection of pathological tissues often started sporadically and out of curiosity, with the advent of public health as a political concern for nation states in the late 18th and early 19th century, collecting pathological tissues took on a broader political significance. In fact, in some European nations collecting pathological tissues was obligated by state health authorities.

Technological advances also played an important role in enabling these first large-scale collections of human tissues. Fixing tissues with formaldehyde and embedding tissue samples in paraffin wax, both methods invented, and perfected, during the first half of the 19th century, provided a simple, low-cost solution to the problem of long-term storage for pathological tissues.

These innovations, together with advances in light microscopy, also helped to turn human tissues into objects of controlled scientific investigation within the laboratory. As a result, during the 19th century, pathology turned into a discipline in its own right at the forefront of research and innovation in medicine.

Some of the tissue collections that have been assembled by pathology institutes over the past hundred years are enormous. The Institute for Pathology at the Medical University of Graz, Austria, assembled over three million paraffin-embedded tissue samples. Today these samples are stored and managed at Biobank Graz, the central biobank of the university. Collections at other pathology institutes throughout Europe similarly store significant numbers of paraffin embedded tissue samples. Embedding tissues in paraffin remains a preferred method for the long-term storage of pathological tissue samples even today. Paraffin-embedding as a method of long-term storage was very much linked to the dominant culture in pathological research since the late 18th century.

For over two hundred years, pathologists have examined tissues mainly through the visual inspection of tissue morphology. Thinly sliced tissue samples are fixed on glass cover slides, stained with various reagents, and examined through standard light microscopy. Inexpensive, accurate, and perfected over more than a century, this approach remains the standard procedure for tissue examination in clinical practice even today. Several decades after the molecular biology revolution, genetic techniques for tissue examination in the clinic are still used only very selectively.

Paraffin-embedded tissue samples can still be examined morphologically even after many years, or even decades of storage. But, while DNA remains at least partly preserved in paraffin-embedded samples, the usefulness of this techniques for storing tissue samples to be analysed by genomic or proteomic techniques is much more limited.

The rise of biobanks was initially linked to the rise of cancer research and, more recently, has accelerated with the advent of large-scale genomics research in the public sector and in industry.

"Biobanks" are of a more recent origin and are largely linked to the rise of cancer research and, more recently, the advent of genomics. "Biobank" is an ambiguous term with more than one meaning, usually referring to a hybrid infrastructure that links collections of biological materials obtained from healthy or diseased individuals to diverse collections of medical or biomedical data, and including patient records.

The large expansion of cancer research during the 1970s motivated some of the first tissues banks, established as a means to supply the growing number of cancer scientists with easy access to human materials. Tissue banks collecting various types of cancer tissues for research purposes have been established at many large research hospitals, and some of these collections have become significant in size.

In the 1990s, the Icelandic genomics company deCODE made headline news with its proposal to link the country's rich genealogical maps with medical records and genetic data in an aggressive effort to unravel the genetic origins of common diseases. [1] For almost a decade, deCODE was synonymous with a new approach in biomedical research, combining rich genealogical and medical data with the latest high-throughput technologies.

At least to some, deCODE was also synonymous with an unprecedented intrusion of venture-capital backed biomedical research into the private lives of ordinary citizens. Thus, the company helped to fuel an intense international debate on the use of medical data and genetic samples in privately funded biomedical research. Following deCODE, a number of countries announced national or regional biobank projects and, over the past decade,

the number of biobanks has multiplied.

Collections of human cells or tissues are not limited to research biobanks. Rather, research biobanks, as they are being built today, constitute just one out of many forms of collecting human cells and tissues.

There exist numerous types of collections of human cells or tissues through the medical world. In fact, the term "biobank" is not strictly technical, but rather refers to a set of practices for collecting and storing biological materials, as well as medical and biomedical data. Biobanks have different origins and are set-up for differing purposes: While some biobanks were started simply with the intention to facilitate the storage and distribution of human cells or tissues for biomedical investigations ("research biobanks"), others were set-up with the purpose of storing tissues for therapeutic applications ("therapeutic biobanks"), while yet others have emerged as by-product of medical "cohort studies" of a given population over extensive period of time ("population-based biobanks").

By far the most widely collected human material is peripheral blood. The use of blood in medicine has a long history and, today, blood is used widely for diagnostic purposes. At least in developed countries, the practice of taking a blood sample is omnipresent throughout the public health systems. Blood is taken for many purposes, from identifying the cause of a simple cold to screening for common diseases, ranging from infectious diseases to more complex diseases, such as cancer.

Blood donations for medical purposes also have an extensive history. [2] Blood is collected in large quantities for medical use as material for transfusion and there exists an extensive infrastructure for the collection and processing of blood serum and plasma. Some agencies that collect and process blood have also built large collections of blood samples with linkages to (anonymised) donor information.

On the background of the troubled history of the blood supply over the past few decades, with thousands of cases of infection with HIV or hepatitis via blood transfusions, to keep a sample of each donation might seem a sensible policy. Yet, like all "biobanks", the collections that have been built by some agencies over the past decade have reached a significant size and pose important ethical and legal questions, notably when it comes to using these samples for other purposes, not related to blood transfusion, such as research.

As part of long-term correlation ("longitudinal") health studies or, else, for screening purposes, the blood samples of the populations of entire regions have been collected and stored for decades. For example, a university hospital in one region in Europe keeps blood samples of all male citizens who have undergone testing for prostate cancer as part of a screening program that is in part funded by the local government.

Extensive collections of human cells, tissues, or DNA samples are also being build for highly specialized purposes, such as law enforcement and forensic investigation. These collections have little in common with research biobanks.

Police and law enforcement agencies throughout the developed world continue to collect increasingly large numbers of DNA samples of people deemed "suspects" in criminal investigations, as well as for forensic purposes. In some countries, these collections have grown very large, covering significant portions of the population. Perhaps the most well known example is the extensive DNA bank built by the Forensic Sciences Service (FSS) in the United Kingdom, which today stores well over 5 million samples.

And, as techniques for extracting and analysing DNA samples become ever cheaper, the question arises of whether to build a

comprehensive database with coverage of *all* individuals living in a given region or country? Taking fingerprints used to be a technique limited to criminal investigations. But, biometric identification using fingerprints has now become widely used and, after 9/11, some countries—such as the US or Japan—now require biometric identification using fingerprints at their borders for all non-citizen or long-term residents. The suggestion that DNA samples could be next is not as far-fetched as it may seem.

Militaries around the world already collect, and store, blood samples of their personnel for various purposes, including identification after combat death. Thus, some of the world's largest collections of human materials are, in fact, managed by military or defence related organization or agencies, such as the US Department of Defence (DoD).

The goal behind the research biobanks of today is to enable a very broad set of scientific investigations and, thus, to make maximum use of the resources collected and stored.

Most of the existing collections of human cells and tissues were built with a *specific* objective in mind—which, in turn, determines the actual practices of collecting, storing, and analysing samples. The usefulness of each collection beyond a selected purpose can be highly limited.

By contrast, some emerging biobanks aim at very broad collections that include samples from patients suffering from (usually) common disease as well as samples from healthy donors used as control. The goal of these collections is to enable a broad range of biomedical investigations that can make use of large collections of samples.

Thus, over the past two decades, biomedical resources collections that were initially built for a specific set of experiments,

have gradually turned into more "universal" collections of human cells, tissues, and information to be used in a much more broader set of medical and biomedical investigations. As we will discuss in the next chapter, this new "universality" of biobanks—and the explicit ambition of biobanks to turn into generic resource collections—is not without its problems.

3. Biobanks as Universal Research Infrastructures

Scientists have been collecting human materials for research purposes for centuries. But, while earlier collections were built for reference purposes or, more recently, were often related to specific research objectives, today biobanks are designed as infrastructures to support a broad range of scientific investigations.

As we have seen, biobanks have a long history, starting with the pathology collections of the late 18th and early 19th century. Further, with the rise of biomedical research during the second half of the 20th century, first in the United States and more recently in Europe, numerous collections of human materials for specific research purposes were created.

There exist several hundred human materials collections in Europe today, and these number does not include smaller collections that individual scientists have gathered during the course of their research. The vast majority of these collections is linked to a single research laboratory, or department, and has been built over time, often as part of a long-term research objective.

The users of these collections are typically limited to a small number of scientists, and rarely extend beyond the immediate collaboration network of those collecting the resources. Most of these small tissue banks were started by scientists in areas such as cancer research, where human tissues are used extensively. Many of these collections remain limited in size, and investment, and are typically known only to insiders, or the agencies or institutions that fund them. And, until very recently, few would actually label themselves as "biobanks".

The advent of genomics, proteomics and various other technologies that make it possible to analyse increasingly large quantities of samples at a reasonable cost has had a significantly impact on the reality of biobanking. Historic collections have been highly case-oriented; that is, the goal had typically been to preserve individual cases and what is unique about them.

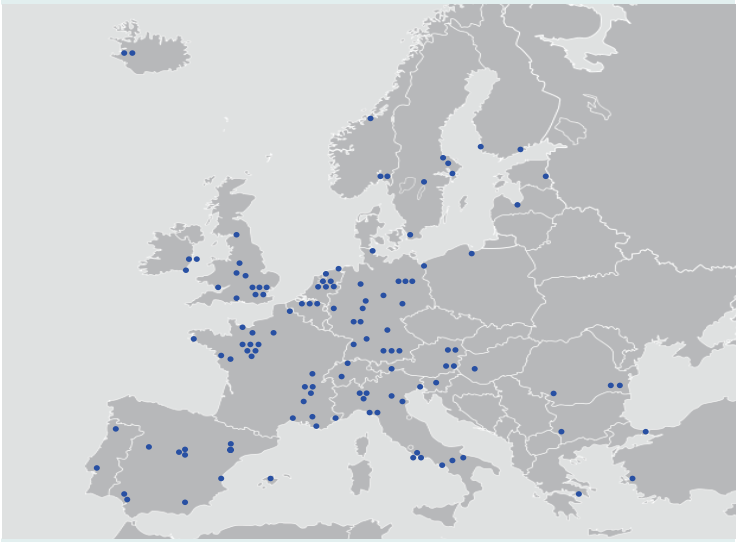
In genomics, the task is often the opposite: large numbers of samples are used to identify statistically significant commonalities, and to establish statistically significant relations between a given phenotype (e.g. a common disease such as prostate cancer) and an underlying genotype. While it is far from clear to what extend such relations do exist, or are indeed significant and meaningful in common diseases, there is no question that very large sample sizes will need to be analysed to understand them. [3]

Thus, the advent of medical genomics has put a new value on sample collections that are large and also provide access to medical records. In some cases, dormant collections were suddenly viewed as potential "treasure troves"—finally to be opened, and accessed, with the help of the new technology of genomics, or whatever flavour of "omic" approach.

Over the past decade, biobanks have become research infrastructures in their own right. Governments in many countries are spending an increasing amount of funding on building repositories of human materials and biobanks, even if immediate scientific is far from certain.

The need for ever larger numbers of samples has raised the bar for investments into resource collections, from tens or hundreds of samples to *tens or even hundreds of thousands of samples.* Thus, over the past few years, funding agencies have started to look at biobanks as an important *common infrastructure for biomedical research*—thus, the emergence of increasingly sizeable "infrastructure" biobanks that collect, store, and distribute large quantities of human blood and tissue samples potentially useful to many

BOX 1: BIOBANKS IN EUROPE



The BBMRI Project: Representing Europe's Biobanks

The *Biobanking and Biomolecular Resources Research Infrastructure* (BBMRI) effort represents over 270 organizations in 33 countries that collect human cells and tissues for research purposes—the vast majority of publicly funded biobanks in Europe. At present, BBMRI is also the largest organization of biobanks and biospecimen collections worldwide. A major objective of the BBMRI effort is to develop technical, operational, ethical, and legal standards and "best practices" for operating research biobanks.[4] The map above dis-plays the location of major biobanks in Europe (Graphic adapted from: Gaskell, G., Gottweis, H., 2011).

different investigative strategies and research purposes.

Despite lingering questions about the actual feasibility of many of the scientific approaches pursued, biobanks have emerged as a new type of "Big Science" undertaking. Biobanks today are increasingly turning into sizeable facilities with large numbers of tanks for cryopreservation, large sequencing or proteom-ics pipelines, and increasingly large computer rooms to store and analyse genomic and proteomic data.

When the first large biobank projects were announced, there was a certain perception—both in research and the general public—that the output in terms of new medical and therapeutic advanced would follow straight. In some countries, such as Estonia, early biobanks projects were sold as a new way to capitalize on the "patrimony", and to catapult backward economies into the new world of the technology fuelled turbo-capitalism of the San Francisco Bay Area.

Today, such naïve views of biobanks—and genomic research—have certainly given way to a more realistic assessment. Yet, governments, research agencies, and private corporations continue to spend significant amounts of funding on biobanks. In fact, some of the largest biobanks projects—such as Biobank UK—are only now becoming available to scientific users. And, it may well take years, if not decades, for the scientific output from the infrastructure investments undertaken today to fully materialize.

