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Biobank Research

Individual Rights and Public Benefit

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Abstract
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The aim of this thesis is to investigate the relationship between individuals and society in the context of healthcare and medical research, more specifically concerning the rights and duties of individuals in regard to biobank-based research. My starting point is that we all have a strong vested interest in improved healthcare, and therefore the possibilities to conduct important research should be optimized. In the first article, I investigate whether individual results from research using samples in large-scale biobanks should be returned. I conclude that there is good reason not to implement such policies, and instead to allocate available resources to pursuing medical advances. In the second article, I compare consent for using stored samples in research with consent for organ donation, whereby many countries have adopted opt-out strategies in order to increase the number of organs available. I claim that the default position should be changed in biobank research as well, i.e. it should be presumed that individuals want to contribute rather than that they do not. In the third article, I argue that safeguarding autonomy by requiring informed consent for using samples in research not only defeats the interests of society but also runs counter to the interests of the individuals the policy purports to protect. Finally, in the fourth article I suggest that it is reasonable to view participation in medical research from the perspective of a social contract, built on our mutual need for medical advances, and that this implies that there is a moral duty to adhere to the contract by allowing one's samples to be used in research. A central conclusion in this thesis is that biobank research should be viewed as a natural part of healthcare, like quality control, method development and teaching, and that as such, it ought to be endorsed and facilitated.

Keywords: Biobank, Ethics, Consent, Returning results, Individual rights, Public good

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"Health is the result of biological and social determinants; both are important. Nature dictates the laws for biological determinants; people create the laws for social determinants. Nature's laws are hard to discover and are eternal whether or not they suit humanity; people's laws are easily written and can be changed at anytime to suit humanity better**."**

Attaran et al. Lancet 2012

In Memoriam
Eva Stjernschantz 1977-2011

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Stjernschantz Forsberg J., Hansson M.G., Eriksson S. (2009) Changing perspectives in biobank research: from individual rights to concerns about public health regarding the return of results. *European Journal of Human Genetics*, 17:1544-49.

II With kind permission of Springer Science and Business Media: Stjernschantz Forsberg J., Eriksson S., Hansson M.G. (2010) Changing defaults in biobank research could save lives too. *European Journal of Epidemiology*, 25:65-68.

III Stjernschantz Forsberg J., Hansson M.G., Eriksson S. (2011) Who benefits from individual consent? *BMJ* 2011;343:d5647.

IV Stjernschantz Forsberg J., Hansson M.G., Eriksson S. Why participating in (certain) scientific research is a moral duty. *Submitted.*

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Other publications by Joanna Stjernschantz Forsberg not included in the thesis:

- Hansson M.G., Simonsson B., Feltelius N., Stjernschantz Forsberg J., Hasford J. (2012) Medical registries represent vital patient interests and should not be dismantled by stricter regulation. *Cancer Epidemiology,* doi:10.1016/j.canep.2012.06.009.
- Hansson M.G., Gattorno M., Stjernschantz Forsberg J., Feltelius N., Martini A., Ruperto N. (2012) Ethics bureaucracy: a significant hurdle for collaborative follow-up of drug effectiveness in rare childhood diseases. *Archives of Diseases in Childhood,* 97(6): 561-3.
- Evers K., Stjernschantz Forsberg J., Hansson M.G. (2012) Commercialization of biobanks. *Biopreservation and biobanking*, 10(1):45-47.

- Stjernschantz Forsberg J., Hansson M.G., Eriksson S. (2011) Biobank research and consent. Authors' reply to Sheehan. *BMJ* 2011;343:d6901.
- Stjernschantz Forsberg J., Hansson M.G., Eriksson S. (2011) The risks and benefits of re-consent. *Science*, 332:306.

Contents

Introduction – Let George do it 9

Personal reflections 11

Background 12
A historical perspective on medical research 12
Why medical research is important 16
The distinction between healthcare and research 18
Different kinds of medical research 22
On consent 23
What is biobank research? 24
Different kinds of biobanks 26
Clinical biobanks 26
Research biobanks 27
Large-scale population-based biobanks 28

What are the ethical concerns in biobank research? 30
Benefits of biobank research 30
Risks involved in biobank research 32
Individual risks 32
Family risks 33
Risks for groups of people 34
Risks in a longer term perspective 34
Ethical and legal means to balance benefits and risks 35
Consent 35
Confidentiality 38
A legal perspective: The Swedish legislation pertaining to biobank research 40
Other ethical issues in biobank research 42
Commercialization and benefit sharing 42
Returning results 43
Public trust 44

Aims 45

Methods 46

Scope 48

Summary of articles 49
Article 1: Changing perspectives in biobank research – from individual rights to concerns about public health regarding the return of results 49
Article 2: Changing defaults in biobank research could save lives too 50
Article 3: Biobank research: Who benefits from individual consent? 52
Article 4: Why participating in (certain) scientific research is a moral duty 53

Discussion 54
Biobank research – Public goods and individual rights 55
A liberal view 56
A communitarian approach 57
Public and private goods 58
Congruent, convergent and common interests 59
What are rights? 60
Is there a right to healthcare? 62
Different contract views 65
Some concluding remarks on the proposed contract view 67

Future work 69

Conclusion 70

Acknowledgements 71

Summary in Swedish – Sammanfattning 72

References 75

Introduction – Let George do it

According to the Stanford Encyclopedia of Philosophy, the popular slogan "Let George do it", in which George typically stands for the rest of the world, captures the logic of collective action and the free-rider problem. [1] It will be central to my thesis.

In a world where millions of people suffer from untreatable diseases, where curable diseases become incurable due to drug resistance and new diseases continuously evolve, there is a clear need for medical advances. Improved healthcare can only be achieved through medical research, which requires competent, devoted researchers, substantial economic resources, a permissive regulatory framework and the participation of individuals.

Much research imposes serious risks on those who participate. This is illustrated by the case of Jesse Gelsinger, an 18-year old boy who suffered from a rare genetic metabolic disorder called ornithine transcarbamylase deficiency syndrome. [2] He died while taking part in a clinical trial, in which an adenoviral vector was used in an attempt to transfer a corrected gene to patients. Another example of the risks involved in invasive research is the phase 1 trial of TGN1412, a monoclonal antibody developed to fight autoimmune disease and leukemia. [3] After infusion of a dose 500 times lower than what had been found to be safe in animal studies, six healthy volunteers rapidly developed life-threatening conditions.

In invasive research it is therefore important that the risks involved are carefully weighed against the benefits, and that individuals receive (and understand) all the information relevant for making an informed decision regarding whether or not to take part in a specific study. International guidelines on research involving human subjects, starting with the first point of the Nuremberg Code: "The voluntary consent of the human subject is absolutely essential", [4] accordingly emphasize the importance of obtaining prior, free and informed consent from prospective research subjects.

However, not all medical research imposes such risks. Biological material and/or data can be used for important research at very low risk. Stored blood samples and tissue samples obtained during routine cervical cytology screening were for instance used to demonstrate an association between HPV infection and cervical cancer, [5, 6] which in turn led to the successful development of vaccines against the disease. [7] Another example is when previously taken blood samples are used to search for predictors of disease that can be detected years before patients develop symptoms. This has been done

for instance in rheumatoid arthritis, where pre-RA markers may be clinically useful because early treatment is important in order to reverse morbidity. [8, 9] The risks associated with this kind of research differ significantly from those imposed by invasive research in that they are not physical but informational, i.e. revolve around sensitive information winding up in the wrong hands.

The need to obtain specific informed consent for non-invasive research is not as clear as for invasive research, because the cost of doing so may outweigh the benefits. That is, when the risks involved in research are low, a scheme that demands consent may be excessively burdensome, and even cause harm. Reusing stored samples that have been taken in previous research projects illustrates this: If specific informed consent is required, researchers must spend time and money on contacting individuals (a procedure that can invalidate the results by imposing bias because the individuals that agree to participate may differ from those who do not). When the research that the individuals originally consented to was similar to the proposed new study, the cost of obtaining consent may be unreasonable: If the participants consented to research on specified biomarkers for cardiovascular disease, and researchers subsequently wish to investigate new biomarkers, allocating resources to obtaining consent not only seems unnecessary, but unethical.

We all have an interest in as much and as effective research as possible being carried out, because we do not know in advance what kind of healthcare we (and our family and friends) will need, and thus which research projects we might benefit from. Even in the unlikely event that we never come to need any healthcare, we benefit from knowing that research is continuously conducted because it gives us hope for the future and makes us feel more secure. [10] However, we obviously have other interests as well, for instance an interest in not being exposed to costs and risks. Therefore many (perhaps all) would rather have others participate in research than take part themselves. This is where George enters the picture.

The aim of this thesis is to investigate the relationship between individuals and society in the context of healthcare and medical research, more specifically concerning the rights and duties of individuals in regard to biobank-based research.

Personal reflections

When I started my PhD journey, I had no idea what lay ahead. On a professional account, when I look back now, I was certainly quite naïve. I was simply a medical doctor with an interest in ethical issues, and a clear picture of the need for advances in healthcare. Although my clinical career had not been long, I had met enough patients to know that there are many people who suffer from diseases that cannot be treated or cured (and from the treatments that are available), and seen a fair amount of both hope and despair.

So in my first article the argument in favor of allocating available resources to pursuing medical advances rather than benefitting individuals directly was based in solidarity, because it was natural to me. However, I soon realized that appeals to solidarity (or public benefit) don't work well, if the starting point is that what matters are individuals and their rights. Therefore, I changed sides, aiming to show that the conclusion that research should be facilitated can be reached even without concerns about the well-being of others. During the process I have come to find the rights-based view increasingly convincing.

On a personal account, I was quite naïve too. I had been spared from experiencing suffering and death in my life, and had adopted the view that certain things just don't happen. But they did, and I was reminded that although medical research may not be the most important thing in the world, to some of us it will be the difference between life and death, our own or that of somebody we care about. To others it will be the difference between living a "normal" life and a life marked by illness. To a lucky few, it might mean nothing more than a decreased risk of side-effects when taking a pill against an occasional headache. But we do not know in advance how (or if) we will benefit.

Therefore it is reasonable that we do what we can to improve the prerequisites for conducting research. I hope that my thesis can contribute to this by helping to break the stalemate between individual rights and public benefit in the debate on what policies that should govern observational research. Because in the end, what matters most is not *why* we support research, but that we *do*.

Background

A historical perspective on medical research

In order to better understand the current regulation of biobank research, and the ethical issues that not only the research but the regulations give rise to, it is helpful to briefly consider the history of medical research. My intention is not to give a comprehensive historical background, but to illustrate some of the circumstances and concerns that have affected the existing norms, i.e. what problems they have been put in place to deal with.

Many guidelines and declarations have been influenced by scandals regarding how human subjects have been treated in research. [11] These include the atrocities of the Nazi doctors, who used concentration camp victims for medical experiments aimed at gaining knowledge about e.g. the effects of freezing, high altitude, sulfanilamide administration, and transplantations. [12] The Nuremberg Code was a result of the trial against the Nazi doctors and consists of 10 principles that establish the requirement to obtain voluntary consent and the need to weigh the benefits and risks of research. [4] However, medical codes existed before Nuremberg, dating as far back as the Hippocratic Oath, written around 400 B.C. Although the oath did not deal directly with research subjects, it established the obligation to benefit the patient and not to inflict harm.

Up to the 20th century almost all medical practice was experimental. Procedures were undertaken in order to save lives, i.e. experimentation carried out in the context of patient care was not considered research. [13] Therefore, most early codes did not make the distinction between therapeutic and non-therapeutic research that is common today. [14] When medicine moved into the age of science and experiments were carried out as research (i.e. to increase knowledge, not primarily to benefit the subject), the difference was not addressed and the distinction between patient and research subject was blurred. [15]

There are isolated examples of early experimentation on human subjects, often conducted on prisoners: In 1721 inmates at a prison in Great Britain were for instance offered free pardon if they agreed to be variolated (i.e. undergo cutaneous inoculation of material from smallpox pustules), which caused a milder disease than natural smallpox, but could spread among susceptible individuals. In 1796 Edward Jenner inoculated a child first with cowpox virus and then with smallpox in order to demonstrate that the former

offered protection against the latter, which paved the way for eradicating the disease as this method of prevention did not imply a risk of infectious spreading. [13]

However, during this time period, most experiments were conducted by physicians on themselves. Examples include self-infections (e.g. swallowing live cultures of vibrio cholera) and ingestions of drugs. [13] This auto-experimentation continued into the 20th century. In 1900 members of Walter Reed's research group in Cuba for instance infected themselves with yellow fever, proving that the disease was transmitted by mosquitoes; knowledge that saved many lives. Another famous example is from 1929 when the German physician Werner Forssmann passed a catheter from his arm into the right ventricle of his heart demonstrating that it could be done safely and without discomfort. [13]

One of the first codes that included directives regarding research ethics (although its main focus was on clinical practice) was written by Thomas Percival, an English physician in 1803. It was explicit about the need for new therapies and focused on demanding good methodology and competent investigators, but did not mention any requirement to protect research subjects or to obtain informed consent. In 1833 William Beaumont, an American physician who carried out non-therapeutic experiments on a patient with an open fistula into his abdomen following a gunshot wound, wrote a code on the ethics of human experimentation. It shared many characteristics with the writings of Percival, but included a demand for voluntary consent as well as discontinuation of experiments that gave rise to distress, likely reflecting the fact that he did not conduct his research on a prisoner, but on a free man. [14] In 1865 Claude Bernard, a French physiologist, wrote: "It is our duty and right to perform an experiment on man whenever it can save his life, cure him or gain him some personal benefit. The principle of medical and surgical morality, therefore, consists in never performing on man an experiment which might be harmful to him to any extent, even though the results might be highly advantageous to science, i.e., to the health of others"… [14] Thus, Bernard demanded personal benefit, which excluded non-therapeutic research, but did not mention any need to obtain consent. Early writings such as these came to underlie the Nuremberg Code, because they influenced the thinking of the prosecutions two primary medical expert witnesses: Leo Alexander and Andrew Ivy. [14]

It should be emphasized that regulations regarding the proper conduct of research existed in Germany prior to the Second World War. [16] The 1900 Preussian directive was issued following a debate on the permissibility of human experimentation brought about by attempts to immunize healthy individuals (children and female prostitutes) against syphilis. It demanded protection of vulnerable populations, information about possible adverse consequences as well as consent. [14] Furthermore, criticism regarding unethical conduct within the German medical profession in the 1920s resulted in the issuing of guidelines for medical experimentation with humans in

1931 by the Reich Minister of the Interior. In many aspects these guidelines were more extensive than the Nuremberg Code or later the Declaration of Helsinki. [14]

A problem with the Nuremberg Code was that it could be dismissed by scientists as irrelevant to their (decent) research efforts. Using the words of Jay Katz, it was viewed as "a good code for barbarians but an unnecessary code for ordinary physician-scientists". [15] In 1964 the World Medical Association promulgated the Declaration of Helsinki, addressed primarily to physicians, as a statement of ethical principles for medical research involving human subjects. [17] The Declaration clearly distinguished between therapeutic and non-therapeutic research, stating that in the latter kind of research "the interest of science and society should never take precedence over considerations related to the well-being of the subject". [17] It has been modified several times and in 1975 a requirement for prior review by an independent committee was included. Since 2000 it explicitly makes reference to research on identifiable human material and data. [18]

In 1979 the Belmont Report was issued in the United States, in part following a number of controversial research projects, e.g. the Tuskegee Syphilis Study, in which poor African American men were used as research subjects without their knowledge, in order to learn more about the natural course of syphilis. The men were left untreated even after it became clear that penicillin was an effective treatment for the disease. [19] The Jewish Chronic Disease case (in which cancer cells were injected into patients without consent) and the Willowbrook case (in which hepatitis virus was injected into mentally retarded children) are two other examples of unethical research conducted before the Belmont Report. [11] The report identified the principles of respect for persons, beneficence and justice as the moral basis for legitimate research involving human subjects. These principles give rise to the requirement to obtain informed consent, the need for an appropriate risk/benefit ratio and an equitable selection of research subjects. [20]

Another issue relevant to biobank research is that of benefit sharing. The newly published book "The Immortal Life of Henrietta Lacks" by Rebecca Skloot has added to the debate on whether or not individuals have a right to share the profits when parts of their bodies are used for research. [21] Henrietta Lacks was a poor black tobacco farmer who died of cervical cancer in 1951. Cells from her tumor were taken without her consent (or knowledge) and used to create the first immortal cell line. These HeLa cells have been used in research all over the world and have contributed to the development of e.g. the polio vaccine, chemotherapy, cloning, in vitro fertilization and gene mapping. They have been bought and sold in large quantities, yet her family has received no economic compensation. [22] The case of John Moore, who underwent treatment for hairy cell leukemia at UCLA in 1976, stirred similar controversy. Cells from his spleen were taken without his consent and used to culture an immortal cell line that was patented in 1984.

