Biobanks
as resources for health

Mats G. Hansson & Marianne Levin (eds.)

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Research Program Ethics in Biomedicine

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Contents

1

Biobanks as resources for health

Associate Professor Mats G. Hansson[1] & Professor Marianne Levin[2]

[1]*Research Program Ethics in Biomedicine, Uppsala University*
[2]*Department of Law, Stockholm University*

The potential benefits of biomedicine and biotechnology are considerable, but this is also an area of science and medicine that is sometimes found controversial. Decisions made by scientists, by health care professionals and by policymakers must be well informed and based on knowledge and sound research. Legal experts concerned with public law and intellectual property rights, philosophers and social pharmacists have been collaborating with geneticists, pathologists and doctors in several research projects in order to seek the kind of biobank management that would satisfy the interests of both the research community and the general public as regards new medicines and forms of treatment, whilst protecting the integrity of the individual. A summary of that research is presented in this book, and in the present chapter we provide a short overview.

1. Introduction

The potential benefits of biomedicine and biotechnology are considerable, but this is also an area of science and medicine that is sometimes found controversial. Value studies both in Sweden and abroad reveal widespread scepticism among the general public about future developments in this sphere. The rapidity of development both attracts and repels. Establishing relationships of trust is vitally important. A minimal requirement for the establishment of trust is that the decisions made by scientists, by health care professionals and by policymakers are well informed and based on knowledge and sound research. This is true not only for biotechnology and medicine, but also for ethics and social policy-making. In 1998 the Vice-Chancellor of Uppsala University initiated the research program *Ethics in Biomedicine* Research Programme in order to enable a disciplined evaluation of ethical values, providing sound research and scholarship. Psychologists and ethics researchers are collaborating with clinical geneticists, oncologists and surgeons to determine how patients and relatives react when told that they are genetically disposed to cancer. In projects about biobanking, legal experts concerned with public law and intellectual property rights, philosophers and social pharmacists have been collaborating with geneticists, pathologists and doctors in seeking the kind of biobank management that would satisfy the interests of both the research community and the general public as regards new medicines and forms of treatment, whilst protecting the integrity of the individual. This book is a report from the projects on biobanking. All publications and activities emanating from the project are listed in the concluding chapter.

The research program *Ethics in Biomedicine* Research Programme has the benefit of a sizeable group of scholars in-house but depends for its success on good relationships with other departments, both at Uppsala University and at other universities. The Department of Law at Stockholm University has been an important collaborator for many years, with its expertise in different areas of private law and public law. The Chalmers University of Technology is another partner of importance. In the projects on biobanking, close contact with natural scientists, both at academic institutions and at pharmaceutical companies, has been essential in order to get the facts straight and acquire first-hand knowledge about the use of biobanks for research purposes.[1] The following scholars and scientists have been involved in the projects on biobanking as partners or as consultants:

- *Associate Professor Mats G. Hansson*, B.A., ThD, (Project Leader), Research Program Ethics in Biomedicine, Uppsala University.
- *Professor Maria Anvret*, PhD, AstraZeneca AB.
- *Ulla Björkman*, LLM, Senior Lecturer, Department of Law, Uppsala University.
- *Jacob Dahl Rendtorff*, PhD., Department of Philosophy, Roskilde University.
- *Associate Professor Bengt Domeij*, LLD, Industrial Economics and Management, Royal Institute of Technology, Stockholm
- *Stefan Eriksson*, ThD, Research Program Ethics in Biomedicine, Uppsala University.
- *Ulrik von Essen*, LLD, Department of Law, Stockholm University.
- *Rebecka Frisk*, LLM, Bird & Bird.
- *Gert Helgesson*, PhD, Research Program Ethics in Biomedicine, Uppsala University.
- *Åsa Hellstadius*, Doctoral Candidate, LLM, Department of Law, Stockholm University
- *Lena Jonsson*, PhD, Amersham Biosciences.
- *Magnus Kaijser*, PhD, Department of Medical Epidemiology, Karolinska Institutet.
- *Åsa Kettis-Lindblad*, PhD, Department of Pharmacy, Uppsala University.

[1] For an earlier report see: Hansson, M.G., (ed.), *The Use of Human Biobanks. Ethical, Social, Economical and Legal Aspects*, Report 1, Uppsala University 2001, ISBN 91-506-1472-X, 93 pp.

- *Associate Professor Jens Laage-Hellman*, PhD, Institute for Management of Innovation and Technology, Chalmers University of Technology, Göteborg.
- *Professor Ulf Landegren*, MD, PhD, Department of Genetics and Pathology, Uppsala University.
- *Professor Marianne Levin*, LLD, Department of Law, Stockholm University.
- *Bo Lindberg*, MD, PhD, Former Medical Director, Akademiska sjukhuset (Uppsala University Hospital).
- *Lena Ring*, PhD, Department of Pharmacy, Uppsala University.
- *Urban Paulsson*, Advocate, Bird & Bird, Member of the Swedish Bar Association
- *Associate Professor Annina Persson*, LLD, Department of Law, Stockholm University.
- *Associate Professor Elisabeth Rynning*, LLD, Department of Law, Uppsala University.
- *Associate Professor Christer Sundström*, MD, PhD, Department of Genetics and Pathology, Uppsala University.
- *Richard Wessman*, LLD, Department of Law, Stockholm University.
- *Li Westerlund*, LLD, Department of Law, Stockholm University.
- *Associate Professor Kerstin Westermark*, Medical Products Agency, Uppsala
- *Sanna Wolk*, Doctoral candidate, LLM, Department of Law, Stockholm University.

As can be seen from the last chapter of this report, the authors have published in scientific journals within their own academic fields. Some titles are forthcoming during 2003. This report represents a summary of the results. Through the research projects a multi-disciplinary basis has been laid for the implementation of ethical and legal praxis regarding biobanking. Thanks to an initiative taken by the Swedish Federation of County Councils in January 2003 a uniform praxis is developing among Swedish health care providers regarding information and consent procedures for collection and storage of human biological specimen. Several questions remain to be solved. There is a need for closer collaboration over national borders and there must be standards of quality and safety that are common to different partners collaborating in diagnosis and research. The new EU Directive (2001/83/EC) setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components will stimulate coordination and collaboration between the member states of the European Union for the benefit of

patient safety. A new directive regarding pharmacogenomics from The European Agency for the Evaluation of Medicinal Products (EMEA), decided in December 2002 (EMEA/cpmp/3070/01)will facilitate collaboration through establishing uniform criteria for genetic tests and coding of genetic information. Of great and obvious concern for the implementation of a European praxis is also to follow closely the progress of the new proposal for a EU Directive (2002/0128(COD) on setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells.

2. Biobanking is not a new phenomenon

Issues related to sampling of human biological material have come to be intensively discussed during the recent five years. Sweden has had new legislation in effect since 1st January 2003 and legislation is expected in other countries as well. Health care professionals, scientists and politicians are involved in discussions related to different aspects of biobanking. In this context it is important to remember that the taking of blood and tissue samples has been a part of routine clinical practice for many years. From the perspective of ordinary health care, biobanking is not a new phenomenon. It is normal procedure in order to perform diagnosis or ascertain the effects of medical treatment. Bo Lindberg's account of biobanking (ch. 2) as a part of clinical practice is a reminder of this fact. In many diseases an exact diagnosis is necessary before treatment starts, and biopsies must be stored in order to diagnose relapses of a disease or for the sake of patient safety. Supply of safe blood products is a prerequisite for most surgical procedures today. It is important also to acknowledge that within the context of ordinary health care these aspects of medical treatment have been guided by common and well-accepted codes of professional conduct, such as giving the patients appropriate information and respecting their self-determination. This practice, which has long been codified in Swedish health care legislation, is an intrinsic element of clinical ethics.

However, even if biobanking as such is not a new phenomenon in clinical practice, it is also important to acknowledge that new scientific knowledge, e.g. genetic research, has turned the samples of blood and tissue into vital means for research. If successful, this research will enable the development of new medical treatments. Lindberg has pointed to the importance of well-managed and accurate clinical data for realising the potential of the clinical biobanks. Reliable clinical data, including a comprehensive and structured anamnesis and family history, the results from clinical examinations and laboratory investigations, are necessary tools if these resources of health are to be realised. Research using human biobanks has so far been dominated by molecular epidemiologists using large cohorts numbering hundreds or thousands of patients. With the progress now being made in functional genomics there is growing interest in having access to clinical data where patients are well-characterised both at the molecular level and with regard to family history and life-style factors. A few well-characterised patients may be more advantageous for some research purposes in functional genomics than access to thousands of patients characterised only in one or two aspects. Good clinical practice and close collaboration between scientists and doctors are essential in order to serve the interests of patient welfare in both the short- and in the long-term perspective.

3. A great variety of research projects for realising the potential of biobanks

There are many kinds of biobanks organised for many different purposes, ranging from small collections of biological specimen assembled from specific patient groups to large biobanks with hundreds of thousands of samples assembled within the framework of different screening programmes. Magnus Kaijser (ch. 3) has suggested a categorisation of these different biobanks distinguishing between (i) material collected for diagnosis, (ii) material collected for future clinical and diagnostic use, (iii) material for mapping of patients with different characteristics such as potential bone marrow donors and (iv) material collected exclusively for research. Whatever the main purpose of collection, all these biobanks have proved to be invaluable tools for biomedical research. Kaijser proves this point with eighteen illustrative examples of different research projects carried out recently. His collection of examples shows that a great variety of research questions can be addressed through the use of biobanks. Each scientific result adds important knowledge that, successfully collated, may be of great benefit for the welfare of patients. One important lesson from this survey is that in order to fully realise the potential of biobanks, biological information from the biological specimen needs to be combined with every kind of medical and personal information available. The use of biobanks for research then implies full access to information available in different kinds of medical registers, access to clinical data for each individual and also access to epidemiologically significant information available in different kinds of public records and scientific databases. One further implication, as will be discussed later, is that all this information must be safely handled so that no harm is done to sample donors, patients or other informants of registers and records.

Some of the concrete examples of research projects also illustrate the possibility of a direct loss of scientific value if explicit and specific informed consent is the rule without exception when using previously collected samples for addressing new research questions. Some questions may not be asked, and there is a cost related to a study's drop-out rate. The scientific value of the study diminishes and with it the value of the knowledge for understanding and curing diseases. There will always be a drop-out when there is a strict requirement of obtaining fresh informed consent from a sample donor. Between 20-40% of the informants will not reply, no matter how many reminders are sent out. It is impossible for the scientists to know if those not responding belong to a group of particular interest for the study or why they don't respond. If great risks of harm are associated with participating in the study, this may be an ethical price that has to be accepted. But if the risks are slight one assumes a great moral responsibility when arguing for informed consent without exception, since the possibility of meeting the needs related to patient welfare are drastically reduced. How this balance between patient interests for new medically important knowledge versus donors' interests of self-determination may be achieved is a key concern in the new Swedish Biobanks Act and is discussed by several of the authors in this report.[2] The Biobanks Act assigns the task of balancing values at stake to the research ethics committees and it should be noted that the relevant provision of the Biobanks Act does not impose any statutory restrictions on the discretion of the research ethics committees. However, as shown by Ulrik von Essen (ch. 6) and

[2] See also Hansson, M.G, Balancing the quality of consent, *Journal of Medical Ethics*, and Hansson, M.G, Combining efficiency and concerns about integrity in the use of human biobanks, forthcoming.

Gert Helgesson (ch. 7), a new Swedish law regulating ethical review of research will influence the praxis of research ethics committees (Government Bill 2002/03:50). This law is expected to come into effect as of January 2004.

4. Partnership for the benefit of patients

In order to realise the potential of human biological material and additional medical and personal information into new medical products and treatment opportunities, public and private partners must collaborate. Doctors and scientists at public universities and hospitals do not have the financial means or the competence to assume responsibility for turning basic scientific knowledge into new medical products and treatments. Different parties in these collaborations may have different interests that may not be easily settled in a common venture. Commercial parties like pharmaceutical and genomic companies have legitimate commercial interests. Scientists want to publish their results openly and the prime duty of doctors is to their patients. Collaboration with commercial partners is nothing new to universities, nor is it unique to biobank research. It is something that has been stimulated with the aid of both local and national initiatives for the transfer of knowledge and technology between universities and industry. Within the context of biobank research a number of initiatives have been taken by pharmaceutical and diagnostic companies in order to search for disease-associated genes and related targets for drug and marker development. Direct collaboration between industrial firms and academic scientists has been frequent both in different kinds of clinical trials and in biobank research. Another option for academia is collaboration with special genomic companies as intermediaries. Jens Laage-Hellman has studied three such commercialisation ventures: deCode Genetics in Iceland, Oxagen in the UK and UmanGenomics in Sweden (ch. 4). One important conclusion for companies interested in this field is that a commercialisation venture is difficult to "organise" in the ordinary sense of that word. The organisation and the resulting performance emerge rather as a result of a complex interplay among many actors, each of which may have different interests. Laage-Hellman notes as one implication of this that an actor's ability to interact with others and build trustworthy relationships is crucial to his own success as well as for the progress of the whole venture. A lesson to be drawn from the Swedish case in Umeå is that all parties concerned must be included in a partnership and agreements must be made both with the universities and with the individual scientists. This is also stressed by Urban Paulsson and Rebecka Frisk (ch. 13). Oxagen has selected a more promising approach in this respect, with a sense of partnership where they can take advantage of the competence and the resources possessed by academic institutions in a large network, while still maintaining a commercially efficient node. There is nothing to suggest that public ownership *per se* would lead to a better and more efficient use of biobanks. The Umeå case if anything illustrates the contrary. With regard to ethical and legal rules, the Biobanks Act only regulates biobanks set up within the professional activities of a health care provider. However, the new Swedish law on ethical review will include all research with biological material. It is therefore recommended that private companies already now adjust their praxis to the provisions of the Biobanks Act.

5. Swedish law recognises both research interests and the interests of integrity

Elisabeth Rynning acknowledges in her report on public law aspects (ch. 5) that both patients and society have an interest in guaranteeing researchers and industry a favourable climate with ready access to research material and not too many cumbersome restrictions. Excessively onerous requirements may prevent the development of better treatment methods for future patients. Rynning also underlines the important point that the preservation of public trust is equally important for the development of science and good health care. Protecting the integrity of the donors and genetically related individuals is definitely in the long-term interest of both science and society. The need to balance research interests with integrity concerns is a central point in the Biobanks Act as well as other legislation. Rynning provides a detailed account of their relevance to human tissue sampling and biobank research. She and others are critical of the Act for being compromised by inconsistencies, general obscurities and other shortcomings, and the Biobanks Act will not be the end of a regulatory process regarding the use of biobanks. New legislation will have to be introduced shortly on the banking of samples from incompetent adults. The lack of regulation is ethically problematic, since it implies discrimination of incompetent persons in both health care and research. However, compared with the hitherto unregulated practice which has allowed room for private solutions and arbitrariness, we are now on more secure ground and eventually practitioners will find that the new law is both pragmatic and sufficient for meeting their needs of foreseeability and security in legal relations as well as in research ventures. The new law on ethical review will further prove this point.

6. The new legislation opens the way to pragmatic solutions and minimises the risk of arbitrariness

The health care providers are assigned the task of approving and registering all biobanks set up. It should be observed that, apart from general requirements of quality, traceability and provisions regarding sharing of samples, the Biobanks Act does not say how biobanks are to be geographically organised. This is an administrative question related to practical concerns and research interests. One and the same biobank may be located at different facilities. The health care provider is free to decide that another organisation, e.g. a research institution or a private company, shall administrate the biobank. However, the formal responsibility for registration still remains with the health care provider.

When the purpose of establishing a biobank is research or when samples already collected and stored will be used for research purposes, the research ethics committee must approve the sampling and the research project. How different interests related to this research should be balanced and what kind of information and consent procedures are appropriate have been much debated issues. Stefan Eriksson (ch. 8) provides an interesting overview of the public debate that preceded the Swedish legislation on biobanking and a broad presentation of standpoints and arguments proposed in the international scholarly debate related to informed consent. Private opinions, academic positions presented in scholarly journals and policy proposals from various ethical committees and bodies are presented. For a detailed account of the debates we refer to Eriksson's chapter. For a doctor, a

scientist, a member of the research ethics committee or a layperson it may be very difficult to set things right on the basis of this debate. It comes as no surprise if they experience a sense of arbitrariness in these ethical advices. However, even if the Biobanks Act does not impose any statutory restrictions on the discretion of the ethics committees, rulings by the committees themselves will not be arbitrary. As Ulrik von Essen describes in his chapter on legal guidelines for ethical practice (ch. 6), under the new Ethical Review Act (Government Bill 2002/03:50) examination by the new Boards for Research Ethics will constitute a task involving exercise of public authority and regulated by statute.

One general and important guideline is the 1996 European Convention on Biomedicine and Human Rights. As stated in the *travaux préparatoires* of the Ethical Review Act, this convention has been a beacon to the legislators. Article 22 of the convention lays down that: "When in the course of an intervention any part of a human body is removed, it may be stored 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". The question still remains, of course, what are *appropriate* information and consent procedures? Some guidance is obtainable from the explanatory report to the Convention, where it is explained concerning Article 22 (comment 137): "The information and consent arrangements may vary according to the circumstances, thus allowing for flexibility since the express consent of an individual to the use of parts of his body is not systematically needed. Thus, sometimes, it will not be possible, or very difficult, to find the persons concerned again in order to ask for their consent. In some cases, it will be sufficient for a patient or his or her representative, who have been duly informed (for instance, by means of leaflets handed to the persons concerned at the hospital), not to express their opposition. In other cases, depending on the nature of the use to which the removed parts are to be put, express and specific consent will be necessary, in particular where sensitive information is collected about identifiable individuals."

The focus in the explanatory report to Article 22 is on risks of damage and the handling of sensitive information. Ulrik von Essen has described the premises on which the ethical review shall be based, and the focus is similar to the explanatory report of the Convention. The central ruling of the Ethical Review Act is that a research project may be approved only if the risks entailed by it to the research subject's health, security and personal integrity are counterbalanced by its scientific value. The Board for Research Ethics will first consider the research on the biological material and then, separately, examine damage risks related to the handling of personal data. Regarding research on the biological material, a risk of harm will only arise in extremely exceptional cases. The only kind of harm is violation of personal integrity, and since the samples will as a rule be coded, this risk is minimal. However, as von Essen observes, if the samples are not coded or if the code may be broken at a later moment, the Board for Research Ethics will also carry out an ethical review of the project including any processing of sensitive data. When determining the risk, the board will assess the security in the processing of data and then acknowledge that if the principal investigator is a public representative, e.g. a university scientist, secrecy will apply to personal information about individuals. The degree of the risk of violation of personal integrity may then be considered low and the counterbalancing between risk of integrity violation and scientific value may normally lead to approval of the research project.

7. A Swedish standard for information and consent procedures

The key issue in the ethical review of biobank research concerns security in connection with the processing of data, and public confidence in biobank research may to a significant extent depend on understanding that sensitive information will not be passed on to insurance companies, employers, the police or other public authorities, or private companies not involved in the research project. Information regarding this kind of research should make clear that data will only be processed for research purposes. As several authors in the report mention, research subjects have a positive attitude to biomedical research and are often altruistically motivated to take part in research for the advancement of knowledge. Lena Ring and Åsa Kettis Lindblad describe in detail two large surveys, one of a representative sample of the general public comprising 6,000 individuals and one of a group of 2,000 diabetes patients (ch. 9). In their pilot study they showed that 89 % of the respondents would consent to donate an extra blood sample for research purposes and a majority of the respondents had a positive attitude towards genetic medical research. With all this and the provisions of the Ethical Review Act in mind, some conclusions may also be drawn regarding appropriate information and consent procedures.

Within the traditions of clinical ethics and research ethics since the Nuremberg trials, risk-exposure is a central element justifying the rules of informed consent. The research subject has a right not to be exposed to risks he has not accepted. In clinical trials the investigator is obliged to check for actual and potential short- and long-term risks to the research subject. After having done this properly and then explained the purpose of the project and carefully informed the research subject of any remaining risk, the investigator asks him if he is willing to assume this risk and participate in the project. When the risks are slight, an information and consent procedure based on an opt-out, or informed refusal model may be appropriate. When the risks are great and time is limited there is a well-established praxis in clinical treatment of presuming consent. Presumed consent is also used for research protocols with minor risks involved. Risk-exposure is a key concern of the ethical review.[3]

With regard to research using human biological material, the only significant potential risks are those related to violation of integrity and the potential spread of personally sensitive information. If these risks can be controlled, different versions of opt-out models of informed consent may be sufficient in most cases. Gert Helgesson (ch. 7) has examined and discussed the arguments regarding information and consent procedures. He suggests a Swedish standard based on the new laws with general information available about biobanking and research using biobanks. There will be four different consent forms: (i) consent to storing biological samples for diagnostic and treatment purposes (the doctor verifies the consent with a signature), (ii) consent to storing samples for future clinical use or for mapping purposes, e.g. the Tobias registry or storing of *ova* and embryos in connection with IVF-treatment, (the donor signs the consent form), (iii) consent to storing and using samples for specific research purposes (the donor signs the consent form) and (iv) consent to using existing samples for research where there is no previous consent (the donor signs the consent form). In all cases it is suggested that the donor may consent to future biomedical research with or without specified exceptions. If samples taken as

[3] Ibid.

part of routine care include a consent to biomedical research the Board for Research Ethics will normally not need to ask for renewed consent later on. Having regard to such security measures as stated in the Swedish Secrecy Act a broad purpose such as "biomedical research" is suggested as an acceptable result of counterbalancing low risk-exposure against the scientific value of the research.

8. The importance of agreements on disposition both over the biobanks and biological material

In the context of biobanks and other organ and tissue transplants we speak of "donors" and "recipients". The act of letting a hospital take samples or donating tissue or organs is in itself based on a positive personal decision or passive acceptance by the involved individual, or his or her close relatives. The person involved has the right to decide over the body or parts thereof. This leads us to think in terms of ownership and disposition rights. The immediate question a lawyer then poses is whether conclusions for these types of donations could be drawn from the terminological similarities and differences between the Gifts Act, including other private law rules on gifts, and the Transplant Surgery Act. The Transplant Surgery Act defines the conditions under which organs may be removed from the body of a living or deceased person for transplant or other medical purposes. However, the Act does not regulate the legal relationship between the donor and the donee. The Gifts Act regulates the validity of various types of gifts in the private sphere, and Annina H. Persson (ch. 11) focuses her study on whether such private law rules could be applied in regard of such donations of human biological material that are not governed by the Transplant Surgery Act or other public law legislation. Is the making of a gift an active giving and that of a donation a passive giving, and what are the similarities and difference between a donor of a gift in this general context and someone who donates human biological material? The main conclusion reached is that the Gifts Act and other general civil law rules on gifts, etc. are not really suitable to be applied to the donation of biological material. Notwithstanding that there are certain similarities between the general gifts and donations of biological material taken from living persons, the differences are nevertheless significant, not least as regards who can be the maker of a gift. Nor are the similarities between a donee of human biological material and the recipient of a general gift particularly striking. The conclusion of this in-depth study is therefore that the Gifts Act cannot be applied to opaque legal questions regarding the donation of biological material. This leaves us with an unregulated relationship between the donor and the donee, which makes the legal focus on the information and consent procedures all the more important.

When it comes to relations between medical companies and holders of biological material, such as researchers at universities and the like, the Biobanks Act has to a certain extent clarified the legal situation. For the perspective of commercial use of the biobank material, it is expected that the number of collaborations between companies and academia in respect of the biobanks will increase. But in order for collaboration to be successful and uncontested a number of problems have to be taken into account, namely: the prohibition under the Transplant Surgery Act and the Biobanks Act of deriving profit from handling donated human biological

material, the rules concerning ethical approval, the requirement of patient consent and the effect of withdrawal of consent. Experience on such issues is to a great extent lacking, and guidelines are obviously needed. So it is especially welcome that some of the most important, critical legal issues of this kind have been analysed by Urban Paulson and Rebecka Frisk (ch. 13). Their study covers both practical and theoretical aspects, including discussions of and proposals for the drafting of key clauses. Their conclusion is that, in particular, such key clauses dealing with rights of use and title to tangible research results, and structure of payments under the agreement, may now be drafted with a higher degree of legal certainty than in the past. But it must at the same time be emphasised that the legislation imposes heavy requirements on the prudent and knowledgeable negotiating and drafting of commercial agreements for valid access to and research on human biological material stored in biobanks.

Also in relation to questions of ownership of and disposition over biobanks, the drafting of agreements has proved to be vitally important. One striking example is the above mentioned case of Uman Genomics and the negotiations with Umeå University and the Umeå County Council. Who owns the biobank is otherwise a question that has so far been little discussed. The answer may in many cases be unexpected, and perhaps not what the holder of the biobank had bargained for (See Ulla Björkman's summary in ch. 12). A starting point is that the creation of a biobank is a work of the mind, and many such works enjoy protection under intellectual property law. In the intellectual property context, biobanks are regarded as protectable compilations, i.e. databases. Hence, the creator or maker of biobanks may be protected by exclusive property rights in the form of copyright or *sui generis* protection, respectively. The extent and the practical effects of such protection of biobanks are of importance to proprietors and users of biobanks, researchers, patients and others, since the rights holder may prevent certain acts involving the samples contained in the biobank. The ownership of intellectual property in biobanks and related materials resulting from scientific research is therefore of special interest and has formed the subject of a special study (ch. 10) by Åsa Hellstadius, Richard Wessman and Sanna Wolk. Not least the intellectual property rights of researchers employed at Swedish universities, governed as they are by the so-called Teacher Exception, require special attention. It is therefore recommended that the intellectual property rights be properly regulated by contracts in advance, just as regulation is needed concerning any other right to the material (right of disposition, use etc.) in a biobank.

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Regeringens proposition 2002/03:50 om lag om etikprövning av forskning som avser människor (2002) Stockholm.

2

Clinical data – a necessary requirement for realising the potential of biobanks

Bo S Lindberg, MD, PhD, former medical director

Akademiska sjukhuset (Uppsala University Hospital)

Advances in medical research result from a series of interrelated steps involving basic science, applied research and clinical investigation. Biological material banks are indispensable for the acquisition of new knowledge that will permit further development of diagnostic and therapeutic methods. Reliable clinical data including a structured anamnesis and family history, and the results of clinical examinations and laboratory investigations are prerequisites for realising the potential of such biobanks. A uniform terminology and computerised medical records make it possible to cross-match patient data with information from genetic studies. The clinicians have an important role to play in helping to make possible the exploitation of these new techniques to the benefit of present and future patients.

1. Introduction

Right on into the middle of the 19th century the dogma of humoral pathology from ancient times stated that diseases were due to an imbalance between the four body fluids: blood, yellow bile, black bile and mucus. One of the founders of modern medicine, the German physician Rudolf Virchow[1], contested that view in a famous publication on cellular pathology published in 1858.

Virchow stated that all diseases start in the cells, and this statement has had a revolutionary influence on medicine ever since. Virchow, a pathologist, used several staining techniques which enabled him to study human tissues in health and disease. Pathologists were the first, *avant la lettre*, to establish biobanks.

Few discoveries have had such a revolutionary influence on everyday medicine as Virchow's cellular pathology during the 19th century. The elucidation of the molecular structure of DNA[2] and the complete sequencing of the human genome are two of the most important achievements since then. Fifty years after Watson and Crick's description of the structure of DNA, the human genome was decoded. The genetic background of diseases has consequently been in focus during the last decades, and the importance of biobanks has grown correspondingly.

[1] Virchow, R. 1858.
[2] Watson, J., Crick, F. 1953

2. Biobanks in clinical praxis

Biobanks of relevance to patients may be categorised as derived from blood and from other tissues.

2.1 Blood

Since 1901, when Karl Landsteiner first reported on the ABO blood groups,[3] several hundred blood groups have been described and the antigens involved characterised. Other blood components such as leucocytes and platelets, as well as various fractions of plasma, have also been separated and stored in blood banks. Preservation techniques make it possible to store blood products for a long time. Supply of safe blood products is a prerequisite for most surgical procedures today. For safe transfusion, the blood groups must be accurately categorised. In rare cases, only a few possible donors in the world are known, but thanks to an international co-operation, their blood can be transported and given to the recipient anywhere.

Blood products can also be used for other purposes than surgery. Leukaemia (first described by Virchow in 1845) and some tumours sometimes call for bone marrow transplants. The Tobias Registry, the national registry of voluntary bone marrow donors in Sweden, was launched in 1992. This is one of many worldwide and there are more than seven million tissue-typed/HLA-typed potential donors in these registers. So far, around 300 members of the Tobias Registry have donated bone marrow containing haematological stem cells.

Long-term preservation(>15 years) of stem cells in blood drawn from the umbilical cord at birth is a new form of biobanks. Such blood can be safely used by the donor much later in life. Nine private banks devoted to the storage of umbilical blood have been founded today.

Analyses of anti-nuclear antibodies in serum are used in the diagnosis of rheumatic diseases and anti-neutrophil cytoplasmatic antibodies in vascular injuries, including glomerulonephritis and vaculitis. Other markers are of value, e.g. in the diagnosis of cardio-vascular and gastro-intestinal diseases, and in endocrinopathies. Samples must then be stored for re-examination for comparison in order to ascertain the effect of treatment and to diagnose relapses of the disease. Samples may also be used to detect new serum factors possibly associated with the disease.

A positive antibody titre may indicate past or current viral infection. Sera drawn within the first two weeks after onset are variably negative for IgG antibodies and should not be used to exclude an infection. The best evidence for infection is a significant change in titres on two appropriately timed specimens, where both tests are done in the same laboratory at the same time. In pregnancy it is important to exclude an infection at certain gestational weeks where the risk of foetal malformations is high. It is then particularly important to have stored sera in order to perform the analysis on paired samples.

2. 2 Other tissues

In many diseases an exact diagnosis is necessary before treatment starts. Biopsies are examined with techniques which have evolved enormously since Virchow's time. At departments of pathology all over the world, millions of tissue samples are stored

[3] Landsteiner, K. 1901

after the diagnostic procedures are completed. This storage is necessary mainly for the safety of the patient: a diagnosis may be questioned and a new analysis of the original sample may be performed, perhaps with a new technique or by another pathologist. New disease entities may also be detected in stored samples.

A patient who has been treated for a tumour may develop a new one. It is then important to establish if the original tumour has recurred or if there is a new disease. This distinction may be of vital importance for the patient. The specimens must then be stored for a very long time.

With modern techniques DNA samples can be prepared from histological material, a possibility that can further increase the value of the specimen.

3. Basic science and translational research

3.1 Genomic and proteomic studies in the diagnostics of diseases

Many diseases have been shown to have genetic causes, though those dependent on a single gene are few in number and concern a relatively small number of patients. When the genotypes of patients with a particular disease are analysed, several subtypes of the disease may evolve. This inhomogeneity of the patient material might be one explanation for the success or lack of success of treatment in some cases. Genetical and environmental factors frequently interact. Complex changes within the genomic environment as well as the external environment play a role. For diseases with late onset, even random biological changes may be of importance. It will be important in the future to provoke gene expression, in order to find which genes are turned on in different health and disease situations. Simple provocation could include diet, drugs and/or exercise. The response could easily be determined by DNA microarray-based techniques, which allow thousands of genes to be detected at once on a single microarray.

Genomic studies during the last few years have given rise to a deluge of information which have necessitated the careful storage, organisation and indexing of sequence information. Information science as applied to biology (bioinformatics and computational biology) involves the following:

- Finding the genes in the DNA sequences.
- Developing methods to predict the structure and function of the encoded proteins (proteomics).
- Clustering protein sequences into families of related sequences and the development of protein models.

3.2 Translational research

Translational research can be defined as applying knowledge gained from basic science to clinically relevant problems. Although recent years have seen an explosion of fundamental insights into the mechanisms of disease, transfer of this knowledge into practical advances in health care has moved more slowly. Translation also means the conveyance of clinical insights into hypotheses which can be validated in the laboratory. Genomic studies may clarify numerous new protein structures, but the function of these proteins for disease development has to be confirmed and established by studies on patients. Reliable clinical data are thus a necessary requirement for realising the potential of the biobanks.

3.3 Clinical trials

A clinical trial is a research study to find better ways of preventing and treating diseases. Clinical trials are usually classified in one of three phases. Phase I evaluates a new therapy for safety; when found safe, Phase II trials determine if the therapy is effective and what doses to use; and Phase III compares the therapy to current, standard therapy, or if possible to placebo. In all these phases, the patient and the doctor have important functions.

4. What kind of clinical information is needed?

The clinician has an important role in making the biobanks reliable as sources of information. What is needed is information about the patient's origin, their filiation, as well as medical, clinical and biological data. Genetic epidemiology needs large cohorts of hundreds or thousands of patients, but studies on well defined patient groups might be more cost-efficient. That requires the patients to be well characterised both at the molecular level and with regard to family history and life-style factors.

The patients do not present themselves with the same high precision as their genes may be sequenced. On the contrary, they appear as a huge group of individuals with varying complaints, influenced by their genetic heritage and social and environmental background factors. The task of the clinician is to find the needle in the haystack, the one that distinguishes one particular patient in a heterogeneous group. This requires the following:

4.1 Case history

All medical students are trained to take a careful anamnesis, but many doctors under time stress nowadays only ask questions which seem to be relevant to patients' present complaints. However, information that seems irrelevant for the moment may be of value later, perhaps many years later when new genetic information is available. When storing biological material from a patient, particular care will be needed in taking the anamnesis. There are certainly many factors, the importance of which is unknown at present, but the following must be paid attention to:

- Family history as stressed otherwise in the chapter.
- Previous diseases, e. g. hepatitis B and C and other infections.
- Diet plays an important role in many disorders[4]; cancer and cardiovascular diseases in particular. About half of all cancer deaths are due to four principal sites: lung, bowel, breast and prostate. These cancers are virtually absent in many developing countries but increase in incidence when migrants move from low to high risk areas. A consistent finding in most studies is that vegetables and fruit as well as a food rich in non-starch polysaccharides such as fibres reduce the risk of the most common cancers. There is also ample evidence that the same factors reduce the risk of cardio-vascular diseases. Similarly there is consistency for increased risk with high consumption of fat and meat, particularly when barbecued or otherwise burnt or fried.
- Smoking is the single lifestyle factor that has the greatest negative influence on health.

[4] Cummings, J.H., Bingham, S.A. 1998.

- Alcohol consumption is also an important health factor, but as with many lifestyle factors, it is difficult to obtain a true estimate of the real intake. Special interview techniques are needed in order to make the patient overcome his feeling of shame.
- An ideal body weight is important for well-being. Overweight increases the risk of premature death due to both cancer and cardio-vascular diseases and an increased body mass index (BMI) is a risk factor correlated to many other diseases as well. BMI is the weight in kilograms divided by height in meters squared (kg/m^2). Ideally the BMI should be between 19 and 25. Underweight increases the risk of certain diseases e.g. osteoporosis. Overweight is defined as a BMI between 25 and 29,9 and obesity above 30 kg/m^2.
- Physical activity decreases the risk of both cardio-vascular diseases and cancer.
- Drug intake (including birth control pills). Adverse drug reactions are an important cause of admittance to hospitals and to death in many countries. Some reactions may become manifest months or years after exposure. Particular vigilance is required to identify adverse reactions in the elderly. They may metabolise medicines less efficiently and be more sensitive to their effect. Also they often take a number of medicines, and are therefore likelier to encounter drug interactions. Children are another group that requires special attention. Many drugs routinely used are not licensed for use in children. An accurate drug intake history is necessary for making full use of the pharmaco-genetic techniques in the biobanks.
- Herbal remedies. Although some herbal medicines are licensed for use, there are many herbal remedies on general sale. Some of them interact with drugs or cause damage to the liver and other organs. In many countries, a substantial number of people use herbal remedies but do not tell their physicians unless explicitly asked. It is important that the use of herbal remedies and all suspected adverse reactions to them be reported so that their safety can be monitored.

4.2 Laboratory investigations

In ordinary laboratory praxis, reference values are given with 95% confidence limits. Accordingly, 5% of the population fall outside this arbitrary limit and are by definition considered extreme cases. This group may conceal patients with some form of important genetic deviation. Their results should therefore not be dismissed as due merely to random variation, but be scrutinised by combining clinical data with bioinformation.

4.3 Uniform terminology

Without a uniform terminology of symptoms, signs and diagnoses, even the most scrupulous anamnesis is of limited value. The medical profession has an obligation to try to agree on common definitions for most of the terms used in clinical praxis.

4.4 Computerised medical records

In most laboratories today computers are used when reporting the results of chemical, bacteriological, viral and other analyses. In order to make clinical data available, electronic information must be used in clinical work, much in the same way as it is used in bioinformatics. Up till now, most medical records have been stored in paper form. Consequently they have not been available for large-scale information searches. Computerised medical records make it possible to search by

specific terms or expressions, which always should have the same meaning in all records. Sweden has more than 20 different data systems in use. They must be made compatible to communicate with each other. These are difficult goals to achieve but are absolutely essential if the full potential of the biobanks is to be realised.

When new mutations or new biochemical markers are found, this information can be cross-matched with the information from previous patients' case histories and laboratory findings in the medical records. In this way, future patients will benefit from new discoveries.

5. Examples of diseases and the need for clinical and related data

Many diseases may be heterogeneous, even if we are unaware of it at the moment. The potential of all new techniques as applied to samples in the biobanks is that the diagnostics will be refined which will lead to a more causal therapy. I will turn now to discuss some diseases in more detail and stress the data that is needed in order to characterise the groups.

5.1 Breast cancer

Breast cancer is considered to be a multifactorial disorder caused by both genetic and non-genetic factors. The risk of an individual developing breast cancer may be estimated from her family history. The following aspects may be used to identify average-risk, moderate-risk and high-risk individuals:

- Number of relatives affected.
- Ratio of affected and unaffected relatives.
- Biological affinity of relatives affected.
- Ages at cancer diagnoses.
- Presence of bilateral/multifocal breast cancer.
- Presence of ovarian cancer.
- Number of children (pregnancies).
- Use of birth control pills.

Individuals with a high risk of developing breast cancer may wish to have a genetic test performed. It is the responsibility of the clinician to provide information before the test. The importance of providing information and obtaining consent prior to performing tests for cancer-predisposing gene mutations has been emphasised by several expert groups.

5.2 Cardiovascular disorders

Cardiovascular diseases are a result of lifestyle factors such as diet, smoking habits, alcohol abuse, stress and lack of exercise, but genetic factors also play a role. It is possible to estimate the risk likelihood by observing the outcomes in other family members, that is the empiric risk. If several members of a family have cardiovascular diseases, the probability increases that there is a genetic component. The possibility of other family members having an increased risk depends on:

- The type of heart problem.
- The number of affected family members.
- The closeness of the relationship.

- At what age the heart problems first occurred (in the individual and his or her relatives).
- The presence of other health problems.

5.3 Metabolic disorders

Metabolic disorders have a great impact on the risk of cardio-vascular diseases. Prominent among these are diabetes and obesity.

5.3.1 Diabetes

5.3.1.1 Diabetes type I (juvenile onset diabetes)

The following factors should be considered:

- Family history. In diabetes type I, the inheritance factor is relatively small, although a family history of diabetes increases the risk of developing the disease, but no single gene has been confirmed to be the main cause.
- Previous infections. Type I diabetes often appears after a virus infection.
- Drugs. Some drugs are thought to cause diabetes, such as pentamidine, used to treat pneumonia and L-asparaginase, used for treatment of cancer.
- Diet. It has been speculated that feeding infants with cow's milk may increase the risk of developing type I diabetes, which is an auto-immune disease. The infant's immune system may produce antibodies against the cow's protein. Due to similarities between this and the protein on the surface of the pancreatic beta cells, these antibodies may destroy the beta cells, causing diabetes.

5.3.1.2 Diabetes type II

Diabetes type II is a genetically complex disease involving multiple genes and multiple gene-environment interactions. In the case history, the following factors should be paid attention to:

- Family history of diabetes.
- Obesity, which is by far the most important cause of type II. Obesity is thought to increase the insulin resistance. People carrying their fat above the hip (apple-shape) with a waist-hip ratio above 0.9 have a greater risk than pear-shaped people with a waist-hip ratio below 0.7.
- Diets high in fat can lead to diabetes, but excess calories in any form are stored as fat, which increases the risk of diabetes.
- Age greater that 45 years increases the risk, but there is now a rapid increase in the juvenile group due to obesity and a diet of products with high glycaemic index.
- Ethnic groups. Some ethnic groups, such as aboriginals, native Americans, African- and Hispanic Americans have an increased incidence of diabetes type II in association with obesity.
- High blood pressure.
- Diabetes during pregnancy or a baby weighing more than 4 kg.

5.3.2 Obesity

Obesity is increasing rapidly in many countries and implies an increased risk of complicating diseases and premature death. The WHO[5] has recently assessed the

[5] WHO World health reports 2002.

global burden of disease from 22 health risk factors. A sedentary lifestyle is one of the ten leading causes of death and disability in the world and also a leading cause of obesity. Physical inactivity is often combined with a high consumption of fat, the obese individuals eating more than they need. The main cause of this overeating is the intake of rapidly absorbed carbohydrates, which leads to a peak in insulin production, which in turn rapidly makes the individual feel hungry again due to low blood sugar levels. This is a global problem and WHO has defined obesity as a worldwide epidemic.

There are several other reasons for obesity, including genetic, psychological, cultural, metabolic and environmental factors. If some environmental variables manifest themselves only in certain genotypes, efforts to prevent obesity at a public health level can be focused on recognition and counselling of susceptible individuals. In addition, appreciating the importance of genetic variation as an underlying cause helps to dispel the notion that obesity represents an individual defect in behaviour with no biological basis at all, and provides a starting point for efforts to identify the genes involved[6]. Why are interventions based on diet and exercise more effective for some people than others? What are the biological differences between these high and low responders? How do we use these insights to tailor interventions to specific needs? Interventions that prevent obesity are important and physicians have an obligation to work in a very systematic way in order to deliver well-categorised material to biobanks devoted to studies of this important health problem.

5.4 Prostate cancer

Prostate cancer is the second most common cancer in many countries. Epidemiological studies indicate that dominantly inherited susceptibility genes with high penetrance cause 5-10 % of all prostate cancer, and as much as 40% of early onset disease. Probably environmental factors play an important role. The risk of prostate cancer is strongly affected by the family history such as:

- The number of relatives affected.
- Ratio of affected and unaffected relatives.
- Biological affinity of relatives affected.
- Age at cancer diagnoses.

A greater number of family members affected and early onset among family members are the most significant predictors of risk of prostate cancer. Current evidence does not justify screening asymptomatic men for prostate cancer, but men with a strong family history must be informed by their physicians of the benefits and risks of early detection and treatment. A methodological approach is needed in taking the family history as well as in the diagnostic procedures. Clinical data and the results from genetic studies give the potential for directed research into the causes of prostate cancer and for refinements in the current screening practices to detect this common disease. Prostate cancer highlights many of the ethical, emotional and pragmatic controversies in medicine concerning screening. It is important to remember that most men die with their cancer, not because of the cancer.

[6] Barash, G.S., Farooqi, S., O´Rahilly, S. 2000.

5.5 Inflammatory disorders

Many inflammatory diseases such as the spondyloarthropathies (ankylosing spondylitis, Reiter syndrome, reactive arthritis, psoriatic arthritis, and spondyloarthropathies associated with inflammatory bowel disease) are linked to the HLA-gene. These diseases instance the fact that the expression of the genetic trait is modified by environment. They are more widespread among people in countries where red meat is commonly eaten (e.g. Europe and USA), but are very rare in those parts of the world (e.g. Asia) where wholegrain, fruits and vegetables make up most of the diet and dairy products are rarely eaten. When people emigrate from Asia to western countries and adapt a westernised diet, arthritis becomes common among them.

5.6 Mental disorders

5.6.1 Mental retardation

Patients with mental retardation belong to a very heterogeneous group and the majority of them do not have a specified diagnosis. It is then particularly important to use biobanks to refine the diagnostic methods in order to find a causal therapy in many more cases than at present. A careful anamnesis and a clinical and laboratory investigation may distinguish a particular group within the large group. An illustrative example of this is patients with Salla disease, a lysosomal storage disorder[7]. Salla disease is named after the area in Finland from which the first patients originated. They were detected thanks to careful clinical investigations. Within the first two years of life the patients present with psychomotor retardation, ataxia and hypotonia. Most patients survive to adulthood, but with severe mental retardation.

5.6.2 Dementia

More than 50 diseases are known to be associated with dementia, Alzheimer's disease being the best known of them. Since the discovery of the amyloid precursor protein in 1991[8] , our understanding of the disease process has increased enormously. Similar progress has occurred in other types of dementia, making it possible to tailor therapies if only the clinical data are good enough to select the right individuals (patients and concerned relatives) for genetic testing and subsequent early treatment. At present, too many patients with dementia do not have a specified diagnosis.

5.6.3 Psychiatric disorders and alcohol abuse

Genetics is a rapidly expanding area of psychiatric research. Understanding the molecular neurobiology of psychiatric disorders may lead to the development of more specific drugs. In many psychiatric disorders and in alcohol abuse, genetic factors are suspected, but so far, a direct genetic link has not been identified. In these disorders, it is particularly important to have great respect for the integrity of the patients.

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[7] Aula, P., Aution, S., Raivio, K.O., Rapola, J., Thoden, C.J., Koskela, S.L., Yamashina, I. 1979.

[8] Goate, A., Chartier-Harlin, M.C., Mullan, M., Brown, J., Crawford, F., Fidani, F., Giuffra, L., Pericak-Vance Haynes, A., Irving, N., James, L., Mant, R., Newton, P., Rooke, K., Roques, P., Talbot C.M., Roses, A,, Williamson, R., Rossor, M., Owen, M., Hardy, J. 1991.

6. Pharmaco-genetics

Clinical trials try to monitor for potential adverse reactions during the development of a drug, but it is inevitable that their limited size will not catch all potential patient-drug interactions.

The effects of drugs vary widely among patients. It is difficult to determine whether a drug has a beneficial effect and is safe for a specific person. One of the first studies where genetics were used in drug development was published in 1997[9] . A drug was tested against Alzheimer's disease. The authors studied 108 subjects and found that the drug had no effect. Then they subdivided the patients into two groups, one of which had a variant of a certain gene while the other did not. The analysis then showed that the beneficial effect of the treatment was confined to the group with the variant gene. Genetic testing is supposed to have a great potential for tailoring drugs in the future. Instead of the trial-and-error medicine of today, doctors will be able to analyse an individual's genetic profile and prescribe the best available therapy from the beginning at a dose based on the patients genetics.

The importance of clinical observance is illustrated by the Thalidomide® tragedy, even if genetic factors were not involved. Thalidomide® was marketed in the late 1950´s as a sleeping pill and to treat morning sickness during pregnancy. In 1961, it was discovered that an increasing number of babies were being born with a new type of malformation. A common denominator was that their mothers had taken Thalidomide®. In fact, just one dose taken early in pregnancy severely affected the growth of foetal limbs and caused injures to the eyes, heart, kidney and other organs.

7. Gene therapy

Many fatally ill people have centred their hopes of cure on gene therapy. So far these hopes have been fulfilled only at a very limited extent, but perhaps the therapy will outgrow its problems, just as other technologies have done.

8. What is the task of the physician?

It should be clear from this overview of some of the more common diseases with a proven or suspected genetic connection that the clinician has a task involving great responsibility. Physicians have a responsibility to remain aware of current advances in biomedical sciences and to understand the application of promising new ideas to clinical medicine. It is their responsibility to ensure that the background factors for the patients delivering samples to the biobanks are collected and presented in a systematic way so that the potentials of the promising new genomic techniques can be fully realised.

Because humans do not form homogenous populations, genetic differences can be found between and within groups, and the borders between health and

[9] Richard, F., Helbecque, N., Neuman, E., Guez, D., Levy, R.1997.

disease are not always distinct. Polymorphism means inter-individual differences in DNA sequence that may underlie differences in health. A few disorders are caused by mutation of a single gene, most have a polygenic background. Polygenic disorders result from the combined action of alleles of more than one gene. Although such disorders are inherited, they depend on the simultaneous presence of several alleles and the hereditary patterns are more complex.

When researchers are studying a group of individuals, they try to find something that is common among the members of the group and that differentiates the group from other groups. The patients must be categorised in such a way that the analyses are performed on those samples that have the greatest chance of explaining why some people get ill and how to prevent it. Both present and future patients will then benefit.

When the human genome was decoded President Bill Clinton said: "Today we are learning the language in which God created life," and proclaimed a new Canon, The Book of Life, written in a four letter language. The genome consists of a complete set of instructions for making an organism. Random changes in this instructions may cause a disease, but diseases in humans are much more than that. The genotype corresponds to one model of disease, and the phenotype to another. In the person who is consulting a physician the genotype is modified by all the social, spiritual, mental, intellectual and environmental factors affecting a human being during his or her life.

Genetic characteristics have a strong symbolic significance. They signify the past (ancestors), the present (representation of self) and the future (descendants). Physicians occupy an intermediary position: they have to mediate between the necessity of scientific progress and the responsibility of ensuring that the patients' human dignity is maintained. How can we reconcile, in practice, the protection of people's integrity and private life with medical imperatives and public health when using the genetic markers? Physicians have to integrate the rules of good care and research practices with ethical values when utilising biobanks.

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3

Examples from Swedish biobank research

Magnus Kaijser, PhD

Karolinska Institutet
Department of Medicine at Karolinska Hospital, Clinical Epidemiology Unit

This article, exemplifying the variety of questions that can be addressed through the use of Swedish biobanks, consists of a categorisation of how Swedish biobank material is collected and examples of studies based on such material. Research methods, consent procedures, and potential causes of misleading results are discussed in commentaries on the studies.

1. Introduction

There is a broad variety of biobanks in Sweden, ranging from small collections of biological specimens assembled from specific subsets of patients, to the hundreds of thousands of samples collected annually within the frames of various screening programmes. A small minority are established exclusively for research purposes, but the purpose of the overwhelming majority is to enable hospitals, medical laboratories, and other health care institutions to provide accurate diagnostics and safe care. Regardless of their main purposes, however, these biobanks have proved to be an invaluable tool for medical research.
Below follows a categorisation of how Swedish biobank material is collected. In connection with each category, examples are given of studies based on such material. For each example there is an explanatory commentary focusing on the additional data required to conduct the study, consent procedures, and how the choice of methods may have influenced the results.

2. Collection of Swedish biobank material:

I. Material collected for diagnostics
a. Screening of healthy (e.g. PKU-tests and cervical cancer screening)
b. Diagnostics of suspected disease (e.g. biopsies and bacteriological tests)
c. Follow-up of known disease (e.g. serological tests of patients with rheumatoid arthritis)
II. Material collected for future clinical and diagnostic use (e.g. stored ova from assisted reproduction and blood samples for testing potential kidney transplant recipients)
III. Material collected for mapping (e.g. register of potential bone marrow donors)
IV. Material collected exclusively for research
a. In health care

i. from patients (e.g. blood from patients with diabetes)
ii. from deceased individuals (e.g. brain tissue)
iii. from healthy individuals (e.g. control material to other studies and health intervention studies)

b. In biomedical companies (still uncommon)

3. Examples

I a) Research on material collected through screening.

Example 1

Background	It is well documented that human papillomavirus (HPV) can often be detected in tumours of the uterine cervix. But what is cause and what is effect? A person with cervical cancer could be predisposed to infection, rather than the virus being a risk factor for cancer.
Methods	Through linkage between a cytology registry and the Swedish Cancer Registry, all women residing in Västerbotten County who had participated in the screening programme for cervical cancer, had cytological smears preserved and later developed cervical cancer could be identified. For each case a control was selected that had also participated in the screening programme but not developed cancer. The cytological smears from cases and controls were then compared with regard to human papillomavirus infection.
Results	There was a sixteen-fold increase in risk of developing cervical cancer among those infected at the time of examination compared to those who were not. The virus is thus more likely to cause cancer than to be an effect of it.
Consent	A press conference was held at which the study plan was presented. Women who did not want to participate were in this way given the option of being excluded. *(Wallin et al., 1999)*

Comments

This study exemplifies the use of biobank material originating from healthy individuals. The material was collected within the frame of a cervical cancer screening programme, and cervical cancer is the topic of the study. Further insights in the aetiology of this cancer form can be expected to lead to improvements of the screening programme per se. The study is also an example of the use of the so-called "opt-out" method of informed consent. Since infection with human papillomavirus can be positively associated with life style factors that by themselves are negatively associated with active participation in studies, the choice of a different consent procedure would probably have led to misleading results.

In order to conduct the study, the authors needed the following information:

1. national registration numbers of all women participating in the screening programme,

2. the results of the screening,
3. archived cytological samples from the screening, and
4. cancer registry data on cervical cancer incidence among the women.

The samples were taken during the period 1969 through 1995 and the results from this screening were linked to cancer registry data from 1995. Since the cancer registry data are upgraded annually, this study would have been impossible if the cytological samples had been stored in coded form and the coding keys destroyed. Adding data at the time of sample collection would be of no help, since cancer registry data were based on events occurring up to 26 years after sample collection.

Example 2

Background	Human papillomavirus is also suspected to be a risk factor for anal cancer. The strength of this alleged risk factor is, however, unknown.
Methods	By use of two large serum banks in Norway and Finland, it was possible to test sera for antibodies against human papillomavirus. In total, sera from 28 cancer cases were compared with sera from 1,500 controls.
Results	There was a three- to fourfold increase in risk of anal cancer among seropositive patients compared with seronegative.
Consent	This study had approval from the ethics committee to be performed without informed consent. *(Bjorge et al., 2002)*

Comments

This study is similar to the previous example, except that the focus has shifted to another cancer form. This study could thus be considered to have a new purpose. It was conducted without informed consent, but the "opt-out method" could have been used. If the researchers had been obliged to obtain fresh informed consent from each of the more than 1,500 patients that participated, practical and economical concerns would probably have made this study impossible. For the same reasons as mentioned in the previous example, it is also likely that the study would have led to misleading results.

Example 3

Background	With the increasing public awareness that smoking is hazardous for health, it can be suspected that a growing number of individuals will be unwilling to tell the truth about their smoking habits. Smoking during pregnancy increases the risk of both growth retardation and miscarriage. In antenatal care, under-reporting of smoking habits could lead to pregnant smokers not being given important information and high-risk pregnancies remaining undetected. It is, however, unclear whether under-reporting of smoking in antenatal

Background (cont.)	care is of such magnitude that it can be considered a problem. It is also unknown to what extent pregnant women are exposed to environmental smoke, and if environmental smoke exposure has consequences for foetal and infant health.
Methods	Cotinine is a metabolite of nicotine that can be detected in the circulation several days after nicotine exposure. By assessing blood levels of cotinine, active as well as passive smokers can be distinguished from non-smokers. Since blood samples are taken from all women participating in antenatal care, the accuracy of self-reported smoking habits can be validated through comparison with cotinine levels in these blood samples.
Results	Of the women professing to be non-smokers, about 6% were likely to be smokers, and at least 3% were likely to be exposed to environmental smoke. For about a third of the women who reported smoking 1 to 10 cigarettes per day, their daily consumption was likely to be higher.
Consent	All women were asked for informed consent, and 97% were willing to participate. *(Lindqvist et al., 2002)*

Comments

This study is interesting in several ways. Many women would probably consider it intrusive if their blood samples were used to check whether they reported smoking habits truthfully or not. On the other hand, the study can be considered as a mere validation study, serving to check how well the diagnostic procedures operate. From this point of view, a study assessing how good questions are for distinguishing smokers from non-smokers can be compared with studies assessing how good a chest x-ray is for detecting pneumonia. The study was based on informed consent, and the non-participation rate was very low. If the non-participation rate had been higher, the results would probably have been misleading. It is noteworthy that the study was conducted with coded blood samples and that the researcher performing the cotinine analysis had no access to the code key. By this procedure, results from the cotinine analysis were kept separate from the identity information, and the risk of invading the participants' privacy was reduced to a minimum.

I b) Research on material collected from tests of suspected disease

Example 4

Background	Bartonella bacteria are known to cause diseases such as cat scratch disease and trench fever. More recently, new Bartonella species have been discovered, but it is insufficiently known to what extent these new species also infect humans.

Methods	All blood samples sent to the clinical microbiology laboratory at the Uppsala University Hospital to be tested for Bartonella were reanalysed using new and improved methods. A tissue sample from a man deceased in myocarditis was also analysed. As controls, blood from healthy blood donors and tissue samples from patients without myocarditis was used.
Results	When analysing the materials by improved methods, a number of samples previously considered free from bacteria were found to be infected. The man who died of myocarditis also proved to be infected. The association between Bartonella infection and myocarditis was previously unknown.
Consent	The reanalysis of the samples was conducted without informed consent. *(Holmberg et al., 1999)*

Comments

Since the blood samples were initially taken in order to be tested for Bartonella, and the task of the investigators was to perform a more thorough Bartonella analysis, this study could be partly considered as pertaining to the original analysis. Under the new legislation on ethical committee evaluation, however, this study is to be considered as research requiring ethical committee approval. To find out whether the newly discovered bacteria infect humans, coded blood samples without any access to the code key would have been sufficient. Such a procedure, on the other hand, would have made it impossible to follow those who were infected, which, in turn, could result in these patients receiving inadequate care.

Example 5

Background	Celiac disease, or gliadin (gluten) intolerance, affects about 1 in 250. The disease entails gastrointestinal symptoms, lesions of the intestinal mucosa, and, if untreated, malabsorption. Treatment consists of life-long abstinence from gliadin containing food. Since such treatment has profound consequences for the patients, the accuracy of the diagnosis must be extremely high. At present, the diagnosis is based on a total of three small intestinal biopsies for children and two biopsies for adults. A large proportion of patients with celiac disease develop the disease as infants, and for these infants, the relatively large number of biopsies are a cause of much suffering. By assessing the levels of antibodies against gliadin, among other substances, patients with low probability of having the disease can be identified and hence the number of unnecessary biopsies reduced. The methods for assessing the antibodies, however, are rather complicated and time-consuming. Newer tests that are easier to handle have been developed, but before using them in clinical practice, it is important to be sure that their quality equals that of the tests used in current praxis.

Methods	In the paediatric wards of Linköping and Umeå University Hospitals, there were 133 children who had undergone celiac disease investigation for which small intestinal biopsies and blood samples were preserved in a biobank. By using the blood samples, two newly developed tests for gliadin antibodies were compared with the methods used in current practice. The results of the biopsies were used as gold standard.
Results	For children who were not on a gliadin-free diet, a negative blood test according to the new methods showed the risk of having the disease to be below 1 per cent. The new tests thus have the same accuracy as the methods currently used.
Consent	The children's parents consented to an initial study on celiac disease and no new consent was obtained for this study. *(Grodzinsky et al., 2001)*

Comments

As in the example above, this study is a reanalysis of tests performed previously. The scope of the study is to assess the accuracy of tests used to decrease the number of unnecessary biopsies. To perform the study, the researchers had to have access to:

1. repeatedly taken blood samples,
2. collected material from three consecutive biopsies, and
3. medical record data.

The study was conducted without obtaining fresh informed consent and therefore had no missing data due to non-participation. Non-participation in this kind of studies could constitute a serious problem, since the non-participation can be associated with other factors capable of affecting the results. A hypothetical example: If children exposed to cigarette smoke at home have lower levels of antibodies in their blood, a new test for antibodies could be of less precision when used on these children. If non-participation is higher among children whose parents smoke, the new test would then appear to be more precise than it actually is. If such a new test is introduced after evaluation in studies that all have the same kind of non-participation, the result may be a lower quality of care for children of smokers, since the celiac disease of these children may pass undetected.

Example 6

Background	Peanut allergy is considered the commonest cause of fatal food anaphylaxis. In spite of peanut consumption in Sweden being relatively low, there are indications of an increasing prevalence of peanut allergy. Whether this is true or not, however, has not been sufficiently studied.

Methods	Approximately 94,000 tests on food allergy were performed at the Allergy Laboratory , Sahlgrenska University Hospital, Göteborg, between 1994 and 1998. Among these, all tests for peanut allergy were identified. A sample of patients with positive results were also contacted and given questionnaires about their age at allergy onset, the type and severity of symptoms etc.
Results	The number of tests for peanut allergy increased during the study period, and so did the proportion of positive tests. Peanut allergy is as common in Sweden, a low consumption area, as it is in countries where consumption is substantially higher. Of those who tested positive, 40% were unaware of their allergy before taking the test.
Consent	For the study of numbers and results from peanut allergy tests, there was no informed consent. For those answering the questionnaires, the researchers first had the referring physician's permission to contact the patients and then the consent of the subjects themselves. *(van Odijk et al., 2001)*

Comments

This study had two aims. The first was to assess whether peanut allergy prevalence has increased over time, and the second was to gain further knowledge of the symptoms associated with peanut allergy. Through the questionnaires, the researchers succeeded in the second aim. The study cannot, however, be considered to have answered the first question with certainty. Since only tests that were originally designated to assess peanut allergy status were included, the study is based on a selected material. It is conceivable that peanut allergy prevalence remained constant during the study period, but the referring physicians have learnt better to decide who is to be tested. In order to assess whether peanut allergy prevalence has increased over the last 5 to 10 years, one should use other material, such as blood samples collected in antenatal care or from blood donors. Such a study could be conducted without any identity information, provided that no additional information is needed from those tested.

I c) Research on material collected in connection with treatment or follow-up of a known disease.

Example 7

Background	Pheochromocytoma and paraganglioma are tumours producing catecholamines such as adrenaline. The great majority of the tumours are benign and are cured by surgery. In approximately 10% of the cases, however, the tumour grows invasively or develops metastases. It would therefore be of great value if a prognostic marker of malignant transformation were to be detected.

Methods	All 85 patients operated for pheochromcytoma or paraganglioma at the Karolinska Hospital, Stockholm, during the period between 1976 and 1999 inclusive were followed with regard to tumour progression and survival. Molecular biology analyses were performed on stored material from removed tumours. Some of the patients were also interviewed through mailed questionnaires.
Results	Two promising markers of malignant transformation were identified. In the future, use of these markers may be a tool for better prediction of which patients with pheochromocytoma or paraganglioma that are at risk for malignant disease.
Consent	The biobank was established on the basis of informed consent, and informed consent was also obtained for this study from all patients who were still alive. *(Edström Elder, 2002)*

Comments

This study exemplifies the use of material collected in connection with treatment. To perform the study, the researchers needed to have access to:

1. the Register of Population and Population Changes,
2. the Cause of Death Register
3. tumour material
4. addresses, and
5. medical record data.

The initial response rate was 89%. Since the number of patients in the study was limited, it was feasible to contact all non-responders by telephone. After this, the response rate increased to an astonishing 100%. Since the total number of patients was small, the number of patients with metastatic disease was even smaller. The smaller the number, the greater is the risk of chance affecting the results. In this study, such chance effects may include promising markers remaining undetected, as well as markers of no clinical value appearing to be associated with metastatic disease. To be certain of the prognostic values of the promising markers identified in this study, larger numbers of patients are needed. This, on the other hand, requires research protocols, including consent procedures, that are feasible on a larger scale.

Example 8

Background	Treatment for breast cancer includes intensive chemotherapy which can be very agonizing for the patient. The effect of this chemotherapy varies between individuals, and to avoid unnecessary use of chemotherapy, better methods for identifying patients who will not respond to treatment are warranted. An important step in cancer development is when there is a mutation in a gene called p53. This gene regulates the production of a protein that prevents

	unlimited cell growth. If there is a mutation in the p53 gene in a cell, this cell may start to grow and divide without cessation, and cancer may follow. There is a theory that the effect of breast cancer chemotherapy depends on where in the p53 gene the mutation has taken place.
Methods	By using the polymerase chain reaction technique (PCR), the p53 gene could be sequenced in stored tumour material from breast cancer patients. This enabled identification of where in the gene the mutation had occurred. The patients were then followed with regard to effect of treatment and survival.
Results	Mutations in some regions of the p53 gene were associated with both poor prognosis and poor effect of treatment. Intensive chemotherapy that seriously affects quality of life can therefore be of less value to patients with these mutations, since the effect of treatment is limited.
Consent	This study had approval from the ethics committee to be performed without obtaining informed consent.
	(Bergh et al., 1995)

Comments

This is a variant of the previous example, but in this study the researchers also wanted to evaluate the effect of currently used therapies. To perform the study, the researchers needed tumour material and medical records. Avoidance of unnecessary suffering must be a primary goal of all medical care, and it is therefore essential that this kind of studies can be performed with high quality also in the future. If the participation rate is associated with treatment, such as women with little effect of treatment being less willing to participate in the study, the results from the study will be flawed. This could lead to women with breast cancer being exposed to agonizing treatments that has little or no effect.

Example 9

Background	Leukaemia is a blood malignancy with an unlimited production of defective leukocytes (white blood cells). Chemotherapy for leukaemia is based on medication that kills leukocytes. If successful, treatment will kill all defective leukocytes, whereas there are enough healthy stem cells left to enable leukocyte production once the chemotherapy is stopped. There is a risk, however, that the killing of leukocytes may have long-standing effects on antibody production. This could lead to loss of immunity to a number of diseases, such as measles and rubella, for example. Measles and rubella are normally quite uncomplicated when affecting children. For adults, however, they may lead to meningitis and sterility.

Methods	Blood samples from 43 children who had been successfully treated for leukaemia were assessed for antibodies against measles and rubella. Prior to disease, all children had been immunised in the national immunisation programme, and they had donated blood samples before, during, and after treatment.
Results	As many as 40% of the children lost immunity against measles, and 30% lost their immunity against rubella. If the children were immunised de novo, however, they regained their immunity.
Consent	The parents of all participating children had given consent to the study. *(Nilsson et al., 2002)*

Comments

The topic of this study is no longer the disease for which the patients were treated, but their immunity against other diseases. If the biobank used in this study was designated for research on leukaemia, this study may be considered as having a new purpose. On the other hand, the study can be regarded as a mere follow-up of the patients who had been treated. It is noteworthy that non-participation in this study may lead to a loss of immunity that goes undetected. To answer the question of whether one can lose immunity after chemotherapy, coded blood samples are sufficient. Such a procedure, however, would have made it impossible to offer re-immunisation to those who had lost their immunity.

II) Research on material collected for future use and diagnostics.

Example 10

Background	In the mid-1990s, a new virus was discovered that was suspected of causing hepatitis. If the virus causes hepatitis, screening all blood donors for this virus may be warranted.
Methods	Blood from blood donors, used in an earlier study on another hepatitis-causing virus, was tested for the new virus. A total of 600 blood samples collected from blood donors in Malmö during the period 1992 to 1994 were tested and of these, 18 were found positive.
Results	Some of the patients who tested positive showed signs of liver disease, but the results as a whole were that there are no reasons for testing all blood donors for this new virus.
Consent	For reanalysing the blood, there was no informed consent, but all who tested positive consented to continued follow-up and 13/18 even consented to undergo a liver biopsy. *(Bjorkman et al., 2000)*

Comments

This study exemplifies routine use of stored biological samples. The risks entailed by not doing this kind of research are obvious, since patients receiving blood thus would be in peril of being infected. In this study, the reanalysis of the blood was done with coded samples and the code was broken only for those who tested positive. By doing so, the researchers could reduce the risk of privacy encroachment to a minimum.

Example 11

Background	It is known that cadmium, lead, and mercury can be accumulated in the kidneys and have negative effects on kidney function. Most earlier studies, however, have used material from autopsies. Since autopsies are performed on a selected material for some prior reason, it remains unknown to what extent cadmium, lead, and mercury are also accumulated in the kidneys of healthy individuals. Kidney levels of these metals can only be assessed through biopsy, a procedure seldom performed without strong reasons.
Methods	Stored biopsies from kidney transplants with living donors were analysed. The kidney donors were also given questionnaires about occupational history and environmental exposures.
Results	The levels of cadmium, lead, and mercury were in concordance with earlier reports, and previously described causes of accumulation were confirmed.
Consent	This study was conducted without informed consent. (Barregard et al., 1999)

Comments

This study raises some interesting questions. Which patient should be asked for consent, the one who donated the kidney or the one who actually carries it? Just as some genetical tests can cause ethical concern by providing information not only about the patient, but also about his or her parents, siblings and offspring, this study does. One can pose a patient a number of questions about the kidney that now belongs to another. Who shall give consent to storage in a biobank?

III) Research on material collected for mapping:

Example 12

Background	Short tandem repeats are sequences of DNA that are abundant throughout the genome and vary widely between individuals. Due to this variety, they can be used to improve the accuracy of kinship and crime investigations. Before using short tandem repeat assessment in such investigations, however, further evaluation is needed.
Methods	In the Tobias Registry, a European registry of potential bone marrow donors, 52 individuals with identical variants of a certain gene were identified, and the inter-individual variation of the short tandem repeats was assessed.

