

Biobanks in Europe: Prospects for Harmonisation and Networking

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EUR 24361 EN - 2010

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JRC57831

EUR 24361 EN
ISBN 978-92-79-15783-7
ISSN 1018-5593
doi:10.2791/41701

Luxembourg: Publications Office of the European Union

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Printed in Spain

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Acknowledgments

IPTS is grateful for the help and input received from Emmanuelle Rial-Sebbag, Anne Bahr, Latifa Bouyakoub, Laurent Bowen-Squires and Francoise Garnier, on the section of biobanking activities in France, and from Pilar Nicolás on the section on biobanking activities in Spain. IPTS would also like to specially thank the experts who took the time to respond to the survey and provided input at the workshops organised in the context of the study.

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Acronyms

For lucidity purposes this list refrains from displaying all national biobank groups, organisation or units referred to in this report.

BIMS	Biobank Information Management System
DNA	Desoxyribo Nuklein Acid
DPA	Data Protection Authority
EATA	Euro-Atlantic Transplant Alliance
EGC	Ethics and Governance Council
EMA	European Medicines Agency
EPIC	European Prospective Investigation into Cancer and Nutrition
ESTO	European Science and Technology Observatory
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	US Food and Drug Administration
GBP	Good Biobanking practice
GMP	Good Manufacturing Practice
HSD	Health Sector Database
HTA	Human Tissue Authority
IP	Integrated Project
IP	Intellectual Property
IPTS	Institute for Prospective Technological Studies
IVF	In Vitro Fertilization-
Jacie	Joint Accreditation Committee-ISCT & EBMT
MCST	Malta Council for Science & Technology
MRC	Medical Research Council
P3G	Public Population Project in Genomics
RBC	Red Blood Cells
RTD	Research, Technology, Development
S&T	Science and Technology
SWOT	Strength, Weaknesses, Opportunities and Threats
ULB	Free University of Brussels
VDI	Verein Deutscher Ingenieure

EXECUTIVE SUMMARY

The sequencing of the human genome has greatly facilitated the shift towards studying multi-factorial disorders rather than rare monogenic diseases and, as a result, has led to the development of more targeted therapeutic models (e.g. personalised drug therapies). These are highly dependent, however, on the ability to establish clear disease-genomic profile associations which requires the availability of large epidemiological studies and samples from well-characterised patient cohorts. For this reason, **biobanks**, i.e. the organised collections consisting of biological samples and associated data, have gained great significance for research and personalised medicine.

While biobanks are increasingly recognised as a crucial infrastructure for research, at the same time the widely varied practices in biobanking regarding for example collection, storage and consent procedures may also pose a barrier to **cross-border research** and collaboration by limiting **access** to samples and data. In this context, a recent study indicates that the limited sharing and linkage of samples is a key barrier for research, such as pharmacogenetics. Wide variation is observed in the implementation of relevant existing regulation, which may add further burden to harnessing the public health benefit of these collections. Therefore, it has been suggested that there is a strong need for a harmonised approach on biobanking practices and improved networking of existing and new collections. Nevertheless, the extent of the actual activities and the impact of the level of networking and harmonisation have not been fully assessed.

To address some of these uncertainties, the Institute for Prospective Technological Studies (IPTS) of the European Commission's Joint Research Centre, in collaboration with the European Science and Technology Observatory (ESTO), launched the present study. Its main objectives were: i) to obtain missing knowledge on the extent of biobanking in Europe and world-wide; ii) to analyse the relevant options and challenges for networking and harmonisation.

(i) **To obtain missing knowledge on the extent of biobanking in Europe and world-wide**, the first stage of this study was a survey of existing European biobanks which are collecting samples for research and their practices regarding both technical aspects (e.g. storage conditions) and aspects of governance and ethics (e.g. sample and data sharing, consent procedures, collaborations etc.). Surveying biobanks is a daunting task given that there is seldom a requirement for declaration of research biobanks in a central registry. In total, 126 biobanks from 23 countries in Europe were surveyed. The vast majority of the biobanks investigated are found in Denmark (14), Sweden (12) and the UK (11). However, surprisingly, significant activity was also identified in Hungary and Romania. About 80% of the surveyed biobanks are **public** collections based either at universities or national/regional agencies and have been setup either for population-based or disease-specific research purposes. Most of the collections are either small- or medium-sized and primarily consist of DNA, serum and whole blood, and/or cellular tissue samples stored at various conditions, and several types of associated data including medical, demographic, genetic and environmental.

Interestingly, almost 70% of the surveyed biobanks were **single collections** (i.e. not forming part of a network or partnership) with database systems which, in most cases, were stand-alone. In addition to this limited networking, at least in terms of existing database infrastructures, only about half of the biobanks participating in the survey

indicated they have a policy for sharing samples across borders either within the EU or world-wide. Nevertheless, **access** to the biobank is, in most cases, either entirely free or restricted to a part of the repository. Fees for granting access to samples and/or data apply to about a third of the cases. Yet, **scientific collaborations** based on the use of each biobank are prominent. Eighty-five per cent (85%) of the survey respondents reported at least two collaborations with other researchers and 45% reported more than 10. Moreover, 52% of the biobanks surveyed are involved in **international collaborations**.

Significant variability emerged with regards to privacy and data protection requirements among biobanks in Europe. The present survey demonstrates that the majority of biobanks have at least one type of consent form that allows tissue (63.5%) and data (69%) sharing. Yet, a significant proportion of them utilise more than one type of consent depending on the sample. The use of samples defined in the consent form is also highly varied, ranging from research on specific diseases to blanket (as practiced for example in the case of the UK biobank). Importantly, 13 respondents indicated that they do not apply consent at all. Six of them belong to Eastern European Countries with the rest based in Western Europe.

Such differences have been observed previously and may be partly attributed to the varied interpretation and implementation of EC directives covering aspects of biobanking by national authorities. One of the main complications being that, although the field of data protection is harmonised through the EC directive on data protection, the collection, storage and sharing of samples is not. Furthermore, in countries that have introduced special biobanks acts it is not always clear where the borderline lies between the scope of these acts and that of the Directive. There seems to be a trend to break down this sample/data dichotomy and to consider under "database" both the physical sample and the information derived from it, but a deeper international understanding and agreement still need to be reached.

As discussed, the variability found with regards to privacy and data protection requirements might reflect diverse interpretations of the EC directives by national authorities. However, it should be noted that, according to the survey, biobanks within the same country reported different practices, suggesting that the problems of harmonization might be higher than expected and claimed. Not only are there different national laws, but apparently within EU member states biobanks do not implement homogenous practices on privacy and data protection issues.

The role of research ethics committees is, in this context, gaining increasing importance, as shown by the large majority of the biobanks surveyed which are governed by an ethics board (86%). Properly addressing the ethical issues raised by vast biobanking projects can determine the successful clinical uptake of genomics. It is therefore important to understand how the different biobanks are actually dealing with these issues.

ii) To analyse the relevant options and challenges for networking and harmonisation, desk research and expert interviews were done to complete the picture presented by the survey and the potential way forward. Experts widely recognised the need to improve collaboration and networking among the numerous existing biobanks, as well as new initiatives in Europe (and world-wide). Efficient organisation of these resources through the development, for example, of an infrastructure would potentially

facilitate financial sustainability and greatly contribute to the rapid progress of research and development of better diagnostic and therapeutic approaches. The model most favoured involved the development of a virtual biobank that would allow networking of biobanks across different countries and centralisation of data rather than samples. However, several organisational challenges (wide variation in biospecimen collection, processing, storage techniques, data comparability, definitions) may hamper such an effort. The lack of uniform regulatory and ethical requirements and/or practices may pose an additional barrier.