After accidentally having learnt what his cells had been used for (when he was instructed to circle "I do" rather than "I do not" grant the University all rights in any cell line on a consent form), Moore sued UCLA, but the California Supreme Court ruled that he had no right to any share of the profits, although his doctor was criticized for not having informed him about his research and economic interests. [23, 24]

In an attempt to protect individuals from various offences, increasing weight has been given to autonomy and individual rights. Some of the more recent international ethical norms pertaining to medical research e.g. by the Council of Europe [25] and UNESCO [26, 27] have explicitly incorporated human rights in their statements, thereby introducing an external set of values by which the conduct of research can be judged. [28] Thus, they can be regarded as an extension of international human rights law into the field of biomedicine. [29] Following previous scandals many guidelines also expressly endorse the primacy of the individual over society in the context of medical research. The Convention of Human Rights and Biomedicine for instance states that: "The interests and welfare of the human being shall prevail over the sole interest of society or science". [25] Although the grounds for his provision are clear in a historical perspective, its exact meaning is difficult to interpret. [30] Individuals have many different interests that can conflict with each other and it is far from obvious what the "sole" interest of society is. Furthermore, even if such statements are well-intended, they are problematic in that they establish and reinforce a way of thinking about research as something that stands opposed to the interests of the individual.

To conclude, the current regulation of medical research is based on ethical principles with a long historical background, although some significant shifts have occurred, e.g. the modern focus on individual rights. A clear distinction has also emerged between medical care and research, according to which human subjects must be protected against research in a way that is not required for patients in clinical care, even if it is experimental. This has recently been questioned, because it can lead to a situation in which research subjects are overprotected and patients under-protected: Individuals in need of promising treatments cannot be included in studies due to the risk of harm, while medical care that is experimental can be given without similar safety requirements. [31] Suggestions of how the ethics review process and information and consent procedures can be adjusted to the levels of risk associated with specific research protocols have recently been put forward, and may have an impact on the future regulation of research using biobanks and medical registries. [32]

Why medical research is important

Up to the end of the eighteenth century medicine had hardly advanced at all. [13] For thousands of years, ever since Hippocrates, it had rested on the thesis that health came from a balance between the bodily liquids (blood, phlegm, black bile and yellow bile) and the "universal cure" of bloodletting. [33, 34] But progress within the medical sciences has been remarkable since then: In less than 200 years these old truths were overthrown and replaced by the sophisticated methods of diagnosing and treating illness that we take for granted today. Between 1945 and 1965 for instance, drugs against bacterial infections, hypertension, psychosis and cancer came into common use, organ transplantation was initiated, and life-sustaining devices such as dialysis machines, pacemakers and ventilators were developed. [35] This was a result of much research.

Similarly, continuous research is a prerequisite for achieving further advances, which is important not only because many people suffer from diseases that cannot be treated or cured, but also because new diseases, and new spectrums of diseases, evolve. Childhood cancer is an example of an area in which research has lead to great improvements. About 300 children are diagnosed with cancer each year in Sweden. Previously most of them died, but today, thanks to research, three out of four survive. However, this still leaves 25 % facing premature death. [36]

An obvious example of evolving new diseases is the swine flu (H1N1) infection that was detected in Mexico in April 2009. By the end of the year, the disease had spread to more than 200 countries, and caused at least 12 220 deaths. [37] Although the pandemic did not reach its feared magnitude, in an increasingly globalized world diseases can spread rapidly and far. Furthermore, recent figures indicate that almost 300 000 individuals may have lost their lives due to H1N1, a number 15 times higher than the officially reported, laboratory confirmed deaths. [38] The increased incidence of narcolepsy among children that were immunized against H1N1 with the vaccine Pandremix (in which an adjuvant component that was added to enhance the effect of the vaccine is suspected to have induced the disease), also serves as a reminder that the more medical knowledge we have, the better situated we are to deal with future public health crisis. [39] Because adjuvanted vaccines are much needed to enhance the immune response, research is necessary to determine if adjuvants are associated with adverse effects such as autoimmunity. [40]

Another reason why medical research is important is the growing problem of drug resistance. Increasing antibiotic resistance in conjunction with lack of antibacterial innovation has long been recognized as a serious threat by the scientific community. [41] The large and increasing number of Meticillin Resistant Staphylycoccus Aureus (MRSA) infections among hospitalized patients around the world is a clear illustration of this. These infections are

caused by normal skin bacteria that have acquired resistance against conventional antibacterial treatment, and can only be treated with a few expensive intravenous antibiotics that can cause serious side-effects. [42] Another example is tuberculosis, which continues to constitute a major challenge to global health. Almost 2 million people die each year from this illness, and the disease is becoming more virulent and resistant to available medications, largely due to inadequate treatment and compliance. Extensively drug-resistant strains have recently emerged which threatens to take us back to the pre-antibiotic era. [43] Likewise, tumor cells can acquire resistance against cancer therapies, as can viruses against antiviral medications, therefore the arsenal of therapeutic approaches available for these kinds of diseases needs to be broadened as well. [44, 45] To conclude, research is necessary both because there are "old" diseases that cannot be treated effectively and because new health hazards continuously evolve.

The efficacy of medical research is sometimes questioned, and thereby its importance in relation to other societal undertakings. Research costs money and imposes risks on those who participate, the argument goes, yet there are no guarantees that it will give rise to advances that will actually benefit anyone. Arguing in such a vein, Daniel Callahan has questioned "the research imperative", stating "…because of its value – social, medical, economic – medical research tempts us to invest too much hope in it as a way of relieving the human condition or leads us to excessively commercialize it, to cut moral corners in pursuit of therapies and cures, or with human research subjects, or to divert attention from the social and economic sources of sickness." [46] Thus, according to Callahan, the research imperative is dangerous because it may fool us to set aside ethical safeguards and principles, and because it imposes opportunity costs, i.e. consumes resources that might be put to better use. He claims that this is harmful especially since both the therapeutic benefits and social implications of medical research are uncertain.

Although it is true that there is no way of knowing in advance if research will lead to better healthcare, the mere hope of achieving medical advances is arguably sufficient to justify at least research that imposes only diminutive risks, because there is no alternative way to increase medical knowledge. However, since patients' hope has previously been abused, questions such as what kind of risks individuals should be allowed to face have been asked within the field of research ethics. This has lead to a demand that there be well-founded hope for scientific advances, and that the risks involved in research be weighed against the scientific benefits. Furthermore, the potential of different research projects to improve health and healthcare must obviously be compared against each other when finite resources (such as money and stored tissue samples) are allocated. The objection also points at the importance of optimizing the regulatory prerequisites for conducting research, so that the risks that are taken by individuals and the money that is spent render the best possible outcome for current and future patients.

Although it is also true that from a societal perspective there may be economically more efficient ways to further the health of a population (and perhaps more important goals than increased health to aim at as well), this is arguably too limited a view. It is important to remember that for the person who succumbs to a serious disease, there is no alternative to research. From the perspective of the individual, medical research is like paying for an insurance; even if it does not guarantee that effective treatments will exist against all diseases (just as insurance does not cover everything), it is the best and in effect the only way of increasing the chances of relevant knowledge existing. Furthermore, although many diseases can be prevented by changes in lifestyle and public health interventions, research is necessary in order to understand how environmental determinants influence health and in what ways they interact with biological factors. This can be done using biobanks and medical registries.

Moreover, the requirement that ethical corners not be cut demands defining what these corners consist in. As long as one individual is not sacrificed for the benefit of others, it seems that there may be good reasons to "cut corners" in order to increase the benefit that can be obtained for all. One corner that arguably *should* be cut (if it is defined as a corner) is the demand that specific informed consent be obtained when stored samples and data are used in research. [Article III]

A counterargument might of course be that although cutting certain corners may lie in the interest of us as individuals, doing so runs counter to the interests of society. Hans Jonas has accordingly argued: "Let us also remember that a slower progress in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having." [47] This is obviously true when it comes to research in which one individual is sacrificed for the benefit of others (such as in the case of the Nazi doctors or the Tuskegee Syphilis study), but it is not equally applicable on well-regulated observational research. Society is not threatened by cutting ethical corners in a way that benefits all; to the contrary, doing so seems to be the ethical choice. [Article IV]

The distinction between healthcare and research

The CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects defines research as: "a class of activity designed to develop or contribute to generalizable knowledge. Generalizable knowledge consists of theories, principles or relationships, or the accumulation of information on which they are based, that can be corroborated by accepted scientific methods of observa-

tion and inference." [48] Clinical care, on the other hand, exists primarily to benefit the individual patient. As the World Medical Association's Declaration of Geneva states: "The health of my patient will be my first consideration". [49] Thus, medical research is pursued for the public good (and thereby for the good of each individual), whereas clinical care is devoted to benefiting individuals directly.

Not acknowledging the difference between research and clinical care is the basis of "the therapeutic misconception", which is characterized by individuals wrongfully attributing research the goal (at least in part) of benefiting the research subjects individually. The term was originally coined by Appelbaum et al. after having demonstrated that individuals who participated in randomized double-blinded studies believed that they received the medication that was best suited for them. [50] However, randomized clinical trials are built on the notion of "equipoise", i.e. genuine uncertainty in the medical community regarding which treatment is best, and in double-blinded studies neither the patient nor the doctor knows which treatment is given. These studies are conducted not to offer individuals better treatment alternatives, but to collect evidence on which of the treatments that is preferable, i.e. has a superior overall risk-benefit ratio.

Such trials are sometimes terminated prematurely when equipoise is "disturbed", i.e. one treatment appears to be better than the other. It has been argued that doing so conflates the ethics of research with the ethics of healthcare, and may lead to unfortunate scientific consequences that ultimately put patients and future research subjects at increased risk. [51] This is illustrated by a 1999 clinical trial of bisoprolol for patients with vascular disease undergoing non-cardiac surgery. [52] The study was terminated in advance due to a (perceived) great reduction in the risk of myocardial infarction and cardiac death. As a consequence, widespread recommendations to use beta blockers were issued, but in 2008 a meta-analysis including more than 12 000 patients concluded that the risk reduction was significantly lower than what had been reported. Furthermore, the risk of suffering non-fatal stroke was increased twofold, and there was a possible increase in overall mortality. [53]

Overestimating the benefit that can realistically result from being included in a study, or underestimating the risk of harm has also been labeled a therapeutic misconception. When conducting phase 1 studies of potential new drugs on cancer patients with advanced disease, it has for instance been argued that a misconceived hope for medical benefit may invalidate the informed consent, because the patients have no alternative treatment options. [54] Others have claimed that the scientific purpose of research does not rule out individual benefit, and therefore, provided that prospective participants are given accurate information, the hope for benefit may not be misconceived. [55] Furthermore, patients may perceive of their participation in research in many different ways, including the question of what constitutes a

benefit. Thus, benefit need not necessarily be defined solely in terms of medical improvement, but can also include other elements such as a feeling of meaningfulness or being taken care of. In our research group studies are currently being conducted to understand on what premises Swedish patients decide to participate in phase 1 and phase 3 oncology trials with emphasis on their attitudes regarding risk, personal benefits and benefits for future patients. [56]

In the context of biobank research the therapeutic misconception may be nurtured by offering brief medical examinations or the disclosure of individual results to participants. Conflating the purposes of research and clinical care in this way may induce individuals to donate tissue samples to biobanks and not only deceive them but give them a false sense of security. This is one reason why policies that recommend direct individual benefits should be reconsidered. [Article I]

Although there is a significant distinction to be made between the immediate purposes of healthcare and research, in the end both aim at improving the health of individuals. In order for research to have a potential to result in relevant medical advances it must be applicable on clinical needs, which is why it must at least partly be situated within healthcare, finding problems and testing possible solutions. Patients as well as healthy volunteers are necessarily involved in this process.

Therefore it is important that medical research is regulated in a way that optimizes the prerequisites for attaining medical advances while protecting the interests of those who participate. In doing so all aspects must be considered, including the dual interests that patients have, as research subjects but also as end-consumers of healthcare. For policy makers, the primary focus has been on the protection of patients when participating in research, in particular by requiring their informed consent. The patients' interest in medical advances has not been catered for to the same extent, as research is perceived of as something optional and exceptional. [57]

A recent example from Sweden illustrates this: Participation in an international multicenter study comparing two different surgical treatments for rupture of the abdominal aorta (IMPROVE - Immediate management of patients with ruptured aneurysm: open versus endovascular repair) was proposed. [58] Each year 700-1000 patients die from this diagnosis in Sweden. The situation is acute and patients are often in chock and pain and are not uncommonly unconscious. There are two treatment options: endovascular or traditional open surgery. Previous studies have indicated higher survival rates among patients who have received endovascular treatment, but these studies are primarily retrospective and non-randomized, and may therefore be biased. The ethics review board approved the study but decided that patients that could not consent could not be included, leading to a clear risk of selection bias. (In Sweden, as opposed to most other European countries, there is no system of proxy consent that would allow for somebody else to

consent for the patient.) Thus, the interests of these individuals as research subjects (in consenting) seemingly outweighed the benefits that could be obtained by conducting an unbiased study to learn if one method was better than the other. However, the same individuals could be treated with either method as patients, assuming that there was no evidence that one treatment was superior to the other.

Another illustrative example is a quality improvement research project that was conducted by researchers at Johns Hopkins University, aiming to reduce catheter related infections in intensive care units. [59] In the study, a protocol of routinely implementing five evidence-based procedures (including removing unnecessary catheters from patients and having doctors wash their hands prior to the insertion of a catheter) was evaluated. No consent for participation was sought from the patients. The project resulted in a dramatic decrease in infections. Following publication of the results however, an investigation by the OHRP (Office for Human Research Protections) was initiated. It concluded that informed consent should have been obtained from the research subjects. But as in the former example, the participating hospitals could have implemented the quality improvement protocol without conducting prior research on its effectiveness, in which case no consent would have been required, because the patients would have been patients and not research subjects. This would nevertheless come at an epistemological price; we would not really *know* the effect, so while these patients might benefit from the improved procedure it would be much harder to argue for a wider implementation that would benefit the many.

Both of these cases illustrate the problem of viewing medical research as something exceptional that individuals must be protected from (and thereby also consent to) in itself*,* even if participating in the study adds no risks; because as a consequence, patients are, and continue to be, exposed to treatments and procedures that have not been scientifically evaluated. This overprotection of research subjects implies an increased risk in clinical practice due to inadequate scientific foundations, exemplified for instance by the weak evidence base of many treatments for pregnant women. [60] Likewise, pediatric research is lagging behind due to the ethical difficulties involved in such research and consequently children are exposed to extra risks in association with ordinary healthcare.

In the context of biobank research a similar overprotective view is arguably expressed when it is claimed that even if samples are completely anonymized (and thus cannot be linked to specific individuals) they should not be used without consent, because doing so may wrong the individuals from whom they were taken.