Results	Some regions of the gene contained several variants of short tandem repeats. By analyzing short tandem repeats, the validity of genetic tests can be improved.
Consent	*This study was based on an informed consent.* *(Vorechovsky et al., 2001)*

Comments

The importance of precision in genetic tests is obvious. The topic of this study is not related to the reason why the Tobias Registry was established, but without such a register, the study would have been impossible. There was no need for identity information except when addressing the blood donors for consent. Since the letters asking for consent were administered through the Tobias Registry, the researchers could perform the study without any knowledge of the identities of the subjects.

IV a i.) Research on material collected exclusively for research, in health care, from patients

Example 13

Background	The pathology of multiple sclerosis (MS) includes destruction of the white matter within the central nervous system. The disease is often limited to one episode, but sometimes it is more aggressive and leads to death. The aetiology is unknown, but human herpesvirus -6 infection has been suggested as a risk factor.
Methods	Cerebrospinal fluid from patients with multiple sclerosis was tested for human herpesvirus-6, and stored blood samples were tested for antibodies against the virus. The same analyses were also performed on blood and cerebrospinal fluid from patients who did not have multiple sclerosis.
Results	Human herpesvirus-6 was not associated with multiple sclerosis.
Consent	This study had approval from the ethical committee to be performed without informed consent. *(Enbom et al., 1999)*

Comments

This study exemplifies the use of material collected for the sole purpose of research. All material, however, was collected from patients who were undergoing treatment either for multiple sclerosis or for another neurological disease. In this case, no identity information was needed, but if herpes virus-6 had been associated with the disease, a blind design would be problematic, since it would then have been impossible to offer the patients any treatment.

Example 14

Background	It is well known that high levels of certain serum lipids increase the risk of coronary heart disease. Less is known about the association between blood lipids and prognosis for those who have already developed coronary heart disease.
Methods	Blood samples were saved from 988 patients who had been investigated through coronary angiography between 1985 and 1987. In 1998, the vital status of these patients was assessed. Levels of serum lipids and some cholesterol variants were assessed, as well as the association between these levels and mortality.
Results	Low levels of HDL- cholesterol were associated with an increased mortality. HDL is a cholesterol variant which is negatively associated with coronary heart disease. Surprisingly, low levels of LDL-cholesterol were also associated with an increased mortality. The increased mortality was mainly due to other reasons than coronary heart disease, and it applied only to men.
Consent	This study was approved by the ethical committee for performance without informed consent. (Lundstam et al., 2002)

Comments

The scope of this study deviates somewhat from the original intention when the samples were collected. The samples were collected when the patients underwent coronary angiography, and were then used to study the association between blood lipids and mortality. To perform the study, the researchers needed access to the patients' names and national registration numbers. Through the use of these, vital status could be assessed in the Causes of Death Register and the Register of Population and Population Changes. Some patients were also followed through medical records. It would therefore have been difficult to perform the study in a blind design. Even though the study was not conducted in total concordance with the original intention when establishing the biobank, it can be considered as a validation study of current therapy. Little is gained by successful treatment of serum lipids if this does not affect mortality. The study is therefore a good example of the importance of being able to change the focus of research when new questions arise.

IV a ii.) Research on material collected exclusively for research, in health care, from deceased individuals.

Example 15

Background	Several genetic risk factors have been suggested in the aetiology of Alzheimer's disease. To be certain of the diagnosis Alzheimer's disease, other reasons for dementia, such as brain tumour or brain infarction, must be excluded. The safest way of doing this is at autopsy.

Methods	Tissue from 188 deceased patients with Alzheimer's was compared with tissue from more than 200 deceased patients without Alzheimer's disease. The prevalence of the suggested genes was assessed.
Results	A gene that had previously been suggested as a risk factor was found not to be associated with Alzheimer's disease.
Consent	The study was based on informed consent from the families of the patients.
	(Blennow et al., 2000)

Comments

This is an example in which material collected at time of autopsy was used. For studying the association between genotype and Alzheimer's disease, only information on disease status was needed.

IV a iii.) Research on material collected exclusively for research, in health care, from healthy individuals.

Example 16

Background	Insulin-like growth factor-1 (IGF-1) is a protein that may stimulate prostatic growth and thereby increase the risk of prostate cancer in animal studies. Less is known of whether this is applicable also to humans.
Methods	Material from two large studies in the county of Västerbotten, the VIP and Monica studies, was used. The VIP-study is a health intervention study on cardiovascular disease and cancer. In this study, all residents in Västerbotten County are invited to a health survey when they reach the ages of 30, 40, 50, and 60 years. In connection with these examinations, blood samples are collected, and so far more than 50,000 women and men have participated. The Monica-study has in a similar fashion included 6,000 persons to study cardiovascular disease. All incident cases of prostate cancer in the two study cohorts were identified through the cancer registry. For each case, two controls were selected. Blood samples taken prior to diagnosis were analysed for IGF-1.
Results	High levels of IGF-1 were associated with an increased risk of prostate cancer also in humans.
Consent	All participants had consented to the initial studies.
	(Stattin et al., 2000)

Comments

This study exemplifies the use of material collected from healthy volunteers consenting to research. To perform the study, the cohorts were linked to the Causes of Death Register, the Cancer Register, and the Register of Population and Population Changes. This linkage requires information about the national registration number. If the biobank register had effected the linkage between the registers and then delivered coded data to the researchers, the study would have been feasible without identity information. The study also exemplifies the question of the limits for the informed consent. Should a new consent be required when focus shifts from one public health concern to another?

Example 17

Background	Serotonin is a neurotransmitter that may have influence on mood, impulse control, and aggression. An enzyme, tryptophan hydroxylase, is instrumental in serotonin regulation. Previous studies have shown different variants of the gene that codes for tryptophan hydroxylase, and there are reports of a certain variant being associated with an increased risk of suicide. If these reports are correct is, however, still unsure.
Methods	In the Swedish Twin Registry, 36 monozygotic twins who had committed suicide were identified. Since monozygotic twins are genetically identical, the surviving siblings could be tested. This was done, and the results were then compared with results from tests of healthy controls residing in Stockholm.
Results	A certain enzyme variant was much more common among siblings of twins tat had committed suicide.
Consent	Of the 36 twins identified, 28 gave consent to the study. *(Roy et al., 2001)*

Comments

This study is based on informed consent. A problematic feature is that one cannot know with certainty that the gene described is associated with an increased risk of suicide. Since the response rate was around 75%, it is possible that the gene has little or no connection with suicidal behaviour, but a strong association with attitudes towards study participation. To exclude this possibility, complete participation would be required.

Example 18

Background	Selenium is a mineral which by many is considered to decrease the risk of cancer. More recently, a selenium containing protein called selenoprotein P has been identified. The protein is suggested to have antioxidant properties. Antioxidants are also considered to decrease cancer risk. A new method has been developed that enables

Background (contd.)	quantification of selenoprotein P. The association between selenoprotein P and cancer can therefore be studied.
Methods	Between 1974 and 1982, 12,500 men participated in a health intervention study in which blood samples were collected. Since then, 400 men had developed cancer. For each cancer case, two controls were selected, and the association between selenoprotein p and cancer was assessed.
Results	Low levels of selenoprotein P were associated with lung cancer and gastrointestinal cancer.
Consent	All participants consented to the initial health intervention study. *(Persson-Moschos et al., 2000)*

Comments

This study is an instance of new questions arising long after the planning of the initial study. To perform the study, the cohorts were linked to the Causes of Death Register, the Cancer Register, and the Register of Population and Population Changes. This linkage requires particulars of national registration numbers. The associations between selenium and cancer were never thought of when the study was planned. Nevertheless, the purpose of the initial study was to do exactly this kind of research.

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4

Clinical genomics companies and biobanks

The use of biosamples in commercial research on the genetics of common diseases

Associate Professor Jens Laage-Hellman

Chalmers University of Technology
and Institute for Management of Innovation and Technology (IMIT)

Pharmaceutical and diagnostics companies are increasingly interested in using human biobanks in searching for disease-predisposing genes and related targets for drug and marker development. Direct co-operation between industrial firms and academic scientists is one way of commercially using biosamples collected by public institutions. Another option, dealt with in the present chapter, is indirect co-operation with a genomics company acting as an intermediary. Three such commercialisation ventures have been studied: deCode Genetics in Iceland, Oxagen in the UK, and UmanGenomics in Sweden. The study, using a network approach, compares the three cases from an organising perspective. The analysis addresses a number of economic, ethical and legal issues that need to be considered by those involved in the commercialisation of biobanks. Due partly to contextual differences, it is impossible to identify one single best way of organising commercialisation ventures of this kind. Nonetheless, the results of the study provide important insights and lessons that should be useful when choosing or developing solutions for a specific venture.

1. Introduction

In August 1996, deCode Genetics, a venture-capital-financed biotech start-up specialising in human genetics, was founded on the initiative of Icelandic clinical neurologist Kari Stefansson and his Harvard Medical School colleague Jeff Gulcher. The basic idea was to conduct research into the inherited causes of common diseases by using certain unique qualities of the Icelandic population. The results in the form of knowledge concerning new disease genes and drug targets, and related services, were to be sold to the pharmaceutical industry and the health care sector. A year and a half later, deCode signed a breakthrough collaborative agreement with F.Hoffmann-La Roche, which could bring in as much as MUSD 200 in research funding and milestone payments, and royalties on future drug sales on top of that. deCode grew rapidly over the following years, and by mid-2002 it had 650 employees, mainly in Iceland, and had reached over MUSD 30 in annual revenue.

deCode was not the first biotech company to use collections of human biological material ("biobanks"[1]) for drug research. But it soon became one of the largest worldwide and it came to attract a lot of international attention (mainly thanks to a licence from the Icelandic government giving it exclusive rights to build and operate a health care database covering the entire Icelandic population). Several other "clinical genomics companies" with similar business ideas were formed during the following years, not least in Europe, which had been lagging behind the US in the commercialisation of gene technology and other modern biotechnologies. It was widely believed that Europe offered more favourable conditions than the US for conducting research on human biobanks, especially with family-based approaches.[2] In 1997, for example, Oxagen was founded in the UK by a group of Oxford scientists. Two years later, in 1999, UmanGenomics was established in Sweden for the purpose of commercialising an existing population-based biobank. More recently, a similar company was founded in Estonia, linked to a national genome research project.

This chapter focuses on clinical genomics companies as an intermediary between the pharmaceutical and diagnostics industry[3] and the public sector, represented by universities and health care institutions. The two latter categories provide the genomics companies with biosamples, which are used in commercial research projects. In the next section below, some basic features of clinical genomics companies will be presented. In the third section, a number of important issues related to the commercialisation of biobanks are identified. This is followed by a short note on the methodology used in the study on which the present chapter is based. Next come three short case descriptions (deCode Genetics, Oxagen, and UmanGenomics), which are subsequently analysed. A couple of short remarks conclude the chapter.

2. The clinical genomics company: some features

As exemplified in the introduction, deCode and other similar companies represent a rather new element in the rapidly growing biotechnology industry. The biotech industry, according to the broad definition commonly used today, consists of a rather heterogeneous group of businesses. One feature common to all is that they are science-based and therefore tend to have close relationships with academic and other scientific institutions. The latter produce much of the new knowledge and new technologies that are commercialised by the biotech industry. It is estimated that

[1] Biobanks are defined as structured collections of biological material, such as tissues specimens and blood samples and extracted DNA. One can distinguish between health care-based (or clinical) biobanks created for diagnostic purposes and research-based biobanks created specifically for the purpose of research. A typical example of clinical biobanks is the pathology archives, which often contain large numbers of tissue specimens collected over a long period of time. The health care-based biobanks are sometimes also used for scientific purposes. The research-based biobanks can be either disease-specific or collected from a population, e.g., for the purpose of prospective studies.

[2] For example, European countries tend to have tighter family groupings, publicly financed health care, and centralised medical records. Compared to the US, there is also less ethnical diversity and geographical spread.

[3] For the sake of simplicity, the terms pharmaceutical industry and pharmaceutical company as used in this chapter will also include firms specialising in diagnostics.

there are some 4,300 biotech companies worldwide. The US is the undisputed world leader. In 2001, there were 1,453 companies employing 141,000 people and with revenues exceeding BUSD 25. By comparison, Europe had 1,879 biotech companies, but they were smaller than their US counterparts, employing around 34,000 people and with sales totalling BUSD 7.5 .[4] The largest number of companies can be found in the UK and Germany, followed by France and Sweden.

Although the potential fields of application are numerous, the main focus of the biotech industry has been on medicine – in particular drugs and diagnostics, where the business opportunities have been perceived to be the most lucrative. In other words, since long companies specialising in drug discovery and development constitute the core of the biotech industry (approximately half of the companies).

In the 1990s, progress in genomics, such as the genome sequencing projects and the emergence of new efficient tools for genetics research (e.g., DNA chips), led to increasing interest in using genomics as starting point for drug development – related not only to the so-called inherited (monogenetic) diseases but also to common, complex (multi-factorial) diseases. It was expected that genomics research, carried out on model organisms and humans, would be an effective way to identify disease-predisposing genes and related biological targets for development of new "genomics-based" drugs and diagnostic markers. SmithKline Beacham's MUSD 125 investment in Human Genome Sciences in 1993 is often regarded as the birth of "the genomics industry". Since then, a large number of genomics firms have been founded, especially in the US, based on the business idea of finding disease genes and selling the results to the pharmaceutical industry. The sequencing of the human genome accelerating towards the end of the decade did much to enhance both interest and expectations. Previously, the pharmaceutical industry had had some 500 known target proteins to work with. It was expected that thanks to the sequencing of the human genome several thousands of new targets would be identified during the coming years. Although it was well understood that it might take up to ten years for the first genomics-based drug to appear on the market, analysts estimated that twenty years later 20-30 per cent of all new drugs would be of that category (see, e.g., *Red Herring*, 2000).

Parallel to this development, leading drug discovery companies such as Millennium Pharmaceuticals and Genzyme, as well as several of the large pharmaceutical companies, have to varying degrees incorporated genomics in their research strategies.

As mentioned in the introduction, a small number of genomics companies have chosen a "clinical (or human) genomics approach", which means that their research is based on collections of human biological material. It can be disease-specific collections or, more rarely, large population-based biobanks. In this category of genomics firms we find, for example, Ardais, DNA Sciences, DzGenes, Genomics Collaborative, Myriad Genetics and Sequenom, all of which are US firms. Signal Gene and Newfoundland Genomics are two Canadian companies working in the same field. Besides the three above-mentioned European companies dedicated to clinical genomics, Genset in France can be mentioned as an example of a major European genomics company that is using biobanks. Gemini Genomics in the UK used to be a major player in the field, but a couple of years ago it was acquired by

[4] The figures are taken from a report published by Ernst & Young (2002).

Sequenom, and the twin-based biobank material was transferred to the US. Before that happened Gemini had acquired Eurona Medical in Sweden, which was a pioneer in pharmacogenomics and a user of several public biobanks. It is now a subsidiary of Sequenom. Undoubtedly, there are other small biotech companies in Europe, such as Estonian Egeen, Swedish Arexis and Icelandic UVS, which use clinical genomics, but to the author's knowledge there is no public data available on this particular industry.

2.1 The use of biobanks

Scientific approaches to genomics vary. Both in academia and industry, much of the research is carried out on model organisms and cell cultures. However, as an alternative and complement the use of human (or clinical) approaches has gained momentum during recent years – partly as a result of the mappings of the human genome and genetic variability among individuals. As already exemplified, several biotech companies have been established based on the specific idea to use research on biobanks as a means to identify disease genes. However, the number of such firms is relatively limited, and they are clearly in the minority among the biotech firms involved in drug research.

The strategies pursued by clinical genomics companies vary a lot with regard both to how they get access to biosamples and how the results are commercialised. Some companies, mainly in the US as it seems, build up their own biobanks, for example, by collecting samples and information from sick or healthy individuals – sometimes but not always via the health care sector (see figure 1). Others choose to work with samples from external biobanks belonging to universities, research institutes or hospitals (see figure 2). This seems to be a common model especially in Europe.

Figure 1. Genomics company with its own biobank

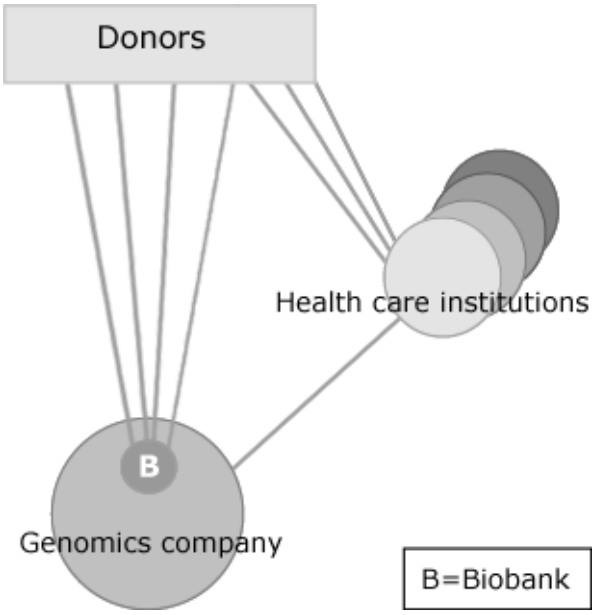
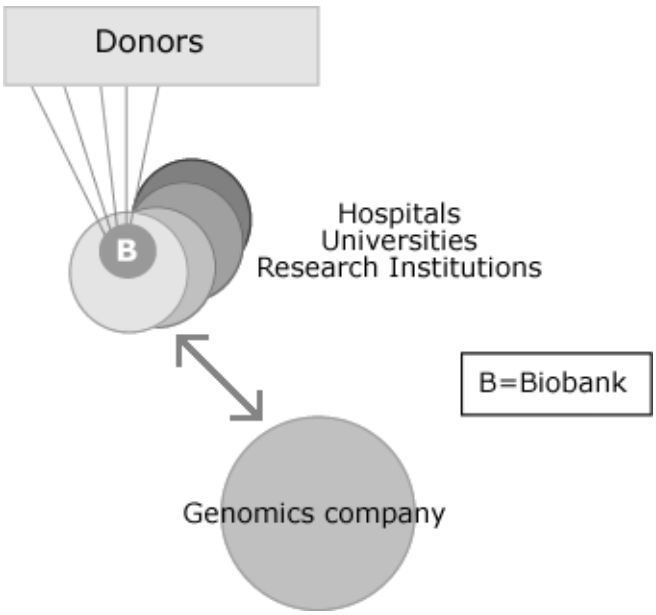


Figure 2. Genomics company without its own biobank



2.2 Exploitation of the research results

When it comes to exploiting the research results, business models and strategies differ from one clinical genomics company to another. Some of them have chosen to be pure research companies selling knowledge to pharmaceutical and diagnostics companies – usually through collaborative and licence agreements. In some cases, the industrial partner comes in early in the research process – as a financier and often also as an active participant in the scientific work. In other cases, the partner comes in at a later stage, when the research has already produced some promising results, such as the identification of chromosomal linkage regions or the location or isolation of a disease gene. For the customer, the latter arrangement means a lower risk, but on the other hand the price is usually higher.

Then again, some research companies go further than others in the innovation process. One option, originally followed by many companies is to concentrate on "gene hunting", that is, the identification and validation of disease genes. The trend now is for genomics companies, not least those dedicated to clinical genomics, to integrate forward into drug targets, lead substances, candidate drugs, and even into clinical trials, carried out either in-house or in collaboration with industrial partners. In other words, they are shifting their business strategy in the direction of becoming "real" drug development companies. This trend has come as a response to two types of changes in the environment. First, the big pharmaceutical companies, being under pressure from the financial markets to speed up growth, are primarily looking for research results that can be turned into new marketable products as quickly as possible. Therefore, many genomics companies have experienced reluctance on the part of potential customers to get engaged in early stage projects. Second, there is growing awareness in the scientific community that finding good targets on the basis of genomics might not be as easy as it was thought some years ago. There is a need for deeper knowledge about the biological pathways through which the genetics, in combination with environmental factors, cause

disease. This makes other nearby bio-scientific research fields, such as proteomics and metabolomics, important tools in the search for functionally validated drug targets.

Some genomics-oriented biotech firms go one step further by developing, producing and marketing their own medical products (instead of licensing out research results). For example, Myriad Genetics in the US has become famous for its patented breast cancer tests, with which the company is trying to monopolise this kind of diagnostic testing.[5] Other firms, such as the previously mentioned Human Genome Sciences, are striving to become pharmaceutical firms.

There are some companies that have chosen to specialise in selling information contained in proprietary genomic databases. Two examples from the US are Celera Genomics and Incyte. The former became famous for its contribution to the sequencing of the human genome. However, Celera is now redirecting its main business focus from information selling to becoming a genomics-based pharmaceutical company.

2.3 The role as intermediary

As has already been explained, the end-users of the knowledge produced by the genomics companies are the pharmaceutical companies. They develop, manufacture and market the final products (drugs and diagnostic tests). They also conduct their own exploratory research as a basis for product development, and many of them have included genomics as one approach to drug discovery.[6]

As we have seen, human biobanks constitute an important resource that, depending on the scientific strategy chosen, can be used by the pharmaceutical companies in their search for disease genes and drug targets. This kind of research builds not only on the samples stored in the biobanks. There is also a need for information about the donors of the samples. This may be clinical information, such as data contained in medical records, and information about lifestyle and other environmental factors. Co-operation with physicians and clinical researchers can be one way of gaining access to samples and information.

A previous study within the present project showed that in Sweden pharmaceutical and biotech companies, with few exceptions, have not invested resources in building up biobanks of their own.[7] Instead, they have chosen to collaborate with academic researchers having similar interests (i.e. understanding the molecular mechanisms behind certain diseases). According to the traditional model of university-industry collaboration, these firms financially support studies carried out by the academics. This gives them the opportunity to patent the results and use the inventions for the purpose of internal product development (often according to the right of first refusal principle). And they can do so without having direct access to biobanks. Although this co-operation is highly valued, pharmaceutical companies

[5] Myriad Genetics, based in Salt Lake City, has collected a large number of samples from the very distinctive Mormon community in Utah. Like the Icelanders, the Mormons are culturally committed to genealogy. (See, e.g., Rose, H. 2001, p. 8)

[6] The goal of *drug discovery*, consisting of an exploratory and an optimisation research phase, is to produce Candidate Drugs. The subsequent *drug development* starts with a pre-clinical development phase, leading to an Investigational New Drug, which goes into clinical testing and registration.

[7] Laage-Hellman, J. 2001a and b.

may sometimes also like to use samples in internal research projects, which are more closely linked to their product development.

This *direct* form of co-operation is the dominant model for the industrial use of biobanks in Sweden, and probably also in other countries (*ibid*.). But as we have already seen, there exists an alternative mode of co-operation which can be characterised as *indirect*. This occurs when there is a clinical genomics company acting as an intermediary between academic and health care institutions on the one side and pharmaceutical companies on the other. It is the genomics company that has direct contact with health care providers and clinical researchers, and from which they gain access to biosamples and information. The research on the biobank material is carried out either by the genomics company itself or as a more or less close collaboration with academic researchers. The funding may come from the genomics company or a customer.

Direct co-operation is a well-established and efficient way for pharmaceutical companies to gain access to knowledge that can be derived from biobank research. In cases where the industrial partner does not work with the biosamples, the commercial element in the (industry-sponsored) research is fairly unproblematic with regard to biobank use. At least, the ethical problems concerned with the protection of the donors' privacy are not very different from those in normal academic projects (e.g., there is no risk of information about individuals being passed on to the company). However, for a few years now pharmaceutical companies have shown increasing interest in using biosamples in more applied studies more closely linked to the internal drug discovery programmes. One conceivable solution is of course to get material from biobanks operated by universities or health care institutions. Another solution is indirect co-operation, that is, through some genomics company. It seems that this model for industrial utilisation of biosamples coming from the public sector is emerging as an important complement to direct co-operation. The establishment of several clinical genomics companies since the mid-1990s supports the assumption that there is such a trend.

Needless to say, the commercial use of biobanks created in the public sector raises a number of issues. As discussed in more detail in other chapters of this book, the use of biobanks for research purposes, generally speaking, means that different interests have to be balanced – in order to use biobanks in ways that are both efficient and ethically acceptable. There are not only ethical but also legal, social and economic issues that have to be dealt with by those involved in different capacities. In the next section, some important issues that are particularly relevant to the role of clinical genomics companies in biobank commercialisation will be identified.

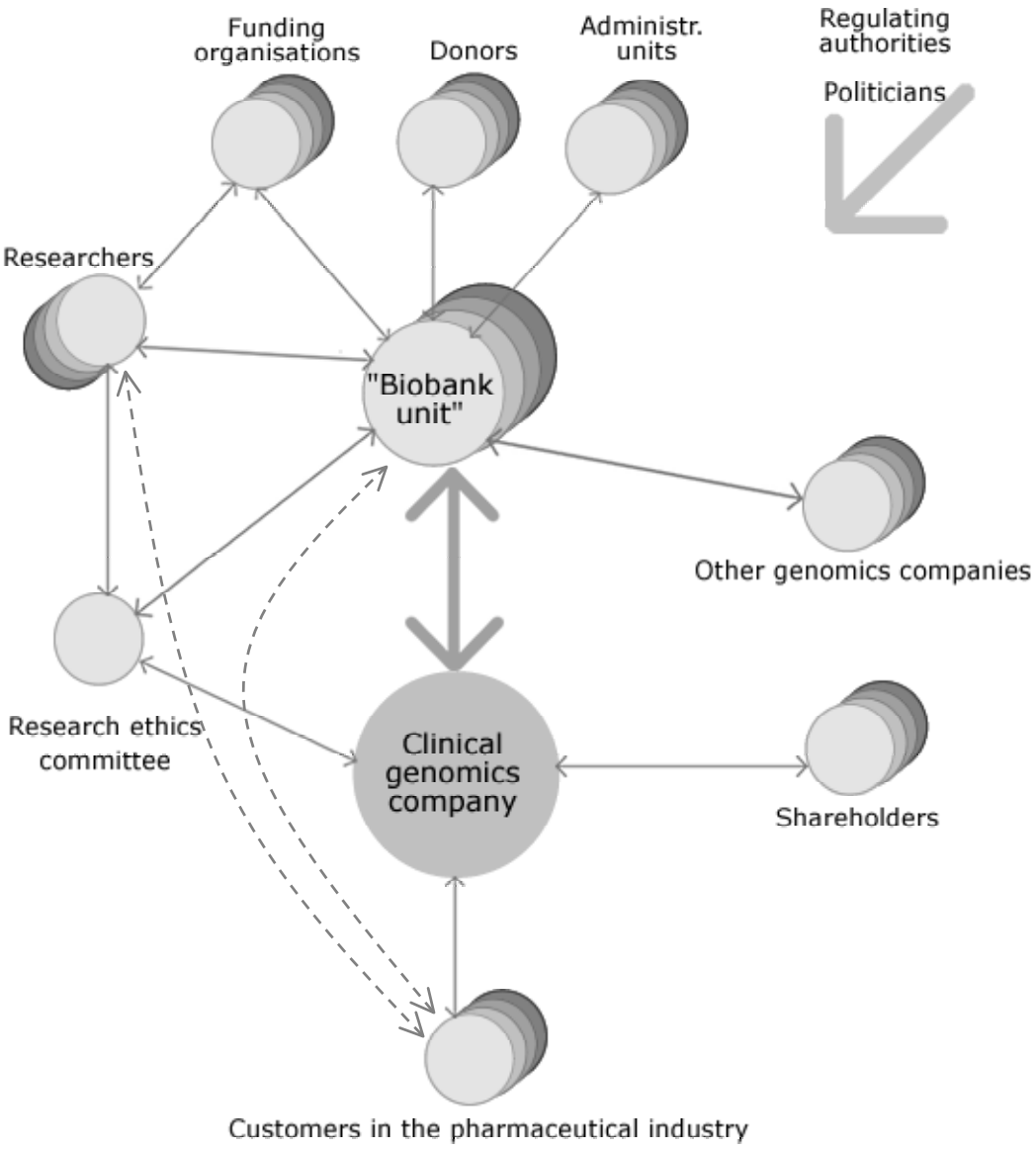
3. The commercial use of biobanks: important issues

The overall question addressed in this chapter is how best to organise, in a broad sense, the commercialisation of biobanks through clinical genomics companies. Let us first establish that this is not an easy question to answer. We have a complex phenomenon to deal with. First, there are many interested parties, with partly conflicting interests, involved in the commercialisation process. Some of the actors are individuals, such as donors of the biosamples, physicians, academic researchers, local politicians, and people who have invested in the genomics company. Other

actors are organisational, such as hospitals, universities, companies, research-funding agencies, institutional investors, and regulating authorities. Second, the question of how to organise the commercialisation of biobanks has economic as well as ethical, legal and social aspects.

As a theoretical starting point, it is assumed that the commercialisation takes place in a network of relationships, within which various actors interact with each other.[8] See figure 3, which schematically illustrates how the different types of actors are related in "the biobank commercialisation network". The relationships, which may be more or less long lasting, function as channels for exchange and transfer of valuable resources. Some of the relationships contain a business exchange, others do not.

Figure 3. Actors and relationships in "the biobank commercialisation network"



[8] The theoretical framework for the study is a network approach, which has proved to be a useful tool for analysing industrial innovation processes. See Laage-Hellman, J. 2003 for more details.

The "biobank unit" in the figure is an actor responsible for collecting, and often also storing and using, biosamples. It can be an academic research group (or even an individual scientist), a university department, a clinic or hospital laboratory, an individual physician, or a special organisation entrusted with administering one or several biobanks. It is the biobank unit that has contact with the donors (e.g. patients). In most cases the biobank unit constitutes part of a larger organisation, such as a hospital or a university. Besides other units in the organisation that use samples for research, the biobank unit may have important relationships with other types of unit, discharging for example administrative and managerial functions.

Some of the actors concerned with commercialisation, such as regulatory authorities and local politicians, may not have direct relationships with other actors in the network. Instead, they may affect the process by making laws and regulations or by other means influencing the actors directly involved.

As emphasised in the figure, the relationship between the biobank unit and the genomics company is central to commercialisation. This focal relationship links the two key actors, responsible for collecting the samples and using them for commercial research respectively. It should be noted that a genomics company can have parallel relationships with several biobank units. Every such unit in turn may have relationships with other genomics companies.

On the basis of the framework illustrated in figure 3, several important organisational issues can be identified with regard to the focal relationship and the two key actors, that is, the biobank unit and the clinical genomics company.

3.1 Organising the focal relationship

The main rationale for establishing this kind of relationship is to give the genomics company access to biosamples and related information, to be used in commercial research projects. A key question is therefore on *what conditions the company gains this access*. Based on the experiences from the commercialisation ventures examined in the present study, the following more specific issues have been found to be of importance:

- Who has the rights of disposal over the samples and the biobank?
- What are the economic conditions for the transfer and use of samples?
- To what extent is the company given exclusive rights to commercialise samples and research results?
- How do laws and regulations affect the relationship (e.g., the content of the agreement between the parties)?
- What are the routines and rules according to which the transfer takes place?

The answering of these questions requires consideration of economic, ethical as well as legal aspects. But all use of biobanks for research, including the commercially oriented kind, also gives rise to other *ethical questions* concerning how to protect the privacy and integrity of the donors. The following more specific issues have been identified:

- Which methods are used to ensure that information about the donors is not misused or passed on to unauthorised persons?

- How are the interests of the donors protected? In particular, what type of information and consent procedure is applied? How can the donors influence the type of purposes for which the samples are used?
- How is society's interest in using biobanks as efficiently as possible for research balanced against the interests and wishes of the individual donors?

3.2 Organising the biobank unit and the genomics company

The *division of labour* between different actors in the network, and especially between the biobank unit(s) and the clinical genomics company, is an important issue. Even if the basic role of the company as a bridge to the pharmaceutical industry is given, the activities and resources can be variously organised. For example, it is not always evident who should carry out a certain step of the scientific work. A related question is where the necessary resources, such as laboratory equipment and specific skills, should be located. Thus:

- Which biobank-related activities are carried out by the biobank unit and the genomics company respectively? (Outsourcing to a third party is another possible solution.)
- Which resources do the two actors have in-house?

It will be readily understood that the division of labour applied in a certain venture affects the characteristics of the focal relationship that binds the two actors. But the pattern of specialisation in the network also has consequences for the *internal organising of the biobank unit and the genomics company* respectively, which we will now turn to consider.

There are a number of organisational and management issues that are relevant from the viewpoint of biobank commercialisation:

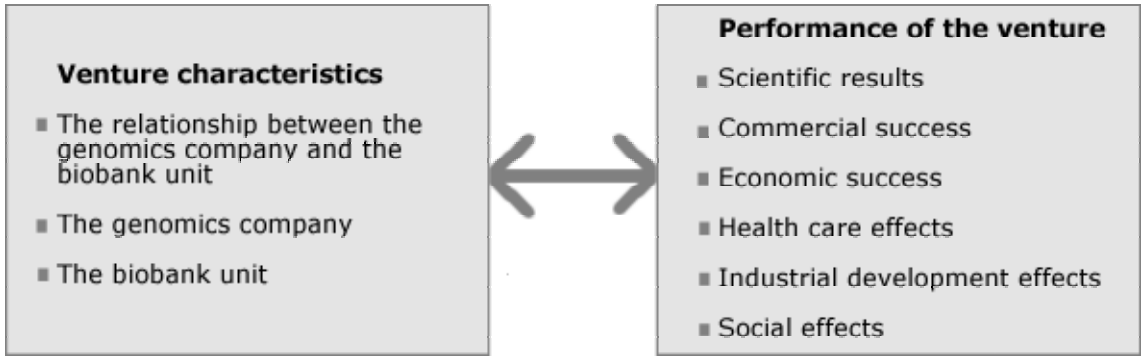
- Financing, ownership and control of the unit/company
- Organisation and management structure
- General visions, goals and ambitions regarding future development
- Scientific goals and strategies (e.g. approach to genetic studies)
- Marketing strategy (e.g. who are the target users/customers?)

All these issues are of relevance to both the biobank unit and the company, but in slightly different ways.

3.3 The performance of biobank ventures

The variables discussed above can be used to characterise a certain commercialisation venture involving a clinical genomics company and one or more biobank units. Depending on how the venture is organised, the outcome will vary. Performance can be measured in different dimensions which to varying degrees are relevant to the interested parties (see figure 4). Important variables are scientific results (knowledge creation), commercial and economic success of the company, effects on health care, and effects on local industrial development and growth. Furthermore, there may be different "social effects" concerned, for example, with how the citizens (primarily the donors and their relatives) are affected by the commercialisation.

Figure 4. The performance of commercialisation ventures



Obviously, different actors have different interests in the venture and therefore make different priorities among these performance variables. As a consequence, the perceived performance differs depending on who makes the evaluation. For example, let us say that a certain way of utilising a biobank for industrial research is scientifically and commercially successful and leads to improvements in health care (thanks to new products developed by the customers of the genomics company). Many actors will perceive this as a good result. But if at the same time there are donors who feel that their integrity is violated, these individuals will not, from their perspectives, have a solely positive attitude to the venture (even though they may be aware of the benefits the research confers). Other actors, such as the physicians treating the patients or academic researchers competing for the (limited) biological material, may also be critical of the venture, from their specific perspectives. In conclusion, this variety of interests has to be taken into account when organising a commercialisation venture.

It must be emphasised that the commercialisation of biobanks (and related resources) is not a static phenomenon. Even though the basic structure in a certain case may remain fairly stable, the network is constantly changing as a result of activities undertaken by actors. That is why the arrow in figure 4 goes in two directions. Hence, the actors involved in the venture will adapt their behaviour depending on the outcome, and this will in turn affect the venture's characteristics.

There may also be changes in the wider environment that affect the venture, and performance. For example, scientific breakthroughs and technological advances may create new opportunities that the actors in the network try to take advantage of – for example, by establishing new businesses or new co-operative relationships. Furthermore, the enactment of new laws and regulations may affect the conditions for certain activities and thereby lead to various adaptations. As a result of such actions by individual actors, the network evolves (more or less rapidly) in directions that may be perceived as positive by some parties and negative by others. In other words, the study of biobank commercialisation must be carried out in a dynamic perspective. This also means that structures are important as well as processes.

4. The methodology of the study

The present chapter is based on a study reported in its entirety in a separate publication.[9] The core of the study consists of an in-depth case study of Uman-Genomics, a company created for the purpose of using a population-based biobank in Northern Sweden for commercial research. This is a pioneering venture with unique characteristics. It has few counterparts in other countries as yet, but there is undoubtedly growing interest in other parts of the world in starting up similar businesses. Presumably, therefore knowledge and insights gained by studying this venture would also be of relevance outside Sweden.

As a complement to the UmanGenomics case study and as a basis for comparative analysis, two other commercialisation ventures already mentioned, namely those centred on Oxagen and deCode, were also studied, though less deeply. These ventures do not constitute true case studies, since their development over time has not been systematically examined.

In the present chapter, space will not permit a lengthy description of the three ventures investigated. The "cases" will be only briefly presented as a starting point for the comparative analysis which follows, dealing with some of the issues identified in the preceding section. For a more extensive description and analysis of the cases, the reader is referred to the full report (*ibid.*).

The data was collected mainly through interviews with key individuals representing the companies, biobank units and researchers they co-operate with, and, to a lesser extent, government agencies and the like. Altogether, close on forty people were interviewed, one or several times each. As a complement, written material from the literature, the press and websites was also used.

5. deCode Genetics

5.1 Background and history

deCode is a "population-based genomics company" whose headquarters and main operations are located in Reykjavik, Iceland. As already stated, it was founded in 1996 by Kari Stefansson and Jeff Gulcher, based on the idea that Iceland offered unique advantages for research into the inherited causes of common diseases. Of particular importance were the relative homogeneity of the Icelandic population and the availability of genealogical records dating back several hundred years. Both these circumstances have been assumed to facilitate the search for disease genes. The facts that Iceland has had a centralised health care system since 1915 and that the population is well educated and generally has a positive attitude to participation in medical research are other advantages thought to benefit a genomics company.

The founders had two different but interconnected objectives. The first was to establish a commercial laboratory to carry out biomedical research in Iceland. It would seek collaboration with clinicians interested in specific diseases and having contact with patients from whom blood or tissue samples could be obtained. deCode differed from other genomics companies using a human genetics approach in that from the very beginning it was planning to link clinical and genetic information into the genealogies. The idea was to use this genealogic approach to

[9] Laage-Hellman, J. 2003.

develop new drugs and diagnostic tests together with pharmaceutical companies. The second and more ambitious objective was to construct a large, computerised database containing genetic, genealogical, and phenotypic information about the Icelandic population. It was thought that such a database would enhance the possibility of radically renewing the management and delivery of health care.

Funded by venture capital raised in the US, deCode started up gene discovery programmes targeting forty common diseases. In 1998, deCode entered into an important agreement, covering twelve of these diseases, with F.Hoffmann-La Roche ("Roche"), a large Swiss pharmaceutical company. The contract gave deCode MUSD 70 in research funding, more than MUSD 130 in possible milestones and the right to royalty on future product sales.

In 2000, two important events occurred. First, the Icelandic government awarded the company a 12-year licence to create an Icelandic Health Sector Database (IHD). This licence allowed deCode to collect data from medical records of public health care institutions and self-employed professionals, and to transfer such data in encrypted form into a centralised database containing non-personally identifiable information. This database would then be used by deCode, in combination with genetic and genealogy data, as a support of the gene discovery programmes and to develop various health care-informatics services.[10] Second, deCode completed its initial public offering and became listed on the Nasdaq and Easdaq stock exchanges.

In January 2002, deCode and Roche unveiled a new collaborative agreement following up the achievements of the first agreement. Building on identified disease genes and drug targets and focusing on four selected diseases, the new phase of the alliance was aimed at developing new therapeutic compounds and taking them into clinical trials. This shift in focus from genetic studies to drug development was possible thanks to deCode's expanding facilities for downstream research, aimed at transforming deCode from a pure genomics company to an integrated drug development firm.

Thanks to the crucial agreements with Roche and success in attracting venture capital deCode has been able to grow rapidly. Earnings in 2001 totalled MUSD 31.6, and in the mid-2002 deCode had some 650 employees, mainly in Iceland. Like many other young biotech firms, deCode was still suffering from big financial losses (MUSD 47.8 in 2001).

5.2 The use of biobanks in deCode's research

Thanks to the IHD project, and the controversy surrounding it, deCode has had enormous publicity internationally. However, outside Iceland there is a great deal of misunderstanding. It is not true, as many seem to believe, that deCode has bought the exclusive rights to "the Icelandic genome". In fact, the database deCode has got a licence for will not contain any genetic data at all, just certain coded information from the medical records. It is true, however, that the licence permits deCode to

[10] The passing in 1998 of the bill granting deCode the right to build, operate and commercialise the IHD had been preceded by a 9-month intensive public debate. Criticism put forward by the Icelandic Medical Association, among others, had led to several changes in the bill compared to the original proposal. Nonetheless, the whole project around the IHD, and the related legislation, is still a subject of criticism and discussion domestically as well as internationally. For example, concern has been expressed regarding such issues as the consenting procedures, confidentiality, and scientific openness.

statistically cross-reference data from the IHD with data from its own proprietary genetic and genealogic databases. Thus, deCode will have to create genetic data by analysing biosamples that it gains access to in other ways. We will return to this matter in due course.

First, though, it has to be made clear that the IHD does not yet exist. In fact, the collection of data has not yet begun. The process of specifying the security targets that the information system will have to meet is still going on. Furthermore, deCode is still negotiating the conditions for information access with the university hospital.

But, independently of the database project deCode has a large number of genetic research studies going on. These are disease-specific. Usually, the research subjects, consisting of patients and healthy relatives in extended families (identified with the help of deCode's genealogy database, "The Book of Icelanders") are recruited through collaboration with physicians. The procedure for selecting the participants, getting their informed consent, taking the blood sample, and collecting the information is quite complicated. It involves the National Bioethics Committee and the Data Protection Authority. At the behest of the latter, deCode has established a special service unit, in the form of a non-profit organisation separated from deCode, which handles the practicalities of collecting samples and information and carries out the coding procedures required to protect the donors' privacy. The activities of this service unit as well as all other work associated with the collection of samples are financed by deCode.

As to the informed consent, the donors have two options. They can opt for the sample to be used only for the study in question, and then destroyed, or for it to be saved for future research. In the latter case the sample will be stored in deCode's own biobank consisting of a number of sub-collections for different diseases. According to public statements made by deCode, 88-96 per cent of the donors choose this latter form of consent. deCode now has a total of 70,000-80,000 samples in its biobank.

The service unit also has a role to play when deCode in some cases wishes to use tissue samples stored in clinical biobanks at hospitals. However, in these cases deCode is only allowed to carry out the planned analysis, according to the protocol approved. Thus, it cannot store this material in the biobank.

The physicians/researchers who are helping deCode to obtain samples and clinical information can be more or less actively involved in deCode's research. It seems that the best scientific results have been achieved when deCode has had close collaboration with clinical researchers at the university hospital. Asthma, schizophrenia, psoriasis, rheumatoid arthritis and stroke are mentioned as examples of diseases where deCode has succeeded well. When there is collaboration, written contracts are signed both with the hospital and the individual scientists involved. It is stated, for example, that deCode will cover all costs of the study. The company will retain all intellectual property rights, but the hospital will get a royalty on possible revenues.

When it comes to deCode's future use of genetic data in connection with the IHD, there is no project in Iceland, as many foreign observers seem to believe, to build up a new population-based biobank (i.e. on similar lines to what is done in Estonia and the UK). Instead, deCode is planning to use data obtained by genotyping samples in the present disease-based collections. However, given the

large number of samples already contained in deCode's existing biobank and the continuing sampling activities, it seems that within the not too distant future deCode will in effect have a biobank covering a very large proportion of the Icelandic population.

5.3 The development of the company and the database project

deCode has pursued an aggressive growth strategy. As mentioned earlier, deCode is now striving to integrate forward and become a fully-fledged drug discovery company. Among other steps, a US company specialising in medicinal chemistry and proteomics was acquired early in 2002. This strategy is very costly, and the company's financial losses are steadily increasing. At the same time, the current problems on capital markets are making it difficult to raise new equity, not least for biotech companies.[11] As a consequence, deCode announced in October 2002 that a major rationalisation programme would be implemented. This meant reducing the total workforce, with immediate effect, from 650 to 450. Most of the reduction concerned people engaged in the Reykjavik-based genetics research operations. The goal was to achieve a positive cash-flow in 2003. It was also stated that, thanks to the rationalisation opportunities offered by new automated laboratory equipment, the pace and breadth of the company's research programmes would not be notably affected.

The IHD project is still being pursued by deCode, although it is apparently not being pushed as hard as previously. For example, rumour has it that many of those working on the database project have been laid off. deCode is now involved in long-lasting and tough discussions with the government regarding the details of the project – for example, how to design the information system. The IHD Act passed by the parliament in December 1998 places very strict demands on the security solutions (this in turn being a consequence of the fact that explicit, informed consent from the individuals will not be required). It seems that the security targets will be so tough that the database will not be as useful as originally intended. This is one reason why many Icelanders, not working for deCode but having good insight into the process, doubt if deCode is really interested in completing the project. It is widely believed at present that the project will never be realised. As several people point out, deCode would not officially admit that the IHD is given lower priority, since the whole project has been used as a key ingredient in the company's marketing.[12]

6. Oxagen

Oxagen (OXford Applied GENetics) was founded in 1997 on the initiative of researchers at the University of Oxford and the Wellcome Trust Centre for Human Genetics. Professor John Bell, one of the co-founders and a prominent scientist, had seen the great possibilities in using human genetics to tackle complex diseases and

[11] When deCode went public in 2000, the share price was USD 18. Now, at the end of 2002 the price has fallen to around USD 2.

[12] One interviewee pointed out that deCode has never tried to correct the misunderstandings. He maintains that for the company the image of having exclusive access to the entire Icelandic genome is good from a PR and marketing point of view.

achieve a major impact on human health. But he also understood that in order to overcome the big scientific challenges and to transform the knowledge produced at universities into new products helping to predict, diagnose and prevent disease, a commercial activity was needed. Thus, the idea was to start up a private genomics company performing complementary research activities directed at commercial applications. The company should raise venture capital, acquire large-scale equipment, build an efficient organisation, and establish collaboration with clinical partners and industrial firms. The aim of the company would be to identify disease genes, novel drug targets, and diagnostic markers by applying innovative genetic analysis. Patents and other intellectual properties related to them, or more ideally to the therapeutic compounds, would be the company's main output.

Oxagen is currently studying nine common disease areas in three major therapeutic fields, viz., cardiovascular disease, inflammatory disease and metabolic/endocrine disorders. The main scientific goal is to identify and validate disease genes by performing large-scale family studies based on collections of clinical samples and data. From the beginning the strategy has been to run these gene discovery programmes together with leading pharmaceutical companies. The first research agreement, focusing on the genetic background to coronary artery disease and lasting for five years, was signed with Astra from Sweden (now AstraZeneca) in 1998. This was for a long time the only commercial partnership, but in 2002 a similar agreement on asthma was made with Pfizer from the US.

From the very beginning it was obvious that the chosen clinical genomic approach to gene discovery would require collaboration with different research groups – not only in Oxford but also in other places. Therefore, within each disease area, Oxagen has selected one or several clinical collaborators contributing samples collected in their respective environments. Today, Oxagen has co-operative agreements with more than thirty research centres, mainly in the UK and other European countries.

Through these collaborations, Oxagen has gained exclusive access to the family collections for commercial applications – in total 34,000 samples. This access to biobanks in combination with the company's own proprietary technology platform constitutes the cornerstone on which the company's competitive power is based.

In 2001, Oxagen had £3.3 million in revenue and R&D expenses amounting to £11.7 million. The resulting net loss amounted to £8.7 million. In the end of 2002, the total staff consisted of around 100 people.

6.1 PROCARDIS: an example

The research project on coronary artery disease (CAD) illustrates one of the cases where Oxagen is working with multiple centres. Here, four different institutions from the UK, Germany, Italy and Sweden have formed a consortium called PROCARDIS. The team is seeking to collect and genotype some 4,000 families (approximately 15,000 individuals) with the purpose of finding CAD-associated gene locus and isolate therapeutic targets.

Normally, Oxagen first establishes a discovery programme and later on seeks a commercial partner. Here, for historical reasons AstraZeneca has been involved from the very start and has close direct contacts with the clinical centres.

The first step was to start collecting samples and information. As always, this was done with appropriate informed consent from the donors. All samples have been coded and sent to Oxagen's facilities, where they are now stored in a biobank. Oxagen has used these samples to make whole genome scanning by using its advanced high-throughput genotyping equipment. The results in the form of interesting chromosomal linkage regions are then investigated in more detail by the academic researchers in collaboration with scientists from Oxagen and AstraZeneca. The latter has some twenty people involved.

In this case, also for historical reasons, the funding of the clinical centres has come directly from AstraZeneca. In other projects, it is Oxagen that funds the sampling activities, but usually not all the research carried out by the clinical partners.

The project has progressed according to the plans and the parties are satisfied with the outcome so far. It is too early to say whether there will be any patentable results.

AstraZeneca expresses great satisfaction with Oxagen's contributions. Besides the infrastructure for biobanking and genotyping and the scientific competence, AstraZeneca appreciates Oxagen's ability to handle relations with the academic partners and the high ethical standards characterising its operations. The last point is especially important since pharmaceutical companies always run the risk of being scrutinised for their behaviour. That is why AstraZeneca always wants to know how its partners handle ethics.

6.2 Some recent changes

Oxagen has found it difficult to get the large pharmaceutical firms interested in funding early stage research projects. In the present situation, "big pharma" is primarily looking for validated drug targets or new substances under development. This market situation has forced Oxagen to follow the main trend in the genomics industry, that is, to run the projects longer in-house before entering into commercial partnerships. That is why a strategic shift was announced in the summer of 2002. The new strategy means increasing focus on target validation and drug discovery. In other words, the company is integrating forward. Instead of just out-licensing discoveries of genes or targets Oxagen will in selected disease areas develop in-house therapeutic compounds and take them to clinical trials – end of phase II as longest. In diagnostics too, Oxagen may develop products or services.

Genetics will remain a core competence, but according to the new strategy the primary efforts will be directed to progressing existing lead gene discoveries through functional biology and on into chemistry. This will require acquisition of additional resources dedicated to these areas.

The transformation of Oxagen into a drug research company unavoidably increases the capital need. At the same time, the current problems in the equity markets make it difficult for biotech firms to raise new venture capital. Therefore Oxagen had to implement a cost-cutting programme whereby 20 per cent of the employees (some twenty people), mainly in genetics and bioinformatics, had to leave the company.

On the other hand, an expected advantage of the new strategy of processing the research findings longer and selling at a later stage is that the price will be higher

and a better return will be achieved on the investments. Whether these expectations will be fulfilled remains to be seen.

7. UmanGenomics

This is a small genomics company located in Umeå in Northern Sweden. It was founded in 1999 on the initiative of Umeå University and the Västerbotten County Council, the principals of the Medical Biobank. The latter is a large, population-based biobank that has been built up since the mid-1980s and now consists of blood samples and lifestyle information from 87,000 individuals. This includes 66,000 people who have donated a blood sample in connection with a still ongoing countywide health-screening programme (the VIP cohort).

At the end of 2002, UmanGenomics had 16 employees. There were at that point in time no ongoing assignments from customers.

7.1 Historical background

The initiative to build a biobank was taken by clinical researchers at the university hospital. Among other scientific opportunities, they saw that the blood samples could be used in the search for biomedical markers for different diseases. A key person was professor Göran Hallmans, who is now head of the Medical Biobank, the organisational unit within the county council that is responsible for operating the biobank. It should be noted, though, that the responsibility for the biobank is shared with Umeå University (to which the biobank belonged organisationally until 2000).

In the beginning, the biobanking and related research activities received little support from the scientific community, and financing was therefore a big hurdle. However, in the mid-1990s attitudes changed as a result of rapid scientific and technological progress in genetics and genomics. It was realised by many that the biobank constituted a valuable asset which could be used for researching the genetic and environmental factors predisposing for common diseases. Thus, the biobank came to be used in an increasing number of academic studies, primarily in Umeå but also elsewhere.

The first ideas for using the biobank for commercial research came up in the early 1990s, partly in response to the funding problems. It was thought that pharmaceutical companies would be interested in using the biosamples in their search for disease genes and genetic markers. The first attempts by Göran Hallmans and some colleagues to start up commercialisation in co-operation with a large biotech company were not realised for various reasons. Instead, Umeå University and the Västerbotten County Council decided in 1998 to start UmanGenomics. The idea was to build up an organisationally independent genomics company that would carry out research on the biobank material on behalf of pharmaceutical companies. UmanGenomics got a strong agreement with the two principals of the biobank giving it exclusive rights to use the VIP-samples for commercial purposes. In order to protect the interests of the donors and the population and make sure that samples are not misused, an ethics model was developed. It consists of three levels. On the individual level, informed consent is received from each donor. Secondly, on the societal level influence is exerted through the regional research ethics committee. Thirdly, the interests of the population should be provided for by giving the public

sector (through the university's holding company) controlling interest in UmanGenomics.

Göran Hallmans and some of his colleagues felt that they had been run over by the university management. They claimed that the researchers behind the biobank should have the right of disposal over the biosamples, and accordingly have the last word on their use. This was important, not least, in order to fulfil obligations towards the donors and the external financiers of the biobank research, it was argued. They also meant that the commercialisation concept had been stolen from them. Thus, a conflict arose regarding the disposal of the biobank and UmanGenomics' access to it.

7.2 The development of the company

To start up the company, Professor Sune Rosell was hired as chief executive officer (CEO). He had retired from Astra, where among other positions he had served as research director. He had been engaged by Umeå University as chairman of the board for the Medical Biobank. In 1999 he started to build up the organisation by recruiting a management team.

Right from the start, UmanGenomics' business idea has been to "discover disease-related genes, explore their function, and market this knowledge". Originally, this would be done by performing contract research on behalf of pharmaceutical companies. Among possible product offerings, validation of candidate genes using SNP analysis was initially thought to offer the most promising prospects (given the access to a unique, population-based biobank and high-quality disease registers). However, the identification of new disease genes was also part of the product strategy.

The marketing initially targeted the pharmaceutical companies behind the SNP Consortium (formed by some ten large companies including AstraZeneca, Pharmacia Corporation and Amersham Biosciences). Contacts were established with several potential customers, but negotiating a deal proved to be more time-consuming than expected. However, in 2000 a first major contract (in the field of proteomics) was signed with a large biotech company, but this partnership soon had to be terminated when the customer changed its business strategy.

In 2001 Sune Rosell resigned as planned, and Dr Wayne Davies took over as CEO. He is a Scottish scientist with long experience of the biotech industry. In the same year, UmanGenomics floated a rights issue (MSEK 30) directed to institutional investors and private individuals, some of whom were employees of the university. After this private placement, Umeå University owned 60 per cent of the shares through its holding company.

Despite its marketing efforts UmanGenomics did not succeed in getting any contracts from pharmaceutical companies. At the same time, there was a trend in the environment whereby research interest in bioscience was shifting from "gene hunting" towards functional genomics and proteomics. These observations triggered a strategic change. The priority previously given to validation studies was abandoned. Disease gene identification became equally important. But at the same time, UmanGenomics decided to integrate forward into drug targets and proteomics, and to run some research projects in-house. To implement this new strategy, which necessitated the hiring of new staff and purchasing of new equipment, more capital had to be raised (estimated to MSEK 200).

To raise this amount of capital it was judged necessary, for a number of reasons, to reduce the university's ownership to below 50 per cent and bring in new money from the venture capital market. This also meant that the original agreement between UmanGenomics, the university and the county council had to be renegotiated, since it presumed majority ownership by the public sector. This condition had been included as part of the ethics model. Since a new Biobanks Act was to be introduced in Sweden from 1 January 2003, the parties judged that public majority ownership would no longer be necessary in order to protect the interests of the population. Early in 2002, a new agreement including some other changes was drafted, and after some modifications, approved by the parties. However, the new agreement aggravated the above-mentioned dispute over control of the biosamples.

7.3 The present situation

Despite a failure by opponents to have the agreement declared unlawful by a court, Göran Hallmans and his associates continue to claim disposal of the biobank and oppose the way in which UmanGenomics gains access to samples. At the present time, this dispute has yet to be resolved.

The dispute has undoubtedly harmed UmanGenomics and the whole commercialisation venture. It is hard for the company to market its services while uncertainties remain regarding its access to the biobank. The planned financing round, intended to bring in the capital needed to implement the new strategy, has also been delayed.

8. Comparative analysis

As described in the preceding sections, the primary business ideas of the three companies are similar. Based on biobanks as a key resource, all of them study the genetic factors behind common diseases with the aim of selling the resulting knowledge to pharmaceutical and diagnostics companies. In recent years, all three of them have made strategic moves in the direction of forward integration in the innovation chain. From an initial focus on discovery or validation of disease genes, they are now striving to run their research projects longer, that is, towards identification of drug targets and development of new drugs.

Despite these similarities it is obvious that in other respects the three ventures are quite different, not least with regard to their way of using biobanks. Some of these fundamental differences are highlighted in table 1 and will be briefly commented on.

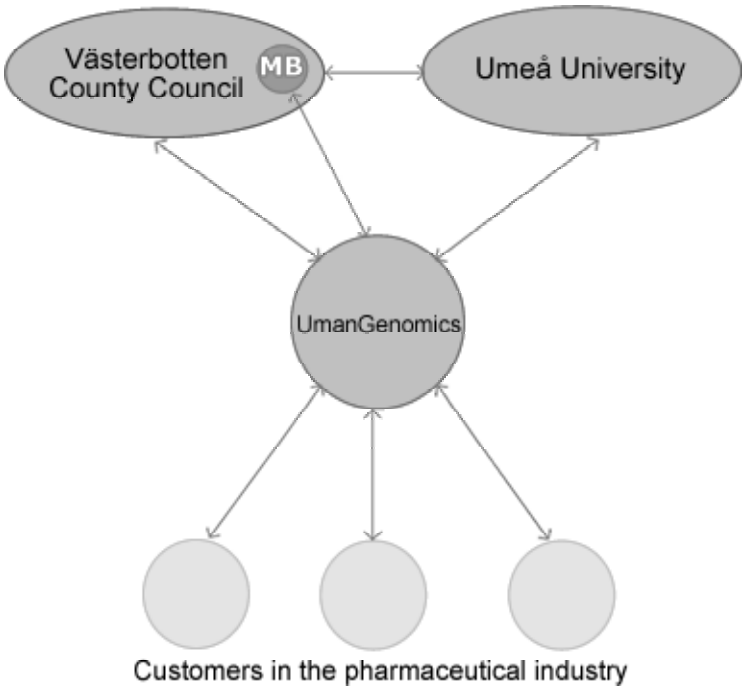
Table 1. Some facts about the commercialisation ventures

	deCode	**Oxagen**	**UmanGenomics**
Type of biobanks	Disease-specific *New*	Disease-specific *New*	Population-based *Pre-existing*
Number of biobanking partners	Many *(Icelandic physicians)*	Approx. 30 *(European academic groups)*	One *(The Medical Biobank)*
Does the company have own biobanks?	Yes	No	No
Where are the biosamples physically stored?	deCode	Oxagen	The Medical Biobank
Does the company have exclusive rights to commercialise?	Yes (without limits)	Yes (2-5 years)	Yes (20 years)
Year of foundation	1996	1997	1999
Number of employees (end of 2002)	Approx. 450	Approx. 100	16
Revenue (2001)	MSEK 290 *(MUSD 32)*	MSEK 50 *(MUSD 5.5)*	0
Net loss (2001)	MSEK 430 *(MUSD 48)*	MSEK 125 *(MUSD 14)*	n.a.
Key industrial partners	Roche Merck	AstraZeneca Pfizer	
Private/public company	Public	Private	Private
University ownership	None	7%	60%

If we start with UmanGenomics, this company was founded for the specific purpose of commercialising one large and already existing biobank (see figure 5). This biobank can be used for conducting prospective studies on a large number of different diseases. The biobank remains under the control of Umeå University and the Västerbotten County Council, but UmanGenomics has a strong agreement with the two principals giving it exclusive rights for twenty years to use the biobank for commercial research.

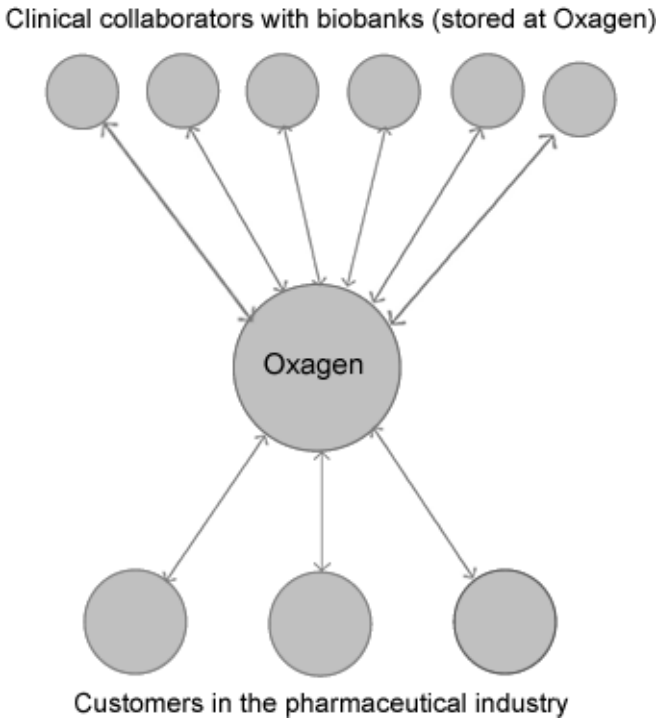
UmanGenomics is still a very small company, and unlike the other two it has not yet concluded any agreement with customers/partners in the pharmaceutical industry. The large public sector ownership (via Umeå University) also distinguishes UmanGenomics from deCode and Oxagen, which were financed by venture capital from the beginning. But as mentioned, UmanGenomics will be further privatised.

Figure 5. Simplified illustration of UmanGenomics in its network



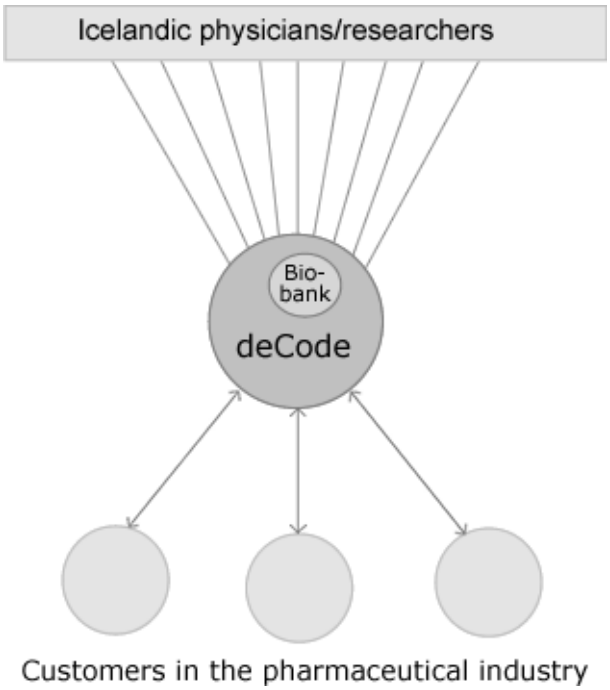
Like UmanGenomics, Oxagen was started up in close contact with a university. But unlike the former it cannot be characterised as a true spin-off. It was academics that took the initiative in establishing the company, but it did not get any start-up access to specific technologies, competencies or biobank resources from the University of Oxford or The Wellcome Trust. Oxagen had to go out and negotiate such access with various clinical partners. From the beginning it was clear that the company would establish collaboration with a number of academic research groups in the UK and abroad. This was necessary, due to the scientific strategy of carrying out disease-specific studies based on family collections. Collaborative agreements have been made with some 30 academic groups within nine different disease areas (see figure 6). In most of these cases, Oxagen is financing the collection of samples, which are specifically intended for the project. Thus, in contrast to UmanGenomics, Oxagen does not normally make use of pre-existing biobanks. Another difference is that Oxagen has close collaboration with the researchers who collect the samples. UmanGenomics is planning to use the samples in-house, without involvement of the Medical Biobank (but in order to gain access to clinical information UmanGenomics will probably need to establish co-operation with clinical researchers).

Figure 6. Simplified illustration of Oxagen in its network



Like Oxagen, deCode is the result of a totally private initiative – that is, it did not spin off from a particular institution. But like UmanGenomics, instead, it has a strong local anchorage in the region where it is located, and from which all research subjects are recruited. Iceland and the County of Västerbotten in fact have roughly the same head of population (some 270,000). However, the scientific approach rather resembles Oxagen's, building as it does on a number of disease-specific collections which are created for each project and with full funding from deCode. The collecting of samples and information is done through collaboration with many individual physicians and clinical researchers who have contact with the patients (see figure 7). A major difference from the other two companies is that deCode has full disposal of the collections, which are stored in the company's own biobank. That is, deCode has unlimited access to the samples. Nonetheless, in many projects deCode has chosen to collaborate with Icelandic clinical researchers who can contribute additional competencies and information.

Figure 7. Simplified illustration of deCode in its network.



The following more systematic comparison of the three cases takes its starting point in the issues identified in section 3. We will start by discussing how the focal relationship between the biobank unit(s) and the genomics company is organised. We will then turn to consider the characteristics of the main actors.

8.1 Conditions for access to biosamples

The conditions for the transfer of biosamples from the biobank unit to the genomics company are a crucial and many-faceted issue. As the UmanGenomics case in particular has illustrated there are several questions that need to be sorted out.

First there is the problem of *disposal of the samples* in the biobank. In all three cases, the samples are collected by or through clinical researchers, physicians or care centres. They have contact with the patients/research subjects and invite them to donate their blood for research. In the case of deCode, the company pays for all the work involved in collecting and handling the samples and the information, which are subsequently transferred to the company's facilities for storage and use. Consequently, in this case, the biobank definitively belongs to deCode. It has the full right of disposal, within the limits given by the informed consent obtained from the donors (i.e., the purpose for which the sample has been donated). The physicians and researchers who helped deCode to get the samples cannot claim to have any rights to control the use of the samples. In other words, the situation is quite straightforward.[13]

[13] In some projects, deCode also uses biosamples stored in a clinical biobank at a hospital or in the biobank of a private research institute (such as the Icelandic Heart Association). In these cases,

Like deCode, Oxagen normally covers all the costs of collecting the samples and building the biobank. The collecting is done by the clinical partners, but sometimes with support from Oxagen's personnel. While deCode carries out most of the scientific work in-house, Oxagen's clinical partners are responsible for the studies together with Oxagen. The collaboration agreements give the researchers the right of disposal over the samples (the "guardianship" as Oxagen prefers to call it) – in spite of the samples, for practical reasons, being physically stored at Oxagen. Oxagen possesses suitable equipment for handling and storage of samples (and donor information) and carries out the genetic analyses. The research carried out by the clinical partners is also funded from other sources, which is why Oxagen cannot claim to be the "owner" of the biobanks. It would, however, prefer such a situation, as conferring stronger and more long-term control of the samples, but then Oxagen would have to pay more and it cannot afford to. Now, in return for its contributions, financially and in kind, Oxagen has got exclusive rights to commercialise the results from the studies as long as the agreement is valid, that is 2-5 years (with a renewal option). Again, it can be concluded that the situation is fairly straightforward, and it seems that so far the disposal issue has not caused any conflict between Oxagen and its partners.

In Umeå, by contrast, the question of who has the right of disposal over the samples has given rise to a profound conflict with detrimental effects on the company. The background is that some of the researchers and other persons behind the Medical Biobank, including the head of that unit, argue that they have the right of disposal over the biosamples. Although they do not oppose the commercialisation as such, they do not like the way it is done and they have not accepted Umeå University and the Västerbotten County Council signing agreements with UmanGenomics without asking for their approval. These persons claim that "the researchers" should control UmanGenomics' use of the samples. This would be necessary in order to discharge obligations towards the donors and the financiers of the biobank research. For example, they maintain that certain grants have been made on condition that samples will be available for the supported projects. Given that the sample volumes are scarce, they fear that commercial use will lead to the exhaustion of certain valuable parts of the biobank – unless the latter is controlled by the researchers.

The counterparty has rejected these claims, arguing, *inter alia*, that the "teacher exception" for Swedish universities, or other intellectual property rights, is not applicable in this case. The teacher exception means that academic researchers have the right to commercialise the intellectual properties resulting from their own "free research".[14]

As the UmanGenomics case illustrates, the question of who has the right of disposal may turn out to be legally complicated when an already existing biobank is to be used for commercial purposes. For example, the question is whether anyone holds copyright protection (*upphovsrätt* in Swedish) for the biobank (i.e., in terms of

deCode only has access to material for analysis, and deCode is supposed to destroy the remaining material when the study is finished.