The European Commission recognised the importance of international biobank projects and many of them have been funded and established in the context of the EU Framework Programmes (e.g. GenomEUtwin¹, EuroBioBank², NUGENOB³, PHOEBE⁴ and BBMRI⁵, among others). The European Commission, DG Research in partnership with two EU-supported biobanking projects, PHOEBE and BBMRI, has recently organised a "Networking Meeting for EU-Funded Biobanking Projects", gathering the coordinators or senior investigators of 28 EU-funded projects with a significant biobanking component. The meeting identified challenges and critical issues to be addressed for the development, success and sustainability of biobanks. Among the recommendations formulated, the adoption of measures in favour of harmonisation was considered one of the most important.

It has been widely recognised by all stakeholders that in order to accelerate scientific discovery it will be critical to improve biobank quality, interoperability and sustainability. The report from the aforementioned "Networking Meeting for EU-Funded Biobanking Projects", also pinpoints this issue raised by the responsible investigators of these projects, and there is a general call for harmonisation of sample and data storage practices (standard operating procedures for both) but also clear procedures for ethical reviews and clarification of legal international requirements for data and sample sharing between different countries. Harmonization was also indicated as the critical process to stimulate and accelerate scientific discovery in a recent workshop jointly organized by P³G, PHOEBE, and BBMRI and sponsored by the European Science Foundation.

To help promote networking of biobanks and thus maximise public health benefits, at least some degree of harmonisation must be achieved. Whether this should be achieved solely at the level of legal/regulatory requirements and practices and/or by technical standardisation requires further investigation. Experts suggested the establishment of an **international** (rather than just a European) **umbrella (or network) organization**, which would establish common operating procedures in e.g. genotyping and phenotyping, quality assurance, information management and common approaches to

¹ <http://www.genomeutwin.org>

² European Network of DNA, cells and tissue banks for Rare Diseases (<http://www.eurobiobank.org>)

³ Nutrient-Gene Interactions in Human Obesity (<http://www.nugenob.com>)

⁴ Promoting Harmonisation of Epidemiological Biobanks in Europe (<http://www.phoebe-eu.org/>)

⁵ Biobanking and Biomolecular Resources Research Infrastructure (<http://www.bbmri.eu>)

Executive summary

ethical and legal requirements such as consent, data protection and privacy, feedback of information to donors, etc. In this context, already existing initiatives with similar objectives should be taken into consideration and are discussed in this report.

1 INTRODUCTION

The sequencing of the human genome as well as non-genomic analyses of various types of biological material has greatly facilitated a shift towards studying multi-factorial disorders rather than rare monogenic diseases and, as a result, has led to the development of more targeted therapeutic models. These are highly dependent, however, on the ability to establish clear disease-genomic profile associations which requires the availability of large epidemiological studies using samples from well-characterised patient cohorts. For this reason, biobanks, i.e. the organised collections consisting of biological samples and associated data, have gained great significance as a resource for research. These collections range widely in scope, from small disease-specific collections to large-scale population based repositories, and may be public or commercial [1].

Although biobanks do not represent a recent development, due to the growing interest in using them for large-scale epidemiological studies on genetic and environmental causes of common diseases, the number of such collections held in different settings (e.g. universities, hospitals, pharmaceutical companies) and countries around the world, has rapidly proliferated. Consequently, there are also a growing number of population-based studies and other collaborative projects carried out, often supported by the EU (e.g. GenomEUtwin⁶, EuroBioBank⁷, NUGENOB⁸, BBMRI). Therefore, biobanks are increasingly recognised as a crucial component of research, in particular, for improving rational drug development and prevention strategies. However, it has also been suggested that they could pose a barrier to cross-border research and collaboration, one of the main reasons being the wide variety of existing practices with regards to e.g. collection and storage of samples, and also to the implementation of relevant regulation. In this context, limited sharing and linkage of samples may pose an additional barrier for research [2].

Thus, it has been suggested that there is a strong need for a harmonised approach on biobanking practices and improved networking of existing and new collections globally [3]. Nevertheless, the extent of the actual activities and impact of the level of networking and harmonisation have not been fully assessed [4]. To address some of these uncertainties, the Institute for Prospective Technological Studies (IPTS) of the European Commission's Joint Research Centre⁹, in collaboration with the European Science and Technology Observatory (ESTO)¹⁰, launched a prospective study in January 2006.

The ESTO group conducting this study consisted of the following experts:

- Anette Braun and Sylvie Rijkers-Defrasne, VDI-FTD¹¹;
- Mylène Deschenes and Isabel Fortier, Public Population Project in Genomics (P³G)¹²

⁶ <http://www.genomeutwin.org/>

⁷ <http://www.genomeutwin.org/>

⁸ <http://www.nugenob.com/>

⁹ www.jrc.es

¹⁰ <http://esto.jrc.es/>

¹¹ <http://www.vdi.de/vdi/english/organisation/schnellauswahl/fgkf/kfbt/organisation/11499/index.php>

¹² <http://www.p3gconsortium.org/>

Introduction

- Jens Laage-Hellman, Vinnova (Swedish Governmental Agency for Innovation Systems)¹³;
- Christian A. Scerri, Malta Council for Science & Technology (MCST, Eurobiobank)¹⁴.

The study was conducted in collaboration with P³G (Public Population Project in Genomics) [5], benefiting from their previous knowledge and using their database for the survey. This initiative is pioneering in providing an international platform for sharing methods and information in the international genomics research arena.

1.1 Objectives

The main objectives of the study were: i) to obtain missing knowledge on the extent of biobanking in Europe and world-wide and ii) to analyse the relevant options and challenges for networking and harmonisation.

A European survey was conducted and complemented by desk research to provide a comprehensive picture of human biobanks world-wide. The study compares the regulatory frameworks and visions world-wide, in order to emphasize similarities and differences and to identify possible strengths, weaknesses, opportunities and threats (SWOT) to improve biobank networking. It also explores the potential for a European harmonized approach to the networking of human biobanks.

1.2 Definition and scope

The study uses a wide definition of biobank, formulated by OECD¹⁵. For the purposes of these Guidelines, human biobanks and genetic research databases (HBGRDs) are structured resources that can be used for the purpose of genetic research, which include: a) human biological materials and/or information generated from the analysis of the same; and b) extensive associated information.

Biobanks vary widely depending on the type of material they store (for example, they may collect DNA, tissue, living cells, associated data and any combination of these) and their purpose (e.g. therapeutic, research, clinical use etc.) (see Figure 0-1). This report has focused primarily on biobanks established for research purposes and, apart from a few exceptions, clinical biobanks created mainly for diagnostic purposes are not covered¹⁶.