While it is far from clear whether the various approaches in "omics" research will indeed live up to their grand promises, biobanks today are already indispensable for medical and biomedical research. Biobanks are no longer seen as collections that can be exploited quickly, and through a clearly delineated series of experiments. Rather, biobanks are increasingly turning into "intermediary" organizations that enable controlled and easy access to human cells and tissues linked to genetic, proteomic, and medical information.

Biobank activities in the private sector have increased considerably over the past two decades and the cell and tissue collections managed by pharmaceutical firms and biotechnology start-up companies will continue to grow.

There is good indication that biobanking activities in the pri-

vate sector continue to grow significantly, yet the sheer extent of private cell and tissue collections, and associated data collections, remains poorly understood.

Biotechnology corporations and large pharmaceutical firms have assembled their own internal repositories of human cells and tissues for a variety of research purposes, from genetics to the toxicological evaluation of new drugs. Also, pharmaceutical firms increasingly keep human cell and tissue samples from patients enrolled in drug trials and clinical studies and are thus building up increasingly large collections.

Industry organizations and consulting firms regularly offer training courses on "best practices" for biobanking and there exist numerous (often commercial) conferences that address issues related to biobanks. Some biotechnology firms have even offered human sample collections for sale, although the business case for selling human tissues appears more complex, and less straightforward, than some entrepreneurs had hoped. [5]

The core activities of research "biobanks" consist of a set of practices to collect, store, distribute, and analyse a broad set of medical and biomedical materials and information. These practices, and the actual protocols used to collect and store samples and information, determine the range of experiments that can be undertaken with the stored material or information.

Whatever their specific background, biobanks are organizations that collect, store, distribute, and analyse (human) biological materials as well as medical and biomedical data associated with these materials. Historically, biobanks have often been linked to a specific issue or question, such as the verification of a diagnostics test, or a specific research question.

The actual "usability" and research value of biobanks is linked to the very content of a biobank and to the specific practices of collecting, and preprocessing, specimens and information.

It is important to note here that the way how samples are collected, processed, and stored determines what these samples can actually be used for. To start with, samples can't be used infinitely. While extracted DNA from human cells can be "amplified"—and, thus copied—almost without limitation, the same is simply not true for the cells as such. For example, a proteomic investigation using mass spectroscopy will require a certain amount of cellular material, thus limiting the type of investigations that can be undertaken with a single sample.

Cyropreservation in liquid nitrogen, a much more expensive approach than paraffin embedding, has become the method of choice for storing fresh tissues as well as peripheral blood used in biological and biomedical research. With cyropreservation much larger sample quantities—even entire organs—can be stored over much longer periods of time and with no, or only very little damage to three-dimensional tissue morphology or cellular macromolecules, such as DNA or RNA. Compared with paraffin-embedding, there exist few limitations when analysing cyropreserved tissue samples. [6]

Further, a number of new technical methods have made it possible to extract, store, or multiply biologically active macromolecules, and notably DNA. And, with advances in both analytic technologies and our understanding of the biology of disease, the range of investigations possible with the collected materials is likely to expand.

For example, until very recently the cost to fully sequence the genome of all donors in a biobank was deemed prohibitively expensive. But, as the cost of sequencing drops, sequencing tens or hundreds of thousand of human genomes is now becoming pos-

sible. Some biobanks, such as the projected "Medical Megabank" in the Tohoku area in Japan, plan to fully sequence hundreds of thousands of samples. Also, new types of proteomic profiling of cells require less materials than was the case only a few years ago, thus expanding the range of proteomic analysis that is possible with a single sample.

With the decreasing cost of genome sequencing, the information content of biobanks is likely to expand considerably. Already, a number of biobanks have announced their intention to fully sequence tens or even hundreds of thousands of individual human genomes and make these data available to medical researchers. In fact, it is quite conceivable that the biobanks in the near future may well have more in common with large server farms and data centres, processing and storing vast amounts of genomic and medical data—rather than the cyropreservation facilities of today.

Of course, as was the case with earlier collections of pathological tissues, biobanks are not "immediately" useful—rather, they *become* useful in relation to certain problems or questions or, simply, as a reference. Making sense and, thus, making use of biobanks is far from trivial. It is relatively easy and straightforward to collect and store thousands of samples; but it is much more difficult to analyse them in a meaningful way.

Because of their sheer size and broad coverage, research biobanks pose a number of ethical, societal, and legal questions related to the collection, long-term storage, data protection, and research and commercial use of biomedical samples and information. Paradoxically, the more useful biobanks are, the more questions are likely to be raised about them.

As we have argued, many of the smaller biobanks in Europe started as small-scale research efforts with the intention to store

fresh human blood or tissues for further biomedical research and analysis. While individual patients most likely signed an informed consent form about providing a blood or tissue sample for further analysis to a pathology department, to make these resources available to a broad variety of investigations was often an afterthought. Most of these efforts remain largely unknown to a broader public, even today.

If biobanks become a subject of public debate, it is because of their increasing scale and scope. Notably, biobanks become problematic and, thus, the subject of concern and debate: (1) when they reach a certain scale—as in the case of Iceland's Health Sector Database (HSD) or the UK Biobank; (2) when the practices they advocate are of a broader significance—as in the case of unrestricted informed consent that would allow a single sample to be used for any kind of future research; (3) when the data and information stored impacts individual donors—as in the case of genetic diseases identified in samples from healthy individuals; or (4) when the use of the material or data stored is of economic value—as may happen in the case of commercial output from research using resources provided by public biobanks. [7] In summary, present day biobanks are not simply problematic *per se*. Rather, biobanks *become* problematic because of the way they are managed and used.

Experiences with biobanks over the past two decades appear to indicate that biobanks are most useful when they are relatively large and, thus, cover a significant number of individual cases; when researchers are able to use samples for many different types of experiments or can follow-up medical histories over a long period of time; and when their use is broad and comprehensive, and includes industry. In other words, there is a high likelihood that biobanks that are actually "useful" for research may also raise important ethical or societal questions.

Research biobanks are built for many purposes, and with nu-

merous objectives in mind. But they share one common goal: the material is collected for the explicit purpose of research, from basic science to drug development, rather than medical use or forensic identification. Research biobanks nonetheless pose a number of important issues and questions. The following list is by no means extensive, but is meant to provide an overview to some of the most pertinent issues that have been raised with respect to research biobanks:

1. *Research ethics and the notion of consent.* The traditional interpretation of informed consent with respect to participation in medical research tends toward a narrow interpretation in the sense that the consent provided by the patient covers only areas of research the patient was informed about, and thus investigations explicitly covered by the consent document. In the case of biobanks this seems increasingly difficult, as it is by no means clear for what type of research a sample—or the data derived from it—will actually be useful. Further, for biobank administrators, there exist many practical issues when dealing with samples that have been obtained with differing informed consent protocols. Thus, not surprisingly, biobank administrators prefer a broad interpretation of informed consent that imposes no, or only few, restrictions on a biobank facility.

2. *Privacy, data protection, and protection of the individual.* Biobanks collect, and store, blood cells or other tissues, as well as personal information and medical records of individual donors. Further, after analysis, biobanks may also store genetic or proteomic information that may have direct implications for the individual donor. In the end, biobanks essentially are extensive collections of all kinds of information related to their donors, which poses numerous questions about access, data protection, and (genetic) privacy. Can information be made truly anonymous? And, just how much of the medical and personal

information is to be made available to users? Too much information may lead to quick identification, while insufficient information may impact the relevance and usefulness of a given sample.

3. *Legal and technical safeguarding of biobank resources.* Data protection for biobanks has important legal and technical aspects that are complex and far from trivial. Legally, biobanks must develop sufficient procedures for data protection but also data sharing. Technically, biobanks must safeguard increasingly large data resources that, in the near future, may comprise the wholly sequenced genomes of tens of thousands of individuals—all while making them available to research users. What technical infrastructure is appropriate? How to ensure that biobanks develop the necessary technical competency to safeguard these vast collections of genetic and medical information?

4. *Re-identification.* While personal and medical information is anonymised, there remain difficult technical questions of when a sample can be, or should be *re*-linked to a given person. Despite the need for protecting anonymity, the potential of discoveries that could benefit a specific donor (e.g. through the early prevention of disease or through tailored therapy) pose the opposite, and equally complex, issues of identification. If an important health-related finding relevant to a given donor (or class of donors) has been made, what should be done? Should donors be informed? And, if yes, how? Who has authority to identify donors and who should make these decisions? These are complex ethical and legal questions that defy a simple answer.

5. *Ownership, benefits, and rights.* Individuals who donate material to biobanks typically are asked to renounce any right of ownership in the donated material. Yet, there remains the more complex question of "benefits" from,

and "rights" to the donated material. What benefits can donors expect? And, should donors have the right to influence what kind of research is (or is not) to be undertaken with their donation? And, further, should donors have a universal right to "opt out" at any time?

6. *Access to resources.* Biobanks are built for scientific research. But, biological resources are not infinite, thus the question arises what research should be supported? Who should make decisions on what research is to be supported and who should have access to the data stored in a large biobanks? How should priorities be determined? Should industry users be granted access and, if yes, under what conditions?

7. *Representation and bias.* Because of their sheer size, because of the size of investment, and because of the potential influence of biobanks on the course of biomedical research, biobanks also pose questions of representation and bias with respect to ethnicity, gender, or disease group. Should a national biobank projects try to mirror the genetic make-up of a nation? Are woman (or men) appropriately represented? What disease, if any, should biobank collections focus on? These are not trivial questions. For example, in some case interest groups for a certain disease have built their own biobank collections. But, are these legitimate means to promote research, or potentially dangerous distortions within the public health research system?

8. *National and international governance.* Biobanks often started as local (or regional) efforts, but are becoming increasingly national as well as global. In a European context, the European Commission has taken a leadership role with respect to research resources, and also biobanks, and there have also been a number of discussions at the international level. But, the increasingly international outlook of bio-

medical, as well as clinical research also raises many questions related to governance, control, and regulation. What is the impact of the globalization of research on biobanks? To what extend can, or should, biobanks be governed internationally? What institutions would be appropriate to guarantee the open and transparent governance of biobanks in a European, or international, context? How should biobanks, and access to biobanks, be regulated internationally and by whom? Should the traffic of information or samples across national (or regional) borders be regulated? What legal framework is appropriate? What are the ethical implications of European, or global, collaboration in the field of biobanks?

9. *Standardization.* Finally, the use of biobanks as "global" resources poses complex and difficult questions about standardization. The quality of the medical histories attached to a sample can determine how useful the sample is for research. But, medical information (and even medical language) is not entirely universal and, furthermore, there exists considerable variation in "local" therapeutic approaches. Thus, global biobanks would benefit from increased standardization of medical histories and treatment strategies, yet both have proven difficult. In fact, some biobanks have go so far as to *re*-process tens of thousands of medical records, since the initial methodology of data collection and preprocessing turned out as problematic in actual investigations.

The above list of questions and issues related to research biobanks is far from exhaustive, but provides a quick guide to the debate about biobanks. As we will see in what follows, the perception of what is problematic, and which of the issues above are actually subject of public debate, is not uniform across Europe, but depends considerable on the local and national context.

Today biobanks are tools for research. But, in future, it is entirely possible that biobanks become increasingly linked to medical practice. Questions around governance and regulation of biobanks will become ever more complex and urgent once biobanks enter the realm of the clinic.

Most biobanks today are designed for research use only. However, if one reads funding proposals or marketing documents carefully, many biobank projects already today point to the potential use of biobanks in medical practices. Of course, not all of these claims should be taken at face value; to claim medical or clinical relevance is often simply used as an argument for getting a research proposal funded. Still, it is important to point out here that the medical relevance of research undertaken with biobank resources will increase over the next years and decades.

Thus, also, the distance to the clinic will likely decrease. To some extend, when considering the clinical and preclinical research undertaken by pharmaceutical companies, this is already happening today. As we have pointed out, pharmaceutical companies often store blood and tissue samples from clinical research—and regulations in the US and other countries increasingly force them to do so.

In future, biobanks will move ever closer to the clinic, which will pose a whole new set of legal and ethical questions that most biobanks today are ill equipped to deal with. This linkage to clinical practice is unlikely to happen over night but, rather, could take years or even decades. Still, new advances in science could quickly lead to new applications for biobanks, well beyond what appears possible today.

The important lesson here is that biobanks are by no means "stable" but, rather, are constantly in flux and changing, depending on the research that is undertaken with the resources that

biobanks collect. Governance regimes for biobanks *must take this evolving nature of biobanks into account.*

4. Public Opinion about Biobanks in Europe

Biobanks constitute a new type of large-scale research infrastructure located at the intersection of biomedical research and information technology, and at the border between research and biomedicine.

Modern biobanks are located at an emerging intersection between medicine, biomedical research, and information technology. Biobanks today are built explicitly as infrastructures for biomedical research. Yet, biobanks are also indicative of emerging practices in medicine and public health that link medical and genetic information into emerging data infrastructures that are becoming increasingly important within the health care system.