Different kinds of medical research

Medical research can broadly be divided into two categories: interventional and non-interventional (i.e. observational) research. Interventional research is experimental in that it involves evaluating the effects of an intervention, for instance by administrating a new drug to patients in a clinical trial. Observational research, to the contrary, does not involve studying the effects of interventions directly. Research using stored tissue samples and/or data in medical records and registries are examples of such research. This distinction is important because the risks that are imposed on the individuals who participate differ significantly, and thereby it is not clear that the same regulations should apply; while interventional research is often invasive, and thus associated with a risk of physical harm, observational research is not. (Although it may impose psychological or informational risks, which will be discussed later)

A cancer patient can be involved in both kinds of research: He or she might be included in a clinical trial comparing a standard treatment with a new cytotoxic agent, which is an interventional study. In this case it is obvious that the individual should receive all the information necessary in order to make an informed decision regarding whether or not to participate, because taking part in such research is associated with significant risks. The same patient may also participate in observational research if a sample that was previously taken from his or her tumor is used in research aiming to detect receptors that could be targets for novel therapies. In this case the risks that are imposed are diminutive, and it is not as clear that informed consent should be obtained, because doing so may hamper research by imposing extra costs and leading to drop-outs. Thus, although obtaining consent respects the autonomy of the patient in both cases, in the context of using tissue samples for research the individual might feel even more respected if consent is not obtained, because it improves the prerequisites for conducting research, and thereby also the chances of attaining medical advances. [61]

It is worth emphasizing that the landscape of medical research has changed significantly during the past decades. There has for instance been a substantial proliferation of multi-site clinical trials, large-scale international data sharing projects and epidemiological research. Simultaneously there has been an increase in the total volume of research, and new entities such as contract research organizations, protocol developers, data analysts and data and safety monitoring committees have emerged. [32] The regulations pertaining to medical research have not kept pace. In the U.S. an advanced notice of proposed rule-making (ANPRM) has therefore been issued, aiming to modernize current research regulations to "better protect human subjects who are involved in research, while facilitating valuable research and reducing burden, delay and ambiguity for investigators." [32] According to the proposal, research

that only involves stored tissue samples or data would be excused from ethics review, provided that mandatory standards for data protection and information security are fulfilled.

On consent

Since the issue of consent has already surfaced several times in this introduction, it is worth recapitulating some basic facts (I will return to a more thorough analysis on consent for biobank research later on). Informed consent has been central to biomedical ethics since the Nuremberg trials, although the term did not appear until a decade after the trials and was not analyzed in detail until the 1970s. [62] Originally its main function was to protect patients and research subjects against serious wrongs such as fraud, deceit and coercion, but more recent justifications of the need for informed consent are based on protecting the autonomy rights of individuals. [63]

Obtaining an informed consent has been defined as including the following elements: 1) competence (an evaluation of the competence of the individual to understand the information and to give consent), 2) voluntariness (an assessment regarding whether the research subject is free and can exercise his or her freedom not to participate in the research), 3) disclosure of information, 4) understanding (trying to make sure that the research subject understands the information) and 5) consent (i.e. authorization by the research subject, orally or in writing). [62]

The most recent version of the Declaration of Helsinki sets the standards for obtaining consent as follows (in its paragraph 24)[1]: [64]

> "In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed."

[1] It should be noted though, that this version of the declaration opens for research on stored tissue samples and data without consent in "situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research". See [64] A prerequisite is that the research has been considered and approved by an ethics committee. The default position however, is still that consent must be sought for collection, analysis, storage and/or reuse of samples.

Rejecting such standardized consent procedures Neil Manson and Onora O'Neill have argued: "Consent is a way of ensuring that those subjected to invasive interventions are not abused, manipulated or undermined, or wronged in comparably serious ways. It seeks to ensure that such action is done only when specific norms are waived, and is not undertaken if it would breach important ethical or legal requirements." [63] From this perspective, there is no obvious need for routine disclosure of sources of funding, any possible conflicts of interest and institutional affiliations etc., even less so for requiring that individuals actually understand this kind of information.

The latter view also fits better with existing empirical evidence showing that people fail to understand many central aspects of the research that they participate in (such as randomization in clinical trials), and therefore in practice, truly informed consent, of the specific kind, is rarely attained. From such a perspective, it has been argued that the ideal of informed consent must be compromised due to empirical reality, and that more weight should be put on other considerations such as beneficence and welfare issues. [65]

In any instance it is clear that consent requirements have escalated during the past decades. This is illustrated by the consent forms that participants in the Framingham Heart Study have been asked to sign over the years.[2] The first consent form (from 1971) read: "I have been fully informed of the nature of this study which includes a medical history, physical examination, blood tests and electrocardiogram and give my consent to be examined. I also authorize the Framingham study staff to secure pertinent medical information from my family, physician, and/or hospital records for the purposes of this study." [66] Subsequent consent forms have become more and more complex, and the latest version (for exam 29 of the original cohort) is six pages long. [66]

What is biobank research?

For the purpose of this thesis I define biobank research as observational research that is carried out using human tissue samples, stored or freshly taken. These samples are stored in biobanks, either before the research is carried out (when existing samples are used for retrospective studies) or during and after the study (when new samples are taken in prospective studies). Often associated personal data, e.g. information available in medical records or registries, or collected via questionnaires, is used as well.

The term "biobank" appeared in PubMed for the first time in 1996, but it became commonly used only after 2000. [67] It has been employed to describe various different collections of human biological material, ranging

[2] The Framingham Heart Study is a large prospective cohort study in the United States that has been running since 1948, aimed at investigating the causes of cardiovascular disease. It will be discussed in more detail later on.

from large population-based repositories that house hundreds of thousands of tissue samples to small "private" collections tucked away in freezers in hospitals and research institutions. In 2009 Time Magazine designated biobanking one of ten ideas that are changing the world right now. [68] So biobanks may seem to be a new and rapidly evolving domain. But the practice of banking tissue samples is not new. Pathologists have studied and stored tissue samples ever since Virchow stated that all disease starts in cells in 1858, and doctors have been taking samples from patients as a part of routine clinical practice for many years. [33]

What is new are the techniques that can be used to gain information from biological material, in particular the recent advances in genetics combined with improved methods to handle large amounts of data. DNA provides data that by far out-does the information that can be derived from samples using conventional methods, which has lead to a debate on "genetic exceptionalism", the idea that genetic information is unique and should be treated differently than other medical information. [69] Before moving on to consider this issue, it is important to emphasize that tissue samples are often used in non-genetic research as well.

Four characteristics of genetic information are commonly proposed to underlie the claim that genetic information is morally different than other medical information. These are: 1) It is predictive of disease before onset, 2) It is transmittable to future generations, 3) It reveals information about other persons than the individual from whom it is taken, 4) It is especially personal or intimate. [70] However, the three first points are true of many kinds of information, e.g. socioeconomic factors (such as income level) and other medical information (such as being HIV-positive). [70] Regarding the fourth point, genes are active in an environment that influences them, so we are not products of our genes alone. For most people differences in health are simply *influenced* by genes, because the effect of genes is modified by behavior, environment and epigenetics. Although we may consider genetic information delicate, this is true of other information as well, such as political views, sexual preferences, or a family history of mental illness. [71] Another reason why genetic information may be viewed as especially sensitive is the history of misuse, illustrated for instance by Nazi Germany's eugenics movement. [72]

Moreover, it is not necessary to study DNA in order to obtain genetic information. Other components of cells can also give information that is relevant when investigating genetic causes of diseases. Proteins and mRNA for instance provide information about the genes that are expressed in cells, and some genetic diagnoses are apparent without any analyses, e.g. Down's syndrome. For these reasons the argument of genetic exceptionalism fails. Nonetheless, in order for many regulative and ethical restrictions on biobank research to make sense it seems that a certain amount of it must underlie them.

Different kinds of biobanks

Millions of previously collected tissue samples are stored all over the world waiting to be used for healthcare, teaching, quality control, method development and research.[3] It has been estimated that there are approximately 100 million samples stored in Sweden, with 2-3 million new samples added each year. [73] Similarly, more than 300 million tissue samples are stored in the United States, a number that increases with 20 million per year. [74]

These collections have been assembled in numerous ways and for diverse reasons, ranging from retained material taken for diagnostic, therapeutic or screening purposes within the healthcare system to samples obtained through voluntary participation in research projects. In the following I will offer examples of different kinds of biobanks, categorized as clinical biobanks, research biobanks and large-scale population-based biobanks. However, since researchers use samples from all of these biobanks, the distinction is arbitrary, based only on the primary cause of the collection.

Clinical biobanks

Blood samples and other tissue samples are routinely taken within healthcare for diagnostic or treatment related purposes. Most of them are analyzed directly and then discarded, but some samples are retained for future use, often for the safety of the patients (so that they can be re-analyzed or compared with future samples). Such tissue samples are commonly stored in pathology, microbiology or cytology biobanks. These biobanks consist of materials such as: cell suspensions, cells mounted on glass slides, cytological brush samples, fresh frozen material, formalin-fixed paraffin embedded tissue samples, serum, cerebrospinal fluid, sore secretion, blister material, bronchoalveolar lavage, conjunctival fluid, urine, buccal swabs, saliva, whole blood, buffy coats and blood clots. [75]

Furthermore, many countries have extensive screening programs for newborns and dried blood spots are often stored for future use. An example is the PKU-biobank in Sweden that has stored samples from 3 million infants starting 1975. [76] The primary purpose of taking these samples is to analyze markers for metabolic diseases that can be treated if diagnosed in an early stage. The samples are stored for quality control purposes, so that they can be re-analyzed if a child later develops any of the diseases that he or she has been screened for, and be used when new tests are developed. They can also be used clinically: if a child is diagnosed with deafness the PKU sample can

[3] The Swedish Biobanks Act distinguishes between development and research in this way. According to the Inquiry that was appointed to review the Act in 2008, the former is a natural extension of healthcare that gives rise to improvements in medical care, while the purpose of the latter is of a different kind. Presumably, method development is thought to be of more direct benefit to patients.

for instance be analyzed to see if he or she was exposed to an intrauterine CMV-infection, rendering further investigations unnecessary (because this is a common cause of congenital deafness). The stored samples can also be used in research, subject to approval from an ethics review board.

Dried blood spots are suitable for genetic epidemiological studies and DNA has been successfully extracted from 25 year old samples. [75] Combining such samples with clinical information from medical registries offers a possibility to conduct large studies on entire populations, avoiding practically any kind of selection bias and reducing costs. [77] Formalin-fixed and paraffin embedded samples (e.g. taken from tumors) are also available in large quantities, but a problem with this kind of material is that derivates such as DNA, RNA and proteins can be of poor quality (although tissue morphology is well preserved). [78] However, recent studies have shown that it is possible to extract high quality genome DNA from such samples as well [79, 80]

An epidemiological study by Wallin et al. illustrates the usefulness of clinical biobanks: It demonstrated that presence of Human Papillomavirus (HPV) DNA in Pap smears taken during routine screening was associated with a 16-fold increase in risk of future cervical cancer. [6] In the study, a cytology biobank registry and the Swedish Cancer Registry were linked in order to find cases and controls. This study design was important because previous research had been conducted on samples taken after the cancer had been diagnosed, and thus the temporal order of events could not be established, i.e. the infection could have been an effect of the cancer as well.

Research biobanks

Samples that have been taken within the context of specific research projects are also stored in biobanks. The World Health Organization's multinational MONICA project, aimed at studying trends in and determinants of cardiovascular disease, serves as an example of such a research project. In 1990 79 % of 2000 randomly selected individuals in Northern Sweden agreed to participate, and their blood samples (donated for research on "cardiovascular disorders and diabetes") have been stored in a biobank for future use. [81] The study population has subsequently been expanded and now includes approximately 12 000 examined individuals, with 18 000 myocardial infarctions and 21 000 strokes registered in associated databases. [82] By linking these registries to each other the risk of developing disease can be related to characteristics that the individuals displayed when they were examined.

Other examples include the ABIS project that has followed 17 000 children in South-Eastern Sweden during more than 10 years, collecting data and samples primarily for research on diabetes. [83] The Framingham Heart Study in the U.S. is an internationally well-known research project that has been running since 1948. The objective of the study was originally to identi-

fy common factors and characteristics that contribute to cardiovascular disease by following a large group of people who had not yet developed symptoms. More than 5000 men and women were recruited, and the study has now included both second and third generations. It has given rise to approximately 1200 publications in leading medical journals during the past 50 years. [66]

Large-scale population-based biobanks

In addition to clinical biobanks and research biobanks, large-scale population-based biobanks are being established widely. Examples include the UK Biobank, LifeGene (in Sweden), DeCode Genetics (in Iceland) and the Estonian Genome Project. The purpose of these biobanks is to investigate how genes interact with people's environment and lifestyle. In order to achieve this goal large associational studies that compare genotypes and phenotypes (i.e. genetic markers and health data) are conducted.

The UK Biobank has collected samples and health data from 500 000 individuals between 40 and 69 years of age. According to the biobank's homepage it is a major national health resource "with the aim of improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses – including cancer, heart diseases, stroke, diabetes, arthritis, osteoporosis, eye disorders, depression and forms of dementia." [84]

LifeGene is a similar population-based project that has been initiated in Sweden. The aim is to recruit half a million individuals and to follow their health in order to study common diseases and health problems such as "asthma, allergies, infections, obesity, repetitive strain injuries, chronic fatigue and pain, and major diseases in later life – cardiovascular diseases and cancer." [85] However, the project has encountered regulatory difficulties based in the fact that it is an infrastructure for future research rather than a research study in itself, and doubts pertaining to the validity of the participants' consent have been raised. [86] In order to facilitate such large-scale cohort studies legislative changes have recently been proposed.

Another well-known population biobank is that of the commercial company DeCode Genetics in Iceland. [87] According to the original proposal, the health records of the entire Icelandic population, 270 000 individuals, would be put into a single database, that could be combined with genealogical information and genetic data obtained from samples donated by volunteers. The health record database stirred great controversy because individuals were to be included under presumed consent. [88-90] According to the company's homepage it has collected genotypic and medical data from more than 140 000 participants, making possible "very large-scale studies of virtually any common disease". [87] However, the controversial health record database has not been established.

The Estonian Genome Project (EGP) was launched in 1999, with the ambition to create a genetic database including virtually all Estonian citizens, but the inclusion rate has been lower than anticipated, and the current aim is to include 5 % of the population. [91] Donors are interviewed, leave a blood sample and are asked to consent to medical data being obtained from other sources, e.g. hospital records. [92] An explicit goal of the project is to grant individuals access to their data so that they can benefit from "the personalized medicine of the future". [93] This stands in contrast to other population-based biobanks, such as the UK biobank and LifeGene, that offer participants some basic clinical results when enrolling, but no individual results from subsequent research.

What are the ethical concerns in biobank research?

There are many stakeholders involved in biobank research, and the interests of all parties need not coincide. As individuals we have an interest in being protected against harm when our samples and data are used for research purposes. However, we also have an interest in medical advances that can only be attained through research. Researchers have an interest in accessing tissue samples and data easily, because it facilitates their work and increases the chances that the results that they obtain will be valid. They can also have economic interests vested in their research, and sometimes make strategic decisions based on promoting their careers or personal agendas. Doctors and hospitals commonly receive monetary compensation for conducting clinical trials. The research community has an interest in establishing and maintaining public trust, because trust is a prerequisite for future research. Society has an interest in furthering healthcare, but in protecting its citizens against wrongdoings and in promoting their trust as well. Furthermore, it must make choices in allocating resources and thus has an interest in what kind of research that is conducted. [94] There can also be commercial interests involved in biobank research, such as when pharmaceutical companies use samples and data for research. These companies obviously strive to increase their profits, which may not seem to be in the best interest of patients. But then again, their existence is necessary for developing new and better drugs.

Thus, there is a need to weigh the different interests of the various stakeholders against each other. In doing so, a basic ethical concern is how the benefits and risks involved for individuals should be balanced. Other ethical issues that will be discussed later on are related to commercialization, returning results and maintaining public trust. First however, we turn to a characterization of the benefits and risks involved in biobank research.