The report covers four geographical regions:

¹³ <http://www.vinnova.se/misc/menyer-och-funktioner/Global-meny/In-English/>

¹⁴ <http://www.mcst.org.mt/> and European Eurobiobank Consortium (www.eurobiobank.org)

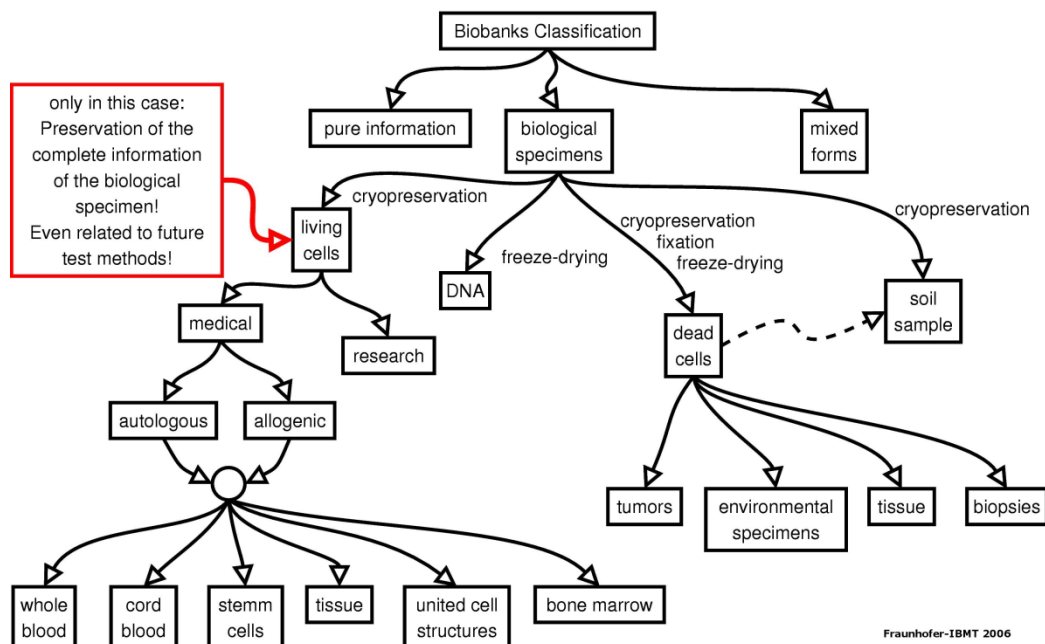
¹⁵ OECD (2009): *Guidelines for Human Biobanks and Genetic Research Databases*.

¹⁶ This report also does not include collections of forensic biobanks, therapeutic biobanks (like blood banks and tissue banks, including umbilical cord blood banks, for allogenic as well as for autologous grafts), and semen banks, as well as organ collections, assembled solely for clinical use. Such biobanks are mostly not designed for research purposes.

- **Northern Europe** in this context comprises the five Nordic countries (Sweden, Norway, Denmark, Finland and Iceland), the three Baltic countries (Estonia, Latvia, Lithuania), the UK and Ireland;
- **Central and Eastern Europe** including Bulgaria, the Czech Republic, Hungary, Poland, Romania, the Slovak Republic, Belgium, the Netherlands, Luxembourg, Germany and Austria;
- **Southern Europe**, which comprises in the context of this study, Cyprus, France, Greece, Italy, Malta, Portugal and Spain;
- **Non European countries**, such as the USA, Canada and Asia.

Representative examples of biobanks are given in section 2.2 for selected countries in each of the regions mentioned above. Annexes 2-4 list all the biobanks identified throughout the study. However, see the ESTO report available at www.jrc.es for the complete analysis

Figure 0-1: Biobanks classification



Source: Fraunhofer-IBMT

1.3 Identification of biobanks and survey

The identification of biobanks was performed using different sources including the early involvement of network leaders of related EU-funded biobank projects (a list of EU-funded projects provided by the EC is found in Annex 2), the P³G website and further available information¹⁷ via search engines like Pubmed and Google, reference websites or published reports, abstracts or proceedings of meetings and references provided by collaborators. A large effort was dedicated to identifying and mapping biobanking activities in Europe in a comprehensive way. After identification of a first list of almost

¹⁷ P³G is not-for profit organization aimed at facilitating collaboration in the field of population genomics. P³G maintains a website with descriptive information about population based research, thanks to information provided directly by the research team (www.p3gobservatory.org).

Introduction

250 potential biobank contacts, eligibility was validated and final selection performed, the main focus being large-scale biobanks established for research purposes. The survey questionnaire developed, aimed at obtaining information relating to the purpose, size, structure and relevant governance aspects of each biobank addressed (see Annex 1). It was sent by e-mail to each respective contact person, with a letter of invitation to participate in the survey from mid-March until mid-May 2006. Any additional and/or missing information was further collected through desk research.

The survey addressed biobanks collecting samples only for research purposes. Complete mapping of all such biobanks existing world-wide was difficult due to the large number of biobanks existing in various settings and there is seldom a requirement for declaration of research biobanks in a registry. Thus, the principal focus was to identify at least the most important biobanks in each of the geographical areas researched. Furthermore, by reason of their potential interest for long-term collaboration, particular attention was allocated to longitudinal studies¹⁸ that included a biobanking component. Moreover, despite their strategic importance in the field of research, it was impossible to obtain information on biobanks collected by private pharmaceutical companies. Finally, the report only includes existing biobanks (i.e. some samples have at least been taken).

The survey was sent by e-mail to 176 European organisations/biobanks: 31 of them no longer existed or had ended their biobank activities; among the remaining 145 active biobanks, 126 replies were received in total. Several factors may have influenced the response behaviour:

- reluctance to divulge commercially-sensitive information;
- sharing information and samples is considered a low priority for a number of the companies commercializing their biobanks;
- sometimes (particularly in Eastern EU countries) general caution about revealing any information on biobank activities has been displayed;
- a serious impediment to the mapping of biobanks is the lack of consistent concepts and terms referring to human biobanks: just as the legislation on biobanks differs in the various countries considered. Terminology is also different (biobanks, biorepositories, cell banks, tissue banks, blood banks, etc.);
- availability of information in English was not always granted;
- the survey depended on the willingness of private biobank investigators to provide information. The complete list of the 145 biobanks identified in Europe is presented in Annex 3.

¹⁸ Please note that the term 'longitudinal studies' in epidemiology or population based research means different things. The most common use of the term in epidemiology, which is the discipline using the large-scale population-based biobanks, is a type of prospective study in which the cohort members are examined multiple times for the same characteristics in order to follow their development or changes over time, e.g. repeated blood 7sampling or measurement of height and weight, in contrast to the more simple cohort or follow-up studies in which there is only a baseline sampling or measurement.

Introduction

The results of the survey, presented in section 2.1, were further complemented by a more in-depth analysis of the most important biobanks in the geographic regions mentioned earlier (the results of this analysis are set out in section 2.2).

2 BIOBANKING ACTIVITY IN EUROPE AND WORLDWIDE

As described, the first objective of this study, to obtain missing knowledge on the extent of biobanking in Europe and world-wide, was first tackled through a survey of biobanks in Europe.

This survey was complemented with desk research and data previously gathered by P³G providing an overview of existing research biobanks in four geographical regions of Europe: Northern, Southern Central and Eastern Europe, as well as major biobanks from non-European regions including the USA, Canada and Asia.

The overview provided a selection of countries (where considerable activity was observed and/or had replied to the survey) within the above mentioned regions including a description of single biobank activities identified, national biobanking characteristics and regulative aspects observed. In addition – where appropriate based on the survey - a brief discussion on sample collections, access availability, sharing of samples, and consent requirements is included.