[14] See Wolk, S. 2002 for a more extensive discussion of the teacher exception and its application in biobank contexts.

its abstract structure – not the physical biosamples as such).[15] In the case of the Medical Biobank it has been preliminarily concluded by civil law researchers that this biobank may not have a sufficiently unique structure to qualify for copyright protection.[16] But instead a similar protection based on the *sui generis* right might possibly apply.[17] Both rights combined could also apply to the biobank.

If the researchers who built the biobank have such a copyright or *sui generis* right, they can object to certain dispositions with the biobank – in some cases including the material contained therein – if they wish. This right does not generally cover the withdrawal of individual samples. However, this may be the case in some situations. For instance, if a withdrawal of samples contains the protected structure of the biobank, the copyright holder must give his or her permission. The extraction of samples may also constitute a breach of the *sui generis* right. In the case of UmanGenomics, each withdrawal would comprise too limited a number of samples – probably less than 1,000 in most studies, compared to the 66,000 samples in the VIP cohort). However, if a large number of samples are used in studies carried out by UmanGenomics over a longer period of time, this may be regarded as an unauthorised extraction of the biobank and thus fall under the *sui generis* protection. It should be noted, however, that this has not yet been tried in court.

These kinds of intellectual property rights arise automatically from the creation of a work or the production of a database. In infringement proceedings, therefore, a court can only establish the existence of the rights. It should be noted that there is no registration procedure as with other types of intellectual properties (patents, trademarks, etc) that could serve as proof of the existence of the rights.

An additional problem in this case is to decide who has this possible right. There are many individuals (and financiers) who have been involved in biobanking since the mid-1980s. Obviously, opinions vary concerning the role played by different individuals and organisations. Resolving this does not look like being an easy task.

Given the present uncertainty surrounding the legal aspects of the disposal of biobank materials in Sweden, it would be useful if a concrete case, such as the conflict in Umeå, were brought before the Court of Justice of the European Communities. That would probably help to clarify the situation.

As to the transfer of individual (physical) samples to genomics companies, another important aspect of the disposal has to do with the "contracts" with the donors. In the deCode and Oxagen cases, the consent form signed by the donors clearly states that the sample will be used by a company (for a specified purpose), so there is no problem in this regard. In Umeå, no commercial use was initially

[15] From an intellectual property rights perspective, a biobank constitutes a database, and under certain conditions it can be protected under the Copyright Act. It should be observed that the copyright and other similar intellectual property rights, like the closely related *sui generis* right, are not concerned with protection of the physical objects as such (e.g. biosamples). What these rights protect is an abstract phenomenon, such as the structure according to which samples in a biobank are organised in the case of copyright. However, the exercise of the rights may concern the physical material as parts of a protected object. See Hellstadius, Å. (2002) for a more detailed discussion of biobanks and intellectual property rights.

[16] Hellstadius, Å. 2002.

[17] The *sui generis* right means that someone who has invested considerable resources in producing a catalogue, table or other similar database can be granted a right to produce copies of the work and make it available for the public (see, e.g., Hellstadius, Å. 2002).

intended. Those who donated blood in the past did it for the purpose of "disease-prevention research". The recipients were Umeå University and the Västerbotten County Council. Now, that UmanGenomics, a profit-driven company, wishes to use "old samples", the agreements will have to be "renegotiated" in some way. One possible solution is to go back to the donors on a project-by-project basis and ask them for a renewed informed consent. This is manageable, of course, but will cost money and probably lead to some research subjects dropping out.

One general conclusion that can be drawn from the Swedish case is that the disposal issue needs to be sorted out before starting the commercialisation of an existing biobank. It is advisable to identify all those who may claim any rights to the biobank and to solve possible disputes in advance, for example, by signing formal agreements with all actors involved. Otherwise, any conflicts arising may jeopardise the whole venture, as we have seen in the case of the Medical Biobank in Umeå. As Urban Paulsson and Rebecka Frisk write in another chapter in this book, given the unclear legal situation with regard to the disposal of biobanks, companies are advised to secure the necessary rights by making agreements both with the university *and* with the researchers.

Another somewhat related issue has to do with the more specific *commercialisation rights*. It is common for clinical genomics companies to be granted exclusivity to use a certain biobank commercially, at least for a certain period of time. We have seen examples of this in all the three cases quoted above (see, e.g., table 1). Given the fact that the samples are collected, in most cases, with the help of employees in the public sector, it is reasonable to question whether this is a good policy. Even if there is no limitation on non-commercial research, such an agreement has the effect of excluding other companies from using the biobank. One possible effect is that certain research projects that might have resulted in valuable new knowledge or health care products will not be carried out. This leads to a welfare loss to society.

But there are also arguments in favour of granting exclusivity. First, when companies like deCode and Oxagen cover the costs of biobanking it is fair, of course, that they should get exclusive rights. The Umeå situation is different. Here, the Medical Biobank has existed for a long time. UmanGenomics will pay only a limited sum (MSEK 2 per year) to cover the additional cost of sample and information handling. Even so, it has got exclusive rights for twenty years. One effect of the deal is that academic researchers at Umeå University who are using the biobank are not allowed to collaborate directly with pharmaceutical firms (unless they get approval from UmanGenomics). This is a disadvantage of the present arrangement. Nonetheless, at least one argument can be put forward in defence of such a deal. When, as in Umeå, the aim is to use the biobank and its commercialisation as a tool to develop the local industry and research environment, the company has to be assured of secure access to samples (which represent a finite resource). This is because a new genomics company established adjacent to the biobank would have to invest in various facilities, which means that it is taking a financial risk. Without granting exclusivity for a reasonably long period, it might be difficult to find private investors prepared to make the requisite investments.

One conceivable solution to this problem would be to let the public sector finance the company by using taxation revenue and without demanding a financial return. Then it would be easier for the company to accept the biobank resource being

shared with other firms. However, such a solution may not be feasible or desirable for a variety of reasons. The public institutions concerned may not have enough money available. It can also be questioned whether it should be the role of public institutions to engage themselves in this kind of risky business venture. Moreover, Swedish law limits the right of public institutions to run businesses.

It can be mentioned that the plan to create a large population-based biobank in the UK does not include the establishment of any business or the favouring of any specific company. Pharmaceutical firms will be able to apply for access to the biobank. But the UK Biobank will carry out all genotyping, on the companies' account. The firms will have to feed back all research results, but they will be given a 6-month grace period for patenting.

To summarise, it can be concluded that despite the drawbacks of giving exclusive commercialisation rights to a selected firm, there may in some cases be valid reasons for doing so. Without such incentives the potential for commercial research based on a certain biobank may not be realised at all, or at least not locally.

The *economic conditions* for access to samples and information have already been touched upon. When new biobanks are created for the purpose of commercial research there is in general no problem. The company pays for the sampling and gets the appropriate rights in return. Again, the question is more complicated when it comes to exploiting existing biobanks. How much should the company pay for the access? UmanGenomics, according to the present agreement with the principals of the Medical Biobank, only covers parts of the biobank's running costs. It does not pay anything towards the heavy investment costs embedded in the biobank. According to a previous agreement, UmanGenomics would have had to pay the principals an additional annual royalty on its sales. However, this clause had to be deleted under a new Swedish Act on Biobanks in Health care, which came into force on 1 January 2003. The Act prohibits the transfer of biosamples for financial gain. The legislators' intention was to prevent individuals or organisations earning money on the trading of biological materials. One consequence of the law is that public institutions building up a biobank for research[18] cannot recover part of their capital expenditure by making companies pay a royalty. But there should be other ways of charging commercial users a price that takes into account the total cost of building the biobank, without violating the law. However, it would not be possible to charge a "mark-up price" corresponding to the market value of the biobank, if that is higher.

The current payment conditions applied in Umeå mean that the commercialisation rights are transferred at a very low price, given the total costs incurred in building the biobank and given its presumed value. In cases where exclusive rights have been granted to one firm, the reasonableness and fairness of such a solution can be questioned. It can be seen as a subsidisation of an individual firm.[19]

There is no doubt that the use of publicly operated biobanks in commercial research is important to society, since it may contribute to the development of new products

[18] A research biobank is covered by the new act if some health care provider is involved in the collecting of samples.

[19] Moreover, it can be argued on the basis of received economic theory that the prohibition of putting a market price on access to biosamples (e.g., translated into a royalty percentage) will lead to ineffective allocation of scarce resources (given the difficulties of appropriating the gains from biobank investments).

that improve health care. However, if private biotech companies should be allowed to make profits on their use of public biobanks it is not unreasonable that they should share their profits with those who place the biobank material at their disposal. This type of industrial use of biosamples cannot be compared with the (unethical) trading of human organs and other biological materials that constitutes the main target of the new Biobanks Act in Sweden (and the older Transplantation Act). It is not the individual sample that is of interest to the receiver, but the result that can be obtained by analysing a large number of samples. Therefore, the profit prohibition in the Swedish law, as it is formulated today, seems to be unwise – at least in the context of the normal use of biosamples in commercial research. For example, the payment of royalty as discussed above should not be regarded as unethical, and therefore be forbidden. It can be noted, incidentally, that this kind of solution is applied in Iceland in the case of the health sector database. That is, deCode will pay a royalty to the Icelandic government for its right to build and operate the database. To the author's knowledge, there have been no protests against this in the heated ethics debate on the project. It is true that deCode's licence does not include access to biosamples, but nonetheless the case illustrates an interesting application of the royalty solution in a similar context.[20]

The discussion of the profit prohibition illustrates one important effect of *legislation and regulation* on the commercialisation of biobanks. This is only one of several rules confirmed by the new Swedish Biobanks Act, which is applicable when a health care provider carries out biobanking. Research biobanks containing samples obtained from a health care provider are also covered by the Act. A more general discussion of the provisions introduced by the new law can be found in Elisabeth Rynning's chapter in this book.

It should be noted that the law does not cover biobanks built up without connection to health care, for example, when companies collect samples directly from people. But when companies gain access to biobanks covered by the law they are concerned in the same way as other users, such as academic researchers. One aspect to be discussed later on is the requirement of informed consent.

The commercialisation of public biobanks may of course also be affected by other laws. In Sweden, for example, the Local Government Act regulates what the county councils can do. Among other things, the Act forbids county councils to engage in industrial activities with a view to financial gain. That is why the Västerbotten County Council cannot be a shareholder of UmanGenomics. The Swedish universities are not allowed to run businesses, but in recent years they have been given the opportunity of starting state-owned holding companies to support commercialisation of research findings. Uminova Holding's shareholding in UmanGenomics is one such example. The issue of publicly owned companies and the commercial use of biobanks is commented on in Ulla Björkman's chapter in this book. In a separate paper, she concludes that arrangements of the type implemented in Umeå are doubtful from a legal point of view.[21]

Needless to say, the transfer of biosamples and information to the genomics company must follow certain *rules and routines* agreed upon by the parties. To some

[20] The prohibition of for-profit transfer of human tissue in the Swedish Biobanks Act is discussed in more detail in Domeij, B. 2000-01 and 2001, and in Björkman, U. 2002.
[21] Björkman, U. 2002

extent the design of the transfer process is affected by legislation, for example, with regard to ethical approval of research on humans.

The routines applied in the three cases are described in some detail in the full report.[22] It shows for example that the Medical Biobank has in recent years developed a system of quality assurance, partly in response to demands from UmanGenomics. The operations of the pharmaceutical and biotechnology industry are strictly controlled by different rules and standards, such as the international principles of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP). It is not unusual that such rules are first introduced in the industry and later on applied by universities. Companies in general are very concerned with such issues as quality, security and ethics. If these are not handled in an appropriate way, the companies may suffer seriously from bad publicity. Therefore, it is not surprising that the involvement of companies in biobanking leads to improvements in the general routines by which biobank work is guided.

When it comes to the specific routines for transferring samples and information to the company, privacy protection – to be elaborated below – is a key issue. Another question is how the results of analysis are to be handled. In the case of deCode, which has its own biobank, the results logically belong to the company. In the case of the Medical Biobank, the principle long since applied is that all results, e.g. from genotyping, should be fed back and stored for future studies. Generally, this is a good practice that increases the value of the biobank for research. But applied to a company like UmanGenomics it poses rather a problem. According to UmanGenomics, potential customers are unwilling to accept the results obtained being made available to other researchers. Understandably so. The solution proposed for the UK Biobank seems to be a good one, in cases where publicly financed biobanks are used commercially. Here, the companies have to report back all analysis results as well as conclusions, but only after they have had time to secure intellectual property rights. This is similar to the practices applied in clinical trials of drugs, where the findings are published after sponsoring companies have had a chance to file patent applications.

8.2 Protecting the donors' integrity

Unless the biosamples are completely anonymised, the *protection of the donors' privacy* becomes an important issue in all kinds of research on biobanks. Security systems and practices are needed to ensure that sensitive information about individuals is not communicated to unauthorised persons. The risk of information about disease predisposition coming to the knowledge of insurance companies and employers has attracted particular attention. It is not unreasonable to suspect that companies with access to biobanks might have a commercial interest in selling such information. Privacy protection ought therefore to be especially important in the context of commercial research. But technically speaking, the problem is principally the same as when biosamples are used by other external researchers.

Coding personal identifiers before transferring samples and information to the company is the dominant mode of protection today. Thus, a decoding key exists, but it is kept secret by the biobank unit or some other public sector organisation. The

[22] Laage-Hellman, J. 2003.

fact is, however, that companies carrying out genomics research do not normally need to know the donors' identity.

Computerised techniques, some more sophisticated than others, are used to encrypt the identity, and sometimes the information as well. In Iceland, not least, a lot of efforts has been put into data protection. Today's use of biosamples by deCode (and other similar companies) has to comply with strict security demands from the authorities. As to the planned health sector database and its combination with genetic data, obtained from deCode's biobank, the security requirements from the government are so far-reaching that many observers believe the database will be of little use for research. This example illustrates the danger of insisting on very high security levels. The danger is that the use of a biobank will be made so complicated and costly as to render the research unprofitable, and also that the biobank's potential for developing new products might not be used to the best possible advantage.

In the Icelandic case one of the motives for requiring such a high level of security is that the health database builds on presumed, as opposed to explicit, consent[23], and must only contain non-personally identifiable data (i.e., there should be no key). However, there are critics who claim that the use of a one-way coding system does not completely eliminate the possibility of tracing identities, and that consent should therefore be obtained a priori.[24]

Ensuring confidentiality of identity is not enough. Good ethical practice according to current international standards for clinical research also requires *protection of the donors' interests*, and especially protection from unwanted risk exposure. That is why the principle of informed consent is often applied both when taking and storing samples and when using them for research later on.[25] In fact, the new Swedish Biobanks Act stipulates explicit informed consent on both occasions. Whether or not the original consent to storage will suffice when a sample is to be used for research at a later point in time is for the research ethics committee to decide. The decision should be based, *inter alia*, on the purpose specified in the first consent.

When samples are used in commercial research it is important that donors be informed of corporate involvement. The implications of this have already been commented on in section 8.1.

When creating a new biobank for the study of a specific disease, as deCode and Oxagen are doing, the purpose of the research can easily be specified. But when pre-existing biobanks, like the one in Umeå, are used, things get more complicated. Depending on the content of the initial consent and the purpose of the study, it may be necessary to go back to the donors for fresh informed consent. Many researchers perceive this to be an inconvenience, but in many situations such a procedure is probably an unavoidable effect of modern ethical guidelines and legislation. It is too early yet to say how the new Swedish Biobanks Act will work in practice. It remains

[23] Given the broad use intended, the concept of informed consent in a true sense might not be possible to implement in this case.
[24] Arnason, E. 2002.
[25] According to the guidelines of the Helsinki Declaration, which began to be developed in the 1960s, informed consent should always be obtained from human research subjects.

to be seen if there will be any change compared with the current (unregulated) practices that have emerged in recent years.[26]

It is interesting to note that Iceland is discussing the introduction of a new type of written consent which would give donors the option of permitting very broad use, if they wish. According to the proponents, this type of explicit consent has the advantage of facilitating the work of ethics committees. Furthermore, it is thought that such a practice would benefit companies collecting biosamples for broad research programmes. But there is some uncertainty whether the Icelandic Biobanks Act will have to be amended, since it requires informed consent for the building of scientific biobanks.[27]

This Icelandic initiative represents a pragmatic attempt to find solutions that make biobank research more efficient at the same time as each individual donor is given the opportunity to decide the scope of the consent. It seems that a majority of the population would be prepared to grant broad consent according to the proposal, but this remains to be seen.

As shown in Lena Ring and Åsa Kettis Lindblad's chapter, based on a pilot study, the general public in Sweden seems to have a positive attitude to the use of biosamples in medical research. To what extent that also pertains to commercial research remains to be examined.

8.3 Organising the genomics company

The *division of labour* between the genomics company and the biobank unit(s) is not given beforehand. The tasks that need to be carried out can be divided up in different ways. deCode and Oxagen represent two opposite approaches. In the former case, the company takes a very active part in the sampling process and is mainly self-sufficient with regard to the subsequent research activities. Oxagen, by contrast, relies to a great extent on the intellectual work carried out by the clinical centres. The deCode way is more expensive, of course, but gives the company a better control over the biobank and the research activities. Oxagen is more dependent on its biobanking partners, but can on the other hand take advantage of the competencies and resources possessed by the academic institutions.

It is not possible to establish, on the basis of the data collected in the present study, which of the two approaches yields the best scientific results (or leads to better commercial and economic success). It can be hypothesised that both models are workable if appropriately implemented. But it is interesting to note that in some disease areas deCode has established co-operation with academic research groups in Iceland. It seems, in fact, that the best results have been obtained in these studies. This shows the great advantage of linking the genomics company to university research.

UmanGenomics have not yet started to use samples from the Medical Biobank, but the present agreement entitles it to use them for in-house projects. UmanGenomics has already established co-operation with clinical scientists in Umeå in the fields of disease registers and familiar diseases. Also when it comes to the future use of the biobank, assuming that the present conflict will be solved in one

[26] A previous study within the project showed that researchers in both industry and academia feared that the new law would bureaucratise the use of biobanks (Laage-Hellman, J. 2001b).

[27] By contrast, presumed consent is sufficient for saving samples in clinical biobanks (but not for their use in research).

way or another, it will be advantageous to team up with clinicians at the university hospital. Actually, this will probably be necessary to some extent in order to access the clinical information needed to conduct the studies.

Many interested parties see UmanGenomics as a tool for developing the local environment. There seems to be a lot of high-quality research in Umeå. But for the long-term development of the company it might be a good idea to broaden the academic base and also establish co-operation with clinical researchers from other parts of Sweden (and maybe abroad). These researchers should be in the forefront in the disease areas targeted by UmanGenomics. They could work with material from the Medical Biobank and/or with other collections. Such an approach would not threaten the local connection of the business activities in Umeå as long as regional interests have a decisive influence on the company's decision-making. But the establishment of collaborative relationships with a greater number of academic partners would strengthen the company's resource base and make it a more attractive partner to the pharmaceutical companies.

It goes without saying that the success of any company is dependent on *the choice of business model, strategies and internal organisation*. This issue is not only of importance to the shareholders and managers of clinical genomics companies. Long-term commercial and economic success is a prerequisite for the company's ability to effectively perform its role in the innovation process and thereby contribute to improvements in health care. In other words, if the company fails in the market, the potential benefits of using biobanks to develop new products might fail to be realised – especially in cases where a single company has exclusive rights to commercialisation. This would be a loss to future patients and society in general.

We can note that the business model and strategies for the core activities are quite similar as between the three companies investigated, despite great differences in their achievements hitherto. They all follow the general trend in the genomics industry to integrate forward into drug development. Given the current changes in the pharmaceutical industry this kind of move seems to be a prerequisite of survival.

deCode today is considerably larger than the other two companies, in terms of both personal strength and earnings (see table 1). Its faster growth can be attributed, among other things, to its raising a large amount of venture capital and to its early alliance with Roche, which gave deCode a flying start. UmanGenomics has been beset with growing pains, which at least partly are a direct consequence of the dispute over access to biosamples. Furthermore, unlike deCode and Oxagen, UmanGenomics has been a company owned and controlled by public sector interests. With hindsight, the commercial wisdom of this arrangement is open to question. With regard both to finance and business competence, it might have been better if a privately owned company had been formed from the beginning. With early financing from the VC market and access to more competence from the biotech industry, e.g. via board members, the preconditions for the company's development and growth might have been better. As we have seen, however, there were specific circumstances related to the Medical Biobank that rendered such a solution difficult, if not impossible. The venture is in fact complicated by a multitude of legal, ethical and economic complexities. It remains to be seen if the ongoing privatisation, aimed at giving UmanGenomics an ownership structure more similar to that of the other two firms, will help to trigger a sound business development. There are still several obstacles to be surmounted.

Just as with other biotech start-ups, early *financing* is crucial to the formation of clinical genomics companies. Generally speaking, the use of venture capital has played an important role for the commercialisation of biobanks. In the 1990s, there was a strong, international VC boom, with plenty of capital searching for investment opportunities. The biotech industry, perceived as offering an attractive potential for growth, thanks to rapid advances in the biosciences and strategic changes in the pharmaceutical industry, became a popular target for the venture capitalists. The high valuation of biotech firms on the stock markets gave promising exit possibilities. It was during this period that deCode and Oxagen were founded. The former especially, turning to the large American VC market, managed to raise a lot of money.

Today, as we all know, market conditions are very different. It has become difficult for biotech companies in general to raise new capital. Besides the general slump in the VC and stock markets, the poor economic performance of many biotech firms has helped to make investors chary of the industry. This includes companies specialising in clinical genomics, since it has turned out to be more difficult than expected to make money out of this business, mainly, as it seems, because the pharmaceutical companies are reluctant to invest externally in early-stage genomics projects. Instead they prefer buying validated drug targets or substances in clinical trials, i.e. research results that can be turned more quickly into marketable products.

This unfavourable situation in the capital market, as well as in the market for the genomics companies' services, means that starting up a new clinical genomics company would be more difficult today – at least if it were to be financed on the VC market.

Apart the purely financial considerations, there are other aspects to the *ownership of the company*. For example, given the key role of public sector institutions in biobanking activities, is public sector ownership necessary for protecting the interests of the donors, society and those who collect the samples? Apparently not. There is nothing to show that public sector ownership *per se* would lead to better use of biobanks – from an ethical or economic point of view. If anything the opposite is true, as witness developments in Umeå. Apart from the legal prerequisites, provided for example by the new biobank laws, the important thing, as we have already discussed, is how the conditions for access are regulated, for example through formal agreements between the actors concerned (see section 8.1).

However, when the aim is to use the commercialisation venture to strengthen the local environment, as in Umeå and Iceland for instance, then locally established ownership may be important. This provides a kind of guarantee of local or regional considerations being taken into account in the company's decision-making, e.g. on location issues. But this does not necessarily mean that the shareholder must come from the public sector. Private owners can fulfil the same function, if they are locally committed.

It should be noted that these (legitimate) ambitions to commercialise biobanks locally, for example as an element of industrial policy, may come into conflict with other performance variables (see figure 4). Thus, it may be that certain samples in a biobank can from a scientific point of view be more effectively used by someone located elsewhere (who has suitable, complementary resources and

competencies). Also from the genomics company's point of view, it does not go without saying that performing all activities locally is the most businesslike solution. In the case of deCode, for example, it seems to be an open question to what extent the company's planned investments in downstream drug research will be located in Iceland or in the US. From a business development point of view, the US might be the best location. However, the Icelandic government, which is expected to support the company by issuing a state guarantee for a convertible bond, is anxious for the investment to be made in Iceland.

8.4 Organising the biobank unit

How to organise biobanking in the public sector – that is, within the health care system and at universities – is an important issue generally, regardless of whether or not commercialisation is planned on, because biobanks, clinical as well as research-based, are expensive to build and operate and because there is a growing interest in using them for scientific purposes. This calls for organisational solutions leading to cost-efficient and quality-assured biobanking and rational and secure procedures for withdrawals. In many places, at least in Sweden, work has been initiated to reorganise existing biobank activities, for example, by creating core facilities or co-ordinating distributed biobanks within hospitals.

New biobank laws and regulations planned or implemented in various countries also imply requirements for organisational changes. For example, the new Biobanks Act in Sweden has given the principals of the health care services (i.e., the county councils) new tasks. The principals have to develop new routines for handling the informed consent for clinical samples to be saved more than two months, which is now required by the new law, to mention just one example. It seems that many of the county councils were poorly prepared for making these stipulated changes when the new law came into force only recently.

These general aspects of biobank organisation are important but have not been addressed in the present study. The relevant question here is how the organising might be affected by commercialisation. In many cases, the implications are not very far-reaching. Actually, most *health care-based biobanks* are not used for commercial purposes. But when they are, this usually means academic researchers who are collaborating with industry using the samples from the biobank.

As has already been remarked, there is a need for routines regulating the withdrawals of samples from the biobank, but there is no great need to treat industrial users differently from other external users (in cases where companies, with or without academic partners, wish to use biosamples in commercial projects). One possible exception pertains to the economic conditions. A widespread rule internationally is to not charge academic researchers, the reason being that scientific criteria, not money, should determine the use of samples. But it is not unreasonable to make companies pay, for example, a fee per sample commensurate with the cost of running the biobank. This principle is now applied in Iceland, where deCode and other companies are using samples from the big national tissue bank at the university hospital. There is, however, a dispute regarding the price, which has limited the number of samples used so far.

The industry is primarily interested in *research-based biobanks* containing well-characterised materials. When new disease-specific biobanks are created for the purpose of commercial (or industrially-sponsored) research. an important

organisational issue is where to locate the biobank physically. It is not unusual for the samples to be stored in the company's facilities. Both Oxagen and deCode do so, for example. This is in many cases a good solution, since companies often have more suitable resources, routines and systems for managing biobanks safely and efficiently (compared to university departments, unless specialised core facilities have been created). Furthermore, this is practical when the company carries out the genetic analyses. It is important, however, that the disposal issue be settled in advance.

This solution works when the research group operates exclusively with one company. If the researchers want to maintain their freedom to collaborate with several companies, then obviously they need to have full control of the samples. But a "strategy" of this kind may also make it hard get companies to pay for the sampling. Since the financing of biobanking is a problem to many academic researchers, the establishment of partnerships with industrial firms, e.g. genomics companies, may be a good solution. But that will also mean some rights having to be renounced.

For population-based biobanks the organisational issue is somewhat different. Unlike the former, such a biobank can be used for studying different diseases. Thus, there are many potential users both in academia and industry. In the UK, as already mentioned, the population-based biobank to be created there will not have special ties to any individual firm. Estonia and Umeå have for various reasons chosen a different approach.

As to the organising of the Medical Biobank in Umeå, it is difficult at present to generalise from their experiences, due to the complex situation caused by the dispute over commercialisation. However, the sharing of responsibility between the university and the county council seems to be a good arrangement. In this way the biobank can probably be used more efficiently both for research and for medical care. Given the value of the biobank, the sensitive information it contains and the large number of interested parties, the control aspect is important. In order to avoid the type of serious conflict that has arisen in Umeå, there is a need for a clear division of roles and responsibilities and an unambiguous management structure.

Everybody agrees that the Medical Biobank should be organisationally separated from the commercial unit. As we have already seen, UmanGenomics today operates as a totally independent company, but with an agreement giving it exclusive access to the biobank. Göran Hallmans and others have proposed an alternative commercialisation model, making commercial activities subordinate to the biobank. That organisational model, described in the main report[28], means that the commercial projects are controlled, and to a large extent carried out, by researchers linked to the biobank. Furthermore, all profits are channelled back to academic research. In short, it can be concluded that this model has different goals from those of the present model. Its main purpose is to support academic research rather than building a thriving biotech company. It is an interesting concept, but it should rather be seen as a novel way of organising direct co-operation between academic research and the pharmaceutical industry. As such it deserves to be taken seriously and critically examined, but for reasons of space that cannot be done here.

[28] Laage-Hellman, J. 2003.

9. Concluding remarks

In section 3, a number of important issues related to the commercialisation of biobanks through dedicated clinical genomics companies were identified. Based on the three cases, these issues have been discussed and certain conclusions drawn. Evidently, all issues have not been dealt with in depth, partly due to the limited space available here. The interested reader is therefore referred to the full report. Furthermore, the empirical data collected in this study has not allowed a thorough examination of all aspects. Thus, there is a need for further research in order to gain a better understanding, for example, of how to build a successful clinical genomics company and how to organise biobanks in the public sector.

The basic question underlying the present study was how best to organise the commercialisation of biobanks through clinical genomics companies. However, as this chapter hopefully shows, there is no universal "best way" of organising commercialisation. No such optimal arrangement exists. First and foremost, the prerequisites for each individual venture will always vary according to differences of local environment and historical context. The solutions chosen need to be adapted accordingly. Second, there are always different parties with varying interests involved. A particular set of solutions, and the associated outcome, may be perceived as good by one party and as unsatisfactory by another. Theoretically, one should try to find a combination of solutions leading to an optimal balance between the different interests. Given the complexity and dynamics of the phenomenon, finding such an optimum looks like being very difficult in practice. Instead, the aim of the present study, summarised in this chapter, has been to provide those involved in biobank commercialisation with a better understanding of the phenomenon and with some help in selecting or designing solutions which will meet different demands and objectives. In each case, there will always be abundant scope for improvement in several performance dimensions.

We may add that a commercialisation venture is never "designed" by one single actor (even if the attempt be made). There will always be several interdependent actors trying to influence the choice of solutions, based on their own interests and means of power. Thus, the characteristics of a certain venture, as it can be observed at a certain point in time, will always be the result of path-dependent interaction processes leading to a lot of compromises. In other words, a commercialisation venture cannot be "organised" in a true sense. Rather, its organisational characteristics and the resulting performance emerge as a result of interplay among many actors who are carrying out parallel organising activities in the network.

It follows that the actors' ability to interact with others and to build relationships in the biobank network is crucial to their own success as well as to the development of the whole venture. It is obvious, for example, that the disappointing development in Umeå at least to some extent is a consequence of poor relationships between certain key actors.

As in other industrial contexts, fruitful interaction with business partners and others always builds on a good understanding of the counterparties (e.g., what makes them tick? What are their goals and visions? What capabilities and other resources do they have?). But this is not enough. It is also important to understand how the counter-parties are linked to and dependent on other actors in the network, and how these

relationships affect the counterparties' behaviour. Given that the commercial use of public biobanks is rather a new phenomenon, it is not surprising that many of those involved do not have sufficient understanding of all the complexities inherent in the commercialisation process. Therefore, if this study can contribute to a better knowledge about the preconditions for effective commercialisation, an important purpose will have been accomplished.

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5

Public law aspects on the use of biobank samples – privacy versus the interests of research

Associate Professor Elisabeth Rynning

Department of Law, Uppsala University

In this Chap., the use of biobanks for research purposes is discussed from the viewpoint of public law. The key issues concern the balancing of the donors' right to privacy with other rights and interests involved, mainly related to freedom of research, the provision of good health care and the protection of property. The new Swedish Biobanks (Health Care) Act (2002:297) is analysed in light of relevant requirements laid down in public international law, and compared to the rules on processing of personal data. A few comparative notes are also made with regard to certain other jurisdictions. It is shown that on certain points the new Swedish biobank legislation is stricter than the corresponding rules on personal data, whereas on other points it fails to provide the privacy protection required in international law. Furthermore, the scope of the Act has not been made sufficiently clear and many biobanks are left unregulated. It is thus argued that the regulatory process must continue, and that legal developments both within and outside the EU should be closely observed.

1. Introduction

As is clear from the various contributions to this report, the construction of a satisfactory regulatory framework for the use of human biobanks requires the careful balancing of a number of rights and interests concerned. Sometimes the interests of individuals coincide with those of other individuals and of society, whereas at other times conflicts of interest arise.[1] In many ways, the conflicts of interests that can be seen in relation to biobanking resemble those that concern the processing of sensitive personal data. Human biological material, however, also has certain characteristics and properties that distinguish it from other sources of personal information. Furthermore, the samples may not be of interest solely for informational purposes, but also as raw material for certain products. New aspects thus add to the complexity of the balancing required in the regulatory process. Nevertheless, it still remains the duty of the legislator to provide appropriate judicial protection to both private and public interests in biobanking. In this process, the shared moral values and basic legal principles of the country or region in question must be considered, as well as state obligations under international law.

Defining the study object of the project, i.e. the concept of a human biobank, might seem to be a simple task. It is clear, however, that the term

[1] Cf. Hermerén, G. 1997, p. 23.

"biobank" is used in both fairly wide and not-so-wide senses.[2] Some biobanks might thus include any size or form of human biological material. Sometimes, the term is even understood to include not only the biological material as such, but also information on the persons who submitted the samples, as well as information obtained from the samples.[3] Less often, the term "biobank" may be used to describe only the narrow conception of a DNA bank. A tissue bank is more often – but not always – perceived as a narrower concept than a biobank.[4]

One general characteristic of biobanks, however, is that the collection should in some sense be structured, and the samples distinguishable from one another. Quite often, it is also required that the biological material be traceable to an identifiable donor. How this requirement should be understood is debatable, however, since in most cases there is at least a theoretical possibility of tracing human material to its donor, by means of genetic analysis and the application of other potent resources. Even in the rare cases where absolute anonymity may be obtained, the anonymous donors and groups related to them will still have certain rights and interests to be observed.

In this report, the wider biobank concept is used, although restricted to the biological material and thereby excluding information registered outside of the samples. All types of human biological material thus fall within the scope of the biobank concept used in the text, and matters of anonymity will also be discussed.

The public law part of the Biobank Project has dealt with a broad set of issues, with regard to judicial protection for the rights of individuals and groups concerned, as well as the need to facilitate efficient management and justifiable use of Swedish biobanks.[5] The study has involved the analysis of relevant areas of both Swedish and international public law, and also comparative aspects regarding the internal law of certain other jurisdictions, primarily the Nordic countries. Due to limitations of space, however, the present report is focused primarily on certain aspects of the use of Swedish biobanks in research.[6]

2. Some rights and interests to consider

2.1. Rights and interests of potential donors

Under Article 8 of the European Convention for the Protection of Human Rights and Fundamental Freedoms (1950),[7] everyone has the right to respect for his or her private life. The scope of the protection afforded by this article is considerable, and in the area of biomedicine made more precise by various Articles in the European Convention on Human Rights and Biomedicine (1997).[8] This latter Convention has

[2] See for example *Research ethics guidelines for using biobanks, especially projects involving genome research*, adopted by the Swedish Medical Research Council (MFR) in June 1999.
[3] See Section 2 of the Norwegian government's proposal, *Odelstingsproposisjon. nr. 56 (2001-2002)*.
[4] See for example EGE 1998.
[5] See report I from the project: Rynning, E. 2001.
[6] A more comprehensive, Swedish report on the results of the public law study will be forthcoming during 2003.
[7] Council of Europe 1950. Also incorporated as a part of Swedish domestic law; see *Lag (1994:1219) om den europeiska konventionen angående skydd för de mänskliga rättigheterna och de grundläggande friheterna*.
[8] Council of Europe 1997 a.

the specific aim of protecting the dignity and identity of all human beings and guaranteeing everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine. The right of privacy is also offered judicial protection in the area of EU law, primarily through Directive 95/46/EC on the protection of personal data. A more general right to the integrity of the person is recognised in Article 3 of the Charter of Fundamental Rights of the European Union (2000),[9] explicitly including the right to respect for physical and mental integrity as well as respect for the free and informed consent of the person concerned, in the fields of medicine and biology. Individual patients and research subjects are thus entitled to have their privacy respected, at least to the extent that infringements of this right are not necessary to protect certain other important interests regulated in national law.[10]

Another important interest of individuals concerns their access to health care of an appropriate standard. This is also considered a right protected, for example, under Article 3 of the Convention on Human Rights and Biomedicine and recognised in Article 35 of the EU Charter of Fundamental Rights. Assuring health care of good quality involves the keeping of medical records, and may also require the preservation of biological samples. Furthermore, patients and research subjects may have a direct or indirect personal interest in research being performed, and better methods developed for the treatment of disease. Even so, respect for privacy and personal integrity still means that the processing of personal information must be subject to certain restrictions and safeguards, and that individuals must as far as possible be allowed to decide what interventions may be performed on them, how parts of their bodies may be used, and whether or not they wish to participate in research and commercial enterprises.

2.2. Rights and interests of researchers and industry

Researchers have a justified interest in freely choosing their scientific problems and methods. This is a freedom recognised in Article 13 of EU Charter on Fundamental Rights and Freedoms and a principle also laid down by Swedish law.[11] In order to pursue this right, researchers need access to the necessary research materials, be it information or biological samples. Openness and freedom of information are thus important to researchers. With regard to information registered in official documents, which include most carriers of information produced in the public sector, the right of access is also a fundamental principle laid down in the Swedish Constitution; see Chap. 2, Section 1 of the Freedom of the Press Act. Just like the individual right to privacy, however, the rights mentioned here are not unlimited. In a conflict of interests, the researcher's freedom may thus have to yield to other important rights and interests. It should of course also be noted that individual researchers might have an interest in keeping their own research materials and

[9] As opposed to the European Convention, however, this Charter has no direct legally binding power.
[10] Restrictions for example on the right to privacy regulated in Article 8.1 of the European Convention on Human Rights and Fundamental Freedoms are only allowed to the extent that they are necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others; see Article 8.2. The restrictions must also be in accordance with the law.
[11] See Chap. 1, Section 6 of *Högskolelagen* (1992:1434) (the Higher Education Act).

registers to themselves, an interest that could come into conflict with the interests of other researchers in being allowed to share them.

Furthermore, research needs to be financed, and the setting up and keeping of biobanks may be expensive. Researchers thus have an interest in not being too restricted with regard to their funding opportunities, but rather having a wide choice of possible financiers, also outside their own country. Collaboration with other research institutions could be one way of facilitating the financing of research, co-operation with industry another.

It is not normally argued that human biological material can be subject to ownership in the ordinary sense of the word,[12] but this is only true as long as the material is not turned into a product. Companies manufacturing products of which human biological materials form part, naturally have an interest in the protection of their property rights with regard to the products. The interest in protection of intellectual property rights may arise even before a product has been fully developed. In the context of biobanking, particular note should be taken of Directive 98/44/EC on the legal protection of biotechnological inventions. Such rights, sometimes of considerable economic value, may be due to individual researchers as well as organisations or private companies. Article 17 of the EU Charter of Fundamental Rights recognises the right to property in more general terms, as does Article 1 of Additional Protocol 1 to the European Convention on Human Rights and Fundamental Freedoms.[13]

2.3. The interests of society

It is clearly in the interest of society to further good biomedical research and the development of science. The generation of better methods for predicting, diagnosing and treating disease is of major importance in the fight against human suffering. The state is interested in having healthy citizens, as well as establishing and maintaining an efficient and economically stable health care sector. The general interest in sound financial development also involves industry, and the introduction of legislation less favourable to industrial operations might also have a detrimental effect on state finances.

With regard to the use of human biobanks, there is also the societal interest of preserving respect for human dignity as such. The European Convention on Human Rights and Biomedicine recognises the need to respect the human being both as an individual and as a member of the human species and the importance of ensuring the dignity of the human being.[14] Certain activities, which could be envisaged as commercialisation or commodification of parts of the human body, are often thought to entail risks in this respect. Society may thus have an interest in limiting the lawful use of human biological material in certain aspects.

2.4 The balancing act

As mentioned above, it is the duty of the state to provide an appropriate legal framework for protecting the rights of individuals as well as other important interests related to the private or the public sector. In this process, a number of basic

[12] Westerlund, L. & Persson, A.H. 2001, p. 77.
[13] Council of Europe 1952.
[14] Preamble of the Convention.

principles must be observed.[15] For example, the powers of public agencies must be clearly defined in law and the implications of the exercise of such powers foreseeable to citizens. Restrictions on the freedom of citizens, as well as the imposition of various types of obligations and burdens, must never be disproportionate to the purpose they are to serve. The law should also be just in the sense of similar rules applying under similar conditions. State obligations under international law must of course be honoured, which among other things involves the protection of human rights and freedoms. In the international human rights documents, it is made clear that they must not be interpreted as implying a right to engage in activity aimed at the destruction of any of the rights and freedoms recognised, or at their limitation to a greater extent than is provided for in the document; see Article 17 of the European Convention on Human Rights and Fundamental Freedoms and Article 54 of the EU Charter on Fundamental Rights.

Guaranteeing researchers and industry a favourable climate, with ready access to valuable research materials and not too many cumbersome restrictions, is in the interests of both society and those more directly engaged in such activities. The introduction of excessive requirements may also be contrary to the interests of future patients, if the development of better treatment methods is obstructed. At the same time, however, preserving the confidence of the public could prove equally important to the development of science and good health care. If people were to feel that their trust and good will were being abused, this could impair their readiness to part with sensitive information to health care providers and to participate in research. The protection of individual privacy may thus also be in the long-term interest of researchers and society. The same applies to measures aimed at securing the impartiality and independence of researchers.

Important tools for the protection of privacy and self-determination of patients and research subjects include appropriate information and consent requirements, as well as the possibility of withdrawing consent given previously. Different solutions may be justifiable in different situations, depending on the perceived risk of integrity infringements as well as the weight of other interests at stake. For example, it would not seem unreasonable if consent requirements for the preservation of tissue samples for health care purposes, in the patient's own interest, were to be less strict than the requirements governing the use of human material in research. Furthermore, research projects also vary considerably, for example, with regard to the potential value to society of the results expected and the risks and degree of privacy infringement. Exceptionally, it may even be justifiable to disregard the wishes of the individual.

A particular issue concerns the situation where the risk of privacy infringements indirectly relates to members of a group, such as the genetic relatives of a donor or persons belonging to a certain population. The group or population also consists of individuals, with rights and interests just as other individuals. At the same time, it is equally obvious that traditional methods for individual information and consent cannot always be applied to groups or populations. This does not mean that the issue can be ignored, but other principles for the protection of privacy may have to be applied in these situations.

[15] See, for example, Strömberg, H. 2002, pp. 64-68.

3. Recent legal developments

3.1. European law and other international regulations

Without any doubt, the Council of Europe must be considered one of the absolutely prime promoters of the protection of human rights. The basic principles laid down in the European Convention on Human Rights and Fundamental Freedoms have already been mentioned, but the Council has also produced several documents more directly relevant to the handling of biobank materials. Most important in this context is the above mentioned Convention on Human Rights and Biomedicine, not least in view of its legally binding character.[16] Article 2 of the Convention prescribes that in the area of biomedicine, the interests and welfare of the human being shall prevail over the sole interest of society or science. Among other things, the Convention defines a number of general prerequisites for biomedical research involving humans, and also includes certain specific rules on human biological material. Thus Article 22 provides that if any part of a human body has been removed in the course of an intervention, it may be stored 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. Under Article 26, restrictions on Article 22 may be prescribed by internal law only to the extent necessary in a democratic society in the interest of public safety, for the prevention of crime, for the protection of public health or for the protection of the rights and freedoms of others. No similar restriction is allowed with regard to Article 21, which lays down that the human body and its parts shall not, as such, give rise to financial gain.

An additional protocol to the Convention, dealing with transplantation of organs and tissues of human origin, was adopted in January 2002.[17] Since the Protocol definition of "transplantation" covers the complete process of removal and implantation of an organ or tissue, including all procedures for preparation, preservation and storage, it also has a bearing on banking issues. The provisions of the protocol include requirements concerning the ensuring of traceability and prohibition of financial gain.[18] The rules on consent, however, only apply to the removal of the organ or tissue.[19] Although the word implantation, in its traditional sense, does not include the use of human material in the form of medical devices or pharmaceuticals, it is stated in the Explanatory Report that professional standards imply that the principles contained in the Protocol regarding safety, traceability, information and consent for such uses should be applicable *mutatis mutandis*.[20] It is clear from the Explanatory Report that the Protocol applies to interventions carried out in connection with experimental transplantation, in which cases the rules governing research must be complied with as well.[21]

[16] The Convention entered into force on 1 December 1999, but has not yet been ratified by Sweden. See also the Explanatory Report, Council of Europe 1996 and Rynning, E. 1997.
[17] Council of Europe 2002.
[18] See Articles 3 and 21-22.
[19] Chap. III of the Protocol. It is recommended that national law or professional standards provide a means of resolving problems concerning the withdrawal of consent to an agreed transplantation after the removal of the organ or tissue; see Section 78 of the Explanatory Report to the Protocol, Council of Europe 2001.
[20] Council of Europe 2001, Section 26.
[21] Council of Europe 2001, Section 42.

An earlier Council of Europe recommendation specifically dealing with human tissue banks proposes *inter alia* that such banking activities should be carried out by non-profit-making institutions.[22] It is also recommended that the distribution of banked materials "take place in such a way as to permit optimal use of the tissues on an equitable basis in accordance with national law, rules and practice and objective selection criteria". In other documents from the early 1990s, the Council of Europe has voiced the idea that human tissue should be considered a source of information and be protected in the same way as other media carrying personal information.[23] Regrettably, the issue would not seem to be discussed in the Recommendation (97) 5 on the protection of medical data.[24]

Looking at European law from a more general perspective, the European Union is of course by far the most powerful and influential organisation. Although there are a number of EC regulations that may be applicable to various aspects or certain types of human biobanks,[25] there is at present no legally binding EC instrument specifically addressing biobanking as such. An opinion on human tissue banking was adopted by the European Group on Ethics in Science and New Technologies (EGE) in 1998. The EGE gives a number of recommendations *inter alia* concerning issues of safety and security, information and consent, confidentiality and the prevention of discrimination, tissue availability and international transfer. It is stressed that while it would be difficult to reserve tissue bank activities strictly for non-profit making organisations, it is important that banks set up by industry be subject to the same licensing and monitoring requirements as non-commercial operators. The EGE opinion covers most types of human tissue, including cells and cell lines, but explicitly excludes some tissues, such as blood, gametes, reproductive tissue and embryos. Nor does the opinion cover genomic banks, also referred to as DNA banks or "biobanks".[26]

In view of the shortcomings and discrepancies in the rules on the therapeutic use of substances of human origin, the Commission has recently drawn up a proposal for a Directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissue and cells.[27] Like the EGE opinion, the proposed Directive is focused on human biological material aimed for application to the human body.[28] With certain exceptions, the proposal covers tissues and cells of human origin for application to the human body during the first phases of their therapeutic use (donation, procurement and testing) and, if the tissues and cells are intended for transplantation, during the processing, preservation, storage and distribution phases.[29] Exceptions mainly concern organs, cells and tissue for autologous use, blood and blood components. Furthermore, Member States will be allowed to take basic decisions on the use of cells posing an ethical problem, such as embryonic stem cells. The proposed measures are aimed at strengthening the requirements relating

[22] Council of Europe 1994.
[23] Council of Europe 1992 a and 1992 b. See also Hondius, 1997, pp. 377–378.
[24] Council of Europe 1997 b.
[25] See, for example, Directive 95/46/EC; Directive 98/79/EC and Directive 2001/20/EC.
[26] EGE 1998, p. 2.
[27] *Proposal for a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, processing, storage, and distribution of human tissue and cells.*.
[28] Article 1 of the proposed Directive.
[29] See "Health and consumer protection" 2002.

to the suitability of donors and the screening of donated substances. Systems will be set up to ensure the traceability of tissues and cells, and to regulate imports of human tissues and cells from third countries. Other aims involve the establishment of comparable national accreditation and monitoring structures, as well as equivalent training of staff.

On the international level, there are many documents that in some way or other are germane to biobanking. They include the UNESCO Universal Declaration on the Human Genome and Human Rights (1997) and the WHO Proposed international guidelines on ethical issues in medical genetics and genetic services (1997). Non-governmental organisations have traditionally provided important guidelines for biomedical research, [30] and such organisations are today developing standards for various types of biobanking.

3.2 Domestic law

With regard to domestic law, new Acts of legislation on human biobanks have been introduced in some countries, and are in preparation in certain others. Most European countries, however, do not seem to have any legislation specifically aimed at regulating human biobanking. This does not mean that such activities are necessarily unregulated, since more general legislation may be applicable and there may be special provisions on biobanking in other Acts. Different biobank activities may, for example, come under regulations dealing with patients' rights, biomedical research, the processing of personal data or donation of human tissue and organs.

The Nordic countries form a geographic region where the legal developments with regard to biobanking have been particularly manifest during the past few years. Iceland was the first to adopt a Biobanks Act (110/2000). This entered into force on 1 January 2001. In September the same year, the new Finnish Use of Human Organs and Tissue (Medical Purposes) Act (101/2001) entered into force,[31] including certain provisions on the taking, collection and further use of human tissue. The Swedish Biobanks (Health Care) Act (2002:297) was passed in May 2002 and is effective as of 1 January 2003.[32] Norway is about to follow the Icelandic and Swedish examples, with a proposed Biobanks Act to be discussed in the Norwegian Parliament by the end of January 2003.[33] The Danes, on the other hand, seem at present to be considering the method of adding certain provisions to existing legislation, primarily to the Danish Legal Status of Patients Act.[34]

It is interesting to note that circumstances such as geographic proximity, a partly common cultural heritage and a tradition of legislative co-operation in many other areas, by no means would seem to guarantee a common legal approach to the area of human biobanking. Not only do the regulatory methods chosen by the different Nordic countries vary, but so do the scope of the legislation and, in a number of aspects, the material contents of the law.

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[30] For a number of such guidelines; see, for example, *Codex – Regler och riktlinjer för forskning.*
[31] *Lag om användning av mänskliga organ och vävnader för medicinska ändamål 2.2.2001/101.*
[32] *Lag (2002:297) om biobanker inom hälso- och sjukvården m.m.*
[33] *Odelstingsproposisjon nr. 56 (2001-2002)* and *Sosialkomiteens Instilling til Odelstinget Nr. 52 (2002-2003).*
[34] *Redegørelse om biobanker. Forslag til retlig regulering af biobanker inden for sundhedsområdet* 2002.

4. Human biological material – a carrier of personal data

4.1. General remarks

When biobank samples are looked upon as a source of valuable, sensitive information, they show substantial similarities to other such sources of information, for example medical records and national health registers. It is therefore of interest to study the rules applied in the processing of such personal information, and to consider whether or not these rules might also be applicable to human biological material.[35] Part of the early criticism against the Swedish Biobanks (Health Care) Act has concerned fears that the collection and storage of biobank samples will be more restricted than the collection and preservation of personal data for medical records and national health registers, and that biobanking may in fact become so difficult and costly that many valuable samples will no longer be saved.[36]

4.2. Swedish law on the protection of personal data in relation to biomedical research

The primary Swedish legislation implementing Directive 95/46/EC on the protection of personal data is the Personal Data Act,[37] complemented by the Personal Data Ordinance.[38] Simultaneously two new laws were introduced for the area of health care and epidemiological research, namely the Medical Care Registers Act and the Health Data Registers Act,[39] both dealing exclusively with certain types of automated processing. There is also an Act on Research Registers for Forensic Psychiatry.[40] The rules of secrecy and confidentiality within the public sector, however, are still mainly to be found in the Secrecy Act .[41]

Medical records within the public health care sector, as well as health data registers, research documents produced at public universities etc., constitute official documents under Chap. 2 of the Swedish Freedom of the Press Act. [42] Databases, recordings, photographs etc. all count as "documents" in this context. Biological samples, however, do not constitute documents under the Freedom of the Press Act, and thus fall outside the scope of this set of rules.[43] The borderline between a biological sample and a document does not seem all that sharp, however, in a time where DNA can be digitalised and many other characteristics of human tissue and cells can be registered in enlarged photographs etc.

The fact that a document is considered to be an official document means that it must be kept and preserved in accordance with the Archives Act and the Archives Ordinance, and may only be destroyed or altered under certain conditions.[44] Furthermore, official documents must be presented on request, unless

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[35] See Rynning, E. 1998.
[36] Adami, H-O et al 2002.
[37] *Personuppgiftslag (1998:204)*. Transitional provisions apply inter alia with regard to certain types of manual processing of personal data; see transitional provision 3.
[38] *Personuppgiftsförordning (1998: 1191)*
[39] *Lag (1998:544) om vårdregister* and *lag (1998:543) om hälsodataregister*.
[40] *Lag (1999:353) om rättspsykiatriskt forskningsregister*.
[41] *Sekretesslag (1989:100)*.
[42] *Tryckfrihetsförordning (KK 1949:105)*.
[43] Ruling of the Supreme Administrative Court, *Regeringsrättens Årsbok 1994* note 465.
[44] *Arkivlag (1990:782)* and *Arkivförordning (1991:446)*. See Rättsliga aspekter på dokumentation och arkivering av material i samband med medicinsk forskning.

there is an applicable provision on secrecy or confidentiality protecting the information registered in the document; see Chap. 2, Section 12 of the Freedom of the Press Act.

Section 13 of the Personal Data Act prohibits the processing of sensitive data, e.g. concerning health, is prohibited, but exceptions are then made for a number of situations. Thus it is lawful to process sensitive data with the express consent of the data subject; see Section 14. Processing of sensitive data for health and hospital purposes may also be lawful without consent, when the processing is necessary for preventive medicine and health care, medical diagnosis, health care or treatment, or management of health and hospital care services; see Section 18.

The registration of sensitive personal data in medical records is thus not subject to the personal wishes of the patient concerned. On the contrary, such keeping of records is a mandatory duty of the health care personnel; see Section 9 of the Medical Records Act.[45] This applies to all types of documentation relevant to the patient's health, treatment etc.; see Sections 2-3. If the health care provider chooses to keep the records in automated form, the patient must be informed of this, but the registration of relevant health information will still take place regardless of the patients' will.[46] The transfer of certain health-related information to national health data registers is also mandatory, under specific legislation, and thus not subject to the will of the patient nor to that of the health care provider; see Section 6 of the Health Data Registers Act.

When it comes to using health-related personal information in biomedical research, however, there is first the matter of gaining access to the information. In some cases, the information needed may be obtained directly from the patient/research subject, but quite often the researcher would like to access information from individual medical records or from national health data registers. Such access may be granted only in accordance with the applicable rules of confidentiality and secrecy. Not even members of the health care personnel who already have access to the medical records in their daily work, are free to use to the information for purposes other than those related to the health care activities.[47]

Within the area of public health care, information about the state of health or other personal circumstances of an individual must not be disclosed unless it is clear that the disclosure will not constitute any harm to the person concerned, or to persons closely related to him or her; see Chap. 7, Section 1 (1) of the Secrecy Act. Similar provisions apply in private health care; see Chap. 2, Section 8 of the Health and Medical Services (Professional Activities) Act (1998:531). Exceptions may apply in certain situations, but it should be noted that there is no general exception regarding research. The rules pertaining to information in national health data registers are no less strict, explicitly providing that personal data be disclosed for research purposes only when it is clear that the disclosure will not cause any harm to the person concerned, or to persons closely related to him or her; see Chap. 9, Section 4 of the Secrecy Act.

[45] *Patientjournallag (1986:203*).

[46] Such automated registers are regulated in the Medical Care Registers Act, where no requirement for the patients' consent is stipulated.

[47] See for example Chap. 1, Section 4 of the Secrecy Act.

It is the responsibility of the person or agency that parts with the information, to establish that the necessary requirements are met.[48] The concept of "harm" should then be perceived from the viewpoint of the individual concerned.[49] It may be sufficient that he or she would feel uncomfortable with the information being disclosed, in order for harm to be caused, although some adjustment would be permissible with regard to information more generally considered to be harmless.[50] In cases where the risk of harm cannot be excluded, however, the person concerned can normally waive the right of secrecy if he or she wishes to do so.[51] Establishing with certainty whether or not disclosure for the intended research will cause no harm, often requires direct consultation with the patient. In practice, however, the rules of confidentiality would not always seem to be applied quite as strictly as that.[52] It should also be noted that the disclosure of depersonalised information is normally not considered to cause harm.

Section 19 (1) of the Personal Data Act provides that sensitive personal data may be processed for research and statistics purposes even without the consent of the data subject, provided the processing is necessary and the interest of society in the project is manifestly greater than the risk of improper violation of the personal integrity of the data subject. These prerequisites shall be deemed satisfied if the processing has been approved by a research ethics committee; see subsection 2. Although the research ethics committee may thus authorise the processing of sensitive data in a certain research project, it should be remembered that the committee does not have the power to grant the researchers *initial access* to the information in question. This is still a matter to be decided in accordance with general rules on secrecy and confidentiality, as described above.

Notification of the Data Inspection Board, regarding the processing of personal data, is not normally required if the data controller has appointed a data representative and given notice of this to the Board; see Section 37 of the Personal Data Act. Nor is such notification required if the data subject has consented to the processing.[53] Processing of personal data within the health care sector, in accordance with Section 18 of the Personal Data Act, is also excepted from the general notification requirement in Section 36.[54]

However, the exemptions which have now been mentioned do not apply to certain types of processing for which prior notice to the Data Inspection Board is *mandatory*. Such requirements are prescribed with regard to two cases of automated processing.[55] The first case concerns processing of sensitive personal data for research purposes without the consent of the person registered which has not been approved by a research ethics committee, in accordance with Section 19 of the Personal Data

[48] Within the public sector, the disclosure of information in official documents is decided upon in accordance with a certain procedure laid down in Chap. 15, Sections 6-8 of the Secrecy Act.
[49] Regner, G, Eliasson, M & Heuman, S. 2002 p. III:14-15.
[50] For a narrower interpretation of the concept of harm; see the chapter by Ulric von Essen in this book.
[51] Chap. 14, Section 4 (1) of the Secrecy Act.
[52] Rynning, E. 2003.
[53] This exemption is found in Section 4 of the Data Inspection Board's Code of Statutes, *Datainspektionens föreskrifter (DIFS 2001:1) om ändring av Datainspektionens föreskrifter i fråga om skyldigheten att anmäla behandlingar av personuppgifter till Datainspektionen*.
[54] Section 5 (e) of the same regulation.
[55] See Section 10 of the Personal Data Ordinance, referring to Section 41 of the Personal Data Act.

Act. If the data controller chooses to perform the balancing of interests himself or herself, the processing of data must thus be notified for prior checking.[56] The second case refers to processing of personal data derived from genetic investigation and concerning a hereditary disposition. Prior notification is not, however, required in cases where the processing is governed by specific regulations, which for example would seem to be the case with automated medical records, health data registers and research registers in forensic psychiatry.

The situation where the data subject withdraws his or her consent to the data processing is regulated in Section 12 (1) of the Personal Data Act. Such withdrawal, however, does not mean that all further processing of the data is prohibited, only that no *additional* personal data may be processed. Updating thus will not be possible, whereas continued processing of the already registered data is still allowed. This was considered a suitable balancing of the conflicting interests of the data subject and the data controller.[57]

4.3. The status of biobank materials

How, then, are biobank materials looked upon in various jurisdictions within the EU/EEA, where Directive 95/46/EC on the protection of personal data should be implemented? Whether or not the biological samples in human biobanks are considered to come under national legislation on the processing of personal data, is of course highly relevant to the perceived need for comprehensive biobank legislation rather than just additional rules addressing certain aspects specific to biological samples. It is equally important that the interpretation of Directive 95/46/EC should not vary between Member States, in such a way that biobank samples are exported on the mistaken supposition that they will be sufficiently protected in the receiving Member State, or withheld under the mistaken apprehension that they will not! The stand taken by various Member States on this issue, however, does not seem to be all that clear. [58] It is naturally observed that legal rules on the processing of personal data must be applied with regard to personal information linked to biobank materials. The uncertainty primarily relates to the status of the biological material as such. [59]

One country where biobank samples have in fact been clearly and officially declared subject to personal data legislation is Denmark.[60] This is also the main reason why the Danes do not seem to plan on introducing any general biobank legislation, only supplementary provisions in certain existing Acts.

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[56] Under Section 3 of the proposed new Ethics Review Act, however, there will be a mandatory requirement of ethics review of research-related processing of sensitive personal data without consent; see the Government Bill *Regeringens proposition 2002/03:50 Etikprövning av forskning*. The data controller will then no longer be able to choose the alternative of performing the balancing of interests himself or herself.

[57] Öman, S. & Lindblom, H-O. 2002, p. 126.

[58] *Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human biobanks*. 2002.

[59] The matter is being studied as part of the European research project PRIVIREAL: Privacy in Research Ethics and Law, co-ordinated by Professor Deryck Beyleveld and David Townend at SIBLE, Sheffield University. Information on this project can be found at <http://www.privireal.org/>.

[60] See e.g. Blume, P. 1996, pp. 29-34 and the English summary of the report *Redegørelse om biobanker. Forslag til retlig regulering af biobanker inden for sundhedsområdet*. 2002 p. 245.

In the *travaux préparatoires* of the Swedish Personal Data Act, the processing of biological samples is not even mentioned.[61] The Swedish Government has since declared that DNA samples and other parts of the human body should in principle be considered to constitute personal data, provided that the material can be traced to identifiable living persons.[62] The Government argues, however, that the mere keeping of samples in a so-called biobank does not come within the definition of such partly automated or manual processing of data as is regulated in the Personal Data Act. Since the keeping of biobanks still constitutes a particularly sensitive activity, and one which should be subject to high standards for the protection of privacy and personal integrity similar to those laid down in Directive 95/46/EC, a special Biobanks (Health Care) Act is needed. As for personal data regarding the samples in a biobank, such information is not considered to formally constitute any part of the biobank as such.[63]

The more precise borderline between the scope of the Swedish Biobanks Act and that of the Personal Data Act still remains rather vague. It is not clear what kind of processing of biobank samples could in fact come under the Personal Data Act, nor which Act should be given precedence in a situation where both Acts could be considered *prima facie* applicable. This could constitute a problem, especially to the extent that the rules of the Biobanks Act are found to differ from those of the Personal Data Act. The Biobanks Act does contain a provision stating that the Act will not apply if there are diverging provisions in other Acts of legislation; see Chap. 1, Section 4. This would seem to give precedence to the Personal Data Act in case of a conflict. Unfortunately, however, Section 2 of the Personal Data Act contains a similar provision, also offering precedence to diverging provisions in other laws and ordinances. The competition is thereby brought to a sort of legal draw. It could perhaps be argued that the Biobanks Act should be given precedence due to its character of special legislation, also enacted after the Personal Data Act. If, however, the biobank provisions are found not to be in conformity with the requirements of Directive 95/46/EC, should not the Personal Data Act be given precedence, since it provides the national transposition of EU legislation that Sweden is under an obligation to implement?

5. Parts of the human body as raw material

Biobank samples may serve not only as information carriers, but also as potential raw material for certain products. Human blood and tissue can be used for a variety of medicinal products, and human stem cells may in the future be cultivated to specific tissue or even organs. This prompts questions on how the human material should be perceived at the various stages of cultivation or manufacture. How long should the original donor be able to withdraw his or her consent, and demand that the sample be destroyed? When does the biobank sample cease to exist, having been used up or turned into something else? Are cells and cell lines cultivated in vitro still just samples of human biological material, or do they constitute medicinal products? If the origin of the new "product" can still be traced to an identifiable donor, at the

[61] Rynning, E. 1998, pp. 318-322.
[62] *Regeringens proposition 2001/02:44* p. 31.
[63] *Regeringens proposition 2001/02:44* p. 32.

point where the biobank regulation no longer applies, how is the privacy of that person then protected? The questions are also related to the commercial interests of manufacturers and others, since the sale of products is generally accepted, whereas the selling and buying of human biological material is subject to considerable restrictions in international as well as domestic law.

The question of when the biological material has undergone sufficient cultivation or manipulation to be no longer looked upon as just a sample, or part of a sample, may be addressed in rather different types of legislation. Does the material, for example, come under provisions regulating medicinal products? Could the biological material as such be patented? Most important in the present context, has the material ceased to be covered by the rules on biobanking? It would of course seem both logical and convenient if the determined point of transition could be the same, regardless of the type of regulation. However, in view of the variation pertaining to the underlying purposes of the different regulations, this does not go without saying. Regulation aimed at guaranteeing the safety of medicinal products might be prone to place the point of transition at an early stage, in order to protect the health of patients and research subjects. If the same approach is taken with regard to biobank regulation, the protection of donor privacy becomes, on the contrary, more limited. Patent law, finally, its primary aim being to stimulate and reward scientific development, requires careful balancing if it is not to become counter-productive by granting exclusive rights too early or to widely.

At present, the European Agency for the Evaluation of Medical Products (EMEA) would seem to recommend the following definition in order for a human somatic cell therapy product to fall within the definition of a medicinal product.[64] The product should be subject to a manufacturing process in vitro, encompassing expansion or more than minimal manipulation designed to alter the characteristics of the resulting cells. Furthermore, the resulting product should be definable in terms of qualitative and quantitative composition.

As regards the patenting of human biological material, the main rule according to Directive 98/44/EC on the protection of biotechnological inventions remains that the simple discovery of an element of the human body cannot constitute a patentable invention; see Article 5.1. Nevertheless, under with Article 5.2 an element isolated from the human body, or otherwise produced by means of a technical process, may constitute a patentable invention, even if the structure of that element is identical to that of the natural element. Under Article 6, however, interventions are not patentable where their commercial exploitation would be contrary to *ordre public* or morality, as would be the case for example with uses of human embryos for industrial or commercial purposes. If for instance a certain stem cell line were to be considered patentable, it should still be noted that the Preamble of Directive 98/44/EC lays down that if an invention is based on biological material of human origin or uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law.[65]

However, the boundaries of justifiable patentability with regard to human biological materials are still subject to a continuing debate, well after the adoption of

[64] CPMP 2001, p. 3.
[65] Recital 26.

Directive 98/44/EC.[66] More than a year after the required date of implementation, the majority of the Member States, including Sweden, have yet to implement the Directive. With regard to human stem cells, the EGE has expressed the opinion that an established but unmodified stem cell line can hardly constitute a patentable product.[67] On the other hand, stem cell lines that have been modified by in vitro treatments or genetically modified so that they have acquired characteristics for specific industrial application, are considered to fulfil the legal requirements for patentability.

At what point a cultured sample of human material will cease to be regarded as a sample under the Swedish Biobanks (Health Care) Act is not clear even from the *travaux préparatoires*. The only statement indicating a certain limitation of the scope of the Act in this respect, concerns the donor's right to withdraw his or her consent and have the sample destroyed.[68] We read, with regard to samples used for research, that what should be destroyed is the sample which has been supplied for research, and not the results of the research. How the results should be distinguished from the sample is not discussed.

6. Using Swedish biobank materials in research

6.1. General rules and recommendations regarding biomedical research on humans

Chap. 1, Section 1 of the new Swedish Biobanks (Health Care) Act, defines the purpose of the Act as being to regulate the collection, storage and use of human biological material for certain purposes, in such a way that the integrity of individual human beings is respected. The scope of the Biobanks Act, then, is restricted in a number of ways, as will be shown below. This means that some biobanks will not be covered at all by the new legislation. The rules governing such banks will still have to be found in other acts of legislation. With regard to the banks that do come under the Biobanks Act, provisions laid down in other laws will still take precedence over the new Act in most cases where there is a discrepancy; see Chap. 1 Section 4 of the Biobanks Act. Individuals and organisations concerned by human biobanking thus need to keep themselves informed also about many other regulations.[69]

Swedish law does not yet lay down any general prerequisites for biomedical research involving humans. The basic principles applied by the legally unregulated, advisory research ethics committees (RECs) are mainly found in national and international ethical guidelines.[70] In response, however, to requirements of international law, Sweden is preparing legislation on ethics review of certain research projects involving humans.[71] It has thus been proposed that a legal requirement for ethics review and authorisation be introduced, with regard to certain types of

[66] See, for example, *Report from the Commission to the European Parliament and the Council – Development and implications of patent law in the field of biotechnology and genetic engineering*. 2002.
[67] EGE. 2002.
[68] *Regeringens proposition 2001/02:44* p. 44.
[69] For a more comprehensive exemplification of such rules and regulations, see Rynning, E. 2001.
[70] See for example *Guidelines for ethical evaluation of medical research involving human subjects. The Policy and organization of research ethics in Sweden*. The Swedish Medical Research Council, MRC report 2 1996, English translation 1999.
[71] *Regeringens proposition 2002/03:50 Etikprövning av forskning.*. See also report from the Ministry of Education, *Etikprövning av forskning som avser människor Ds 2001:62*.

research. The new rules will, for example, cover the use of identifiable human biological material for research purposes, and also research on sensitive personal data in cases where the informed consent of the data subject is not procured. A framework of basic principles for justifiable research will be laid down in the legislation, including traditional requirements concerning respect for human dignity, informed consent, risk-benefit-evaluation etc. The review will be performed by a new organisation of independent Regional Boards for Research Ethics and a National Board will try the appeals.