In the preceding chapter, we have seen that biobanks are both diverse and unstable. Biobanks differ in background, research objectives and rationale, collection strategy and practice, and even in the way resources are distributed and shared. Further, as we have argued in the preceding chapter, biobanks change over time and their objectives evolve. Clearly, the biobanks today different significantly—in scale, scope, organization, research target, and governance—from the early tissue exchange programs set up during the 1970s and 1980s. Large-scale genetics has had a profound impact on biobanks and the advent of inexpensive genome sequencing will further alter what biobanks do, and how they manage, store, and distribute their resources. [8]

A key hypothesis in what follows is that, for the long term success of a large biobank project, *public debate tends to have a positive, rather than negative, impact.* As a matter of fact, public debate rarely kills a project—even one as ambitious as the Icelandic Health

Database. It is true that, to "open up" the debate about a large biobank project to a broader audience (rather then just government funding committees or bioethics boards), is an additional burden that may well impact project schedules. Yet, public debate is also a way to build a broad momentum and public support for biobanks.

What is known about these emerging infrastructures and how are they viewed by the general public? What concerns do citizens in various European countries have, and how are these concerns expressed?

Opinion surveys in Europe indicate that the European public, in general, is cautiously supportive of biobanks and research undertaken with biobanks.

While regional differences remain, the European public tends to be positive about both information technology and biotechnology. According to the Eurobarometer surveys, the European public has mostly optimist views on computers and IT. The support for biotechnology in general tends to be significantly lower, but has been increasing steadily from a minimum in 2000. Specific questions related to biobanks were included in the 2010 Eurobarometer survey on "Life Science and Biotechnology" (for detailed results see Box 2), and the results of the survey indicate cautious support for biobanks, but reluctance toward the notion of "broad", or unrestricted, consent.

While indicative of broader shifts in public opinion in Europe, the questions asked by general opinion surveys such as the Eurobarometer are somewhat too general to provide reliable guidance on how public opinions about biobanks are formed. A more specific, and more focused comparative investigation was thus necessary.

BOX 2: The 2010 EUROBAROMETER SURVEY

The 2010 Eurobarometer survey "Life Sciences and Biotechnology" included 8 questions on biobanks. The results were released in November 2010 and are available in a report from the European Commission: "While approximately one in three Europeans have heard about biobanks before, nearly one in two Europeans say they would definitely or probably participate in one, with Scandinavian countries showing the most enthusiasm. And people do not seem to have particular worries about providing certain types of information to biobanks: blood samples, tissue samples, genetic profile, medical records and lifestyle data elicit similar levels of concern. However, amongst those similar levels there are some nuances. In twelve countries, providing one's medical records provokes the most worry, and in ten countries it is the genetic profile that is most worrying. Asked about who should be responsible for protecting the public interest with regard to biobanks, we find a split between those countries opting for self-regulation (by medical doctors, researchers, public institutions such as universities or hospitals) and those opting for external regulation (ethics committees, national governments, international organizations and national data protection authorities). Broadly speaking, respondents in those countries which show higher levels of support for biobanks tend to favour external regulation more than self-regulation. In those countries where biobanks are unfamiliar, self-regulation is a more popular way of guarding the public interest. On the issue of consent, almost seven in ten Europeans opt for specific permission sought for every new piece of research, one in five for broad consent, and one in sixteen for unrestricted. But of those more likely to participate in the biobank, some four in ten opt for either unrestricted or broad consent".[9]

To better understand public opinion, and public concerns, about biobanks, the BBMRI project has undertaken "focus group" discussions with members of the general public in six European countries.

As part of the BBMRI project, over 60 "focus group" meetings were undertaken in various European countries. A "focus group" is a monitored discussion by a selected group of individuals, usually moderated, about a given topic. Focus groups are widely used in social science research, as well as in the advertising

industry, to gain qualitative insights into the formation of public opinions about a topic, product, or advertising strategy. The goal of the focus groups was to gain an in-depth understanding of opinions within the wider public about biobanks.

Focus groups were undertaken in six European countries—the Netherlands, the UK, Austria, Greece, Finland, and France—in order to better understand public opinions and arguments about biobanks and, also, to gain insights into how public opinions differ amount EU countries.

All focus groups have followed the same approach. Up to twelve individuals—including lay people without prior exposure to biobanks, individuals who had donated blood to biobanks, and patients of specific diseases targeted in research related to biobanks—were preselected for a focus group discussion. Discussions typically lasted between two and three hours and were managed by a skilled moderator. Discussion were held in the local language.

All discussions were recorded and fully transcribed for further quantitative and qualitative analysis. Software for automated correspondence analysis between central notions in the discussions (such as "trust in public institutions" or "informed consent") was used to provide a qualitative understanding of public opinions on biobanks.

Knowledge about biobanks within the European public is fairly limited. While public opinions about biobanks appear positive in most European countries, some concerns exist in all countries where focus groups were undertaken.

One immediate output from the focus groups was that the European public knows relatively little about biobanks. While some may have heard about certain controversial cases that have

BOX 3: BIOBANK FOCUS GROUPS

Focus groups as a research methodology are widely used in advertising and opinion research. Because of the small sample size (typically a few docent participants for a given study), focus groups do not provide data about the statistical distribution of opinions or believes. Rather, focus groups provide insights about how opinions, views, and arguments are shaped in an argumentative process and with reference to a wider social, cultural, and political context. [10]

Case and Participant Selection. Representative biobank cases in the various countries were pre-selected by the study organizers. Multiple focus groups were then held in each country. Focus groups were typically separated into two groups: Those comprising participants in a given biobank projects, and those comprising only lay people without prior history of donating to a biobank effort.

Focus Group Discussions. A skilled moderator conducted each focus group. Focus groups typically lasted between 90 and 120 min. To ensure comparability, a common template script was developed in advance and tested on pilot focus groups conducted in Austria and the Netherlands in 2009. These semi-structured scripts were then tailored to each national focus group by adding relevant examples and topics. Following a brief introduction on biobanks by the moderator, participants were then guided through a discussion centering on the following topics: (1) privacy and data linkage; (2) informed consent; (3) benefit sharing and commercialization; and (4) internationalization. While all focus groups did follow a common guideline, participants were provided with the opportunity to add topics or questions to the discussion. All sessions ended with a discussion of the governance of biobanks.

Data Analysis. All focus groups were transcribed and partially translated. A quantitative data management and analysis software was used for structured content analysis. The output from the quantitative data analysis was then used as an input for a qualitative, interpretative analysis.

been highly publicized, the general public has very limited knowledge about biobanks. In fact, most members of the general public have only a very limited understanding about what biobanks

actually *do*. Also, most people know very little about biobank projects within their own country or region. Thus, there exists a clear knowledge gap about biobanks and, as we will see later, this knowledge gap is not without its risks.

Further, there exist wide differences among countries in Europe as concerns public understanding and knowledge related to biobanks. According to an opinion survey carried out within the BBMRI project, 65%-75% of respondents in the Nordic countries (Finland, Sweden, Norway) and 80% in Island say they have heard of biobanks. By contrast, knowledge about biobanks is significantly lower in Germany and France, and drops further in southern European countries.

Despite this knowledge gap, public attitudes toward biobanks appear overall positive. Typically, biobanks are viewed as a "public good": a shared resource to which individuals contribute through their blood donations and that will, eventually, result in a reciprocal benefit in the form of better and more effective medical treatment options.

Support for biobanks, however, is not unconditional and there exist concerns in all countries where focus group meetings were undertaken. Concerns differ among European countries and there is a great deal of variation in the support for biobanks among countries and social groups. Concerns over privacy and data protection are prominent in all countries yet, again, there remain important differences among European countries. While participants in most countries prefer a narrow consent model, broad consent is acceptable in some countries. Also, despite strong opinions about benefits sharing in some countries, participants in most countries have expressed little concern about benefit sharing.

Overall, as we will argue, trust in public institutions and governance constitutes a key indicator for public support for

biobanks and the perception of different governance frameworks for biobanks—at the national, EU, and international level—seem highly dependent upon public trust in the underlying public institutions.

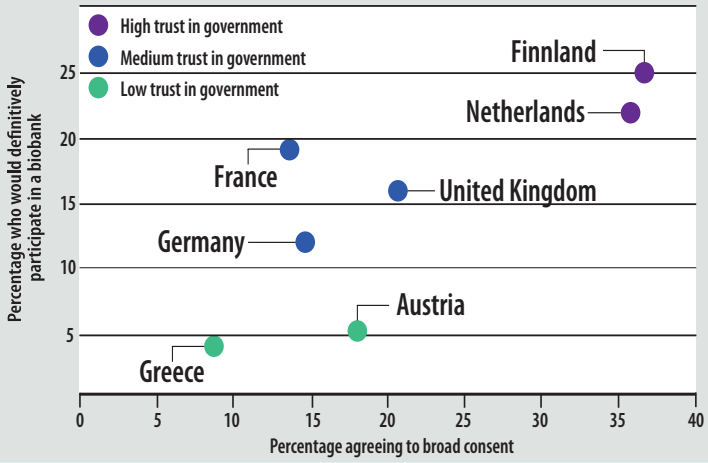
While a "narrow consent" model seemed favoured by most participants, "broad consent" was deemed acceptable in some countries. Individuals, or groups, affected by research that relates to, or uses, biobanks generally appear to be more favourable to "broad consensus". Further, broad consensus does require clarity and openness about goals and institutions and a clear notion of "reciprocity".

Consent remains the most hotly debated issues with respect to biobanks. Existing research ethics frameworks tend to define consent in medical research in a "narrow" fashion, and covering only those experiments that research participants have been informed about.

As generic research infrastructures typically not linked to a specific research endeavour, biobanks inherently pose the question of "broad" and unlimited consent, meaning consent to *any* kind of future research to be undertaken with the biological resources donated and the data derived from these resources. Biobank administrators have argued for broad consent, simply on the ground that it is often not practical to foresee what kind of research could actually be undertake with the resources (blood, extracted DNA, various kinds of biomedical data) stored in a biobank.

In the United Kingdom a broad consensus model was deemed acceptable by many participants. In turn, however, participants argued for the need of transparent governance structures and very clear and precise goals regarding the research undertaken by biobank users. In Finland, there was a clear split among participants—while broad consent, with clear boundaries, was seen as

BOX 4: ATTITUDES TOWARD PARTICIPATION



Trust in Government as Basis for Participation

There appears to be a clear correspondence between positive attitudes toward participation in biobanks—and also acceptance of a broad consent framework—and high trust in government organizations. In countries where trust in government is low, the willingness to participate in biobanks is equally low, as is the willingness to agree to a broad consent framework. By contrast, high trust in government corresponds with the willingness to participate in biobanks and, thus, also to accept a broad consent framework. Graphic adapted from: Gaskell, G., Gottweis, H. (2011).

sufficient by some, others have argued for a kind of "expanded" narrow consent model where participants are re-contacted in case experiments undertaken with biobank resources clearly go beyond the initial consent framework.

By contrast, in Germany, Austria, and Greece, participants expressed a preference for "narrow" consent. In these countries, broad consent was typically associated with a loss of control over data and future developments in research. More importantly, participants in these countries expressed a clear desire to be informed about the nature of research activities, all while wanting to retain

a certain amount of control over "their" data in the form of a "right of withdrawal". Still, at least in Austria and the Netherlands, broad consensus seemed acceptable to some. And, in all countries actual biobank donors and those more directly affected by biobank research (such as patients with a specific disease, or members of a risk group related to a given disease) had generally voiced much more favourable opinions about broad consensus.

In summary, the focus group interviews indicated that broad consent does require transparency, openness, and clarity about goals, trust in institutions, and a notion of reciprocity. In the absence of any of these conditions, broad consent is unlikely to be granted by participating individuals.

Privacy, anonymity, and data protection are key concerns in all European countries and there exist substantial doubts in all countries, but also a fair amount of "positive" resignation. Overall, the trust in biobanks seems to a large degree dependent upon trust in the ability of governance regimes and institutions to protect genetic and personal data.

While privacy, anonymity, and data protection are crucial concerns in all European countries, there exist significant differences on how these concerns are perceived and expressed.

Participants in continental Europe tend to see data protection as an important issue, yet there are clear differences in how these concerns were expressed. In Austria, privacy and data protection are a mayor concern and many participants argued for the need of clear regulations and restricted access. But, also there appeared to be a good deal of "positive" resignation motivated by the observation—gained from participants own life world—that strict data protection is simply no more practically feasible.

In the Netherlands, participants often seemed to think of privacy as an acceptable risk outweighed by the potential benefits of

biobank research. But, there remains a good deal of ambivalence toward biobanks and, with it, the constant risk of an *erosion of trust*. In Finland, trust in the ability to protect privacy coexisted with critical attitudes and questions about data protection and regulation as well as clear concerns about the use of social security numbers for identification and access to biobanks by insurance companies. But, the overwhelming attitude appeared to be one of "positive" resignation.

By contrast, in Greece, the public had no trust whatsoever in the ability of the government (or any governance structure) to guarantee anonymity and privacy and there remained substantial concerns. As a result, participants in the focus groups had argued that there is no necessity to link biological data and personal information.

The situation was very different in the UK, where participants often argued that the data and information given to biobanks is hardly different from the information that people already give away every day. Thus, privacy is rarely seen as a valid concern, and concerns over privacy were often labelled as far removed from reality or even "paranoia". Privacy and data security is, however, seen as a general concern, if not a concern of particular importance. Many participants in the UK argued for a right to obtain information and output from the research conducted and this kind of "return" was generally seen as favourable.