Benefits of biobank research

Contrary to much medical research, biobank research offers a possibility to advance healthcare at diminutive individual cost or risk, if appropriate safeguards are put in place. In part this is due to the fact that the risks are known in advance and therefore measures can be taken to eliminate or at least sub-

stantially decrease them, i.e. they are not unpredictable as when a new drug is injected into the body of a research subject and it is more or less impossible to anticipate exactly what consequences may follow from cascade reactions etc. The risks that are imposed by biobank research also differ from those that are associated with much other medical research, in that they are not physical. So even if the safeguards that have been put in place fail, the consequences are not comparable to those that invasive research might give rise to; people simply do not die or suffer serious bodily harm from participating.

Biobanks can be used for basic research aimed at understanding fundamental biological principles such as molecular mechanisms etc., but also for clinical and epidemiological research. They are a prerequisite for conducting Genome Wide Association Studies (GWAS) that explore connections between genotypes and phenotypes in order to identify genetic risk factors for common diseases (e.g. heart diseases, autoimmune diseases and psychiatric disorders). [95] These kinds of studies have increased dramatically in the past years: A PubMed search using the term "GWAS" or "genome wide association study" in August 2012 rendered more than 11 000 hits, almost 90 % of which were from 2009 or later.

It is sometimes argued that biobank research has been hyped. [96, 97] Progress in identifying factors associated with common diseases has been disappointingly slow (and many of the genetic factors that have been identified are associated only with a slightly increased risk of disease) which has lead to skepticism regarding the potential of biobank based research to give rise to actual improvements in healthcare. Mark Rothstein has for instance compared biobank research to gene therapy, pharmacogenomics and embryonic stem cell research, and concluded that "the timing and nature of the payoffs from the research are currently unclear". [74]

Although this is true, the benefit of biobank research stands: medical knowledge can be attained without imposing more than diminutive risks, and we cannot know in advance what good it may lead to. In less than five years the GWAS experimental design has led to discoveries of genes involved in many common diseases and traits and facilitated basic research, which has given much new biological insight. [98] According to Hunter et al. the "first wave of genomewide association studies is producing an impressive list of unexpected associations between genes or chromosomal regions and a broad range of diseases. There have been few, if any, similar bursts of discovery in the history of medical research." [99] It is not reasonable to demand that this knowledge be transformed into improvements in healthcare directly; it takes time to translate findings in basic research into medical practice.

Furthermore, biobank research *has* already contributed to significant clinical benefits, such as the HPV-vaccine against cervical cancer that is estimated to save about 200 lives each year in Sweden alone. [6, 7, 100] Promising research is also being conducted in order to find predictors of rheumatoid

arthritis so that treatment can be started “in advance” which is essential since early therapy is critical in order to optimize long-term results. [8, 9]

Another important kind of research that can be carried out using biobanks is exemplified by a post marketing surveillance study of the monoclonal antibody natalizumab, used against multiple sclerosis. [101] In this study long-term data on efficacy and adverse events are collected, and samples are taken and stored for future use. The study is important because natalizumab interferes with the immune system and is therefore potentially very dangerous, and serious side effects such as progressive multifocal leukoencephalopathy have been reported. However, post marketing studies are also useful for other drugs, because although randomized clinical trials are the golden standard in medical research, and have a high internal validity (i.e. the results are valid under the studied conditions), their external validity (i.e. the applicability of the results on patients treated in routine healthcare) is more uncertain, due to e.g. differences in inclusion and exclusion criteria. [102]

A final example of beneficial research that has been conducted on stored tissue samples is a study in which gene expression in tumor samples from breast cancer patients was related to survival data. [103] The researchers were thereby able to identify gene expression signatures associated with poor prognosis, providing a strategy to select patients likely to benefit from adjuvant chemotherapy or hormonal therapy. This is important because in the absence of adequate selection criteria 70-80 % of patients receive superfluous treatment with unnecessary side-effects. [103]

When considering the benefits of biobank research it should be emphasized that in order to maximize the good that can be obtained, collaboration between researchers both nationally and internationally is required. This is because sufficient numbers of samples must be available in order for the results to be valid, and often single-center studies cannot achieve them. Even when large-scale biobanks are used, they may not contain enough samples to study rare diseases. This demand for collaboration implies that standardization is necessary, i.e. the processing and storage of samples must be similar, the associated data must be comparable and the ethical and legal standards need to be harmonized. [104]

Risks involved in biobank research

Individual risks

The risks that are involved in biobank research are seldom physical. Often, previously taken samples are used, and when new samples are taken for research purposes they are obtained through minimally invasive procedures such as blood draws or cheek swabs. There is a risk of indirect physical harm

if clinical samples are used to the extent that there is not enough left for the patient's own future use. [105] An example would be if a doctor wishes to compare a newly taken sample of a tumor with a previously taken one, and there is none left because it has been used in research. However, this risk can be handled by restricting the use of scarce samples.

Instead, the main risks associated with biobank research are informational, stemming from breeches of confidentiality, i.e. sensitive information winding up in the wrong hands. The resulting harm may be social, economic or psychological. [105] It is often argued that employers or insurance companies could gain information about individuals in this way. [106-109] Another risk is that individuals may be harmed by research if the results lead to stigmatization or discrimination. [106-109]

It has also been suggested that individuals may be "wronged" if material that has been taken from their bodies is used for purposes that they do not support or perhaps even oppose. [105, 106] Thus, if a sample that I donated for research on diabetes is subsequently used to investigate whether there is a genetic basis for drug addiction, I am wronged if I would have opposed contributing to such research (even if I am not aware that my sample is used in this way). From a similar perspective it has been claimed that individuals are wronged if they are treated solely as a means to an end that they have not chosen. [106] On this line of reasoning any usage of samples or data that the person has not consented to would seemingly constitute wronging.

Family risks

Genetic research is different from much other research in that we share our genes with our (biological) relatives, and therefore the results that are obtained can have direct consequences for others than ourselves. This gives rise to ethical issues concerning for instance the right to know and the right not to know, which are commonly used as arguments for and against returning results to individuals. [Article I] They acquire an additional level of complexity when it is not only the donor but also his or her family that allegedly has such rights. A related concern is the adequacy of individual informed consent. [110] In short, the difficulty lies in how to handle a situation in which one person wants to participate in research that is likely to have direct implications for another, who in turn perhaps does not want for the research to be carried out.

However, it is worth noting that family risks are directly coupled to whether or not individual results are returned, in that if no results are disclosed, there can be no direct harm from the research being carried out for the members of a specific family (although harm may arise from the general results of the research, for instance by leading to discrimination of groups of people, i.e. those suffering from the disease in question, which will be discussed below).

Risks for groups of people

Another aspect of the risks that are associated with biobank research is that the research in itself and the results that are obtained can have negative consequences for groups of people. This can for instance be the case if study results potentially stigmatize individuals belonging to the group, or lead to discrimination. Furthermore, results from research may disturb traditional understandings of origin or disease. In these cases, not only the individuals who contributed samples to the research project, but all members of the group can be harmed. [105, 106] A recent example is the case of the Havasupai Indian Tribe. Members of the tribe sued Arizona State University because samples that they had originally donated for research on diabetes ("the causes of behavioral/medical disorders" in the consent form) were subsequently used for research that they opposed, e.g. studies on schizophrenia, inbreeding and evolutionary genetics. Among other things they claimed that the research could lead to stigmatization. After a long legal process the University agreed to settle and formally apologized. [111] It is noteworthy though, that even if the research had been carried out with appropriate consent, it could have led to this kind of harm.

Risks in a longer term perspective

Another issue to consider when analyzing the risks involved in biobank research is the fact that we cannot know what use our stored samples and data may be put to in the future and by whom. Living in free democratic societies it may be difficult to envisage a future in which states or governments misuse genetic information, but history has shown that it can happen. [108]

This problem is not specific to biobank research, but pertains to many other kinds of research as well, and in fact to all storing of data about individuals and groups of people. From such a perspective it would obviously be safer not to allow any data storage at all, but this would not only hamper research but also infringe on our way of living our lives. It is also worth noting that a need for this kind of precaution is usually not invoked for instance against keeping medical records or storing tissue samples in clinical biobanks, although the information that could be attained from them by maliciously oriented persons or states is the same.

To conclude, biobank research imposes risks on individuals, mainly associated to breaches of confidentiality. However, these risks can be minimized for instance by implementing adequate coding mechanisms and secrecy legislation. The risks can be further decreased by requiring prior ethics review of proposed research projects, whereby not only the risk of informational harm, but also that of stigmatization, discrimination or wronging individuals or groups of people may be taken into consideration. I will now turn to a

discussion on ethical and legal means to balance the risks and benefits of biobank research.

Ethical and legal means to balance benefits and risks

From the point of view of the individual, balancing the benefits and risks involved in biobank research largely translates into a need to weigh the risks imposed by biobank research against the risks imposed by not conducting research, or by conducting poorer research. This is so, because hampered research leads to suboptimal healthcare, which implies that one set of risks is substituted for another. [112]

From a similar perspective, it has been argued that a time-consuming system of ethics review (that has been put in place to protect the interests of individuals) may cost lives because research results are published later than they otherwise would be, and thereby people whose lives could have been saved, die waiting. [113] A bureaucratic system of ethics review may also prevent research from being carried out altogether, or affect its quality for instance by distorting the representativeness of samples. [113] The same applies to other regulations that have a negative impact on research, e.g. by not permitting sharing of samples and data across borders or disallowing the use of medical registries and patient records without consent. [114] Therefore it is important that risks and benefits involved in biobank research are thoroughly balanced, so that the interests that individuals have in medical advances are promoted while other interests (e.g. in privacy) are adequately protected.

In practice this has come to imply requiring consent, ethics review and strict confidentiality. In the following I will first discuss the issues of consent and confidentiality and thereafter use the Swedish legislation pertaining to biobank research as an illustration of a legal attempt to balance benefits and risks.

Consent

The following consent modalities are commonly referred to in the debate on what constitutes appropriate consent for biobank research:

1. Specific consent: Individuals receive information about the specific study that their samples are going to be used in, and consent to this study only.

2. Broad consent: Individuals receive information about what kind of research their samples may be used in within a broader range, e.g.

for research on cardiovascular diseases or cancer research, and consent to this purpose.

3. Blanket consent: Individuals consent to their samples being used for research purposes in general.

4. Tiered consent: Individuals are given the opportunity to narrow down their consent to e.g. a certain kind of research or a specific study, but also have the possibility to consent broadly if they wish to do so.

5. Presumed consent: Individuals are presumed to consent unless they opt-out.

6. No consent: Research is carried out without consent

It is commonly claimed that the same arguments that underlie the requirement to obtain consent in interventional research are valid in the context of biobank research, e.g. that it shows respect to the autonomy of individuals. Thus, it has been argued that informed consent "allows individuals to exercise their fundamental right to decide whether and how their body, body parts and associated data will be used in research". [115] This seems to be the general view in international guidelines pertaining to biobank research. However, due to the fact that obtaining consent can be difficult and costly, all guidelines allow for deviations from the ideal to varying degrees. The recent CIOMS International Ethical Guidelines for Epidemiological Studies for instance claim that the best solution to the consent dilemma is to seek new consent every time a new hypothesis is tested, but acknowledge that this may not always be practicable, and recommend a somewhat broader consent in such cases. According to the guidelines: "A third conceivable solution would be consent to an open-ended donation of the sample to be used for biomedical and epidemiological research, conditional upon the approval of an ethical review committee. This solution is highly debatable and [likely to be] unacceptable under the ethical standards applied in several countries." [116] The International Bioethics Committee of UNESCO on the other hand, states that blanket consent for future research may be preferable, provided that the consent that is given explicitly recognizes this. [117]

Obtaining informed consent for biobank research is problematic for at least two reasons. [Article III] First, it imposes a cost in time and money for researchers. When considering retrospective research on stored samples this is evident. If there is no consent for research or if re-consent must be obtained, researchers must attempt to contact the sources of the samples. If on the other hand, research is prospective, there is a cost involved because intricate systems must be built up and maintained in order to allow for tracing of

the specific uses each sample may be put to. Second, requiring informed consent imposes a risk of bias because the individuals that consent to having their samples used in research may differ in significant aspects from those who do not, or who do not respond to requests for consent. It is known that responders in epidemiological studies often differ in many ways from non-responders, e.g. regarding demographic, socioeconomic, cultural, lifestyle and medical characteristics. [118] Therefore, it is important to keep non-response to a minimum because when no information is obtained about non-responders, it may introduce bias that is difficult to assess. An example of a research study that might have been biased had specific informed consent been required is the previously mentioned HPV study in which an association to cervical cancer was demonstrated. [6] Because HPV infection might be positively associated with life style factors that in turn are negatively associated with active participation in research, the results could have been misleading if specific consent had been required. [119]

Biased research may lead to results that are unreliable or invalid (due to a low response rate), misleading (if selection bias has occurred) or lacking (due to costs and administrative burden). [120] In examining the effects of requiring explicit informed consent for inclusion in an observational disease register Al-Shahi et al. found that the individuals who consented were significantly different from those who did not in both predictable and unpredictable ways. They concluded that consent bias probably invalidates the findings of many observational studies, and that there may be an argument for "complete and representative data collection for observational and non-intrusive epidemiological research, as is currently the case for medical audit (which does not require consent)". [121]

In the bioethical debate on informed consent much attention has been devoted to the appropriate width of the initial consent, i.e. if individuals should be allowed to give broad or even blanket consent for research when samples are taken, or if specific consent should be required for all research. The question of what kind of consent that should be obtained when samples are collected obviously also has implications for the possibility to use the samples in future research projects.

Arguing against broader versions of consent, Vilhjalmur Arnason has stated that "The more general the consent is, the less informed it becomes. It is misleading to use the notion of informed consent for participation in research that is unforeseen and has not been specified in a research protocol." [90] Others have similarly claimed that broad consent does not fulfill the criteria for being a valid informed consent. [122-124] However, from the opposite perspective it has been argued that if the information that is given covers everything that is important for an individual's decision then the person's consent is appropriately informed. [125] On this line of reasoning, if the risks and benefits are common to many studies, general information may be sufficient for the donor to make an informed decision. Furthermore, obtaining consent is gener-

ally regarded as a way of respecting the autonomy of individuals. However, if the goal is to respect autonomy it seems inconsistent that individuals should not have a right to consent to research broadly, if they choose to do so. In general broad consent seems to be the emerging solution regarding consent for biobank based research. [126]

Several surveys have been conducted in order to investigate the public's perceptions of adequate consent procedures for using tissue samples in research. [81, 127, 128] Generally, such studies have indicated that the importance of specific informed consent may be overemphasized in the bioethical debate, in that a majority of donors do not want to be re-contacted for all future use of their samples. [81] There is also evidence that handling of medical records and clinical data, (i.e. protecting confidentiality) seems to be of greater concern to the public, than the specific purpose of the research that their samples are used in. [127] Thus, there is an apparent discrepancy between what individuals think is important and the corresponding view of legislators. David Wendler recently compiled 30 studies conducted on the views of more than 33 000 individuals around the world and found that the data support offering people the simple choice of whether or not their samples can be used in research, provided that an ethics review board approves the projects. [129]

It is important to consider that the consequences of offering individuals the opportunity to choose whether or not to take part in research by requiring informed consent, may not be evident to people. Thus, caution should arguably be taken when interpreting the results of public surveys on topics such as what kind of consent should be obtained for observational research. Junghans et al. accordingly note that while ethics review boards enforce opt-in policies, and it seems that this is what patients prefer, "there is no evidence that patients would chose improved confidentiality over improved health, if asked to make a cost-benefit trade-off between poor medical research and the risk of intrusion of privacy". [120] Furthermore, a discrepancy between hypothetical attitudes in public surveys concerning willingness to participate in biobank research, and factual participation rates has recently been demonstrated, with higher rates in practice than in theory. [130]

Confidentiality

The issue of confidentiality has also been debated intensely. In order to protect confidentiality samples can either be completely anonymized or coded in different ways. Completely anonymizing samples (so that there is no link left between them and the individuals from whom they have been taken) obviously minimizes the risk of harm. However, this approach makes it impossible for individuals to withdraw their samples from biobanks, and a right to withdraw from participating in research is considered fundamental in most declarations and guidelines. Furthermore, samples that have been

anonymized cannot be linked to other data or samples from the same individual, which decreases their scientific or patient perspective usability. Nor can the source of the sample be re-contacted should a need to do so arise. If on the other hand samples are coded (so that they can be linked to the individual from whom they were taken but the researcher has no direct access to his or her identity because the code key is stored in a secure place apart from the samples), the risk of harm due to breaches of confidentiality increases but the negative effects of complete anonymization are circumvented.