Provisions on the taking of biological materials from humans for research purposes can be found in the Transplants Act and in the Autopsy Act,[72] supplemented by regulations and recommendations in the Code of Statutes of the National Board of Health and Welfare.[73] There is also the Fertilised Human Ova (Research or Treatment Activities involving) Act, and the Medical Screening (Use of Certain Genetic Technology) Act.[74] Specific provisions on the performance of clinical drug trials can be found in Sections 13-14 of the Medicinal Products Act,[75] in addition to which there are regulations issued by the Medical Products Agency, e.g. on clinical trials of medicinal products.[76] There is also a Medical Devices Act.[77]

Provisions more specifically aimed at biobank activities are laid down in the already mentioned Biobanks (Health Care) Act, supplemented by an Ordinance and the Code of Statutes issued by the National Board of Health and Welfare on the same subject.[78]

Depending on the type of research that is to be performed, as well as the origin of the samples, provisions in some or several of the above mentioned laws and regulations may be applicable.

6.2. Different types of biobanks

When a new biobank is set up for purposes of research, the rules applicable will depend on who formally decides to set up the bank and also on the origin of the samples, or rather, the circumstances under which they are collected. If a biobank is set up within the professional activities of a health care provider, the bank will come under the new Biobanks (Health Care) Act; see Chap. 1, Section 3, point 1. Any type of human biological material may qualify as a biobank sample, as long as it can be traced to an identifiable human being or foetus.[79] This means that organs and tissue as well as cells and DNA strings will be covered by the regulation, provided that all other prerequisites for the application of the Act are met. The health care provider is free to decide that another organisation or agency, for example a research institution or even a private company, should administrate the biobank, in which

[72] *Lag (1995:831) om transplantation* and *lag (1995:832) om obduktion*.
[73] See, for example, *Socialstyrelsens föreskrifter och allmänna råd (SOSFS M) Organ- och vävnadstagning för transplantation eller för annat medicinskt ändamål* and *Socialstyrelsens föreskrifter och allmänna råd (1996:28) om kliniska obduktioner m.m.*
[74] *Lag (1991:115) om åtgärder i forsknings- och behandlingssyfte med befruktade ägg från människa* and *Lag (1991:114) om användning av viss genteknik i samband med allmänna hälsoundersökningar*
[75] *Läkemedelslag (1992:859)*.
[76] *Läkemedelsverkets föreskrifter och allmänna råd (LVFS 1996:17) om klinisk läkemedelsprövning.*
[77] *Lag (1993:584) om medicinsk-tekniska produkter.*
[78] *Förordning (2002:746) om biobanker inom hälso- och sjukvården m.m.* and *Socialstyrelsens föreskrifter och allmänna råd (SOSFS 2002:11 M) om biobanker i hälso- och sjukvården m.m.*
[79] Biobanks (Health Care) Act, Chap. 1 Section 2.

case the formal responsibility for the bank still remains with the health care provider.

The Biobanks Act also applies to banks that contain samples handed out from the biobank of a health care provider, i.e. a sort of secondary biobanks; see Chap. 1, Section 3, point 2. Such banks may be set up by other health care providers, research institutions, pharmaceutical companies or other juridical person.

A new biobank for research purposes, which is set up either within the professional activities of a health care provider or by the receipt of samples from such a bank, will thus come under the Biobanks (Health Care) Act, provided the samples can be traced to an identifiable donor. Other biobanks for research will not be covered by the new legislation. This means that samples collected directly by e.g. pharmaceutical companies, biotech companies or research institutions, without any connection to health care activities, will not be covered by the new legislation. Nor will samples collected in the area of forensic medicine come under the Biobanks Act. The rules applicable to such banks will thus have to be sought in other laws and regulations, not specifically addressing biobanking.[80] With the introduction of the forthcoming legislation on ethics review, however, a complementary set of consent requirements will apply to all research on such biobank materials as do not come under the Biobanks (Health Care) Act, provided there is an identifiable donor.

For those biobanks which do come under the new legislation, a whole new set of rules will have to be applied. To some extent the rules differ between health care provider biobanks and the type of banks that are here referred to as secondary biobanks. Unless otherwise stated, the rules described below apply to both categories. The special provisions regarding the so-called PKU biobank, which are laid down in Chap. 5 of the Biobanks Act, will not be discussed in this report.

6.3. Setting up a new biobank

A biobank under the new legislation is thus set up through a decision by the responsible principal (i.e. the health care provider or, in the case of secondary banks, the juridical person to which the samples have been handed out); see Chap. 2, Section 1 of the Biobanks Act. When the purpose of the biobank concerns research or clinical trials, such a decision must not be taken without the prior approval of a research ethics committee; see Section 3. The decision to set up the bank, including some further information, must then be notified to the National Board of Health and Welfare, which will keep a register of existing biobanks; see Sections 5 and 6.

With regard to the collection and preservation of biobank samples, the requirements for information and consent are quite strict. Thus under Chap. 3, Section 1 of the Biobanks Act, explicit consent must normally be procured, after the donor has been informed of the purpose or purposes for which the biobank may be used. The consent need not necessarily be given in writing, but it must be appropriately documented.[81] If the donor is a deceased person, the laws on transplantation and autopsies apply, giving the relatives a certain right of veto.[82] Incompetent minors are represented by their custody holders, and foetuses by the

[80] See Rynning, E. 2001, pp. 88-90.
[81] Chap. 3, Section 7.
[82] Chap. 3 Section 4.

(once) pregnant woman.[83] When the biobank samples consist of fertilised human eggs, the consent requirements are laid down in the relevant special legislation.[84]

A considerable flaw in Swedish legislation concerns the fact that vicarious decision-making for incompetent adults in health care and biomedical research is yet to be regulated.[85] An official commission is currently investigating the matter,[86] but until new legislation is introduced, the Biobanks (Health Care) Act does not allow any banking of samples collected from incompetent adults.[87] This will of course have very serious negative effects, amounting to the discrimination of incompetent persons in both health care and research.[88]

According to Chap. 3, Section 6 of the Biobanks Act, the person who has consented to the use of a biobank sample may at any time withdraw his or her consent. If the withdrawal concerns all further use, the sample shall be immediately destroyed *or de-personalised*. From the viewpoint of the donor, de-personalisation would perhaps not seem to be quite the equivalent of destruction,[89] even if is done in such a way that the donor can no longer be traced. It is clear, however, from the *travaux préparatoires* that the choice between destruction and de-personalisation is not up to the donor.[90] It is also stated that destruction would only concern the sample and not the results of the research.

6.4. Older biobanks

The older biobanks, already existing at the entry into force of the Biobanks (Health Care) Act, may also come under the new legislation, provided they belong to one of the two categories mentioned above (health care provider banks and secondary banks). The existence of such a biobank must be notified to the National Board of Health and Welfare within a two-year time limit, if the bank is to be preserved.[91] The Biobanks Act will be applicable to measures that are taken with the samples or the biobank as such after the Act has entered into force.[92] As already mentioned, it could constitute a problem that some of the older biobanks may not have been set up in accordance with the new rules on decision-making by the responsible health care provider or other principal. If formalities are unclear, it might be difficult to decide, for example, whether the bank is a health care provider biobank administrated by a research institution, or a secondary biobank set up by the research institution itself, with samples received from a health care provider biobank. The original purpose of an old biobank may be vague and the origin of the samples may vary within the same biobank. It would be desirable for such

[83] Chap. 3, Sections 2-3.
[84] *Lag (1991:115) om åtgärder i forsknings- och behandlingssyfte med befruktade ägg från människa* (The Fertilised Human Ova (Research or Treatment Activities Involving) Act).
[85] See Rynning, E. 2001.
[86] See the terms of reference provided in *Förmyndare, gode män och förvaltare. Direktiv 2002:55.*
[87] *Regeringens proposition 2001/2002:44* p. 42.
[88] Seeking to modify this problem at least with regard to such preservation of samples as is considered necessary for the safety of the patient, the National Board of Health and Welfare has made an exemption for this situation in its own regulation, se Chap. 4, Section 4 of the regulation *Socialstyrelsens föreskrifter och allmänna råd (SOSFS 2002:11 M)*. The legality of this provision, which is inconsistent with the Act passed by the Parliament, is highly dubious to say the least.
[89] See discussion below, on coding and anonymisation.
[90] *Regeringens proposition 2001/2002:44* p. 44.
[91] Transitional provision 2.
[92] Transitional provision 3.

complications to be somehow dealt with by the National Board of Health and Welfare, at the time when the bank is registered. If, however, the principal mistakenly does not consider the biobank to come under the new Act, the Board is unlikely to be notified at all.

6.5. Safety and security requirements

The Biobanks (Health Care) Act does not really provide much guidance with regard to safety and security measures. Chap. 2, Section 4 lays down that a biobank shall be kept in such a manner that the samples do not risk being destroyed and that unauthorised persons do not obtain access to them.[93] On the other hand, the samples must not be preserved for a longer time than is needed in view of the purpose of the biobank.[94] Discontinuing a health care provider biobank as such, however, and destroying the samples, will require the authorisation of the National Board of Health and Welfare; see Chap. 4, Section 9. Such authorisation may be granted only if the material is no longer of importance to the purpose for which the bank was set up, and there is no public interest that would motivate the preservation of the samples. The corresponding rule regarding secondary banks is somewhat less strict, allowing the principal to decide that the bank shall be discontinued when it is no longer needed for the purpose for which it was set up. The samples shall then be destroyed or returned to the original bank.

The Biobanks Act also contains provisions aimed at protecting the privacy of donors, by means of coding etc. It is prescribed that code keys shall be securely kept by the health care provider who decided to set up the biobank.[95]

6.6. Coding and anonymisation

In order to protect the privacy of donors, different arrangements for encoding of samples and data recorded may be used. There are several provisions in the Biobanks Act where such coding is recommended or even prescribed. The coding or anonymisation that is required for example when samples are transferred abroad and/or passed on from a secondary biobank, in accordance with Chap. 4, Section 5, is also recommended as the standard procedure in other situations. Unless otherwise is explicitly decided, samples released by a health care provider biobank shall also be de-personalised or coded; see Chap. 4, Section 4.

In some cases, the alternative to coding may thus be the complete de-personalisation of the samples, in such a way that they can no longer be traced back to the original donors. The de-personalised or anonymous samples will then no longer come under the Biobanks (Health Care) Act. As mentioned above, the Act only applies to samples that can be traced to an identifiable, living or deceased human being or foetus; see Chap. 1 Section 2. Although the anonymisation may be aimed to protect the privacy of the donor, it does not prevent every kind of privacy infringement and in effect renders further exercise of self-determination impossible as regards that particular sample. Another consideration is of course that the use of

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[93] Some rather limited additional provisions can be found in Chap. 5 of the regulation *Socialstyrelsens föreskrifter och allmänna råd (SOSFS 2002:11 M)* issued by the National Board of Health and Welfare.

[94] *Regeringens proposition* 2001/2002:44 pp. 54-55 and Chap. 5, Sections 5 and 6 of the regulation *Socialstyrelsens föreskrifter och allmänna råd (SOSFS 2002:11 M)*.

[95] Chap. 4, Section 4, paragraph 2 of the Biobanks Act. See also Chap. 5, Sections 1-2 of the regulation *Socialstyrelsens föreskrifter och allmänna råd (SOSFS 2002:11 M)* .

anonymous material is not really an option in many types of biomedical research, in view of the need for safety and quality control etc. With regard to human material aimed for application to other human beings, the requirement of traceability is being stressed in several European documents of relevance.[96]

Without doubt, it would seem important that concepts such as identifiability, anonymity and coding are clearly defined, both with regard to their prerequisites and their consequences. It is unfortunate that no European consensus has been reached on this point. With regard to the processing of personal data, different approaches can be seen in literature.[97] Some argue a *criterion of reasonableness*, according to which the individual should not be regarded as identifiable if identification would require an *unreasonable* amount of time and manpower. This means that encoded data would sometimes be considered anonymous, depending on who has access to the code. Others argue that there should be no theoretical possibility of identifying the person concerned, regardless of the cost and time involved (*the absolute anonymity criterion*). In that case, encoded data can never be considered anonymous as long as someone has access to the code. Both interpretations have been argued with regard to Article 2 (a) of Directive 95/94/EC on the protection of personal data.[98] Recital 26 of the Directive, however, does refer to "all the means likely reasonable to be used either by the data controller or by *any other person* to identify" the data subject, and the Explanatory Memorandum adds that the cost and time required for the identification need not be given any consideration.[99] This would certainly seem to indicate an interpretation fairly close to the absolute criterion mentioned above.

A new attempt at obtaining European consensus is currently being made by EMEA, with regard to terminology in pharmacogenetics. A position paper is thus in preparation, stating *inter alia* definitions of concepts such as identified samples and data, single-coded and double-coded samples and data, anonymised and anonymous samples and data.[100] The effort is certainly praiseworthy, although it remains to be seen if consensus can also be reached in a wider application of this terminology, nationally and internationally.

Under the Swedish Personal Data Act, an individual is considered to be identifiable if *anyone* can directly or indirectly identify him or her in relation to the data. It does not matter if the person performing the processing does not himself or herself have access to the all the information necessary for the identification.[101] Nor does it matter if the process of identification should require a considerable amount of time, money or other resources. This means that encoded data will be considered identifiable as long as someone has access to the code key.[102] The *travaux*

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[96] See for example the above mentioned *Proposal for a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, processing, storage, and distribution of human tissue and cells*, 2002.
[97] See for example Callens, S.1995, pp. 314-316 and Arnardottir, Björgvinsson & Matthiasson, 1999, pp. 329-340.
[98] For the stricter view, see e.g. Dute, J.1998, p. 179.
[99] Explanatory Memorandum to Directive 95/46/EC, p. 9.
[100] Personal information from Sighild Westman Naeser at the Swedish Medical Products Agency, November 2002.
[101] Öman, S & Lindblom, H-O. 2002, p. 52 and *Integritet – offentlighet – informationsteknik*. (1997); p. 338.
[102] Öman, S & Lindblom, H-O. 2002, pp. 52-53.

préparatoires of the Biobanks (Health Care) Act state that identifiable samples of human material should be afforded the same protection as personal data in other information carriers.[103] The question remains, however, whether the absolute anonymity criterion is really intended to apply in the context of the Biobanks (Health Care) Act. Such an interpretation would make the prerequisites for de-personalisation or anonymisation of biological samples extremely difficult to fulfil. On the other hand, using different definitions of anonymity and identifiability in these two acts of legislation, both aimed at protecting the privacy of individuals, would be bound to cause misunderstandings.

If, on the other hand, a less strict criterion for anonymity is applied, a number of samples will not receive any protection under the Biobanks Act. Nor is it proposed that research involving anonymous samples be subject to any mandatory ethics review under the forthcoming legislation.[104] It could well be questioned whether such lack of protection is really consistent with the individual's right to privacy and self-determination, at least if the conclusion is that anonymous material could be used for any purpose, even contrary to the donor's wishes. Even without the risk of having sensitive personal information disclosed, other aspects of the right to privacy might risk being infringed if the donor is given no opportunity to decide about the future use of material removed from his or her body. The donor may not wish to contribute to certain types of research, or may even risk harm in the way of stigmatisation or discrimination, if he or she belongs to a certain identifiable group or population.

Those provisions of the Biobanks Act regulating the breaking of codes and disclosure of personal data do nothing to make things clearer.[105] As described above, under the Personal Data Act, encoded data is considered to constitute personal data as long as someone has access to the code. In many cases it would thus be possible for a recipient of samples also to receive coded personal data concerning the donors of individual samples, without necessarily being able to identify the donors directly. In other cases, however, the recipient might need to identify the donors, for reasons of quality control or in order to apply for information from medical records etc. The relevant provisions in the Biobanks Act, however, do not distinguish between these two situations.

It is thus prescribed that a request to have the code broken "in order to gain access to personal data about an individual donor", shall be handled according to the same procedure as an application for access to samples; see Chap. 4, Section 4, paragraph 3. Furthermore, it is required that "if personal data concerning a donor is handed out simultaneously with a coded sample from the same person, this shall be done in such a way that the personal data cannot be connected to the sample"; see Chap. 4, Section 10. It is certainly difficult to understand what interest the recipient could have in data that cannot be connected to a specific sample. An altogether different matter is the possibility, stated above, of the recipient not needing to ascertain the *identity* of the donor.

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[103] *Regeringens proposition 2001/02:44* p. 31-32. As mentioned above, this is also the position taken by the Council of Europe in several documents.
[104] See Section 4 of the proposed Ethics Review Act, *Regeringens proposition 2002/03:50*.
[105] See Chap. 4, Sections 4 and 10.

6.7. Using biobank materials for new purposes

If a biobank sample is to be used for a purpose other than that which the donor has been informed about and consented to, then normally the person who gave the original consent will first have to be informed of the new purpose and consent to it; see Chap. 3, Section 5 of the Biobanks Act. If the donor is deceased, his or her close relatives must be informed and must not have objected to the new purpose, after being allowed appropriate time to consider the matter. With regard to research, however, a considerably more flexible rule is provided. If the new purpose thus concerns research or a clinical trial, the REC approving the new purpose shall also decide the requirements regarding information and consent, for using the biobank samples for this purpose.[106] It is explicitly stated in the *travaux préparatoires* that the REC is thereby empowered to use its discretion in deciding whether or not a renewed informed consent should be required.[107] The Government refers to the ethical guidelines issued by the Swedish Medical Research Council, according to which certain exceptions from the informed consent requirement may be justifiable.[108] Alternatives mentioned include, for example, the use of an opt-out model for obtaining consent. It should be noted, however, that the relevant provision in the Biobanks Act does not impose any statutory restrictions on the discretion of the ethics committees. Compared to the corresponding provision in Section 19 of the Personal Data Act, where a certain balancing of interests is explicitly required, the Biobanks Act is surprisingly generous in this respect.

6.8. Transfer of biobanks, samples and personal data

An important distinction is made between the transfer of a biobank or part of a biobank as such, on the one hand, and the release or transfer of biobank samples on the other. Under Chap. 4, Section 7 of the Biobanks Act, the transfer of a biobank or part of a biobank requires authorisation by the National Board of Health and Welfare. Such authorisation is only granted if there are special reasons, such as organisational changes or bankruptcy.[109] A biobank or part of a bank must never be transferred to a recipient in another country. This standpoint is motivated by the fact that the human biological material in a biobank offers unlimited possibilities of charting and analysing genetic information about individuals and groups of citizens.[110]

The release of samples from a biobank, however, is less restricted, especially as regards health care provider biobanks. It is thus for the person responsible for the biobank to consider applications for access to samples in the bank; see Chap. 4, Section 1 of the Act. Samples in secondary banks should not normally be passed on, but there are also substantial exceptions to that rule, as will be shown.

If samples are to be transferred to a recipient in another country, for research purposes, the application must be made by a Swedish research institution.[111] The foreign recipient must undertake to return the samples or destroy them when they are no longer needed for the purpose for which they were handed out. It is

[106] Chap. 3, Section 5, paragraph 3.
[107] *Regeringens proposition 2001/02:44* p. 39.
[108] Cf. *Research ethics guidelines for using biobanks, especially projects involving genome research*, adopted by the Swedish Medical Research Council (MFR) in June 1999.
[109] Chap. 6, Section 5 of the regulation *Socialstyrelsens föreskrifter och allmänna råd (SOSFS 2002:11 M)*.
[110] *Regeringens proposition 2001/02:44* p. 56.
[111] Chap. 4, Section 3.

stated that this is the only situation where samples may be released to a recipient in another country.

However, Chap. 4, Section 5 of the Biobanks Act provides several exemptions from the stricter rules described above. Under certain conditions, it is thus lawful to hand over samples to recipients in other countries as well as in Sweden, both from health care provider biobanks and from secondary banks. The prerequisites are that the donor consents, that the samples are coded or anonymised, and that the samples are returned or destroyed when no longer needed for the purpose for which they were transferred. Transfer is then allowed for certain specified purposes, two of which concern research and clinical trials respectively. It may thus be lawful to transfer samples from a biobank used in a research project, to another unit for research, inside or outside the country. Furthermore, it is permissible to transfer samples that have been released to a company for a clinical trial, to be analysed at another unit within the company or another company with which an agreement regarding analysis has been made. This also applies when the recipient is located in another country.

Obviously, the rules regarding the transfer of a *biobank*, or part of a bank, are stricter than the rules applying to the release or transfer of *samples*. Much will thus depend on how different transfer activities are defined. If, for example, the samples of a health care provider biobank set up for a certain research project are gradually transferred to a research partner abroad, will this constitute transfer of part of the biobank or just a release of samples? Will the answer depend on the number of samples – if any – which are left in the health care provider bank? Will it be of relevance whether or not the samples are ever returned from abroad, or just destroyed or used up? The *travaux préparatoires* do not discuss how this line should be drawn.

Is there then any right of access to samples in a biobank? No, not even the donor would seem to have any such immediate right. As stated above, the person in charge of the biobank, or ultimately the principal, decides who will have access to the samples, within the limits defined by the purpose of the biobank. If, however, the health care provider and the person responsible for the biobank do not consider that an application should be granted, the case shall be referred to the National Board of Health and Welfare; see Chap. 4, Section 6. This might be perceived as an opportunity to appeal, but the Board has no formal power to order the granting of access to biobank samples.[112] Any decision of the Board on such a matter will thus be no more than advisory.

6.9. Issues of commercialisation

Chap. 4, Section 8 of the Biobanks Act prohibits the transfer or release of biobank samples or part of samples with a view to financial gain. A similar provision can be found in Section 15 of the Transplants Act, where the taking, delivering, receiving or procuring of biological material from a living or deceased person, or tissue from an aborted foetus, with a view to gain, is criminalised. The same applies to intentional use or collection of such material, in the knowledge of previous measures for the purpose of gain. The Transplants Act, however, makes exceptions for blood, hair, breast milk and teeth, due to certain traditional commercial activities involving such materials.

[112] *Regeringens proposition 2001/02:44* p. 49.

The corresponding provision in Article 21 of the Convention on Human Rights and Biomedicine prescribes that the human body and its parts shall not, as such, give rise to financial gain. No exception is mentioned in the Article, but it is stated in the Explanatory Report that the provision does not refer to such products as hair and nails, which are discarded tissues, and the sale of which is not an affront to human dignity.[113]

It is the biological material itself – e.g. the organs, the tissue or the cells etc. – that may not be bought or sold, whereas technical acts such as sampling, testing, storage, culture, transport etc., may legitimately give rise to reasonable remuneration.[114] Nor do the rules prohibit the sale of a medical device incorporating human tissue which has been subjected to a manufacturing process. Once again, the interesting borderline between sample and product is stressed. Defining the concept "with a view to financial gain" is also proving to be a challenge.[115]

6.10. Supervision and sanctions

When it comes to the monitoring or supervision of biobank activities related to research, there are several public agencies with different, sometimes overlapping responsibilities. The National Board of Health and Welfare, which already monitors clinical research in connection with the treatment of patients, will thus supervise activities that come under the new Biobanks (Health Care) Act.[116] The Board also monitors clinical trials regarding medical devices, whereas the Medical Products Agency monitors all clinical drug trials.[117] The Swedish Data Inspection Board, however, monitors the processing of personal data in all the areas mentioned.[118] Some types of biomedical research that is conducted, for example, by private companies would at present seem to escape any real monitoring, except as regards personal data processing. When the new legislation on ethics review is passed, however, it seems likely that the National Board for Research Ethics will be given the powers to supervise such research activities as do not come under the responsibilities of any other supervisory agency.[119]

Although formally no research activities related to the use of human biobanks will be left unsupervised, the number of supervisory agencies involved would certainly seem to indicate a certain risk of responsibilities being confused, and thus perhaps even neglected. On the other hand, biobank principals and users could also risk being faced with varying and perhaps even incompatible requirements from the different agencies. At least, supervision of the biobanks will constitute a considerable challenge with regard to the necessary co-ordination and co-operation between the agencies concerned.

In order to facilitate its supervisory duties, the National Board of Health and Welfare has been provided with certain powers regulated in Chap. 6, Sections 3-6 of the

[113] Council of Europe 1996, section 133.
[114] Council of Europe 1996, section 132.
[115] See for example the chapter by Jens Lage Hellman in this book, and Domeij, B 2001 pp. 83-86.
[116] Chap. 6, Section 1 of the Health and Medical Services (Professional Activity) Act, *Lag (1998:531) om yrkesverksamhet på hälso- och sjukvårdens område*
[117] Section 11 of the Medical Devices Ordinance, *Förordning (1993:876) om medicinsk-tekniska produkter*, and Section 23 of the Medicinal Products Act, *Läkemedelslagen (1992:859)*, respectively.
[118] *Biobankers behandling av personuppgifter*. 2000.
[119] Sections 34-35 of the Act proposed in the Government Bill, *Regeringens proposition 2002/03:50*.

Biobanks Act. These powers include, for example, a right of access to premises as well as samples, relevant documents, other materials, information and any other assistance needed for the performance of an inspection. The Board is empowered to issue injunctions, even in combination with default fines, and if necessary may request police assistance in carrying out an inspection.

The penal sanction stipulated in Chap. 6, Section 1 of the Biobanks Act is limited to a fine, and only applies to such breaches of the Act as are explicitly enumerated. Thus as regards the prohibition of transfer with a view to financial gain, laid down in Chap. 3, Section 8, no sanction is prescribed in the Biobanks Act itself, which simply makes reference to the sanctions stipulated in Sections 15-16 of the Transplants Act. Since the prohibition of financial gain in the Transplants Act explicitly excludes blood, which the corresponding prohibition in the Biobanks Act does not, there does not seem to be any sanction applicable to unlawful commercial transfers of blood samples or biobanks consisting of such samples.

To the extent that a breach of the provisions laid down in the Biobanks Act causes damage to the donor or constitutes an infringement of his or her personal integrity, the donor is entitled to compensation from the principal of the bank; see Chap. 6, Section 2 of the Biobanks Act. Damages may be adjusted if the principal is able to prove that he or she was not at fault.

7. Conclusions

7.1. The scope of the Swedish Biobanks (Health Care) Act

The primary and perhaps most obvious drawback of the Swedish Biobanks Act concerns the obscurity of its intended scope. Concepts of decisive importance for determining the scope, such as identifiability and anonymity, are not defined in the Act, or even discussed in the *travaux préparatoires*. It does not seem to have been considered what degree of cultivation or processing will be required in order for the biological material to lose its status as a sample under the Act. The applicability of individual provisions in the Biobanks Act is also unclear in relation to the scope of some other Acts, such as the Personal Data Act.

Some biobanks may, furthermore, have been set up in a manner that is not consistent with the requirements laid down in the new Act. This will certainly be the case with some of the old banks, but may exceptionally also apply to new ones. If, for instance, a biobank for research is set up "within the professional activities of a health care provider", but the decision to do so is taken by an unauthorised employee rather than by the responsible principal, will the bank still come under the new Biobanks Act? The employee will be likely to risk some kind of sanction, at least in relation to his or her employer, but regardless of this the donors as well as the principal of the health care institution concerned will be interested to know whether or not the Biobanks Act is applicable to the samples collected.

Another serious shortcoming related to the scope of the Biobanks Act is the remaining unclarity regarding what rules should be applied to biobanks *not* covered by the Act, and the consequent inferior protection offered to identifiable donors concerned. As has already been made clear, biobanks set up by other principals than health care providers are only covered by the Act if the samples have been released from a health care provider biobank. This problem was pointed out by a number of

bodies to which the proposal was referred, and introduction of complementary legislation regarding the biobanks that are left out was mentioned in the Government Bill.[120] So far, however, no such legislation would seem to be in preparation.

Yet another problem concerns the lack of protection for donors of samples that are considered unidentifiable. As pointed out in sections 2.4 and 6.6, above, anonymisation does not mean that the donor is protected against all types of privacy infringements, and may even make it impossible for him or her to exercise right to self-determination, exactly *because* the sample cannot be traced. When anonymous samples are used in research, no ethics review is required under the Biobanks Act, nor under the proposed new Act on Ethics Review.[121]

7.2. Swedish law on the use of biobank samples versus personal data

To a certain extent, biobank samples can be compared to other carriers of sensitive personal data. It is also clear that legislation in both areas are based on the balancing of interests related to the protection of individual privacy on the one hand, and justified interests of access and openness on the other.

The setting up of a biobank under the Biobanks Act, must be notified to the supervisory agency. A similar notification procedure exists under the Personal Data Act, but the exemptions from the general notification requirement are numerous. However, it should be remembered that there is a mandatory requirement for *prior* notification with regard to processing of data concerning a hereditary disposition that has been derived from genetic investigation. One reason for keeping a close eye on human biobanks is of course the fact that the samples can be used for genetic analysis.

Consent requirements for the initial collection of samples for a biobank are clearly more strict than the rules pertaining to the collection of sensitive personal data for certain registers, such as medical records or national health data registers. The patient has no right of refusal when it comes to having his or her health data registered, whereas the Biobanks Act sets up a mandatory requirement for explicit informed consent with regard to the collection and storage of biological samples. It should be noted that the new Act does not apply to routine samples taken solely for analysis in relation to health care measures concerning the donor himself/herself, unless the samples are preserved for more than two months, but the difference is still considerable. It can hardly be justified by a lesser interest in preserving biological samples than, for example, X-ray pictures, so the tipping of the balance must be due to a perceived higher risk of privacy infringement. The information embedded in a sample of human material is in a way both endless and unforeseeable. From the very outset, this argument for a strict informed consent requirement seems somewhat questionable when samples are preserved in the best interests of the patient himself. Could not an opt-out-based consent model be sufficient for such banking? With regard to biobanking for research purposes, the argument of higher risk could be considered more tenable, but with the possibility of digitalising DNA and thus transferring the biological information to a document, the difference between documents and biological material does seem to dwindle.

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[120] *Regeringens proposition 2001/02:44,* pp 33-34.

[121] This would not seem to be the stand taken by the present, legally unregulated RECs; see Research ethics guidelines for using biobanks, especially projects involving genome research. 1999

When registered data is to be accessed or used for research purposes, consent of the data subject would seem to be more or less a standard requirement, as regards both rules on secrecy and rules on data processing. It is true that Swedish law on secrecy and confidentiality does not lay down any explicit consent requirements for the disclosure of health-related information, but in order to establish with certainty that disclosure will not cause the individual any harm, consultation with the person concerned would often seem necessary. Thus the main rules do not really differ much from the provisions laid down in the new Biobanks Act, although in practice the application of the secrecy rules seems somewhat laxer than the statutory provisions imply.[122] On the other hand, the new Biobanks Act leaves the question of renewed consent completely at the discretion of the RECs, whereas the Personal Data Act includes an explicit provision on the balancing of interests required in such situations.

Another aspect of the access issue, however, is that with regard to personal data in an official document, the person whom the information concerns may normally waive the protection of secrecy, and the document must then be presented on demand. With biobank samples, there is no similar right of access even if the donor were to give his or her explicit consent. The principal of a biobank is thus under no obligation to grant researchers access to samples, regardless of the donor's wishes.[123] This could perhaps be motivated by the fact that biological samples do not constitute an endless resource, and some prioritisation between different project is required, but it might also be argued that access to these valuable resources should be equitable.

So is the law stricter when it comes to sending biological samples abroad, compared to the transfer of personal data? The disclosure of health-related personal data to a recipient abroad would come under the same rules on secrecy and confidentiality as disclosure to a recipient within the country. The transfer of personal data must also follow the general rules laid down in the Personal Data Act. Only transfer of personal data to so-called third countries, outside the EU/EEA, is subject to any special safeguards.[124] This means that the transfer of biobank samples to recipients in other countries is clearly more restricted than such transfer of personal data, provided that the samples come under the new Biobanks Act. In whatever country the recipient is situated, samples from a biobank may never be sent abroad for purposes other than those enumerated in Chap. 4, Sections 3 and 5 of the Act, even if the donor were to give his or her consent.[125] Furthermore, samples sent abroad must always be returned or destroyed after having been used for the purpose for which they are released. Unless the samples come under Chap. 4, Section 3, regarding certain transfer abroad for research purposes, there is also a mandatory requirement of the samples being encoded or anonymised. A whole biobank, or part of a bank, may not under any circumstances be transferred to a recipient abroad.

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[122] Rynning, E. 2003.

[123] Even the donor himself or herself would not seem to have any right of access to the material, under the Biobanks (Health Care) Act.

[124] See Sections 33-35 of the Personal Data Act.

[125] It should for example be noted that there is at present no provision in the Biobanks Act allowing the transfer abroad of biological material for transplantation purposes, which would seem to imply that such transfer is formally, unlawful as of January 1, 2003. Considering the international co-operation taking place in this area, such a provision will certainly be necessary.

The restrictions on sending biobanks and samples abroad have been prompted by the fact that human biological material offers unlimited possibilities of charting and analysing genetic information about individuals and groups of citizens.[126] Provided that the same judicial protection is still offered the privacy of donors, however, the crossing of a national border should not constitute such a risk of privacy infringements. The real problem would thus seem to lie in the existing uncertainty regarding the legal regulation of biobanks in other countries, and the possible lack of uniformity with regard to the protection guaranteed.

7.3. A few comparative notes concerning the domestic law of certain other jurisdictions

As mentioned above, the Nordic countries have all taken an interest in investigating and regulating the use of human biobanks, although the legal solutions preferred vary considerably. When comparing Sweden to the other Nordic countries, it should also be remembered that they all have basic legislation on patients' rights and,[127] with the exception of Norway, general legislation on biomedical research involving humans.[128] Such legislation is so far still absent in Sweden.

Thus the Icelandic Biobanks Act only regulates more permanent biobanks, where the samples are to be kept for more than five years. Research biobanks of a more temporary character are governed by the general rules on biomedical research and the processing of personal data.[129] Many projects using biological samples will thus never come under the requirements of the Biobanks Act, even though this Act is not limited to cover only banks with samples collected within the activities of a health care provider.

Norway is also considering a special Biobanks Act, but more similar to the Swedish Act than to the Icelandic.[130] The proposed Norwegian Act, however, is not restricted to samples collected within the activities of a health care provider, and with regard to biobanks for research, even covers information extracted from the samples.

Finland has chosen not to introduce any Act specifically regulating biobanks, but has supplemented the new Act on the Use of Human Organs and Tissue for Medical Purposes with certain provisions on the collection and further use of human tissue. A similar solution is being considered in Denmark, but there the complementary rules will be introduced in the Act on the Legal Status of Patients and in the Act on Ethics Review. As has been stressed above, under Danish law the biobank samples are also covered by general rules on the processing of personal data.

Generally speaking, the consent requirements for collection and preservation of biological samples for health care purposes are less strict in the other Nordic

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[126] *Regeringens proposition 2001/02:44* p. 56.

[127] See *Lag om patientens ställning och rättigheter 17.8.1992/785* (Finnish Act on the Status and Rights of Patients); the Icelandic *Act on the Rights of Patients No. 74/1997*; *Lov om patienters retsstilling LOV nr 482 af 01/07/1998* (Danish Act on the Legal Status of Patients) and *Lov om pasientrettigheter (pasientrettighetsloven). LOV-1999-07-02-63* (Norwegian Act (63/1999) on Patients' Rights).

[128] See the Danish Act *Lov om et videnskabsetisk komitésystem og behandling af biomedicinske forskningsprojekter LBK nr 69 af 08/01/1999*; the Finnish Act *Lag om medicinsk forskning 9.4.1999/488* and the Icelandic *Regulation on Scientific Research in the Health Sector No. 552/1999.*

[129] See Articles 2 and 15 of the Act on the Rights of Patients No. 74/1997.

[130] *Odelstingets proposisjon nr 56 (2001-2002) Lov om biobanker (biobankloven)* and *Sosialkomitéens Instilling til Odelstinget nr. 52 (2002-2003).*

countries, compared to the new Swedish rules. Biological samples from patients would seem to constitute a more or less integrated part of the medical records, which are kept regardless of the patients' wishes.[131] In the proposed Norwegian Biobanks Act, samples from patients may be preserved in accordance with presumed consent under the legislation on patients' rights. Sweden is thus the only Nordic country where explicit informed consent is required for the banking of samples stored for health care purposes, in the best interests of the patient.

Sweden would also seem to be the only Nordic country where the donor may require the sample to be destroyed or depersonalised even when it is being kept for the health care of the donor. With regard to samples used for research purposes, however, all the other countries seem to entitle the donor to withdraw his or her consent and have the sample destroyed.[132] In Norway, it is even suggested that the donor may insist on information extracted from the sample also being erased.[133]

In general, the rules related to the collection or use of biological samples for research purposes seem to be less divergent. The main rules in all the Nordic countries thus include requirements for ethics review and informed donor consent. At the same time, all the Nordic countries allow certain exceptions to the consent requirements, with regard to use for new purposes of samples already banked. These exceptions vary somewhat with regard to both their prerequisites and their consequences but, as in Sweden, exemptions from the consent requirements need to be approved by the REC, and in the proposed Norwegian legislation also by the Ministry.[134]

Looking beyond the Nordic region, the United Kingdom is an example of a country where substantial investments in new biobanks are at present being made,[135] without the existence of any specific legislation regulating such activities. Instead, several guidelines have been issued by various agencies, such as the Nuffield Council on Bioethics, the Medical Research Council and the Department of Health.[136]

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[131] See, for example, Section 11 of the proposed Norwegian Act, and concerning Denmark, *Redegørelse om biobanker. Forslag til retlig regulering af biobanker inden for sundhedsområdet*. 2002, pp 195-196.

[132] Section 7 of the Icelandic Biobank Act; Section 7 of the Finnish Act on the Use of Human Organs and Tissue for Medical Purposes, Section 14 of the proposed Norwegian Act and the proposed new Section 18 f. of the Danish Act on the Legal Status of Patients.

[133] Section 14 of the proposed Norwegian Act.

[134] Section 13 of the proposed Act.

[135] See, for example, the UK Biobank.

[136] See *Human Tissue - Ethical and Legal Issues*, 1995; *Human tissue and biological samples for use in research. Operational and Ethical Guidelines* 2001 and *A Code of Practice for Tissue Banks: providing tissues of human origin for therapeutic purposes*, 2001. The guidelines of the Medical Research Council require informed consent whenever samples are taken wholly or partly for use in research. Consent must also be obtained for storage and potential future use of samples. Unless the sample is to be anonymised and unlinked prior to storage, it is not acceptable to seek unconditional blanket consent (for example covering "all biological or medical research"). With regard to use of so-called surplus materials removed in the course of medical treatment etc., it is required that individual consent be obtained wherever practicable, and that at the very least an opt-out model should be applied. Although access by the commercial sector to biobank materials collected in the course of MRC-funded research is encouraged, it is stressed that no company should be given exclusive rights of access to a collection of samples made with the benefit of public funds. Donors should be informed if their samples might be used in commercial research. Approval by an appropriately constituted ethics committee is also a mandatory requirement of the MRC, for all research using samples of human biological material.

According to the Nuffield Report, there is limited UK statute law relating to human tissue and the common law leaves its status uncertain in many respects.[137] Many aspects of the law relating to the use of human biological material may thus be difficult to determine with certainty, as is also pointed out in a recent consultation report concerning the law on human organs and tissue in England and Wales.[138] Following the period of consultation, comprehensive proposals will now be prepared for the regulation of the storage and use of human tissue and organs.[139] Among other issues, the consultation report considers the legal and ethical principles of consent, and states that according to the main rule donors must be provided with suitable information and give their voluntary, explicit consent (or, in some instances, register an objection).[140] For children under the age of 16, parents may give consent,[141] whereas the law relating to incapacitated adults is less clear.[142] It is also found that "patients should be asked whether organs or tissue left over following diagnosis or treatment may be retained and/or used for research", and that "all research using samples of human organs or tissue must be approved by a properly constituted research ethics committee".[143] Also with regard to the use of existing samples, "consideration should be given as to whether it is possible (or, depending on the nature of the research, necessary) to seek consent from the person concerned".[144] It is stressed that assumptions about such prospects should really be tested, and that it must not be taken for granted that organs or tissue obtained before a certain date are likely to have been "abandoned". It would thus seem that the English rules on consent show many similarities to Sweden's, and that in England even donors of anonymous materials are offered some protection.

7.4. Compliance with European requirements and standards

Does Swedish law concerning human biobanks comply with the standards laid down in European law? To start with, the Swedish rules vary depending on the circumstances under which the biobank samples are collected. The lack of clear judicial protection for certain donors would not seem to be in keeping with the requirements laid down in Article 22 of the European Convention on Human Rights and Biomedicine and Article 8 of the European Convention on Human Rights and Fundamental Freedoms, nor with Article 3 of the EU Charter on Fundamental Rights and the opinion of the EGE. The fact that no protection of privacy is offered with regard to biological material that is anonymous or anonymised also constitutes an infringement of the rights protected by Article 22. If a restriction of, say, Article 22 is considered necessary in view of other interests at stake, this would need to be clearly stated and defined in accordance with Article 26.1. It should also be noted that relevant binding EU regulations, such as Directive 98/79/EC on in vitro diagnostic medical devices and the proposed Directive on setting standards of quality

[137] *Human Tissue - Ethical and Legal Issues* 1995, Introduction Section 13.8.
[138] *Human Bodies, Human Choices* 2002.
[139] *Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human biobanks* 2002, pp 32-33.
[140] *Human Bodies, Human Choices* 2002 Section 6.1.
[141] *Ibid*, Section 6.2.
[142] *Ibid*, Section 7.4-5.
[143] *Ibid*, Section 10.13.
[144] *Ibid*, Section 10.22.

and safety for human tissues and cells, explicitly refer to the consent requirements of the European Convention on Human Rights and Biomedicine.

As yet, there is no general legal requirement for ethics review of Swedish biomedical research involving humans or human biological material. The European Convention on Human Rights and Biomedicine, as well as Directive 2001/20/EC on good clinical practice in the conduct of clinical trials, sets a standard that calls for adjustments in Swedish law. Legislation on ethics review may be introduced within the near future, and new rules on proxy consent for incompetent patients and research subjects are also under preparation.[145]

An important question is whether Swedish law on biobanks is consistent with Directive 95/46/EC on the protection of personal data. The Directive requires a certain degree of privacy protection, but it is also clear from Article 1.2 that Member States shall neither restrict nor prohibit the free flow of personal data between Member States, for reasons connected to this protection. To the extent that samples of human biological material might come under the Directive – which is an issue yet to be clarified – the Swedish restrictions on the transfer of biobank samples to other Member States would thus be contrary to EU law.[146]

8. Closing remarks

The aim of the Swedish Biobanks (Health Care) Act is to facilitate access to human biological material for both health care purposes and important research, while at the same time offering appropriate protection to privacy of individuals concerned.[147] The requisite balancing of interests has not resulted in quite the same rules for biobank materials as apply to the processing of personal data. It could well be argued that some differences are justified, for example by the fact that human biological material is not only a source of information but can also be used as raw material for products. On the other hand, to the extent that human biological material is only used in a way similar to other carriers of personal data, differences in regulation might seem unreasonable and out of keeping with general ambitions for consistency and coherence in the legal system.

The Swedish Biobanks (Health Care) Act does not manage to clarify the borderline and differences between personal data and human biological material, nor which rules should be applied in certain situations of possible conflict. To some extent, this should not be regarded as a problem to be finally solved by Sweden alone, but as a matter to be discussed and agreed on by the EU countries jointly. The same could be said concerning definitions of such concepts as anonymity and coding. Until such time as these problems can be given a harmonised European solution, however, the Swedish legislator must provide rules that are sufficiently clear at least for domestic use. At present, the scope of the new Biobanks Act remains rather obscure, to the detriment of all parties in any way affected by the legislation. There are also several problems with the Swedish biobank legislation that cannot be

[145] See *Regeringens proposition 2002/03:50 Etikprövning av forskning* and the terms of reference issued in *Förmyndare, gode män och förvaltare,* Direktiv 2002:55.
[146] See Wessman, R. 2003.
[147] *Regeringens proposition 2001/02:44* pp. 29 and 67.

blamed on uncertainty related to European law, such as the fact that many biobanks are left partly unregulated.

The framing of legislation on the use of human biobanks, which in a well-balanced way fulfils international requirements as well as domestic needs, has certainly been an urgent task, but it should also have been recognised as a highly demanding one. It would seem that the Swedish government did not take this issue seriously enough at the outset, and thus failed to secure the thorough and qualified investigation that was needed. The resulting Swedish Biobanks (Health Care) Act is unfortunately compromised by inconsistencies, general obscurities and other shortcomings.[148] We have succeeded in introducing regulation of human biobanks, but it is a regulation that may require more adjustment and supplementation than would normally be desirable. It is therefore important that the present Biobanks (Health Care) Act should not be considered the end point of this regulatory process. The legal developments and debate both within and outside the EU need to be followed closely and carefully considered, if we are to achieve our objective: a just and appropriate balance between privacy and interests of research, in compliance with our duties under international and European law.

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6

Focusing on personal integrity violation – legal guidelines for ethical practice[1]

Ulrik von Essen, LLD

Department of Law, Stockholm university

The rapid pace of development in science has activated ethical questions in connection with research. Studies of these questions in Sweden have resulted in a draft Ethical Review Act concerning research which entails processing of personal data and studies of biological material. Since examination by the Boards for Research Ethics will constitute a task involving exercise of public authority regulated by statute, future assessments must lie within the limits determined by the statutory provisions. This paper discusses the legal premises on which these ethical reviews should be based on.

1. Introduction

The rapid pace of development in science has activated ethical questions in connection with national and international research. Studies of these questions have resulted in a draft Ethical Review (Research Concerning People) Act (Ethical Review Act).[2] This Act will apply to all research disciplines, but ought to be of primary importance for medical research.

Even today, medical research is examined from the ethical point of view. In every health care region there are medical research committees on ethics whose work is based on the Helsinki Declaration and other ethical guidelines.[3] The Declaration, which has been adopted by the World Medical Association, contains ethical guidelines for research on people. Inspection of medical research is not, however, legally regulated nowadays. This is considered to be a serious shortcoming which will be remedied by the entry into force of the Ethical Review Act.

Since examination by the Boards for Research Ethics will constitute a task involving exercise of public authority regulated by statute, future assessments must conform to the limits determined by the statutory provisions. When determining the

[1] This paper is based on an earlier article, von Essen, Ulrik (2002). *Biobanks- och Registerforskning.* Förvaltningsrättslig tidskrift, häfte 5-6, 2002, pp. 351-380.

[2] At the time of writing (January 2003) the Government had submitted a Proposal for consideration by the Council on legislation, and the latter had returned an opinion. A Government Bill 2002/03:50 (*Regeringens proposition 2002/03:50 Etikprövning av forskning)* was proposed in February. The Act is expected to come into force in January 2004.

[3] See the guidelines of Medicinska forskningsrådet (2000). *Riktlinjer för etisk värdering av medicinsk humanforskning* (MFR rapport 2/2000). (Medical Research Council – now Working Group for Research on Genetics in Medicine of the Scientific Council – *ethical evaluation of medical human research*, report 2/2000).

limits, consideration must be paid not only to the wording of the statutory provisions, but also of the intentions expressed in the *travaux préparatoires*. Care must be taken here to avoid collisions between the various statutes in the area.

2. The Ethical Review Act

2.1 Purpose and terminology

The *purpose* of the Ethical Review Act is to protect the individual and guarantee respect for human dignity in connection with research. Private individuals shall be protected against violations of personal integrity and physical injuries or emotional harm. What is intended here is not so much provision of absolute protection against the foregoing, but rather, since a research project may entail risks to the test subjects, a *balancing* of these risks against the expected gain in knowledge.[4] A generally accepted balance therefore needs to be struck between the quality of research and the risks it entails to individual subjects and the value of human dignity.

Research refers here to scientific research as well as development projects based on scientific grounds. The government authority or the natural or legal person under whose auspices research is conducted is referred to in the legislative proposal as *research representative*, whereas the living person affected by the research is called *research subject*. Regarding other matters, the legislative proposal contains certain concepts which are defined in other statutes, especially in the Personal Data Act (1998:204)(see below).

2.2 Scope

The scope of the Ethical Review Act is regulated by Sections 3-5 of the Act. Section 5 lays down that the Act shall apply to research which is *conducted in Sweden*. Regarding international research projects, ethical examination shall apply to that part of the project which is to be conducted in Sweden. Sections 3 and 4 of the Act determine the substantive area of the Act's application by laying down that ethical examination shall be conducted with regard to research concerning the handling of certain *personal data*, or entailing either physical *handling of people* or concerning studies of *biological material* obtained from people. Research of these kinds may be conducted only if it has been approved following ethical examination. Approval under the law does not entail that the research may be conducted if it is in violation of another statute, for example, the Human Fertilised Ova (Measures for Research and Treatment Purposes) Act (1991:115).

2.2.1 Research entailing processing of personal data

The Ethical Review Act shall be applicable to research entailing, *inter alia*, processing of sensitive personal data. One of the prerequisites for the application of the Act is that the research subject shall *not* have given his or her *explicit consent* to the processing of data. Moreover, the Act applies only to research concerning information about *living* persons. The term *sensitive personal data* is defined in Section 13 of the Personal Data Act – to which the Ethical Review Act makes reference – and embraces, among other things, personal data which reveals race or

[4] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)* p. 79.

ethnic origin and which concerns health or sex life. An example of research that would be covered by the Act is when a researcher wishes to use data from the National Board of Health and Welfare's health register.

General provisions concerning processing of personal data can be found in the Personal Data Act, the object of which is to protect people from violations of personal integrity, first and foremost by means of automatic personal data processing.[5] The more precise meaning of the term *integrity* has not been discussed in the *travaux préparatoires*.[6] The term *processing* refers in this context to any measure or series of measures taken in respect of personal data. All handling of such data – e.g. collection, registration, storing, processing, use, and destruction – falls, in principle, within the scope of the Act, . *Personal data* is defined as any type of information directly or indirectly referable to a living, natural person. Information that can be referred to individual persons but only in their capacity as members of a larger group, for example, smokers or breast cancer patients, should not be considered as personal data. On the other hand, encrypted or encoded data is covered by the Act, as long as there is someone who can make the data readable and in this way make possible the identification of individual persons. A person who decides the purpose and means of personal data processing is called *controller of personal data* in legal terms. The Act applies, with few exceptions, exclusively to controllers established in Sweden.

The Personal Data Act is *subsidiary* in relation to other statutes or statutory instruments, but not to regulations issued by public authorities (Section 2). Such divergent provisions can often be found in so-called *data file statutes*, which regulate the setting up and maintaining of more important data files, primarily in the public sector. A data file statute therefore constitutes a special regulation in relation to the Personal Data Act, which it is intended to supplement or override to some extent. A large number of such statutes are to be found,[7] with varying taxonomy and structure. Perhaps the most important in this context is the Health Data Registers Act (1998:543). Under the provisions of the Act and the corresponding statutory instruments, the health care personnel responsible must provide information to a central administrative authority, primarily the National Board of Health and Welfare, so that it can be entered in the national data file. The information in this data file may be used,, for example for purposes of research or epidemiological studies, on which occasions the national data file may be run concurrently with other data files. Once a legality test has been carried out and passed, the information may be forwarded to the researchers involved in the project, in both the public and the private sectors. It should be observed that the provisions regulating disclosure of information by authorities or individuals have precedence over the provisions of the Personal Data Act.[8] Such a duty is set out in the Freedom of the Press Act (1949:105), the Medical Records Act (1985:562), the Secrecy Act (1980:100), and the Health and Medical Services (Professional Activity) Act (1998:531).

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[5] This Act transposes Directive 95/46/EC of the European Parliament and the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

[6] Cf. Government Bill 1997/98:44 *(Regeringens proposition 1997/98:44)*, p. 115. See also Öman, Sören & Lindblom, Hans-Olof, *Personuppgiftslagen*, 2nd ed., p. 43 f.

[7] Cf. the Ministry publications series, Ds 2000:34, p. 58.

[8] Government Bill 1997/98:44 *(Regeringens proposition 1997/98:44)*, p. 116.

The principal requirements concerning the processing of personal data and situations in which such processing is *permissible* are defined in Sections 9 and 10 of the Personal Data Act. These sections lay down quite obvious requirements, e.g. that personal data shall be processed only if the processing is lawful and shall be processed in a correct manner. It is further stipulated that personal data may only be collected for specific, explicitly stated and justified purposes and that personal data shall not be processed for any purpose that is incompatible with that for which the information is collected. Personal data may be processed only if the person registered has given his or her consent to the processing. There are, however, a number of exceptions to the requirement of consent. For example, personal data may be processed where necessary for the performance of a task of public interest, such as research.[9]

More restrictive rules apply to the processing of *sensitive personal data*, regarding health, for example. The main rule is that processing of such data is *prohibited* if the person registered has not given his or her *explicit consent* to the processing (Section 15 of the Personal Data Act). In addition to the above-mentioned right to the processing of personal data pursuant to different data file statutes, a number of exceptions can be found. For example, processing of personal data for the purposes of health care and medical treatment is permitted.

Sensitive personal data may further be processed without consent in connection with *research*, subject to certain conditions. Thus Section 19 (1) of the Personal Data Act sanctions the processing of sensitive personal data for the purposes of research, provided the processing is *necessary* in the manner stated in Section 10 and the interest of society in the research project is manifestly greater than the risk of improper violation of the personal integrity of the individual involved in the processing. The provisions are justified by the fact that research may be so important that it should not be dependent on informing and obtaining consent from every individual.[10] A controller of personal data, e.g. a researcher or a research institution, may decide on their own to notify the Data Inspection Board of their decision, or else submit the research project to a *research ethics committee*. If the processing of personal data has been approved by the research committee, the prerequisites under Section 19 (1) of the Act shall be deemed satisfied.

The above-described regulatory framework will change after the implementation of the Ethical Review Act. The new Act stipulates instead an *obligatory ethical review* of research projects in which sensitive personal data are included, and where consent has not been obtained. Research may not be undertaken if the research project has not been approved by a Board for Research Ethics. In this way the researcher will no longer be able to make his own decision on the basis of Section 19 of the Personal Data Act. In consequence, when examining research containing sensitive personal data, the Board for Research Ethics will also have to give an opinion on the processing of these data. Assessing the project and the processing of data should often be the same, but it cannot be ruled out that certain processing measures may be considered too far-reaching, even if the project and the general procedures are regarded as acceptable. In its decision – which will be made in accordance with the provisions of the Ethical Review Act (see Section 4) – the Board shall make use of the *assessment prerequisites* which are today expressed in

[9] Swedish Government Official Reports, SOU 1997:39, p. 305, 355 and 361.
[10] Government Bill 1997/98:44 *(Regeringens proposition 1997/98:44)*, p. 71.

Section 19 of the Personal Data Act.[11] The Personal Data Act will therefore be supplemented by a new provision stipulating that sensitive personal data may be processed for the purposes of research, provided the processing has been approved by a Board for Research Ethics according to the Ethical Review Act.

2.2.2 Research entailing intrusive demands on people and studies of biological material

In addition to research entailing processing of certain personal data, the Ethical Review Act shall apply to research entailing physical intrusion on a research subject and carried out in a way which will influence the research subject physically or mentally, research concerning studies of biological material taken from a living person and identifiable as originating from that person, research entailing physical intrusion on a deceased person or concerning studies of biological material taken for medical purposes from, for example, a deceased person, and identifiable as originating from that person (Section 4 of the Ethical Review Act). Research concerning fertilised ova, embryos and foetuses inside the mother's body entails physical intrusion on the person of the mother, whereas research on fertilised eggs outside the female body, for example in the case of embryonic cell research, constitutes research on biological material. In both cases ethical review shall be performed. If, on the other hand, research consists in the fact that certain biological material from a person is developed into something more than it originally was, for example when DNA is isolated, or when a part of a fertilised human egg is developed into an embryonic cell line, the individual connection no longer exists and no ethical review is therefore necessary.[12] Opinions may differ, however, as regards the exact point in time at which the tissue ceases to be part of the original material.

What is interesting in this context is research done on pre-existing biological material. Interest in such collections of human biological material has grown very strong in recent years.[13] This is associated with the rapid development of biomedical research and genetic technology both in Sweden and abroad, which opens the doors to tremendous possibilities in both biomedicine and other research. The development process is being accompanied, however, by fears that information about individual persons' genetic material may be misused, and that people will be treated differently, depending on their genetic condition.[14] In the general debate, protection of an individual person's integrity has come into focus, and it is considered important to create safeguards guaranteeing that integrity-sensitive information is not disseminated in an uncontrolled and undesirable way. This protection of individuals shall be safeguarded, *inter alia*, by means of the new Biobanks (Health Care) Act (2002:297) (the Biobanks Act) which enters into force on 1 January 2003, and in turn is supplemented by the Ethical Review Act.

The purpose of the Biobanks Act, as already intimated, is regulation of the use of human biological material from the point of view of respect for personal integrity of individuals. The exact meaning of the term 'integrity' has not been discussed in the *travaux préparatoires*, but it is indicated that protection of

[11] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, pp. 164 and 185.
[12] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, p. 99 f.
[13] See Rynning, Elisabeth (1998). *Biobankerna – hög tid för bankinspektion*? Förvaltningsrättslig tidskrift, no. 6, 1998, pp. 303-333.
[14] See in this context Radetzki, Marcus, Radetzki, Marian & Juth, Niklas *Att nyttja genetisk information*, with references.

individuals shall be weighed against society's need of the biological material in question for the purposes of research.[15] The Act shall be applicable to biobanks in Sweden. The term *biobank* refers to biological material from one or several persons – living, deceased or foetuses – which is collected and kept to be used at a later date, whose origins can be traced to the person or persons concerned. Not all biobanks will be covered by the new regulatory framework, however.

The first condition for a bank to come under the Biobanks Act is for the material to be *traceable* to the individual sample givers, for example, by being able to break the encoding key. It is further required that the material has been obtained from patients or others in the context of health care or medical treatment or in connection therewith for the purposes of research, and that it is to be *stored* for an indefinite or definite period. Samples which have been collected independently from health care activities, for example samples taken by research institutions, come outside the scope of the Act. The Act applies, however, to biobanks containing material obtained from biobanks kept by medical and health care institutions, and material stored at research institutes or pharmaceutical companies, for example. Samples taken for the purposes of medical treatment and not kept for "a longer period of time" are not covered by the provisions of the Act. The Act does not specify the meaning of the term "a longer period of time", but a period of two months has been indicated in the *travaux préparatoires* as such.[16] This will probably entail a number of problems for health care services, since samples taken for treatment purposes must often be kept longer than that.[17] Regarding biobanks containing samples obtained from newborns special rules apply under Chap. 5 of the Act.[18] The Act is *subsidiary* in relation to other legislation, with the exception of the provisions concerning the PKU register, which shall apply before all other legislation.

A biobank is *established* by a decision of a health care provider or some other institution, such as, for example, a research institute or a pharmaceutical company, which has received tissue samples from the biobank of a health care provider. In connection therewith the representative of the biobank shall also determine the purposes of the biobank. If a biobank is established for the purposes of research or clinical testing, it shall always be examined and approved by a Board for Research Ethics. This examination procedure must be completed before samples can be submitted for research purposes.[19] A decision to set up a biobank shall be communicated by the research representative to the National Welfare Board, which shall keep a register of biobanks.

The Act stipulates that tissue samples may not be *collected* and stored in the biobank unless the sample provider has been *informed* of the reason for it and the objective or objectives for which the biobank may be used, and unless he has given

[15] Government Bill 2001/02:44 *(Regeringens proposition 2001/02:44)*, p. 18 ff., and 67.
[16] Government Bill 2001/02:44 *(Regeringens proposition 2001/02:44)*, p. 30.
[17] See Lindberg, Bo, *Clinical data – a necessary requirement for realising the potential of biobanks*, in this final report.
[18] The so-called PKU test is a routine blood test performed on all newborns in Swedish hospitals in order to uncover a relatively rare disease which may cause serious brain damage if the child is not supplied with a special diet. After a screening analysis, the samples are stored in the so-called PKU register at the Huddinge University Hospital AB.
[19] Government Bill 2001/02:44 *(Regeringens proposition 2001/02:44)*, p. 71.

his or her *consent*.[20] Consent can be revoked wholly or partially at any time. If the revocation refers to all use, the sample shall be destroyed or all identification labels removed. In this respect the regulatory framework differs from what normally applies to personal data under different data file statutes in the area of medicine, where an individual subject normally has no right to request his or her removal from such files. This is because the right to be struck off a register would mean that the activities for which the data file is supposed to be used – health care, research, statistics, etc. – could not be satisfactorily performed. Frequently, the importance of access to large amounts of material for medical research purposes is also stressed, as well as the need for research activities extending over a long period of time.[21] The same arguments can, naturally, be invoked against the right of revocation of consent to the use of biological material in a biobank. If the material in the bank is to be used for *another purpose* than the original purpose of the collection, it is up to the Boards for Research Ethics to examine the research project in order to determine what shall apply regarding information and consent (see also Sections 2.3 and 4.4).

If a researcher wishes to use material from a biobank he must obtain approval from a Boards for Research Ethics under Section 4 of the Ethical Review Act. In contrast to research entailing processing of sensitive personal data, ethical review in these cases is not dependent on the consent of the sample providers.

2.3 Information and consent

Sections 13-22 of the Ethical Review Act contain provisions on information and consent. The main application area of these provisions relates to research which entails physical intrusion on individuals, because the provisions apply only insofar as there are no other special provisions on information and consent in any other statute.

When the biological material is stored in biobanks *and comes from health and medical services*, the provisions of the Biobanks Act concerning information and consent shall thus be applicable. Under this Act, tissue samples may not be collected and stored in a biobank without informing the sample provider of the purpose and objectives for which the bank may be used, and without obtaining his or her consent. If a researcher wishes to use the material in a biobank for *another purpose* than that embraced by the information provided earlier and for which consent has been obtained, the sample provider has to be *informed and his or her consent* obtained for this new purpose. An exception is made regarding the requirement of consent in cases of *research and clinical testing*. If the new purpose concerns such activities, it is instead *the Board for Research Ethics* which has to grant approval for the new purpose and also determine the requirements concerning information and consent if the tissue samples stored in the bank are to be allowed to be used for the new purpose (see Section 4.4.). The *travaux préparatoires* do not discuss the issue of when a sample is to be considered to be used for a new purpose, which can lead to various demarcation problems.

The question that comes to mind concerns the type of information that an individual person must receive in order to give his or her legally valid consent to the storage of the material in a biobank. The *travaux préparatoires* indicate that it is

[20] Special rules apply to information and consent as regards minors, foetuses and deceased persons, as well as persons who by reason of unconsciousness, mental illness or similar are unable to give consent.
[21] See, for example, Government Bill 1997/98:108 *(Regeringens proposition 1997/98:108)*, pp. 39, 42 f. and 83 f.

impossible to regulate exactly the requirements of information and consent in each individual case, but that the sample provider should always be informed about 'the intention to keep a sample in a biobank and the purpose for which is shall be used'.[22] In the light of the aforesaid and in reference to the ethical review which will be obligatory for research on human biological material, it should be sufficient, in my opinion, to inform a patient briefly what a biobank is and what rules *apply to* it, requesting that the patient decide to either give or withhold his or her consent to storage of the sample and its use for the purposes of 'research'. Requesting that a patient consent to a specific research project is quite unrealistic, since it is rarely known at the time of the sample taking which research project will be involved. The patient will not be particularly inconvenienced, since ethical review will have to be made once the research project is underway, and if any component of the research project seems controversial the Board for Research Ethics may then decide that consent must be obtained again.

Collections of biological material that have been gathered primarily by *someone else than the health care provider in health care and medical services*, for example, a research institute or a pharmaceutical company, do not come under the Biobanks Act. In those cases the provisions of the Ethical Review Act apply as regards information and consent, but have the same implications as the provisions of the Biobanks Act. Even in those cases it is the Board for Research Ethics that shall determine the requirements to apply in respect of information about and consent to the use of the material.

As regards research entailing processing of sensitive personal data, the question of the research subject's *consent* never arises. If the consent has been given, processing is permitted under the provisions of the Personal Data Act, and an ethical review pursuant to the provisions of the Ethical Review Act is not necessary.[23] The researcher will not need to provide information on the processing (Section 24 of the Personal Data Act; cf. Section 6 of the Ethical Review Act).[24] On the other hand, the Board for Research Ethics may lay down conditions concerning information in connection with the ethical review (see Section 4.4).

3 Access to research material

3.1 Access to biological material

The requirements which have to be satisfied by a researcher in order to gain access to the material stored in a biobank are defined in Chap. 4 of the Biobanks Act. The person requiring access to tissue samples has to apply for it to the person responsible for the bank in question, who may refer the matter to the principal party A refusal may be reviewed by the National Welfare Board, but its decision will constitute only a non-binding recommendation,[25] the reason being that no statutory right determines access to samples stored in a biobank, and accordingly a health care provider is under no obligation to hand over the samples. The aforesaid applies to biobanks in

[22] Government Bill 2001/02:44 *(Regeringens proposition 2001/02:44)*, p. 38.
[23] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, p. 115.
[24] The formulation and content of Section 6 of the Ethical Review Act have been criticised by the Council on Legislation (see the Council's opinion, p. 4 f.).
[25] Government Bill 2001/02:44 *(Regeringens proposition 2001/02:44)*, p. 49.

both the public and private health care sectors. For newly created biobanks – secondary biobanks – at research institutes or suchlike, which contain material gathered from the biobanks of various health-care providers, there is no possibility of 'appeal', since samples stored in such banks may never be passed on to other parties.[26] Tissue samples collected primarily from outside the health care sector, for example by pharmaceutical companies, are not covered by the provisions of the Biobanks Act and it is up to the 'owner' to decide whether and on what conditions samples may be handed out. Other rules apply to tissue samples which are to be handed over to recipients in another country for the purposes of research (see, Chap. 4, Section 3 of the Biobanks Act).

Unless otherwise provided, tissue samples shall not be identifiable, i.e. they must be *coded* before they are released. An application to break the code in order to gain access to personal data concerning an individual sample provider shall undergo the same procedure as applications for access to samples in a biobank. As mentioned earlier, a research project including studies of sensitive personal data shall undergo ethical review. Approval obtained from the aforesaid means that the processing is permissible, but the question of whether information shall or may actually be disclosed shall be decided on the basis of the rules concerning secrecy and confidentiality (see Section 3.2).

3.2 Access to personal data

Section 6 of the Ethical Review Act provides that personal data may be disclosed in order to be used in research projects unless otherwise indicated by provisions concerning secrecy and confidentiality. It is important to note that the provisions do not entail an obligation to disclose personal information. This is expressed in the *travaux préparatoires* in such a way that the provisions 'allow the person in possession of the information to disclose it only if he or she wishes to do so',[27], provided it is not contrary to the provisions governing secrecy and confidentiality. This statement does not really reflect the true situation, because a distinction has to be made between a situation in which the information is in the possession of a public authority, and cases in which it is in the possession of a private subject.

The right of access to official documents is constitutionally regulated, and the provisions concerning the issue may be found in the Freedom of the Press Act. These provisions apply, in principle, solely to *public* (government or municipal) *authorities*, and not to private parties, such as, for example, private health care or research institutions. A document is regarded as official if it is in the possession of a public authority and if is has been received by the authority or drawn up by it. The main rule is that anybody may request access to an official document. The right to the aforesaid – *the principle of public access to official documents* – is restricted, however, by means of secrecy provisions. It must be emphasised that public bodies have an unconditional duty of disclosure of official documents which are not restricted by secrecy provisions. No equivalent duty of disclosure of documents applies to individual parties, such as, for example, private health care institutions.[28]

[26] Within the framework of research co-operation, material may be passed on to another research unit for research purposes in Sweden or abroad.
[27] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, p. 183.
[28] Some measure of obligation to disclose information follows from the provisions of Section 16 of the Medical Records Act, but this obligation applies to the patient alone.

The provisions of the Secrecy Act concerning *secrecy* are directed, with few exceptions, at *public bodies*. Observing secrecy means a prohibition to disclose information, whether orally or by means of making an official document available, or in any other way. The Secrecy Act has thus been designed to regulate the issues of *secrecy* and *confidentiality* in the sphere of public activities. Secrecy applies not only in relation to individuals but also *between different authorities* and to different spheres of activities within one and the same authority if they are considered as independent from one another. The principal rule that secrecy applies between authorities is subject, however, to many exceptions. The most important exception in this context is the one laying down that the provisions on secrecy do not prevent disclosure of information to another authority when the obligation to provide information follows from a law or a statutory instrument. Such provisions on obligation to provide information can be found, for example, in the many different data file statutes.

Regarding *certain particular subjects* equivalent rules on confidentiality apply which can be found in other statutes. Concerning private doctors and the like, such provisions can be found in the Health and Medical Services (Professional Activity) Act. There are no similar regulations relating to a number of other private subjects, such as, for example, companies, institutes and foundations; these can be bound, however, by prohibitions under the Secrecy Act, since an authority supplying a confidential item of information will stipulate that the information may not be passed on or used in another way (Chap. 14, Section 9 of the Secrecy Act).