Participants in Greece also argued for the importance of benefits sharing. Yet, research results—personal and general—were seen as only one form of benefit among others, including more direct benefits, such as lower medical fees or free examinations.

Overall, the focus group discussions clearly illustrate that the trust in data protection by biobanks is not unconditional, but rather dependent on general opinions regarding privacy and data security and, at least in continental Europe, also trust in the ability

of general governance structures to protect genetic and personal data. Thus, where privacy and data protection are seen as problematic, and where trust in the ability to protect personal data and anonymity is breaking down, favourable opinions about biobanks are likely to change quickly and, under certain circumstances, may even turn into resistance.

Focus group interviews clearly indicate that trust in governance structures is perhaps the single, most important variable that determines support for, and trust in biobanks.

Perhaps the most important conclusion from the focus group interviews points to the *importance of governance and trust in governance.* In all countries, participants argued for independent public oversight of biobanks and biobank research. In fact, the trust in biobanks is largely dependent on the trust in the governing institutions of a given biobank project. These need to be "transparent" and "independent" (UK) or, else, should be recruited from among trusted organizations, such as universities, university hospitals, or public research organizations (Netherlands). Trust in biobanks is lowest where trust in public governance is low, as is the case in Greece, where trust in the government, or government appointed committees, in general is extremely low.

This result has important implications for the governance of biobanks but, in itself, is perhaps not very surprising. Giving the limited knowledge about biobanks, it isn't so much biobanks or biobank research *per se* that is questioned, but rather the institutional arrangements and regulations that govern biobanks. Thus, trust in the institutions and regulations supporting a given biobank project will likely result in broad support. By contrast, where this trust is absent (as is the case in Greece), concerns and negative opinions are more likely to arise.

A computerized analysis of affinities among key words used

in the focus group discussions point to a similar conclusion. Trust in institutions is an important factor for the support of broad consent and determines overall attitudes toward biobanks, while issues such as compensation or doubts about research feasibility appear to be relatively isolated concerns.

The European public overall tends to have positive opinions about European approaches toward biobank regulation and research. Opinions about European biobank activities reflect the status of trust—in a given country or region—in European organizations.

The European public is overall rather positive about a *European* approach toward biobank research and regulation. However, the degree of support differs widely among countries. European or international cooperation in biobanks is largely seen as a *cooperation of national organizations*—rather than as a delegation of responsibility to an organization at the European level; only in Greece did focus group participants express a preference for EU or international governance models over national governance.

For example, in Finland and Austria participants tended to see EU cooperation (and thus some shift of governance responsibility to EU organizations) largely positive and also preferable to arrangements at the international level. There remained some scepticism in Austria, and when discussing practical matters participants quickly shifted toward a preference for a national solution. However, the same participants still preferred international arrangements when it came to setting research goals.

But, in the UK and he Netherlands, participants argued that there was essentially no difference between governance at an EU or international level. Overall, there appears to be a clear preference for *a EU-level or international arrangement that has a strong grounding in national institutions*—with Greece being an exception where limited trust in national institutions seems to motivate a prefer-

ence for governance at an international level.

While opinions about biobanks are overall positive, support for biobanks is not unconditional but, rather, appears highly dependent upon trust in the institutions, and regulations, that govern biobanks.

The results of the focus group interviews confirm that citizens in Europe tend to have positive views about biobanks. Narrow consent appears to be the default position, especially in the absence of detailed knowledge about biobanks, or a given biobank effort. Further, European approaches toward biobank governance are seen largely as positive.

Yet, there remains a good deal of variation among countries and social groups, and support for biobanks is hardly unconditional. There exist important concerns regarding governance, privacy, and data protection. Finally, and this is perhaps the key finding for policy makers and biobank administrators: *Support for biobanks is largely dependent on trust in the governance of biobanks, whether at the national or international level.* It is important to keep this finding in mind when discussing, in the next chapter, the need for new notions of "consent" and "benefit" with respect to biobanks.

Arguably, consent—whether limited or broad—should always be a matter of individual choice. The questions that arises, thus, is not so much *what level* of consent biobanks should chose, or what notion of consent is ethically responsible and offering sufficient protection for biobank donors. After all, any biobank donation is useless and of no value whatsoever if it is remains unused. Rather, the more pertinent questions is *what kind of governance regime is necessary to generate sufficient trust in biobanks to enable, and facilitate, the most productive consent framework for both participants and researchers.*

5. Ethics for Biobanks: A New Notion of Consent?

Following the raise of biobanks, the classic notion of informed consent has increasingly been questioned and new definitions of informed consent tailored to the needs of research biobanks have emerged.

The notion of informed consent was shaped in the aftermath of World War II, and as response to the abuse of human beings (inhabitants of concentration camps, prisoners of war, soldiers, civilians, etc.) in medical research and experimentation before and during the war. Informed consent is a legal procedure to ensure that a patient knows, and understands, the risks involved in a given therapy or treatment.

The elements of informed consents include informing the patient of the nature of the treatment, possible alternative treatments, and the potential risks and benefits of the treatment. In order for informed consent to be considered valid, the patient must be mentally competent and the consent must be given voluntarily.

The idea behind informed consent was to enable a patient, or a volunteer participant in any kind of medical or clinical research, to make his or her own choice of whether to accept a given treatment, based on a clear understanding of benefits and risks. In return, informed consent also provides legal protection for the medical doctors who undertake a treatment, or conduct a clinical experiment. Since the patient was informed about potential risks and benefits, and has agreed on the treatment up front, the options for legal action against the physician, in case the outcome is not as expected, are much more limited.

The difficulties with informed consent are in the details. What does it really mean to "properly inform" a patient about risks and benefits? It is well known from many psychological experiments that the perception of risks and benefits depends heavily on the specific way in which risks and benefits are presented. Also, it is widely accepted that most human beings, including professional statisticians, are unable to intuitively grasp the meaning of even fairly simple statistical data. [11]

How does a patient with a life-threatening disease react to different treatment options, carrying different risks, explained by a physician who, by definition, knows significantly more about the treatment envisaged than the patient? When is a patient "competent" and, what, if the patient is underage?

A large number of studies on the practice of informed consent have demonstrated that the outcome of informed consent depends on many fine details, from the language of the consent form to the specific process for obtaining consent. There exist significant cultural differences in the way informed consent is presented in, say, the United States, which has a long history of both informed consent and legal challenge to informed consent than is the case in Japan, where informed consent has been a surprisingly recent addition to the physician-patient relationship.

Informed consent in its traditional form is "narrow" in the sense that it is strictly limited to *a given intervention or research effort presented to, and agreed upon by the patient*. But, biobanks are costly investments in infrastructure, and to obtain the maximum output from biobank collections, "broad" informed consent seems inevitable. "Broad" here means that consent is given to a class of medical experiments or, in fact, any kind of medical or biomedical experiment to be undertaken with the samples, or the accompanying information collected in a biobank.

At least today, biobanks are in no way a "treatment strategy"

and, thus, do not pose an immediate physical risk to a participant. But, early biospecimen collections often failed to obtain informed consent or, in case they did, the informed consent process for obtaining samples was similar to the minimum informed consent used when a sample is sent to a pathology laboratory for further analysis. In other words, in the early days of research biobanks, large numbers of samples were obtained without proper informed consent and, in some cases, without *any* consent at all. Thus, this poses the question of *retroactive* consent with respect to research undertaken with a cell or tissue sample collected in the past, and without proper informed consent.

As we will argue in the following, it is important that the notion of consent is not simply treated as an ethical question but, rather, is linked to the governance regime of a biobank.

Biobank resources enable large numbers of experiments in numerous locations, beyond organisational, national, or even European borders. Adequate notions of informed consent are necessary to enable research, all while fully protecting donors, and their rights, and genetic identity.

Traditional bioethics guidelines have generally expressed concern with respect to both retroactive and broad consent, but for biobanks both seem crucial. Biobanks differ from traditional medical and biological research in the sense that biobanks are not about single experiments at a single location. In fact biobanks typically do not undertake any experiments at all. Thus, biobank operators have argued for the necessity of a new notion of informed consent that takes into consideration the reality of present-day biobanks as large-scale research infrastructures that *enable* research, rather than as a research endeavours with a clearly delineated scope.

Biobank administrators tend to be very clear and outspoken about the need for a reasonably broad consent regime—meaning

consent that is not limited to a single experiment or clinical study, but rather allows for the usage of biobank resources in a broad variety of experiments. After all, biobank resources are likely to be used over an extensive period of time (in the case of information resources potentially several decades), and it is far from obvious today what the state of science will be only a few years from now, and what experiments scientists may want to undertake with these samples. in fact, biobanks operators typically would prefer consent to be without *any* specific limitation whatsoever.

Of course, "broad consent" is not without its problems. Some bioethicists have criticised the very notion of "broad consent", and have even argued that "broad" consent may lead to an erosion of the very notion of "consent" in medical research. Still, many would agree that broad consent is a practical necessity for biobanks. What is to be done here?

To start with, "broad consent" does not mean that any kind of experiment is allowable, based on a single act of consent. Rather, a sensitive notion of "broad consent" will imply that multiple (and even: unlimited) experiments within a clearly defined class of experiments are allowable. Thus, the important question that arises is how to define, and delineate, what experiments fall within the scope of the informed consent provided, and what experiments don't—or, at least, what experiments should be excluded. This can be a tricky question that defies a simple answer. Note also that the boundary of what is an "allowable" experiment may shift over time, as new research strategies become available.

Retroactive consent has been an especially difficult, and hotly debated issue, but it is importance is clearly decreasing over time—as new biobank resources become available, the importance of early sample collections is decreasing rapidly. Ethics committees have provided biobanks with a reasonably solid instrument to deal with retroactive consent, and to provide biobanks with guidance on when to allow the use of samples that were obtained

without proper informed consent.

> *"Informed consent" in the case of biobanks means that donors entrust the biobank to both utilize and safeguard the material and data provided. Biobanks must provide donors with the possibility to "opt out" and have the donated material destroyed and any data deleted.*

In some way, and our empirical research confirms this view, informed consent in the case of biobanks is quite different from informed consent in a given experiment or medical procedure. In the case of biobanks, what informed consent really means is that participants entrust the biobank organization—and its governing bodies—with the safeguarding and proper handling of their medical and physical and genetic information.

Conversely, by accepting a "donation", biobanks also accept the responsibilty to safeguard information and samples, and to use them properly and with due respect to the overall scientific agenda and governing framework of a biobank. Arguably, in this view, biobanks are somewhat similar to organizations that manage public goods.

Should donors be given the option to "opt out", this is, not to allow samples to be used in certain investigations? Or, should informed consent be simply limited to experiments undertaken within a given period of time? It is important to note here that the risk to privacy exists as long as information, or cell and tissue samples, remain stored within the biobank. Thus, in any case, biobanks must provide donors with the choice to "opt out", revoke their initial consent and, subsequently, require the biobank to delete, or destroy, all information and samples. In fact, and while details differ, the vast majority of biobanks in Europe do provide such an option already today.

Interestingly, this very issues has been hotly debated over the

past few years with respect to social media web sites, such as Facebook or Google, some of which do not provide users with the choice to "opt out"—user information remains stored potentially for many years. It is yet too early to judge how the existence of web 2.0 companies that store large amounts of private information on literally billions of individuals will impact both culturally accepted notions of "privacy" and regulations aiming at the protection of privacy. Yet, there is good indication that, at least in Europe, biobanks can only benefit from empowering donors by providing them with the choice to "opt out" at any given time.

As the size of biobank projects increases, questions of participation, research focus, gender, and representation become increasingly important. Biobanks must develop sensitive approaches to deal with these issues, and with the requests or needs of specific groups of participants.

Most research biobanks have started at a relatively modest size. But, the largest biobanks now hold hundreds of thousands of samples and, in some cases, even cover a significant percentage of the population in a given area. As biobanks approach a scale that matters at the level of populations, question of selection and representation will become increasingly important. People who participate in biobanks are not simply anonymous "donors", but specific human beings with specific interest that may include gender, age, genetic differences, or even social status.

Biobanks focused on specific diseases already define enrolment targets that take into account demographic variables, including age and gender. Also, special interest groups—such as patient organization—have occasionally used biobanks as a way to pursue their agenda and interests (see Box 5).

Should biobanks take the question of representation into account when defining their ethics standards and governance principles? While there is no easy answer, and while the actual answer

BOX 5: "OUR BLOOD": PATIENT ORGANIZATIONS AND BIOBANKS

There exist numerous cases where patient organization, research charities, and other interest groups have been directly involved in a biobank effort. The aim of these groups is to influence public research and research spending through public opinion, targeted funding, or political lobbying, and to increase research efforts and funding for research on a given disease condition. Some of these groups understood early on that linkages to patients, and the ability to recruit large numbers of individuals to participate in a study or clinical trial, is an important asset in biomedical research—as a consequence, some of these organizations have become involved in building-up, and administrating, large sample collections related to a given disease condition and, in this way, actively influence public sector research. [12]

may vary among biobank projects, we believe that, at a minimum, all biobanks must develop a certain sensitivity toward this question, and especially toward the requests of certain social or ethnical groups or minorities.