The state-of-the-art regarding human biobanks for research purposes in Europe and world-wide, as described in this chapter is based on data collected by May 2006.

2.1 Survey of European biobanks

At the time of this survey no comprehensive list of biobanks in Europe exists. A survey was sent to 176 European biobanks/organisations identified as described earlier, and a total of 126 completed questionnaires were received (a response rate of about 72%). Table 2-1 lists the number of sent and returned questionnaires per country.

Table 2-1: Number of respondents per country

Country	Biobanks Surveyed		Country	Biobanks Surveyed	
	Sent	Response		Sent	Response
Austria	6	1	Latvia	1	1
Belgium	5	2	Malta	1	1
Bulgaria	2	1	Netherlands	11	8
Denmark	15	14	Norway	9	9
Estonia	1	1	Poland	3	3
Finland	5	5	Romania	12	12
France	2	2	Slovakia	1	1
Germany	10	9	Slovenia	1	1
Greece	1	1	Spain	2	2
Hungary	17	17	Sweden	14	12
Iceland	5	4	UK	12	11
Italy	9	8	Total	145	126

Since a number of the biobanks addressed were found to have ended their activity, the response rate of active biobanks is nearly 87 %. The vast majority of the biobanks surveyed are found in Denmark (14), Sweden (12) and the UK (11). However, surprisingly, significant activity was also identified in Hungary and Romania.

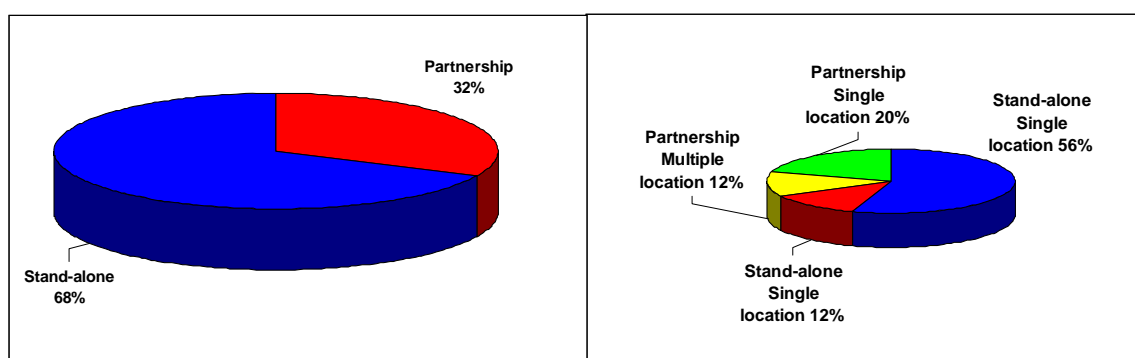
The response rate was homogeneously high for almost all countries (between 90 and 100%), with the exception of Austria (16%), Belgium (40%), Bulgaria (50%), and The Netherlands (73%).

The variability in the number of biobanks per country could be at least partially explained by the existence in some countries of network infrastructures or consortia that provide visibility to individual biobanks. For example, the "Genomic Research for Human Health Consortium" supported by the EU 6th Framework Programme and the foundation of the Hungarian National Biobank Network¹⁹ were the reasons behind the inclusion of an unexpectedly high number of Hungarian biobanks in the sample.

2.1.1 Biobanks composition and purpose

The majority of the surveyed biobanks (68%) are single (stand-alone) banks²⁰, whereas thirty-two percent (32%) have instead formed a partnership with other biobanks located either in the same (20%) or in a different (12%) country, for sharing samples and/or for carrying out research (see Figure 2-1). Within the last category 62,5% (20% of the whole sample) is involved in a partnership with biobanks in the same geographical location, and 37,5% (12% of the whole sample) form a partnership with banks in different locations. The data available indicate that the formation of trans-national biobanks partnerships or networks is rather limited, even if we cannot specify the type of collaboration.

Figure 2-1: Biobank partnerships (left panel) and geographical location (right panel)



¹⁹ www.biobank.hu

²⁰ As stand-alone biobank we mean a biobank that does not consist of a partnership of banks (See Annex 1 – Question 5)

Biobanking activity

92% of the responding biobanks (116) sampled have a clear ownership (see Figure 2-2). The majority of these are owned by universities (39%), national/regional agencies (39%) or non-profit organisations (19%) and only few (3%) are private. Moreover, when asked the principal reason for the creation of the biobank, the majority of the respondents replied that it was created for public research only (36%) or for both public and clinical research (mainly aiming at diagnosis, 24%) (see Figure 2-3).

Figure 2-2: Ownership

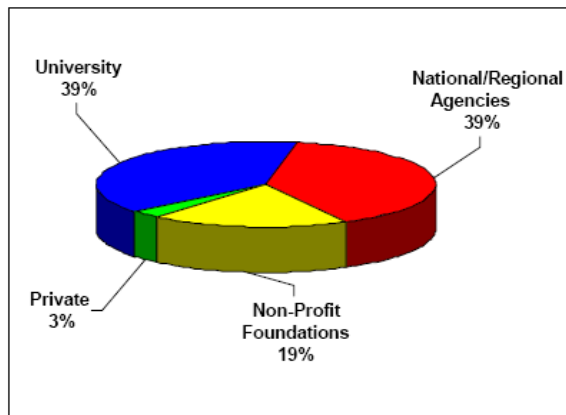
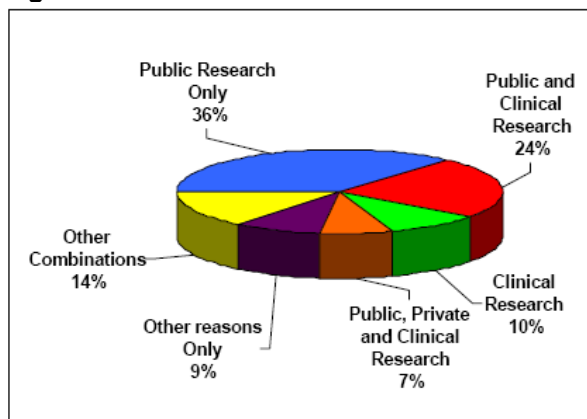


Figure 2-3: Research models



To gain further insight regarding the purpose of the sampled biobanks, a question in the survey considered participant selection. Table 2-2 lists the answers received per category (including combinations). The majority of the collections are either disease specific (27%) or from a random population (21%) but a considerable number of them are collecting both types of samples (16%). About a fourth of the responding biobanks stated they additionally collect samples of specific demographic characteristics (e.g. isolates or healthy elderly). 17 respondents further specified the other types of sample collection. Table 2-3 summarises these answers.