There is considerable confusion regarding the terminology of different levels of identifiability of samples and data. [131] Elger and Caplan have compiled a list of 29 terms used to describe different degrees of anonymization relevant to biobank research, including expressions such as "completely anonymized", "unlinked anonymized", "de-identified", "traceable" and "encoded". [67] This lack of consensus creates uncertainty and has a negative impact on the efficacy of important national and international research collaborations. In an attempt to evade such problems the EMA (The European Medicines Agency) has recently suggested the following nomenclature: [132]

1. Identifiable: Samples that are directly identifiable, e.g. those that are marked with names or social security numbers.

2. Single coded: No directly identifiable information is retained with the samples, however there is a code on them that can be broken using a code key and thus the possibility to identify the sources of the samples persists.

3. Double coded: There are two codes, and two code keys that are stored separately.

4. Anonymized: Samples that have previously either been identifiable or coded, but where the information linking a sample to an individual has been destroyed.

5. Anonymous: Samples that have never been possible to trace back to an individual, even though some general information about the source of the sample may exist (e.g. female, 20-30 years old, healthy).

To conclude, requiring informed consent and protecting the confidentiality of samples and data through coding or anonymization have become standard measures taken to protect the interests of individuals. However, they also imply a risk of impeding research. In order to compensate for this partly different strategies have been adopted in Europe and the United States. In

2004 the OHRP (Office for Human Research Protection) in the U.S. expanded the definition of "non-identifiable" to include samples that are coded, where the researcher does not have access to the code key. [67] Consequently, such research does not require informed consent or approval by an ethics review board, since it is not classified as human subjects research. In Europe, the consent and ethics review processes can generally not be circumvented in this manner, but on the other hand European guidelines are more supportive of broad consent for unspecified future research.

A legal perspective: The Swedish legislation pertaining to biobank research

It is difficult to compare regulations pertaining to biobank research in different countries. In part this is due to the complexity of the situation, with data and samples collected both within the healthcare system and exclusively for research purposes. Also, tissue samples are commonly protected by specific laws, while other laws apply to the data that is used, and the legal situation is often ambiguous. In the following I will offer a brief overview of the Swedish legislation (that is largely built on the Convention on Human Rights and Biomedicine by the Council of Europe [25]) as an example of a legislative attempt to weigh the benefits against the risks involved in biobank research.

In Sweden the usage of stored samples is regulated in the Biobanks in Medical Care Act (2002:297), [133] while access to personal information is regulated in the Personal Data Act (1998:204) [134] and other legislation such as the Public Access to Information and Secrecy Act (2009:400). [135] Furthermore, all research on stored identifiable biological material must be reviewed and approved by an Ethics Review Board according to the Act Concerning the Ethical Review of Research Involving Humans (2003:460). [136] The Ethics Review Board is, under this act, responsible for determining what information and consent procedures are appropriate for the proposed research.

The Biobanks Act

The Swedish Biobanks Act regulates "how human biological material is to be collected, stored and used for certain purposes with respect for the personal integrity of the individual" and defines a biobank as "biological material from one or more human beings that is collected and preserved for an indefinite or limited period, and whose origin is traceable to an individual or individuals". [133]

According to the act, the basic principle is that individuals must consent to their samples being stored and used for certain purposes.[4] These purposes

[4] This echoes Article 22 of the Convention of Human Rights and Biomedicine, that states: "When in the course of an intervention any part of a human body is removed, it may be stored

are limited to the care and treatment of the donor, quality assurance, training, research, clinical trials, development, or other equivalent activities. The act does not apply to samples that are routinely collected within healthcare for the diagnosis or treatment of patients, and that are not stored for a longer period of time. However, the exception does not apply to samples that are taken for research purposes. If a stored sample is subsequently to be used for research, an Ethics Review Board shall decide what information and consent procedures are appropriate.

An Inquiry was appointed to review the Biobanks Act in 2008. In part this was due to complaints from both the healthcare system and research enterprise regarding the increased costs and administration following the introduction of the current act in 2003. [137] The Inquiry now proposes a differentiation of the regulations for consent, so that samples taken within healthcare for the care and treatment of a patient can be stored (also for later use in research) provided that the individual does not object (i.e. an opt-out model). However, when samples are taken for other than clinical purposes express consent is required, "especially when tissue samples are collected for research, including clinical trials." [137] The Inquiry also proposes that the donor should have an unconditional right to have his or her tissue sample destroyed, as opposed to the current situation, where biobanks can decide whether to destroy or anonymize such samples. Thus, compared to the current act, this increases the individual's right to self-determination.

The Ethical Review Act

According to the Ethics Review Act, all research on identifiable tissue samples must undergo ethics review. The ethics review board shall decide what information and consent procedures are appropriate for each proposed study. The main rule is that specific informed consent is required. However, the board can allow research without (renewed) consent in certain cases if the benefit of the research is judged to significantly outweigh the risk of violating the integrity of individuals or groups of people. [138] Research that is conducted on material that is anonymous does not require ethics review.

The Personal Data Act

According to the Personal Data Act sensitive personal data (including personal data that concerns the health of individuals) may be processed for research purposes, provided that the processing is necessary for a work task of public interest and that the interest of society in the research project within which the processing is included "is manifestly greater than the risk of improper violation of the personal integrity of the individual that the processing may involve".

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and used for a purpose other than that for which it was removed, only if this is done in conformity with appropriate information and consent procedures." See [25]

[134] These prerequisites are deemed satisfied if an ethics review board has approved the research.

Other ethical issues in biobank research

Commercialization and benefit sharing

Benefit sharing is a fairly new concept in the context of biobank research. It is based on the notions of justice, solidarity and equity and mandates recognizing the contributions of the individuals, populations and societies that participate in research, by "giving back" to them. [131] Various mechanisms to share benefits have been proposed but even the guiding principles remain unclear. [115] The HUGO Ethics Committee provides a notable exception, in recommending that at a minimum, all participants should receive an indication of appreciation and understandable information about the general research outcomes, and that profit-making entities dedicate a small percentage of their profit to healthcare infrastructure or humanitarian efforts. The committee emphasizes that prior consultation with and involvement of individuals and communities in research design is a preliminary basis for the future distribution of benefits and that it may be considered a benefit in itself. [139]

When it comes to commercialization, i.e. the possibility to buy and sell tissue samples on a market, the Convention of Human Rights and Biomedicine issued by the Council of Europe states: "The human body and its parts shall not, as such, give rise to financial gain". [25] Thus, in Europe commercialization is categorically prohibited. In the United States the situation is different and commercialization is possible.

From an ethical point of view there seem to be two distinct aspects of biobank commercialization to consider. [140] First, the material in itself can be bought and sold. This is controversial since the individuals from whom the samples were taken have generally not received any monetary compensation, i.e. the samples were donated by them (or taken as a part of routine healthcare). Allowing researchers to sell such samples may therefore be inappropriate. Selling material may also conflict with the principle that samples should be put to the best possible use, since the financially strongest research groups do not necessarily have this aim, or the ability to produce the best research. Second, the knowledge that is attained through research can be commercialized. This aspect is not specific to biobank research, but concerns all medical research, and has given rise to intense debates on e.g. patenting of genes. On the one hand such commercialization can increase the incitement to invest money in research, on the other hand it can lead to reluc-

tance to share data and samples in the quest for patents, and thereby stifle research. [140]

A related question is whether or not individuals should have a right to economic compensation when their samples are used in research that generates profits. Research regulations are generally not built on property rights of individuals, but rather on their right to decide whether or not to take part in research, for instance by donating samples. [141] In several U.S. court cases (e.g. the previously mentioned case of John Moore [23] and the Greenberg case, where investigators patented a predictive prenatal genetic test for Canavan disease that was developed using samples that had been donated for research [142]), it has been decided that they do not.

Returning results

Biobank research generates results and other types of information that may be of clinical relevance or interest to the individual patient or donor (and potentially also to other parties such as genetic relatives, employers, insurance companies, the police, the biobanks themselves etc.). This information may for instance be a result concerning a hereditary disposition or environmental risk factors. It can also be an incidental finding that has nothing to do with the research project and is therefore unforeseeable.

How such information should be handled has not been clarified and diverging recommendations have been issued by authorities and other interested parties. Some factors that can influence the importance of returning information are 1) the analytic validity (the probability that the information is correct), 2) the clinical validity (the probability that the individual actually develops the disease), and 3) the clinical utility of the results (e.g. how serious the illness is and whether or not there is a possibility to intervene). [143]

In favor of returning results to participants it has been argued that individuals have a right based in autonomy to know what is known about them and that researchers have a duty of beneficence or respect toward sample donors [143-145]. Arguments against returning results include that doing so consumes resources that could be allocated to research instead, and that it conflates the ethics of research with that of medical care. [145, 146] [Article I]

In practice it seems that many biobanks have implemented policies that imply that individual research results are not returned to donors (e.g. UK Biobank and LifeGene). However, according to recent recommendations issued by a working group funded by the United States' National Institutes of Health (NIH), biobanks should introduce policies that encourage the return of individual results and both secondary researchers (i.e. those who conduct research on material that has been collected by others) and the biobanks themselves are attributed responsibilities for this. [145]

Public trust

Public trust is necessary in order to optimize the prerequisites for conducting medical research. In biobank research the trust of patients and other potential donors of samples is vital, because without access to large amounts of representative samples and data research is seriously inhibited. It is therefore important that scandals are avoided, and that research is conducted under transparency and accountability.

What happened following the revelation that the police had gained access to the Swedish PKU biobank after the killing of foreign minister Anna Lindh in 2003, illustrates the consequences of distrust. As described earlier, the PKU biobank contains samples from virtually all individuals born in Sweden during the past 35 years. [76] During the investigations following the murder, the police requested that a stored sample that had been taken from a suspect be handed over to them so that they could compare traces of blood from the scene of the crime with DNA in the PKU sample, in order to confirm the identity of the killer. This forensic use of the biobank received much media coverage (although using the sample was not necessary, because according to Swedish law the police could have taken a new DNA sample from the suspect as well). Previously very few individuals had demanded that their samples be removed from the biobank (17 persons from January 2003 until the murder on September 10), but during the following year the number of withdrawals increased to 445. [147]

Another example of the consequences of loss of public trust is what happened after the Alder Hey scandal in the UK, where organs from children were systematically removed and retained, often without consent, after post-mortem examinations. [148] It has been demonstrated that both autopsy and organ donation rates were negatively affected following the controversy, as was the recruitment of pathologists. It has also been shown that the intensity of the media coverage was inversely related to the number of tumor samples deposited in a national children's tumor bank. [149]

Aims

Biobank research is important because it offers a means to increase medical knowledge, and thereby further healthcare, without imposing significant costs or risks on individuals. However, as citizens we have many different interests that must be balanced: although we clearly have an interest in improved healthcare, we also have democratic interests. Therefore, samples cannot simply be appropriated; rather, we need to reach a common understanding of what constitutes a reasonable contribution to the public good of increased medical knowledge.

The aim of this thesis is to explore the relationship between individuals and society in the context of medical research and healthcare, regarding possible rights and duties of individuals in biobank based research. More specifically I want to investigate if the apparent conflict between individual rights and public benefit can be reconciled and whether or not individuals have a moral duty to participate in this kind of observational research. The overarching aim of the thesis is to contribute to a constructive debate on what policies concerning biobank research that best serve individuals and society alike.

To reach these goals, I set out to answer the following research questions:

1. What interests are at stake in biobank research, with particular emphasis on the issues of consent and returning results?

2. How can the interests of individuals and society, pertaining to medical research and healthcare be balanced?

3. Can a social contract view offer a justification of a duty to participate in biobank research?

4. What are the policy implications of applying a contract view on biobank research?

This research project is undertaken from a bioethical perspective, and its focus will be on practical consequences and policy implications of different philosophical positions.

Methods

I write this thesis from the perspective of a medical doctor engaging in a bioethical enquiry on the relationship between individuals and society in healthcare and medical research, more specifically in the context of biobank research, aiming to bring a perspective based in patient care and needs to the interdisciplinary field of bioethics. My approach is problem oriented, in that my reasoning takes its stance in existing problems (such as the issues of what constitutes adequate consent and whether or not research results should be returned to individuals). Moreover, I apply a pluralistic perspective, i.e. I do not claim that the explanations and justifications of moral judgments that I put forward, exclude the possibility of there being other as plausible accounts.

I appeal to intuitions about right and wrong and to everyday use of language when I examine concepts and different normative positions on issues of interest. The various ethical principles that are elaborated and applied in the debate always stand in a relationship to our intuitions. Sometimes principled arguments are strong enough to make us want to change our intuitions, viewing them as premature rather than well-reflected, at other times intuitions resist change, presumably because they are based on convictions or basic premises in terms of facts or moral ideas that we are not willing to give up.

Different ethical theories provide different reasons for changing or holding on to a normative position, e.g. because more good for all people will be attained or because there are limits to maximizing the good, say by respecting certain rights or not breaking an agreement or promise. My aim is not to write a comprehensive overview of different possible normative positions and their theoretical underpinnings but to provide a well-reasoned, critical and constructive account of some of the standpoints related to biobank research and the balancing of interests in this context.

The articles and comprehensive summary are based on studies of literature on previous and current research within the field. I aim to analyze whether the arguments that have been put forward are consistent, coherent and based on relevant facts. I also attempt to examine if the conclusions that are drawn from them are plausible, valid and sound and if counterarguments can be made.

An example of how coherence can be analyzed:

1. According to the Swedish Biobanks Act samples can be used for method development and quality control without obtaining specific informed consent from the individual that the material has been taken from.

2. However, if samples are to be used for research purposes, an ethics review board must approve the research project and shall decide what information and consent procedures are appropriate. The default position is that specific informed consent must be obtained.

This does not seem coherent, since in both cases the reason for using the samples is to improve healthcare.

An example of how consistency can be analyzed, by way of a possible contradiction in how we deal with issues of informed consent:

1. Individuals that take part in research have a right to decide what their samples can be used for (when it comes to choosing specific studies).

2. Individuals that take part in research do not have a right to decide what their samples can be used for (when it comes to choosing that they can be used for research in general).

Can the contradiction be alleviated?

1. It ceases to exist if the premise that specificity is required in order for consent to be informed is added.

2. But remains if it can be shown that consent can be informed even if it does not include all details about a specific study, i.e. it depends on how "informed" is defined.

Scope

For the purpose of this thesis I define biobank research as an activity that is carried out using human tissue samples, either stored or newly taken, in an effort to increase medical knowledge in order to contribute to better healthcare. I exclude research that is conducted on embryonic material, including stem cells derived from embryos, because such research gives rise to specific ethical issues that are not relevant to consider in the context of other kinds of research using human tissue samples. For reasons of clarity I also exclude samples taken post-mortem.

Often data about the individual from whom the sample was obtained, e.g. information recorded in medical records, registries or questionnaires, is also used in this kind of research. A researcher interested in studying the role of a specific gene for the development of a tumor might for instance want to investigate the prevalence of the gene in a population and then link the results to possible data on the same individuals in a cancer registry. Although handling of data in research gives rise to ethical issues in itself, [150] my main focus lies on the ethical aspects of using tissue samples, i.e. material that has been taken from the bodies of individuals, for research purposes. However, many of the conclusions that are drawn from using stored tissue samples for research clearly apply to research on stored data as well.