The objective of the secrecy laws is to protect public and private interests. The secrecy provisions have been therefore generally formulated in such a way that a risk of harm must be assessed in each individual case in connection with their application. There are two types of so-called *harm conditions*: 'straight' and 'converse'. The first means that the right of access to information is the main rule, and secrecy applies only if *it disclosure will presumably lead to harm*, whereas the second means that secrecy is the main rule and always applies when *it is not clear* that the information can be disclosed *without any risk of harm*. The latter harm condition, i.e. a more strict form of secrecy, applies to the health care sector and to information supply from certain authorities' registers, such as the National Board of Health and Welfare, for purposes of research.

Usually, the secrecy provisions are formulated in such a way that secrecy is restricted to information which appears in a certain type of case, for example, within a certain sphere of activity or a particular authority. If an item of information is passed on from one authority to another, the main rule is that secrecy rules applicable to the information supplying authority (the primary secrecy) do not extend to the receiving authority. Whether a document will or will not become subject to secrecy in the receiving authority depends on whether secrecy concerning information disclosure applies to this authority or not. Sometimes, however, when it is especially provided *secrecy protection is transferred* to the receiving authority, where so-called secondary secrecy will apply. The cases in which such transfer is applicable are regulated in Chaps. 11 – 13 of the Secrecy Act. Secondary secrecy applies, *inter alia*, when one authority receives confidential information from another for the purposes of research. Authorities may receive such information under statutory provisions or regulations by statutory order (Chap. 14, Section 1 of the Secrecy Act), upon exemption from the Government (Chap. 14, Section 8 of the Secrecy Act), or upon harm assessment in accordance with some secrecy provision, for

example, pursuant to Chap. 7, Section 1 of the Secrecy Act (health care). The provisions on secrecy transfer shall not apply, however, if a secrecy rule for the protection of the same interest is in any case applied to the information by the receiving authority. The receiving authority shall then act according to its own secrecy provisions, which means that secrecy protection may become weaker or stronger than that applied by the original authority supplying the information.

Consequently, if a researcher wishes to obtain personal data from, say, a medical file or a register kept by a *public authority*, the documents containing the information are, as a rule, to be considered as official documents. The request will then be examined by the authority, for example a public health care service or a central administrative authority, in accordance with the provisions of the Secrecy Act and the Personal Data Act. As stated before, every research project which includes the processing of sensitive personal data has to undergo an ethical review. Approval means that processing is permissible under the Personal Data Act, but the question of whether the information may be disclosed (concerning public health care providers) will be determined on the basis of the Secrecy Act. If it cannot be said with certainty that the information may be disclosed without causing harm to the individual subject, the information may not be passed on – otherwise, it may. If the information is intended for research purposes, the examination will most often lead to the conclusion that the information may and shall be disclosed.[29] A decision denying a request to obtain documents may be appealed in the Administrative Court of Appeal under the provisions of the Secrecy Act.

If a researcher to whom information is submitted works for a public authority, for example a public health care provider, the secrecy rules of the supplying authority will accompany the information, if the information would not be confidential under the secrecy provisions applied by the receiving authority. Whatever the exact case may be, in the context of medical research it is practically always the stricter form of secrecy which applies. If the recipient is a private health care provider, the information will be confidential under the Health and Medical Services (Professional Activity) Act. If the recipient researcher represents another type of private subject, e.g. a pharmaceutical company, the information is not subject to any secrecy provisions there. The supplying authority may make a proviso, however, that the information may not be passed on to anyone else.

In the case of *private health care providers*, medical files and other documents concerning patients do not constitute official documents, which is why these institutions are not obligated to disclose any information deriving from them. There is nothing to prevent disclosure of information, however, provided secrecy provisions do not apply, which is seldom the case when information is requested for research purposes. But even if a given health care provider should decide that disclosure of information would not cause any harm to the individual, he has no obligation to disclose information, and his decision cannot be appealed against.

If information is disclosed by a private health care provider to a researcher working in the public or private health care sector, the information will be subject to secrecy provisions applicable in the recipient institution. If the information is disclosed to private subjects outside the health care sector, it normally loses its

[29] Bohlin, Alf, *Offentlighet & sekretess i myndighets forskningsverksamhet (Riksarkivet, Report 1997:2)* p. 28 and *Offentlighetsprincipen*, 6th ed. p. 203 f.

secrecy protection and the supplier of information – the private health care provider – has no possibility of making provisos concerning its dissemination.

It should finally be added that the provisions of the Secrecy Act and the Health and Medical Services (Professional Activity) Act for the protection of the individual's integrity are supplemented by what are usually referred to as *internal secrecy* rules. Under the provisions, for example, of Section 7 of the Medical Records Act (1985:562), medical documents shall be handled and stored in such a way that no unauthorised persons can gain access to them. It is thus only the personnel actually needing access to a patient's files in their work who shall have the possibility of accessing the patient's files.[30]

4. Review by the Boards for Research Ethics

4.1 The premises on which ethical review is based

The provisions of Sections 8-11 of the Ethical Review Act stipulate premises for ethical review concerning research entailing intrusive demands on human beings or studies of human biological material, or entailing the processing of sensitive personal data. The provisions have been formulated on the basis of Article 16 of the European Convention on Human Rights and Biomedicine, which in turn is supported by the Helsinki Declaration. The aim of an ethical review is to decide whether the research project as such, including any processing of personal data, can be approved from the ethical point of view. If the Board for Research Ethics approves the project it may also determine the rules concerning information and consent. This issue is treated below in section 4.4.

The proposed legislation contains only certain general and rather vague premises as to what shall be taken into consideration in connection with an ethical review. This is because it is the organisation and form of the ethical review which have been considered in need of regulation. The review of the substantive content has not been found as suitable for detailed regulation by means of legislation.[31] Since reviews by the Boards for Research Ethics will constitute statutorily regulated tasks, their future decisions must observe the restrictions of the framework determined by the statutory text and the intentions expressed in the *travaux préparatoires*.

The first requirement that has to be satisfied is that research may be approved only if it can be conducted with respect for *human dignity* (Section 8 of the Ethical Review Act). This requirement is partly connected with the provisions of Section 9 of the same Act, providing that *human rights and fundamental freedoms* shall always be considered in connection with ethical reviews, at the same time as regard shall be paid to the development of *new insights* by means of research; people's well-being, however, shall always be given priority over society's needs and research interests. What does this mean? The *travaux préparatoires* stipulate only that protection of the participants in a research project is of major importance, and that this concern for the individual can be expressed in that research may be approved only if it respects human dignity. It is further laid down that these interests do not always, or even frequently, have to be contradictory. On many occasions research can be the very thing that best promotes people's interests. In general, it is

[30] Government Bill 1984/85:189 *(Regeringens proposition 1984/85:189)*, p. 43.
[31] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, p. 93.

stated that the balancing of interests should be done in the light of more general considerations, e.g. that the fundamental rights and freedoms shall be observed in connection with research in terms of a long-time perspective and not only in terms of direct risks incurred by the participants. What this refers to, for example, is research that may entail genetic influence on future generations. Here again it is held that these requirements may speak both for and against research, since people's welfare is in general promoted by research, and since from the societal point of view it is very important to create possibilities for the advancement of knowledge by means of research.[32] Neither the Convention on Biomedicine nor the Helsinki Declaration provide more precise guidelines for the interpretation of these provisions.

The provisions presented above constitute in reality a political manifesto of limited legal importance. The provisions can thus be compared to those of the Social Services Act (2001:453) stipulating that 'the social services shall promote equality in the people's … living conditions for the purposes of democracy and solidarity', or the requirements of the Health and Medical Services Act (1982:763) that health care shall 'be of good quality and meet the patient's needs of security'. Thus no legal restrictions for the approval of research projects are imposed by these provisions, other than in extreme cases.

Under the provisions of Section 11 of the Ethical Review Act, a research project may not be approved if the expected result can be achieved in *another way which is less hazardous to* the research subject's health, security and personal integrity. Regarding processing of sensitive personal data, approval may be granted only if the processing is *necessary* for the carrying out of the research project. The first phrase in italics expresses the principle that research relating to people may be conducted only if no alternative, equivalent methods exist which do not entail experiments on people or which are less risky. This will therefore not apply to research on material from biobanks. The requirement of necessity, which corresponds to Section 10 of the Personal Data Act, should normally be satisfied in connection with the research in question.

Section 10 of the Ethical Review Act defines special prerequisites under which research may be approved only if the risks entailed by it to the research subject's health, security and personal integrity are counterbalanced by its *scientific value*. This should be considered as the most important provision in this context[33]. The Act permits research subjects to face certain risks, but these must be proportionate to scientific gain. Ethical review proceeds by two stages. First comes an assessment of what is called *scientific cogency*. This means that the researcher has to be able to show that his research project can generate well-substantiated knowledge. The determination of scientific cogency is of decisive importance, since the special prerequisites mentioned above mean the expected *value* of knowledge that may be generated by the research being posited against the risk of harm. As regards the *assessment of risk*, the *travaux préparatoires* state that it is in the nature of things that in a normal case the risks ought to be restricted. Regarding the assessment of risk itself, one has to determine first the extent to which any negative consequences can be *predicted*. Uncertainty concerning harm that may ensue is said to constitute an important argument against approval. Next, the *probability* of

[32] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, pp. 90 and 185.
[33] Cf. Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, p. 91.

identifiable negative consequences must be determined. Finally, the *degree* of inconvenience or harm that these consequences may entail to people who participate in or are in some other way involved in the research shall be established.[34]

4.2 Review of research concerning studies of biological material

As regards research on material from *biobanks*, the researcher has to show, as has been demonstrated in the previous section, that the research project satisfies the necessary conditions for the generation of important new insights. If this is the case, the project should be approved from the ethical point of view, since only in extremely exceptional cases will a risk of harm arise in the legal sense. Research of this kind does not entail any physical intrusion on human beings and there is no risk of psychological harm involved. The only type of harm that may become relevant is *violation of personal integrity*. As mentioned earlier, tissue samples delivered by a biobank shall as a rule be coded. If they are not, or if the code may be allowed to be broken later on, the Board for Research Ethics will *also* have to carry out an ethical review of the research project, including the processing of sensitive data (see below). Since the material in connection with 'pure' biobank research, i.e. research which does not involve personal data, cannot be associated with any individual persons, there is no risk of their integrity being violated.[35]

The meaning of the term *integrity* has not been defined in the statute or the *travaux préparatoires*, and the term takes on different meanings in different contexts and statutes. Arguably, then, research on material which has been submitted by persons who have not given their consent to a specific project already constitutes a violation of integrity. It has not been the legislator's intention, however, to give the term this interpretation,[36] and this should also be clear from the fact that no ethical review under the provisions of the Ethical Review Act is necessary if biological material cannot be linked with an individual person.[37] If such a view should nevertheless be taken, the above-described appraisal ought to demonstrate that research should be permitted as long as it has the potential for increasing our knowledge. Predictably, there is a risk here of some individuals feeling that the research can be prejudicial to their integrity. Indeed, these persons may possibly find the research offensive. The degree of this inconvenience must be termed fairly limited, however, since data from a biobank cannot be linked to any particular individual.

The conclusion must be that research on material from biobanks is normally ethically acceptable for the purposes of the Ethical Review Act. Exceptions will refer to cases when the researcher cannot show that his or her research project has any scientific value, and cases where the research as such can be said to express a view of people which is incompatible with the views and attitudes prevailing in our society.

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[34] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, p. 91. Cf. Medical Research Council's Report, MFR report, 2/200, p. 13 f., based on the Helsinki Declaration.

[35] Against this view it can be stated that human material containing DNA which is intact is always, in principle, traceable back to the provider. In my opinion it is not enough, however, at least at present, to claim that because of this there is a risk of integrity damage.

[36] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, p. 89 f.

[37] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, p. 99 f.

4.3 Review of research entailing processing of sensitive personal data

As regards the use of *sensitive personal data*, the value of the research must be weighed against the risk which it entails. As a rule, access to personal data plays an important role in the generation of new, valuable knowledge in the course of research. Determination of risk should obviously be performed on the basis of the above-described rules, and additionally, the provisions that – until the coming into force of the Ethical Review Act – follow from Section 19 of the Personal Data Act.[38] The *travaux préparatoires* of this section stipulate that when comparing the research project's importance and the risk of violation of personal integrity, the processing *security* shall be taken into account, the *expense and time* necessary to obtain consent, and, to a certain extent, the degree of difficulty involved if someone should attempt to *identify* individual persons on the basis of the personal data undergoing processing. It shall further be considered whether information is forwarded in any form to the persons in question, for example by advertising or notification, and whether the person who so requests has the right to be excluded.[39]

When determining the risk under the Ethical Review Act, one must first determine the *predictability* of any possible negative consequences. This should not present any major problems, since the risk usually consists 'only' in the possibility of individuals being offended by information about them having been used in a project. Moreover, the *likelihood* of this happening shall be assessed, i.e. whether individual sample providers may really feel that their integrity has been violated. It is hardly possible to generalise on this issue, hinging as it does partly on how important the persons in question consider the project to be, and partly on the types of data which are to be processed. If the information refers to abortion or drug abuse, the likelihood of a person feeling offended will be greater than if the information concerns allergies, child diseases or exercise routines. Finally, the *degree* of inconvenience or harm entailed by the processing shall be estimated.

As regards the degree of the expected violation of personal integrity – which is the important issue in this context – it must be emphasised that the individual's perception cannot be wholly decisive, and that a more objective assessment has to be made. In other words, an individual has no 'right' to consider just anything as a serious violation of his or her personal integrity. Secrecy legislation normally stipulates that information about an individual may only be disclosed if this is not detrimental or harmful to the individual. The individual's perception of such detriment constitutes an indication of whether the information is to be regarded as sensitive or not, but those in possession of the information are not bound by it, and have to make their own assessment as to whether disclosure of the information shall be regarded as detrimental to the person in question.[40] The equivalent approach ought to be applicable to the review under discussion.

The absolutely decisive factor with regard to the determination of the degree of violation of personal integrity must be the issue of who may gain access to the information. The key issue therefore concerns security in connection with the processing of data. From the point of view of personal integrity there must be a considerable difference if only a restricted number of researchers have access to the

[38] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, p. 92.
[39] Government Bill 1997/98:44 *(Regeringens proposition 1997/98:44)*, p. 127.
[40] See, for example, JO 1982/83, p. 22 (the Parliamentary Ombudsman) and Bohlin, Alf, *Offentlighetsprincipen*, 6th ed., p. 178.

data, compared with the situation in which other parties, such as employers or insurance companies, may also gain access to it.[41] The extent to which different parties may access information is regulated, as described in section 3.2, by secrecy legislation. The secrecy provisions play usually a decisive role in this type of decisions. In the *travaux préparatoires* concerning the regulation of medical data files and hospital records, it is stated that personal integrity cannot be regarded as an absolute criterion in the sense of protective regulations applying without exception or irrespective of conflicting interests. Instead, safeguards must be created against activities that may be judged to constitute infringement of personal integrity. Protection against such infringements is provided by means of the provisions on secrecy.[42] With regard to medical files and hospital records, the provisions of the Secrecy Act (and the Health and Medical Services (Professional Activity) Act), together with the provisions of the Medical Records Act concerning internal secrecy, are thought to provide sufficient and well-considered protection for individuals.[43]There are good reasons for applying the same view to the case under discussion.[44]

The discussion above indicates that if the principal research representative is a *public authority*, secrecy will apply to the information in the authority's possession concerning individuals. Even though the secrecy provisions do not imply any unconditional prohibition to disclose information, examination of integrity damage will, as a rule, result in its non-disclosure. Since personal data which has been obtained and processed for the purposes of research cannot in practice be passed on, the *degree of personal integrity violation* ought to be considered as moderately restricted. Provided that a research project can be considered capable of furthering the advancement of knowledge, application of the provisions of the Ethical Review Act should normally lead to the approval of the research project from the ethical point of view.

If instead the personal data is in the possession of an *individual subject*, for example, a pharmaceutical company, a research institute or an individual researcher, no secrecy provisions apply as a rule. If the data comes from a public authority, e.g. a public health care institution, a reservation may be imposed, stipulating that the information may not be passed on (Chap. 14, Section 9 of the Secrecy Act), whereupon secrecy will also apply to the private subject's activities. Such reservations are also assumed to be regularly imposed when individual researchers request information from medical data files.[45] It should be noted that a Board for Research Ethics cannot influence the decision as to the foregoing. On the other hand, the Board for Research Ethics may lay down a *condition* in connection with its own ethical review under the Ethical Review Act, stipulating that no personal data shall be disclosed. Since the ethical review must be made before the research commences, the Board for Research Ethics cannot know for sure that such a proviso will be made. It is therefore justifiable for the Boards for Research Ethics to prohibit dissemination of the information as a matter of course, by imposing such conditions. If this is indeed done, the *degree of violation of personal integrity* can be considered

[41] Cf. Government Bill 1997/98:108 *(Regeringens proposition 1997/98:108)*, p. 48.
[42] Government Bill 1997/98:108 *(Regeringens proposition 1997/98:108)*, p. 27 and 47.
[43] Government Bill 1997/98:108 *(Regeringens proposition 1997/98:108)*, p. 88.
[44] Cf. Government Bill 1997/98:44 *(Regeringens proposition 1997/98:44)*, p. 69.
[45] Government Bill 1997/98:108 *(Regeringens proposition 1997/98:108)*, p. 59.

fairly small, even as regards research in private hands, and therefore also as acceptable from the point of view of the Ethical Review Act.

It should be added that usually a large number of individuals are included in such studies, and that researchers are normally interested in their subjects as members of a certain group, not as private individuals. As mentioned earlier, the possibility of identification is something which, in accordance with the *travaux préparatoires*, can be taken into consideration when determining whether a given research project shall be approved or not, which should normally speak in favour of approval in cases now under discussion.

4.4 The requirement of information and consent

As mentioned earlier, a Board for Research Ethics has to decide the rules that shall apply in respect of information and consent. The legislator has thus entrusted the Boards with the task of working out suitable practice in this respect. It must be noted that the Boards for Research Ethics may lay down requirements concerning consent in respect of research on biological material only, and not as regards research entailing processing of sensitive personal data for which consent is not required.[46] When examining the latter, the Board must only decide whether the research project and the processing of data shall be approved or not, and if approval is given, whether any requirements shall be formulated regarding information. Since such research projects often entail both studies of biological material and processing of personal data, these decisions must frequently be taken in conjunction with one another.

It is important to remember the basic premise of the Biobanks Act, as well as the Personal Data Act and the Ethical Review Act, stipulating that important research *shall not be hampered* by means of statutory provisions. The *travaux préparatoires* of the Biobanks Act stipulate that the idea behind the rule in question is that the Board for Research Ethics shall be able to make deviations from the fundamental principle requiring that the persons concerned must give informed consent. It shall therefore be possible also in the future, much the same as it is today,[47] to provide information in special situations by notice, applying the so-called opt-out principle, on the assumption that consent has been given, as long as the party concerned given no indication to the contrary.[48]

When do such 'special situations' apply? This question is important, since one of the great advantages of research on material from biobanks is that the researcher gains access to large groups of patients which have been followed up for a long time, and where the percentage of dropout cases is very small. If a researcher is required to obtain consent from the persons affected, his access to relevant material will certainly be constricted to a significant degree, as a result of which the research results will not be equally well substantiated, or, at worst, may be misleading. The value of the research will therefore seriously diminish if consent is required in other than just exceptional cases. What is more, if consent has to be obtained, or, as stipulated in the *travaux préparatoires* of the Personal Data Act,[49] if more individual

[46] Government Bill 1997/98:108 *(Regeringens proposition 1997/98:108)*, p. 59.
[47] Proposal referred to the Council on Legislation for consideration *(Lagrådsremiss 2002)*, p. 115.
[48] See MFR Report 2/2000, p. 86.
[49] Government Bill 1997/98:44 *(Regeringens proposition 1997/98:44)*, p. 127.

information has to be given, this can impose an unreasonably heavy, and in certain cases prohibitive workload on the research representative.[50]

The only factor that should be taken into account here is personal integrity. As mentioned earlier, a risk of violation of personal integrity will arise only when research also entails processing of personal data, but for this activity consent should not be required. As transpires from the earlier sections, research will normally be conducted on biological material to which personal data may be linked in situations where it is ethically acceptable with regard to the strict confidentiality provisions surrounding such research activities. In these cases there is no reason to request consent. Nor is there any reason to impose stricter requirements on information in these cases, except that it be provided in a more general form, e.g. in brochure form or through the mass media. More individual information or consent from persons concerned should be requested only in those special circumstances when the research project itself is controversial in some respect, and the adequacy of the existing legal rules concerning secrecy in order to protect the personal integrity can therefore be called into question. This concerns cases in which, despite the safety measures involved, it is not clear that the balancing of scientific value and risk will lead to approval of the research project.

[50] Cf. also Government Bill 1997/98:108 *(Regeringens proposition 1997/98:108)*, p. 82.

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7

A Swedish standard for information and consent procedures in biobank research

Gert Helgesson, PhD

Research Program Ethics in Biomedicine, Uppsala University

The Swedish Biobanks Act forbids the storage of human biological samples in biobanks without the patients' informed consent. This paper suggests a Swedish standard for informed consent procedures concerning storage and use of biobank samples, and argues that the suggested procedures are recommendable from an ethical perspective.

1. Introduction

Under the Swedish Biobanks Act, which entered into force on January 1 2003, it is no longer permissible to store human biological samples in biobanks without prior informed consent from the patients.[1] The Act calls for new biobank information routines and the registration of patients' consent at hospitals and care centres. These routines have to meet both legal and ethical requirements.

In this paper, I suggest informed consent procedures that meet these requirements in a way which is satisfactory in terms of the integrity interests of patients, the ability of the Swedish health care system to provide high-quality care, and research interests of society at large, while being legally acceptable and sufficiently down-to-earth to be practically feasible.

A description of biobanks and the information tied to them is given in section 2 of this paper, the meaning of "informed consent" is discussed in section 3, and the question of what values are at stake is addressed in section 4. The kind of biobank information to be given to potential donors is suggested in section 5, while informed consent procedures for biobanking, based on the value considerations, are presented in section 6. Finally, arguments against the suggested procedures are discussed in section 7.

2. Biobanks and information on individuals[2]

Biobanks contain human biological samples in various forms – for example, whole organs, tumours, parts of tissues, blood, plasma, cells, DNA, or RNA. The storage

[1] Chap. 3, Section 1 of the Biobanks Act.

[2] I am grateful to Magnus Kaijser for helpful comments and suggestions for this section.

techniques vary: samples may, for instance, be stored in freezers or in paraffin blocks, on microscope slides, or in test tubes.

A vast majority of the samples in Swedish hospital biobanks have been collected for diagnostic purposes, such as cancer screening and serological examinations. Apart from this, samples are collected for "mapping", for instance of potential marrow donors, and for future clinical purposes. One example of the latter is when patients on transplant waiting lists donate serum to be used for testing against potential organ donors. Finally, a small minority of the biobank samples are collected exclusively for research purposes.[3]

Through the use of samples preserved in biobanks, a variety of information can be obtained, ranging from current and previous infection status and blood cholesterol levels, to information about the genetic code. This information is primarily used in clinical practice, for example in cancer therapy, where the choice of treatment often depends on whether the cancer is a relapse or is developed de novo. For patients developing cancer a second time, comparisons with previously collected tumour material are thus essential.

Biobanks have also proved to be a valuable tool in medical research. For example, preserved material from screening for cervical cancer has been used to establish the etiological role of human papilloma virus. In the search for disease-causing agents such as viruses, bacteria, or environmental exposure, for instance, to lead, cadmium, and pesticides, blood samples collected long before onset of the disease are often instrumental.

To be useful for research, information from biobanks often has to be combined with other information, such as disease status or exposure information.[4] To assess whether high levels of cholesterol increase the risk for ischaemic heart disease, a blood sample analysis is not sufficient. No questions can be answered without knowing whether the patient developed heart disease or not. Since a variety of factors, such as sex, age, and smoking, can affect both cholesterol levels and risk of heart disease, this information may also be needed. Thus, some biobank research contains other information than that extracted from the biobank samples themselves. This "other" information is not part of the biobank, as defined in the Biobanks Act, but it may be relevant when consent is to be obtained.

A number of precautions are taken to prevent information on patients and research subjects from getting into the wrong hands, for example coding of the biobank samples and strict limitation of access to these samples and to the code keys. This is also stipulated by the Biobanks Act.[5] Personal data is protected under the Personal Data Act and the Secrecy Act.

Up till now, samples in biobanks have mainly been collected without informing patients that they will be stored, nor have patients consented to the storage (samples collected for research being the exception). The Biobanks Act changes this. A sample can no longer be stored in a biobank without the donor's informed consent.

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[3] Kaijser (2003). For detailed references to the clinical use of human biological material, see Lindberg (2003).
[4] A number of examples of biobank research are presented in Kaijser (2003).
[5] Chap. 4, Section 4 of the Biobanks Act.

3. Informed consent

To consent to something means to give assent or approval, to agree to something and to comply with it. Consent is an agreement as to action (or opinion), or an approval of what is done or proposed.[6]

As is often pointed out, to be able to give informed consent a person must have a certain competence. Further, he or she must understand what the consent is about.[7]

Consent is of little moral relevance if it is not sufficiently informed. For example, if I agree to take part in an experiment, and the researcher does not inform me that I am very likely to get hurt in it, but on the contrary pretends that my participation will bring me great personal benefits, then I have been deceived. That I have consented is beside the point, since I have not consented to what actually takes place but to what I was misleadingly informed would take place. Sincere and well-informed consent, on the other hand, is morally relevant, since it means that the person consenting has had a say on the issue at hand and thus has exercised his or her autonomy. More specifically, the person giving informed consent means that he or she agrees to the action taken, whatever reasons he or she may have for doing so.[8]

Being well-informed here means having relevant and sufficient information about that which one is about to consent to. Much of the information about the action at hand may be irrelevant to the consent, while some of it is not. For example, if I consider letting a friend borrow my car to do some grocery shopping, then I do not need to know what brand of cereals he will buy, or whether he is going to buy tomatoes, cucumbers, or both. But I do need to know whether he is going to drive carefully and make sure that the car is returned in good condition.

What is sufficient information in a certain situation is not always clear, not least because different persons may have different views in the matter. What is sufficient information for one person may be far from sufficient for another. A practical consequence of this for consent routines concerning biobanks is that patients and research subjects should be given the opportunity to ask questions possibly going beyond the information that is given to everyone. To allow for this is to show respect for individual differences.

Informed consent, in the context of biobanks, concerns a process in which a potential sample donor gets the relevant information and decides whether or not to authorise storage and various uses of the sample, based on that information and his or her own values.[9]

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[6] See e.g. Longman Dictionary and The Oxford Thesaurus.

[7] See, for instance, Faden & Beauchamp (1986), pp. 287–294, on competence. Chapter 9 is mainly devoted to a discussion of understanding. On p. 155, the principles of the Nuremberg Code are discussed. The first principle of the code states that consent must be voluntary, competent, informed, and comprehending.

[8] Some of the complexities of informed consent are disregarded here. For a fuller account, see e.g. Brock (1993), Faden & Beauchamp (1986).

[9] Cf. Eriksson (2001), pp. 44–45.

4. Values at stake

What values are at stake with biobanks? Clearly there are both positive and negative values involved. The positive values stem from the usefulness of biobanks for diagnostic, other medical, and research purposes. Biobanks have been used for diagnostic purposes for many years, and the rapid development of biomedical research techniques has increased research interest in biobank material. Biobanks are already now being used for research, but a considerable increase in these activities can be expected. This is likely to lead to new knowledge concerning human health and diseases, which in turn may lead to new ways of improving health care.

Thus, developments in recent years inspire hopes of considerable progress. But they also bring fears that the new opportunities, not least those of gene technology, will be misused or simply get out of hand. Apart from nightmare visions of ecological disasters being caused by genetic manipulation of crops, plants, insects, or animals, there is a harsh anticipation that genetic information may be used in ways that will have dire consequences for society. For example, some people fear that insurance companies and employers will use it for genetic discrimination, unless such information is protected by rigorous regulations.[10]

Storing a sample in a biobank involves no direct physical risk once the sample is taken. But having samples stored in a biobank involves a certain, although small, risk of sensitive information ending up in the wrong hands and being used to the disadvantage of the sample donor. This information may be either extracted from the samples or tied to them, as is the case when biobank research is combined with register research. The more people that have access to such information in an uncoded form, the greater the risk of such harm, which means that research on uncoded biobank material involves a certain risk to the donors. If the information is well protected, and not misused, by biobank researchers, this risk remains very small. Since informed consent has to be obtained from the donor in order to store the sample in a biobank, it is up to that person to judge whether the regulations and routines concerning biobank material, and accordingly the risk exposure, are acceptable.

Another cautionary aspect of biobanks is that their use may violate the donor's integrity. Spelling out in detail what it takes for someone's integrity to be violated is a controversial and complicated matter, but at least it concerns an infringement of an individual's personal sphere by not allowing them to decide, or have a say, about things central to their own life.[11] What actions involve such

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[10] For an example, see Dagens Nyheter 2002-12-15, p. 2. Cf. Korn (1999), pp. 31, 44–45, 73, Radetzki, Radetzki & Juth (2002).

[11] Some readers may object that I am discussing privacy, not integrity. "Privacy" is, for instance, the term used in Korn (1999). I leave the terminology question aside, including what the connections are between privacy and integrity, since my use of "integrity" is sufficiently clear for present purposes. A close connection between the two concepts is indicated by their use, for instance, in Article 21 of the *Helsinki Declaration*. There are also connections between "autonomy" and "integrity", and between these two concepts and "self-determination". See Hansson (1998), p. 183, where it is claimed that the "value of self-determination is the fundamental motivation of rules about obtaining informed consent". Brock (1993), p. 28, writes: "A patient's interest in self-determination reflects the common desire to make important decisions about one's life oneself and according to one's own aims and values. Self-determination involves the capacities of individuals to form, revise over time, and pursue

infringement is, in part, for the individual to judge. Views on what is a violation of a person's integrity can therefore be expected to vary from one individual to another.

It is easy to imagine cases in which researchers would be said to go too far in this respect. For example, any detailed research, without consent, into people's sexual habits, religious beliefs, or political affiliations would probably be regarded as an integrity breach by most people, as would research where participants are manipulated in certain ways.[12] However, since the Biobanks Act leaves it to the potential sample donor to consider whatever reasons he or she might have for and against giving consent, there is sufficient room for integrity considerations – a potential donor finding, say, research on his samples unacceptable from an integrity perspective can simply withhold consent. Thus, people's integrity is respected and protected by the Biobanks Act.

Sample donors have an interest in receiving certain information. They may also have an interest in not receiving certain information. Receiving that information anyway may be harmful and may involve a violation of the person's integrity. Similarly, donors may have an interest not only in having a say about certain things but also in *not* having a say about certain things. This will sometimes make it hard to decide whether to pass on certain information or not.[13]

For the sake of clarity, let us reiterate the value aspects of biobanking that are mainly of interest here. On the positive side, there are the advantages of using biobanks for diagnostic, other medical, and research purposes. On the negative side, there are the risks of genetic and other personal information ending up in the wrong hands and harming the sample donors, and of storage and uses of samples without consent violating the donors' integrity. In the first case it is the effects of sensitive information getting into the wrong hands that are harmful, in the second case, storage or use in itself is harmful, as an instance of integrity violation.[14]

With these considerations in mind, let us see what information is needed for potential sample donors to be sufficiently informed, and thus capable of giving informed consent.

5. General and specific information

It is practical and reasonable to divide information to be given to potential donors on storage and use of samples in biobanks into two main categories: *general information* and *specific information*.

5.1. General information

General information raises aspects of biobanks, their clinical and research uses, relevant laws and regulations, etc. that are of general relevance to consent to the storage and use of individual samples in a biobank.

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a plan of life or conception of the good." Cf. Hermerén (1999), p. 102. All these terms are used in the discussion. In the Swedish debate, the relevant term is "*integritet*".

[12] Milgram's much-discussed studies of obedience in the 1960s are arguably an example of integrity-breaching manipulation of research subjects. See Milgram (1997). For further examples, see Faden & Beauchamp (1986).

[13] Wendler (2002), p. 50.

[14] Cf. Eriksson (2001), p. 45.

General information ought preferably to be presented in readable brochure form. Brief, verbal information may be sufficient in many clinical routine situations, and is also preferable for practical reasons – in most cases, it would be far too time-consuming to give each patient detailed information when the sample is taken. However, in such cases the verbal information should be supplemented by written information. This is where the brochure comes in handy.

Brochures containing general information on biobanks should have the following components:

- what biobanks are,
- how biobanks are handled – biobanking practice,
- clinical and research points of having biobanks
- how information about individuals is treated in and, in connection with biobanks: what measures are taken to protect the information, for example that the samples are coded, the code keys are well protected and can be accessed only by a few persons, and information delivered from biobanks to external researchers is normally coded or deidentified,
- that biobank samples may be released uncoded if researchers need to connect personal records to biobank information so as to be able to reach an interesting result,
- that all research on biobanks is reviewed beforehand by ethical research review committees, the utility of research here being balanced against effects on personal security and integrity,
- that the review committees also decide whether new consent must be obtained for new uses of existing biobanks, for example new research projects,
- that storage of samples in biobanks is optional,
- that consent given previously can be withdrawn at any time, in which case the sample must be destroyed or deidentified immediately,
- that research sometimes involves international co-operation, that there may be instances when biological samples from Swedish citizens are analysed in foreign laboratories, and that samples analysed abroad must be returned or destroyed when the work is completed,
- that biobank research may lead to the development of new methods for preventing and treating various diseases, and that some of the discoveries made may need to be patented for the development of new medicines,
- the essence of what is stated in the most relevant acts and regulations,
- where to turn in order to get more information or put questions directly to the authorities.

5.2. Specific information

The specific information concerns a particular purpose for taking or using certain biobank samples, and the attendant circumstances concerning this, for example, the clinical reason for taking a certain sample or facts about a specific research project. When a sample is taken for routine diagnostic reasons, the specific information may be given verbally: before taking the sample, the doctor explains, in simple terms, why it is being taken, and the patient may ask questions if he or she requires further explanations.

In consent situations concerning the use of biobank samples for a particular research project, the specific information should be in written form – there are no

strong practical reasons against having it this way, while there may be some advantages, not least that such information should go into some detail and may be difficult to comprehend. Written information is therefore likely to make things clearer. Information on a specific research project ought to be presented with the consent form.

Information of this kind should contain the following:

- the title of the research project,
- the research group, university department, or equivalent carrying out the study,
- how potential participants have been selected,
- what question or questions the study is intended to answer and why this is interesting,
- what kind of samples will be used,
- whether the researchers wish to store the samples when the study has been carried out,
- the consequences of participating in the project – are there any risks involved?
- how information about the participants will be handled,
- where the potential participant may turn for more information about the project.[15]

6. Consent

Let us begin here with some of the considerations leading up to the suggested forms of consent, before looking at the forms themselves.

6.1. Consent categories

As we have already noted, the samples in biobanks are collected for one of the following primary purposes: diagnostic purposes, future clinical purposes, mapping, or research. While there are four grounds for collecting samples in biobanks, it is reasonable to sort them into three different consent categories:

1. Samples taken for diagnostic purposes.
2. Samples taken for future clinical purposes or for mapping.
3. Samples taken for research purposes.

When samples are collected and stored for diagnostic purposes (category 1), the information as well as the consent may be given verbally: the doctor explains the purpose of taking the sample, that the biobank material is well protected, etc., and the patient tells the doctor whether he or she consents, with or without restrictions, to having the material stored in biobanks and used in specified ways. When doing so, the patient should have the opportunity of consenting, not only to storage for diagnostic and other medical purposes, but also to research.

Documentation of consent may be handled by adding it to the patient's medical record. The exact content of the consent, including any restrictions, must be clearly stated. The doctor must also certify that the patient has given consent by

[15] Cf. this list with the one in Beskow et al (2001). Some writers go much further and suggest that patients should be informed, for instance, of the researchers' personal characteristics and their views relative to the research. See e.g. Wilkinson (2001).

signing or initialling the consent documentation. It is important for the patient's consent status to be available in all the circumstances where it is of relevance.

When samples are collected and stored for future clinical purposes, or mapping, (category 2), the practical objections to obtaining written consent are of limited importance, since this takes place much less frequently than the collection of biobank samples for diagnostic purposes. Therefore written consent should be obtained. Here again, the doctor may briefly explain, by word of mouth, the purpose and the procedures and routines, supplementing this by written information – both general information on biobanking and specific information on the purpose of taking the sample.

New consent is not always needed for research on already existing biobanks – it is up to the ethical research review committees to decide. But informed consent is needed when samples are collected and stored for research purposes (category 3), . In such cases, it is strongly recommended that the potential donor be given clear and easily comprehensible written information on the specific research project for which the samples are being collected, and told that there is an opportunity for asking more detailed questions. The information should be presented with the consent form. As in previous cases, a brochure with general information on biobanking should also be available.[16]

6.2. Consent forms

I suggest the following consent forms. Note that the first form is to be handled by the medical doctor only, while the next three are to be signed by the sample donor.

Form 1: Documentation of consent to storage of biological samples in a biobank for diagnostic purposes

Documentation of consent to storage of biological samples in a biobank for diagnostic purposes

Patient _____

Sample _____ Date _____

The patient has been informed of the routines for handling human biological samples in biobanks. Consent has been given for storage and the following uses:

☐ Care and treatment, and activities associated therewith

☐ Other medical purposes

☐ Biomedical research *Exception(s)* _____

Doctor's signature or initials: _____

[16] The discussion in von Essen (2002) supports my view that the consent forms I am about to suggest are fully acceptable from a Swedish legal perspective.

Form 2: Consent to storage of samples in a biobank for future clinical use or for mapping purposes

Consent to storage of samples in a biobank for future clinical use or for mapping purposes

Concerning storage of _____ (type of sample) in a biobank

☐ I consent to the sample being stored and used for _____ (purpose)

☐ I consent to the sample being stored and used for _____ (purpose)

It may also be used for biomedical research

Exception(s) _____

Date _____

Patient's signature _____

Anyone who consents to having his or her samples (blood samples, tissue samples, etc.) stored in a biobank is entitled, under the Swedish Biobanks Act, to withdraw the consent at any time. When the withdrawal is expressed to responsible authorities, the samples will be deidentified or destroyed.[17]

[17] The concluding paragraph is optional, but reminds the donor that consent can be withdrawn later.

Form 3: Consent to storage and use of samples in a biobank for research purposes

Consent to storage and use of samples in a biobank for research purposes

To be used when biological samples from humans are collected for research

Consent form for _____ (research project)

I have been informed of the present study and have been given an opportunity to ask questions.

☐ I consent to _____ (sample)

being stored and used for _____ (purpose)

☐ I consent to _____ (sample)

being stored and used for _____ (purpose)

and for other kinds of biomedical research

Exception(s) _____

Date _____

Patient's signature _____

Anyone who consents to having his or her samples (blood samples, tissue samples, etc.) stored in a biobank is entitled, under the Swedish Biobanks Act, to withdraw the consent at any time. When the withdrawal is expressed to responsible authorities, the samples will be deidentified or destroyed.[18]

[18] Optional, see previous footnote.

Form 4: Consent to the use of samples in a biobank for research purposes

Consent to the use of samples in a biobank for research purposes

To be completed when research is to be done on existing biobanks

Consent form for _____ (research project)

I have been informed of the present study and have been given an opportunity to ask questions.

☐ I consent to _____ (sample)

being used for _____ (purpose)

☐ I consent to _____ (sample)

being used for _____ (purpose)

and for other kinds of biomedical research

Exception(s) _____

Date _____

Patient's signature _____

Anyone who consents to having his or her samples (blood samples, tissue samples, etc.) stored in a biobank is entitled, under the Swedish Biobanks Act, to withdraw the consent at any time. When the withdrawal is expressed to responsible authorities, the samples will be deidentified or destroyed.[19]

7. Discussion

The consent forms that I suggest show due respect for both kinds of individually tied values discussed above, since the patient may bring in any kind of consideration when contemplating whether to consent to the storage and suggested uses of his or her samples. That is, if only the risk for personal harm is found to be relevant to the choice, then only that factor will be considered. If, on the other hand, integrity

[19] Optional, see footnote 17.

reasons beyond that are found to be relevant, then they will also be taken into consideration.

The same applies in cases where a sample donor is considering withdrawal of consent given previously . Since the right to withdraw consent is independent of the donor's reasons, risk of harm as well as integrity reasons may carry any weight whatever in the decision that the donor makes. Patients concerned only with risk of harm may want to withdraw their consent either because of new facts concerning the risk or because they have re-evaluated the negative value of the possible harm, while those who also find integrity reasons relevant may find new facts about integrity effects a reason to reconsider the consent.

Let us now turn to consider some objections to the consent procedures I have proposed.

7.1. "Informed consent shall be written"

It might be argued that consent shall always be documented in writing and signed by the sample donor. This demand goes against the first consent form suggested, which the medical practitioner fills in after having received verbal consent from the patient.

Reply: From legal and ethical perspectives, it makes no difference how consent is documented. Unless doctors are unreliable, and taking into consideration the vast number of routine samples taken in ordinary health care, the suggested practice is the most practical one.

7.2. "Open-ended consent to research is not acceptable"

Both lawyers and philosophers have suggested that open-ended consent to research – that is, unspecified consent to research in general – should not be allowed on the ground that it is unacceptably broad.[20] Instead, different kinds of research should be distinguished. This would mean a number of research categories, such as cancer research, cardiac research, research on arthritis, diabetes, obesity, etc., having to be presented in the consent forms. It has also been argued that one must distinguish between different research methods.[21] According to this latter view, it is not acceptable to let donors consent, say, to cardiac research; instead, consent must concern cardiac research using this or that method. Even if this view is rejected, long lists of research to which we may or may not consent would be needed.[22] This would give us consent situations quite different from what I am suggesting.

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[20] Thus Hermerén (1999), p. 100, argues that unspecified consent to use "blood spots" for research purposes is "too general", mainly because of (1) "the rapid developments in molecular biology", (2) "the import and export of data across national borders", and (3) "the commercial interests of blood samples and other human tissues for the pharmaceutical industry".

[21] Göran Hermerén recently expressed this view in an interview in Svenska Dagbladet, 2002-12-22, p. 17. See, e.g., also Gustafsson Stolt (2003), paper VI. It might be thought that the *Helsinki Declaration* requires research methods to be specified in consent forms. It does say that in "any research *on human beings*, each potential subject must be adequately informed of the aims, methods..." (my italics), but research on biobank samples is not research on human beings and does not involve many of the possible risks that research on humans does.

[22] Critics of open-ended consent to research rarely state how specific these categories must be in order to be acceptable; for instance, whether cancer research is an acceptable category or whether different sorts of cancer should be distinguished, and if so, to what extent (for instance, should there be

One argument for this position is that unless consent to research is quite specified, it is not clear to what one is expected to consent. How can you give an informed consent to research that you have never been informed about? is the rhetorical question raised by critics of open-ended consent to research. A second argument is that sample donors, for integrity reasons, should be allowed to have a say in detail about for what kinds of research their samples are used.

Reply: All research projects are different in some respect. If all information about research were relevant to informed consent, then informed consent could not be given to any research not yet planned. But not all information is relevant to what is at stake for the sample donor in the consent situation, namely that the storage and use of the samples involve a certain risk of harm and may violate his or her integrity. These are the aspects of biobanks that are morally relevant to the donor's consent.[23] Therefore it is information concerning these aspects that the donor is entitled to. It is not normally the actual research content or specific characteristics of the researchers or their methods that the donor should consent to.

Critics may object that integrity questions concern not only how and to what extent research interferes with individual lives – having a say on what research is carried out on one's biological samples may, as such, be part of what integrity is about. On this matter, I share the view taken by David Wendler:

> *The weight of individuals' claim to a say over whether they contribute to a particular research project depends upon how central making this contribution is to their lives. In the majority of cases, it seems plausible to assume that it is important for individuals to determine whether their samples are used for research purposes since doing so allows sources to decide whether they contribute to the general project of increasing medical knowledge and helping others. ... It seems less important, in most cases, for individuals to control whether their samples are used to study one disease or another. Whether I contribute to medical research at all says something important about my life; whether I contribute to research on arthritis as opposed to research on diabetes says less about my life. ... However, the specific nature of certain research projects can give sources a weighty interest in determining whether their samples are used. For instance, some oppose abortion and dedicate their lives to ending its provision. Such individuals have a weighty interest in controlling whether they contribute to research projects involving abortion.*[24]

Wendler concludes that "individuals can ethically give consent for future research purposes in general without having to know about and approve every individual use of their samples".[25] However, some individuals may have reason to turn to local biobank authorities to give more specified consents.

One may agree with this but insist that not all research has the same integrity effects or involves similar risks to sample donors. This is correct. It is, for instance, relevant to distinguish between research that has access to uncoded samples and research that only uses coded samples. Besides, some research topics are

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different consents to different kinds of cancer in a certain organ?). Even a list with broad categories covering only our commonest diseases will be quite extensive.

[23] The social value of research is also at stake for the individual sample donor, and not only those aspects that concern him or her exclusively, but I disregard that point here.

[24] Wendler (2002), pp. 49–50.

[25] Wendler (2002), pp. 53–54.

more sensitive than others, for example research concerning venereal diseases and alcoholism. Is not this sufficient to show that one cannot allow open-ended consent to research?

This would have been a correct remark, had it not been for the ethical research review committees. It will be part of their job to review research projects in terms of risk exposure and integrity effects on sample donors. These committees can be expected to demand that new, specific informed consent is obtained whenever a planned research project involves higher than normal risk for the sample donors, or is more likely than otherwise to violate their personal integrity.

7.3. "Violation of integrity a matter for the individual to judge"

It may be argued that this is to miss a very important point, namely that the members of the ethical review committees cannot make such judgments, because it is entirely up to the individual to judge what constitutes a violation of integrity.

Reply: This can only be correct if "integrity" is used in such a broad sense that it is no longer of any particular moral relevance. Even if there were people eager to cry out that their integrity is violated each time they were not given the right to veto any action that somehow might affect their lives, this would give us no reason to agree with them, if "integrity" is used in its ordinary sense. As I have stated earlier, integrity matters are personal matters; they concern things of great concern to a person. Not everything that a person may want to have a say about is of that kind.

I have also said in an earlier section that what is taken to be a violation of integrity may vary between individuals. Is this view consistent? I think so. This, briefly, is how I see it: Some actions involve violation of a person's integrity, regardless of whether that person thinks so or not, while some actions involve a violation of integrity only if the person thinks so. Other actions involve no violation of integrity even if the person thinks they do.[26] If this is correct, some matters of integrity violation are up to the individual, while others are not. I see no reason why ethical review committees cannot identify which cases are of which kind.

7.4. "Specified consents to research are more practical than open-ended consents"

One may still wish to argue that specified consents to research are more *practical* than unspecified consents. The basic assumption behind this claim is that people, for integrity reasons, will be unwilling to give open-ended consents to research, while consents are much more likely to be given if the span is more restricted.

Reply: On the contrary, it is much more practical to use consent forms with an open-ended consent alternative than forms with restricted consent alternatives. There are at least two reasons for this. First, if one asks for more restricted consents, then a large number of alternatives will have to be presented on the consent forms. This will make it difficult for most people to reach a decision, which makes it more likely that they will not consent to research at all. And even if they do consent to research, much research will not be consented to, either because these alternatives are not on the list, because they are far down on a long list that many donors may not bother to read through, or understand, or because there will be a tendency to choose a few of

[26] Some remarks by Hermerén, (1999), p. 102, lend some support to this view.

the alternatives just because there are so many to choose from. In other words, there is a risk that donors will consent to the research they feel most strongly for, or find early on in the list, instead of to all research that they have no objections to.

A second reason why open-ended consents to research are more practical than narrower consents is that with open-ended ones there will be fewer occasions when researchers will have to return to sample donors to ask for new consent. This is good, since the scientific disadvantage of missing data due to non-participation may be considerable.[27] Further, obtaining consent from many donors is expensive. There is also a considerable risk that donors with "popular" samples will eventually get tired of reading research information and filling in consent forms. One can therefore expect that an increasing number of these donors will not answer new requests for consent. Signs of such an exhaustion effect are claimed to be seen in Iceland.[28]

The information and consent procedures to be implemented depend, in part, on the attitudes of potential sample donors. Critics of open-ended consent procedures argue as if they presuppose a general negative attitude, or at least a lack of trust, regarding Swedish medical research. I believe this empirical assumption to be mistaken. My suggestions rest on the assumption that most people in Sweden find medical research valuable and necessary, and trust the research community and the regulations it has to abide by.[29] If this assumption is correct, then the suggestions made here are better for all parts than an alternative where consent forms must specify research in some detail.

Admittedly, some people are likely to demand detailed information, not only about biobanks in general but about particular research projects, if they are to consent to any research. But there is no perfect solution to a situation where some potential donors want detailed information about everything that might happen to their samples, while others do not want to be bothered with information and consent forms, or do not want to make the decisions, and therefore want to give consent to research once and for all. An advantage of the consent forms suggested here is that the integrity of all donors is respected, since those who want to can require that certain kinds of research be excluded from their consent.

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[27] Cf. Kaijser (2003).
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8

Mapping the debate on informed consent

Stefan Eriksson, ThD

Research Program Ethics in Biomedicine, Uppsala University

This paper describes the major issues concerning informed consent that have emerged during the Swedish debate on biobanks. The process leading to the Biobanks Act and the debate on each major issue are outlined. May biobanks be collected and used without informed consent from donors? Is there a duty to participate in such research? The extent of information required in the informed consent process is outlined, and some complications are mentioned. Then I ponder questions such as when consent is needed for new research on archived specimens, and whether donors should be able to revoke consent. Lastly, an overview is given regarding consent for specimens taken from foetuses, minors, deceased and non-competent persons. The discussion shows that the Swedish Biobanks Act leaves a lot of the ethical deliberations to the ethics committees, and that some difficult questions remain to be addressed.

1. Introduction

The point of storing human specimens in biobanks is for important knowledge to be readily available for research and treatment, but at the same time the knowledge may be intimate and sensitive, and therefore we must take care not to let individuals and their relatives suffer any harm because of such storage. People's integrity may be safeguarded by their specimens and personal data being coded, by a duty of confidentiality on the part of employees of such a bank, through the exercise of supervision and control, and by various other means. One important way of protecting people is by telling them what they will be taking part in and letting them decide whether to agree to the retention and use of their specimens, *i.e.* by using *informed consent*.

Different models of informed consent may be used. The basic variety consists of presumed consent without information, informed refusal (or "opt-out"), and informed consent proper ("opt-in"). In the first case it is enough to have reason to believe that someone *would* agree *if* asked, in the second a person is informed personally or by posters, for example, that he or she will participate unless refusing to. In this last case information is given before inclusion in a study, and participation is possible only after a positive decision to participate. (There is much confusion about these terms in the legislative proposals and debate. I have used the terms in the above sense to *describe* the positions taken by different debaters instead of reproducing the way they *use* them.)

In this paper I will describe the major issues concerning informed consent that have emerged during the Swedish debate on biobanks. The process which have led to the Biobanks Act and the debate on each major issue are outlined. I will elucidate how the Act and ethical research guidelines address those issues, sometimes with reflections on the justifiability of the solutions adopted.[1]

2. Short overview of the debate leading up to the Biobanks Act

A biobank consists of biological material from one or more humans that is collected and kept indefinitely or for a definite time and whose origin can be traced to the human or those humans from which the material comes.[2] In Sweden biobanks have existed for decades without particular attention being paid to them. One exception was a governmental report on genetic integrity in 1984.[3] One of the first to raise questions again was the ethicist Göran Hermerén, *e.g.* in a couple of articles.[4] In May 1997 a seminar entitled "Human biobanks — ethical and social issues" was held in Iceland by the Nordic Council of Ministers, with Hermerén taking part.[5] In the same year physician Bo Lindberg asked who owned the specimens in a biobank[6] and in 1998 Elisabeth Rynning provided an overview of current legislation relevant to biobanking and asked whether the time had now come for setting up a "bank inspectorate".[7] At the time Rynning had been tasked by the research ethics committee in Uppsala with reviewing a contract between Uppsala University and a company named Eurona which wanted to use the pathological biobank. At this time more and more medical companies were beginning to understand the possibilities of biobanking. Apparently Eurona had already had access to the pathological bank for years. One of the changes demanded by the committee and made by Eurona was that specimen donors were to be informed and their consent obtained. A worried researcher in Lund wrote a letter to the National Board of Health and Welfare asking about Eurona and its access to the Uppsala biobank.[8]

The debate gathered further momentum when the Icelandic Parliament decided to give a company, deCode, a licence to use de-identified data from patients, collected in Icelandic public health registers, for research. deCode's plan was to link such data to genealogical registers and biobanks, thus making possible the collection of genetic data that might explain the outbreak of disease and point the way towards new treatments and medicines. deCode being a commercial enterprise, other companies may buy a dispositional right to such data.[9] An initiative, in some

[1] The so-called PKU biobank, for which special provisions were made in the Act, will not be discussed in this paper. Please note that the proposed legislation refers solely to biobanks containing biological material whose origin is traceable to a certain individual. Non-identifiable specimens and personal data are not included in the definition of biobank; the latter are regulated by the Personal Data Act (SFS 1998:204).
[2] *Regeringens proposition 2001/02:44*.
[3] *Genetisk integritet* 1984, pp. 217–218.
[4] Hermerén 1997a and Hermerén 1997b.
[5] Sorsa & Eyfjörd eds. 1997
[6] Lindberg 1997.
[7] Rynning 1998.
[8] Trägårdh & Ringman 1999.
[9] I will not retell the debate about deCode here, but to indicate the strength of opposition suffice it to say that even the World Medical Association denounced the initiative. See Duncan 1999.

respects similar to deCode's, was taken in Umeå shortly thereafter, in March 1999, when the County Council and the University started a company, UmanGenomics, to start exploit the biobank which the University and the County Council had been operating since the 80s.[10] It was to be publicly owned and all results were to be returned to the biobank (thereby becoming public domain).[11] In the daily newspaper *Västerbottens-Kuriren* a debate raged on during the spring. Protagonists included the politician Barbro Westerholm, who demanded that the future of biobanking be investigated as soon as possible and claimed that legislation was badly needed.[12] Concurrently the Government's Medical Ethics Advisory Board (SMER) pointed out that the Government give further consideration to biobanks at the earliest possible opportunity.[13] Commercial interests should not be allowed to infringe human integrity. This demand for an inquiry into biobanks had also been put forward by a parliamentary investigation into research ethics, led by Westerholm.[14] Pressure began to build up: in a placard which created a stir, the evening newspaper *Aftonbladet* proclaimed on April 10 1999 that "Researchers are performing secret experiments on parts of your body".[15] The paper heavily criticised the National Board of Health and Welfare for not blowing the whistle in spite of knowing about Eurona's access to human biological specimens. In an appeal in *Aftonbladet*, a number of representatives from patient organisations now also demanded an inquiry.[16]

The Government reacted to all this on June 17 by instructing the National Board of Health and Welfare to review questions regarding biobanks and to propose a new Biobanks Act, supposedly as a direct consequence of the articles published in *Aftonbladet*,[17] although the Medical Research Council had also asked for an inquiry. Special attention was to be paid to the question of whether new consent was needed when old specimens were to be used for a "new purpose". Nevertheless, most debaters would surely have preferred a thorough and comprehensive official parliamentary report by a government commission of inquiry to a swift one-man inquiry. That was not to be, which in turn helped to bring about the problems outlined below.

Before that inquiry was finished, however, more work was done elsewhere. Insecurity had spread among scientists. Individual scientists, as well as representatives of the pharmaceutical industry, had for a while asked the Committee for Research Ethics at the Medical Research Council (MRC) for advice, and research ethics guidelines for biobanks were presented in June 1999.[18] In these guidelines it was noted among other things that individuals have an interest in research capable of identifying markers for diseases for which some form of intervention may be available. Another point was that biobank material should not be allowed to be used

[10] Similar initiatives have been taken in Italy (locally in a small village), Estonia (a huge biobank), and in the Tonga Islands (national biobank as in Iceland), as well as in Newfoundland. See, for example, Greely 2001.
[11] See Jens Laage-Hellman's forthcoming book C*ommercialization of Biobanks. A Study of biotech companies dedicated to human genetics*, for a further discussion of the feasibility of these claims.
[12] Westerholm 1999.
[13] *Åtgärder kring biobanker* 1999. For a resumé, see Ahlgren 1999.
[14] *God sed i forskningen* 1999, p. 212.
[15] The Aftonbladet articles were published between April 10 and 15. The journalists, Maria Trädgårdh and Magnus Ringman, were later awarded *Stora Journalistpriset* for the series.
[16] Bjöörn et al. 1999.
[17] As stated by Social Minister Lars Engqvist in *Aftonbladet*, April 15, 1999, p. 10.
[18] *Research ethics guidelines* 1999.

up. Meanwhile, the Nordic Committee on Bioethics organised an international conference in Estonia (which has inaugurated the most ambitious biobank project of its kind worldwide, at least until Biobank U.K. was announced in 2002), on the subject of "Who Owns our Genes?", which discussed biobanks in a number of respects, not least questions of buying and selling specimens and whole biobanks.[19] Further conferences have followed. The Swedish Data Inspection Board, which by this point had received many questions regarding biobanks, also set up an inquiry. After extensive field inspections, at the Medical Biobank in Umeå for example, a report was published at the beginning of 2000, indicating various deficiencies in the biobanks investigated, mostly to do with informed consent.[20]

The National Board of Health and Welfare presented its report in May 2000, after almost a year's work.[21] It was proposed that biobanks which in a health care setting had been collected from patients or specimen providers in order to reach a certain objective should be regulated by the Bill. Secondary banks collected from such a primary bank were also included. Central positions were allotted to the ethical guidelines from the MRC and to the research ethics committees. The informed consent procedure endorsed by an ethics committee should apply when someone wanted to use specimens for research or for a clinical trial. The Board stressed that legislation was needed and that many interested parties were asking for regulation as soon as possible. The Bill was deliberately brought as close as possible into line with the Council of Europe Convention on Human Rights and Biomedicine, to facilitate subsequent ratification.[22] A biobank may not be transferred to another country, nor shall any transfer or release of material take place for commercial gain, suggestions later retained through all stages of the process towards a new Act.[23] One controversial and somewhat unclear suggestion made in the Bill was that a caregiver in the health care sector should be obliged to provide both tissue specimens and personal data to any biobank set up in accordance with the law (subject to donor consent). It was suggested that special advisory boards should be introduced, to prioritise between projects requiring access to specimens in a bank. The Act was meant to come into force on July 1, 2001, but the process was to be much delayed.

An important statement on this report was made by the Swedish Society for Clinical Cytology, which drew attention to the fact of pathology departments handling and storing thousands of specimens every day. It seemed somewhat unclear whether the National Board of Health and Welfare had at all noticed that for many routine diagnostic purposes the specimens had to be stored for longer than two months (the limit for retention, after which, in the Bills and the subsequent Act, the specimens are seen as belonging to a biobank). Great difficulties arise if the Act applies to tissue collections of this kind.[24] If informed consent is needed as soon as a specimen has been kept for over two months, this will be expensive and may prolong waiting times for diagnostic results. The society also asked for a provision

[19] *"Who Owns our Genes?"* 2000.
[20] *Biobankers behandling av personuppgifter* 2000.
[21] *Biobanker i hälso- och sjukvården m.m.* 2000.
[22] *Convention* 1997. This convention has been signed by Sweden but not yet ratified, and so is not (yet) legally binding.
[23] But this statute is still being discussed and challenged in different ways; see, for example, Österberg 2002.
[24] *Angående förslag till lagstiftning* 2000.

whereby specimens taken and stored for the purpose of health care should only be released for another purpose if this can be done without compromising the patient interest. A patient may for his or her whole life have an interest in using old specimens for diagnostic purposes, for example. Similar criticism emerged in comments by some County Councils, the Lund Medical Faculty and the Karolinska Institute.[25] This was never addressed in the subsequent Act, but the MRC guidelines say that if the material "is collected for clinical purposes [and may be of] significance for such purposes in the future, these must be given precedence." The proposal that advisory boards be introduced was shot down in the consultation process, not least because the regular research ethics committees were already supposed under the new MRC guidelines to prioritise between projects.

Elisabeth Rynning criticised the Bill for not including biobanks unconnected with health care,[26] a criticism echoed in many, many statements,[27] including the later report by the Riksdag (Parliamentary) Standing Committee on Social Affairs (see below).[28] An important point mentioned by Rynning was that it is unclear how one should understand the distinction, drawn by the National Board of Health and Welfare, between identifiable and non-identifiable material, or whether such a distinction was really meaningful.[29]

On August 23, 2001 a proposal was referred to the Council on Legislation for consideration.[30] The plan now was for the new Act to come into force on July 1, 2002. The controversial suggestion that a caregiver in the health care sector should be obliged to provide tissue specimens to any biobank set up in accordance with the Act had by now been dropped, as had the suggestion that special advisory boards should be created. The Government bluntly stated that the Act should be written as to harmonise with the Convention on Human Rights and Biomedicine,[31] and furthermore that the Helsinki Declaration serves both as the prime guidance for biomedical research in Sweden and as the foundation for ethical reviews by research ethics committees. The Biobanks Act should give tissue specimens the same protection regarding the individual's integrity as the Personal Data Act.[32] The Government declared its intention of returning to the question of biobanks outside the health care sector.

The Swedish Council on Legislation thoroughly revised the proposal,[33] and most of its suggestions for improvement were adopted by the Government in their Government Bill, dated November 29, 2001.[34] This Government Bill was worked out in co-operation with the Swedish Left and Green Parties, which may explain some of the alterations made. Now the Act was to come into force on January 1, 2003. The Swedish Council on Legislation noted that the relationship between the

[25] See *Lagrådsremiss* 2001, section 10:2, as well as Dillner 2002.
[26] Rynning 2000.
[27] *Regeringens proposition 2001/02:44*, "Övervägande och förslag", section 10:3.
[28] *Socialutskottets betänkande* 2002.
[29] This was again forcefully brought to our attention when Rynning, with Stellan Welin, wrote yet another contribution to the debate; see Welin & Rynning 2002.
[30] *Lagrådsremiss* 2001.
[31] Ibid., section 10:1.
[32] Ibid., section 10:2.
[33] *Regeringens proposition 2001/02:44*, "Bilaga 5: Lagrådets yttrande".
[34] *Regeringens proposition 2001/02:44*.

Biobanks Act and other laws, notably the Personal Data Act, was unclear, an observation to which the Government showed no response.[35]
Meanwhile the debate raged on in the papers. Quite a few misunderstandings were revealed, but a number of important points were made. One is the question of when research results consisting of biological material cease to be "biological material" from humans, traceable back to the humans it comes from.[36] If such results were to be considered as material in the sense of the Bill, they would have to be destroyed (or de-identified, which might come to the same thing) as soon as the donor demanded it.

Another important point is how the huge task of collecting informed consent for the taking of at least 2 million specimens each year is to be carried out in practice without patient security being compromised. To refuse the inclusion of one's specimen in a pathological bank will remove the possibilities of verifying results, comparing new specimens with old ones, and investigating possible misjudgements or mix-ups.[37] If instead the specimens are taken without consent, they will have to be discarded after two months, with the very same consequences. It seems as though patients are almost compelled to submit their samples to biobanks, which then may be used for research without patients exercising much control. An answer from representatives of the Institute for Biomedical Laboratory Science (IBL) challenged these fears. The Act shall first and foremost safeguard patients' integrity, not promote research. This is in line with the Health and Medical Services Act and also with the ethical guidelines for biomedical laboratory technologists, in which patient integrity and the right of self-determination come first. The writers therefore commended the Bill.[38]

UmanGenomics in Umeå provoked a debate on its own.[39] Pharmaceutical companies were reluctant to make deals with UmanGenomics, since all results became accessible to competitors (according to the company). UmanGenomics wanted increased protection against competitors and to be able to open up the company to more owners who could contribute risk capital, but the proposed contract was not accepted by the County Council.[40] This threatened to drive UmanGenomics bankrupt.

Events followed thick and fast, with new versions of a contract being presented almost daily. Much of the debate concerned who owns, controls, and shall be administratively responsible for the biobank. The researchers who collected the blood specimens for the biobank felt that they were being left out of the picture. Representatives of granting organisations protested that a change could mean grants

[35] Later, the Swedish Data Inspection Board also criticised the unclear relationship between the Biobanks Act and The Personal Data Act. The principal of a biobank must consider two different acts at the same time, without always being clear about how they stand in relation to each other. See Wärngård 2002.
[36] See Welin & Persson 2001, who discuss the problem with regard to stem cells. See also Welin & Rynning 2002.
[37] Some examples: Adami 2002; Hedbäck 2002; and Nilsson 2002. Similar criticism was voiced by several patient groups; see, for example, Knifström Nordén 2002.
[38] Silvestri & Ericson 2002.
[39] As part of this project, Jens Laage-Hellman has studied UmanGenomics, and a comprehensive overview of the debate is to be found in his forthcoming book *Commercialization of biobanks. A study of biotech companies dedicated to human genetics*.
[40] See *Rätten till proverna olöst* 2002 and *Lundaprofessor föreslår alternativ lösning* 2002, as well as Hellman's forthcoming book.

being used for unintended purposes. Many felt it important that part of the material should be reserved for public research. On April 22, after many revisions, the contract was finally accepted by the County Council. Now results could be kept secret until commercially used, and outside forces could buy into the company (which has since happened).[41] The idea now was to find genes important for sickness and health and to seek patents for them.

The contract was not signed, however, and about ten appeals against the decision were soon lodged with the County Administrative Court, based on a whole array of different reasons, not least that donors had had no intention of supporting commercial interests when donating specimens.[42] All appeals were rejected in October 2002, a decision not altogether satisfactory from a legal point of view.[43] Professor Gisela Dahlquist of Umeå, a member of the ethics committee of the Swedish Science Council (formerly MRC), wrote a paper urging everyone to stop arguing about ownership. Now was the time to make sure that biobanks were rationally utilised.[44]

The Riksdag Standing Committee on Social Affairs processed the Government Bill and presented its report on April 25.[45] The main difficulty for the parliamentary majority was the provision on how to shut down a biobank. The Bill was otherwise left unchanged, although the Committee remarked that it was important to follow up the practical outcome of the Act, and especially that the possibility of epidemiological research must not be jeopardised. This was later endorsed by the Riksdag (Parliament). The Conservative Party, as well as the Centre Party, introduced Private Members' Bills to exclude biobanks used primarily for health care and diagnostics from the scope of the Act, regardless of how long specimens are stored, but were voted down.[46] In the ensuing parliamentary debate the majority was accused of "almost astonishing nonchalance" because of its reluctance to acknowledge the problems placed in the path of epidemiology and routine health care diagnostics by their proposal.[47] The Biobanks (Health Care) Act (SFS 2002:297) was passed by the Riksdag on May 16, 2002 in the form proposed by the Standing Committee on Social Affairs. It was supported by the Social Democrats, the Left Party and the Greens.

The National Board of Health and Welfare then drafted a regulation and recommendations which were circulated for comment in October 2002 and adopted in December.[48] One peculiar feature of the regulation is its definition of 'specimen'. This includes organs and tissue, or parts thereof, cells and cell lines, genes or parts thereof, and other forms of biological material. The question is how far on in the process of refinement something is to fall under the concept of "biological material".[49] Clearly the National Board of Health and Welfare's attention was drawn to this problem, since the final version included the statement that a "result" from a

[41] Eriksson 2002; and Lillkvist 2002.
[42] See Lövtrup 2002a; Lövtrup 2002b; *Dramat om västerbottningarnas blod fortsätter* 2002, and Stattin et al. 2002.
[43] Lövtrup 2002c.
[44] Dahlquist 2002.
[45] *Socialutskottets betänkande* 2002.
[46] Ibid.
[47] *Snabbprotokoll 2001/02:107*, anförande 20 Leif Carlsson (m).
[48] *SOSFS 2002:11 (M)*.
[49] For more on this topic, see Rynning's article in this volume.

measure taken with a specimen does not fall under the regulation. This addition puts the demarcation line earlier in the process, but a difficult interpretative task remains: when *does* the specimen turn into a result?