Biobanking activity

Table 2-2: Sample/Participant selection

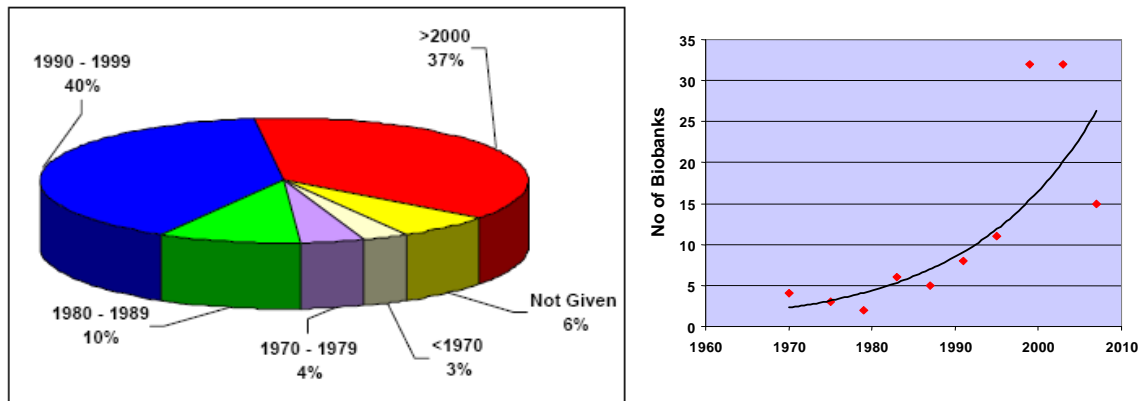
Objective	Number
Random Population	26
Disease Specific	31
Random Population & Disease Specific	20
Demographic	4
Random Population & Demographic	13
Disease & Demographic	4
Random Population, Disease Specific & Demographic	8
Other objectives	7
Disease specific and Other reasons	6
Other combinations of objectives	4
No answer	3
Total	126

Table 2-3: "Other" activities

Type of activity	Number
Blood donors	2
Controls/Healthy volunteers	3
Pregnant women	1
Research projects	2
Stem cells	1
Tissue specific	2
Twins	2
Birth Cohort	1
Embryos	1
No description Given	2
Total	17

Our data suggest an acceleration in biobanking activities in recent years. While a few of the biobanks identified started collection in the 70's, they have been built up relatively recently (during the 90s) with 37% of the surveyed biobanks starting their activity after 2000 (see Figure 2-4), obviously reflecting the burst of genome-wide association studies and the search for disease susceptibility genes and diagnostic biomarkers after the completion of the human genome sequencing project.. The majority of the biobanks (>74%) of the biobanks do not foresee an end to their sampling activities and indicate a high potential for growth, showing the dynamic nature of biobanking and an increasing role in research

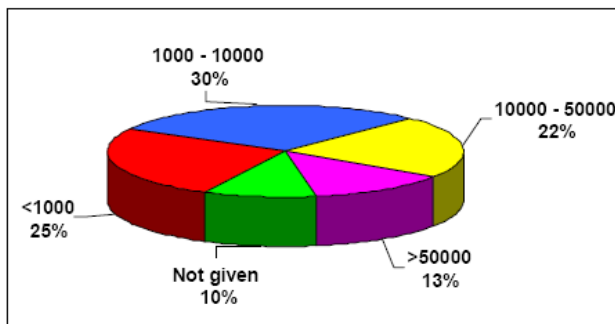
Figure 2-4: Year biobank started



2.1.2 Sample and data collection

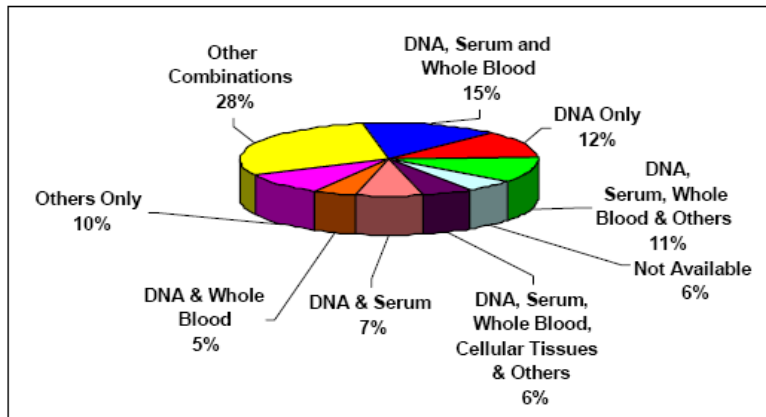
Regarding the targeted size of the biobanks that participated in the survey, the majority of the respondents seem to be small (less than 1000 samples) or medium sized repositories (up to 10000 samples) (see Figure 2-5). This might reflect the fact that most of the biobanks surveyed are disease specific and that population based biobanks have been instituted rather more recently. Nevertheless, about a third of the respondents indicated they collect up to 50000 samples or more. 57% of the repositories also reported that they do not have any specific sample target number for the future.

Figure 2-5: Number of samples



Participants to the survey were also asked to specify the type of material stored in the respective biobanks. Types included DNA, serum, whole blood, tissues or other, and respondents could select any answer that applied. The survey shows that most biobanks store DNA combined with serum, whole blood and/or different types of tissue (see Figure 2-6), whereas only 12% store DNA alone. Other tissues stored (as specified by the respondents) include, for example, stem cells and RNA, urine, dried blood and red blood cells.

Figure 2-6: Type of material stored

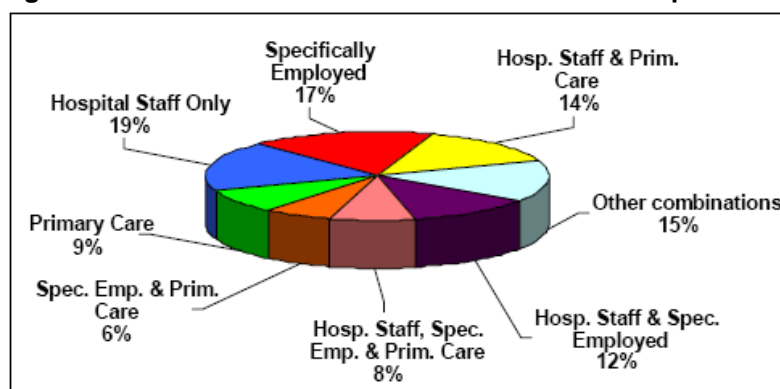


Finally, the survey investigated who carries out the collection of samples (e.g. hospital staff, patient interest groups, staff specifically employed for the respective project/biobank). Interestingly, in the majority of the cases, sample collection was carried out either by associated hospital staff, primary care workers or a combination of both (see

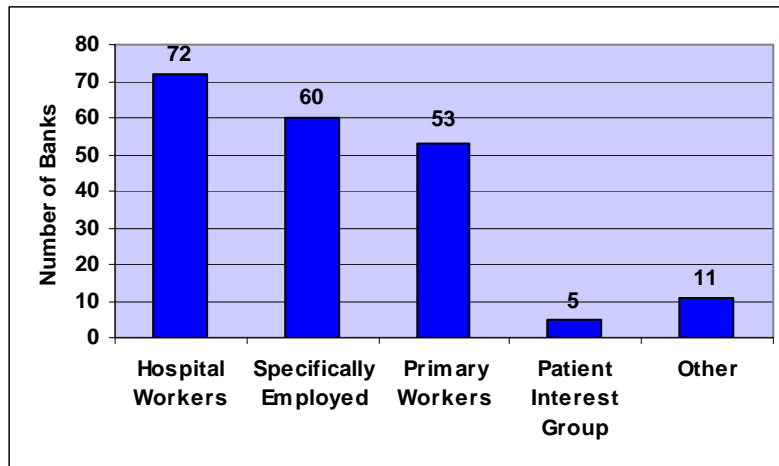
Figure 2-7). Approximately half of the respondents (60) stated that sample collection is carried out by staff specifically employed for the project, either alone or with other staff (e.g. primary care workers, hospital staff etc.) (see

Figure 2-7, bottom panel). This is perhaps not surprising as the biobanks surveyed are largely public (either owned by national agencies/hospitals or universities) (see Figure 2-2). Interestingly, some respondents indicated that data collection may also be carried out by patient interest groups.