Summary of articles

Article 1: Changing perspectives in biobank research – from individual rights to concerns about public health regarding the return of results

During the last decade, various guidelines that imply a duty for researchers to disclose information obtained through research to participants have emerged. The character and extent of this obligation have been debated extensively, with much attention devoted to the decisiveness of the validity and utility of the results in question.

This article argues that individual results from research on materials stored in large-scale biobanks, consisting of samples taken within healthcare or of altruistically donated material, should not be returned. Rather, medical research using such biobanks should be viewed as a collective project to improve public health, and available resources should be utilized to pursue this goal.

The samples in biobanks consisting of material collected within the healthcare system have been taken specifically in order to benefit an individual. Once this material has been used as planned, it can be discarded or used for research. In either case the source of the sample has already benefited from it as intended, and it is not obvious that he or she can legitimately claim a right to further direct gain. To the contrary, since the individual has utilized the healthcare system, i.e. the medical advances that largely result from past research on human beings, healthcare and research can (and should) maintain the right to use materials – that otherwise would be disposed of – for the purpose of further progress.

When it comes to large-scale biobanks consisting of altruistically donated material, the purpose of the donation is to enhance scientific knowledge in order to promote people's health. Autonomous agents have chosen to act, knowing that it will be of no direct medical benefit to them. They have no relationship with the researchers. Their donation has not been asked for on the grounds of their specific health status or any other central feature of their lives and they could easily be replaced by other random persons in the population without impairing the quality of research. Failing to use such donations for the intended purpose is arguably disrespectful, whether the samples are used in an inappropriate manner (e.g. for research projects that are not

scientifically justified) or not used to their full potential due to wrongful allocation of resources.

Proponents of a duty to return results often base their line of reasoning on autonomy. It is claimed that individuals have a right to know what is known about them, so that they can lead their lives according to their life plans. Obviously, a policy of returning results may make individuals feel respected. On the other hand, returning preliminary results from ongoing epidemiological studies may jeopardize the scientific validity of the study due to changes in behavior or selective drop outs. In this case, participants may rather feel disrespected since their general research interests are less likely to be fulfilled. Based on a duty to do good and avoid harm one could argue that at least incidental findings that are of medical significance should be communicated to donors of biobank material. However, disclosing individual results of factors thought to imply risk for a population may cause unjustified concern since an odds ratio expressing risk cannot be directly translated into an individual prognosis. Thus, for most people such information would be of no or questionable benefit, but it would impose a risk through hampering the research that can be done as well as potentially causing direct harm.

This article concludes that returning individual results fails to respect the premises under which the public health project of large-scale biobank research is undertaken as it inevitably reduces the prospect of achieving advances by consuming resources that should be allocated to benefiting the public good. Principally, results should therefore not be returned.

Article 2: Changing defaults in biobank research could save lives too

In an effort to increase the amount of organs available for transplantation, many countries have implemented presumed consent for organ donation. It has repeatedly been shown that presumed consent legislation has a positive effect on organ donation. Presuming a wish to contribute to medical advances through biobank research on stored tissue samples could similarly improve health and wellbeing.

Currently however, informed consent is generally deemed necessary for research on stored samples (unless they have been completely anonymized). The default position is that individuals do not wish to contribute by allowing leftover samples to be used for biobank research. Yet many of the arguments put forward in favor of presumed consent for organ donation also seem applicable on consent for biobank research.

While demanding informed consent for organ donation results in fewer organs being available, selecting informed consent as the default position for biobank research risks generating collections of samples that are not repre-

sentative of the population. Routinely obtaining informed consent for research on previously taken materials also imposes practical and financial difficulties.

In this article common arguments for and against presumed consent for organ donation (listed in the table below) are analyzed and applied on biobank research.

Table 1. *Arguments in favor of and against presumed consent for organ donation*

Arguments in favor of presumed consent for organ donation	Arguments against presumed consent for organ donation
Presuming consent would increase the amount of organs available.	There are other ways to increase the amount of organs available that do not restrict autonomy.
Presuming consent would be doing the right thing most of the time, since most people have a positive attitude toward organ donation.	Presuming consent would lead to mistaken removals, i.e. organs would be taken from individuals who do not wish to be donors.
Presuming consent would not impose the burden of changing status on the majority.	Shifting defaults implies that society has a right to use or interfere with our bodies.
Presuming consent could lead to a genuine cultural change over time.	Presuming consent may negatively alter the very meaning of donating organs.

In spite of obvious differences between biobank research and organ transplantation the cases for implementing presumption of a positive attitude appear quite analogous. In both instances more of the valued material would be available at a lower cost and in biobank research the collections of samples would likely also be more representative of the population. Some individuals who wish to opt-out may fail to do so under presumed consent, but a majority of the population has repeatedly been shown to support these projects, and individuals fail to opt-in under informed consent as well. Moreover, presuming a positive attitude does not impose the cost of changing status on the majority and could result in donation becoming the norm, additionally facilitating procurement.

This article concludes that instead of presuming that individuals do not wish to contribute to the advancement of healthcare through biobank research, ethics review boards should presume that they do, and evaluate the need for consent accordingly. If consent is considered necessary, an opt-out system should be selected, imposing the cost of changing status on those who, although they have taken advantage of the healthcare system, do not wish to contribute to further advances.

Article 3: Biobank research: Who benefits from individual consent?

Individuals are often claimed to have a right to control how their personal data and samples are used, even if no risks are involved. However, demanding informed consent for biobank research causes problems for at least two reasons. First, obtaining consent for research on stored samples and data consumes resources that could be used for more research or healthcare instead. Second, well-documented differences between individuals who consent to participating in biobank research and those who do not may threaten the validity of the results by introducing selection bias. Both of these problems can be reduced if broad, presumed or no consent for research on leftover material is accepted, but even the least controversial of these proposals, that of broad consent, has been extensively criticized, partly because it is claimed to breach autonomy.

This article emphasizes the importance of recognizing that individuals do not only have interests as research subjects but also as patients and citizens. Given that nobody knows how much and what kind of medical care they and their family and friends will need everybody has an interest vested in research. Since the risks imposed by biobank research are minimal (with appropriate safeguards such as adequate data protection and approval by an ethics review board) the interest of the individual as a research subject, in deciding what use a sample can be put to, is arguably outweighed by his or her interest in medical advances. Furthermore, because robust research depends on access to samples and data from as many individuals as possible, a system that facilitates general contribution is in the interest of all.

It is often argued that using a sample without informed consent cannot be justified by claiming that it will benefit the person from whom it was taken, since it is unlikely that the knowledge that is obtained will be relevant to him or her. However, it is not clear why the benefit must be generated by research on material from the specific individual, it could as well be the result of research on any other sample—that is, a result of the existence of the research enterprise or the biobank, as such. Just as I benefit from a clean environment regardless of who has refrained from polluting it, I benefit from increased medical knowledge obtained through biobank research regardless of whose sample has been used.

Accepting the proposed view on biobank research implies that this kind of research is considered to be a natural component of healthcare that is endorsed and facilitated, just like quality control, method development, and teaching. Leftover material, stored tissue samples, and associated data can be used without consent, if approved by an ethics review board, because the minimal risk of harm is clearly outweighed for each individual by the increased chance of benefiting, directly or indirectly, from healthcare.

Article 4: Why participating in (certain) scientific research is a moral duty

Lately there has been a scholarly debate between John Harris (in part together with Sarah Chan) and Iain Brassington on whether or not participating in scientific research is a moral duty. Harris and Chan have argued that it is, based on a duty to rescue and the unfairness of being a free-rider, and while Brassington has not denied that such a duty might exist, he has claimed that the arguments that have been put forward do not establish it.

This article argues that there is a moral duty to participate in research that involves diminutive risks, imposes no burdens or costs and is potentially beneficial, e.g. research that is conducted on stored tissue samples and data in medical records and registries.

The proposed duty is based on a social contract view: since for many diseases effective treatments and cures do not exist, and we do not know in advance what kind of medical care we (and those we care about) will come to need, we all have an interest in medical advances. Such advances can only be achieved through research. Research requires co-operation, and in order for us to co-operate as efficiently as possible, unnecessary hurdles must be avoided.

Therefore, it is rational to accept a (hypothetical) contract imposing a duty to participate in certain research. Accepting the contract implies that there is a moral duty to adhere to it, that can either be justified by a pre-existing duty to honor one's agreements and keep one's promises (a widely endorsed moral principle), or by referring to the contract itself, i.e. the rationality of doing so.

It is important to note that the purpose of the proposed contract is not to maximize the public benefit that can be achieved, but to optimize the outcome for each individual, as compared to a situation in which all pursue their own best interest independently. Therefore, it does not collide with the widely endorsed principle that the interest of the individual should always prevail over that of society in medical research.

Discussion

In this project I set out to investigate the relationship between individuals and the public in the context of biobank research. More specifically, I was interested in how practical issues such as obtaining consent and handling individual results should be dealt with in order to best promote the interests of all.

In the first article I considered the issue of returning individual results obtained in large-scale biobank research from a perspective based in solidarity, i.e. I argued that such research should be viewed as a collective undertaking aimed at achieving public benefit. I concluded that in principle results should not be disclosed, but that resources should be allocated toward maximizing the public good of increased medical knowledge instead. In the second article I argued that changing defaults from an opt-in policy to an opt-out policy for research using stored tissue samples would be beneficial from the perspective of pursuing medical advances, and preferable from an ethical point of view. I concluded that the cost of actively making a decision should be imposed on those who do not want to contribute to this kind of medical research, rather than on those who do. In the third article the aim was to demonstrate that requiring informed consent for research on stored samples in order to safeguard the autonomy of individuals not only defeats the interests of society, but also runs counter to the interests of the individuals that the policy purports to protect. Finally, the fourth article aimed to demonstrate that a duty to contribute to biobank research can be defended from the perspective of a contract based in self-interest.

Thus, I have started from both rights-based and solidarity oriented perspectives, and reached the conclusion that the goals of biobank research can outweigh certain individual interests. In what follows I will attempt to reconcile the rights of individuals with the good of the public, because regardless of whether the benefits of biobank research are thought of in individual or other-regarding terms, it seems clear that the more knowledge that is attained, the better. Therefore, a stalemate based on disagreements as to *why* people ought to contribute is self-defeating.

Biobank research – Public goods and individual rights

In the political and moral debate, a line is often drawn between communitarianism and individualism (most commonly thought of as liberalism). Individualists emphasize individual rights and freedoms, and defend the priority of individuals over society, while communitarians argue that people are embedded in networks of social relationships and that individuals are constituted by the community of which they are part.[5] [151]

The communitarian approach allows accepting individual obligations for the benefit of the public, whereas from the liberal perspective individual rights should not be sacrificed for the public good. Much contemporary medical ethics is built on the liberal view, giving priority to autonomy and non-interference over values such as solidarity and equity. [152] This is evident for instance in the field of public health ethics, where interventions aiming to further the health of a population (such as requiring people to wear bicycle helmets or imposing extra taxes on unhealthy food) are commonly criticized because they restrict individual freedom and interfere with people's choices.

Similar conflicts exist in the context of medical research: In the case of biobank research, a communitarian approach might be that individuals have a duty out of solidarity to accept that leftover material is used for research aiming to advance medicine, at least when it can be done at insignificant risks. The standpoint of individualism, on the other hand, is typically that even under such circumstances, the individual has a right to decide whether or not to allow for his or her samples to be used.

These opposed starting points may give rise to a deadlock, in which individual rights and the public good seem irreconcilable. But it should be kept in mind, that the public good can, and often does, coincide with the good of the individual, and in these instances there is no clash: certain individual benefits (that are simultaneously public benefits) can only be achieved through co-operation that requires that people give up some of their individual freedom.

This coincidence of ends may not exist when it comes to choosing what to eat or whether or not to wear a bicycle helmet, but it arguably does in the context of medical research. Although it is clearly in the interest of the public that research is carried out so that healthcare can be furthered; it is also in the interest of each individual. [Article III] In part this is attributable to the fact that people do not know in advance what kind of research they will benefit from. Using the metaphor of John Rawls, individuals actually stand be-

[5] There are of course other political philosophical views than individualism and communitarianism to consider (e.g. utilitarianism, feminism, Marxism and liberal egalitarianism), but I have chosen these two in order to illustrate the alleged collisions between individuals and society in the context of medical research as distinctly as possible.

hind a "veil of ignorance"[6] as to their future medical needs, and behind this veil, what is in the interest of one individual cannot be distinguished from what is in the interest of another. [153] Also, some goals simply cannot be obtained by individuals themselves, i.e. even if they knew what medical advances they would come to need, attaining them would not be possible because doing so requires a public effort.

In short, individual rights and the public good are often portrayed as conflicting in the context of biobank research. Previously, much debate has revolved around a perceived need to strengthen the rights side of the equation, [Article III] but the pendulum seems to have swung. In what follows I hope to demonstrate that although notions such as solidarity are relevant from the communitarian perspective, they are not necessary to justify a duty to participate in biobank research, because the same conclusions can be reached from an individualist point of view. First however, I will consider how the interests involved in biobank research are balanced by liberalism and communitarianism in more detail.

A liberal view

From the liberal point of view individuals have a right to pursue their own conception of the good, and society should remain neutral when it comes to how individuals choose to live their lives. Self-determination is crucial, and rights are given a prominent position. The harm principle derived from John Stuart Mill illustrates this point: "…the only purpose for which power can be rightfully exercised over any member of a civilized community, against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant."[7] [154] Thus it seems clear that from a liberal perspective individuals should have a right to choose whether or not to take part in research and thereby arguably also to decide what can be done with their tissue samples.

In the context of biobank research such a rights-based stance has been taken by Henry Greely who, in discussing large-scale genetic databases and biobanks, has stated: "New methods of consent will need to be created to replace the blanket consent common to such endeavors, with a consent procedure that gives subjects some real control over what they might consider inappropriate use of their information and biological material. Through their use, these biobanks are also likely to yield information that will be of some clinical significance to the subjects, information that they should have access to." [155] From this point of view, individuals have a right to decide what can be done with their samples, as well

[6] The veil is set up to assure that the principles agreed upon in the original position will be just. Behind this veil individuals evaluate principles solely on the basis of general considerations related to self-interest and do not know how various alternatives will affect them in real life.

[7] I understand "to prevent harm to others" in the sense of prohibiting actively causing harm, i.e. not requiring measures to be taken to prevent harm that may occur if one remains passive.

as a right to obtain individual results. [Articles I and III] Timothy Caulfield has similarly emphasized the importance of individual autonomy, claiming that in the context of biobanks, "autonomy is largely about the maintenance of *control* over something that implicates personal integrity. It implies that the research participant should retain a right of control over their genetic and personal information." [156] According to both of these views, individual rights seem to outweigh considerations of the public good.

However, there is a problem with the traditional liberal view from the perspective of the individual, in that it obstructs the prospect of attaining mutual benefits that can only be realized if all co-operate. [Article IV] This is because, given the choice, some people will likely not contribute to collective efforts, however minimal the associated costs and risks are, due to the fact that they can free-ride on the contributions of others.

A communitarian approach

Communitarians reject the liberal focus on individual freedom, and the view that society should be neutral between different conceptions of the good life; leaving to individuals to determine for themselves what constitutes their welfare. From the communitarian perspective, liberalism results in a neglect of various communal goods and values. This is because communities consist of the interconnected lives of people with shared interests and responsibilities, rather than merely being constituted of separate individuals. [157] Communitarianism thereby highlights the social nature of our lives, identities, relationships and institutions: a community is a union that has its own intrinsic value. Michael Sandel has accordingly argued that some allegiances (such as families, communities and nations) "allow that to some I owe more than justice requires or even permits, not by reason of agreements I have made but instead in virtue of those more or less enduring attachments and commitments that, taken together, partly define the person I am." [158] According to Sandel the liberal "unencumbered self" is a person "wholly without character, without moral depth." [158] This is because from the communitarian perspectives there are social attachments that determine the self.