Lastly, mention must be made of the proposal for new ethical review legislation in Sweden. This is intended to take effect on January 1, 2004. Biobanks not regulated by the Biobanks Act will have to comply with the rules laid down in the new Act, provided that the donor of biobank material is identifiable. It remains to be seen whether the new Act will have even greater impact, making *e.g.* the research ethics guidelines regarding biobanks obsolete in certain respects.[50] Briefly, the new Act says that, just as with biobanks collected in a health care setting, research using other biobanks shall be reviewed by an ethics research committee, which will decide appropriate procedures of information and consent. An interesting addition to the present regulation is the provision that if the donor stands in a dependent relationship to the researcher or has difficulties in claiming his or her rights, as is the case when the researcher is also the donor's doctor, or is a student's supervisor, special consideration shall be given to questions of information and consent during the ethical review.[51]

3. Some topics debated during the legislation process

I now propose to describe some of the major points of discussion which have emerged during the debate on biobank regulation in Sweden. I will also address these issues and briefly evaluate the merit of suggested solutions. The conclusion I come to is that the Swedish Biobanks Act leaves a lot of the ethical deliberations to the ethics committees, and that some difficult questions remain to be addressed.

3.1. Consent to the taking and storage of biological specimens

The outcry in *Aftonbladet* had much to do with the fact that people were not commonly aware that their specimens were being kept in biobanks and could be used for research. Formerly, according to the National Board of Health and Welfare most specimens have been stored without informed consent.[52] When the Data Inspection Board asked blood banks about their use of blood and about the information given to blood donors, some blood banks admitted that for research they used blood which had been collected for health care only, sometimes without consent from donors.

This has been commonly rejected as a wrongful approach. When specimens are taken in a health care setting, common principles regarding volition as well as provisions in that sector concerning information, self-determination and secrecy, etc., are applicable. The same demands should govern the storage, retention and use of specimens taken.[53] The statutory instrument issued by the National Board of

[50] Further to this topic, see Ulrik von Essen's contribution to this volume.

[51] Throughout the debate one question has been avoided by all participants. How long shall the demand for informed consent apply? No one has discussed this question, it has only been said that *perhaps* the demand made in the official secrets legislation can furnish guidance (see *Lagrådsremiss* 2001, section 10:5). There it is said that public domain documents containing personal data about a donor remain secret for not more than 70 years.

[52] *Biobanker i hälso- och sjukvården m.m.* 2000, "Förord" & "Principer för information och samtycke".

[53] *Regeringens proposition 2001/02:44*, Chapter 6: "Principer för information och samtycke".

Health and Welfare had as its first rule regarding informed consent that when tissue specimens are taken and collected for a certain purpose, the informed donor must have consented to this, a rule which has been almost unanimously endorsed in the later discussion. (Disposal of old specimens is discussed in section 3.3.)

Not everyone agrees with this rule, however. For example, thirteen prominent Swedish scholars wrote an article in which they expressed the conviction that it should not be necessary to ask for consent to storage when taking a specimen.[54] Instead consent may be presumed. To do otherwise would pose a threat both to individual and public health. We must guard the possibilities of verifying individual results, to compare new specimens with old ones, and to investigate possible misjudgements or mix-ups, they wrote. Furthermore, we have a global obligation to promote research on the Swedish biobanks. It is only in the Nordic countries that we find almost complete biobanks and health data registers amenable to interlinkage. It would also be better to use our resources for good health care rather than to collect informed consent where previously none was needed. Now perhaps only well-to-do hospitals will believe that the end justifies the cost, thereby the principle of equal right to health care is threatened. The writers conclude that in order to do good research, biobanks must be complete, and the only way of ensuring that is by including specimens from everyone.

These arguments are all good reasons why biobanks should be promoted. The obvious counter-argument is that more strictly controlled biobanks may have higher quality and thus may actually *promote* individual and public health. It is of course hard to say at this point whether the negative or optimistic view is closer to the truth, much depends on the funds available for biobank activities. In the *travaux préparatoires* it is said that in many cases a standard, printed information sheet is surely sufficient to enable a patient to decide, and that general written information is surely sufficient in many cases. Thus the cost of collecting informed consent when a specimen is taken for health care and treatment need not be as high as some have suggested. Nevertheless, the concern expressed by those scholars underlines what was stated by the Standing Committee on Social Affairs, namely that it is important to follow up the practical outcome of the Act. If the disadvantages are too many, we will need to get back to the basic premises for an effective use of biobanks.

There is another ethical argument for not using the opt-in model of informed consent in medical research. This often takes the form of an argument for a general moral obligation to participate in medical research. As we are called upon in many countries to serve in the army in order to defend society against military threats, so we should be called upon to serve as research subjects in order to defend us all against threats to our health. We have to sacrifice some autonomy and put ourselves to some inconveniences for the public good. When you use the health care system you take advantage of the work done by prior generations. Why should you take gain from this and not put something back in for future patients? If you expect to receive the best possible treatment, you should contribute to the processes by which such treatment is established. If you don't, you are a "*free rider*".[55] The question, then, is seen to be one of *fairness*. The argument undoubtedly carries considerable weight. No system can tolerate more than a certain number of free riders without breaking down.

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[54] Adami 2002.

[55] See Harris & Woods 2001; and viewpoints tendered in *Committee on Ethical Issues* 1999.

However, as a general argument for the right of an government to include citizens in medical research, this is open to question. Firstly, the whole picture of a free rider may be misguided. Empirical research exists which suggests that participation in medical trials may actually be beneficial to patients.[56] If so, it is no burden on a patient to take part in clinical research: on the contrary, to refuse to do so is to decline a potential health benefit. But surely, that only strengthens the moral obligation? In therapeutic research it may do so. But even when it comes to therapeutic research this line of reasoning is too suggestive of a reciprocal relation between the health care system and the individuals who both contribute to and use it. Research is most often done by commercial enterprises. Of course, those enterprises are necessary in order to get new medicines, but on the other hand the research subject may be seen as a "resource" who in many cases won't benefit from the results of research without paying for it. Perhaps, then, the subject does not find himself in a reciprocal relation but is rather in the position of being a potential customer who participates as a possible customer and commercial resource. And of course it is not too uncommon to find volunteers participating in research principally for financial reasons.[57]

Also, such an obligation cannot be attributed to just anyone and everyone. The argument arises out of a predominantly western perspective. People in the developing world most often have not and in many cases will not gain access to the results of medical research. This fact will sometimes be disturbing even in an affluent western country like Sweden. Depending on the relationship between a Swedish research study and the international presence of the drug company responsible, an obligation may be felt more or less strongly, or not at all. If, for example, a drug company won't make a drug as accessible to Third World countries as to westerners, this may for example be perceived of as a breach of the UN Convention on Social, Economic and Cultural Rights, which recognises the right to enjoyment of the highest attainable standards of health. In such a case people have, of course, no duty to participate in such an endeavour.

We conclude that a moral obligation *may* carry considerable weight for a certain individual patient, but we cannot assume outright that it does and therefore in general drop the demand for voluntary participation. The government has no right to introduce a universal duty of participation in research on the basis of an assumed moral obligation. That obligation may exist, but not in such a way as to justify forcing the public into participation. Rather, the argument shows that there may be cases where after joint examination (in an ethics committee, that is) we find it reasonable for research to be done even without consent being obtained. In order to see whether such an obligation may be presumed, we need to examine each particular case on its merits. When biobank research in Sweden is concerned, we find both a relation between patients and the health care system which may be partly described as reciprocal, and patients who often express their willingness to contribute to research for altruistic reasons.[58] When specimens are taken from patients for health care purposes and, moreover, may be used for research, we

[56] 22 studies supporting this conclusion are mentioned in Chalmers & Lindley 2001. See also Lantos 1999.
[57] When Germans participating in research were asked in an anonymous questionnaire to give their reasons for doing so, 76% put financial motives first in their answer. See van Gelderen et al. 1993.
[58] See, for example, Gustafsson Stolt et al. 2002.

undoubtedly have a prime example of a situation where the patient gains directly from this and at the same time can contribute to the common good and the future well-being of others. Therefore it does not seem unlikely that we may find such an obligation as described by the free rider argument to possibly exist in some cases.

3.2. The extent of information needed

What are the information requirements when someone wants to collect specimens from donors or patients? The Government's Medical Ethics Advisory Board (SMER) criticised the report from the National Board of Health and Welfare for its very failure to specify such requirements.[59] Some clues are given in the *travaux préparatoires*, where it is said that in many cases a standard, printed information sheet is surely sufficient to enable a patient decide, and that the procedure to be followed in a particular case cannot be legislated on in detail. General written information is surely sufficient in many cases, while some purposes demand specific information, adjusted to the individual. So it seems possible in many cases to give general, written information concerning a broad purpose.

The SOSFS 2002:11 (M) guidelines and recommendations say that the consenting party should be informed that approval by an ethics committee is necessary in order to use a biobank for research or clinical trials, that new informed consent has to be collected if one's specimen is to be used for another purpose than has hitherto been the case, and that one's consent may be withdrawn at any time (in which case the specimen shall be destroyed or de-identified if the withdrawal concerns all use of it). The recommendations state that the informed party should consider for what purposes the specimen may be transferred to other parties.

Government Bill also says that the information usually given should not be less than is required by Section 25 of the Personal Data Act. That section provides that information shall include information on the use of personal data (for which read: specimens), but also that it shall include information on the identity of the person responsible for the personal data, and all other information the person needs for the assertion of his or her rights, e.g. who will receive the data and the fact that a person is entitled to know what is being done to their data. As Rynning remarks in this volume, similar demands have been made at various times by the Council of Europe.

If personal data are processed additional demands have to be met, as presented in the Personal Data Act. In a recent report, the Data Inspection Board revealed that in quite a few ways genetic researchers at present do not seem to fully comply with the regulative demands.[60] In the report the following aspects of informed consent were mentioned as mandatory in addition to the ones mentioned above: consent shall be given to a specific processing of personal data (this is not satisfied by a person consenting to the study as such) and to a transfer of data to a third country, and information given should include the obligation to release data; the right to rectify erroneous data; and whether data will be transferred to another country.[61] As mentioned elsewhere, if the purpose of processing is research, an ethics committee may decide upon the appropriate level of informed consent and may waive some of the requirements.

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[59] *Remissyttrande över Socialstyrelsens rapport* 2000.
[60] *Personuppgifter i genforskning* 2002.
[61] See also *SOSFS 2002:11 (M)*, Chap. 4, Section 5.

In the MRC research ethics guidelines it is said that donors should have the right to be told how the specimens will be stored, for how long, and how they will remain registered. Information should include the uses of the specimens that can be predicted and what will be done to prevent unauthorised parties from accessing the information. If specimens may later be used for a new research purpose, an ethics committee will review and approve the research and decide the requirements for informed consent. The MRC have much stronger demands on human subjects research of the experimental kind, and so it seems clear that a distinction is at work here between this kind of research and biobank research.

The MRC also wrote that it is important to ensure the individual's interest if the research can identify a marker for a disease for which some form of intervention may be available. If so, this is a "use" of the specimen which requires particular attention: Regarding relatives, they wrote that a research ethics committee "must also carefully consider situations such as when gene markers may have individual or group interest for concerned relatives of the person who has submitted the specimen. In such cases informed consent should be obtained from anyone who can be directly affected by research results."[62] This guideline was endorsed by the National Board of Health and Welfare and the Government.[63] The topic remains highly controversial and the Government has appointed a committee to inquire *e.g.* into the matter of information to relatives.[64]

There is also a peculiar section of the Act which has not been debated hitherto. Chap. 4, Section 5 provides that if the donor consents, specimens in coded form may be released to another unit inside or outside the country for analysis etc.[65] So, if you collect specimens for a bank and plan to make use of a laboratory somewhere else you will have to inform each donor of this when taking of the specimen, otherwise you will face a tremendous task of re-contacting everyone later. This demand seems somewhat overstated, since it is the only one given explicit legal backing in the Act, whereas many other information requirements are usually perceived as more important in various ethical guidelines.

To conclude, a regular version of an information sheet should usually include the following in order to comply with the standards issued by the MRC, the National Board of Health and Welfare, and the Government:

- For what uses is the material collected?
- Who is responsible for the biobank?
- Who will have access to or be provided with the specimen?
- Will the specimen be sent somewhere else? (Consent under Chap. 4, Section 5 of the Biobanks Act)
- New informed consent is to be obtained if the specimen is used for another purpose.

[62] *Research ethics guidelines* 1999.
[63] *Biobanker i hälso- och sjukvården m.m.* 2000, "Socialstyrelsens överväganden och förslag", section 5, and *Lagrådsremiss* 2001, section 10:6. In a forthcoming article, "Should results from genetic research be returned to research subjects and their next-of-kin?", I discuss this topic further. See the website of the research program for updates on publications, or my website at <http://www.teol.uu.se/homepage/stefan_eriksson/publikationer.htm>
[64] See *Genetiska undersökningar m.m.* 2001.
[65] For a detailed exposé, see Rynning's article in this volume.

- If the new purpose is research, an ethics committee will review and approve the research and define the requirements for informed consent.
- The possibility of revoking one's consent
- Additional demands occasioned by the processing of personal data (with specific consent)
- When the purpose is research: How will the specimens be stored? For how long? How will they be registered?
- What will be done to prevent unauthorised parties from accessing information gathered in the project?
- May research results be returned if important for the subject's health? Is consent from relatives needed?

More items can be added to this list of course. For example, it is important to keep in mind the ongoing discussion of whether there is a need to obtain informed consent for the taking of a specimen, if an invention based on the material taken is later to be patented (see contributions by Rynning and Wessman for more on this topic).

To conclude this section I will present three complications of the discussion above. First, the status and content of the Helsinki Declaration complicate things a little. Previously the declaration was said to consist of "recommendations". Section nine of the new 2000 version states that even if research investigators should be aware of ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements, "no national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration." Consider, then, that in the first section it is stated that medical research involving human subjects "includes research on identifiable human material or identifiable data". This means that the above distinction between human subjects experimentation and general biobank research does not hold. All the requirements defined concerning information shall apply to biobank research, which means that "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" (section 22). To take these requirements seriously will be at odds with current practice in Sweden and with the various guidelines presented here so far.[66]

The second complication concerns the distinction also used in the declaration above, that between identifiable and non-identifiable specimens. First we should note that the Data Inspection Board saw a common misconception amongst biobank principals: they thought that coded material was de-identified. The Board made clear that this is not the case: information is de-identified only when there is no possibility of tracing it to a person.[67] So according to the Swedish Data Inspection Board, a solution which consists in the coding of material is insufficient *e.g.* for genetic material. Such material is a form of personal data as long as it is traceable to

[66] One problem is that the guidelines from the MRC do not discuss the Helsinki Declaration of 2000, even though the MRC revised the paragraphs about biobanks in 2002!

[67] *Biobankers behandling av personuppgifter* 2000, p. 14. Such a misleading use of "de-identified" is common, for example the UNESCO International Bioethics Committee uses the term to refer to coded specimens (see *Draft Report on Collection* 2001).

a person, and when it is processed this makes the Personal Data Act applicable. Thus normally neither presumed consent, nor an informed refusal, are acceptable for such processing (unless the exceptions made by the Personal Data Act are applicable, as when the purpose is research).

So, what if you get rid of the code? This does not of necessity imply that specimens are de-identified. Rynning and Lindberg, among others, both note that it is possible to identify specimens containing genetical information even if they are de-identified.[68] If you have a particular gene sequence, for example, and can run it against identified genetical information elsewhere, you may identify the person the sequence comes from. This is known as "computer profiling". Consider Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, which says that "Whereas the principles of protection must apply to any information concerning an identified or identifiable person; whereas, to determine whether a person is identifiable, account should be taken of *all the means likely reasonably to be used* either by the controller or by *any other person* to identify the said person…" (my italics).[69] The National Board of Health and Welfare also noted that this was the case. Nevertheless they seemed to assume throughout the report that it was meaningful to differentiate between identifiable or coded material on the one hand and de-identified material on the other, as did the Government in the proposal referred to the Swedish Council on Legislation. But this differentiation rests on shaky foundations, as we see here.

There will probably be no new smart way of de-identifying specimens, if anything the opposite may be the case (the invention of new means to identify specimens), so I think the only solution to this dilemma is to stop focusing on the properties of the specimen itself. The important thing isn't whether it has been completely stripped of identifiers or not, but whether it will be used in such a way as to make an identification possible. If DNA is kept and used in such a way that the information cannot be compared to "outside" sources of DNA, the chances of identification are very, very small. But if the specimen is represented in digital format on the Internet, the risk is considerably higher, even if it is still small. In other words, a specific description of what will be done with specimens, not least from a technological point of view, is needed in order for an ethics committee to decide on appropriate measures.

Lastly, there is a paramount problem regarding the level of understanding on the part of patients.[70] In a French study, patients who had consented to specimens being stored in a DNA bank was later sent a questionnaire in order to assess their perceptions of storage and consent. Of the patients who replied, none was aware that his or her samples were being stored in a bank, and none remembered signing a consent form.[71] In recent literature on informed consent there has been a shift from emphasis on the *documentation* of informed consent to the *process* of giving information and ensuring comprehension.[72] Great communicative skill is needed if

[68] Rynning 1998; and again in Rynning 2000, p. 458; Lindberg 1997. See also for example Gostin 1995, p. 494.
[69] For further discussion of the directive, see Zoëga & Andersen 2000.
[70] See Werkö 2002, which describes the comprehension problem and gives references to some empirical studies on the subject.
[71] Moutel et al. 2001.
[72] On this subject, see for example National Bioethics Advisory Commission 2001.

patients are to get the advice and assistance they need in order to be as autonomous in their decision as they can be. Today's advanced research is very difficult for many people to comprehend, not least since modern genetics is such a complex endeavour and is so bound up with probabilities. If the information isn't understood, the idea of an autonomous and well-informed decision has rather a hollow ring to it. I am not suggesting this makes the consent invalid, but I do think it puts before us an ethical challenge to try and improve patient information and comprehension. Not least patients who have been stricken with bad news may have a hard time taking in information and deciding upon the possible inclusion of their specimen in a biobank. If they say No it may prejudice their future care, which can be hard for a person in such a state to understand. In order to improve the possibility of true understanding which enables people to make autonomous choices, we need to implement strategies which enable each party to the informed consent process to partake in this process in a fruitful manner. Very briefly, something along these lines is called for:

Education policies. The general public must learn more about effective health care and research, as well as be educated about genetics.

Professional training. The general practitioner will often be the person who meets the patient and thus will need a more thorough understanding of research and genetics in order to give guidance to his or her patients. He or she must also be knowledgeable about the risks, both to the patient and the patient's relatives, entailed by a decision not to store, for example, a cytological specimen. Both general practitioners and qualified experts will need to develop their communication skills.[73] A simple but effective tool for assessing patients' comprehension is to ask them to re-word the information given. Genetic counselling may be appropriate in more instances than those for which it is currently provided.

Better instruments. We need more empirical knowledge about information readability in order to present information in the best possible way. Hermeneutics experts should join forces with research professionals. Furthermore, the process of informed consent should not be considered as over when the statement is signed and the specimen has been stored. People's preferences change over time and understanding sometimes takes time too, therefore information should often be given on a more or less regular basis and new ways developed of supporting an effective ongoing process of two-way-information. If a contact is maintained, it will also be much easier to return results or to re-contact the patient when new consent is needed for a new study.

3.3. The need for consent to new research on existing specimens

Do you need to have new informed consent from donors if their specimens are to be used for *new purposes*?[74] Purposes recognised in the law are care and treatment, quality assurance, teaching, research, clinical trial, method and competence development or similar endeavours. But when the purpose is research, a rather different notion of "purpose" comes into play. In research ethics there is a common demand that the specifics of each and every research project be described to the subject before he or she consents to it. Although this notion is not spelled out in the Act, it is easy to see that it is presumed.

[73] See Hall 2001, for an introduction to this theme and for a comprehensive bibliography on the subject.

[74] This question was first broached by Bo Lindberg in Lindberg 1997.

Rynning, as well as the Swedish Medical Research Council, remarks that since it is difficult to predict what future analyses that will be possible and desirable, it is hard to ask for a traditional consent where all circumstances are outlined in detail.[75] Is it then enough just to consent to the specimen being taken for an unspecified research purpose, just as UmanGenomics initially used an information sheet merely stating that the specimens would be used for research concerning prevention, diagnosis, and treatment of heart attacks, stroke, and diabetes, but also to find out about these and other diseases, for example cancer?[76]

This problem is equivalent to the one about old specimens collected ages ago, probably without consent. Now, when measures are taken with specimens collected before the act come into force, they come under the Act. So no distinction is made between old and new material in this respect. Still, as noted by Rynning, it may be hard to decide whether a particular biobank is to count as a primary or secondary biobank and what the purpose originally was. Furthermore, different specimens in the bank may have different origins.

Gisela Dahlquist, chairperson of the MRC at the time, held that to not again ask donors that once gave their specimens for future research, is contrary to the research ethics guidelines in force in Sweden. Although there are exceptions, they are very strict.[77] The guidelines issued by the MRC say that "informed consent for each new purpose is the main rule, which means that general information where the patient consents to the use of collected material for unspecified future research cannot be accepted."[78] Göran Hermerén noted that even if an opt-in or opt-out model of informed consent is preferable in many cases, this has its problems. Many biobanks are very large and a research project using many specimens would then need to contact so many people that it would be unmanageable. Some biobanks have existed for many decades and most donors are by now deceased.[79] The statements requiring new consent for each new research project were of grave concern to scientists. Researchers worried, for example in the referral from the Karolinska Institute,[80] about having to collect new consent for every changed analysis, something which will be hard to do, will cost a lot, and will cause a high drop-out rate.[81]

The National Board of Health and Welfare suggested in the Bill that specimen donors should consent to "other uses" of their specimens. But if the purpose was research then the ethics committee should decide on appropriate information and consent. This of course was ambiguous, as it can be taken to mean that the committee shall check whether the demand has been satisfied, or that the task is to decide whether new informed consent is needed at all. The first interpretation gains support from another passage where the Board speaks of the committee as deciding *how* informed consent shall be collected. But in another passage they say that it is customary for the ethics committee to examine both the

[75] Rynning 1998, p. 307; *Research ethics guidelines* 1999.
[76] *Information om medicinska biobanken* 2000.
[77] Dahlquist 1999.
[78] Even if only "the patient" is mentioned, MFR also says that the guidelines "also apply, where appropriate, when biological material is collected mainly for an identified research project." (*Research ethics guidelines* 1999).
[79] Hermerén 1997a, p. 31.
[80] *Lagrådsremiss* 2001, section 10:8.
[81] For more on this topic, See Magnus Kaiser's contribution to this volume.

level of informed consent and *whether it is needed*.[82] It is hard to see whether the writers have deliberately addressed the problem.

In the proposal referred to the Swedish Council on Legislation, the wording of the section had been changed to the first alternative above ("how"). Nevertheless, in the commentary they wrote that a research ethics committee may depart from the principle of informed consent, something which is in line with the ethical guidelines of the Medical Research Council. The remark that it is customary for the ethics committee to examine both the level of informed consent and whether it is needed was still retained in the commentary. Decisions would thus be guided, they wrote, by the ethical guidelines of the Medical Research Council, not a detailed law.[83] This was endorsed by the Government.[84] Thus, some critics who argued that new informed consent was now to be needed at all times had misunderstood the proposal. To conclude, the current guidelines state that: (a) consent to unspecified future research is controversial and according to the MRC cannot be accepted, (b) informed consent for each new purpose is the main rule, and (c) the ethics committee may depart from the principle of informed consent when certain criteria are met.

It has long been customary to approve certain kinds of research without donors having consented to specific purposes. While there are many variations on the theme, broadly speaking two models may be distinguished: the *review model* and the *professional conduct model*. The review model puts the emphasis on review by an ethics committee, an IRB or the like. The committee shall ensure that certain criteria are fulfilled before approving a research project where informed consent is waived. Criteria usually require among other things (a) that individuals concerned may be thought to give presumed consent; (b) that participants are only subject to minimal risk; (c) that data or specimens are coded or de-identified and (d) that public interest in the research clearly outweighs any harms and risks to participants. Something along these lines is the usual procedure for information-sensitive research, and basically the one agreed upon in the former contract between UmanGenomics and Umeå University/Västerbotten County Council, where only coded or de-identified specimens and data are supposed to be given by the biobank to the company.[85] The governmental department memorandum *Genetic Integrity*,[86] as well as the report by the National Board of Health and Welfare, likewise stressed that information concerning an individual's genes used for research usually should be de-identified (or coded).

The professional conduct model can be instanced with the British Royal College of Physicians, which stated in its guidelines that neither review by a committee, nor informed consent is needed as long as access is obtained from the custodian of the material, if confidentiality issues are solved reassuringly, and if the recipient of the material is a senior professional who is subject to "an effective disciplinary code enforced by his or her professional body over any breach of confidentiality".[87]

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[82] *Biobanker i hälso- och sjukvården m.m.* 2000, "Socialstyrelsens överväganden och förslag, section 8".
[83] *Lagrådsremiss* 2001, section 10:9.
[84] *Regeringens proposition 2001/02:44*, Chapter 10: "Överväganden och förslag", section 10:9.
[85] *Forsknings- och utvecklingsavtal* 1999.
[86] *Genetisk integritet* 1996.
[87] *Guidelines on the Practice of Ethics Committees* 1996, Appendix B.

But there is another possible position which is often based on the notion of "the dignity of the human being" found in the Convention on Human Rights and Biomedicine. This position basically says that human tissue cannot be treated like other sources of information. Human tissue is an intrinsic part of the body, and the body is an integral part of a person. It is therefore plain wrong for others to use a person's tissue without explicit consent.[88] Another way of putting it is to compare such a study to an intruder getting into a house when no-one is home, without disturbing anything. Even so, the house inhabitant has been wronged. By the same token, to do research without explicit consent is to invade your privacy without consent, what in law is known as trespass,[89] and therefore should not be allowed. This kind of position is supported by various guidelines. For example, in the Report on Confidentiality and Genetic Data made by the International Bioethics Committee (IBC) in 1999, roughly the same idea is expounded.[90] The human right to privacy,[91] so heavily emphasised in various human rights instruments, is applied there to the use of genetic data, although traditionally it is connected first and foremost with honour and reputation, family, home and correspondence. One version of this argument is put forward by Sheila McLean, who says that good research should always respect the subject by seeking consent and the giving of "full information". Any failure, she writes, "to offer this respect is in itself a harm, even if its consequences are not physical".[92]

Now, research ethics attempts to safeguard the privacy and self-determination of individuals, but who is the person subjected to an experiment when the research scientist studies a genetic sequence? *Aftonbladet* wrote that "nobody knows who owns *you*," but is it really *me* they see in the experiment?[93] So long as a specimen is identifiable, there is a question of me being a subject in a more palpable sense. When on the other hand the material lacks any identifying information, the fact remains that I am the *source* or the *origin* of the material, but it seems far-fetched to say that it is *me* the experiment is being performed on. In Iceland, a spokesperson for the Government Bill to set up an Icelandic health sector database said that research "carried out with the database would not represent human investigation and hence the Helsinki Declaration simply did not apply to database research."[94] Swedish researchers retorted that most people can distinguish between themselves and, say, a blood specimen![95]

These responses may oversimplify things but, for one thing, one must, like the IBC, differentiate between kinds of genetic data. Some data are common to all humanity, some differences pertain to a group of people, others to an individual. Data may be linked to an individual or may not. To say that all tissue is an integral part of the person is a gross overstatement which neglects the differences between

[88] This position was defended by Jacob Dahl Rendtorff in the first report published from this research project, see Rendtorff 2001.
[89] Nielsen 1997, p. 123.
[90] *Report on Confidentiality* 2000.
[91] About the concept of privacy: defined relationally, it is the ways and circumstances under which other people access information from me. Defined subjectively, it is the right of the individual to limit access by others to some aspects of their persons.
[92] McLean 1997.
[93] See *Aftonbladet*, Saturday 10 April 1999, p. 6.
[94] As reported in Zoëga & Andersen 2000, p. 41.
[95] Welin & Persson 2001.

culturally sensitive material and material seen as mere waste, between de-identified material and material associated with an identifiable individual, as well as the differences between material that can be viewed as an intrinsic part of a particular person and material that is interesting because it contains DNA which is "the heritage of humanity".[96]

This position uses a particular image, in which tissue is compared to one's home and both can be subjected to invasions of privacy. This image, suggestive as it may be, is misleading. When a person builds a house he thereby builds a private sphere which in one respect is an extension of his own identity. We rightly feel that we can lock the door and that we do not have to let anyone in who isn't invited. But building a biobank for research isn't really comparable to this. A more appropriate image is that of people together building a public office which is for the use of everyone, and not an instrument of one's own privacy. When turning to health care we turn to a jointly built institution and co-operate with it to promote health, my own as well as others'. Some data may need to be protected by confidentiality, of course, but there is no logic in assuming that every use of the data is tantamount to trespass. We can see that the analogy holds in certain cases, but it may as well be drawn otherwise.

Contrary to this picture, one may hold that the important thing isn't my specimen but the wishes I have regarding the use to which it may be put. If I support medical research and want my specimen to be a contribution to it, having respect for my person may involve keeping unnecessary contact to a minimum. McLean thinks seeking consent is necessary in order to show respect, but cannot avoidance of unnecessary contacts be seen as equally respectful? In such a case it is the *new* contact for consent which may be seen as an intrusion of privacy. Also, as pointed out by representatives of the Swedish Moderate (conservative) Party, a further problem arises when new consent is sought. More persons than previously have to be involved in contacting donors, accordingly sensitive information is exposed more than would otherwise be the case, which presents the donors with an increased risk of breaches of confidentiality.[97]

A large part of the conflict concerning the ethics of biobanks has its origin in the conflating of different models of research ethics. On the one hand, there is the Helsinki Declaration and other similar documents on the integrity of the experimental subject, which some have seen as also valid for biobank activities. On the other hand you have either the sort of ethical considerations made for epidemiology and register research, or the principles that apply to donation.[98] The absolute right to decide for oneself and to protect one's integrity is almost indispensable in the former case, but seems rather out of place in the latter. Take a researcher who isn't interested in you at all but by surveying data from perhaps thousands of people is seeking statistical results on a national level, for example. Register research is sometimes regulated in law so that participation is a legal requirement. The individual person's interest in self-determination is then given no room at all.

Argument on these lines remains open to the objection that putting the public interest before the individual right "amounts to justifying exploitation of

[96] *The Universal Declaration* 1997.
[97] See *Socialutskottets betänkande* 2002, "Reservationer".
[98] As noted in Welin & Persson 2001.

individuals and ignore the objective harm that is inflicted upon them by disrespect for their autonomy", or that is "to embrace the dogma of scientific progress at any price".[99] But there is a basic flaw to such an attack. While it is true that different models of research ethics are conflated in the debate, the right of the individual should not be automatically viewed in contradistinction to the public interest or to various social projects, for the self-same individuals proclaimed to be invested with rights can also obtain provision for their interests indirectly, through social institutions. The prime distinction to be made, therefore, is between a direct and an indirect *form* of exercising individual interests. An individual can directly assert his interests by exercising his autonomy in various ways, but he can also obtain provision for them indirectly, through elected or appointed representatives. When a law thus impinges on his right as an individual to influence a particular matter, this need not necessarily be deemed prejudicial to his interests. After all, as a democratic subject he has (or should have) elected a certain order of things in order to bring about legislation which provides both for his own interests and for other people's. Therefore the second article of the Convention on Human Rights and Biomedicine, mentioned above, runs the risk of making us oversimplify our thoughts on the matter, and all too easily forget that what is in the interest of science or society may very well be in the particular person's interest too.

The conflict between two different ways of understanding personal involvement in research runs through all the debates concerning informed consent. It seems obvious that proper use of the Act by the research ethics committees must be aimed at doing justice to our intuitions here and firmly make room both for situations where persons are involved as experimental subjects, and those where we all want scientists and health care personnel to have effectual access to broad data.[100]

3.4. Should the donor be able to revoke his consent?

In Sweden, The Medical Research Council, the National Board of Health and Welfare and the Biotechnology Committee[101] all wished to make the donor fully entitled to revoke his consent. Their standpoint tallies with the Helsinki Declaration, the Convention on Human Rights and Biomedicine, and Section 12 of the Personal Data Act which stipulates that in cases where processing of personal data is only permitted when the person registered has given consent as the Act provides, the person registered is entitled at any time to revoke the consent he has given. This principle is derived from research ethics concerning human experimentation, where it is mandatory to declare that each and every subject has the right to withdraw from participation in an experiment or a study. This is sometimes conceived of as a human right. Speaking of Icelandic patients who choose to participate in the health sector database, thereby renouncing the possibility of later withdrawal, Zoëga and Andersen write that they "are required to give up a fundamental human right: the right to withdraw from research studies".[102] The National Board of Health and Welfare calls it an "unconditional right".[103]

[99] Doyal 1997, and Doyal 1998, respectively.
[100] In a forthcoming article (in Swedish) I discuss how to understand and make use of the notion of "new" or "other" purpose; see of the research programme website for updates on publications, or my website at <http://www.teol.uu.se/homepage/stefan_eriksson/publikationer.htm>.
[101] *Att spränga gränser* 2000, Section 5 of draft enactment on biomedical research on humans, p. 315.
[102] Zoëga & Andersen 2000, p. 47.
[103] *Biobanker i hälso- och sjukvården m.m.* 2000, "Socialstyrelsens överväganden och förslag, section 6".

On the other hand, I have claimed that a right of this kind runs contrary to the established practice of research ethics in connection with register research.[104] First, as noted above, it is questionable in many instances whether it is relevant to speak of a person taking part in a study where epidemiological research and register research are concerned. Further, if individuals could recall the data/specimens they have supplied to registers, this would detract from the scientific value of the register concerned. If we use the donation model, donors are not usually allowed to ask for the destruction of what they have donated, as long as it is used in the way intended by the donor. The devaluation of the register is not only negative in itself: setting up a good-quality biobank, with adequate security etc., costs large sums of money, and so failure to use it as effectively as possible would be a waste of resources. It should further be noted that, if the specimen has been made a subject of research, destruction of the specimen eliminates the possibility of subsequently verifying and otherwise following up the research, which without doubt is a palpable deficiency.

These considerations have formerly guided the creation of registers and tissue banks in Sweden. For example, in the general recommendations by the National Board of Health and Welfare concerning routines for saving test material at pathology departments, it is claimed that test specimens do not belong to patients, rather they belong to whoever has taken them. Nevertheless, the National Board of Health and Welfare wrote in their Biobanks Bill that if a donor revokes his or her consent, the specimen shall be destroyed. The proposal referred to the Swedish Council on Legislation went further still, requiring the specimen to be destroyed *immediately*. The MRC have had a similar idea: donors must be informed of the possibility that their specimens may be destroyed at any time on their request.

The Swedish Society for Clinical Cytology found this provision unacceptable. Someone consenting to a specimen being taken for diagnostic purposes should not be allowed to withdraw that consent: doing so will jeopardise the efficiency of health care for the future.[105] Further criticism of the same kind came from other commentators. The idea behind the Bill was that if continued storage of specimens is important for health care purposes, the donor's doctor should discuss the matter with the patient before the specimen is destroyed.

By the time the Bill came to be enacted, a change had occurred. Now the provision was that after someone has revoked consent, the specimen shall be destroyed *or de-identified*. This is no doubt a concession to the critics, but comes as a mixed blessing. An Act in which revocation of consent includes destruction of the tissue specimen has the effect of establishing by law the donor's right to have the specimen destroyed, an arrangement which, in the light of our previous discussion, seems rather ill-advised and ought not to be recommended. There is no precedent for any such inalienable right. As we have already seen, it is abandoned in the statutory requirements, introduced previously by the National Board of Health and Welfare and other authorities, concerning the supply of data to various registers. Research with the aid of these registers has been judged so valuable as to warrant a circumscription of the individual person's right of direct control over his participation. Similarly, research with the aid of biobanks appears to be of such great interest to broad groups of patients and to society as to make it reasonable for the

[104] Eriksson 2001.
[105] *Angående förslag till lagstiftning* 2000.

researchers to be able to de-identify the specimens in order to keep the biobank intact.

But the provision has a flip side. Basically, it provides a way round the law as opposed to a law having some logic to it. If someone has been given the right to withdraw his specimen and uses that right, that person may now find that as soon as they ask for the specimen to be destroyed the researcher instead de-identifies the specimen and refuses to give it back or to destroy it. This may easily be seen as deceitful behaviour and it is hard to understand how it can further the lawgiver's overriding concern of preserving public confidence in health care and research, especially in light of the above considerations of what is to count as a de-identified specimen in the first place.[106] The present provision thus works against Article 4 of the international instrument on human genetic data proposed by the International Bioethics Committee, calling for "transparent procedures providing for the informed participation by society as a whole" when it comes to genetic data.[107]

Thus, instead of the statute as it now stands, the nature of each purpose should govern what is agreed on through the informed consent procedure. On the strength of information supplied to them concerning the value of registers and research, as well as possible clinical value, the majority of donors hopefully can accept the passing of full control over the specimens to the biobank (although confidentiality must not be compromised). From an efficiency viewpoint this should be the normal course of things. It is also perfectly possible to anticipate this in the conditions but to give anyone wishing to do so the possibility of making a written proviso. Otherwise, of course, it may sometimes only be possible to take specimens from those accepting the biobank's full right of disposal, without prejudicing the success of research. In other cases, perhaps the possibility of verifying results does not require the specimens to be retained, and the donor's right of recovering the specimens or having them destroyed can be part of the initial conditions. Sometimes an agreement on possible de-identification is suitable.

In short, the circumstances of the individual case should be allowed to decide the procedure to be followed, and a decision on this question should be included in the informed consent procedure, thus making donors involved in the decision of whether to destroy or de-identify in the case of revoked consent.

3.5. Consent for specimens taken from foetuses, minors, deceased and non-competent persons

In this last section we will consider special provisions regarding informed consent, for specimens taken from foetuses and from deceased and non-competent persons. The National Board of Health and Welfare wrote in their Bill that in the case of *foetuses* the mother gives consent. The research ethics committee at the Karolinska Institute suggested that the father should also have a say, a view shared by the Moderate Party members of the Riksdag Standing Committee on Social Affairs. This

[106] See the preliminary findings by Ring and Kettis Lindblad in this volume, one of which is that the public has great trust in the ability of university-based researchers and health care personnel to evaluate the risks and benefits of genetic research. The high level of confidence is confirmed elsewhere. In Sweden, 9 people out of 10 have great confidence in research and researchers, according to a public survey made by TEMO, *Svensken tror på forskarna* 2002.

[107] *Outline of the International Instrument* 2002. Note that this outline (in contrast to the author of this paper) does not use the said article to challenge a right of withdrawal of consent; on the contrary, such a right is strongly accentuated.

was rejected by the Government, however. But the Government was also apprised of the possibility of a case of which no provision had been made: if the mother dies, who will then decide about the taking of a specimen from her foetus? Therefore they included a provision stating that a "near relative" shall give informed consent before a specimen can legally be taken in such cases.

The emphasis put on the mother reflects common values about the woman's right to decide concerning her body and the child she has carried. What seems to have been overlooked is that the genetical information extractable from a specimen in equal measure reflects the genetical constitution of the mother and father and their families. The criticism levelled against the Act therefore seems relevant and perhaps even justified. If the specimen is to be used for another person's care, it seems acceptable for the mother alone to decide, but if the purpose is genetical research, the father's and his family's integrity seem as important to safeguard as the mother's. Accordingly, this provision should be revised.

Regarding *specimens from deceased* persons, the National Board of Health and Welfare suggested that the Act should include a provision that when specimens are *taken* from diseased persons this should be done "with respect" for the diseased. In the discussion on consent from relatives they stated that the model regarded as customary in this situation was that of opt-out consent. Sometimes consent may even be presumed. The National Association of Disabled Persons objected that most people are unaware that specimens are taken and therefore consent cannot be assumed. They went on to say that relatives may disagree among themselves and that such a situation had yet to be addressed by the Bill.[108] The Government answered the last point by stating as their view that in such a case specimens shall not be taken (a statement that pertains to the next section as well). In the Government Bill, however, the Government had omitted the provision on "respect" and now had only a reference to the Acts on transplantation and post-mortem examinations respectively.[109] This basically means that specimens may be taken if there are grounds for assuming this to be the will of the deceased. If you do not know whether the deceased would have accepted the operation you may proceed on two conditions: that there are no grounds for assuming that the deceased was *against* such an operation, and that near relatives have been notified and do not object. Should relatives disagree, no specimen can be taken.[110] If no near relative can be reached, an autopsy may only be performed for special reasons.[111]

The research guidelines from the Medical Research Council state that if you want to use *previously collected* material from now deceased persons, the research ethics committee must determine whether relatives of the deceased should be informed or not. The National Board of Health and Welfare, and later the Government, held the view that consent from a relative *may* be of current interest when using such a specimen for a new purpose, especially if the relative's integrity may be affected by it. In accordance with the ethical guidelines, the Board concluded that relatives, when it was "judged to be necessary" [by an ethics committee, that is], shall be informed and asked for consent "in a suitable manner",

[108] *Remissyttrande över: Biobanker i hälso- och sjukvården m.m.* 2000.
[109] *Regeringens proposition 2001/02:44*, Chap. 3, Section 4.
[110] See *SFS (1995:831) Lag om transplantation m.m.* (The Transplant Surgery Act).
[111] See SFS *(1995:832) Lag om obduktion m.m.* (The Post-Mortem Examinations Act).

if specimens from a diseased are to be used for a new purpose.[112] Both these expressions were to be deleted, though. "In a suitable manner" was deleted at the suggestion of the Swedish Council on Legislation. Instead a new reference to the Medical Records Act (SFS 1985:562) was made, to the effect that if information or consent is given according to the Biobanks Act, this shall be stated in the patient's medical record. In the Government Bill, the expression "when judged to be necessary" was also absent. Instead relatives shall have been informed and not have objected to the new purpose. Still, a research ethics committee may decide upon the requirements deemed suitable when the new purpose is research. Which is all to the good, I think, since relatives may find it offensive to be contacted in this matter for trivial reasons.

The matter of *specimens from minors* was regulated by the National Board of Health and Welfare in the usual way: it is from the custodian that written consent must be obtained, but the minor shall be informed and have his or her say as deemed suitable according to age and maturity. In the case of an older child, its own consent is often sufficient for taking and storing a specimen in a biobank, the Board commented. The statute was heavily criticised. On the one hand, the research ethics committee at the Karolinska Institute believed the minor's own view to be insufficiently considered in the proposal. On the other hand, the Medical Research Council thought both parents/custodians should be required to give permission (this is required under the Code of Parenthood and Guardianship). Others had similar remarks to make. The Government accepted the latter objection, that consent should be obtained from both parents or custodians.

The Swedish Council on Legislation favoured of the former suggestion and wanted to add a provision that if minors oppose the taking of a specimen the consent of custodians will not be sufficient. However, the Government did not accept any such provision in the later Government Bill. Instead they added a provision whereby, age and maturity permitting, the minor himself may decide. This is somewhat surprising, considering that there is "a strong consensus" in professional guidelines against carrying out research on an child who objects even if its parents consent.[113] Ethics committees must decide whether the nature of biobank research is such as to warrant a departure from this principle, and may very well be more reluctant than the law on this point because of common standards in research ethics.

There is also an inverse problem: what if a minor has a rightful need for a specimen to be stored, for health care purposes, and the custodian(s) says no? Should the minor's care be compromised because of this?[114] This problem has yet to be solved except for cases where the anticipated damage is so severe so that the Care of Young Persons (Special Provisions) Act becomes applicable. Questions of care aside, a basic principle which has evolved concerning the ethics of *research* on minors is that research should only involve children when it is essential for the study to do so and when comparable data are unobtainable from adults. Whether such a presumption should guide biobank research in Sweden has unfortunately not been

[112] *Biobanker i hälso- och sjukvården m.m.* 2000, "Författningsförslag", Chap. 2, Section 5.
[113] Montgomery 2001, p. 179.
[114] As pointed out by the Moderate Party; see *Socialutskottets betänkande* 2002, "Reservationer". Of course, in cases of urgent need a sample may still be taken under the Care of Young Persons (Special Provisions) Act (SFS 1990:52), but most often such urgent needs are not of the kind making the Biobanks Act applicable to the operation, *i.e.* there is no need to store them for more than two months.

addressed hitherto.[115] Lastly, we may note that in the regulation and recommendations on biobanks it is said that minors who are not mature enough to decide for themselves whether a specimen should be included in a bank shall be given the opportunity to do so as soon as maturity has been attained.[116]

The National Board of Health and Welfare wrote that for *non-competent persons*, a near relative or proxy can give informed, written consent. The National Association of Disabled Persons disagreed: for the maintenance of personal integrity, no one should have to leave specimens for a purpose which he or she does not understand.[117] Also, the vague notion of 'near relative' was criticised by the bodies taking part in the consultation process. In the proposal referred to the Swedish Council on Legislation there were no statutory provisions on this matter at all, only a reference to the Code of Parenthood and Guardianship. In the accompanying report, however, the Government said that a non-competent person shall himself agree to the donation of a specimen in order for a proxy to give acceptable consent. Also, relatives are not permitted to decide, only a legal trustee or a guardian (someone who voluntarily acts as a non-competent person's advocate) can do so. If the non-competent person's condition prevents him from giving an opinion, a trustee or guardian may give legitimate consent, provided there are no reasons for assuming that the non-competent person would disagree.[118] The Swedish Council on Legislation criticised the imprecise reference to the Code of Parenthood and Guardianship and at their suggestion it was then wholly omitted from the Government Bill. In the commentary the Government accordingly stated that if the patient or a custodian has not given informed consent, no specimen can be taken (for inclusion in a biobank), which is in line with the Medicinal Products Act (SFS 1992:859) governing clinical research.

The problem is that it may be of the utmost importance for specimens to be taken from a non-competent person (a cancer patient, say) to provide good quality health care. There is a crucial dissimilarity here: whereas clinical research is of no critical interest to such a patient, the taking and storage of a specimen for more than two months may very well be! The omission of this point is a matter for grave concern, and we must hope that the Commission on the Swedish 1995 guardianship reform which has been appointed by the Government will address these questions and give workable guidelines.[119] In the later SOSFS 2002:11 (M) regulations and recommendations, a statement was included to the effect that a specimen may be saved in a biobank if the attending physician considers it necessary in order for safe health care and treatment of the patient. It is unclear whether this regulation is compatible with the Biobanks Act.

In all the above cases, the National Board of Health and Welfare wrote, the consent given by a proxy, or if relevant, a relative, may *be revoked* if it is "in the interest of the specimen provider". SMER drew attention to a peculiar non-symmetrical feature of the provisions, since a relative or proxy may say No to the inclusion of a specimen in a biobank *even though* such inclusion is in the patient's

[115] Another such basic principle which has not been debated is that research on older children is preferable to research on young ones.
[116] *SOSFS 2002:11 (M)*, Chap. 4, Section 5.
[117] *Remissyttrande över: Biobanker i hälso- och sjukvården m.m.* 2000.
[118] *Lagrådsremiss* 2001, section 10:5.
[119] This was fiercely debated in the Riksdag both on May 16, see *Snabbprotokoll 2001/02:107*, and on May 27, see *Snabbprotokoll 2001/02:113*.

best interest. As in the revocation rule, they should not be allowed to do so, according to SMER. This was not endorsed by the Government, however. In the Bill referred to the Swedish Council on Legislation they simply dropped the wording about the provider's interest, with the result that the right to withdraw consent was even more accentuated in the resulting Act (a matter criticised earlier in this paper).

Lastly, the Government writes that when the specimens are taken for research, in all the cases mentioned above a research ethics committee shall review the research project and decide what requirements of informed consent are necessary.[120] Also, in the proposal for new ethical review legislation there are some differences to the Biobanks Act that will be of importance for biobanks *not* collected in a health care setting or derived from such a bank. Regarding *minors* considered for inclusion in research through the donation of a biological specimen, if they are under 15 and mature enough to understand the research project and its implications, and say No to it, the specimen shall not be taken. In the case of *non-competent* persons, specimens may be taken when certain provisos are met and neither the non-competent person, near relatives nor a legal trustee or guardian disapprove – a more satisfactory solution than is found in the Biobanks Act.

[120] *Lagrådsremiss* 2001, section 13:1; and *Regeringens proposition 2001/02:44*, Chap. 13: "Författningskommentar", Chap. 3, Section 5.

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9

Public and patient perception of biobanks and informed consent

Lena Ring, PhD[1] & Åsa Kettis Lindblad, PhD[2]

[1]*Department of Psychology, Royal College of Surgeons, Ireland*
[2]*Department of Pharmacy, Uppsala University, Sweden*

This chapter provides international examples of empirical research on public and patient perception of research on biobank material, including procedures of obtaining informed consent. Few such studies have been conducted in the Swedish context, but preliminary data from a pilot study of the general public in Sweden will be presented as well as the design of ongoing full-scale studies of the general public and diabetic patients.

1. Introduction

The rapid development of biotechnological research has stimulated the establishment of new biobanks and the use of existing biobanks. Questions that keep coming up, and that have been debated in both the scientific and the public community, are about the safety and risk of the participants/sample donors in this research, including issues concerning informed consent[1].

The basic principle in medical research and in research using human biobanks is that informed consent from research subjects and sample donors should be obtained. However, the research ethics committees can make exceptions and are committed to strike a balance between the value of research and the requirement of informed consent. According to the Swedish Biobank Act, the research ethics committees shall select appropriate information and consent procedures after this balancing and after taking other legislation, e.g. the Personal Data Act into consideration.

The challenge lies in how to obtain informed consent from the donors, in a way that takes many different values, such as altruism, integrity and research quality, into account. It is important to balance the integrity/autonomy of the donor and the common good that medical research may result in. Some researchers fear that restricted regulations will hinder research in human genetics "with highly detrimental consequences to ultimate public benefit"[2]. Others claim that skewed overprotection of subjects may also cause problems. One example is when warnings in the information are geared to genes that entail high risk of developing a disease,

[1] Ashcroft, 2000, McQueen, 1998, Pelias & Markward, 2001, Prime et al., 2000, Steinberg, 2001, Wendler, 2002, Williams, 2001
[2] Wadman, 2000

although these genes are relatively uncommon[3]. Such warnings may distract study participants from other important information and unnecessarily discourage participation in research studies. Additionally, informed consent procedures and withdrawals may lead to missing data and thereby jeopardize the quality of the research[4]. Swedish researchers have claimed that the new law is an expression of an exaggerated consideration for the donors. Especially, since they have the personal experience that most patients' are willing to contribute to research for the common good, even if they get exposed to personal risks. This is what the researchers believe, but what is the opinion of the potential sample donor, i.e. the general public and patients? Knowledge of potential sample donors' perceptions regarding the use of biobanks is invaluable in developing appropriate informed consent procedures for use in clinical practice and in research settings.

2. Empirical research on the views of the general public and patients regarding research on biobank material and informed consent procedures – an international perspective

2.1 The public's willingness to contribute to genetic research

Several studies indicate that the public's willingness to contribute to genetic research is relatively high. In an American study of prospective jury members, 60% would donate a tissue sample for genetic research[5]. Another American study showed that 42% of the public was in favor of blood donation and long term storage for genetic research[6]. These figures correspond to that found in a study of the public's willingness to participate in medical research in general, i.e. 46%[7]. Characteristics of those in favor of donation include higher education and a positive family history of a genetic disorder, a belief that genetic research will prevent disease and belief in genetic determinism[8]. A study by Malone et al, found higher assent rates for patients aged at least 65 years versus those younger[9]. It has also been found that the willingness to provide consent is greater when the sample has been collected in a research setting rather than clinical setting[10]. Individuals assessments of the risks and benefits of genetic research has been found to be unrelated to their stated willingness to donate[11]. Many persons appear to be willing to donate for research purposes, even though they gain nothing personal from it[12]. Participants have been found to be significantly less willing to participate in research that examine stereotypical or potentially stigmatizing traits, as opposed to research that examine medical or mental illnesses[13].

[3] Wilcox et al., 1999
[4] Wilcox et al., 1999
[5] Merz & Sankar, 1998
[6] Wang et al., 2001
[7] Trauth et al., 2000
[8] Wang et al., 2001
[9] Malone et al., 2002
[10] Schwartz et al., 2001
[11] Merz & Sankar, 1998
[12] *ibid*
[13] Schwartz et al., 2001

Swedish researchers have also found that peoples' readiness to contribute to genetic research is high, at least in the framework of a carefully conducted study that is well known to the population[14]. They reported actual data on the willingness to give consent for a new purpose. Of initial 1494 donors, 1409 (93%) were alive and possible to locate eleven years later. Of these 1409, 1345 (95%) responded to the letter seeking informed consent, and 1311 (93%) gave their informed consent. This means that 1311 of 1494 (88%) of the original tissue samples could be used. Stegmayr and Asplund concluded that it is feasible to obtain individual consent for genetic research a decade after blood was donated[15].

2.2 Does the public require informed consent?

Few studies have explored the donor's perceptions of informed consent procedures and the results are partially contradictory. Stegmayr and Asplund found that a large proportion of the respondents wanted to be contacted before every new research project in which their blood sample is intended to be used[16]. However, based on the views of 504 elderly respondents in another study, Wendler at al propose that consent is needed only the first time samples are used for research purposes, thereafter, identified samples could be used for further research without specific consent[17]. Most respondents thought that anonymous samples could be used for research irrespective of if informed consent had been previously obtained or not. Clayton et al[18] also conclude that informed consent is required for linkable samples but not anonymous samples, based on a consensus process involving scientists, ethicists, lawyers and consumers.

Preliminary findings from another study indicate that the lay public and medical professionals may have different attitudes towards the use of archived information and samples without specific informed consent[19]. This hypothesis, however, is derived from focus groups interviews, and requires validation through research using a larger sample. The public expressed several essential preconditions that had to be met if researchers were to have access to samples used for research, without obtaining specific informed consent of the subjects. These preconditions included the protection of a subject's privacy, maintaining confidentiality, and communicating the outcomes of studies to research subjects. Although physicians thought that some kind of prior permission from subjects was desirable, they pointed out the difficulties involved in obtaining individual informed consent in each case.

Schwartz found that written informed consent is preferred in genetic studies. For example, a survey of Jewish individuals about their attitudes regarding the practice of using stored DNA samples for genetic research, found that overall, most respondents reported that written informed consent should be required and that they would be willing to provide such consent. The participants were more likely to endorse the need for obtaining consent when the sample was collected in a clinical setting[20]. However, Wendler and Emanuel recommend a policy of not

[14] Stegmayr & Asplund, 2002
[15] *ibid*
[16] *ibid*
[17] Wendler & Emanuel, 2002
[18] Clayton et al., 1995
[19] Asai et al., 2002
[20] Schwartz et al., 2001

requiring consent to new research purposes, because most respondents thought consent to be unnecessary[21].

The above studies give raise to questions such as: Is it reasonable that every research subject is given an opportunity to decline to participate in any research project? Does every research subject consider this option as necessary in all contexts? Can there be exceptions to the call for informed consent? Sade raises the following questions: What is the justification for removing autonomous choice for the minority group? What size majority is needed to override research subjects' right to self-determination, that is, to deny their right to say yes or no to the use of their bodies, body parts, or personal information in research?[22]. He states that regardless if samples are identified or anonymized human samples or information, subjects can be and should be located and asked for their consent to protect the fundamental right of self-determination. Research subjects' reasons not to want their biological materials or information used in a study may be plausible or implausible, reasonable or unreasonable, in the view of the investigators. He means that only the subjects can weigh the severity of potential harms to themselves or to their communities, in terms of their own values, preferences, and concerns. Should Sade's principle be sustained no matter how great the value (as perceived by the investigator or a research ethics committee) of the new knowledge that might be obtained from such a study? Or should the common good be considered? An additional question is if there exist truly anonymized samples in genetic research? Every tissue sample, even the smallest fraction of them, can be used to obtain the individuals whole genetic profile.

2.3. Validity of the informed consent

In a study that followed up on donors, none of the patients contacted was aware that they had samples stored in a DNA bank, that genetic analyses had been undertaken or remembered that they had signed a consent (which indeed existed)[23]. Another study showed that only a minority of the donors recalled that samples might be used for future research and that the release of research records could affect their insurance status[24]. One reason might be that consent forms often are written at a higher reading level than is appropriate for the intended population[25].

This implies that the validity of a given consent is doubted. If the information is not understandable by the patients, it is questionable whether the decision-making is well informed. The findings also stress the importance of strategies to help subjects remember when forgetting important aspects of their research participation[26].

2.4. The donors whish for feedback of results

Questions concerning feedback of research information cannot be neglected, although cumbersome to carry out. Feedback of research results may be a motivating factor for some people. Mertz et al. found that 79% of the participants indicated a

[21] Wendler & Emanuel, 2002
[22] Sade, 2002
[23] Moutel et al., 2001
[24] Wendler et al., 2002
[25] Ogloff & Otto, 1991
[26] Wendler et al., 2002

desire to receive research results under a linked model[27]. However, Fuller et al mean that providing genetic information to subjects may entail significant risks and cause erroneous conclusions that could result in physical, psychosocial, or economic harms. If genetic research results are to be given to the subjects, the protocol must provide for counseling before and after the test. They conclude that if a policy mandating return of clinically meaningless data were implemented, associated costs and personnel might provide an obstacle to doing the study. Thus, in the absence of clinical validity there should not be an absolute requirement for data to be returned to subjects. For research in which data are not provided to subjects, the researcher should demonstrate absence of clinical validity, a research ethics committee should be required to review and approve the exception, and the informed consent document should state explicitly that the data will not be returned to the research subject[28].

2.5 Recommendations for obtaining adequate informed consent in genetic studies

Clayton et al have developed recommendations for obtaining adequate informed consent when gathering tissue samples that may be used for genetic studies[29]. Their recommendations were partially based on opinions elicited from the general public. They conclude that (1) informed consent is required for all genetic research using linkable samples unless conditions for limitation or waiver are met; (2) informed consent is not required for genetic research using anonymous samples but may be considered if identifiers are to be removed from currently linkable samples; (3) institutional review boards could usefully review all protocols that propose to use samples for genetic research; and (4) further work regarding these issues is warranted.

Recommendations as to how the consent form can be designed has been presented by Beskow et al. They have created an informed consent template for population-based studies using tissue samples[30] and provide detailed suggestions regarding the language to be used and what information to give prospective participants[31]. However, alongside the development of forms, there is a need to reform the informed consent and focus more on the process itself than the form, i.e. to ensure that participants really have given their voluntary informed consent[32].

3. The Swedish public's perceptions of research using biobanks and informed consent procedures – a pilot study

The aim of our study is to identify perceptions of the general public and patients regarding: (1) research involving storage and use of human tissues from which genetic materials may be derived and, (2) procedures of informed consent in relation to the use of material from biobanks

[27] Merz & Sankar, 1998
[28] Fuller et al., 1999
[29] Clayton et al., 1995
[30] Beskow et al., 2001
[31] *ibid*
[32] Annas, 2001

3.1 Methods

The data will be collected by means of a self-administrated questionnaire. The development of the questionnaire was a demanding process given the complexity of the topic. Stored tissue samples, genetic research, informed consent, and integrity are issues that the average citizen hardly relates to on a daily basis. Most people are likely to be unaware of several of these concepts or only have a vague perception of them. Even people with experience in this field find it difficult to take sides against or with different biobanking issues.

The content validity and the feasibility of the questionnaire was ensured by letting different experts (researchers, physicians, ethicists, and lay men) see if any important areas were missed, and suggest revision or deletion of irrelevant or unclear questions. This procedure was repeated after every revision of the questionnaire. We also carried out an extensive pilot study to allow evaluation of the questions, identification of misinterpretations and analysis of the distribution of answers. In the pilot study, we also evaluated the questionnaire itself by adding some questions at the end of the questionnaire, for example, whether the questions were difficult to understand or if they felt irrelevant. The local research ethics committee approved of the study and the questionnaire.

The pilot study consisted of a self-administered questionnaire sent to a random sample (n=500) of the general public in Sweden in May 2002. The background data included information that we hypothesised had an impact on the attitude towards genetic research and biobanking, e.g., age, gender, education, health status, and overall experiences of the health care system. The questionnaire also included questions on: genetic diseases in the family, whether the respondent had ever been a blood donor, attitudes towards genetic research and trust in different authorities capability to evaluate the risks and benefits of genetic research, attitudes towards genetic research, willingness to donate a blood sample for research, preferences for informed consent procedures, feed-back of research results and potential exceptions from the call for informed consent. A hypothetical question was constructed to ask about the respondents' willingness to donate a blood sample for research purposes.

All data were coded and analysed with the SPSS software program. Below we present some preliminary results from the pilot questionnaire.

3.2 Preliminary results from the pilot study

3.2.1 Response rate and representativeness

The response rate was 30% (n=154) with no reminders. A similar study, carried out in the northern part of Sweden during the spring of 2002, had a response rate of 59.6% after three reminders[33]. Compared to the general public, women and respondents over 45 years of age were slightly over-represented among the respondents. However, the level of education among the respondents reflected that of the general Swedish population.

3.2.2 Evaluation of the questionnaire itself

A majority of the respondents thought that it was important to have a say in these matters (79%), i.e. that they appreciate that the public is listened to by inviting

[33] Klaus Høyer, PhD-student, Umeå University, Sweden, e-mail, January 24, 2003.

them to surveys. A majority thought that the questions were easy to understand (95%) and that the number of questions was about right (82%). Most of the respondents also felt that the questions were relevant to them (87%). This is surprising given the complexity of the topic. However, it is important to keep in mind that 70% of the respondents chose not to respond, and that one reason might be that the questionnaire was too difficult, long and irrelevant to them.

3.2.3. Perceptions of genetic research

A minority of the respondents (23%) were aware of that some of their tissue samples may be stored. A majority of the respondents had a positive attitude towards genetic research concerning mapping of the genome (78%), assessing risk for disease (89%), diagnostics (92%) and treatments (94%). In the open-ended questions several respondents noted that they where pro medical genetic research, as long as it did not involve any "Frankenstein" tendencies, such as attempts to create the perfect human being. When asked about their trust in different authorities capability to evaluate the risks and benefits of genetic research, university-based researchers (80%) ranked highest while local health care politicians (27%) were found at the bottom.

3.2.4 Willingness to contribute to genetic research

A majority of the respondents (89%) would consent to donate an extra blood sample for research purposes. Of these, a majority (68%) approved of their sample being used for genetic research. The most common motive was for the benefit of future patients. Some 16% of those who consented to give an extra blood sample said that their decision would be influenced by the financial source of the research. However, the majority (66%), were indifferent of the financial source and delegated the decision to the research ethics committee.

3.2.5 Requirement for informed consent

Women and those in higher ages were significantly more likely to want to be asked for their consent if their sample was to be used in research. However, almost half (46%) of the respondents expressed no need to be asked for informed consent in relation to new projects, if the research ethics committee had approved of the project. Another 18% wanted to be asked for informed consent if the purpose is entirely different from the original purpose. They also wanted oral or written information. Yet another 18% called for the strictest informed consent procedure. They wanted to be asked for informed consent for all new projects, and to be valid, the consent has to be signed by the donor. They also wanted oral or written information about the project.

If asked for informed consent in relation to every new project a majority of the respondents would feel respected (68%), some 25% would think that it is a waste of resources that should be invested in research, about 8 percent would feel indifferent about being asked, and 9 percent would feel that they got unnecessary information. Only 6 percent would be reminded about illness and worried about their health

About half (52%) of the respondents' thought that samples from deceased donors might be used if the research ethics committee approves. However, 37 percent thought that relatives have to make the decision.

Many (53%) of the respondents think that there are situations when the research ethics committee can approve of research using stored samples without obtaining informed consent from the donor or relatives. Exceptions to the call for informed consent was due if prior consent has been given (46%), if it is an old sample that has been given in relation to care/treatment (34%) or if the research ethics committee thinks that asking for consent will worry the donor (29%) or if the donor is dead and relatives have to be asked (20%). Hardly anybody (<1%) thought that reduced research quality due to missing data or increased costs for follow-up would legitimate exception from informed consent

3.2.6 Relative importance of information

The most important information to be given when asked to donate a sample was if care and treatment will be affected by the research results (86%), while the right to withdraw the consent and get the sample destroyed was found to be the relatively least important information (62%).

Some 39 percent would like to get feedback of research results and to get information about their risk for hereditary diseases. Another 44 percent wanted to have this information only if the disease was preventable or possible to treat. Only some 6 percent would prefer not to get informed at all. Half of the respondents wanted to decide themselves whether their relatives should be informed about that the respondent carries a risk for a hereditary disease. About 30% preferred that the health care personnel should make this decision

3.2.7 Conclusion

This pilot study has revealed some tentative findings, apart from serving the purpose of further validating the questionnaire for the full-scale studies. These preliminary results indicate, that the general public seems to support the use of stored samples. The trust in researchers, and most other authorities, is high and the respondents are relatively prone to delegate decisions about the use of their samples to the research ethics committee. However, due to the low response rate it is impossible to generalize our results, the risk for selection bias is apparent. Consequently, results from the full-scale studies will be needed to confirm these results. The two full-scale studies will also provide enough statistical power, to allow for multivariate regression analyses to identify factors that influence, for example, the willingness to donate a sample and the preference for different consent procedures.

3.3 The full-scale studies of the Swedish public and diabetic patients

Both full-scale studies employ the modified version of the self-administered questionnaire used in the pilot study. It was sent to a random sample (n=6000) of the general public in Sweden in late October 2002. The response rate has reached 50% after two reminders (the first reminder with a letter only, and the second with a new questionnaire and envelope), and will hopefully increase further after the third and last reminder (letter only) that was sent in mid January 2003. Analysis will be conducted during the spring 2003. In parallel, a second full-scale study is running in which the same questionnaire is used to identify diabetic patients perceptions. In this study, diabetic patients visiting the diabetic clinic at a major hospital in Sweden are consecutively approached until a satisfying number of patients have accepted to participate. The analysis of these data will be carried out during the fall of 2003. The

results from both full-scale studies will be published in peer-reviewed international scientific journals.

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Intellectual property and biobanks

Åsa Hellstadius, LLM, Sanna Wolk, LLM & Richard Wessman, LLD

Department of Law, Stockholm University

The exploitation of biobanks creates interactions between various legal disciplines. The rights to information, consent and withdrawal, established by the recent Swedish legislation on biobanks and granted to protect the patient's or donor's integrity when supplying the biobank with material, are contrasted with the rights of the proprietor or user of a biobank. The latter include intellectual property rights acquired as a result of biobank-related research and development and possible commercialisation. Such proprietary rights are clearly needed in order to create incentives for companies to invest in research, but their application may collide with other types of rights and interests. In the intellectual property context, biobanks are regarded as protectable compilations, i.e. databases. Hence, biobanks may be protected by intellectual property in the form of copyright or sui generis protection. The extent and the practical effects of protection of biobanks are of importance to proprietors and users of biobanks, researchers, patients and others, since the rights holder may prevent certain acts with the samples contained in the biobank. The ownership of intellectual property in biobanks and related materials resulting from scientific research is therefore of special interest. The intellectual property rights of researchers employed at Swedish universities are governed by the so-called teacher exception. This specific system concerns academic research, and is a both statutory and a traditional system giving university teachers ownership title to their patentable copyrightable works. It is therefore recommended that the intellectual property rights be properly regulated by contracts, just as any other right to the material (i.e. right to disposition, use etc.) in a biobank needs to be regulated.

1. Introduction

As a result of biotechnological developments, collections of biotechnological material are of obviously growing value and importance for research and development purposes. In particular against the backdrop of the swift biotechnological development, biobanks must be considered as important and valuable assets. In such a perspective, questions of ownership, rights in and control of the material as such are of sudden and crucial interest.

The system of intellectual property law offers certain possibilities for creators of biobanks to enjoy an exclusive right to the structure of the bank, as well as protection against extractions or re-utilisation of the data. In the event of commercialisation of biobanks and their content either as data or as collections of data (databases), the importance of trademark or trade name protection should not be forgotten as another examples of valuable exclusive rights. Where the rights

holder is an employee of a commercial company, it depends on the employment contract whether the exclusive rights in a biobank structure or the collection are transferred to the employer. In principle, however, this is not the case when the creator of a biobank structure is active as a university teacher, as special rules by law and tradition apply in the university environment. In both cases problems may occur that demand consideration of the situation aimed for, and contractual regulation is often of vital importance to prevent legal problems or disagreements occurring later on.

Although intellectual property rights in the light of recent years' technological developments have been intensely debated in many forums, nationally and internationally, intellectual property questions in relation to biobanks have as yet been little discussed. The following summary of some new studies on biobanks and intellectual property aims to fill that gap. It is obvious that the existence of exclusive rights in biobank structures, or rights to forbid extraction from or re-utilisation of the collection in a biobank, or to hold a biobank trademark or trade name to an exclusive basis always restricts the access of other parties to the protected objects. This is why intellectual property rights are sometimes questioned and can never be regarded in isolation, i.e. without also taking due account of competition structures and the balancing of rights. The system as such exists to promote socially beneficial developments of various kinds and to inspire competition.