Research biobanks must develop clear policies that specify how to handle cases of scientific success or advancement, or findings that may have direct implications for individual participants, or classes of participants.

Advances in research and technology itself may actually change the very conditions and assumptions upon which consent was provided. For example, informed consent is usually given in exchange for the promises of anonymity and protection of genetic and medical information. Yet, in the near future, advances in technology, together with the broad availability of patient information within the health care system, will make it ever easier to *re*-identify a given sample and link it to an individual—and, thus, to identify an individual. For certain cases, this possibility exists already today.

The explicit goal of research biobanks is to contribute to the advancement of medical research, and to the development of new diagnostic or therapeutic approaches. While advancements may be still years, or decades away, biobanks must consider scenarios where research undertaken with the resources provided actually leads to clinically relevant advancements. But, how should biobanks "share" actual progress that may have clinical implications for their donors? This is a very difficult and challenging question, especially when considering the trans-national use of biobanks, since regulations on what medical scientists legally can communicate to participants in research differ among countries.

For example, consider a case where it is found that a subgroup of donors with a certain disposition would benefit from a new therapeutic strategy. Should these patients be identified and informed of this advancement? Also, how to handle cases where research undertaken with biobank resources yields important diagnostics findings that may have immediate implications for individual donors, or classes of donors? Certainly, biobanks have an ethical responsibility to develop clear guidelines to handle such cases and these guidelines should be an integral part of the informed consent process.

Note also that, in this case, "donors" actually turn into "patients". As some observers have pointed out, the legal status of participants in a biobank is complex, and can oscillate between different position, depending on what type of research is performed with a sample:

> "The legal qualification of the source-person cannot be the same when samples are obtained within the health care context or within the research context. On the one hand, when samples are used for diagnosis or treatment, people are considered as patients and are protected through the implementation of patients' rights. On the other hand, when samples are gathered from research participants, these persons are considered as donors of body elements and are specifi-

> cally protected by the rules governing donation, which are quite different from patients' rights." [13]

Thus, in the case of biobanks, it isn't just the biobanks themselves that are unstable and changing—the legal status of participants, or "source-persons" may equally evolve over time, and depending upon the outcome of research undertaken with biobank resources.

Donors see biobanks as a "public good" that belongs to humanity, rather than any specific organization. Biobanks, thus, must share their "benefits" with donors and the general public and we believe this is best done by providing donors with open, and transparent information on the research undertaken with biobank resources.

As we have pointed out, many biobank donors see biobanks as a "public good", and their donation as a contribution that, eventually, will benefit society at large. Immediate personal benefit is rarely a main motivation to donate a sample. Still, our interviews clearly indicate that many donors do actually have an active interest in the research that is undertaken with their donation and, more generally, in research progress enabled by biobanks.

So far, most biobanks provide only a fairly limited amount of information on the research that has been undertaken with their resources. In fact, few biobanks have a dedicated PR approach. By contrast, we believe it is an *ethical duty* of biobanks to provide donors and the general public with timely, transparent, and precise information about their activities, and about the research undertaken by their scientific users. This "reciprocity", as Gottweis *et al.* argue is crucial for connecting the public with biobanks:

> "People need to feel that they are part of something larger and that their donation feeds into a mutual, respectful relationship. This cannot be done simply by talking in abstract terms about the potentially significant medical ben-

> efits that might result from biobank research at some unspecified point in the future. Certainly, medical advances are relevant, but our research shows that participants in many countries expect individual feed-back from check-ups and also expect the possibility of gaining information about research advances that result from the biobanks in which they are participating, as long as their tissue or DNA is part of the biobank. They rarely expect money in return, but want to be appreciated as donors and be treated well." [14]

The concept behind informed consent was to provide information that will enable patients to make their own informed decisions about benefits and risks. But, in the case of biobanks, notions of benefits and risks take on a very different meaning.

The main "risk" for biobank donors is a breach of privacy and this risk remains present as long as a sample and information is stored in a biobank. Leaving aside the specific case where participation in a biobank has a diagnostic output that was not foreseen by the donor, there usually are no immediate benefits that biobanks provide to their donors. At best, there is the satisfaction of having contributed to the advancement of medical research. The main benefit to donors is thus, simply, information and the notion of taking part in a medical research effort with potential benefits for all of us.

Arguably, the ethics of informed consent in the case of research biobanks is, thus, rather distinct: What motivates donors to make their samples and medical information available to scientific users over extensive periods of time, rather than opting out, is continuing information about activities and research progress and, in the case of a diseased individual, information about the relevance of these advances to their specific condition.

6. A Legal and Technical Framework for Biobanks

Biobank governance poses various legal questions, including questions of ownership, rights, and contractual obligations of the parties involved. Rethinking biobanks as a "public good" will help resolving some of the legal tensions surrounding biobanks.

Located at the intersection of research and clinical practice, of human biological materials and information, and between the public sector and private interests, the legal status of biobanks is equally complex.

The donation of blood or tissues to a biobank by an individual implies a "contract" between a donor and a biobank organization. The biobank then utilizes the donated cells and tissues, as well as medical data or data derived through various types of scientific analysis, and makes these available to researchers.

But, while informed consent forms tend to be simple and straightforward, the actual "contract" behind them often simply isn't. Typically, biobanks require participants to grant the biobank, and its users, a number of rights, including the right to patent scientific findings derived from research with biobank resources. In the US a series of legal disputes over the past two decades have resulted in a body of case law that is now reflected in the actual contract documents that personal genomics companies, such as 23andMe, require their donors to sign.

Arguably, the simplicity of the informed consent procedures used by biobanks, and of the informed consent documents signed off by institutional ethics boards, "masks" many of these complex legal questions, and some observers have called informed

consent a "broken contract." [15]

Other questions relate to issues such as sharing research outcomes with participants. For example, in some countries, such as the UK, investigators are legally barred from sharing specific result of genetic research with the individual donors or patients, even when these results could benefit individual patients.

As we have argued in the preceding chapter, notions such as participation and trust can provide a new framework for rethinking the link between biobanks and donors—and, thus also to rethink the contractual relationship between donors or participants, intermediary agents such as biobanks, and research users of human materials.

Of course, a more participatory approach toward biobank governance will not immediately resolve all legal questions raised by cell and tissue donations to biobanks. But, rethinking biobanks as a "public good" will help to restore the balance between research users and donors and, eventually, could lead to a new legal framework for biobanks.

The amount of data processed and stored at major biobank facilities will increase significantly over the next years and decades. Biobanks have already entered the area of "Big Data" and are increasingly turning into large data centre facilities or "cloud" environments.

In many ways, biobanks are simply large, and continuously growing collections of biological and medical data. Even the sample itself—which contains DNA—can be viewed as an information product. Also, most biobank projects focused on disease research have attempted to gather adequate medical records from donors. The patient information stored in biobanks is often far more sensitive than information typically used in research, and requires adequate anonymisation and additional layers of security.

As the costs of sequencing and analysis decrease, and with the increasing amount of data being stored at biobank facilities, many large biobank are effectively turning into data centre facilities, rather than more traditional cell or tissue banks, with server farms and data storage equipment replacing liquid nitrogen tanks as the key imagery of a biobanks.

This shift from biological materials to information as the main ingredient of biobanks, while gradual, is already well under way. Increasingly, what biobanks will provide to researchers is not a blood or tissue sample, but rather a data set for further analysis. While samples need to be physically shipped to an end user, data is much more versatile. Large quantities of data can be easily downloaded over a fast network and replicated at many locations across the Internet. As biobanks turn into data centres and "clouds", data security and data protection will become increasingly important.

Data protection is perhaps the most prominent legal question related to biobanks and biobanks utilization. The cross-border access to data stored within biobanks in Europe requires a data management framework that must comply with both the EU Data Protection Directive and its various implementations in EU member states.

At least in Europe, privacy and data security remain perhaps the issue that cause most concerns about biobanks among the public. Cross-border sharing of samples or data among European Union member countries, or with other countries outside of Europe, poses additional questions.

Within the European Union, data protection has been harmonized through the EU Data Protection Directive. Yet, this directive leaves some margin for implementation by EU member states and there exist a number of differences in member states with respect to data protection and privacy.

For the cross-border exchange of samples and data, a data access policy respecting both EU and national law is thus crucial. As part of the BBMRI project, a "General Information Management System" has been proposed and we have reviewed this framework from a legal perspective. Further, we have proposed a BBMRI-EU Data Protection Standard that incorporates a number of technical and legal or contractual measures, such as the European Union's Model Data Access Policy as well as Standard Contractual Clauses (SCCs) for data transmission.

Data protection for biobanks is not simply a legal question. Adequate standards and technical "best practice" guides are necessary to ensure that biobanks use the best data security technologies available today.

The technical implementation of data protection and anonymisation for a consortium of biobanks—such as BBMRI—is by no means trivial. There exist practical hurdles and potential pitfalls and there remain numerous risks. Questions of data anonymisation and data security have important technical aspects; a legal framework that is implemented with an inadequate technical approach can easily result in a breach of security.

Biobanks may seem unlikely targets for cybercriminals, yet the risk is very real and is likely to increase as the amount of digital information stored at biobank facilities surges. A technical failure at a single site could have important repercussions for any BBMRI project. Continuous monitoring and review of data management and data protection practices is thus necessary at any biobank.

While many scientific institutions, both in the US and Europe, have implemented increasingly strict data security policies, the approach toward security at many research organizations and universities typically remains below the standards implemented

by commercial organizations that safeguard large amounts of sen-sitive personal data, such as financial institutions, insurance com-panies, or health-care providers.

Medical information networks, and the sharing of medical record data among health care providers, are probably the best reference case for biobanks. Of course, biobanks are not heath care providers; but, similar to health care providers that share medical information, biobanks are providing increasingly large data sets—associated with human cells and tissues—to biomedical researchers at various locations, including foreign countries.

Within the BBMRI project, we are developing technical best-practice guides for data protection, data anonymisation, and data security. While voluntary, these guidelines will provide biobanks with an immediate approach toward data protection and data security.

Information technology can help strengthen interactions with donors, increase the information flow from biobanks to donors, and even facilitate participatory governance.

Data protection and security are not the only areas where technology can help. As we have already pointed out, information technology also provides interesting approaches for rethinking the notion of participation in biobanks.

For example, one could easily imagine an approach where biobanks use on-line tools to inform donors about research progress, or even invite them to participate in important decisions about future directions. Of course, information technology rarely solves an organisational problem that cannot be solved by other means; at best, information technology can facilitate the implementation of practical, inexpensive solutions.

7. Governing Biobanks in Europe Today

Governance, and trust in governance, are the most important ingredients for biobank success. Our research shows with surprising clarity that individuals will only make donations, and allow their medical histories to be stored in a biobank, if they have trust in the organization and governance of the biobank.

Throughout our interviews and focus group meetings, we have observed, again and again, that trust in the institutions that govern a biobank and, more generally, trust in government and public sector institutions, is the single most important ingredient for biobank success (at least, if success is defined as donor recruitment). Further, its appears that actual trust is not simply motivated by the specific arrangements of a given biobank project, but rather is often a reflection of a more general form of trust in the broader organisational framework into which a given biobank project is embedded.

In short, when individuals have trust in the broader organisational arrangements of a biobank project, they are likely to volunteer as participants. By contrast, if this form of trust is absent, collecting and storing samples *at scale* is likely to be difficult, if not impossible.

For donor recruitment to be successful in a "hostile" environment, biobank operators need to build a "micro-environment" that provides potential donors with sufficient transparency and accountability, while also offering a certain degree of participation. Examples in a variety of countries, from France to Japan, suggest that participation, and participatory governance, are powerful approaches toward re-establishing trust in an environ-

ment where trust in public institutions is relatively low.

Japan is an example of a country where trust in governance has been eroding over the past decades, and where medical scientists in the public sector themselves have expressed concerns about the ability to recruit donors. A large biobank project nonetheless succeeded in obtaining hundreds of thousands of samples. It did so mostly by relying on well establish private hospital groups and through an aggressive recruitment strategy aimed at informing patients about the research to be undertaken and, in this way successfully managed to involve, if only partially, donors in the biobank effort. [16]

The advancement of biobanks, and of biomedical research using large amounts of data, requires an extensive rethinking of governance models for biomedical research.

Traditional research ethics, and even notions such as privacy, are stretched to their limit when dealing with today's biobanks. New approaches appear necessary. The ethical framework for the governance of biomedical research was initially conceived several decades ago and its key notions—notably "informed consent", "privacy", and "benefits"—reflect a set of distinct concerns common in clinical research and medical practice.

Biobanks, and research facilitated through biobanks, increasingly differ. The sheer amount of data used, and generated, in some areas of biomedical research today, combined with the increasingly global nature of the research enterprise, means that both informed consent and privacy protection have turned into a highly complex task.

Even a single human cell contains the entire genetic information of an individual. DNA extracted from cells can easily be stored almost infinitely and, with the technique of PCR, can be

copied indefinitely. As a simple piece of information, genetic data may me used, or distributed, for extensive periods of time and without restrictions. A singular act of informed consent, one might conclude, is hardly adequate to cover the full potential contained in even a *single* human cell.