Figure 2-7: Staff involved in the collection of samples

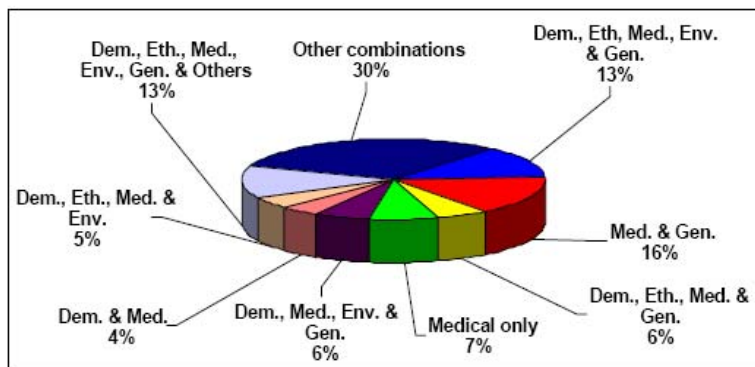
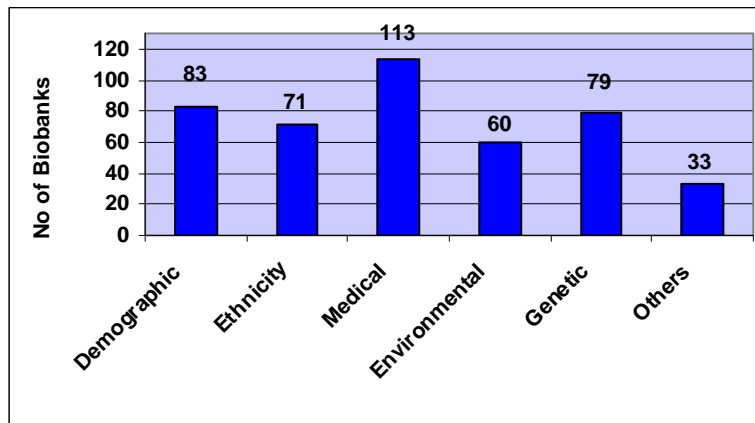


Biobanking activity



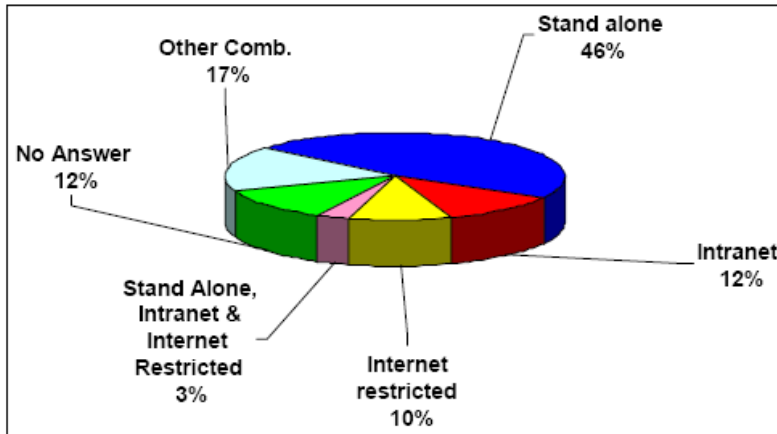
The survey also addressed the types of data that are stored and associated with the collected samples (see Figure 2-8). By far, the most commonly stored data are medical (113 replies), genetic (79 replies) and demographic (83 replies), potentially reflecting the type of research activities undertaken by the respective biobanks. About half of the surveyed biobanks stated they also collect environmental data (60 replies). Respondents were asked to include all types that applied. The bottom panel of Figure 2-8 breaks down the shares of the replies by all the combinations provided.

Figure 2-8: Type of data collected and stored



Regarding data connectivity, a stand-alone database system is the type mostly utilised by the biobanks that responded to the survey (46%) although, at times, they may be networked through a restricted intranet and/or an internet system as well (see Figure 2-9). This may not be too surprising though as most of the responding biobanks are not part of a network (see Figure 2-1).

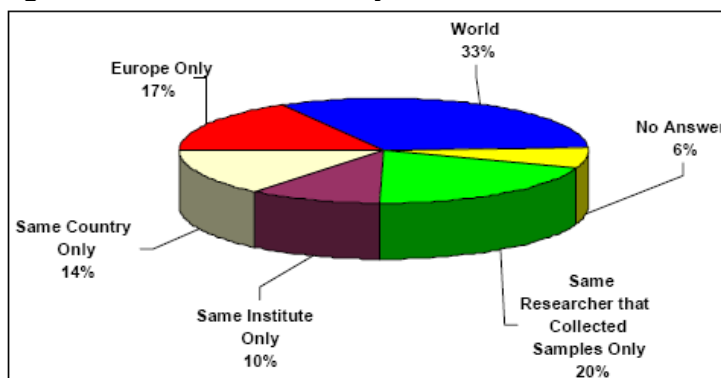
Figure 2-9: Types of data storage systems



2.1.3 Access

The majority of biobanks sampled have a policy that allows sharing samples across country borders either within the EU (17%) or world-wide (33%) (see Figure 2-10). However, a considerable share of the respondents indicate that biobanks may only be accessed by the researchers who collected the samples (20%) or all researchers that belong to the same institute (10%). The lack of proper networking (see Figure 2-9) may provide an explanation for the limited access to certain biobanks beyond other legal restrictions.

Figure 2-10: Biobank use by location



As most biobanks sampled are publicly funded and owned either by public agencies or universities, it is not too surprising that, by far, the largest majority (see Figure 2-2), (84%) offer their samples either totally free or offer a part of their repositories free (see Figure 2-11). Though free, most institutions have some restrictions mostly in terms of the mode and extent of use of the biobank, as well as specific ethical requirements.

Biobanking activity

Decision on the granting of access for the utilisation of samples, is split between the governing body (39%) and the curator of the biobank (27%) (see Figure 2-12).