To understand the full effects of intellectual property rights as just mentioned in this specific biobank context, a little more explanation of the system as such is needed. To start with, intellectual property is the part of the legal universe that regulates the protection of art and literature, science and technology, industrial designs, trademarks and other distinctive signs and related subjects. But all these objects have to be taken in a broad sense today. Literary should be understood as merely "descriptive" and what modern art stands for is much more than the classical works; a visit to any modern art exhibition will make this clear. A trademark is not only a word or a pictorial label, it may even consist of a smell.

The notion of Intellectual Property is thus fairly expressive of what it is all about. The legal protection given resembles proprietary rights to tangible objects in many respects, but concerns non-tangible matters, works of the mind. An intellectual property right is not a right to a physical object, but rather an abstract phenomenon of the mind. However, the right must be manifested in physical objects which function as carriers of the intellectual product. For instance, a literary work or an invention can be observed in its concrete form, but the object of protection is the work as such. The intellectual property system confers, for example, on the author a copyright, on the inventor a patent right or on the trader a trademark right, etc., which is a type of monopoly. The exclusive right can be transferred as a whole or partly (under licence) to others in a similar way to other objects of ownership.

Even if legislation is national or today to a certain extent regional within Europe, as for example with trademark and design rights existing on a national as well as a regional basis, protection can transcend national borders, thanks to a system of international conventions. Due to the special character of intellectual property, effective international agreements and systems of protection are particularly important, and thanks to harmonisation at both European and global level, such

rights can to a large extent be enjoyed in a similar way from country to country. The object, subject, scope and duration of protection differ according to the various rights, and to a certain extent at least the scope of protection may differ from country to country. This is especially true outside Europe.

Intellectual Property Law has traditionally been closely connected with technical developments, and normally, where there is a new technology, rapid adaptation of the intellectual property system takes place, in addition to new types of rights being developed. This is not least the case where considerable investments are involved. Intellectual property law in our days has moved towards a system for protection of investments. Nevertheless, when introducing intellectual property rights in novel environments and surroundings, new situations and problems may arise. One such example is the introduction in society of information technology, digitalisation and the Internet, where intellectual property rights have had to be adapted to work in new settings. The existence of such rights in biotechnology and gene technology research is natural and a consequence of the traditional mutual dependence of the intellectual property system and scientific and societal development.

2. The biobank, the market and the law

There are many new and interesting legal questions concerning the use and exploitation of biobanks. Different types of rights exist in and around the collections of human biological material. Some of these may merely seem to conflict with each other, other actually do so. But basically, the rights exist on different levels; for instance, the rights of the patient or donor to be informed of the preservation of the sample and to consent to its preservation, the rights of proprietors or the users of a biobank to make use of the samples, the copyright protection of the biobank as such, and the patenting of inventions resulting from use of samples in research.

The legal demarcations which sooner or later have to be made between the rights of different persons (in particular between, on one hand, the donors of human material and, on the other, the owners or users of biobanks) are at the present time far from clear or precise. In this particular context, it is important to define clearly the right of the patient or donor to be informed of the preservation of the sample, to consent to this preservation and to withdraw a consent previously given.[1] The establishment of such rights may not only affect the collection and use of samples in biobanks, but also the possibility to assign or transfer a biobank to another party,[2] and the possibility of patenting inventions which are derived from the use of biobanks.[3] Furthermore, questions regarding the rights of the proprietors or the users of the biobanks are of great importance. The commercially important possibility of deriving valuable intellectual property rights from the use of biobanks has to be considered. In this context not only patent law, but also copyright law and trademark law, are important.

[1] Chap. 3, Sections 1 and 6 of *Lag (2002:297) om biobanker I hälso- och sjukvården m.m.*
[2] *Ibid*, Chap. 4, Section 7.
[3] Beyleveld 2000, p. 1 and Sterckx 1998 p. 123.

The use of biobanks in research and development may result in inventions that are patentable.[4] In the fields of biotechnology and genetic engineering, the possibility of acquiring an exclusive right through the rules of patent law serves as an important incentive for investment in research. The systematic approach taken by the biobank proprietor in the compilation and administration of the biobank may often be eligible for protection under copyright law, or come under special protection for compilations.[5]

Furthermore, the proprietor may attempt to secure the goodwill or reputation of the biobank by registering its name as a trademark. The trademark may serve to guarantee the biobank's reliability and quality.

The trade name or trademark of the biobank may be protected in various ways. If it becomes well known in the relevant public sector or in the particular field of trade, it may be protected under the Swedish Trademarks Act, regardless of registration. It must at present be considered unclear whether the mark has to be well known among researchers and medical practitioners in the field of biobank research or among the patients or donors supplying the biobank with material.

Nevertheless, due especially to the burden of proof in a potential infringement proceeding, registration is to be preferred under normal conditions. In order to acquire a trademark right in Sweden by way of registration, one may register the trademark on either a national basis[6] or a European basis[7]. In the latter case, the trademark is protected in the European Union in its entirety. The registration of the trade name in accordance with the Swedish Trade Names Act will protect the trade name from being used by others as a trade name or trademark in Sweden.

The aim of strengthening the goodwill of the proprietor of the biobank, represented by its trade name or trademark, may in itself – regardless of legal obligations – be a sufficient incentive to improve ethical aspects. Ethical questions are no doubt important in the field concerned. Only if a biobank collects and handles its material in an ethically proper way, will it be viewed in a positive light by researchers and donors. The reflection of the ethical standards in the trade name or trademark will serve as an economic incentive for investments in information and quality control.

In this context, with a view to the commercial exploitation of biobanks, an important distinction must be made between, on the one hand, biobanks created within the frame of public health and medical services, and on the other, those created by private companies, e.g. biobanks owned by pharmaceutical companies. The Swedish Biobanks Act applies only to biobanks within the sector of public health and medical services,[8] and legislation prohibiting the exploitation of a biobank for commercial gain, or preventing the assignment of a biobank to another party, may affect the value of a biobank to its proprietor or user.

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[4] Markl 2002, p. 1, Holzapfel/Schneider 2001, p. 860, Ng-Loy Wee Loon 2002, p. 393 and Sena 1999, p. 731.

[5] *See* Section 3 "Exclusive rights to Biobanks".

[6] The application should be made to the Patent and Registration Office (PRV) in Söderhamn.

[7] The application is made to Office for Harmonization of the Internal Market in Alicante or via the PRV in return for an additional charge.

[8] Chap. 1, Section 3.

A dividing line may be drawn between the rights of the person supplying the biobank with its material, e.g. a patient or a donor, and the rights of the person who is the proprietor of the biobank or is using it for research and development. While the proprietor of the biobank may acquire exclusive rights to the bank as such or its name or develop patentable products, there is no sharing of benefits with the patient or donor. With this dividing line in mind and with an eye to potential conflicts of interest between the persons situated on different sides of the line one may, on the one hand, consider the integrity of the patient or donor and the right a person has over his own body and material collected from it, and on the other, take into account the need to support and encourage research and development, by the use of biobanks, in the fields of biotechnology and genetic engineering.

The conflict just mentioned is, however, at least to some extent illusory. The patient or donor, in other words the person who supplies material, e.g. a blood sample, to the biobank, is not only a "supplier" in the market in question. He is at the same time a "consumer" of the end product, e.g. a pharmaceutical, resulting from biotechnological research made possible by the use of a biobank. One may in this sense speak of a dual role. The patient or donor may be seen not only as a producer of raw material for a particular biobank, but also as a potential consumer of products stemming from the research made possible by the biobank in question. When determining whether or not the legislation is efficient one cannot avoid taking this "dual role" into account. In doing so, it has to be considered that an overprotective view of the patient/donor, resulting in an unbalanced emphasis on rights of information, consent and withdrawal, may on the whole lead to negative effects, not only for the proprietors or users of biobanks but also for the patients/donors themselves, in their capacity as consumers of pharmaceuticals and other products resulting from biobank-related research and development.

Firstly, such overprotection may weaken the incentives to invest in biobank-related research and development. The need to inform and acquire consent, in addition to the risk of a later withdrawal of a consent already given, may lead not only to a rise in development costs but also to insecurity as to the present and future capacity and value of a particular biobank. When deciding whether or not to invest in a biobank, the investor must consider the costs of informing and acquiring consent and furthermore the insecurity related to the risk of future withdrawals of consent.

Secondly, excessive protection of the patient/donor may increase transaction costs. In order to inform and obtain consent, the proprietor of a biobank has to take certain measures, e.g. information pamphlets supplied to the patient/donor, special information activities among the staff and forms securing consent. The cost of administrative measures, in economic terms – transaction costs – may be so significant as to prevent transactions which in themselves would have been efficient.

The Biobanks Act ought to be viewed against the backdrop of the above argument concerning the dual role of the patient/donor. It requires the proprietor of the biobank to inform the patients/donors and obtain their consent, but the closer interpretation of these requirements, is, at least to a certain extent, left for the courts or certain expert committees[9] to decide. Clearly, the requirements cannot be construed in an overly strict manner, since this would lessen the incentives to invest in biobanks and increase the transaction costs involved in creating them.

[9] Chap. 1 Section 2 and Chap. 2 Section 3 of the Biobanks Act.

When a biobank is created outside the area of public health and care service, e.g. a private biobank owned and administered by a pharmaceutical company, the Biobanks Act is not applicable. But there is still a requirement of consent, in the sense that the proprietor of the private biobank must obtain the consent of those who supply the biobank with samples. Normally, this will be administered by way of special agreements through which consent is secured. Under certain conditions, e.g. when a company uses samples from employees in its own biobank, the difficult demarcation of the requirements of information and consent, mentioned above, may still have to be made.

Even if it follows from the Biobanks Act that a patient/donor may withdraw consent already given, it is not clear whether a right of withdrawal exists in relation to privately owned biobanks outside the area of health and medical services. Normally, this must be taken to hinge on the interpretation of the agreement between the patient/donor and the proprietor of the biobank. Undoubtedly, this represents an important difference between the regulation of biobanks within public health and medical services and biobanks created privately, for example by pharmaceutical companies. Such a difference may be justified by differences in the way in which material is collected.

3. Exclusive rights to biobanks

The creator/producer of a biobank has often invested time and money in its creation, and therefore wishes intellectual property protection of the results. What he has achieved in the intellectual property sense is probably a "database". Since a biobank may constitute a database, the principles for the protection of databases under intellectual property law are examined regarding their application in the domain of biobanks.

The intellectual property rights of interest for a database producer are copyright and/or *sui generis*[10] protection. Generally, two types of protection are conceivable:

- The database is protected independently by **copyright**, on account of the **structure** of the database, which is protected as an original work under Section 1 of the Copyright Act.
- The database is protected by the so-called ***sui generis* right** under Section 49 of the Copyright Act, on account of the **investment** involved in the creation of the database.[11]

A combination of these rights is possible, depending on originality and the investments made in the compilation and the structure of the material. It should be noted that also, the registers appurtenant to the biobanks, with information of the samples, might fulfil the requirements for copyright or *sui generis* protection.

[10] Literally, "of its own kind".
[11] Section 49 of *Lag (1960:729) om upphovsrätt till litterära och konstnärliga verk*.

Where a biobank is protected, the creator/producer of a biobank is protected against unauthorised use of the protected object (i.e. the bank). Questions arise as to what constitutes infringement of the right. Can the use of samples in the biobank infringe such a right, e.g. the release of samples for research purposes? The answer depends on which type of right protects the material. If the bank is eligible for copyright, the arrangement of material will be protected against copying, public distribution or display. If on the other hand it is merely something that corresponds to the requirements of a *sui generis right*, the protection prevents against the extraction and/or re-utilisation of the whole or a substantial part of a compilation's contents, but not more.

3.1 Biobanks as "Databases"

The legal definition of a "biobank" is "*biological material from one or several humans that is collected and stored […]*".[12] According to the Biobanks Act, the material need not be stored in a certain structure. However, the samples must be contained without risk of destruction. Furthermore, unauthorised persons must be prevented from accessing the material. The same goes for the appurtenant registers. Consequently, the arrangement of samples in a certain order is a prerequisite for the functionality and the fulfilment of the legal requirements of a biobank.

The legal conception of a "database" refers to the storage of information – usually electronic – in a memory. However, the word "data" is by no means limited to computerised storage of information. The notion of "data" only refers to information contained. This view is reflected in the EC Directive's definition of a database:

> *"'Database' shall mean a compilation of independent works, data or other materials arranged in a systematic or methodical way and individually accessible by electronic means."*[13]

According to the legal definition, a database is a compilation of independent data with individually accessible elements. So it need not be electronic. The intellectual property protection of databases covers every compilation of material stored by any means. The user of a base must be able to find relevant information by using individual search criteria, and should not have to search through the whole collection of information to find the information he or she wants.[14]

Protection is not dependent on the size of the base. Even a small collection of material is a database qualifying for protection under Swedish law. With regard to biobanks, a bank with a limited number of samples is just as eligible for protection as a bank containing thousands of items. As a general rule, biological material stored in a certain structure is a database, with due regard for the structuring of the material, and the means of searching the compilation.

In order to enjoy copyright protection a database must fulfil the criteria of "originality" and "individuality" to be a "work" within the meaning of copyright law.

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[12] Chap. 1, Section 2 of *Lag (2002:297) om biobanker i hälso- och sjukvården m.m.* (the Biobanks Act), *Regeringens proposition 2001/02:44, Biobanker i hälso- och sjukvården m.m.* (Government Bill 2001/02:44) p. 21.
[13] Art. 1(2), Directive 96/9/EC.
[14] Andersen 2001, p. 403 et seq.

The protection afforded under the *sui generis* right differs in some respects from protection under copyright. A database protected under the *sui generis* right does not possess the necessary degree of originality for copyright protection.

The delimitation between the two kinds of protection depends on an evaluation of the work laid down in the database of interest. Copyright protects intellectual creativity in the selection or arrangement of the contents of a database, while the *sui generis* right protects investments in the obtaining, verification or presentation of a database's content. The rights function either separately or combined.[15]

3.2 Copyright

Copyright, as the term suggest, is a right to prevent others from copying a literary or artistic work. The protection under copyright law of collections of biological material can be seen as an extension of the objects traditionally protected. Copyright originated in the eighteenth century, with authors and artists seeking protection for their literary and artistic works. But over the following centuries new needs have been felt, and modern copyright has developed towards a broad right for a variety of individual expressions that are sometimes quite commonplace. Today copyright in literary and artistic works should be taken in a very broad sense. The development of new technologies, not least, has profoundly affected the legal framework. Of course, traditional works like novels, musical compositions and paintings are still covered, but so too are various modern and technologically related phenomena such as computer programs, and databases.

As a result of this development, copyright has come to play an important role in today's society, as intellectual property protection of technical equipment and products is crucial. The protection of databases, not least, is important from an economic perspective. European as well as national legislation has therefore been enacted in this domain. Swedish legislation on the protection of databases is harmonised with that of the other EC countries under Directive 96/9/EC, the Database Directive.

Copyright protection is regulated in the Copyright Act of 1960.[16] This right is cheap to administer and easy to access. Copyright requires no formal registration. On the contrary, formal requirements for copyright protection are precluded by international law. The right arises as soon as a work is created. Copyright protects, not ideas but the form in which an idea is expressed. The ideas need not be new but the form – be it literary or artistic – must be an original creation, e.g. not a copy of somebody else's work. Thus, the basic criterion for protection is originality. Protection depends neither on the quality of the work nor on the purpose of its creation. But a qualified originality, in the sense of the work differing from what was previously known or what could be expected, will earn such a work more extensive scope of protection.

One prerequisite of copyright protection is that the author's work originates from him personally. It must have its origin in the author's labour, and must be the result of a personal intellectual creation. There is no novelty requirement, it suffices that the work emanates from the author and is new to him or her. Thus, the subjective state of the individual author is decisive. This means – at least in theory –

[15] Koktvedgaard/Levin 2000, p. 93.
[16] *Lag (1960:729) om upphovsrätt till litterära och konstnärliga verk* (the Copyright Act).

that two persons who create two identical works independently are both entitled to copyright protection, i.e. protection against copying. In real life, works are rarely identical, but they may be similar. This is true not least of works that are more functional in character, e.g. biobanks and other databases.

Whereas a legal person may acquire copyright by the transfer of rights from a natural person, it is always the author or creator of a work, the natural person, who is also the initial owner of the copyright in the work.[17] Nor may machines be holders of copyright.[18] If a work is created by a group of persons jointly, the exclusive rights shall be owned jointly.[19] In addition to traditional copyright protection, it is also possible to protect certain kind of objects under what are called neighbouring rights.[20] The *sui generis* right already mentioned is just such a neighbouring right under which databases and other compilations may be protected.

As mentioned earlier, the copyright protection conferred concerns the database's structural elements, i.e. the inherent organisation of the samples in a biobank. Similarly, an encyclopaedia may be protected as such for the choice and structure of its content, whereas a biobank is protected for the selection and arrangement of samples. A biobank is protected even though its content (the samples) consists of non-protected material. The biological samples can never qualify as "works" within the meaning of copyright law, and are not protected as such under copyright. Consequently, the protection relates only to the (original) structure of the biobank, not its contents.

For protection of a biobank, its samples should be selected and arranged according to a certain method of structure. The organisational structure needs to be original and creative. In addition, it must be the author's own intellectual creation, with regard to the selection and disposition of the material. A biobank with too simple a way of organising the samples, without any individual principle of selection or arrangement of the material, will not enjoy copyright protection.[21]

The rights bestowed by law on the owner of copyright in a protected work are exclusive rights to use the protected work, or authorise others to use it. Copyright may be separated into two parts: "economic rights", and "moral rights".[22]

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[17] Section 1 of *Lag (1960:729) om upphovsrätt till litterära och konstnärliga verk*. The legal right may be transferred through contracts. There are also rules governing the employer's right to the works or inventions of employees, *see ibid* Section 40(a). *See further* Wolk, section 4.

[18] Lindberg/Westman 2001, p. 247.

[19] Section 6 of *Lag (1960:729) om upphovsrätt till litterära och konstnärliga verk*.

[20] The neighbouring rights protect *inter alia* the rights of producers and performers and non-artistic photographs.

[21] *See Regeringens proposition 1996:111, Rättsligt skydd för databaser m.m.* (Government Bill 1996/97:111) p. 28. *See also* Art. 2(5) of the Berne Convention, Art. 10(2) of the TRIPS Agreement, and Art. 5 of the WIPO Copyright Treaty.

[22] The "moral rights" are independent of the economic rights and cannot be transferred. The moral rights consist firstly in an author's right to be named, when the work is being reproduced or made available to the public. Secondly, the author has a right to object to the work being used in a way that would be prejudicial to the author's reputation.
The moral rights are found in Section 3 of *Lag (1960:729) om upphovsrätt till litterära och konstnärliga verk*. An exception to the principle of non-transfer of moral rights is when a computer program is created by an employee in the execution of his duties or on the instructions of his employer, the latter shall be entitled, unless otherwise provided by a contract, to exclusively exercise all economic rights in the program so created. (Section 40(a) of *Lag (1960:729) om upphovsrätt till litterära och konstnärliga verk*).

The economic rights are limited to reproduction of the work and making the work available to the public. These rights are covered in the following acts:

- the making of copies of the work,
- the distribution of copies to the public,
- the public performance of a work,
- the public display of a work.[23]

A copy is perceived as each medium in which the work is fixated, no matter by what technique. The fixation of a work must be independent from the original work. Copies and other reproductions of the work are regarded as samples of the original work, even if they are not identical with the original. Total identity is not required. The scope of protection for a protected work corresponds to its originality. If the work is highly original, the scope of protection will accordingly be assessed quite broadly, and vice versa. The possibilities of creative variation are limited in certain contexts, due to the materials, functions etc. of the work. For instance, the options for structuring a biobank are generally quite limited, and consequently the scope of protection for biobanks will be quite narrow.

The scope of copyright protection includes not only the making of identical copies of a work, but also the work in an altered form, in translation, adaptation, arrangement and any other alteration, in another literary or artistic form or by other technical means. For infringement to be established, the probability must be shown of the infringing work being derived (copied) from the protected work. Assessment of the scope of protection is based on the delimitation between adaptations of the work, which are comprised in the scope of protection, and other freely connected works, which fall outside the copyright protected domain.[24] If the structural elements of a biobank are copyright protected, copying of the structure is not allowed. Copyright infringement may occur even if only a part of the structure is copied, provided that the part contains the original, protected structure.

The second part of the economic rights conferred by copyright consists in making the work available to the public. A work is made available in three ways: by the distribution of copies to the public, by the public performance of a work, and by the public display of a work.

The public performance of a work is of importance to makers of music, films and plays. It consists of the right to play, read or transmit the work to the public, but could in this context be relevant to screen displays to an unknown audience. The distribution right is a right to distribute a work through sale, rental or lending. The public display of a work is a right to show the original work, or a copy of it, in public.

Only acts taking place within the public sphere are protected under copyright. The work may be displayed within the private sphere, or within a limited circle of persons, without authorisation from the rights holder. A prerequisite is that the circle of persons should consist of a limited unit with a concrete, individual

[23] Section 2 of *Lag (1960:729) om upphovsrätt till litterära och konstnärliga verk*. *See* also Arts. 2-4 of Directive *2001/29/EC of the European Parliament and of the Council of 22 May 2001 on the harmonisation of certain aspects of copyright and related rights in the information society*.
[24] *See* Koktvedgaard/Levin 2000, p. 143 et seq.

connection between its members, e.g. a company's employees, students at a school, delegates at a conference or members of an association.

Copyright is limited by a number of exceptions. It is not eternal, but is today fairly long-lasting, and probably much longer than needed for most of the works protected: 70 years from the author's death year. Other exceptions are copying for private use and exhaustion of the right by the marketing of a product with the consent of the copyright holder.[25] One important caveat in this context, however, is that a digital database may not be copied to a digital format, even privately.[26]

3.3 *Sui generis* protection of biobanks

As mentioned earlier, the right *sui generis* exists irrespective of possible copyright (or other) protection of a database. As has also been mentioned, the Database directive has been transposed to Swedish Law by amendments to the Copyright Act. The sui generis right is found in Section 49, and the Directive is an important source for interpretation of the rules. The protected compilations are not "works" in the meaning of the Copyright Act. The *sui generis* right provided under the Directive protects not only the compilation of material but also the data contents of the base. Thus, the different parts of the database are protected as well as the whole database as such.

In this context, the decisive criterion for protection is the presence of a (qualitatively and/or quantitatively) substantial investment in the obtaining, verification or presentation of the contents of a compilation. The conception of "substantial investment" is defined neither in the Copyright Act nor in the Database Directive. When assessing the criterion of substantial investment, economic as well as other investments are evaluated.[27] The deployment of financial resources and/or the expenditure of time, effort and energy in the making of the biobank/database are seen as investments in the terms of the Directive.[28]

The *sui generis* right protects the maker of a biobank/database from extraction and/or re-utilisation of the whole or a substantial part of its contents. The term "extraction" means the permanent or temporary transfer of all or a substantial part of the contents of a compilation to another medium by any means or in any form. "Re-utilisation" means any form of making available to the public all or a substantial part of the contents of a database by the distribution of copies, by renting, by on-line or other forms of transmission.[29] Thus the difference between "extraction" and "re-utilisation" is that the former refers to the right to make copies of the database while the latter concerns the right of making it available to the public.

Apart from "substantial" being used as a criterion for protection, the concept is also of pivotal importance for assessing infringement of the right. Only the use of substantial parts of a compilation is regarded as an infringement. It has

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[25] The limitations are contained in Chap. 2 of *Lag (1960:729) om upphovsrätt till litterära och konstnärliga verk*. *See* Koktvedgaard/Levin 2000, p. 112 et seq.
[26] Section 12 para 2 no. 3 of *Lag (1960:729) om upphovsrätt till litterära och konstnärliga verk*.
[27] *Regeringens proposition 1996/97:111, Rättsligt skydd för databaser m.m.* (Government Bill 1996/97:111) p. 55.
[28] Recital 48 of Directive *96/9/EC*.
[29] Art. 7(2) of Directive *96/9/EC*.

been proposed in the legal literature that the term "substantial" with regard to the interpretation of "extraction" and "re-utilisation" could mean the use of more than 50 % of the compilation. However, an interpretation of the terms by a competent court, such as the European Court of Justice, is needed to establish the exact content of the term "substantial".

The rights holder is the "maker" or "producer" of a database.[30] The maker of a database is the person who takes the initiative and the risk of investing. Subcontractors, however, are specifically excluded from the definition of maker. The producer could be a physical as well as a juridical person (for instance a company). The compilation need not be the result of a creative, intellectual effort. Instead the work laid down is protected.

Protection under *sui generis* right of databases may be summarised as follows:

- the *sui generis* right applies to all compilations, whatever their form, provided they are compilations of independent works, data or other materials arranged in systematic or methodical way and individually accessible by electronic or other means;
- it protects only compilations where there has been a substantial investment in either the obtaining, verification or presentation of the contents of the database;
- it protects against unauthorised extraction and/or re-utilisation of the whole or of a substantial part of the compilation; and
- it is available only for compilations whose makers or rights holders are EEA (European Economic Area) nationals or corporations.[31]

The term of *sui generis* protection is fifteen years from the date of completion of the making of the compilation. A substantial change of the contents of the database qualifies the resulting database for its own term of protection. In practice, the term of protection can thus be prolonged quite easy by substantial new investments. But the limitation with regard to digital copying also applies to non-copyrightable compilations of data .

3.4 Practical implications

If a biobank is protected under either copyright or *sui generis* protection – or under both rights in combination – certain acts constitute infringement. The holder of the rights may prevent those acts. Considering that conflicting interests may exist regarding a biobank, the existence and exercise of intellectual property rights is certainly important.

A biobank is copyright protected if its structure fulfils the criteria of selection and originality needed for copyright. The structure could be visualised in the form of a so-called mind-map. If the biological samples are structured in accordance to a certain system and with a selection of samples, copyright protection may apply. However, the compilation of samples must not be too simple or of a routine nature. Registers containing personal data are also eligible for copyright protection according to the same criteria, but structuring in chronological or consecutive order may not be detailed enough for protection. Differing levels of

[30] Art. 8 of Directive *96/9/EC*.
[31] Art. 11 of Directive *96/9/EC*.

samples, or a certain scheme for identification of sample numbers, make the structure more advanced and should enhance its eligibility for protection. Due regard must, of course, be had to the practical possibilities of numbering and marking the samples.

The Biobanks Act contains standards for the labelling of samples in a biobank. The material must always be traceable back to a certain individual. However, the samples released for research must be coded.[32] A coding system for the biobank and its registers is therefore needed to fulfil the integrity demands in the Biobanks Act. Such a coding system may also qualify for copyright or *sui generis* protection.

Copies of the work can only be made if the structure of the biobank is copied and used, for instance in the making of another biobank. The issuing of samples from a biobank is not an act of copying. Instead, their release may constitute acts of making the protected work available to the public, which is also reserved for the copyright holder.

For an issuing of samples to be regarded as an act of making the protected structure available to the public, a copy of the protected work needs to be either distributed or displayed. The release of samples generally concerns only parts of the whole biobank. However, it is not necessary for the protection to apply that the whole work is distributed or displayed. As stated above, it is the structure that is protected under copyright. It is sufficient for only a part of the biobank to be used, if that part contains the protected structure. Thus, if the samples released from a biobank suffice to form the protected structure, the release of the former may constitute distribution of the latter. In such cases the rights holder's permission must be obtained before the release.

Public – as opposed to private – display of the work is conceivable if the protected structure is made available for observation by the public. The work – the protected structure – need not be in original form. A photograph showing the structure of the biobank may be enough. If the public has access to the biobank, so that the protected structure is available for everyone to see, then the bank is displayed to the public, and the act requires the rights holder's permission. However, it could be difficult for the public to assimilate the protected structure just by visiting the biobank as such. It is more a matter of showing the structure in the form of mind-maps and the like.

For protection according to the right *sui generis* a substantial investment – economic or by other means – is required. The collection of material and data for most biobanks may be enough to qualify them for the *sui generis* protection.

The use of samples in a *sui generis* protected biobank could be seen as either extraction or re-utilisation of the bank. The assessment of infringement is based on whether the part extracted is substantial or not. However, the number of samples issued in most biobanks may not be large enough to satisfy the criterion of "substantial part". A complementary protection is found in the Database Directive. The repeated and systematic extraction and/or re-utilisation of insubstantial parts of the contents of the database may also constitute infringement. Thus a complementary protection may be applicable in most cases. However, those acts

[32] *See* Chap. 4, Section 4 of *Lag (2002:297) om biobanker I hälso- och sjukvården m.m., Regeringens proposition 2001/02:44 om biobanker i hälso- och sjukvården m.m.* (Government Bill 2001/02:44) p. 46 et seq.

must be proved to conflict with a normal exploitation of that database, or unreasonably prejudice the legitimate interests of the maker of the database. This could be difficult, since the samples are unique, and are released mainly for research. The rule is clearly designed for digital databases, and the problems of applying such rules to non-electronic databases are abundantly visible in this context.

4. Who owns the biobank?

Since today employees are responsible for a large proportion of creative work in general, and most inventions, it is important and interesting to know who becomes the owner of the intellectual property rights in a biobank that is created in the course of employment. But there is no precise answer to this question.

Swedish intellectual property law provides that the creators of copyrightable works, patentable inventions or protectable industrial designs have the initial title to the intellectual property rights.[33] Therefore, the starting point is that an employer may only obtain copyright, patent or design rights by a contractual assignment in contract or by law. This is especially true in a university environment.

4.1 Ownership of employees' copyright

In Sweden there is no equivalent to the Anglo-Saxon "*contracts of service*" or the Anglo-American "*works made for hire*", whereby the copyright generally belongs to the employer. There is basically only one exception to this principle, following from the European Directive 91/250/EEC on the Legal Protection of Computer Programs, which is included in Section 40(a) of the Copyright Act. That Section deals with computer programs created within the scope of employment, or when following instructions given by an employer.[34] It tells us that, in the absence of any agreement to the contrary, the copyright in such computer programmes is transferred to the employer, and as a consequence of Section 40(a) of the Copyright Act the employer holds both the economic and the moral rights in a computer program.[35]

For works other than computer programmes there are no explicit provisions governing copyrights in employment relationships. The Swedish copyright tradition follows the continental European systems, and an employer may only be entitled to employees' copyright by an agreed transfer.[36] However, even if no transfer of rights has been explicitly agreed, an agreement between the parties may be inferred. The general rule is that the employer may exploit employees' works within his normal field of activities.[37]

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[33] *See* Section 1(1) of *Lag (1960:729) om upphovsrätt till litterära och konstnärliga verk*, Section 1(1) of *Patentlag (1967:837)* and Section 1(2) of *Mönsterskyddslag (1970:485)*.
[34] See Art. 2(3) of Directive *91/250/EEC*. *Cf.* Art. 13(3) of the *Regulation (EC) 6/2002 on Community Design*.
[35] *See* Section 3.5.1 "Copyright protection".
[36] *See further* Svensäter, p. 331 et seq.
[37] *See* Swedish Labour Court case 2002 No. 87.

4.2 Ownership of employees' patentable inventions

Patentable inventions occurring in the course of employment are regulated in the Employee's Inventions (Entitlement) Act (1949:345).[38] This Act is mainly non-mandatory and its main provisions can be – and are in the private sector – overridden by collective agreements. The Act applies to patentable inventions made by employees in the course of their private or public employment, Section 1(1). Depending on the employees' duties in relation to the inventions made, the Act defines three different categories of inventions, to which an employer has a greater or lesser right, Section 3. But even where the law stipulates a total transfer of the invention to the employer, the employee has a mandatory right to a reasonable recompense for the rights transferred to the employer, Section 6(1). The amount of remuneration is to be decided by the parties involved. The value of the invention, the scope of the rights that the employer acquires, the terms of employment and the significance that the employment may have had in the making of the invention are factors taken into consideration when deciding the remuneration.

4.3 Ownership of intellectual property rights by university employees

The Employee's Inventions (Entitlement) Act, however, is not applicable to inventions made by teachers employed at universities or equivalent institutions (*teacher exception*), Section 1(2).[39] Employed teachers own the rights in their patentable inventions and are entitled such inventions as their private property, unless otherwise provided by contract.[40] Similarly, the implied agreement applied to copyrights within the employer' s normal field of activities in other environments than the university has no bearing on university teaching staff. As regards works made by non-teaching staff, the university may variously claim the patent or copyright to objects developed in the course of their duties in the same way as for employees in general.

The underlying concept of the teacher exception is academic freedom. It should be noted that the question of ownership is not affected by whether the university's research funding comes from industry, a funding research council or some other source.

As an effect of the teacher exception, where a database, for instance a biobank, is protected as a literary work under Section 1 of the Copyright Act, and it has been made by a university researcher or a group of such teachers, the structure belongs to the creators of the base, i.e. the university teachers. It should be emphasised that intellectual property laws, of course, do not protect the human biosamples as such in that database and the material is not covered by the exception.[41]

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[38] *See further* Dennemark 1950 and Jacobsson/Tersmeden/Törnroth 1980, p. 630 et seq.

[39] In Sweden there is an ongoing discussion regarding rights and wrongs of the teacher exception, *see further* Government Official Reports 1996:70, Government Bill 2000/2001:3 p. 195 and Government Bill 2001/2002:2 p. 47 et seq. *Cf.* the Danish Act 347/1999 on inventions at public research institutions, Section 42 of the German Law on Employee Inventions of 1957, as amended 7.2.2002, Section 12(3) of the Netherlands Patents Act of 1995 and Chap. 1, Section 1 of the French Decree on Employees´ Inventions of 1979. *See also* Section 24[bis] of the Italian Law on Patents for Inventions, Royal Decree of 1939, as amended 18.10.2001.

[40] About the teacher exception in the Nordic Countries *see* Andersen 2000, p. 602 et seq. Bruun 2000, p. 611 et seq. and Lund 2002, p. 618 et seq.

[41] *See further* the Norwegian case from Asker og Bærum herredsrett, judgement 29.9.1999.

When several persons have collected human biosamples for a biobank, only those who have made a creative contribution to the construction of the biobank's structure can enjoy copyright in the work. An assistant to the creation of such a database will not be a holder of the copyright. But, admittedly, it is not always easy to draw a distinction between authorship and assistance.

If on the other hand a biobank has no original structure, and is protected as a database only under the special provision in Section 49 of the Copyright Act (*sui generis* right), the holder of this neighbouring right is the maker of the database, generally the investor.[42] In some situations the investor may be a university researcher or a group of researchers, and in others it is the university department or a funding party. Even co-ownership of a biobank is possible, e.g. by university employees and the university.

Where there is an overlap of protection for a biobank, e.g. the rules on full copyright and *sui generis* protection are both applicable, and the creators and the maker/investor are different persons, the creators' individual rights have priority and limit the database maker's right *sui generis*. The database maker may only exercise his right with the copyright owner's consent, while the copyright owner's rights to a work are in no way limited by the *sui generis* right.

Therefore, and as a consequence of the teacher exception, it is important for universities, contributors etc. to define (early on) the relationship between the parties in a project, and especially to settle questions that may arise concerning ownership of intellectual property. Without such agreements, or explicit renunciation of the rights by the teaching staff involved in the creation of biobanks, the latter will become the holders of the copyright.

[42] *See also* Chap. III of Directive 96/9/EC *on the legal protection of databases*.

5. Summary

HANDLING OF INTELLECTUAL PROPERTY RIGHTS IN BIOBANKS

Copyright protection:	***Sui generis* protection:**
What is protected?	**What is protected?**
The structure in which the samples are organised in the bank.	The investment in the making of the biobank.
Who is the rights holder?	**Who is the rights holder?**
The creator (physical person) of the structure in the biobank.	The maker/producer/investor of the biobank.
Which acts may the rights holder prevent?	**Which acts may the rights holder prevent?**
Making a new biobank with an identical structure. Releasing samples in the form of the protected structure. Displaying the biobank's structure to the public. Displaying the structure on a screen, for the public to see.	The unauthorised extraction/re-utilisation of the contents of the bank, *i.e.:* Releasing samples from the bank. Displaying the biobank to the public.
Recommendations in employment relations?	**Recommendations in employment relations?**
Agreements on transfer of rights are recommended. The general rule is that the employer may exploit employees' works within the employer's normal field of activities. If no transfer of rights has been explicitly agreed, an implied agreement between the parties may be considered to exist. University employees are subject to the Teacher Exception. Agreements on transfer of rights are recommended.	Agreements on transfer of rights are recommended. The investor is the rights holder and in general that is the employer. In university environments, in some siutations the investor may be a university researcher or a group of researchers, and it others it is the university.

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11

Gifts and donations

Associate Professor Annina H Persson

Department of Law, Stockholm University

Sometimes the only way of treating certain serious illnesses or physical injuries is by organ or tissue transplant. In the context of organ and tissue transplantation, the following concepts are often used: making a gift of or donating organs or tissue, gifts, donations, makers of gifts and donors. Sweden is home to a number of biobanks, in which millions of samples of blood, tissue and cells are stored. These biobanks are under either private or public management and the material stored may have been taken from a patient, for example in order to make a diagnosis, treat the patient himself or for other medical purposes, e.g. research. The sample may also have been taken in order to clinically test pharmaceuticals or other medical products. The stored samples are taken from living, deceased or as yet unborn persons. How, then, does the recipient take possession of the material? Is it a question of gift or donation in this context too? The aim of this presentation is to look into these two concepts, donations and gifts, from a civil law perspective, and above all to see whether the civil law rules for gifts can be applied to legal issues regarding donations of human material.

1. Introduction

Sometimes the only way of treating certain serious illnesses or physical injuries is by organ or tissue transplant. In the context of organ and tissue transplantation, the following concepts are often used: making a gift of or donating organs or tissue, gifts, donations, makers of gifts and donors. Sweden is home to a number of biobanks,[1] in which millions of samples of blood, tissue and cells are stored. These biobanks are under either private or public management and the material stored may have been taken from a patient, for example in order to make a diagnosis, treat the patient himself or for other medical purposes, e.g. research.[2] The sample may also have been taken in order to clinically test pharmaceuticals or other medical products. The stored samples are taken from living, deceased or as yet unborn persons. How, then, does the recipient take possession of the material? Is it a question of gift or donation in this context too?

The aim of this presentation is to look into these two concepts, donations and gifts, from a civil law perspective, where the concept of a gift at least is legally

[1] A biobank can be a tissue bank or a collection of blood samples, or the information, which has been obtained from such a bank. Cf. Chap. 1, Section 2 of the Biobanks (Health Care etc.) Act (SFS 2002:297), Prop. 2001/02:44 pp. 1, p. 6, p. 21 and p. 67.

[2] See Rynning, E., Biobankerna – hög tid för bankinspektion? 1998, Förvaltningsrättslig tidskrift, 1998, häfte 6, p. 305.

technically limited. The donation of biological samples is regulated by statute in the field of health and medical care law. These statutes, for example the Transplant Surgery Act,[3] are of a public law, rather than a civil law, character. The Transplant Surgery Act provides, for example, the conditions under which organs may be removed from the body of a living or deceased person for transplant or other medical purposes. However, the Act does not regulate the legal relationship between the donor and the donee.[4] The question is, therefore, whether the civil law rules for gifts can be applied to legal issues regarding donations of human material, which are not governed by the Transplant Surgery Act or other public law legislation. What are the terminological similarities and differences between the two? Is the making of a gift an active giving and that of a donation a passive giving? Can the two concepts mean the same thing in certain contexts and different things in others? Further, what are the similarities and differences between a donor of a gift in its general context and someone who donates human biological material? What are the similarities and differences between a donee in its general context and a donee of human biological material? What legitimates a gift transaction in its legal sense? Can the civil law rules regarding gifts in general be applied to donations of human biological material?

2. Terminology

Let us begin by considering the terminological similarities and differences between the concepts of gifts and donations. In its general context, a gift is defined as a transfer of property without remuneration.[5] The classic example is when someone gives something away without receiving any service in return (i.e. consideration), e.g. a present. Legally, unlike purchase and exchange, a gift is a beneficial agreement since transfer is made without remuneration.[6] The prerequisites for a gift are as follows: 1) a transfer of property[7], 2) made voluntarily[8] and 3) a beneficial intention on the part of the donor for a gift to be made.[9] The making of a gift must be seen to be an act of generosity or such-like.[10] It can be hard to draw the line between beneficial and onerous[11] agreements on the one hand, and gifts and other legal

[3] See *Lag (1995:831) om transplantation m.m.* (the Transplant Surgery Act), *Lag* (1995:832) om obduktioner m.m. (the Post-Mortem Examinations Act). Cf. also *Hälso- och sjukvårdslag* (1982:763)(the Health and Medical Services Act) and *Lag (1998:531) om yrkesverksamhet på hälso- och sjukvårdens område* (the Health and Medical Services (Professional Activity) Act).
[4] See SOU 1989:98 p. 255.
[5] See Bonniers stora lexikon, Gam-Hon,1986. See also Stora Svenska Ordboken, 1996, Bengtsson, B., Särskilda avtalstyper I, 1971, p. 20.
[6] Cf. Bergström, S. & Eek, H. & Håstad, T. & Lindblom P H., Juridikens Termer, 8th edition., 1993.
[7] The donee shall be enriched at the donor´s expense. See Bengtsson, B., Om gåvobegreppet i civilrätten, SvJT 1962 p. 694.
[8] The transfer of wealth shall not be made by reason of a legal duty. See Bengtsson, B., op. cit. SvJT 1962 p. 694.
[9] See Bengtsson, B., Särskilda avtalstyper I, 1971, p. 21 and the same author in op. cit. SvJT 1962 pp. 694. The gift concept does not include transfers of wealth with no consideration, where the transaction is clearly dictated by business interests.
[10] See Bengtsson, B., Särskilda avtalstyper I, 1971, p. 22.
[11] An onerous agreement is one in which a burden is imposed on both parties, e.g. a purchase. See Bergström, S. et al., Juridikens termer, 8th edition, 1993.

concepts on the other. Agreements which formally seem to be beneficial can, in fact, often involve consideration.[12] One example is an agreement (known as a remuneratory gift) whereby an undertaking has been given because a donee has carried out certain services on behalf of the donor, in spite of no legal claim to remuneration having been made. Further, a gift to an heir can be considered an advance on his inheritance.[13]

The Svenska Akademiens Ordlista (standard Swedish dictionary) defines the verb "to donate" as "to give by deed of gift for purposes to the benefit of everyone".[14] Another reference book defines a donation as a larger gift, usually made in a legal form, e.g. in a will.[15] A donation can therefore be a gift by deed of gift to an authority or foundation, for example.[16] The above definition of donation is relatively common in dictionaries,[17] but the word can also be said to be used more "generally, particularly in medical contexts".[18] Terminologically, there does not appear to be any difference between a general donation and the donation of human biological material. However, the forms and legal consequences of the two can differ depending on the purpose and object of the donation.

Furthermore, it is also important to determine the parties involved in the different legal relationships. As regards a gift in a general context, there is a legal relationship between a donor and donee. Parties on either side may be natural or legal persons. The gift transaction often takes place without the involvement of any intermediary, and the gift is generally transferred directly from the donor to the recipient. Instead of the object of the gift being transmitted directly to the recipient, the donor can also provide the recipient with a promissory note, in which he undertakes to transfer the property.[19] The object of the gift may also be in the hands of a third party. In this case, the donor can inform the third party that the property shall now be at the disposal of the recipient.[20] A gift from a natural person can only be made by a living donor; in other words, a gift which can only be valid on the donor's death and which cannot be classed as being bequeathed under a will, is in principle invalid.[21] Of course, a donor can leave a gift to someone after his death, but in order for the recipient to be able to validate the gift on the donor's death, the gift must be bequeathed under a will. It will therefore no longer be a question of a gift,

[12] See Hellner, J., Speciell avtalsrätt II, Kontraktsrätt, 3 uppl., 1 häftet, särskilda avtal, 1996, p. 234.
[13] See 6:1 *Ärvdabalk* (Inheritance Code, SFS 1958:637).
[14] See Svenska akademiens ordlista över svenska språket, 1998.
[15] See Bonniers stora lexikon, Chr-Emp, 1985.
[16] See Förklarade Ord 1960. Compare *donationsförordning (SFS 1998:140*) where donation is defined as any transfer of property to a public authority through gift or testamentary provision and which does not require any quid pro quo or status as a beneficiary and where the property does not constitute a foundation.
[17] See Stora svenska ordboken, 1996, Bonniers svenska ordbok, nya skolupplagan, 1992. Cf. Svenska ord - med uttal och förklaringar, 2 uppl., 1993, p. 132, where donation is defined as "officially giving something away".
[18] See Stora svenska ordboken, 1996.
[19] See Bengtsson, B., Särskilda avtalstyper I, 1971, p. 22.
[20] See Bengtsson, B., Särskilda avtalstyper I, 1971, p. 22.
[21] See 17:3 *Ärvdabalk* (Inheritance Code, SFS 1958:637). See also Walin, G., Kommentar till ärvdabalken, Del 1 (1-17 Kap) 5 uppl., 2000, pp. 419. Cf. pp. 203. See also Bergström, S. et al., Juridikens Termer. 8th edition, 1993.

but of a testamentary devise.[22] A similar situation applies to general donations, the difference being that the donor may be living or deceased when the donation is effected, since the donation is either made by way of deed of gift during the donor's lifetime or in the form of a will if it is made after the donor's death.

As mentioned above, human biological material can be taken from a living, deceased or as yet unborn person. As regards the legal relationship between the parties, the donor is clearly a natural person. In human biological terms, the donor is defined in the same way as a maker of a gift; e.g. a blood donor, sperm donor or a person from whom organs are removed on transplant.[23] However, the recipient can be a natural or a legal person. Sometimes the donation transaction is carried out by a legal intermediary, in spite of a natural person being intended as the ultimate recipient of the material, e.g. when human biological material is taken for transplant without being transferred directly to the recipient. The material is instead stored at the relevant medical institution for a short period until such time as the right recipient can receive it. This is not uncommon.

3. Who donates human biological material?

The Transplant Commission's interim report[24] included a discussion of how to define the term 'donor'. It was conceded that it is difficult to find an adequately neutral term to describe the person who undergoes an operation in order for another person to receive an organ for transplant. Where a living person was involved, it was felt to be clear that that person should be called the maker of a gift or donor. However, where a deceased person was involved, these concepts met with some difficulties, since in principle these words would require the rules regarding consent to be such that organs could only be removed if a positive declaration of consent to that effect had been given during the deceased persons´s lifetime. The Commission went on to say that it was questionable whether such a declaration of consent could even suffice in order for a person to be reasonably characterised as the maker of a gift or as a donor.[25] The Commission found that there should be a certain linguistic difference between a gift in its real sense and mere acceptance or consent, but it failed to come up with any other suitable general term, which could be used irrespective of the form of the rules of consent. The Commission therefore determined to employ the term 'donor' in respect of both living persons and deceased persons from whom an organ is removed, irrespective of whether they had or had not during their lifetime positively made known their intention to make a gift or in any other way indicated that their organs were to be removed. Further, the Commission determined to employ the term 'organ donation' to denote the taking of organs in a broad sense, and thus not only to situations in which the deceased, or his surviving relatives, clearly make it known that they are donating organs as gifts after death or where they otherwise expressly consent thereto.

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[22] See 11:10 *Ärvdabalk* (Inheritance Code, SFS 1958:637). Bequest refers to a particular benefit granted by a will, such as specific tangible property or a specific pecuniary sum or a right of use in the property or a right to enjoy the interest thereon or the proceeds thereof.
[23] See Bonniers stora lexikon, Chr-Emp, 1985.
[24] See SOU 1989:98 p. 39. Other legislative proposals by The Transplant Commission are SOU 1989:99, SOU 1991:42 and SOU 1992:16.
[25] Cf. SOU 1984:79 p. 33.

As indicated above, the question of who can be defined as a donor is linked to the rules on consent to the donation of human biological material. The current rules in the area of health and medical care law are relatively precise as regards which situations require consent and also concerning the type of material involved. Consent can either be written or oral, depending on the situation. Swedish law currently considers that medical steps can only be taken once consent has been given by the relevant person. If the human biological material is part of a patient´s medical treatment,[26] Chap. 2, Section 1 of the Health and Medical Services Professional Activity Act (1998:531) provides that the patient shall be provided with careful expert health and medical care in accordance with scientific practices and practical experience.[27] As far as is possible, a care programme shall be designed and put into practice in consultation with the patient, who shall also be shown consideration and respect.

If the biological material is not taken as part of the medical treatment of the patient himself, but for some other purpose, e.g. transplant surgery, medical research or pharmaceutical production, the principle rule as stated in the first line of Section 6 of the Transplant Surgery Act (1995:831) is that organs or other such biological material coming under the Act shall not be removed from living donors without consent.[28]

If the organ or material which is to be taken cannot be recreated or if the operation is liable to cause considerable harm to or difficulties to the donor, the second sentence, in Section 6 of the same Act, requires consent to be in writing. Further, the operation may only be carried out if there is no serious risk to the donor's life or health (Section 5). As regards the transplant of material, which cannot be recreated, the donor is required to be a relative of the proposed recipient, or otherwise to be particularly close to him (Section 7). Otherwise, specific reasons are required before the operation can be performed on other persons. If the material is not recreated or if the operation may otherwise involve considerable harm to or difficulties for the donor, permission from the National Board of Health and Welfare is also required Section 9), if the material is to be taken for medical purposes other than for transplant. Specific rules also apply as regards material taken from minors and from mentally disabled persons.[29]

Where the donor of organs or tissue is deceased, his views on removal of biological material prior to death will be decisive. Therefore, under Section 3 (1) of the Transplant Surgery Act, biological material intended for transplant or some other medical purpose may be taken from a deceased if he has agreed to the operation or if it can otherwise be shown that such a step would have been in

[26] It should be noted that the Transplant Surgery Act is not applicable to biological matter excised for the purpose of treating the person upon whom the incision was performed. See Section 2 (2) of *Lag (1995:831) om transplantation m.m.* (The Transplant Surgery Act).

[27] Cf. also Sections 2, 2a, and 2b of *Hälso- och sjukvårdslag* (1982:763)(the Health and Medical Services Act).

[28] See the statutory text and Prop. 1994/95:148 pp. 31, pp. 79. Cf. SOU 1997:154 p. 422, Rynning, E., Samtycke till medicinsk vård och behandling, En rättsvetenskaplig studie, 1994, p. 125. SOU 1989:98 pp. 198.

[29] See Sections 8 and 9 (2) of *Lag (1995:831) om transplantation m.m.* (The Transplant Surgery Act). See also Prop. 1994/95:148 pp. 34, pp. 81.

accordance with the deceased's views.[30] Permission can be inferred, e.g. from information in a will or a donor's card. It should be noted that permission need not be writing. Further, if the donor has not expressed any views to the contrary, his consent will be deemed to have been given. However, biological material may not be removed where the deceased has in writing expressed that he is against such an operation or where there are other reasons to believe that such an operation would be contrary to the deceased's wishes, (Section 3 (2)). If there is conflicting information as to the deceased's point of view on this matter, or if there is any other particular reason why such an operation should not proceed, the operation must not be performed (Section 3 (3)). Finally, persons close to the deceased may also prohibit the operation if the wishes of the deceased are not known (Section 4). However, it can also be noted that organs and other material may be taken under the Post-Mortem Examinations Act, should the purpose of the post mortem require it.[31]

If the biological material is tissue from an aborted foetus, the woman who carried the foetus must give her consent if the tissue from the foetus is to be used for medical purposes, Section 11 of the Transplant Surgery Act.[32] The term "medical purposes" means that the tissue is to be used for treating illnesses or injuries or medical research.[33] Permission from the National Board of Health and Welfare is also required in order for the tissue to be taken, and that permission can only be given where there are special reasons for doing so. Such reasons will be found where the application for consent is made for extremely urgent purposes such as the treatment of serious illnesses, e.g. Parkinsons´s disease. Special reasons can also be found where established methods involving serious side effects can be avoided or where there are no alternative methods available.[34] When the operation is performed, the woman can determine whether the tissue from the foetus may only be used for some specific purpose. She can therefore exclude certain uses of the material and so has the initial right of disposal over the material. If the woman has consented to the material being used in a certain way, she cannot later lay down further conditions as to how the tissue is to be used.

Consent is also required if the biological material is to be used for research into or treatment of fertilised eggs.[35] The consent of the egg and sperm donors is required, but it does not have to be in writing.[36] It should be noted that the Transplant Surgery Act does not apply to the transplant of gametes or organs

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[30] See the statutory text and Prop. 1994/95:148 pp. 23, pp. 75.

[31] See *Lag (1995:832) om obduktion m.m.* (the Post-Mortem Examinations Act). See also Section 21 of the same Act regarding anatomical dissection for purposes of research or teaching. See Prop. 1994/95:148 pp. 100 and *SOSFS 1996:28 om kliniska obduktioner m.m .(* Clinical autopsies etc.) p. 11.

[32] See Prop. 1994/95:148 pp. 41, pp. 84. Cf. SOU 1991:42 pp. 69.

[33] See *SOSFS 1997:4 Socialstyrelsens föreskrifter om organ och vävnadstagning för transplantation eller för annat medicinskt ändamål* (Provisions of the National Board of Health and Welfare on the collection of organs and tissue for transplant surgery or other medical purposes), p. 16.

[34] See SOSFS 1997:4 p. 16.

[35] See Sections 1 and 2 of *Lag (1991:115) om åtgärder i forsknings- eller behandlingssyfte med befruktade ägg från människa* (the Fertilised Human Ova (Research or Treatment Measures) Act).

[36] See Section 1 of *Lag (1991:115) om åtgärder i forsknings- eller behandlingssyfte med befruktade ägg från människa* (the Fertilised Human Ova (Research or Treatment Measures) Act). See also Rynning, E, Samtycke till medicinsk vård och behandling, 1994, pp. 125.

producing gametes.[37] These are regulated *inter alia* by the Insemination Act (SFS 1984:1140) and the Fertilisation Outside the Body Act (SFS 1988:711).[38] Summing up, current legislation provides that a living, deceased or as yet unborn person can be a donor. In general terms, all human biological material can be donated to different recipients for different purposes.

4. Who receives human biological material?

As indicated above, a donor of human biological material can provide that material for different purposes. The specific purpose for which the material is provided is determined by the identity of the intended recipient. If someone provides an organ or tissue for transplant, the recipient is another natural person, but the transaction process whereby the donation is made is often carried out by a legal intermediary, that is to say the medical institution where the operations are performed on the donor and the donee. If the biological material is removed from a person in order, for example, to make a diagnosis or treat the patient himself and the sample is then stored, the recipient is the legal person where the treatment is given/where the sample is stored.[39] Pathology departments in hospitals around the country store cell samples and tissue samples which are used to diagnose patients' illnesses. The tissue samples are often stored for use, for example, as a basis for comparison when new samples are taken.[40] The biological material may also have been removed from a person for medical purposes other than those mentioned above, e.g. for transplant[41] or research. As regards the latter, the sample may have been taken by researchers at research institutes which are either under private or public management. In these

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[37] See Section 2 of *Lag (1995:831) om transplantation m.m.* (The Transplant Surgery Act).

[38] See *SOSFS 1987:6 Socialstyrelsens föreskrifter och allmänna råd om inseminationer* (Provisions and general guidelines of the National Board of Health and Welfare on insemination) pp. 14, and *SOSFS 1989:35 Socialstyrelsens föreskrifter och allmänna råd om befruktning utanför kroppen m.m.* (Provisions and general guidelines of the National Board of Health and Welfare on Fertilisation Outside the Body) pp. 5.

[39] See Sections 3 and 18 of *Hälso- och sjukvårdslag (1982:763*)(the Health and Medical Services Act). See *SOSFS 2001:8 Socialstyrelsens allmänna råd om försiktighetsmått vid hantering och märkning av sådant biologiskt avfall som kan medföra olägenhet för människors hälsa enligt miljöbalken* (General guidelines of the National Board of Health and Welfare on caution when handling and marking biological waste etc.), *SOSFS 1999:27 Socialstyrelsens föreskrifter och allmänna råd om hantering av smittförande avfall från hälso- och sjukvården* (Provisions and general guidelines of the National Board of Health and Welfare on handling infectious waste from the health and medical sector), *SOSFS 1989:38 Socialstyrelsens föreskrifter om blodgivning, blodtransfusioner m.m.* (Provisions of the National Board of Health and Welfare on blood transfusions etc.*)*, *SOSFS 1990:8 Socialstyrelsens allmänna råd rörande omhändertagande av foster efter abort* (General guidelines of the National Board of Health and Welfare regarding care of aborted foetus), *SOSFS 1996:28 Kliniska obduktioner m.m.*(Clinical autopsies etc.), *SOSFS 1996:29 Socialstyrelsens föreskrifter och allmänna råd: Vissa åtgärder inom hälso- och sjukvården vid dödsfall (*Provisions and general guidelines of the National Board of Health and Welfare: Death and deceased persons – certain measures in the health and medical sector).

[40] See *SOSFS 1995:9 Socialstyrelsens allmänna råd: rutiner för bevarande av provmaterial vid patologavdelningar m.m.* (General guidelines of the National Board of Health and Welfare on routines for preserving tissue samples at pathology departments etc.).

[41] See *SOSFS 1997:4 Socialstyrelsens föreskrifter och allmänna råd avseende organ och vävnadstagning för transplantation eller för annat medicinskt ändamål* (Provisions of the National Board of Health and Welfare on the collection of organs and tissue for transplant surgery or other medical purposes), p. 15 regarding institutions and other units where incisions can be performed.

circumstances, the recipients may be natural as well as legal persons. Samples may also be taken in order to clinically test pharmaceuticals or other medical products. In this case, the recipient may be a researcher with a pharmaceutical company or a company as a legal person.

5. Gifts

The legal concept of a gift is regulated by several different statutes,[42] one of which is the Certain Undertakings in respect of Gifts Act (SFS 1936:83) ('Gifts Act'). However, this Act governs only one particular issue, namely the conditions under which an undertaking to make a gift has legal effect.[43] Other Acts encompassing rules on gifts include the Land Code[44] (Chap. 4, Sections 29-31), the Air Traffic Act[45] (Chap. 9), and the Trading Companies Act,[46] but these statutes are not particularly detailed as regards rules on gifts. Other legislation governing onerous agreements, e.g. the Sale of Goods Act,[47] must therefore be consulted in order to determine what does not apply to gifts in any given case.[48] If there is any uncertainty as to whether an agreement is of a beneficial nature, it should be determined whether the maker of the gift did indeed have such an intention. If the maker of a gift expressly undertook to make a gift, no particular problems arise,[49] but if the recipient cannot rely on any such undertaking it becomes necessary to interpret the agreement and look in particular to the circumstances surrounding the agreement as well as to custom.[50] The general principles of interpretation, validity and amendment apply when determining whether an agreement is beneficial or not, but application may differ if an agreement is found to be beneficial. When interpreting the intention of the parties, for example, the intention and wishes of the maker of the gift will be decisive, whereas the recipient´s intention will be irrelevant.[51] If an undertaking to make a gift has legal effect, the maker of the gift can be legally required to fulfil his obligations and make the gift. If the maker of a gift retains the right to dispose of something encompassed by the gift – contrary to the undertaking – the general legal principles on the illegal reselling of goods are the only recourse open to the maker of a gift.[52]

Section 1 (1) of the Gifts Act provides that an undertaking to make a gift of a chattel is invalid if the gift is not complete, as long as the undertaking has not been

[42] The following is based on Walin, G., Lagen om skuldebrev, 2 uppl., 1997, pp. 233, Hessler, H., Allmän sakrätt, 1973, pp. 532, Hellner, J, Speciell avtalsrätt II, Kontraktsrätt, 3 ed., 1 häftet, särskilda avtal, 1996, pp. 234, Bengtsson, B., Särskilda avtalstyper I, 1971, pp. 20. For a historical retrospect of the legal institute of gift, see Eschelsson, E, Om begreppet gåfva enligt svensk rätt, 1897, and the same author in: Fullbordandet av gåfva af lös egendom enligt svensk rättspraxis., Uppsala, 1906.
[43] See Walin, G., Lagen om skuldebrev, 2 uppl., 1997, p. 233.
[44] See *Jordabalk*, SFS 1970:994.
[45] See *Luftfartslag* (SFS 1957:297)(Civil Aviation Act).
[46] See *Lag (1980:1102) om handelsbolag och enkla bolag* (Limited Partnerships Act). Cf. NJA 1986 p. 402.
[47] See *Köplag*, SFS 1990:931.
[48] See Hellner, J., Speciell avtalsrätt II, Kontraktsrätt, 3 uppl., 1 häftet, särskilda avtal, 1996, p. 235.
[49] See Hellner, J., op. cit. p. 235.
[50] See Hellner, J., op. cit. p. 235.
[51] See Hellner, J., op. cit. p. 244.
[52] See Walin, G., Lagen om skuldebrev, 2 uppl., 1997, p. 233.

made in a promissory note or other written document which has been handed to the recipient.[53] An undertaking to make a gift can also be made orally. Should the circumstances surrounding the origin of the gift be such that the oral undertaking was intended to be made general knowledge, it may be binding.[54]

The rule set out in Section 1 (1) of the Gifts Act applies only to the contractual effect of the gift agreement, i.e. the relationship between the maker of a gift and recipient. However, Section1 (2) of the Gifts Act regulates the effect of the gift agreement on third parties, i.e. whether it will have effect against the creditors of the maker of a gift, for example, in the event of bankruptcy. This section provides that if the gift is not complete it cannot be enforced against the maker of a gift's creditors, in spite of the fact that the requirements in Section 1 (1) of the Gifts Act may have been fulfilled. On the other hand, it is possible to turn this rule on its head and assert that if the gift is complete it is immaterial as regards the validity of the gift whether one has acted in accordance with the formal requirement set out in subsection one.[55] In the first instance, the recipient does not even have the right to make an unprivileged claim in the maker of a gift's bankruptcy. In general, the Gifts Act also provides that an undertaking to make a gift is not even contractually binding where the gift is incomplete. The rule in Section1 therefore aims to determine the point at which a binding undertaking by the maker of a gift becomes valid as against third party creditors so that the transaction cannot be rendered voidable except, for example, under the rules on recovery as laid down in the Bankruptcy Act.[56]

The object of a gift transaction can be different types of chattel. The Gifts Act, however, is not intended to regulate all types of gift, only those which have as their object money, tangible chattels, oral or written claims and certain types of shares or securities.[57] Gifts of real property are governed by Chap. 6, Section 4 of the Housing Act.[58] The form of the object of the gift transaction is of importance as regards the point at which the gift is to be considered complete. The creditors of the maker of a gift are generally protected once the gift comes into the recipient´s possession. Under Section 2 (1) of, line 1 of the Gifts Act, a gift such as money or a tangible chattel is not complete until it comes into the recipient´s possession. On the other hand, the gift may be considered complete in another way, since the substance of the transfer requirements differs depending on the type of property concerned.

The principle rule provides that the maker of a gift can change his mind right up until the time when the gift or deed of gift has been transferred. Once the gift is complete, however, it cannot be withdrawn unless the gift document is invalid in some way, see for example Chap. 3 of the Contracts Act.[59] However, if, after the undertaking has been made, the financial position of the maker of a gift has deteriorated to such a degree that, even taking into account the recipient's situation,

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[53] See Walin, G., op. cit.. p. 233.
[54] See Walin, G., op. cit. p. 233. See also Lagberedningens förslag till Lag om skuldebrev m.m., 1935, p. 132, NJA II 1936 p. 141.
[55] See Walin, Lagen om skuldebrev, 2 uppl., 1997, p. 234.
[56] See Lagberedningens förslag till Lag om skuldebrev m.m., 1935, pp. 131, NJA II 1936 p. 146. See also *Konkurslag* (SFS *1987:672*)(Bankruptcy Act).
[57] See Lagberedningens förslag till Lag om skuldebrev m.m., 1935, pp. 130 and Walin, G., Lagen om skuldebrev, 2 uppl., 1997, p. 228.
[58] See B*ostadsrättslag* (SFS 1991:614). Cf. NJA 1993 p. 560.
[59] See *Lag (SFS 1915:218) om avtal och andra rättshandlingar på förmögenhetsrättens område.*

the demand for the gift is unreasonable, the gift can be reduced or withdrawn in accordance with Section 5 (1) of the Gifts Act. The gift can also be withdrawn under Section 5 (2) of the Gifts Act if, after the undertaking is made but prior to completion, the recipient seriously wrongs the maker of a gift.[60] In this case the maker of a gift must notify the recipient of the withdrawal within one year of the wrong coming to his knowledge.

A gift may be subject to instructions as to how it is to be employed.[61] These instructions may constitute conditions[62], i.e. a transfer ban or other testamentary clause concerning the handling of received property.[63] The legal position regarding such instructions is rather opaque in certain areas,[64] but from a contractual perspective, it is established law that these conditions may be declared invalid if they are contrary to good and accepted practice or are unreasonable under Section 36 of the Contracts Act.[65] Further, as regards third parties it is established that a transfer ban, for example, can be valid against them as regards gifts,[66] but invalid on purchase.[67] A transfer ban of a mixed beneficial and onerous character is considered to be valid against third parties if the transfer is clearly a gift transaction.[68]

6. Object of gifts

Under the Gifts Act the object of a gift transaction can be different types of chattel, including tangible chattels, buildings on another's land, shares and other securities, intellectual property rights etc. Animals are also considered to be tangible chattels; that is to say, they are legal subjects.[69] However, there remains the question as to whether humans/the human body can be the object of a gift within the meaning of the Gifts Act. This question can only be answered first by analysing whether it is possible to own one's own body and its parts, since no one can really give away something that does not belong to them. Literature on the subject takes as a starting point the fact that every person is a subject of the law.[70] A person, therefore, cannot

[60] *Märklig orätt* in Swedish. See NJA 1961 p. 105, where the donee commits a serious crime against the donor. Cf. also NJA 1977 p. 717.
[61] See Hellner, J., Speciell avtalsrätt II, Kontraktsrätt, 3 uppl. 1 häftet, särskilda avtal, 1996, p. 246.
[62] Substantive law sometimes makes a systemic distinction between different property rights, such as ownership, right of claim, participation right or special right. The last mentioned group can comprise three forms, namely rights of user, rights of security and qualification (*betingelse*). The last of these denotes a power of some kind over another person´s property which does not come under the other categories of special right. There are various kinds of *betingelse*, namely rights qualifications (right of repurchase, options etc.), negative qualifications (prohibition of the transfer or grant of certain property) and purposive provisions.
[63] See Hessler, H., Allmän sakrätt, 1973, p. 26, pp. 54, 446.
[64] See, for example, Supreme Court Justice Bengtsson´s rider in NJA 1990 p. 18.
[65] See Hellner, J., Speciell avtalsrätt II, Kontraktsrätt, 3 uppl. 1 häftet, särskilda avtal, 1996 p. 246.
[66] See NJA 1986 p. 16, NJA 1989 p. 696 och NJA 1993 p. 529.
[67] See NJA 1974 p. 376 and NJA 1993 p. 468.
[68] See NJA 1998 p. 135 and NJA 1991 p. 376.
[69] See Malmström, Å. & Agell, A., Civilrätt, 16 uppl., 1999 pp. 59, 76.
[70] See Malmström, Å. & Agell, A., Civilrätt, 16 uppl., 1999 p. 59, Inger, G., Rätten över eget liv och över egen kropp, Kungl. Humanistiska Vetenskaps-Samfundet i Uppsala, Årsbok 1985, p. 97. See also SOU 1989:98 p. 68.

be the object of another's ownership.[71] This is also true of deceased persons.[72] Every human being has legal personality, from the moment of birth until death, but on death, a human being is no longer considered to be a subject of the law and therefore loses his legal personality. The deceased can therefore no longer acquire any rights. Those rights which the deceased had during his lifetime are transferred to another or are extinguished completely.[73] However, it should be noted that the fact of the deceased no longer being a legal subject does not make him a legal object. Further, the deceased's relatives/estate cannot claim title to his corpse or any parts of it. A corpse cannot form part of an estate and it should not be possible to set a price on it financially.[74] A corpse cannot be considered to be an object legally speaking, and therefore someone who removes a corpse without permission cannot be said to have committed a crime against property.[75] This would also apply where someone removed parts of a corpse.[76] However, it must be conceded that during his lifetime the individual can decide to a great extent how his body will be dealt with on his death. This is true both of arrangements as to his funeral as well as possibilities of removing organs by way of transplant operations and post mortems. Alternatively, the deceased's relatives will also be able to determine these issues, but they cannot 'own' a corpse. Museums and medical institutions, however are capable of owning an entire corpse.[77]

What, then, is the situation as regards ownership of parts of a human body? It is said that "parts of a living human (hair, beards etc) belong to the person from whom they have been taken, as long as that person has not given them up. The same should also be true of other materials such as blood and internal organs which have been removed on the operating table".[78] Of deceased persons it is said that "in the same way as a living person's hair, beard etc. can be passed on to another, the same cannot be said as regards the same type of biological material from a deceased".[79]

As indicated above, gifts are generally beneficial agreements and are based on the premise that the maker of the gift has the legal right to transfer. Applying this concept to the human body, the question arises as to whether the owner can give away his body or any part of it.[80] Doctrine provides that even if it is not possible to

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[71] Seee SOU 1989:98 p. 68. Cf. Alexius, K., Något om äganderätt, angrepp på egen rättssfär och en eventuell kriminalisering av prostitution, SvJT 1995 p. 599, arguing that a person´s right to their own body, generally speaking, is probably of a simple kind, i.e. a non-transferable right of ownership, unaccompanied by any unconditional right of disposal over the object.