We have argued that the very nature of biobanks as "public goods" offers a potentially interesting strategy toward formulating a new ethics and governance framework for biobanks. In fact, most donors see biobanks as exemplary "public goods", and their donation of cells, tissues, and information as a means to participate in the advancement of a broader goal, well beyond personal interests or wellbeing, but rather as an investment that will eventually pay back a dividend to a broader community.

This offers a way to rethink research ethics *around the notion of participation*, rather than simply cost-benefit sharing. Participation is, in itself, a simple way to reap the "benefits" from the donations to a biobank facility.

Transparency and accountability are crucial for biobank governance. But, while these are necessary ingredients, we believe biobanks also need to engage more directly with participants and donors.

The very nature of biobanks as infrastructures that enable a broad variety of investigations over extensive periods of time means that the interaction with donors must not be seen as a single interaction during which an informed consent form is signed, and a sample provided. Rather, donors entrust information, and including information that is dormant within the cells and tissues provided by the donor, to the biobank that, then, makes samples and information available to scientists.

In some way, thus, a biobank is not so much the opposite party in an informed consent procedure, and in most cases any-

way not the party that is undertaking the actual research. Rather, a biobank is almost like an agent for its donors or, at least, an intermediary between donors and scientist and, as such, biobanks must also represent the interests of their donors—rather then simply the interests of the scientific community.

And, as research with biobanks resources moves closer to the clinic, the diagnostic and medical relevance of research will increase, which poses a whole new set of question; but, it also reinforces the notion that the link between a biobank and its donors (and including the relatives of a donor, in case a donor dies) is not simply momentary. To the contrary, we believe the relation between biobanks and donors needs to be consciously managed over the entire lifetime of the biobank.

But, this is only possible if biobanks are actively engaged in a constant dialogue with the individuals who donate samples. One has to conclude, then, that the governance principle for biobanks is, not so much "informed consent", but rather "*informed trust*"—a long-term relationship of trust between biobanks and donors that is based on, and motivated by, a continuous stream of information about the activities of a biobank project and, in some cases, ways for donors to, at least, partly influence the governance and directions of a biobank effort. There exists numerous models for such an approach, from organizations that collect blood to organizations aimed at protecting the environment.

The act of "informed consent", seen this way, is not so much a one-off interaction that simply enables the biobank to do any kind of science with the donated sample and information. But, rather, it constitutes the entry point into a long-term relationship between a biobank and a donor that should last as long as the sample (or DNA or information derived from it) is actively used in medical research.

Further, in future, it is entirely possible that biobanks become

BOX 6: RECOMMENDATIONS FOR BIOBANK GOVERNANCE

The following recommendations are taken from the summary report "Biobanks for Europe - A Challenge for Governance" released by the European Commission (Gottweis, 2012).

1. Member states and European institutions should develop a consistent and coherent legal framework for biobanking that should protect participants' fundamental rights, in particular in the areas of privacy, data protection and the use of human tissue in research.

2. There should be better coordination and collaboration between national oversight bodies (e.g. data protection authorities and ethics committees) as well as mutual recognition of decision-making to eliminate unnecessary duplication of oversight and compliance requirements, with training to support this.

3. For European biobanks to operate successfully there need to be sustainable governance mechanisms to involve and engage the public, and in doing so ensure their continual participation, trust and support.

4. Sustainable governance mechanisms for creating a relationship of reciprocity between biobanks and European society need to be encouraged so that Europeans can understand and obtain the benefits from biobank research.

5. The new governance bodies that have emerged specifically for biobanks should be integrated into the existing governance system to help to develop a meta-governance system for biobanking within Europe.

6. To ensure their sustainability, biobanks need to become embedded in the public healthcare structure as valuable resources that can be used for clinical care, personalized medicine and translational research.

7. Greater investment should be made in the development of e-governance tools to embed "ELSI by design" solutions, which can be used to augment existing governance structures and facilitate the sharing of samples and information between biobanks and researchers at a meta-level.

8. The potential to use web 2.0 technologies to involve patients, research participants and the wider public, in the governance of biobanks should be supported to ensure that Europeans can have trust in biobank research and those organizations that establish and maintain biobanks.

9. New accreditation systems need to be developed to reward and acknowledge the effort of scientists who establish and build biobanks.

ever more integrated into the health care system itself, which will only reinforce a notion of biobanks as an *intermediary* between participating citizens and, in some cases, patients, and the medical research community. Arguably, it may well take some time before most biobanks can indeed take on such a role. But, it is beyond questions that biobanks who want to be successful in the long-term will need to prepare themselves today.

Participation and participatory governance offer new approaches toward biobank governance. While there is no single model for participatory governance, we encourage managers of biobank facilities to investigate, and develop, new ways of interacting with the individuals who donate samples.

We have argued throughout this report that standard ethics approaches—such as "informed consent"—or even general data protection policies, while certainly important, are unlikely to provide a long-term solution to biobank governance. One reason is that biobanks are simply unlike any other medical research en-deavour. *Biobanks often do not undertake research themselves but, rather, provide for an infrastructure to enable investigations in some of the fastest-moving areas of biomedical inquiry*. Thus, the research undertaken 5 or 10 years from now with samples from the Biobank UK or, for that matter, any other biobank, may differ significantly from research under way today. Biobanks have to adapt to these changes—and they must communicate these changes to their donors, if they want to retain trust.

It is important to note here that there exists no single approach that will guarantee trust. As we have pointed out, trust in institutions *is not easily generated*; neither can specific institutions be set apart from their overall political context. For example, the trust in government organizations in Greece is extremely low, neither do people in Greece believe that "committees" can be trusted to pursue interests other than the interests of those who

crated a committee. By contrast, there appears to be more trust in organization with a European, or even international grounding.

Thus, aspiring biobank administrators in Greece might find it difficult to obtain the confidence and trust of the public, unless their efforts are strongly linked to European or International initiatives, or else have the backing of a recognized, and trusted, patient support group. But, the association with European efforts or a patient organization alone is unlikely to instil trust. Rather, to build trust is likely to involve a long-term effort to connect with individuals who donate samples, inform donors about activities and progress, and provide them with opportunities to participate in the governance of the biobank.

Research biobanks, as we have argued, often started as a sideline activity by medical investigators using human cells and tissues in their research. When, what started as collection of cell cultures in a refrigerator in a research lab then turned into an expensive shared facility storing thousands of cyropreserved tissue samples from patients or donors, few organizations realized the potential implications.

Loose oversight rules for scientific research in most countries meant that there were few incentives to review the potential implications of these collections. As a result, in the past many biobanks had indeed pursued— intentionally or unintentionally—an "under the radar" approach of providing no, or only a minimal amount of information to donors, while all but abstaining from interactions with a wider public.

But, in future, we believe, biobanks must engage more directly with the public—and not a kind of anonymous, undefined "public", but rather the specific public constituted by their donors, participants, and research users. In future, we believe, biobanks must find innovative ways to interact with, and engage their donors and even consult with donors on such questions and issues

as "governance", "access" to biobank resources, or the "benefits" created by biobank research.

It is likely that, in future, biobanks will increasingly turn into public "mediators" that link individuals donating blood, tissues, or information with the "users" of the donated materials in biomedical and clinical research.

The idea behind most large biobank projects has been to facilitate, and simplify, access to human cells and tissues and, also, to reduce the cost of collecting, processing, and storing human-derived materials as well as individual genetic and medical information in a standardized fashion. Arguably, biobanks also reduce the potential ethical and social risk and pitfalls for individual scientists when dealing with human-derived materials and information. Thus, apart from a few exceptions, biobanks were often seen as primarily representing the interests of its scientific users, rather than the interests of the individuals who participate in a biobank.

We believe that this situation will change and that biobanks will increasingly turn in organizations that *mediate* between the public and science, and between participants and researchers. It is for this very reason that, in future, successful biobank governance will require public participation. At a minimum, biobanks must prepare themselves to *pro-actively interact and engage with their donors and donor communities as well as with the general public.* And this, in short, is what this booklet is all about.

8. Recommendations: From Ethics Towards Participation

Biobanks are omnipresent in biomedical research today, yet their reality is constantly changing and evolving. New technologies to retrieve, store, and analyse biologically relevant data from human cells and tissues will profoundly reshape biobanks over the next decades.

The long-term storage of ever increasing amounts of human biological materials and biomedical data for research purposes in the form of broadly accessible "biobanks" is a reality in present-day biomedical research.

What started decades, or centuries, ago in the form of pathology collections, today has become a global activity undertaken in research hospitals, universities, dedicated biobanking facilities, as well as numerous biotechnology or pharmaceutical corporations. Human cell and tissue collections provide important resources to many branches of medical research and, further, are increasingly important in the regulation of new pharmaceuticals and therapeutic approaches.

As we have argued, the term "biobank" remains ambiguous and subsumes a broad variety of human specimen collections. Even within the scientific community, biobanks often remain ambiguous: While there is a broad consensus in the biomedical research community on the importance of systematic collections of human cells and tissues, there remains considerable debate on what should be collected and how. Also, the actual scientific value of a given biobank project may subject to controversy.

Nor is the term biobank in itself "stable". As research objec-

tives and research tools evolve, practices of collecting, preparing, analysing, storing, and distributing human cells and tissues will also change and evolve. Spectacular as it may have been, the case of the Icelandic Health Sector Database is but one instance of a biobank effort, and certainly not a very representative one. To the contrary, even today, most biobank efforts remain relatively modest in scale and often unknown to the public.

Still, while a decade or two ago biobanks were mostly "local" enterprises limited to a single laboratory or department, since the emergence of "megabanks" the average size of biobanks continues to grow. Also, biobanks are increasingly linked on a regional or global scale, as the case of the BBMRI initiative demonstrates. The increase in the number of samples and the number of banks, the growing diversity of samples and the sheer amount of information collected or produced, together with new technologies for sample analysis and growing international linkages all pose important challenges to the management, and governance, of biobanks.

Ethics, and ethical oversight through ethics committees, have been the primary mode of governance for biobanks over the past decade. But, while necessary, this approach may no longer be sufficient, or adequate, to deal with the complex realities of today's biobanks.

Biobanks today manage large technical infrastructures that link together samples with medical and biomedical and genetic data. The practicalities of storing, anonymising, and distributing cell and tissue samples and corresponding medical or biomedical information are, as we have noted, complex and intricate. The ethics of informed consent, initially formulated by the Helsinki Declaration, remains the fundament for biobank governance. Still, biobanks today need to take into account a number of other factors when formulating their governance regime.

As we have argued, until recently the governance of biobanks has been largely discussed with reference to the *ethics of participation* in medical and clinical research, and with respect to issues such as recruitment, informed consent, privacy, and ownership. Notions of consent, as many observers have noted, have drifted from consent to a single experiment or a small series of experiments, to a much broader and inclusive notion of consent covering many classes of experiment or, even, quite simply all possible experiments that can be undertaken during the lifetime of a human cell or tissue sample. This kind of "broad consent" is often combined with the possibility to "opt out" at any given time.

Informed consent is not simply a monolithic notion, and its implementation in the case of biobanks differs across Europe. And, as we have noted, informed consent with respect to biobanks has evolved considerably over the past twenty years, and is likely to continue to evolve in future. Somewhat similar to preferences, and sensitivities toward informed consent rules for organ transplants, some countries are relatively open to a broad notion of consent for the sake of research, while more narrow definitions are preferred in other EU member states. Further, members of affected communities—such as disease support groups—appear more likely to agree to a broad consent regime than individuals without any connection to the research that is undertaken with the samples provided.

The informed consent process will remain a cornerstone of biobank governance. Yet, we conclude from our investigations into biobank governance that informed consent alone is no longer enough. The uncertainty inherent in scientific research means that samples collected for a certain type of investigation may eventually be used in a very different area of research.

Particularly difficult problems can arise when samples or data are shared across countries with distinct legal cultures or data protection regimes, or when samples or data move from the

public to the private sector. Adequate data access policies for exchanging biobank samples and associated information in Europe is crucial for research.

Further, at least for biobanks with samples from diseased individuals, the medical information needed for one type of investigation may differ from the information needed for a different type of investigation, thus the value of a biobank collection may eventually depend on the ability to re-identify a sample, which poses yet another set of questions.

Finally, the donor selection and recruitment strategy chosen remains a crucial issue that is easily overlooked when considering consent only. As biobanks—or networks of biobanks—grow larger, questions regarding populations, race, minorities, and discrimination will become more pertinent.

The attitudes toward biobanks in Europe are overall positive. However, most biobanks remain largely unknown to the public. Singular events, such as a security breach, or even a controversial scientific finding, could easily trigger a change in public opinion. It is crucial for biobanks to pro-actively engage in an on-going dialogue with the public.

The attitudes of the European public toward biobanks are largely positive and most European citizens appear confident about biobank research and regulation. Different from what one might expect, biobanks are rarely controversial. Quite to the contrary, most biobanks projects in Europe remain rather obscure and are often barely known to the general public. Iceland, it now appears, was the exception, rather than the rule.