Figure 2-11: Type of access

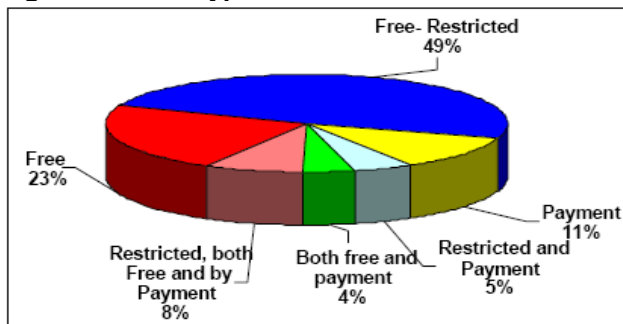
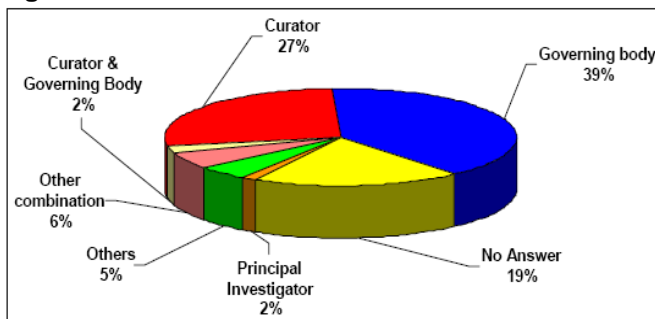


Figure 2-12: Decision on access



2.1.4 Consent and privacy

Significant variability emerged with regards to privacy and data protection requirements among biobanks in Europe. Although informed consent for approval of biobank-based research is almost ubiquitously required, the actual consent requirements and related procedures vary widely among biobanks, depending on the national laws and guidelines applied. The present survey demonstrates that the majority of biobanks have at least one type of consent form that allows tissue (63.5%) and data (69%) sharing. Yet, a significant proportion of them utilise more than one type of consent depending on the sample. The use of samples defined in the consent form is also highly varied, ranging from research on specific diseases to blanket (as practiced for example in the case of the UK biobank). Importantly, 13 respondents indicated that they do not apply consent at all. Six of them belong to Eastern European Countries with the rest based in Western Europe.

As would be expected (in view of the various legislative directives) almost all biobanks sampled are regulated by an Ethics board approval. A large majority of the biobanks have a legal consent structure allowing tissue (63.5%) and data (69.0%) sharing. Most of the banks have at least one type of consent form, though many (40%) utilise more the one type, depending on the sample.

Figure 2-13: Ethics board

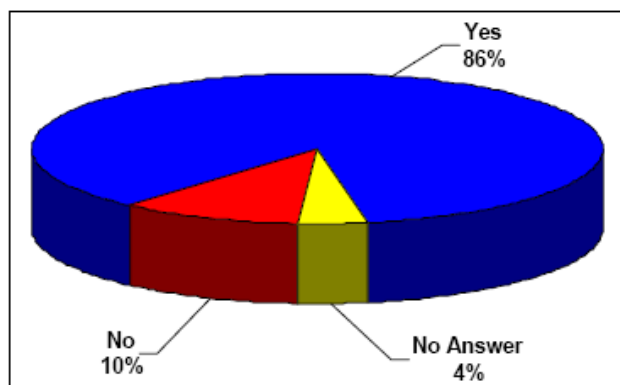
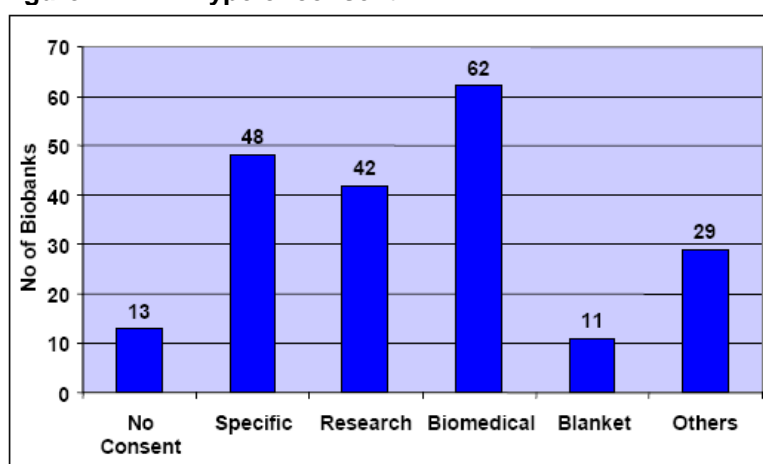
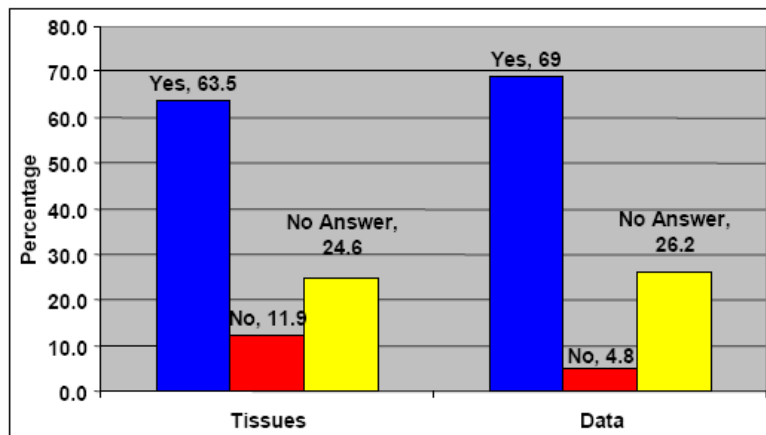


Figure 2-14: Type of consent



The consent forming 72.2% of banks allows the donor to withdraw his/her consent for the storage of the donated sample, whilst 15.1% withdrawal of consent is not allowed (12.7 % of the sampled biobanks chose not to answer this question).

Figure 2-15: Does consent form allow sharing with researchers from other countries?



Information gathered from any tests carried out on samples is referred back to the donor. This is the case for 37% of the banks if consented to and 6% in all cases. 57% of the biobanks would never refer back any data to the donor. Most of the biobanks (76%) protect the privacy of their donors by coding the samples. Most probably this reflects the fact that, in most of the banks samples are disease related or are specific population where, either feedback or data retrieval are considered necessary and, as such, the possibility of identifying the donor is a prerequisite.

Figure 2-16: Is information referred back to the donor?

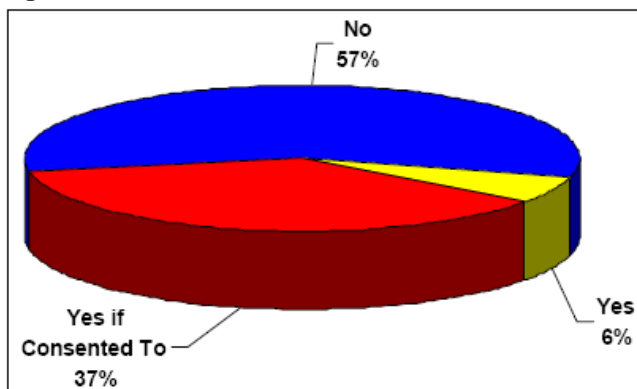
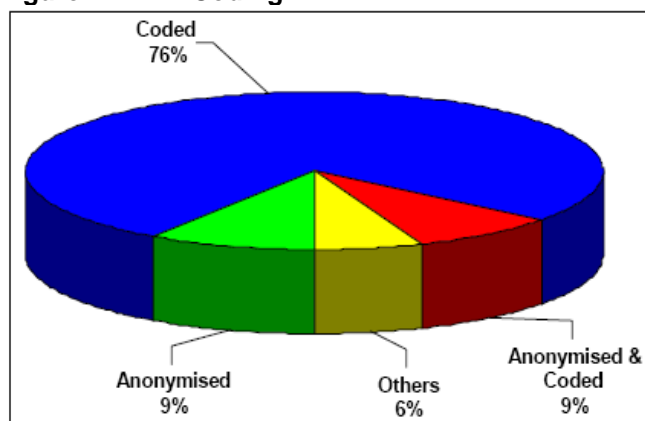