In the context of medical research it has been proposed that the values of solidarity (defined as participation in research for the benefit of others) and equity (sharing the benefits of research) should govern genetic databases. [159] Similarly, the ethical principles of reciprocity, mutuality, solidarity, citizenry and universality have been identified as emerging trends in genetic research. [160]

From a related perspective Ursin and Solberg have argued that the Norwegian concept "dugnad" offers a way of understanding a moral obligation to take part in certain research projects. [161] The concept stems historically from neighboring farmers helping each other to accomplish large tasks such as haying or roofing, and as such, dugnad is an informal duty to take turns to

assist each other. The authors state that "The *dugnad spirit* denotes that the values of liberty, equality and fraternity are actively promoted by a group and its members in freely committing themselves to work together as equals for the benefit of all". [161] They conclude that normative recruitment of research participants can be justified on this basis, provided that certain criteria are fulfilled regarding the design, context and intention of the research project.

However, in distinguishing between traditional dugnad projects among farmers, and the modern project of biobanking (using the example of the Norwegian HUNT-biobank[8] [162]) they state that a major disparity is "that while stepping outside the traditional dugnad institution might have implied grave and direct social and economic consequences for a farmer in the nineteenth century, a person declining to take part in the HUNT study today should, as a matter of principle, expect no personal consequences from his decision in the future provision of healthcare." [161] This, arguably, points at the possibility that what is envisaged as a reason to participate namely solidarity, can also (and sometimes perhaps more accurately) be a form of self-interest. But the authors contend that "To benefit from or take part in dugnad should be motivated by a shared and acquired social conscience rather than by calculations of profit or from fear of sanctions." [161]

Thus, although it is possible that the farmers helped each other for altruistic reasons, it is also conceivable that what they did was enter an implicit agreement that resulted in mutual benefit (i.e. promoted their self-interest).

Another aspect to consider is that there should be no personal consequences regarding provision of future healthcare from the decision to contribute or not. According to the World Medical Association's Declaration of Helsinki, the refusal of a patient to participate in a study or the patient's decision to withdraw must never interfere with the patient-physician relationship. [64] However, this does not imply that there will be no personal consequences from opting out. Medical advances depend on research, and if research is impaired, so will the level of healthcare that can be provided to patients be. [Article III]

Having considered the liberal and communitarian approaches and found that individualism poses problems for effectively attaining mutual benefits, and that the communitarian view may harbor elements of self-interest, I move on to investigate whether the two perspectives can be reconciled. In order to do so, I first turn to a brief discussion on goods, interests and rights.

Public and private goods

In the field of economics, a public good is commonly defined as a good that is non-rival (i.e. one person consuming it does not hinder others from doing

[8] The Nord-Trondelag health study (HUNT) in Norway has collected health data and samples during 30 years in three phases from a regional cohort of 130 000 individuals. See [162]

so) and non-excludable (i.e. people cannot be excluded from having access to it). Clean air is an example of a public good: My breathing it does not hinder anyone else from doing so, and people cannot be excluded from having air to breathe. Another example of a public good is the herd immunity that results from a sufficient proportion of the population being vaccinated against a disease, thereby decreasing the probability of spreading the infection. When herd immunity has been established, all individuals are protected by it, regardless of whether they have contributed or not. In the context of healthcare it has similarly been argued that e.g. genetic information, public health [163] and the knowledge produced by medical research [164] should be considered public goods.

The opposite of a public good is a private good, which is a good that is rivalry and excludable, e.g. a car. My buying it implies that you cannot buy it and only people with enough money can buy cars.[9]

In economics, public goods are problematic because there is little incentive to produce goods that people have unlimited access to, and therefore markets alone cannot be expected to supply them. This is because they commonly give rise to the free-rider problem, which is characterized by individuals not paying for the goods that they consume. Analogously, individuals have little incentive to contribute to goods that are attainable through co-operation if they can gain access to them anyway. I argue that this line of reasoning adds to the view that there is no duty to participate in biobank research: If healthcare is thought of as a human right (which arguably implies that we *should* have access to it), the incentive to contribute decreases, because the right is the same whether we contribute or not.

The difference in degree of incentive to contribute to public and private goods can be illustrated by returning to the example of clean air: Since we have access to common air regardless of whether we do our share to keep it clean, we can pollute and hope that others will refrain from doing so. If, however, each individual had a specific lot of air to breathe (i.e. air was in effect a private good), then we would have a strong incentive not to pollute, because else all our air would be contaminated.

Congruent, convergent and common interests

A related aspect is what kinds of interests individuals have. In the field of public health ethics, Angus Dawson (following Postema) has pointed out three sets of collective interest that individuals have (as opposed to their private interests): congruent, convergent and common interests. [152] Con-

[9] Furthermore, there are common goods (or common resources), that are non-excludable but rival, i.e. access to them cannot be restricted, but one person's using a common good may hinder others from doing so. Common goods can give rise to the tragedy of the commons, originally exemplified by farmers letting their cows graze on public land too much, thereby depleting the common resource.

gruent interests are interests that we all have as individuals in the same things, but that require a public structure to be met: e.g. our interest in education that requires that schools are put in place. Convergent interests are individual interests that can only be fulfilled by production and maintenance of a public good: e.g. our interest in living in a clean environment. These interests require a higher degree of collaboration than mere public provision to be met. Common interests, in turn, are interests that we share as societies or groups of people in values, norms and attitudes that sustain the collective: e.g. our attitudes as a society, and they are properties rather than products. We may for instance have a common interest in living in a community where individuals are not discriminated against on the basis of their sex, ethnicity, wealth, position etc., and where our lifestyles and attitudes further our health. The communitarian view has no problem incorporating this, but from the liberal perspective there is a clear risk that interventions aiming to change our behavior in order to e.g. promote our health will be deemed unacceptable because they conflict with our freedom to live our lives as we wish, so long as we do not harm others. [154]

In applying this structure on healthcare I argue that our interests in healthcare may at a first glance seem to be congruent: i.e. we have an interest in having access to healthcare, which requires that public structures (e.g. hospitals) exist. This is akin to the situation concerning education. But since effective healthcare depends on medical research being conducted, which requires a public effort (illustrated for instance by epidemiological research conducted on data in medical registries or samples in population-based biobanks), our individual interests in healthcare must be considered convergent as well.

This brings us to the question of whether we can have rights that protect such convergent interests, i.e. whether other individuals can have a duty to co-operate in order to fulfill them. Consider the case of vaccinations. Some might regard immunization against tetanus as a right (protecting our congruent interests not to succumb to the disease). But they could not as reasonably claim that herd immunity against for instance measles is a right (protecting our convergent interests in decreasing the risk of succumbing to the disease). Establishing herd immunity requires that almost all individuals are vaccinated, which not only demands economic resources, as in the tetanus example, but may necessitate compulsion as well.

What are rights?

The Cambridge Dictionary of Philosophy defines rights as "advantageous positions conferred on some possessor by law, morals, rules or other norms". [165] According to Hohfeld rights function in four different ways: as privileges (you have no duty not to), claims (somebody else has a duty toward you), powers (an ability to alter privileges and claims) and immunities (others lack

ability to alter your privileges and claims). [166] Rights are commonly understood as either favoring the will of the holder against the will of others or as protecting the interests of the possessor. They can be divided into positive and negative rights, where the former are rights to something, and the latter are rights to be left alone: a right to healthcare is a positive right, while a right to freely choose one's religion is a negative right.

There are three common justifications of rights: 1) natural right theories, 2) instrumental theories and 3) contractual rights. From the first perspective individuals have rights based in features that they share as humans. This standpoint has been defended by philosophers such as Hobbes, Locke, and Nozick. According to Nozick for instance, rights impose side-constraints on what others may do in the pursuit of their goals, because all people possess an inviolability that others must respect. [167] Locke similarly states that reason is the law of nature that teaches mankind that "being all equal and independent, no one ought to harm another in his life, health, liberty or possessions". [168]

From the second point of view rights protect interests that individuals have, i.e. they are instruments to achieve a desired goal. This goal can be based for instance in maximizing utility or in egalitarian concerns. An obvious difficulty with basing rights in consequences is that different interests must be measured against each other, both between individuals and within the same person.

The third justification is that rights are based in principles that individuals would agree upon under certain circumstances. Rawls for instance justifies rights as those that individuals would assign to themselves and others if they were not aware of their own particular interests. [153]

Irrespective of how rights are justified, different rights can conflict with each other. In the context of biobank research this is illustrated for instance by the right to confidentiality and the right to withdraw from research: confidentiality is best protected if samples are anonymized, but anonymizing them implies that individuals cannot demand that they be returned or destroyed, because there is no link left between the individual and the sample.

Thus, rights can be thought of in a variety of ways. Although they are obviously central for us as individuals living together in a society, it is important to recognize that they are not the whole story. As James Griffin has put it: "We have constantly to remind ourselves of the destructive modern tendency to turn all important moral matters into matters of rights, especially of human rights. We have to recover our sense of the power of the rest of our moral vocabulary – for example the language of justice and fairness." [169] From here we turn to considering whether or not healthcare is a right, and if so, what kind of right it is. This is relevant because as the previous discussion on goods and interests demonstrated, our view on healthcare may affect how we look upon a duty to participate in medical research.

Is there a right to healthcare?

In attempting to deal with this question, it is at least clear that there can be no right whatsoever to the healthcare that we desire, defined as access to effective treatments when we need them, because they may not exist. It also seems doubtful that we can have a human right (i.e. a right based solely in the fact that we are human) to those aspects of healthcare that constitute our convergent interests, e.g. advances in medicine grounded in research, because this would imply that others could be forced to contribute against their will. What remains is a possible right to the healthcare that can be publically supplied as a means of fulfilling our congruent interests, i.e. a right to provision of the necessary "infrastructure" (e.g. hospitals, doctors, nurses and existing medicines).

When considering whether a right to such healthcare exists, three alternative views seem possible. First, it can be thought of as a human right, i.e. a right that all individuals have simply in virtue of being human. Second, it can be conceived of as a social contract right, i.e. a right appointed to individuals as members of a society. Third, it can be argued that there is no right to healthcare, but that healthcare is merely a commodity, bought and sold on the market.

Healthcare as a human right

According to the Office of the High Commissioner for Human Rights, human rights are "rights inherent to all human beings, whatever our nationality, place of residence, sex, national or ethnic origin, color, religion, language, or any other status". [170] Article 24 of the Universal Declaration of Human Rights includes the right to medical care [171] and the International Covenant on Economic, Social and Cultural Rights of the United Nations states that we have a right to "the highest attainable standard of physical and mental health". [172] However, as James Griffin has pointed out, the highest attainable standard of health seems not even to be a reasonable social aim. [169] According to Griffin we do, nonetheless, have a human right to the health support necessary for our functioning as normative agents. The obvious question that arises is then: who has the corresponding duty to provide it?

Following a Kantian scheme obligations can be divided into three categories. First, obligations can be universal and perfect, i.e. owed by all individuals to all others, based on respecting individuals as moral agents. These obligations correlate to for instance the negative rights expressed in the Declaration of Human Rights, such as the right to freedom of opinion and expression. Second, obligations can be perfect but non-universal, i.e. owed by specific individuals toward other specific individuals. Obligations of this kind are grounded in contracts or special relationships, e.g. the duty of healthcare personnel to care for their patients, and are also associated with specific rights. Third, there are universal imperfect obligations that are wider

obligations, e.g. the duty to be charitable. Such obligations cannot be translated into rights, i.e. although I should donate money to people in need, nobody can claim a *right* against me that I do it.

The traditional negative human rights correlate to obligations of the first category, whereas positive human rights seem not to, i.e. it can hardly be the duty of every individual to contribute to the healthcare of every other person in the world. Rather, these obligations seem to be of the third category, which would imply that there actually are no corresponding rights. However, Griffin argues that human rights can impose duties on particular agents because simple ability may entail moral responsibility. When poor countries lack the capacity to provide healthcare for their citizens, the duty to do so may fall on other agents such as the pharmaceutical industry or the rich countries of the world. [169] James Nickel has similarly argued that although governments are the primary addressees of the human rights of their residents, other governments, international organizations and individuals have back-up responsibilities for the fulfillment of human rights around the world. [173]

However, this line of reasoning inevitably involves a potential conflict between the negative rights of those that allegedly have a duty to act and the positive rights of the people in need. While such conflicting rights are commonly handled within the framework of a social contract, it is not clear that they can be solved in the absence of one. Thus, compelling individuals to change their life plans (e.g. by accepting a duty to serve in the military or to pay taxes) is possible in the former situation, but seems far less legitimate in the latter. It can of course be argued that human rights are in fact social contract rights, the society in question being the world community, but in order for such a contract to be effective, an apparatus regulating and implementing the various rights and duties would seemingly be required. Arguably, a human right to healthcare cannot be based on ad hoc solutions that cast duties on whoever happens to have the ability to help.

Healthcare as a social contract right

An alternative interpretation of human rights is that they do not include positive welfare rights such as a right to healthcare. [174, 175] From this standpoint, human rights are restricted to negative autonomy rights that are universal claims of all individuals against all others, e.g. the right to freedom of opinion and expression. Accordingly, all the welfare rights that an individual may have are social contract rights, often civil rights appointed to him or her as a citizen in a particular country (although it is possible to conceive of larger social contracts as well).

Besides the obvious benefit of incorporating a clearly identifiable duty bearer, e.g. the society that the individual belongs to, at least one consideration seems to favor this view: It is reasonable to suppose that an individual choosing to “opt-out” of society would retain his negative rights, e.g. the

right to freedom of thought, conscience and religion as well as the right to freedom of opinion and expression, but give up his welfare rights. Thus, as a human being he would still have a right to hold any opinion or belief, but placing himself outside the community he would have no right to the benefits co-operatively produced within it (e.g. healthcare). This seems to indicate that the latter rights are not grounded solely in an individual's being human, but also in his being a member of a specific community.

Viewing healthcare as a social contract right illuminates the fact that healthcare is not "manna from heaven" by emphasizing the reciprocity of a contract, i.e. the right to healthcare is naturally coupled with a duty to contribute. Hence, it is clarified that the right to healthcare is not an absolute right to healthcare in general, but a right to specific healthcare, the limits of which are set by factors such as availability, funding and medical research.

Healthcare as a commodity

From the third perspective, there is no right to healthcare. Instead, all individuals have a right to buy their healthcare on the market if it happens to exist, and if it is not available or they do not have the resources to pay for it they simply have to make do without it. Robert Sade has accordingly argued that medical care is "neither a right nor a privilege: it is a service that is provided by doctors and others to people who wish to purchase it". [176]

However, a right to buy healthcare can at most be a right to buy healthcare based on the current level of medical knowledge. Consider the case of orphan diseases. Orphan diseases are diseases that are not deemed lucrative enough for the pharmaceutical industry to invest in, either because they are rare or because they predominantly affect individuals that cannot afford to pay for their medication. Hence, individuals affected by such diseases cannot have a right to buy the healthcare that they need since it does not exist, and the same is obviously true of those who are affected by other diseases for which no effective treatments are available.[10]

Although proponents of the "healthcare is a commodity" view can claim that they have a right to buy healthcare without associated obligations, their line of reasoning fails if the premise that they wish to have access to better healthcare is added. Then, since advances in medicine depend on robust research being carried out, all individuals arguably have a reason to contribute and a contract imposing a duty to do so (at least when no costs or significant risks are involved), is the best means of attaining this goal.

To conclude, it seems that the most reasonable justification of a right to healthcare, even when it is considered merely as a right to the necessary "infrastructure", is that of a social contract. This does *not* imply that all peo-

[10] This is why we collectively sponsor such research by creating economic incentives, e.g. extended marketing exclusivity or easier approval.

ple *should* not have a right to healthcare. To the contrary, the right to healthcare is arguably too important to be swept away in grandiose terms that are not rooted in reality: a praiseworthy goal is not the same as a right. If we want healthcare to be a right, then we have to make it one by agreeing upon who is to have the right and who is to have the corresponding duties. And if we want it to be a right to more than infrastructure, then the duties must include contributing to research. This leads us to closer consider the social contract view.