But, this does not mean that everything is just fine, or that biobanks should best avoid publicity and continue to operate in relative obscurity, as some would argue. The lack of knowledge about biobanks in the general public also carries the risk of a

BOX 7: BIOBANKS AND THE PUBLIC: A SUMMARY

1. The European public is, for the most part, positive about biobanks and biobank regulation. Yet, there also remains a lack of information about biobank efforts, and the positive attitude about biobanks may be, at least partly, simply ignorance. Neither is the overall confidence in biobanks (and biobank regulation) a reason for complacency. For example, even a single security breach at a single biobank site can negatively impact all other biobanks in Europe!

2. Informed consent and ethical review remain a crucial fundament for biobank governance. However, the sensitivity toward, and acceptance of broad consensus rules varies among EU countries. We thus encourage biobanks in Europe to design, in consultation with societal stakeholders, appropriate and sensitive informed consent regimes tailored to a given environment, rather than so simply use standard formulas.[17]

3. Trust is crucial for biobank governance. Direct engagement with donors as well as concerned and affected groups and members of the public is an important, and relatively inexpensive means to build trust. Activities in this direction might include specifically designed education programs and regular outreach activities or events that involve patients and donors and the scientists who design, build, and use the biobank. We also encourage biobanks to explore new forms of communication, including Internet and web-based technologies, as a means to better, and more directly, engage with the public. Most importantly, public participation in biobank governance is a potentially very powerful means of building trust.

4. Given the increasing scope of present-day biobanks, and the potential for further expansion, considerations about participation, and the balanced representation of various societal groups including patient organization, as well as considerations of age, gender, and even race will become increasingly important. We thus encourage biobanks in Europe to continuously review, monitor, and improve their recruitment strategies.

5. Biobanks are massive collections of highly sensitive medical and biological data about individual human beings. And, different from databases used in hospitals, it is the very mission of biobanks to make these data—in anonymised form—broadly available to research users. The importance of data protection cannot be overstated. Enforcing rigorous and credible data protection, as well as anonymity, across Europe will be vital for the future of biobanks. Biobanks must strife to continuously improve technical, legal, and organizational means to protect, and safeguard, medical and biomedical data.

sudden backlash in public opinion *against* biobanks. But, neither should biobanks simply start launching publicity campaigns to inform the public about their activities.

Rather, in our opinion, biobanks are probably best served by a measured and targeted model of engagement with the public. The focus group interviews undertaken in various European countries clearly point to *trust* in public institutions as a key variable influencing attitudes toward biobanks. Trust cannot be earned through advertising campaigns only. Rather, biobanks must engage the general public and its various constituencies in a more direct and open approach.

One straightforward way of engaging the public is by focusing on specific groups of concerned individuals, such as biobank donors or group of patients affected by a disease targeted by the biobank's research agenda. Such groups have an immediate interest in a biobank and will typically see their donation as a direct contribution to relevant research.

Building trust with such constituencies will need to go well beyond standardised informed consent procedures. For example, patients and their families will be most interested in obtaining in-depth information about the research undertaken with samples donated—and this information is unlikely to be featured in a generic informed consent form. More generally, biobanks can provide an important service to its scientific users by linking scientists and donors and, in this way, contributing to the public understanding of biomedical research.

The "contract" between donors and biobanks and their users is thus subtly shifting from an obligation to obtain "consent"—and do so in a mostly defensive and protective fashion—toward a model where *donors play a more active role as "participants" in a biobank effort.* In this model, *biobanks effectively take on a role as mediators between "participants" (or donors) and scientific "users".*

Implementing these changes may well take years or decades. Yet, we are convinced that successful biobanks will increasingly adopt such an approach—and, in turn, identify new and innovative ways to more directly involve the public in their efforts.

Notes

1. The anthropologist Gisli Pálsson has written extensively on deCODE and the case of Island. See e.g. his essay "The Rise and Fall of Biobanks", in: Gottweis & Petersen, *eds.* (2008), p. 41-55.

2. Hermitte (1996) provides a fascinating discussion of the legal history of blood transfusions in France.

3. An early assessment is provided in Cambon-Thomsen A. (2003). For a good overview of the state of biobanks in various countries see e.g.: Gottweis & Petersen, *eds.* (2008).

4. A comprehensive list of biobanks in Europe is provided by Wichmann *et al.* (2010). See also Appendix 3 for a list of members in the BBMRI project and Appendix 4 for the BBMRI member charter.

5. Over the past decade, a number of start-up companies in the US and elsewhere have attempted to capitalize on biobanks. Interestingly, several of these efforts seem to have failed commercially or, else, have turned into active research endeavors.

6. New technologies may help to overcome the limitations of paraffin-embedding of tissue samples. See e.g. Viertler *et al.* (2012).

7. For a discussion of sample sizes needed for genetic epidemiology see e.g. Burton *at al.* (2009).

8. Michaela Mayrhofer provides empirical evidence for this argument in her doctoral research. See: Mayrhofer (2010, 2011).

9. Quoted from G. Gaskell *et al.*, *Europeans and Biotechnology in 2010: Winds of change?* Accessed on 2012/3/15 at: http://ec.europa.eu/research/science-society/document_library/pdf_06/europeans-biotechnology-in-2010_en.pdf.

10. For a more detailed discussion of the focus group methodology see: Gottweis, H. *et al.* (2012).

11. There exists a large body of behavioral research on risk perception. For an easy accessible introduction see e.g. Kahneman (2011).

12. For a fascinating case study of a French patient organization that had a considerable impact on genetics research in France see: Callon & Rabeharisoa (2003).

13. Quoted from Rial-Sebbag & Cambon-Thomsen (2012), p. 118.

14. Quoted from Gottweis, Gaskell & Starkbaum (2011), p. 739.

15. See e.g. the article in *Nature* by the San Francisco based science journalist Erika Hayden (2012).

16. The case of Biobank Japan is discussed in some detail in Gottweis & Petersen, *eds.* (2008), p. 123-139.

17. The BBMRI Stakeholder's Forum solicitaes inputs and requirements from the broad and heterogeneous stakeholder community of BBMRI, comprising patients, clinicians, funding organizations, associated project partners, industry, and users. See also: http://www.bbmri.eu/images/stories/Reports/Consultation_Document_010810.pdf.

APPENDIX 1: Bibliography and References

Allsop, J. (2006) "Regaining Trust in Medicine." *Current Sociology* **54** (4): 621-636.

BBMRI's Stakeholder Forum (2010) *The European Biobanking Research Infrastructure: A Step Closer*, June 9th 2010, report accessible at: www.bbmri.eu.

Bevilacqua, G., *et al.* (2010) "The Role of the Pathologist in Tissue Banking: European Consensus Expert Group Report." *Virchows Arch.* **456** (4):449-454.

Bexelius, C., Hoeyer, K.e *et al.* (2007) "Will Forensic Use of Medical Biobanks Decrease Public Trust in Healthcare Services? Some Empirical Observations." *Scandinavian Journal of Public Health* **35** (4): 442.

Brothers, K. B., Clayton, E. W. (2009) "Biobanks: Too Long to Wait for Consent". *Science* **326**: 798.

Burton, R. B. *et al.* (2009) Size Matters: Just How Big is BIG? Quantifying Realistic Sample Size Requirements for Human Genome Epidemiology. *Int J Epidemiol.* **38,** 1: 263–273.

Callon, M., Rabeharisoa, V. (2003) "Research 'in the Wild' and the Shaping of New Social Identities." *Technology in Society* 25 (2003) 193–204.

Calnan, M. W., Sanford, E. (2004) "Public Trust in Health Care: The System or the Doctor?" *Quality and Safety in Health Care* **13** (2): 92-97.

Caulfield, T., Kaye, J. (2009) "Broad Consent in Biobanking: Reflections on Seemingly Insurmountable Dilemmas." *Medical Law International* **10**: 85-100.

Cambon-Thomsen, A. (2003) Assessing the Impact of Biobanks. *Nature Genetics* **34**: 25-26.

Chadwick, R., Berg, K. (2001) "Solidarity and Equity: New Ethical Frameworks for Genetic Databases." *Nature Review of Genetics* **2** (4): 318-321.

Chen, D. T., Rosenstein, D. L. *et al.* (2005) "Research with Stored Biological Samples: What Do Research Participants Want?" *Archives of Internal Medicine* **165** (6): 652-655.

Condit, C. (2001) "What Is 'Public Opinion' About Genetics?" *Nature Review Genetics* **2** (10): 811-815.

Dierickx, K., Borry, P. *eds.* (2009) *New Challenges for Biobanks. Ethics, Law and Governance.* Antwerp: Intersentia.

Kaye, J., Stranger, M. *eds.* (2009). *Principles and Practice in Biobank Governance.* Farnham, Surrey: Ashgate.

European Science Foundation (2008) "Population Surveys and Biobanking. Science Policy Briefing". Makarow, M., Hoejgaard, L., Vanommen, G. J. & Skorpen, F.

European Science Foundation **32**: 1-10.

Felt, U., Fochler, M. *et al.* (2008) "Visions and Versions of Governing Biomedicine: Narratives of Power, Structures, Decision-Making and Public Participation in the Field of Biomedical Technology in The Austrian Context." *Social Studies of Science* **38** (2): 233-257.

Gaskell, G. *eds.* (2010) *Europeans and Biotechnology in 2010. Winds of Change? Eurobarometer.* European Union.

Gaskell, G., Gottweis, H. (2011) "Biobanks need Publicity", *Nature* **471**: 161-162.

Godard, B., Marshall, J. *et al.* (2007) "Community Engagement in Genetic Research: Results of the First Public Consultation for the Quebec CARTaGENE Project." *Community Genetics* **10** (3): 147-158.

Godard, B., Ozdemir, V. *et al.* (2010). "Ethnocultural Community Leaders' Views and Perceptions on Biobanks and Population Specific Genomic Research: A Qualitative Research Study." *Public Understanding of Science* **19** (4): 469.

Gottweis, H. (2008) "Participation and the New Governance of Life." *Biosocieties* **3**: 265-285.

Gottweis, H. Petersen, A, *eds.* (2008) *Biobanks. Governance in Comparative Perspective.* London, Routledge.

Gottweis, H. *et al.* (2012) *Biobanks for Europe - A Challenge for Governance.* Luxembourg: Publications Office of the European Union

Gottweis, H., Lauss, G. (2010) "Biobank Governance in the Post-Genomic Age?" *Personalized Medicine* **7** (2): 187-195.

Gottweis, H., Gaskell, G., Starkbaum, J. (2011) "Connecting the Public with Biobank Research: Reciprocity Matters." *Nature Review Genetics* **12**: 738-739.

Gottweis, H., Chen, H., Starkbaum, J. (2011) "Biobanks and the Phantom Public." *Human Genetics* **130**: 433-40.

Hermitte, M. A. (1996) *Le Sang et le Droit, Essai sur la Transfusion Sanguine.* Paris: Seuil.

Haddow, G., Laurie, G. *et al.* (2007) "Tackling Community Concerns About Commercialisation and Genetic Research: A Modest Interdisciplinary Proposal." *Social Science & Medicine* **64** (2): 272-282.

Hayden, E. C. (2012) "Informed Consent: A Broken Contract." *Nature* **486**, 312–314.

Heard, E., Tishkoff, S. *et al.* (2010) "Ten Years of Genetics and Genomics: What Have We Achieved and Where Are We Heading?" *Nature Review of Genetics* **2 11** (10): 723-733.

Hemminki, E., Tupasela, S. *et al.* (2009) "Finnish People's Attitudes Towards Biomedical Research and its Sponsorship." *Genomics, Society and Policy* **5** (2): 67-79.

Hens, K., Wright, J., Dierickx, K. (2009) "Biobanks: Oversight Offers Protection". *Science* **326**:798.

Hewitt, R. E. (2010) "Biobanking: The Foundation of Personalized Medicine". *Curr Opin Oncol.* **23**:112-119.

Hirtzlin, I., Dubreuil, C. *et al.* (2003) "An Empirical Survey on Biobanking of Human Genetic Material and Data in Six EU Countries." *Eur J Hum Genet* **11** (6): 475-488.

Hobbs, A. *et al.* (2012) "The Privacy-Reciprocity Connection in Biobanking: Comparing German with UK Strategies." *Public Health Genomics* **15**: 272–284

Hoeyer, K. (2008) "The Ethics of Research Biobanking. A Critical Review of the Literature." *Biotechnology and Genetic Engineering Reviews* **25**: 429-452.

Hoeyer, K., B. O. Olofsson, *et al.* (2004) "Informed Consent and Biobanks: A Population-Based Study of Attitudes Towards Tissue Donation for Genetic Research." *Scandinavian Journal of Public Health* **32** (3): 224-229.

Kahneman, D. (2011) *Thinking Fast and Slow.* New York: Farrar, Straus & Giroux.

Kauffman, F., Cambon-Thomsen, A. (2008) "Tracing Biological Collections: Between books and clinical trials." *JAMA* **299**: 2316-2318

Kaufman, D., Murphy-Bollinger, J. *et al.* (2009) "Public Opinion About the Importance of Privacy in Biobank Research." *The American Journal of Human Genetics* **85**(5): 643-654.

Knoppers, B. M., Chadwick, R. (2005) "Human Genetic Research: Emerging Trends in Ethics." *Nature Review of Genetics* **6** (1): 75-79.