[72] See SOU 1989:98 p. 70.

[73] See SOU 1989:98 p. 69.

[74] See Inger, G., Rätten över eget liv och över egen kropp, Kungl. Humanistiska Vetenskaps-Samfundet i Uppsala, Årsbok 1985, p. 97. See also SOU 1992:16 p. 66.

[75] Cf. Chapter 8, Section 8 of *Brottsbalk* (the Penal Code, SFS 1962:700). See also Holmqvist, L., & Leijonhufvud, M., Träskman, P O., Wennberg, S., Brottsbalken. En kommentar. Del 1 (1-12 kap.) p. 367, Jareborg, N., Brotten, andra häftet, Förmögenhetsbrotten, 2 uppl., 1986, pp. 42, 82, 122.

[76] See SOU 1992:16 p. 66.

[77] See Jareborg, N., Brotten, andra häftet, Förmögenhetsbrotten, 2 uppl., 1986, p. 49. There would not, however, appear to be any impediment to private persons occupying skeletal parts. See ib., p. 49.

[78] See SOU 1989:98 p. 68. See also Jareborg, N., Brotten, andra häftet, Förmögenhetsbrotten, 2 uppl., 1986, p. 49.

[79] See SOU 1989:98 p. 70.

[80] Cf. Sågänger, J., Organhandel, Kroppsdelar till salu, 1994, p. 80.

own someone's body or parts of it, the person in question does have the right to dispose of it within certain parameters.[81]

Swedish law includes several statutes governing what can be done with a human body respectively in life and in death.[82] Most of the relevant legislation focuses on medical procedures such as transplant,[83] post mortem[84], criteria for determining whether someone is dead,[85] insemination,[86] research on fertilised eggs[87] etc. So what can one do with a corpse? On this particular point the legislation only says than that certain procedures regarding corpses are prohibited.[88] The possibilities of using the corpse for different purposes are limited, as long as the operation is not entrenched in an act or other statute.[89] The exact situation outside the legislated fields, however, is rather unclear.

Do the body and its parts form part of the owner's estate as assets and therefore constitute a basis for those liabilities which he subsequently takes on? From what has been stated above, the answer to that question ought, *prima facie*, to be no. On the other hand, there is no doubt that a person can cut off his hair and sell it for a specific sum of money to a wigmaker.[90] Arguably, then, it should be possible for a body part separated from the body to be given away in the same way as objects in general. The *travaux préparatoires*, however, seems to distinguish between body parts which can be recreated, such as blood and hair, and parts whose removal would be to the permanent detriment of the individual. As regards the latter case, it appears that were an agreement to sell a kidney to come under the scrutiny of a court, the court would probably find the agreement out of keeping with good practice and therefore declare it invalid. As to the question of whether a body part is an asset of the person who owns it, the answer will depend on the body part in question.

The *travaux préparatoires* of the Transplant Surgery Act discuss how to deal with agreements on body parts where the agreement has been made before the body part has been removed from the body. Discussion also focuses on how the person entitled to the body part can enforce performance of such an agreement. As regards the legal analysis, it should however be noted that it makes no difference which body part is involved. Should the person entitled to the hair sold enforce performance himself, i.e. cut off the owner's hair without his consent, he will have committed bodily harm and may be liable for battery. Of course, the same will be

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[81] See Machado, N., Using the bodies of the dead, Studies in Organization, Law and Social Process Related to Organ Transplant, 1996, p. 170.
[82] See Machado, N., Using the bodies of the dead, Studies in Organization, Law and Social Process Related to Organ Transplant, 1996, p. 166.
[83] See *Lag (1995:831) om transplantation m.m.* (the Transplant Surgery Act).
[84] See *Lag (1995:832) om obduktion m.m.* (the Post-Mortem Examinations Act).
[85] See *Lag (1987:269) om kriterier för bestämmande av människans död* (the Human Death Criteria of Determination Act). See prop. 1986/87:79.
[86] See *Lag (1984:1140) om insemination.* (Insemination Act).
[87] See *Lag (1991:115) om åtgärder i forsknings- eller behandlingssyfte med befruktade ägg från människa* (the Fertilised Human Ova (Research or Treatment Measures) Act).
[88] See SOU 1989:98 p. 70.
[89] See, for example. *begravningslag (SFS 1990:1144*)(the Burials Act), *begravningsförordningen (1990:1147*)(the Burials Ordinance), *Lag (1995:832) om obduktion m.m.* (the Post-Mortem Examinations Act). See also SOU 1989:98 p. 71 and SOU 1992:16 p. 60.
[90] For the following three parts, see SOU 1992:16 pp. 58-59.

true as regards other body parts. Performance should not be enforceable by coercive means.

The only possible conclusion is that the general civil law rules on gifts are not very pertinent to the donation of human biological material. The object of a gift in general differs from a donation of human biological material. The first case concerns an object – property or a 'thing'– which on transfer is the subject of a transfer of property. The second case concerns a legal subject or, at all events, something which is not to be considered an object of the law. There is no question here of any transfer of property. Generally, a gift is an asset both to the maker of the gift and the recipient. However, the body and its parts cannot be considered to be an asset forming part of the owner's property, thereby creating obligations incumbent upon him.[91]

7. Donations

The term 'donation' generally involves a person giving away an object or money for a purpose that benefits everyone. One example could be where someone leaves a donation of 20 million SEK to a university for a new student union building, another where a donation of paintings or other works of art is left to a museum. A person who donates human biological material does so by allowing the removal of blood, cells, tissue or organs, for example, and the reason for doing so may be to enable the doctor to make a diagnosis or treat the patient. Material may also be removed for other medical purposes, e.g. research.[92] Or again, the sample may be provided for use in the clinical testing of pharmaceuticals or other medical products.

As mentioned above, the donation of biological material is governed by statute in the area of health and medical care. These statutes, e.g. the Transplant Surgery Act,[93] are of a public law, as opposed to a civil law, nature. The Transplant Surgery Act, for example, defines the conditions under which organs may be removed from a living or deceased person's body in order to be used for transplant or other medical purpose. However, this Act does not regulate the legal relationship between the donor and donee.[94]

The donation of biological material is in principle not made for remuneration,[95] and one could therefore characterise the agreement as a beneficial agreement. But is the agreement more in line with an agreement to make a gift or a donation in general? The interim report of the Transplants Committee[96] indicates that even if an organ donation were to be characterised as a gift, the donor's express

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[91] See, regarding ownership of human biological material, Westerlund, L., & Persson., H. A., Civilrättsliga reflektioner på användningen av mänskligt biologiskt material, 2000, pp. 23.
[92] See Rynning, E., Biobankerna – hög tid för bankinspektion? Förvaltningsrättslig tidskrift, häfte 6, 1998, p. 305.
[93] See *Lag (1995:831) om transplantation m.m.* (the Transplant Surgery Act), *Lag (1995:832) om obduktioner m.m.* (the Post-Mortem Examinations Act). Compare also *Hälso- och sjukvårdslag* (1982:763)(the Health and Medical Services Act) and *Lag (1998:531) om yrkesverksamhet på hälso- och sjukvårdens område* (the Health and Medical Services (Professional Activity) Act).
[94] See SOU 1989:98 p. 255.
[95] It should be noted that a token sum of money is given to the donor in connection with donation of blood.
[96] See SOU 1989:98 p. 150.

(active) consent is not required in order for the transplant operation to be carried out. Further, if a person during his lifetime has passed on an organ to another, he has thereby made a "considerable sacrifice and such a donation without remuneration can certainly be characterised as a gift". However, should the donated organ not be claimed until the demise of the maker of the gift, the situation is somewhat different: "In this case, it is not as natural to regard the surrender of the organ as a sacrifice on the part of the maker of the gift. He no longer requires it, and if it is not used for transplant, it will still be destroyed together with the rest of the body either on cremation or during the decaying process. Those reasons which, as regards a living person, lead one to conclude that he did not wish to donate an organ in the absence of his express consent to do so do not have the same force once the proposed donor has died".[97]

The above passage can be used as a basis for discussing the following propositions: first, that the beneficial character of donations as a concept regarding human biological material may change, depending on whether the maker of a gift provides the material on his death or whether he provides it during his lifetime, and second, whether the donation of human biological material can be placed on an equal footing, from a legal perspective, with a gift or donation in general.

Addressing the first question, I doubt that the beneficial nature of the donation arises only where the donor has provided the material during his lifetime. Comparing this situation with that of gifts in general, it is arguable that an agreement should not in fact be considered beneficial simply because it was not linked with a sacrifice on the part of the maker of a gift. The fact that the surrender of the object does not involve any particular loss suffered by the maker of a gift can hardly be said to change the substance of the agreement. A person can wish to give away something for which he no longer has any use, but which in the eyes of the recipient has considerable value. In this case there is nothing to suggest that the agreement cannot be considered to be a gift. Comparing donations in general, the maker of a gift can be a living or deceased at the performance of the donation. If the donation is made during the lifetime of the maker of a gift, it is effected by deed of gift. If it is made after death, it is effected in the form of a will.

In the latter case, it is clear that the donation does not involve any sacrifice on the part of the deceased. However, the donation is considered to have a beneficial character since the maker of the gift is giving away a means or object for a person to the benefit of everyone instead of letting it fall to the relatives of the deceased. The fact that a deceased no longer requires the biological material does not, it is submitted, have sufficient force – any more than in the above cases – to change the beneficial character of the donation transaction. That a person, up until his death – and his relatives thereafter – can refuse to provide biological material for the benefit of another, serves only to underpin the fact that when a donation is in fact made, it is an act (albeit passive)[98] of a clearly beneficial character.

As regards the second question – whether the donation of human biological material can be equated with an agreement on gifts or donations in general, the answer is no. As mentioned above, in order for there to be a gift in the first place, there must be a transfer of property from the maker of a gift to the recipient. Under Section 15 of the Transplant Surgery Act, human biological

[97] See SOU 1989:98 p. 150.
[98] See further details about this question under the subheading "Conclusions".

material may not be provided, received or procured for financial gain, and this provision precludes the sale or purchase of such material in return for payment, which in turn makes it very difficult to put a financial value on such material. Since human biological material does not have any financial value, there will be no transfer of property when the material passes from the maker of a gift to the recipient.[99] Gifts in general and donations of human biological material are therefore not on an equal footing. Comparing the donation of human biological material with donations in general, the whole purpose of the latter transaction is for there to be a transfer of property from the maker of a gift to the recipient. Bearing this in mind, neither donations in general nor donations of human biological material are comparable, since in the latter case, as mentioned above, there is no transfer of property at all.

Within this context, however, it may be interesting to consider another type of agreement, namely that of a deposit. This question is particularly pertinent as regards samples which have been stored for the care of the patient himself. Is it the case that when the biological material is handed over to the recipient, the act of handing over can be characterised as a deposit? A deposit generally refers to an agreement whereby an object is left in the care of another.[100] In the context of a general deposit, the person who leaves the object in the care of another keeps his/her ownership of that object.[101] Further, use of the object is generally not permitted. The nature of a deposit is that the object is merely held for safe-keeping, and there is no question of the property changing hands or being used. If this does happen, the person holding the object may be liable in damages. A deposit agreement does not have to comply with any formalities in order to be valid. The parties may make an agreement that remuneration may be provided in return for storage (agreement of an onerous character), but the agreement may also be of a beneficial nature. The most striking characteristic of a deposit is that the person storing the property takes the property in the interests of the person making the deposit. It depends on the purpose for which the material was provided as to whether one can speak of a deposit of biological material. If the biological material was removed, for example in order to make a diagnosis or treat the patient himself, and the sample is later stored, one can say that a deposit has been effected. The material is handled, for example, by a pathology department in the patient's own interests. With transplants of biological material, however, there can be no question of a deposit. If the contrary were the case, the recipient of, say an organ would simply be storing it for the donor and the donor could therefore recover it whenever he desired. Biological material provided for research purposes cannot be said to constitute deposits either, since in that case the researcher would not be able to use the material.

Having regard to the above, therefore, a transaction involving transplant or research on biological material cannot be characterised as a deposit. One should therefore avoid characterising as a deposit an agreement between a donor and recipient of such material. However, it is possible to use the term 'deposit' where it is simply a question of storing the sample in the interests of the patient.

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[99] See further details under the subheading "Recipients of gifts and donees".
[100] See Bergström, S. et. al., Juridikens Termer, 8th ed., 1993.
[101] The following is based on Bengtsson, B., Särskilda avtalstyper I, 1971, pp. 80, Malmström, Å & Agell, A., Civilrätt, 16 uppl., 1999, p. 123, Helldén, M. & Millqvist, G., Krediträtt, Sveriges Rikes Lag, Lagbokskommentaren, 2000, pp. 241.

8. Object of donations

The object of a general donation, as stated above, is usually money or a chattel. As regards the donation of biological material the potential objects differ depending on whether it is taken from a living or deceased person. The object of a donation from a living person can be a kidney or a lung or possibly part of the liver. As a rule there is a strong connection between the donor and recipient in the sense that the two are related by blood.[102] A living maker of a gift can of course also donate tissue, blood, other bodily fluids, cells, breast milk and teeth.

As regards a deceased maker of a gift there are several possible objects of donation. A deceased maker of a gift can donate all types of human biological material as long as it is technically feasible. Further, someone may not want to donate simply a single organ or specific tissue but his whole body for medical research. In this case, special rules apply.[103]

9. Comparison between gifts and donations

The difference between a general gift and a donation of biological material can be summarised as follows: the maker of a general gift can change his mind about making that gift right up until the moment that the gift or deed of gift is handed over to the recipient. However, once the gift is complete, it cannot be withdrawn unless the gift document is invalid in some way. Otherwise, the deed of gift is binding both on the maker of a gift and on others parties. A general gift will become complete, in the case of tangible chattels, for example, when the property comes into the recipient's possession. As indicated above, however, the gift may be withdrawn if the gift document is invalid in some way. This is true even where the gift is complete. When is the donation of biological material deemed complete? When the biological material is removed from the body? If one assumes that the donation of the biological material becomes complete in removal from the body, it is necessary to distinguish between different situations as regards the right to withdraw the donated material.

If the biological material has been provided for transplant and the necessary operation has been performed so that the relevant organ is already in the recipient's body, it will not be possible to withdraw the donation on the basis that, for example, the maker of a gift can show that the donation document was somehow invalid due to error, imprudence etc.

If biological material is provided for research purposes, the general rule is that the donor can require the sample to be destroyed if for some reason he no longer wishes to be involved in the research project. Further, the donor can require that the material be returned if it is not to be used for those purposes for which the maker of a gift provided it. If the donor, due to error, imprudence or some similar

[102] See Section 7 of *Lag (1995:831) om transplantation m.m.* (the Transplant Surgery Act). See also Prop. 1994/95:148 pp. 80. See also *SOSFS 1997:4 Socialstyrelsens föreskrifter och allmänna råd avseende organ och vävnadstagning för transplantation eller för annat medicinskt ändamål* (Provisions of the National Board of Health and Welfare on the collection of organs and tissue for transplant surgery or other medical purposes), p. 12.

[103] See Section 21 of *Lag (1995:832) om obduktioner m.m.* (the Post-Mortem Examinations Act).

reason, has not understood the purpose for which the material was to be used, he is permitted to require its return. There should, therefore, be a right in both cases to withdraw biological material which has been provided for research purposes, even though the donation must be considered to be complete. However, certain technical problems may arise where the donor wants the sample to be destroyed. Suppose one manages to derive a new product from that sample. What is it that the donor can require to be destroyed? Just the sample itself or the new product as well? Chap. 3, Section 6 of the Biobanks (Health Care etc.) Act (SFS 2002:297) provides that a person who has given his consent to the use of a tissue sample may withdraw his consent at any time. If the withdrawal applies to all uses the tissue sample shall be destroyed or depersonalised with immediate effect. The Government Bill on the Act[104] states that the person who gives his consent to storing the sample in a biobank for certain purposes shall have the unqualified right to withdraw that consent. This right also extends to those persons who have the legal right to represent that person. The consequence of a withdrawal which bears upon all uses of the sample is, as highlighted above, that the tissue sample will either be destroyed or depersonalised. The bill indicates that if the withdrawn consent bears only on the use of a sample for one of several purposes, the sample should not be destroyed in its entirety. Instead appropriate measures should be taken, e.g. special markings to ensure that the sample is not used at variance with the donor´s consent. Further, as regards withdrawal of consent for samples which have been taken for research purposes, it should be the actual tissue sample provided for the research that is to be destroyed, and not the results of that research. The question as to what is to be destroyed if a new product is derived from research involving the tissue sample is not clear from the Biobanks Act. However, it is submitted that in this case there should be a test whereby different interests are reasonably balanced, that is to say the maker of a gift's right to withdraw consent and the researcher's right to exploit material for which consent was given in the name of research. Conversely, a rule that does not taken into account the researcher's interests as well as the interests of the maker of a gift may have serious consequences for research and large projects may come to nothing or have to be started again from scratch.

10. A comparative analysis of deeds of gift and donors' forms

There are similarities in form between a deed of gift and a donation form for biological material; as regards a donation form completed by a living donor, the intention to donate can either be oral or be found in a written document.[105] For example, the text of a written donation form for blood or tissue provided by a living donor can be formed in such a way that the donor consents to give the sample to a specific recipient for research purposes.[106]

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[104] See Prop. 2001/02:44 p. 9, p. 44, p. 75.

[105] Cf. Sections 6–9 of *Lag (1995:831) om transplantation m.m.* (the Transplant Surgery Act), Chap. 2, Section 1 of *Lag (1998:531) om yrkesverksamhet på hälso- och sjukvårdens område* (the Health and Medical Services (Professional Activity) Act), Sections 2, 2a and 2b of *Hälso- och sjukvårdslag* (1982:763)(the Health and Medical Services Act).

[106] This example is taken from a donation form - issued by the Medical Biobank at Norrland University Hospital and Umeå University, 2000.

As regards deceased donors, an intention to donate can be expressed in a written document, e.g. a donor's card, or can be oral, e.g. by informing a close relative of that desire[107] or by signing up with the National Donors' Register.[108] Information given either on a donor's card or on the National Donors' Register can be amended at any time and as many times as is desired. Whether the donor uses a card or the register is immaterial, since there is no "difference in 'value' between these two forms" by which the donor can make known his position regarding human biological material.[109] Irrespective of how the donor makes known his standpoint, it will be the information provided most recently that will be used to determine the donor's wishes regarding donation and will therefore 'bind' both the donor and third parties.

The deed of gift must have been made in writing, in the form of a promissory note or other written document drawn up for the specific purpose of showing that the relevant undertaking has been made.[110] Furthermore, a binding undertaking can be implied where a person indicates in a normal letter that he intends to leave a gift, if it is clear from the circumstances that the letter-writer has intended that the recipient should be able to rely on the letter as proof of an undertaking of a gift. In this case, the letter is deemed to constitute a deed.[111] An undertaking to make a gift may also be oral if, for example, the maker of a gift has made known his intention to a group or association of a number of persons.[112] Under certain circumstances a gift must also be registered in order to be valid (cf. Chap. 8, Section 1 of the Marriage Code, SFS 1987:230).

Summing up, then, it appears, *prima facie*, that donation forms and deeds of gift are similar in form, but the two types of document have very different legal consequences. If an undertaking to make a general gift has legal effect, then legal avenues may be pursued in order to hold the maker of a gift to his obligations regarding that gift. A person who makes known a desire or a refusal to donate human biological material is deemed to have expressed a "manifestation of will, and not a point of view".[113] Will such a manifestation of will provided in a written agreement – a declaration given to the recipient, that a donation is to be made – be binding? In spite of the donation having been made through a written document, it is unlikely to be enforced on civil law grounds where it is considered at variance with principles of good practice.[114] Furthermore, this would conflict with the provisions of the Transplant Surgery Act on consent and any such undertaking should therefore be declared invalid.[115] Having regard to these facts, a deed of gift and a donation form/donor's card can hardly be said to be on an equal footing, even though the letter can be adduced as written proof of the desire of the maker of a gift to "give away" biological material.

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[107] Cf. Section 3 of *Lag (1995:831) om transplantation m.m.* (the Transplant Surgery Act).
[108] See *SOSFS 1997:4 Socialstyrelsens föreskrifter och allmänna råd avseende organ och vävnadstagning för transplantation eller för annat medicinskt ändamål* (Provisions of the National Board of Health and Welfare on the collection of organs and tissue for transplant surgery or other medical purposes), p. 6.
[109] See Socialstyrelsen (National Board of Health and Welfare), Donation av organ och vävnader: Frågor och svar, 2000, p. 23.
[110] See Walin, G., Lagen om skuldebrev, 2 uppl., 1997, p. 233.
[111] See Walin, op. cit. p. 233.
[112] See Lagberedningens förslag till Lag om skuldebrev m.m. 1935, p. 132, NJA II 1936 p. 141.
[113] See SOU 1989:98 p. 220.
[114] See op. cit. p. 39 p. 69.
[115] Cf. SOU 1989:98 p. 58.

There are further differences between a general deed of gift and a donation form for biological material. As regards general gifts, there is, in principle, always a specific recipient. Deceased donors of human biological material can never indicate on their donor's card that a specific organ must be donated to a specific identified recipient. However, a deceased person does have the right to decide which material may be taken and for what purposes. Living donors may decide on a specific identified recipient of their transplanted material. If the maker of a gift provides human biological material for other medical purposes he may, in the same way as a deceased donor, direct which material may be taken and for what purposes it shall be used. A living maker of a gift is also able to determine whether the material should be donated to a specific recipient for research purposes.[116] Secondly, a deed of gift may be linked with remuneration from the recipient to the donor, e.g. the recipient of the gift must provide the maker of a gift with a promissory note of X SEK. In principle, the donation of biological material should never be made in return for remuneration to the donor. Thirdly, a deed of gift may have tax implications for the recipient, something which is not possible when donating biological material. Fourthly, if a person becomes a donor or donee, that information will be protected by confidentiality,[117] whereas the contrary is true of general gifts. As regards gifts, there are rules on publication, whereby in order to be valid against third parties, the gift will only become valid on registration. If, for example, a man wishes to make a gift of something to his wife, then either the rules applying to the completion of gifts in general have to be complied with, or else the gift must be registered in what is known as the National Marriage Register. Otherwise the gift will not be valid as between the parties, Chap. 8, Section 1 (1) of the Marriage Code (SFS 1987:230). For protection against the donor´s creditors, the gift has to be registered in the National Marriage Register, Chap. 8, Section 1 (2) of the Marriage Code. Any creditors will then be apprised of the gift, since the register entry is published in the official journal Post- och Inrikes Tidningar and in local newspapers.

11. Makers of gifts and donors

A comparison of the similarities and differences between the maker of a gift and a donor of biological material leads to the following conclusions. As regards general beneficial agreements, in principle the owner has the legal right to dispose of his assets as he desires. He can therefore hand them over to whomsoever he wishes in the form of a gift. In the case of a donation, the maker of a gift also has the legal right to decide what should happen to his body and its parts. However, if a maker of a gift consents to biological material being donated after his death, he can neither prohibit nor require it to be used for the benefit of a specific person or group of

[116] Cf. donation form, issued by the Medical Biobank at Norrland University Hospital and Umeå University. The donation form clearly stipulates that the biological material is given to that particular biobank. Furthermore, it is stipulated in the donation form that the biological material will not be sold.

[117] See, for example, *Sekretesslag (1980:100*) (the Secrecy Act), *Personuppgiftslag (1998:204*)(the Personal Data Act).

persons of a certain nationality or particular ethnic origin, since this would act as an obstruction to the operation.[118]

The maker of a general gift can lay down instructions to the recipient as to how the gift should be employed. The question is, however, whether one can set conditions for the use of a donation of biological material in the same way. As has already been shown, certain types of condition can be imposed, for example the donor may stipulate that the biological material may not be used for anything other than a specific purpose, or that only a certain type of biological material may be taken.[119]

In principle, anyone can be a donor of human biological material. A living maker of a gift should be able to provide human biological material irrespective of age. Biological material may also be taken from as yet unborn or deceased persons. However, certain donors are excluded from donating organs or tissue to another person where the recipient is in risk of infection or illness.

The Gifts Act does not place any particular requirements on the maker of a gift. However, the gift may be null and void owing to a formal defect whereby the maker of a gift, owing to lack of legal capacity, has no possibility of performing this legal act, the reason being that 1) the maker of a gift is a minor,[120] 2) the maker of a gift is under guardianship,[121] 3) the maker of a gift is mentally disturbed.[122] The maker of a general gift commences the gift transaction. This is also the case where human biological material is donated, by the donor expressing his will to make a donation.

12. Recipients of gifts and donees

A further question requiring analysis is that of the similarities and differences between the recipient of a general gift and the donee of human biological material. The doctrine on general gifts discusses the concept of the requirement of acceptance by the recipient.[123] The general rule is that actual acceptance by the recipient is not required, as long as the gift does not impose any obligations on the recipient. Despite there being no requirement of acceptance, there must be some sort of co-operation by the recipient in order for the gift to be considered final, either implicitly or passively by receipt of the promise of a gift or the completion of the gift. There is no requirement for the recipient to take receipt of the gift. This means that the promise of a gift may be inoperative – even though the promise of a gift is

[118] See *SOSFS 1997:4 Socialstyrelsens föreskrifter och allmänna råd avseende organ och vävnadstagning för transplantation eller för annat medicinskt ändamål* (Provisions of the National Board of Health and Welfare on the collection of organs and tissue for transplant surgery or other medical purposes), p. 12.
[119] See above under subheading – "Object of donations".
[120] See Chap. 9 of the Code of Parenthood and Guardianship (*Föräldrabalk*)(SFS 1949:381, reprinted SFS 1995:974).
[121] See Chap. 11 of the Code of Parenthood and Guardianship (*Föräldrabalk*)(SFS 1949:381, reprinted SFS 1995:974).
[122] See, for example *Lag (1924:323) om verkan av avtal som slutits under påverkan av psykisk störning* (Effects of Contract when Concluded under the Influence of Mental Disturbance Act).
[123] See Hellner, J., Speciell avtalsrätt II, Kontraktsrätt, 3 uppl., 1 häftet, särskilda avtal, 1996 pp. 240. Bengtsson, B., Särskilda avtalstyper 1, 1971, pp. 25. Cf. Håstad, Tjänster utan uppdrag, 1973, pp. 224.

binding on the maker of a gift – if the gift is not accepted by the recipient. Unlike general gifts, as a rule there should be express acceptance by the recipient as regards donating human biological material, for example, where a transplant requires a medical operation, it is clear that the recipient must have expressed his desire to receive the organ/tissue. If the material is taken for research purposes, it seems natural to conclude that the recipient – having asked the maker of a gift whether he has consented to the material being used for that purpose – has expressly made known his desire to receive the material. If the sample is taken in order to make a diagnosis of or treat the patient himself, it should be implicit from the Health and Medical Care Act that the sample is to be used for the benefit of that patient.[124]

As indicated above, a general gift can be withdrawn if, having given the undertaking, the financial situation of the maker of a gift deteriorates to such a degree that, also taking into account the recipient's conditions, the enforcement of the gift is clearly unreasonable. The gift may also be withdrawn under Section 5 (2) of the Gifts Act where the recipient, after the undertaking but prior to completion, does the maker of a gift considerable (significant) wrong.[125] This provision is not particularly suitable for application to the donation of human biological material either. In the first place, human biological material, with the exception of blood, hair, breast milk and teeth, may not be sold or provided to the maker of a gift in return for payment,[126] nor may the recipient receive or transmit biological material from a living, deceased or aborted foetus for financial gain.[127]

Since biological material does not have a financial value, it becomes pertinent to ask the significance in this context for the maker of a gift of a right of withdrawal as provided in Section 5 (1) of the Gifts Act. As regards the second exception, namely the withdrawal of the promise of a gift on the basis that the recipient does the maker of a gift significant wrong, it can be said that the maker of a gift of biological material must always be able to change his mind. The maker of a gift who has consented to donate biological material has the right to change his mind, irrespective of whether or not the recipient has significantly wronged him. If a person has undertaken to donate, say, tissue to a research project, he is entitled to change his mind up until the point that the tissue is actually donated. Moreover, the

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[124] See Sections 3 and 18 of *Hälso- och sjukvårdslag* (1982:763) (the Health and Medical Services Act). Cf. also *SOSFS 2001:8 Socialstyrelsens allmänna råd om försiktighetsmått vid hantering och märkning av sådant biologiskt avfall som kan medföra olägenhet för människors hälsa enligt miljöbalken* (General guidelines of the National Board of Health and Welfare on caution when handling and marking biological waste etc.), *SOSFS 1999:27 Socialstyrelsens föreskrifter och allmänna råd om hantering av smittförande avfall från hälso- och sjukvården* (Provisions and general guidelines of the National Board of Health and Welfare on handling infectious waste from the Health and Medical Sector), *SOSFS 1989:38 Socialstyrelsens föreskrifter om blodgivning, blodtransfusioner m.m.* (Provisions of the National Board of Health and Welfare on blood transfusions etc.), *SOSFS 1990:8 Socialstyrelsens allmänna råd rörande omhändertagande av foster efter abort* (General guidelines of the National Board of Health and Welfare regarding care of aborted foetus), *SOSFS 1996:28 Kliniska obduktioner m.m.* (Clinical autopsies etc.), *SOSFS 1996:29 Socialstyrelsens föreskrifter och allmänna råd: Vissa åtgärder inom hälso- och sjukvården vid dödsfall* (Provisions and general guidelines of the National Board of Health and Welfare: Death and deceased persons – certain measures in the Health and Medical Sector).

[125] See Walin, G., Lagen om skuldebrev, 2 uppl., 1997, p. 248.

[126] See Section 15 of *Lag (1995:831) om transplantation m.m.* (the Transplant Surgery Act). See Prop. 1994/95:148 pp. 87.

[127] See Section 15 of *Lag (1995:831) om transplantation m.m.* (the Transplant Surgery Act).

maker of a gift can also withdraw the tissue sample after donation if the sample is not employed in a way for which consent was given or the maker of the gift has changed his/her mind regarding participation in the research project. A "significant wrong" should never be able to arise regarding the donation of organs taken from a deceased, because the end recipient and the maker of a gift do not generally know each other. Bearing in this in mind, it is unlikely that the recipient can do the maker of a gift "significant wrong" in a way that could be construed as the maker of a gift no longer wishing to donate his organ to that person. If the maker and recipient of a gift are related or acquainted, or otherwise know each other and the recipient is said to have done the maker of a gift significant wrong, the rule must also apply that the maker of a gift can change his mind right up until the operation and after the operation if the material is not used in the way which he consented to.

13. Conclusions

The following conclusions can be drawn from the above. The first conclusion must be that the Gifts Act and other general civil law rules on gifts etc. are not really suitable to be applied to the donation of biological material.[128] Secondly, both general gifts and donations of biological material taken from living persons constitute acts of active giving. Organ donations from deceased persons could possibly be construed as an act of active giving. Sections 3 and 4 of the Transplant Surgery Act provide that, in the absence of any indication to the contrary by the maker of a gift, consent to donate will be presumed as long as relatives do not refuse to go ahead with the operation.[129] It is therefore presumed that the deceased wanted to help a fellow human being in need of organs and that the donor would therefore have been in favour of the donation.[130] In this respect the act of giving can be deemed to be passive. Thirdly, a donation form/donor's card regarding biological material and a general deed of gift do not rank equally in a legal perspective. In principle, general gifts always have a specific, identified recipient, whereas deceased donors of human biological material can never indicate on their donor's card a specific, identified recipient to whom a particular organ should be donated. However, a deceased person does have the right to determine which material may be taken and for what purposes. Living donors should also be able to determine that the material should be donated to specific recipients for research purposes. Fourthly, the concepts do not have the same terminological substance. There is generally considered to be no difference between the concepts of general gifts and donations of human biological material. If there is any difference, it is only legislative, i.e. differences between the Gifts Act and the Transplant Surgery Act, and in everyday speech donations are referred to as gifts. Another interpretation is that the concepts are used differently depending on whether it is a donor or donee that is referred to. A natural person who receives human biological material receives a gift. Such a person receives a gift without obligations and the material then belongs to him. The term 'donation' refers to the person who gives away the gift. The absence of terminological distinction between the concepts of gift and donation is not particularly serious in itself, but it

[128] Cf. SOU 1989:98 p. 69.
[129] See statutory text and Prop. 1994/95:148 pp. 23, pp. 75.
[130] See Socialutskottets betänkande 1994/95:SoU21 Transplantationer och obduktioner m.m. p. 13.

may give rise to some confusion between the two legal concepts in a legal perspective. Authorities, organisations or other bodies providing information to the general public should therefore make it quite clear that the donation of biological material is not linked, in legal terms, to gifts in general. Fifthly, gifts differ from donations depending on the position of the maker of a gift and the donor. The differences include who can be, respectively, the maker of a gift, and the donor. Sixthly, the similarities between a donee and the recipient of a general gift are not particularly striking either; if anything the opposite applies. In short, we may conclude that the Gifts Act cannot be applied to opaque legal questions regarding the donation of biological material.

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12

Commercial engagement and public research in the biomedical area[1]

Ulla Björkman, LLM, Senior Lecturer

Department of Law, Uppsala University.

Among the many legal aspects of the biomedical area, the commercial ones are of special interest to those engaged in research work, i.e. the scientists, the hospitals and hospital authorities as well as the universities, the crucial question being that of the possibilities and limits to making a profit out of the scientific results. The new Swedish Biobank Act (2002:297) addresses the problem, but a number of questions remain unanswered.

Briefly, national as well as international laws firmly discountenance any financial gain out of the human body and its parts as such; a commercial market for such material is unwanted for several reasons, principal among them being human dignity. However, national as well as international laws also make exceptions for "discarded tissues" (ETS 1997/164, art. 21) or even for blood (Section 15 of the Swedish Transplants Act). On the other hand, Sweden's new Biobank Act lays down that tissues or parts of tissues that are kept in a biobank under its provisions must not be sold or otherwise transferred for financial gain (Chap. 4, Section 8). As the new Act refers to the older Transplants Act when it comes to the sanctions against illegal conduct, it remains uncertain whether blood really is excepted or not. Defining the different human materials in this context and also "financial gain" is therefore a major legal task.

In this process it should be noted that the Swedish legislation also limits the ability of public institutions as such to take part in profit-making business, whatever the context. As the universities as well as public medical care institutions, hospitals etc. are normally part of the public system under this obligation, a further impediment to financial profit is made evident.

It should also be noted that, according to Swedish law, a scientist, even if he or she is on the payroll of an university, is granted the exclusive intellectual right to develop the invention or discovery resulting from his or her research-work.

An interesting case is now pending before the Administrative Court of Appeal in Sundsvall. The Court is expected to deal with the questions whether or not the Västerbotten County Council, as mandator of the hospital in the university town of Umeå in the north of Sweden, a) broke the basic prohibition in the Local

[1] An English summary of *Kommersiell verksamhet inom biomedområdet och den offentliga forskningen*, forthcoming, 2003

Government Act of financial support to a private enterprise, or even b) broke the same Act's prohibition of financial gain in a body coming under the Act, the County Council being such a body, when the County Council, as one of the parties forming a private enterprise, Uman Genomics AB (the University of Umeå being one other party), granted Uman Genomics AB a favoured position for using the human material in a biobank collected at County Council-run Umeå Hospital. The Administrative Court of first instance in Umeå (Dom i Länsrätten i Västerbottens län 2002-10-04, mål nr 668-02) did not find the charges made by County residents proved, but we are still awaiting the decision by the Court of Appeal.

In my opus I recommend that

- the County Council in charge of a biobank keep it and run it according to the Biobanks Act and not show favour to any user,
- scientists from all universities be given equal rights to use the material under the law without gaining any monopoly status,
- the research be openly funded, whether by taxpayers' money, specially earmarked, or by the medical industry on a commission basis,
- scientist develop their results freely under the law.

13

Agreements concerning human biological material

Urban Paulsson, Advocate & Rebecka Frisk, LLM

Bird & Bird

This article addresses some of the more critical legal issues that arise in connection with the negotiation and drafting of commercial agreements for access to and research on human biological material stored in biobanks. Now that Sweden has enacted a law regulating the handling of biobanks within healthcare organizations, which clarifies the legal situation regarding commercial use of the biobank material, it is expected that the number of collaborations between companies and academia in respect of the biobanks will increase. When negotiating and drafting the collaboration agreements there are a number of critical legal issues that need to be considered. The legal issues specific to biobank research collaboration are: (i) the prohibition of deriving profit from handling donated human biological material, (ii) the requirement of patient consent to donation of material, and (iii) the requirement of ethics committee approval for research on human biological material. These issues and their impact on the key clauses in a commercial agreement regarding access to and research on human biological material are discussed in this article. The key clauses that are addressed concern: (i) considerations paid under the agreement, (ii) rights to research material and results, and (iii) the content of the research.

1. Background

Due to the rapid development of biomedical research and genetic engineering both in Sweden and internationally, interest in collections of human biological material has dramatically increased during recent years. Every day biological material is taken from humans in the form of specimens for different reasons and for different purposes. Valuable information, for example regarding disease mechanisms and genetic causes, can then be extracted from this biological material. Therefore the biological material enables research that was not possible to carry out before, research that might lead to new methods of treatment and new drugs. In this way the biological material also acquires a commercial value which impels research companies to enter into agreements with universities and county councils concerning access to human biological material in biobanks.

2. General overview – agreements and scope of article

By way of background, it should be emphasised that an agreement regarding access to biological material is in many respects no different from agreements within other

areas. The agreement is built upon the presumption that two or more parties agree on a suitable form of collaboration and from this try to reach a reasonable distribution of rights and obligations. Many different parties may enter into agreements regarding biological material. The agreements may be oral or in writing, short-lived or long-term.

In this article we will focus on the issues that will surface when a commercial entity and a university/county council are about to enter into a written agreement concerning access to and research on biological material from a biobank. It should be noted that general contractual issues will not be discussed any further. Typically, both universities and county councils might be the other party to the commercial agreement, but for the sake of simplicity we will hereafter only refer to universities, even though county councils might also be involved.

The particular problems with agreements concerning human biological material in biobanks that we intend to discuss in this article appears in relation to a number of statutory provisions described below, namely:

- The prohibition under the Transplants Act (1995:831) and the Biobanks Act (2002:297), of deriving profit from the handling of donated human biological material
- The rules of ethical approval.
- The requirement of patient consent and the effect of withdrawing consent.

These provisions and their effects on the content of the agreement define the scope of this article.

2.1 The prohibition of deriving profit

Section 15 of the Transplants Act contains a prohibition of deriving profits that covers handling of human biological material for profit purposes. Under the law it is a criminal offence to take, deliver, receive or handle biological material from a living or deceased human being or tissue from an aborted foetus with the intent of deriving profit. All human biological material is included, with the exception of blood, hair, mother's milk and teeth, and the prohibition is intended for unprocessed biological material.

One important exception to the prohibition concerns refined or processed human biological material that is included in a product, for example a drug, and that becomes an object of sale or other assignment for a consideration. This processed biological material is not covered by the prohibition.[1]

The legal acts that are covered by the prohibition are first of all purchase or sale of the material. But the prohibition is general in nature and is not limited to certain parties or situations. In the *travaux* préparatoires it is stated that the prohibition does not have any limitation concerning the purpose of the handling, but that a wide formulation was used to cover all forms of taking, delivery, receipt or mediation of biological material for the purpose of deriving profit. [2]

[1] Prop. 1994/95:148 p. 88 and Domeij, Humanbiologiskt material och vinningsförbud. 2001 p.775.
[2] Prop. 1994/95:148 p. 52, 87 f. See Domeij, Humanbiologiskt material och vinningsförbud. 2001 p. 778 ff.

The Biobanks Act, which came into force on 1 January 2003,[3] prohibits the gainful assignment and distribution of tissue specimens stored in biobanks.[4] Chap. 4, Section of the same Act lays down a rule making the assignment of a biobank as such possible, wholly or partly, and focusing on the situation where a biobank is assigned primarily for, say, organisational reasons. To make such an assignment possible, special circumstances are required and the National Swedish Board of Health and Welfare has to give permission. However, such assignment may not be undertaken for gain.

The fact that Swedish law prohibits the handling of human biological material for profit purposes should cause any party desiring to enter into an agreement concerning that kind of material to carefully consider the particular problems that arise and the impact on contract terms, such as the structure of payment and cost calculation models used in the agreement. We will be returning to these questions presently.

2.2 Ethical approvals

Before giving its approval to a particular project, a research ethics committee shall examine the project from a scientific as well as from a general ethical point of view.[5] Any conditions imposed by the committee shall be evident from the decision.

The research ethical examination refers to the scientific durability of the project and the ethical problems that the project poses. It also examines the adequacy of the procedures for collecting patients' consent and the information provided to the patients. The research ethics committees shall make a risk/profit estimate and in doing so ascertain that the project concerns an essential question which can be appropriately answered through the proposed research.[6]

The ethics committees consider applications before the research begins, but cannot examine the performance of the research as such. The scientist involved in the research is therefore obliged to follow the project description that has been given at the time of application and to report any changes in the project as well as complications and new information with a bearing on the risk assessment. Finally, the scientists have to report the result of the project. The ethics committee shall further approve possible modifications of the project before they are carried out.[7]

It is also important to note that, pursuant to the pending legislation on ethical approval for research, research that falls within the scope of the proposed law requires ethical approval in order to be permissible. To carry out such research without the relevant approval has been made a criminal offence. Further, it is a condition for approval under the law that the research be carried out or supervised by an appropriately qualified researcher. As has already been shown, a research

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[3] *Lag (2002:297) om biobanker i hälso- och sjukvården* (the Biobanks Act).
[4] Chap. 4, Section 8 of *Lag (2002:297) om biobanker i hälso- och sjukvården* (the Biobanks Act).
[5] Research ethics committees appraise and judge research ethical questions. Both the general public and the research community shall be represented on such a committee. Usually the committee is affiliated to a university or a college, or to some other authority prominently concerned with funding the research. See Chap. 1, Section 2 of *Lag (2002:297) om biobanker i hälso- och sjukvården* (the Biobanks Act). According to Chap. 2 , Section 3 of the Biobanks Act, a research ethics committee shall test and approve the establishment of a biobank if it shall be used for the purpose of research or clinical testing. See also Chap. 3 , Section 5 (3).
[6] Prop 2002/03:50, p. 95 ff.
[7] *ibid*.

collaboration agreement with a university will need to address issues relating to the scientific personnel involved in the research and mechanisms for obtaining the requisite approval. [8] We will return to this question below.

2.3 The patient's consent

Biological material may be taken from a living human being for the purpose of research only if he or she has consented. The consent shall be freely given and can be given either verbally or in writing. Consent once given may at any time be withdrawn. The consent shall be specific and clearly state the research that is to be carried out with the material and, in the event of new areas of use being found for the material in question, new consent shall be obtained. The research ethics committee determines the requirements that will be applicable for information and consent in order for the tissue specimen to be used for the new purpose.[9]

It follows from the above that the research area specified in the patient's consent will constitute the frame for the research that can be contracted. It is also to be noted that a withdrawal of consent only relates to the donated material as such. Thus, it does not affect the research results that have been generated with the use of the material. In that context, it remains to draw the line between the biobank material and the research results. We will return to this below.

3. Key clauses

Before drafting an agreement for access to and research on biobank material, it is important to carefully think through all the different issues that may arise between the parties in the future. The more issues that are addressed beforehand in the contract, the more likely it is that the co-operation will work out. The statutory provisions described briefly above obviously affect the drafting of a number of key clauses in the agreement. In this connection, we have elected to confine the present article to discussing their impact on the contract provisions that are typically the key clauses for a commercial entity. These key clauses address:

- compensation,
- rights to biobank material and research results, and
- the content of the research.

3.1 Compensation clauses

The parties may violate the above described prohibition of financial gain when drafting the compensation clauses.[10] A party intending to enter into an agreement concerning access to biobank material should investigate the following two questions in particular:

(i) what is the compensation intended to cover and
(ii) how is the compensation to be calculated?

[8] Ds 2001:62 Etikprövning av forskning som avser människor, p. 95 ff.
[9] Chap. 3 , Sections 1 and 6 of *Lag (2002:297) om biobanker i hälso- och sjukvården* (the Biobanks Act). Prop. 2001/02:44, pp. 24 f, 35 ff.
[10] See Chap. 4, Section 8 of *Lag (2002:297) om biobanker i hälso- och sjukvården* (the Biobanks Act).

To start with, one can establish that co-operation between academic and commercial entity may contain several different kinds of compensation mechanisms. The most frequent compensations are:

- *(i)* compensation for the handling by the universities of the biobank and distribution of material,
- *(ii)* compensation for contract research carried out by the university scientists on the biobank material on the company's behalf,
- *(iii)* unrestricted research grants to the university, which may or may not fall due for payment at agreed milestone events, and
- *(iv)* compensation, primarily royalties, the size of which depends on the commercial success of the products developed by the commercial entity from the biobank material.

Before going into these questions in detail we would like to note the limited case law in Sweden on the subject., With the exception of the recent judgment by the county administrative court in Västerbotten concerning Uman Genomics AB, case law, to the best of our knowledge, is non-existent. [11] Added to which, the doctrine in this field is meagre. [12]

Compensation for contractual research, item (ii) above, is more seldom problematic. The prohibition of profit is aimed at payments for transfer of the biological material.[13] The compensation in item *(ii)* refers to a research service supplied by the university and not access to biological material.

Payments under items *(i)*, *(iii)* and *(iv)* above may, however, cause greater problems, depending on how the compensation is constructed.

Regarding compensation for the handling of biobanks and distribution of material, i.e. item *(i)* above, the provisions have to be transparent enough for it to be clear that the compensation does not contain any mark-up but is calculated on the basis of the actual costs of the universities. In this context it is interesting to note that within the university world there is a steady trend towards, as it is hoped, abandonment of the fixed percentage-based fees for administration, premises and other costs, that have so far has been applied to externally funded research. Instead, many universities want to reach a solution where an overall price is applied which may include a profit element. Such a model may be less suitable to apply in agreements concerning biobank material, since the overall price quoted may well exceed direct and indirect costs to the university.

Proposed wording of a compensation clause for handling of biobanks is given below:

> *"The company shall compensate the University for its costs and expenses as a result of storage, handling and administration of the biobank. The scope of the compensation and other payment terms are shown in Appendix [ ]. At the same time, the University confirms that the compensation paid by the Company for the work of the University, as stated above, to no extent comprises any profit to the University."*

[11] Case No. 668-02, länsrätten in Västerbottens län.
[12] Domeij, Humanbiologiskt material och vinningsförbud. 2001. p. 773 ff.
[13] Chap. 4 , Section 8 of *Lag (2002:297) om biobanker i hälso- och sjukvården* (the Biobanks Act). Prop. 2001/02:44 p. 56 f.

Whether or not research grants in agreements regarding access to biobanks, i.e. item *(iii)* above, are consistent with the law will, to a great extent, depend on whether or not the payment is connected in any way with the handling of the biobank. If, for instance, a company undertakes in an agreement concerning biobanks to pay a research grant, the size of which is dependent on the quantity of biological material that the company gains access to, there is an evident risk of the university being considered to have distributed the material for the purpose of gain.

Likewise, it should be difficult to undertake to pay a research grant at a certain rate for every year that the biobank agreement is in force. An example of such a clause is given below:

> *"For the duration of this agreement, the Company undertakes to support the research of the University within the area [ ] at a rate of SEK [ ] annually and the University undertakes to allocate the said grant for such research."*

If on the other hand the research grant is paid as a reward for successful contractual research carried out by the university, where possibly also intellectual property rights have been transferred, it is less probable that the prohibition of profit will be considered to have been violated. Even if the biobank material has made contractual research possible, the connection between the two is diluted. It is here relevant to note the exception stated in the Transplants Act concerning processed biological products. The diluted connection, coupled with the fact that the prohibition of profits should as penal legislation be interpreted restrictively, should lead to the conclusion that the last mentioned form of contribution falls outside the prohibition area. An example of such a clause is given below:

> *"As a reward to the University for successful contract research, the Company undertakes to support the research of the University within the area [ ] by the amounts set out below, to be paid out on the milestone events set out below, and the University undertakes to allocate the said amounts for research in the said area.*
>
> *(i) SEK [ ] at the initiation by the Company of clinical trial in phase III with the first product resulting from the contractual research,*
> *(ii)* SEK [ ] at the grant to the Company of all necessary regulatory approval required for the commercial sale of products referred in i) above in the first country or region of either the EU or the U.S."

Finally the question remains whether a university can agree to compensation based on the commercial success of the company with products developed from the biobank material. In accordance with the above, we believe this question should be answered in the negative if the surrender of biological material is the sum total of the University's performance. The compensation in that case cannot reasonably be considered to relate to anything but the actual transfer of biological material.

On the other hand, if royalties or milestones are granted in return for successful contract research accomplished by the university, where in many cases valuable intellectual property rights are also created, the prohibition of profit should not reasonably apply. The exception stated in the Transplants Act for biological products should also be noted in this regard.

Summary: *the prohibition of profit*

- The prohibition of profit targets transfers of the material for the purpose of financial gain.
- The agreement has to be transparent, so that different services and the pricing of the same are clear.
- Compensation with "an element of profit" should be possible insofar as it relates to other performance by the university than the handling and distribution of material from the biobank.
- The prohibition of profits constitutes penal legislation and shall therefore be interpreted restrictively.

3.2 Ownership and use of biological material

The problems that a drafter of an agreement is confronted with concerning property rights to human biological material result from the unclear legal situation in Sweden.[14] There are fewer uncertainties regarding biological material that constitutes research results, and not biobank material. For this reason, not least, it is suitable when structuring an agreement to divide the material into two categories, i.e. biobank material and biological material that constitute research results, respectively.

Examples of such definitions are given below:

> *"**Biobank material** shall mean the donated human biological material that is made available under this Agreement for the Research."*
>
> *"**Resulting material** shall mean the human biological material and other material that has been created in the Research and which is derived from the Biobank material"*

Regarding biobank material the doctrine appears unanimous in that ownership cannot be used as a legal concept. The right by which a university or a scientist possesses a donated human biological material is rather a right of disposal, the extent of which is largely determined by the content of the patient's consent and the ethical approval that has been given for the research on the material. [15]

From a contractual point of view it is important to ensure:

(i) that the content of the research that is intended to be executed with the donated material is well defined in the agreement and that it is consistent with the research that has been specified in the ethical approval and patient's consent, respectively,

(ii) that the key scientists who are to carry out the research in question are specified in the agreement and that the *same* scientists have been specified in the ethical application,

[14] See, for example, Westerlund/Persson, Civilrättsliga reflektioner på användningen av mänskligt biologiskt material. 2000 pp. 23 ff, 32, 62. Prop. 2001/02:44 p. 25 f.
[15] Westerlund/Persson, Civilrättsliga reflektioner på användningen av mänskligt biologiskt material. 2000 p. 23 ff.

(iii) that it is clear from the agreement whether the donated material is surrendered to scientists in coded form, which makes it retraceable, or in an un-identified form that does not make it traceable back to a donor.

The extent of the right of disposal of the biobank material is affected by what has been agreed concerning:

(i) whether the biobank material is to be surrendered in coded or an un-identified form and
(ii) the consequences of a withdrawal of patient's consent, applying only to coded material

It is clear from Chap. 4, Section 4 of the Biobanks Act that the biobank material, when surrendered to scientists, shall be in either coded or un-identified form. For tissue specimen in a biobank to be covered by the Biobanks Act the material must be traceable back to the donor. Consequently, the Act will not cover un-identified material. It should be noted that a donor has an unrestricted right to, at any time, withdraw consent. Withdrawal of consent shall lead to destruction of the tissue specimen that has been donated for research. When consent is withdrawn, it may be decided that the tissue specimen, instead of being destroyed, shall be un-identified, whereupon the Biobanks Act ceases to be applicable. It is important to observe that the withdrawal of consent does not include the result of the research on the material. Thus, appropriate wording is important in this context, and the wording must be adapted to the need for disposal, also in the event of the donor withdrawing consent. Different wordings of the contract and of patients' consent can be used to regulate the scope of the right of disposal.

Concerning the biological material that constitutes research results from the use of the biobank material, defined as "Resulting Material" above, a number of questions need to be considered in the contract, for example:

(i) how to draw the line between the biobank material and the material constituting research results, and
(ii) how to allocate the rights to the biological material constituting research results.

Firstly, as regards item *(i)*, the debated embryonic stem cell research may serve as an example. The stem cells, which are the adaptable primordial cells of the body, can be isolated from a donated embryo. Then, by applying a number of techniques, media and tools, these isolated cells can be made to divide themselves without changing character. At this point a stem cell line is considered to be established.

The question then is at what point in this process stem cells are transformed from donated material to a research result. The answer to this question will decide which rights can be obtained through an agreement for the respective material. In our opinion, the transition from donated material to research result takes place when the embryonic stem cells have been isolated and made to multiply outside the embryo. It is worth noting that neither the Biobanks Act or its *travaux préparatoires* furnish any guidance on these questions, beyond saying that the biobank material

does not include research results. However, it appears from the *travaux préparatoires* of the Transplants Act that a certain level of processing of the biological material is necessary in order for the material to constitute a product and thus be excepted from the Act's prohibition of profit. A similar view is stated by the EMEA (European Agency for the Evaluation of Medical Products), in their recommendations for a definition of a human somatic cell therapy product.[16]

There are some fairly complicated questions that the author of the agreement needs to consider, not least when the contract deals with material that multiplies through cell division.

When the demarcation is made in the agreement, which of course presupposes detailed discussions with scientifically initiated persons, the parties can agree on the rights to the resulting research material. As far as we understand, the same rules apply for biological research material as for other, more traditional, research results, i.e. they can be possessed with full property rights for the proprietor.

However, whether such a property right initially belongs to the university or the university scientists who have created the result, in our example above the stem cell line, is a separate question. Insofar as patentable inventions, and not tangible results, are concerned, it follows from Swedish law that the patentable invention is owned by the university scientists. [17]

When it comes to the actual tangible result, the issue is not regulated in Swedish law. The question of the right to biological research material has been examined by a Norwegian district court.[18] The case concerned a dispute between two hospitals about the right of disposal of research material, among other things in the form of blood tests, DNA extracts and personal information relating to the specimen. The court established that in the absence of directly applicable rules, an overall assessment had to be made of the circumstances in the case. The starting point of the court's assessment was the patient interest.

Since the court found that the patient interest, as it had been expressed in the consent, was to be satisfied regardless of who had the right to the material, the question was decided by balancing the interests of the parties. In this balancing of interests, the court found that the degree of connection of each party to the project and the disputed material would be decisive and it ruled in the favour of the scientist. In its judgment the court considered among other things who had managed the financing of the project and the contact with third parties who supplied and controlled resources for the project as well as the intentions of the parties.

Since it seem to be unclear in Swedish law whether biological research results initially belong to the scientist or to the university, our advice to an outside contracting party, for example a company, is to ensure that ownership is assigned by both the university and the scientist.

[16] Points to consider on manufacture and quality control of human somatic cell therapy medicinal products. Adopted by the committee for Proprietary Medicinal Products (CPMP), May 2001, p. 3.
[17] See Section 1 (2) of *Lag (1949:345) om rätten till arbetstagares uppfinningar* (the Employees' Inventions (Entitlement) Act).
[18] Asker and Baerum Herredsrett, Nordiskt Immateriellt Rättsskydd (NIR). 2000, p. 688.

Summary: *ownership and right of use*
- Different rules apply, respectively, to biobank material and biological material constituting research material.
- Use careful definitions in the agreement to draw the line between these categories of biological material.
- Since it is uncertain in Swedish law whether biological research results belong to the university or the scientist, an outside party should secure rights from both.

3.3 The research content

As regards the content and performance of the research, the patient's consent and ethical approval constitute two limiting factors. In an agreement regarding access to and research on biobank material, therefore, the content of the research plan, which is normally attached to the agreement, must fully correspond to the patient's consent and the ethical approval. Since the purpose of the Biobanks Act is to protect the interests of patients and not least the patients' integrity, we recommend that the patient information clearly state what can be expected in terms of results and their potential use in the future.

The following should also be regulated in the agreement:

(i) which appropriately qualified university researcher is to carry out or supervise the research,
(ii) who is responsible for obtaining new ethical approvals and patient consents as a result of changes in the content of the research,
(iii) the consequences of non-conformity between the approved specified research and the research actually carried out, and consequences if no appropriately qualified researcher is available to carry out or supervise the research.

Also concerning the content and execution of the research, it is important to distinguish clearly between the biobank materials on the one hand and the biological research results on the other. The limitations that follow from the ethical approval and the patient consent are typically related to the donated material and not the research results. Further research on the human biological material that constitute research results might demand new ethical approvals, but that is a different issue.

Summary: *the research content*
- The ethical approval and the patient consent constitute the framework for the research that the agreement may cover.
- The appropriately qualified researcher conducting or supervising the research should be identified in the agreement.
- Responsibility for obtaining new ethical approvals and/or patient consents in the event of changed research and responsibility for ensuring that an appropriately qualified researcher is available to carry out or supervise the research, need to be regulated in the agreement.

4. Conclusion

The enactment of the Swedish Biobanks Act has helped to clarify some of the previously unclear legal issues that the contracting parties need to consider when entering into an agreement for access to and research on donated human biological material stored in a biobank held by a health care organisation. In particular, key clauses dealing with i) rights of use and title to tangible research results, and ii) the structure of payments under the agreement, may now be drafted with a higher degree of legal certainty than in the past.

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14

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4. Conference and seminar contributions

Anvret, M., Guldgruva eller huvudvärk? Vilken nytta har läkemedelsindustrin av biobankerna? Vilken betydelse har det att lagen inte gäller privata biobanker? Lecture on the course entitled "Biobankslagen", March 20-21, 2003, Uppsala. Kurssekretariatet, Uppsala University

Eriksson, S., Etiska regler för biboanker. Lecture on the course entitled "Biobankslagen", March 20-21, 2003, Uppsala. Kurssekretariatet, Uppsala University.

Eriksson, S., The Use of Human Biobanks, Lecture at SSF-funded research school for PhD students in cellular coummunication, August 19, 2002.

Eriksson, S., Development of – and chairman for – the entitled "Biobankslagen", March 20-21, 2003, Uppsala. Kurssekretariatet, Uppsala University.

von Essen, U., Den nya biobankslagen., lagens innehåll och användning. Lecture on the course entitled "Biobankslagen", March 20-21, 2003, Uppsala. Kurssekretariatet, Uppsala University.

Hansson, M.G., Annual meeting of the Swedish Oncology Association, in Jönköping March 24, 2000.

Hansson, MG., Seminar for Group leaders at Amersham Pharmacia Biotech, Uppsala, June 8, 2000.

Hansson, M.G., Lecture on biobanks and ethics at the Scandinavian Healthcare Authorities Congress, Reykjavik, Iceland, August 31 – September 1, 2000.

Hansson, M.G., Seminar at Linköping University, October 4, 2000.

Hansson, M.G., Lecture on genetic research and biobanks, Biotechnology Trade Show and Pharmaceutical Congress, Stockholm International Fairs, Älvsjö, October 9, 2000.

Hansson, M.G., Lecture on the ethics of biobank research, University of Newcastle, UK, November 22, 2000.

Hansson, M.G., Lecture on the genetics of DNA-testing and biobanks, Åmic Inc., Uppsala, January 17, 2001.

Hansson, M.G., Seminar on gene technology and biobanking, Videndus AB, Stockholm, January 26, 2001.

Hansson, M.G., Lecture on ethical aspects of biobanking, Linköping University, April 23, 2001.

Hansson, M.G., Seminar with scientists on the use of biobanks, Uppsala University, May 16, 2001.

Hansson, M.G., Lecture on the ethics of biortechnology, The Foundation for Technology Transfer, Stockholm, June 12, 2001.

Hansson, M.G., Lecture on Pharmacogenomics, biobanks and ethics, Swedish Pharmaceutical Society, Stockholm, August 22, 2001.

Hansson, M.G., Lecture on ethical and legal aspects of biobanking, Meeting with all scientists at the Dept. of Medicine, Uppsala University, Skokloster, August 30, 2001.

Hansson, M.G., Lecture on the ethics of stem cell research, Huddinge University Hospital, September 19, 2001.

Hansson, M.G., Lecture on ethical and legal aspects of biobanking, The Federation of County Councils, Stockholm, September 28, 2001.

Hansson, M.G., Seminar regarding ethical review of biobank research, Uppsala Research Ethics Committee, October 17, 2001.

Hansson, M.G., Seminar on biobanking, Wallenberg Consortium North, Uppsala, November 9, 2001.

Hansson, M.G., Seminar on ethical and legal aspects of biobanking, Executive Directors, Uppsala University Hospital, January 10, 2002.

Hansson, M.G., Seminar for the Parliamentary Standing Committee on Social Affairs concerning the Government's Biobanks Bill, the Riksdag (Swedish Parliament), January 29, 2002.

Hansson, M.G., Lecture on Gen-Ethics and biobanks, Students in molecular biology, BMC, Uppsala University, February 27, 2002.

Hansson, M.G., Lecture on integrity, the Royal Academy of Arts and Sciences of Uppsala, March 6, 2002.

Hansson, M.G., Seminar on biobanking, SweGene & Wallenberg Consortium North, Sigtuna, May 29, 2001.

Hansson, M.G., Conference with a session on biobanking arranged by the Wellcome Trust, York, UK, July 31 – August 3, 2002.

Hansson, M.G., International workshop on biobanking at Uppsala University, September 12-13, 2002.

Hansson, M.G., Seminar for Clinic Superintendents at Uppsala University Hospital, September, 25, 2002.

Hansson, M.G., Seminar on biobanking, SweGene & Wallenberg Consortium North, Såstaholm, October 1, 2002.

Hansson, M.G., Seminar on the ethical and legal issues of biobanking, Stockholm County Council, October 8, 2002.

Hansson, M.G., Stig Wahlqvist Symposium, Saltsjöbaden, November 4-5, 2002.

Hansson, M.G., Lecture on the ethics of biobank research, Bioethics Seminar at Fudan University, Shanghai, November 15, 2002.

Hansson, M.G., Lecture on the ethics of biobank research for medical students, Peking Union Medical College, Beijing, November 19, 2002.

Hansson, M.G., Seminar on ethical and legal issues related to biobank research, AstraZeneca, Södertälje, January 17, 2003.

Hansson, M.G., Seminar on biobanking, The Federation of County Councils, Stockholm, January 31, 2003.

Hellstadius, Å., Wessman, R., Wolk, S., En för alla – alla för en? Om forskaren, företaget, sjukhuset och biobanken. Frågor om konkurrens, upphovs- och arbetsrätt. Lecture on the course entitled "Biobankslagen", March 20-21, 2003, Uppsala. Kurssekretariatet, Uppsala University.

Hellstadius, Å, Lecture on copyright protection of biobanks. VJS conference Upphovsrätt, varumärke, patent 2002. 17 December 2002, Norra Latin, Stockholm.

Laage-Hellman, J., Høring om biobanker (Hearing on Biobanks) organised by Teknologirådet in association with Det Etiske Råd for Folketingets Sundhedsudvalg, Forskingsutvalg og Udvalget vedr. det etiske Råd, Copenhagen 2/10 2002

Laage-Hellman, J. & Hansson, M.G., The use of biobanks in research, Chalmers Bioscience Workshop May 10, 2001.

Laage-Hellman, Jens, Medicon Valley Bio-Conference 19 September 2001. Session on Ethics and Medical Biotechnology: Title: Commercialisation of biobanks through dedicated genomics companies.

Lindberg, B., Lecture, Pensionärsuniversitetet, Biobanker som Hälsoresurs, Uppsala 11 February 2003.

Paulsson, U., Tillgång till proverna. Om avtal för industrin. Lecture on the course entitled "Biobankslagen", March 20-21, 2003, Uppsala. Kurssekretariatet, Uppsala University.

Persson, A. H., Vem äger provet – om äganderätten till proverna. Lecture on the course entitled "Biobankslagen", March 20-21, 2003, Uppsala. Kurssekretariatet, Uppsala University.

Ring L. &Kettis Lindblad Å., Empirical research on informed consent and biobanks. EASST 2002 (European Association for the study of science and technology). York, 31st July-3rd Aug. 2002.

Rynning, E., Hearing on biobanks, arranged by the Swedish Research Council, the Ministry of Education and the Ministry of Health and Social Affairs, Stockholm, April 20, 2001.

Rynning, E., Lecture on forthcoming legislation on biobanking and research ethics review, Legal Department of the University Administration, Uppsala University, November 29, 2001.

Rynning, E., Symposium on biobanks and health data research, Läkarstämman, Stockholm, November 30, 2001.

Rynning, E., Lecture on the new Swedish Biobanks Act, Biotech Forum, Stockholm, November 30, 2001.

Rynning, E., Lecture on forthcoming legislation on biobanking and research ethics review, Research ethics committee of the Faculty of Medicine, Uppsala University, December 12, 2001.

Rynning, E., Lecture on the New Swedish Biobanks (Health Care) Act – Privacy Versus Freedom of Research Revisited, 14th World Congress on Medical Law, Maastricht, August 14, 2002.

Rynning, E., Lecture on forthcoming legislation on biobanking and other legal aspects of research ethics review, Research Ethics Committee of the Faculty of Medicine, Uppsala University, September 9, 2002.

Rynning, E., Lecture concerning legal issues on biobanking – privacy versus freedom of research and property rights, International workshop on biobanking, Uppsala University, September 13, 2002.

Rynning, E., Seminar on stem cell research, arranged by the Swedish Research Council, the Book and Library Fair (*Bok- och biblioteksmässan*), Gothenburg, September 20, 2002.

Rynning, E., Lecture on Swedish legislation for stem cell research, International conference on the commercialization of stem cell research, London, September 24, 2002.

Rynning, E., Hearing on biobanks, the Danish Parliament (*Teknologirådet i samarbete med Det Etiske Råd for Folketingets Sundhedsudvalg, Forskingsutvalg og Udvalget vedr. det etiske*
Råd), Copenhagen, October 2, 2002.

Rynning, E., Lecture on the protection of integrity and the interests of research – with regard to the new biobank legislation, Symposium on biobanks, Umeå University, December 17, 2002.

Sundström, C., Biobanker i den kliniska vardagen. Hur används biobanker i klinisk verksamhet? Vilka svårigheter ställer den nya lagen klinikern inför? Lecture on the course entitled "Biobankslagen", March 20-21, 2003, Uppsala. Kurssekretariatet, Uppsala University.

Westermark, K., Erfarenhter från kliniska prövningar. Lecture on the course entitled "Biobankslagen", March 20-21, 2003, Uppsala. Kurssekretariatet, Uppsala University.

5. Project activities

Hearing of representatives of industry, Swedish authorities and representatives from Iceland, Uppsala, September 16, 1999.

Public Hearing in Göteborg on Biobanks, ethics and law, May 11, 2000.

Public Hearing in Göteborg on Biobanks, ethics and law, March 12, 2001.

Exhibition at Biotech Forum, Annual Biotechnology fair, Stockholmsmässan, November 28-30, 2001.

Exhibition at the Biotech Forum, Annual Biotechnology fair, Malmömässan, October 8-10, 2002.

16 maj 2001, Vem äger mina celler? Public Hearing on ethical and legal aspects of biobank research. Uppsala University.

10-11 mars 2003, Biobanker som hälsoresurs – Etiska, juridiska och ekonomiska förutsättningar för en effektiv och integritetssäker användning av biobanker (Biobanks as Health Resources – Ethical, legal and economic prerequisites for efficiency and integrity), Uppsala Slott, Uppsala.

The potential benefits of biomedicine and biotechnology are considerable, but this is also an area of science and medicine that is sometimes found controversial. Decisions made by scientists, by health care professionals and by policymakers must be well informed and based on knowledge and sound research. Legal experts concerned with public law and intellectual property rights, philosophers and social pharmacists have been collaborating with geneticists, pathologists and doctors in several research projects in order to seek the kind of biobank management that would satisfy the interests of both the research community and the general public as regards new medicines and forms of treatment, whilst protecting the integrity of the individual. A summary of that research is presented in this book.

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