Different contract views

From the contract perspective, what is right and wrong depends on principles that would be agreed upon by equals in a hypothetical situation. In contractarian theories, these equals are simply rational self-interested individuals, whereas contractualist theories are built on reasonable reciprocity, i.e. fairness between moral equals. [177] Hobbes and Gauthier represent the first view, while Kant, Rousseau and Rawls are examples of philosophers that have applied a contractualist perspective. Rousseau for instance states: "Since no man has a natural authority over his fellow, and since strength does not confer any right, it follows that the basis remaining for all legitimate authority among men must be agreed convention." [178]

In exploring whether a contract view can justify a duty to contribute to biobank research both the contractarian and contractualist perspectives are relevant to consider. However, since the contractarian account rests solely on self-interest, it seems that a duty to contribute, if it can be defended by contractarianism, should also be justified by a theory that allows for considerations of fairness to enter the picture.[11] Therefore, my main focus will be contractarian, although I will also briefly discuss some appealing aspects of Rawls' theory of justice.

Agreeing upon a contract

A contractarian theory starts with the assumption that there are circumstances in which each individual benefits from co-operating with others compared to the situation in which all pursue their self-interest independently. If the good that can be attained is important enough, it is rational even for purely self-interested individuals to agree to mutually constrain their freedom to acquire it. All would prefer schemes in which others bear more of the costs, but are prepared to do their share according to principles that rational individuals would agree upon. [177]

[11] The difference can be illustrated by contrasting the perspectives of Hobbes and Rawls. Hobbes' theory rests on pure self-interest, while an intrinsic element of Rawls' theory is that individuals have a moral duty to support and act on the principles that are chosen behind the veil of ignorance, because they are fair, even if they turn out not to promote their actual interests when the veil is lifted.

In the case of biobank research, the benefit that can be obtained through co-operation is medical knowledge that may lead to improvements in healthcare. The cost for each individual is the risk that is imposed by the research. From the perspective of pure self-interest it seems that the rational course of action would be not to participate, because the benefit of improved healthcare is available to all regardless of whether they have participated or not, and offhand it seems unlikely that one's sample would be the specific sample necessary for obtaining the specific knowledge that would later lead to the specific advances in healthcare that one would come to need. However, since this is true for everybody, it gives rise to the worst prerequisites for advancing healthcare.

It might be objected that most individuals consent to their samples being used, so there is no need for a contract. However, requiring consent for using stored samples in research imposes a risk of selection bias, because when participation is not universal, biobanks and registries are affected by both those who are included and those who are not, leading to incomplete information and data-bank bias. [179] Furthermore, obtaining consent consumes time and money that could else be spent on conducting research. [Article III] That is, even if everyone that was asked to consent actually did consent, research would be hampered compared to a situation in which samples are used without consent. So a contractarian view can seemingly be applied on biobank research, because it is reasonable to assume that the self-interest of all individuals is better served by accepting a contract imposing a duty to participate by allowing stored samples to be used, than by the no-contract situation. There is also another reason why individuals have an interest in their samples being used in biobank research: As personalized medicine moves forward, future treatments are likely to be compromised for those whose genes are not represented in research, because new therapies will not be developed for their gene profiles. [180]

A duty to adhere

There are two central notions regarding how moral duties arise in association with contracts. The first presupposes an obligation to honor agreements that exists prior to specifying the content of the contract. From this perspective a person who accepts a contract has a moral duty to adhere analogous to the duty to keep one's promises. According to the second notion, the contract is a ground for complying, i.e. the contract in itself explains the duty to adhere to its contents.

A central problem for contractarian theories is then that they must be able to explain why self-interested individuals would adhere to the contract even if not complying would confer a greater benefit. That is, although individuals may have a reason based in self-interest to sign a contract, why would they have a reason based in self-interest to stick to it, if they could benefit even more by defecting?

There seem to be two possible solutions: either some kind of external governance mechanism with the power to impose punishments must be brought in (e.g. the Sovereign of Hobbes); or it must be demonstrated that cheating would not be in the best interest of the individual after all, due to considerations that are internal to co-operating. In the context of biobank research the first alternative can be achieved by converting the moral duty to a legal one, and thereby discouraging individuals from free-riding on the contributions of others.

From the second perspective David Gauthier, in attempting to build a moral theory on rational constraint, has introduced the concept of "constrained maximizers", distinguishing between persons who are disposed to straightforwardly fulfill their interests in the particular choices that they make, and constrained maximizers, who are disposed to comply with mutually advantageous moral constraints, provided they expect similar compliance from others. He argues that the net advantage that constrained maximizers gain from co-operating is larger than that which persons who exploit others may expect, and thus it is rational to "be disposed to constrain maximizing behavior by internalizing moral principles to govern one's choices". [181]

The contractualist perspective does not give rise to the problem of why to adhere, since on this view moral principles are rules that individuals would agree upon from a common perspective, all being free and equal persons. That is, they define what is right to do, rather than merely what lies in one's self-interest to do. Briefly, Rawls argues that individuals would agree upon two principles to govern their conduct if they were ignorant of their own individual interests. The first requires equality in the assignment of basic rights and duties. The second holds that social and economic inequalities are just only if they result in benefits for all, in particular for those worst off. [153] The idea is "that since everyone's well-being depends upon a scheme of cooperation without which no one could have a satisfactory life, the division of advantages should be such as to draw forth the willing cooperation of everyone taking part in it, including those less well situated." [153] This view opens the door to favoring the interests of those who are worst off. In the context of healthcare and medical research those worst situated are arguably the patients. Accordingly, the interest of an individual in not allowing a sample to be used in research e.g. due to a negative attitude toward a specific project or a certain disease, may be outweighed by the interest of patients to have access to new treatments. [61] Erik Christensen has recently applied such a view on biobank research, arguing that participating in this kind of research is a natural extension of our liberal values and democratic principles. [182]

Some concluding remarks on the proposed contract view

To summarize, I put forward that a duty to participate in biobank research can be defended from the perspective of a social contract (based in self-

interest) that is rational for all individuals to accept. This rests on the assumption that the risks involved in the research are diminutive and outweighed by benefits that can only be attained through co-operation. The moral duty to adhere can either be justified by a pre-existing duty to honor one's agreements and keep promises, or by referring to the rationality of doing so. [Article IV]

However, I do not suggest that a contract view is the only, or even the best, way of accounting for rights and duties of individuals in the context of healthcare and medical research. It does though arguably offer a relevant picture of the conflicting interests that are involved, and also concurs with many of our intuitions, e.g. that individuals ought not to hinder usage of samples that does not impose risks, when it could benefit both themselves and others.

Furthermore, I do not propose that such a contract exists, or ought to exist, in reality (implying for instance that those not signing it would have no right to healthcare). Rather, I argue that the theoretical view justifies implementing regulations that facilitate this kind of research. That is, since a moral duty to contribute can be demonstrated, the regulations that govern our interaction should encourage us to act accordingly. Basing legislation and other regulations on a contract view implies that there is a need for public education and debate in order to secure understanding and acceptance of the policy. If individuals are made aware of the fact that it lies in their own interest to co-operate, they are likely to accept policies that facilitate this end.

However, if there was an actual contract to sign, people *could* choose not to, thereby giving up their right to the benefits that are produced. Since this option does not exist if a hypothetical contract underlies regulations that must be followed, it may be appropriate to grant individuals a possibility to opt out. This in order to avoid charges of coercion, which could result in negative consequences from a wider societal point of view. (Although from a moral perspective the individuals that choose not to contribute should arguably be willing to forego the benefits that result from the co-operation, i.e. the advances in healthcare that are achieved.)

I conclude that viewing biobank research from the perspective of a social contract offers a way to reconcile the rights of individuals with the benefit of the public.

Future work

A common feature of large-scale biobanks is that they are created as research infrastructures rather than as tools for specific research projects. Samples are stored for future unspecified studies, and often personal data (e.g. from medical registries, medical records or questionnaires) is linked, or linkable, to them. Current research regulations, including the ethics review process, have not kept pace with these developments, so there is much work to be done when it comes to improving the prerequisites for conducting this kind of research. Some of it is obviously legal, i.e. laws and regulations need to be adjusted to the changing realities that we face. However, such changes should arguably be based on sound ethical arguments, so continued bioethical analysis of the different interests at stake is important.

Furthermore there is a need for public education and debate, in order to create a deeper understanding of the relationship between medical research and healthcare, so that awareness is raised on the consequences of acting in what seems to be one's self-interest. In short, it should be conveyed that there can be no right to effective healthcare, unless a corresponding duty to contribute to research is acknowledged. In this thesis I have restricted myself to arguing that there is a moral duty to accept that stored tissue samples and data are used for research purposes, but it could also be analyzed whether a duty to donate new samples can be defended from the same perspective.

Another issue that has not been settled is how individual results and incidental findings should be handled. According to a recent consensus statement by a working group funded by the United States' National Institutes of Health (NIH), biobanks should accept "significant responsibilities" for the management of such findings from genetic and genomic research. [145] Others have pointed out that this could be costly and difficult, and may not even lie in the best interest of participants. [183, 184] More research is required in order to evaluate the consequences of implementing such policies. Research is also needed on risk perception and communication, since often risk information based on biobank research is complex and ambiguous.

Conclusion

Starting with the practical implications of this thesis, I conclude that there are good reasons why:

- Individual results from research using samples stored in large-scale biobanks should not be returned.

- Ethics review boards should presume that individuals want to contribute to medical advances through biobank research, rather than that they do not, and therefore more often allow for opt-out strategies.

- Biobank research should be thought of as a natural component of healthcare, like quality control, method development and teaching, that ought to be endorsed and facilitated.

From a theoretical perspective I conclude that:

- A moral duty to contribute to medical advances by accepting that stored tissue samples and associated data are used for research can be defended from the perspective of a social contract based in self-interest.

- No arguments based in societal benefit are necessary to justify such a duty, and thereby, it cannot be rejected by appealing to the primacy of individual rights over the public good.

- Applying a social contract view on biobank research offers a means of reconciling individual rights with public benefit.

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Summary in Swedish – Sammanfattning

Biobanksforskning är medicinsk forskning som använder sig av vävnadsprover som härrör från människor. Proverna kan antingen vara tagna inom hälso- och sjukvården (t.ex. som ett led i en utredning eller behandling), eller vara donerade för forskningsändamål. Ofta används också annan information om personen i fråga i forskningen, t.ex. data ur register, journaler eller enkäter.

Medicinsk forskning är viktig, eftersom många människor lider av sjukdomar som inte går att bota eller behandla, nya sjukdomar utvecklas och gamla sjukdomar blir motståndskraftiga mot de mediciner som finns. Vi har alla ett intresse av att forskning kontinuerligt bedrivs, eftersom vi inte vet vilken sjukvård vi och de som står oss nära kommer att behöva och därför inte heller vilka medicinska framsteg vi kommer att ha nytta av. Jämfört med många andra slags forskning medför biobanksforskning endast små risker för dem som deltar. I allmänhet är riskerna inte fysiska, utan de består av möjliga intrång i integriteten som uppkommer genom att information om personen hamnar i orätta händer. Denna risk minimeras genom att prover och data kodas eller anonymiseras, så att man inte omedelbart kan koppla samman dem med individerna som de tagits från. En annan risk är att prover används för ändamål som individen inte vill medverka till, t.ex. forskning om psykiska sjukdomar eller drogmissbruk.

I den här avhandlingen vill jag utreda förhållandet mellan individen och samhället då det gäller sjukvård och medicinsk forskning, särskilt vilka rättigheter och skyldigheter individer har med avseende på biobanksforskning.

I den första artikeln undersöker jag argumenten för och emot att återföra resultat som erhålls vid forskning som använder sig av prover som tagits inom sjukvården eller donerats till storskaliga biobanker (som t.ex. LifeGene). I debatten om återförande av resultat anges ofta att individer har en ”rätt att veta” och att forskare har en plikt att göra gott och inte skada. Men individer kan även ha en ”rätt att inte veta” och att återföra resultat kan hämma viktig forskning, och därigenom i förlängningen också orsaka skada. Jag drar slutsatsen att individuella resultat generellt sett inte bör återrapporteras, istället bör tillgängliga resurser läggas på mer (eller bättre) forskning, för att öka den medicinska kunskapen och på så sätt förbättra sjukvården för alla.

I den andra artikeln jämför jag samtycke för organdonation med samtycke till användning av prover för biobanksforskning. Många länder har infört presumerat samtycke för organdonation, d.v.s. man antas samtycka om man

inte aktivt har sagt nej medan man levde, och det har visat sig att detta leder till ett ökat antal donatorer. Flera av argumenten som stödjer ett sådant förfarande är även applicerbara på biobanksforskning. De flesta är exempelvis positiva till att deras prover används i forskning och om man utgår från att människor vill medverka kommer man därför oftast att göra rätt. Om de som inte vill att deras prover används får säga ifrån, så tvingas ingen delta och de som inte vill bidra får bära kostnaden associerad med att göra ett aktivt val.

Det hävdas ofta att individer har rätt att bestämma över hur deras prover och data får användas, även om forskningen inte medför några kostnader eller risker. I den tredje artikeln pekar jag på problemen med denna syn då det gäller biobanksforskning. För det första innebär kravet på att inhämta ett nytt samtycke för varje studie en risk för att urvalet blir snett. Detta kan ske om individerna som samtycker skiljer sig åt jämfört med de som inte samtycker eller inte svarar på förfrågan om samtycke överhuvudtaget. Ett uppenbart exempel är om prover från avlidna inte får användas eftersom de inte kan samtycka. En forskare som vill studera en sjukdom kommer då att få ett snett urval, där de som var mest sjuka och avled av sin sjukdom inte finns representerade. För det andra innebär kravet på samtycke en kostnad i både tid och pengar. I artikeln argumenterar jag för att intresset av att bestämma vad ens prover får användas till måste vägas mot intresset av medicinska framsteg - och att biobanksforskning därför bör kunna utföras utan samtycke.

Målsättningen med den fjärde artikeln är att visa att en plikt att delta i biobanksforskning kan rättfärdigas utifrån ett ”socialt kontrakt”. Denna syn baserar sig på att individer (hypotetiskt) kommer överens om att inskränka sin frihet för att uppnå ett mål som ingen kan uppnå själv. Man sluter en överenskommelse som är grundad i självintresse: eftersom medicinska framsteg förutsätter forskning och effektiv forskning förutsätter att så många som möjligt ställer upp, är det rationellt att acceptera en plikt att delta genom att låta sina prover och data användas (under noga reglerade förhållanden). Om man accepterar ett sådant kontrakt i teorin har man också en moralisk plikt att delta i praktiken.

Sammanfattningsvis har jag i den här avhandlingen dragit slutsatsen att biobanksforskning är viktig och bör stödjas, både utgående från ett individuellt och ett kollektivt perspektiv. Jag har argumenterat för att en kontraktssyn på biobanksforskning är rimlig, och att den har fördelen att den kan förlika individens rättigheter med allmännyttan och underlätta för forskare att använda sparade prover och data.

De praktiska slutsatserna i denna avhandling är:

- Att individuella resultat från storskalig biobanksforskning generellt sett inte bör återföras.

- Att etikprövningsnämnder bör utgå från att människor vill medverka till medicinska framsteg.
- Att biobanksforskning bör ses som en naturlig del av sjukvården.

De teoretiska slutsatserna i denna avhandling är:

- Att en moralisk plikt att delta i biobanksforskning kan rättfärdigas med hänvisning till ett socialt kontrakt grundat på självintresse.
- Att inga argument baserade på andras välfärd krävs för detta.
- Att kontraktssynen innebär att individens rättigheter och allmännyttan inte står i konflikt med varandra.

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