Knoppers. B. M., Joly, Y., Simard, J., Durocher, F. (2006) "The Emergence of an Ethical Duty to Disclose Genetic Research Results: International Perspectives. *Eur J Hum Genet* **13**:1170-1178.

Korts, K., Weldon, S. *et al.* (2004) "Genetic Database and Public Attitudes. A Comparison of Iceland, Estonia and The UK." *Trames* **1-2**: 131-149.

Lue, L. (2009) "The Value of The Use of Biotechnology. Public Views in China and Europe." *Public Understanding of Science* 18: 481-492.

Lunshof, J., Chadwick, R. *et al.* (2008) "From Genetic Privacy to Open Consent." *Nature Review Genetics* **9**: 406 - 411.

Mayrhofer, M. (2010) *Biobanks in Practice. A Comparative Perspective.* PhD Dissertation. University of Vienna and École des Hautes Études en Sciences Sociales, Paris.

Mayrhofer, M. (2011) "Biobanks in Practice: The Contingent Meaning of Collected Bodily Material." In: Löwy, I. *ed. Microscope Slides. Reassessing a Neglected Historical Ressource.* Berlin: Max Planck Institute for the History of Science.

Mayrhofer, M., Prainsack, B. (2009) "Being a Member of the Club: The Transnational (Self-)Governance of Networks of Biobanks." *International J Risk Assessment and Management* **12**: 64-81.

Mcguire, A., Caulfield, *et al.* (2008) "Research Ethics and the Challenge of Whole-Genome Sequencing." *Nature Review Genetics* **9** (2): 152-156.

Nilstun, T., Hermerén, G. (2006) "Human Tissue Samples and Ethics." *Medicine,*

Health Care and Philosophy **9** (1): 81-86.

Pardo, R., Midden, C. *et al.* (2002) "Attitudes Toward Biotechnology in the European Union." *Journal of Biotechnology* **98** (1): 9-24.

Pulley, J., Brace, M. *et al.* (2008) "Attitudes and Perceptions of Patients Towards Methods of Establishing a DNA Biobank." *Cell and Tissue Banking* **9** (1): 55-65.

Pálsson, G., Harðardóttir, K. E. *et al.* (2002) "For Whom The Cell Tolls." *Current Anthropology* **43** (3): 271-301.

Ries, N., LeGrander, J., Caulfield, J. (2010) "Handling Ethical, Legal and Social Issues in Birth Cohort Studies Involving Genetic Research: Responses from Studies in Six Countries". *BMC Medical Ethics* **11**:4.

Rial-Sebbag, E., Cambon-Thomsen, A. (2012) "The Emergence of Biobanks in the Legal Landscape: Towards a New Model of Governance." *Journal of Law and Society Volume* **39** (1): 113-130.

Stranger, M., Bell, *E. et al.* (2008) "Human Genetic Databanks in Australia. Indications of Inconsistency and Confusion." *New Genetics and Society* **27** (4): 311-321.

Tupasela, A., Sihvo, S. *et al.* (2010) "Attitudes Towards Biomedical Use of Tissue Sample Collections, Consent, and Biobanks Among Finns." *Scandinavian Journal of Public Health* **38** (46): 45-52.

Tutton, R. (2002) "Gift Relationships in Genetics Research." *Science As Culture* **11** (4): 523-542.

Tutton, R. (2007) "Constructing Participation in Genetic Databases: Citizenship, Governance, and Ambivalence." *Science, Technology & Human* **32** (2): 172-195.

UK Biobank (2002) *Biobank UK: A Question of Trust: A Consultation Exploring and Addressing Questions of Public Trust*. London, People Science & Policy Ltd.

UK Biobank (2003) *UK Biobank Consultation On The Ethical and Governance Framework*. London, People Science & Policy Ltd.

Wichmann, H. E. *et al.* (2010) "Comprehensive Catalog of European Biobanks." *Nat Biotechnol.* **29** (9):795-7.

Viertler C., *et al.* (2012) "A new Technology for Stabilization of Biomolecules in Tissues for Combined Histological and Molecular Analyses." *J Mol Diagn.* **14** (5):458-66.

Zatloukal, K., Hainaut, P. (2010) "Human Tissue Biobanks as Instruments for Drug Discovery and Development: Impact on Personalized Medicine." *Biomark Med.* **4** (6):895-903.

Appendix 2: Relevant Legislation, Regulations, and Guidelines

Relevant EU Legislation

The Charter of Fundamental Rights of the EU.

Directive 95/46/EC of 24 October 1995 on the protection of individuals with regards to processing of personal data and the movement of such data.

Directive 2001/20/EC of 4 April 2001 on clinical good practice.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Directive 2004/33/EC concerning information to be provided to prospective donors, information required from donors, eligibility of donors; storage, transport and distribution conditions for blood and blood components; quality and safety requirements for blood and blood components.

Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions.

Directive 86/609/EEC of 24 November 1986 on the protection of animals.

Directive 86/609/EEC of 24 November 1986 on the protection of animals used for experimental and other scientific purposes.

Protocol on the Protection and Welfare of Animals (protocol to the Amsterdam Treaty).

Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000, on the protection of workers from the risks related to exposure to biological agents at work (7th individual directive, Article 16 (1) of Directive 89/391/EC).

Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells", code number 2002/0128 (COD), Strasbourg, 31 March 2004.

Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components.

Directive 98/44/EC on the legal protection of biotechnological inventions.

International Conventions, Declarations, and Guidelines

Helsinki Declaration.

Convention of the Council of Europe on Human Rights and Biomedicine signed in Oviedo on April 4, 1997, and the Additional Protocol on the Prohibition of Cloning Human Beings signed in Paris on 12 January 1998.

Recommendation Rec (2006) 4 of the Committee of Ministers to member states on research on biological material of human origin.

UN Convention on the Rights of the Child.
Universal Declaration on the Human Genome and Human Rights adopted by UNESCO.
OECD Best Practice Guidelines for Biological Resource Centres, OECD 2007.
OECD Guidelines on Human Biobanks and Genetic Research Databases, OECD 2009.

APPENDIX 3: BBMRI Member Organizations

Research Partners

Academisch Ziekenhuis Leiden, The Netherlands
Babraham Bioscience Technologies, United Kingdom
Biomedical Research Foundation of the Academy of Athens, Greece
Center for Economics and Social Aspects of Genomics, United Kingdom
Dutch Federation of University Medical Centers, The Netherlands
EGP of the University of Tartu, Estonia
Ensembl Functional Genomics, European Genotype Achive, United Kingdom
Erasmus MC Rotterdam, The Netherlands
Hellenic Republic Ministry of Development, General Secretariat for Research & Technology, Greece
Helmholtz Gemeinschaft, Germany
IPPOSI, Ireland
IPRI, France
Institut Mérieux, France
Institute for Biomedical Technologies, Italy
International Agency for Research on Cancer, France
Istituto Nazionale per la Ricerca sul Cancro, Biological Bank and Cell Factory, Italy
Karolinska Institute, Sweden
Legal Pathways B.V., The Netherlands
Life Science Governance Institute, Austria
Medical University of Graz, Austria
National DNA Bank, University of Salamanca, Spain
National Institute for Health and Welfare, Finland
National Research Center for Environment and Health, Germany
Norwegian Institute of Public Health, Norway
Norwegian University of Science and Technology, Norway
Semmelweis University, Hungary
UK Biobank Ltd., United Kingdom
University Hospital Groningen, The Netherlands
University of Klagenfurt, Austria
University of Malta, Malta
University of Turku, Finland
University of Manchester, United Kingdom
Uppsala University, Sweden
VITRO Ltd., Spain
deCODE Genetics, Iceland

Participating Funding Organizations

Alleanza Contro il Cancro, Italy
Bundesministerium für Bildung und Foschung, Germany
Bundesministerium für Wissenschaft und Forschung, Austria
Comitato Nazionale per la Biosicurezza, le Biotecnologie e le Scienze della Vita, Istituto Superiore di Sanita, Italy
Fraunhofer IBMT
Fundación para el desarrollo de la investigación en Genómica y Proteómica, Spain
Fondazione Telethon, Italy
Féderation hospitalière de France – FHF, France
INSERM, France
Institut National du Cancer, France
Instituto de Salud Carlos III, Spain
Irish Clinical Research Infrastructure Network, Ireland
Max-Planck-Institut für Molekulare Genetik, Germany
Medical Research Council, United Kingdom
Ministry of Education and Research, Estonia
Ministry of Education, Culture and Science, The Netherlands
Research Infrastructure and Special Initiatives Unit, Health Research Board, Ireland
The Icelandic Centre for Research, Iceland
The Netherlands Organisation for Health Research and Development, The Netherlands

APPENDIX 4: BBMRI Partner Charter

MMBRI Partner Charter
Draft version 5; 18.6.2012

Purpose and Applicability

The BBMRI-ERIC Partner Charter should define the most important cornerstones for the participation of biobanks or biological resource centres (Partner) that are associated with BBMRI-ERIC to foster scientific excellence, guarantee interoperability, and compliance with ethical and legal requirements. The Partner Charter is binding for any Partner of the BBMRI-ERIC and shall be agreed between national BBMRI-ERIC nodes and the Partners. Participation of a Partner in BBMRI-ERIC is non- exclusive and has no effect on any activity of a Partner outside of BBMRI-ERIC.

Principles

Primacy

BBMRI-ERIC acknowledges the primacy of national and European legislation and respects the jurisdiction of competent authorities.

Access Policy

Samples and data need to be accessible through a clear access procedure compliant with the general access procedures and conditions of BBMRI-ERIC. BBMRI-ERIC will foster the establishment of scientific collaborations between authenticated scientific users and Partners. Special access policies can be established for industrial users.

Access to samples and data will honour commitments to donors and follow the principles of "fair access" and scientific excellence. Access in the context of research projects performed within BBMRI- ERIC will only be provided for specified research projects, in accordance with the terms of the consent given by the participant and after approval of the research project by a Research Ethics Committee (REC). Access has to be compliant with regulations of BBMRI-ERIC Partner biobanks, and Partner biobanks have to decide whether access can be granted for a specific project. This decision has to follow transparent and non-discriminating decision making procedures. Noteworthy, the establishment of high quality research collaboration is

the preferred format for access.

Data Protection and Management Policy

BBMRI-ERIC and Partners will not make public any information of research projects performed through BBMRI-ERIC that can be directly related to an individual. Information on individuals will only be made accessible to authenticated scientific users in a coded or anonymised fashion in the context of specific research projects and upon approval by a competent Research Ethics Committee (REC) in compliance with national and EU legislation, and subject to the BBMRI data access conditions. Partners will support integration of their data management system with that of BBMRI-ERIC by complying with the BBMRI-ERIC information requirements. The initial information requirements are realized as the expected minimal common data content and data structure in relevant databases. No access will be provided for non-research purposes (such as forensic, insurance or employment purposes), except pursuant to a court order.

Informed Consent

BBMRI-ERIC and Partners will, at any time, honour commitments owed to donors. Partners shall aim at prospectively implementing the OECD Guidelines for Human Biobanks and Genetic Research.

Infrastructure and Management

Partners will commit themselves to future implementation of the OECD best practice guidelines for Global Biological Resource Centres Networks. These guidelines define in particular requirements concerning the following issues:

. Infrastructure (building, facility)
. Management (responsibilities and qualifications)
. Traceability
. Biosecurity
. Data protection
. Minimal and recommended datasets
. Quality management and certification
. Quality management

All Partners should commit themselves to implement quality management/assurance procedures compliant with OECD best practice guidelines for Global Biological Resource Centres Networks. SOPs should be established and made publicly available for all processes related to sample collection, processing, storage, retrieval and despatch. It is recommended that SOPs should follow the procedures as specified in the WHO/IARC guidelines for biological resource centres for cancer research whenever feasible. A unique BBMRI biobank (collection) identifier should be provided (see: Kauffman, F & Cambon-Thomsen, A. *Tracing biological collections: Between books and clinical trials*. JAMA 2008, 299: 2316-2318). Criteria for the identifier will be provided by BBMRI-ERIC. Partners should allow external audits by BBMRI-ERIC.

Reporting

Partners will provide annual reports to the National Node Director on which

research projects have been supported and information on the outcome that partners have received (e.g., publications, patents). Projects that have been supported by BBMRI-ERIC should acknowledge the contribution of BBMRI-ERIC in any publication according to the principles of good scientific practice. Partners will provide a yearly updated inventory to the National Node Director on the type, content and quality of collections and resources they are holding.

Charges

BBMRI-ERIC will pursue its principal task on a non-economic basis. However, it may carry out limited economic activities, provided that they are closely related to its principal task and that they do not jeopardise the achievement thereof. Biobanking-related services might be subject to cost recovery. Costs can be recovered for staffing, consumables, licensing, equipment servicing/maintenance. No patient samples or data are sold for profit. Supply of samples by or to external commercial organisations shall be conducted in accordance with the Community Framework for State Aid for Research and Development and Innovation (2006/C 323/01).

Biobanks and the Public.
Governing Biomedical Research Resources in Europe.

Funded by the European Commission.
Project GA 212111.

Text and Layout, TRI Inc.
Printed in Austria, 2013.