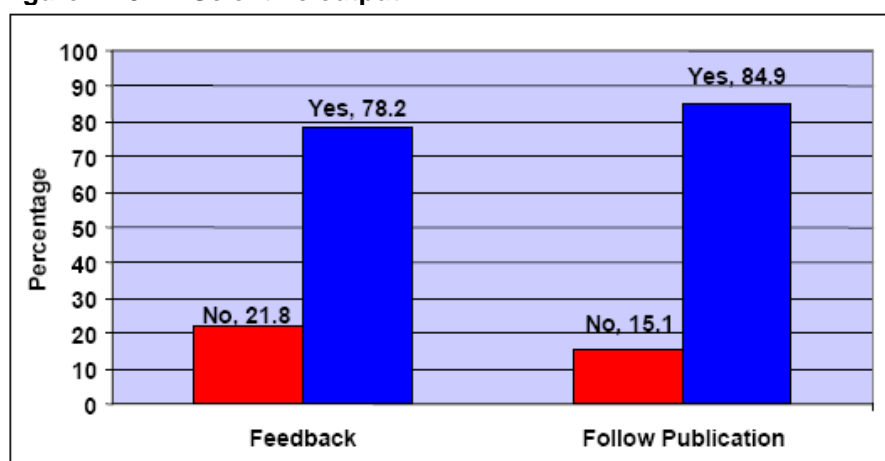
Figure 2-17: Coding



2.1.5 Scientific Output

The majority of biobanks (78.2%) require researchers utilising samples of the bank to feedback on the outcome of tests and results. Similarly, the largest majority of biobanks (84.9%) follow the publications emerging from the tests and research carried out on their samples.

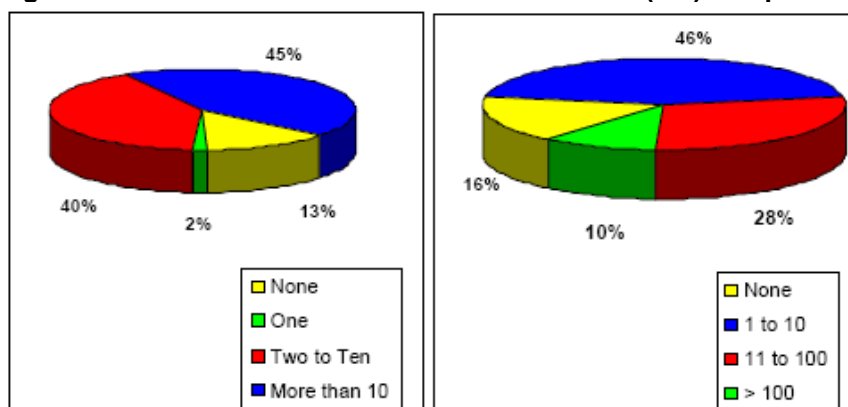
Figure 2-18: Scientific output



Biobanks also have good records of collaboration with outside researchers: 85% reporting at least two collaborations and 45% more than 10. This is also reflected by the number of papers published with 84% showing at least one, 38% more than 10 and 10% more than 100 publications. 52% of the biobanks report having been involved in international collaboration and only 26% report having had some problems in sharing samples.

Most of these problems relate to the storing of samples, dry ice shipments and legislative barriers especially in countries (e.g. Hungary) where the transfer of samples to foreign countries is not permitted. Most of the biobanks sampled (75%) allow both sending and receiving samples from other countries, with 16.4% from the EU and 83.6% from the rest of the world.

Figure 2-19: Number of scientific collaborations (left) and publications (right)



The fact that only 16% of biobanks have not produced any scientific publication is a positive sign of the contribution of biobanks to medical research, though ideally, the efficiency of this type of investment (in terms of money and sample donation) should be evaluated taking into account the impact of the research published, investigating bibliometric indexes of biobank publications.

2.2 Biobanks world-wide

2.2.1 Biobanks in Northern Europe

Northern Europe, in the context of this report, comprises the following countries: the five Nordic countries (Sweden, Norway, Denmark, Finland and Iceland), the three Baltic countries (Estonia, Latvia, Lithuania), the UK and Ireland.

Regarding the Nordic countries, the identification of biobanks was mainly done by using previous knowledge and existing contacts. Sweden has been used as a particular case to illustrate the phenomena also present in other Nordic countries, based on their existing similarities. It was easy to identify two important biobanks in the Baltic countries, since these are associated with well-known genome projects in Estonia and Latvia. Our contacts have confirmed that there are no other biobanking activities in these countries worthwhile covering in this study. Several research biobanks exist in the UK at universities and university hospitals, the main of which have been identified. However, given the short time-frame during which this study was carried out, the mapping is not exhaustive. No major biobanks dedicated specifically to research were identified in Ireland at the time of the survey. However, there was a proposal to establish a network of clinical biobanks involving several hospitals: Biobank Ireland²¹. They have started their networking activity in February, with the Department of Pathology in the Galway University Hospital as a first step forward for the establishment of the network.

Information on relevant laws and regulations in different countries has been gathered in a compilation carried out in 2005 by the Department of Health and Human Services in the UK: International Compilation of Human Subject Research Protections (Second Edition, October 1, 2005). Additional information on specific laws has been obtained from various websites and other publications.

²¹ <http://biobankireland.com/>

The mapping of biobanks in Northern Europe has focused primarily on *research biobanks*, and apart from a few exceptions, clinical biobanks created mainly for diagnostic purposes are not covered. There are very large numbers of samples stored in clinical biobanks, not least in the Nordic countries since there has been a long-standing tradition to save tissues and other samples taken during routine medical care. In Sweden, for example, it is estimated that there are 50-100 million human samples stored in biobanks of the healthcare system, increasing by 3-4 million samples every year.²² The majority of these samples are stored in departments of clinical pathology, cytology and microbiology. Similarly in the UK, it is estimated that 150 million tissue samples are taken every year during medical operations and procedures.²³

The situation found in the different countries is described in the following sections, starting with Sweden, which is given some more space than the others due to the reasons mentioned above.

2.2.1.1 Biobanks in Sweden

Biobanks identified

The following 13 biobanks, in Sweden, are covered in this study:

- ⇒ Medical Biobank
- ⇒ Northern Sweden Maternity Cohort
- ⇒ Malmö Preventive Medicine
- ⇒ Malmö Diet & Cancer
- ⇒ Malmö Microbiology Biobank
- ⇒ Botnia Study
- ⇒ "Biobank SC153"
- ⇒ Karolinska Institutet Biobank
- ⇒ Swedish Institute for Infectious Disease Control Biobank
- ⇒ PKU Biobank
- ⇒ ULSAM
- ⇒ ABIS (All babies in Southeast Sweden)
- ⇒ Epidemiology Group, Sahlgrenska University Hospital

The list comprises all large research biobanks in Sweden, although a few clinical biobanks are also included.

In accordance with the Swedish Biobanks in the Medical Care Act, in force since January 2003, all biobanks originating in the healthcare system are to be registered regionally, and under supervision by the National Board for Health and Welfare. This ongoing registration work shows that there is an incredibly large number of biosamples stored at the large hospitals. The main purpose of 25 of these biobanks/collections is diagnostics and treatment. However, according to this national register, many of them are also used for research. The majority of the biobanks have been created specifically for the purpose of research or clinical trials (often a combination of these). However,

²² www.biobank.se

²³ BBC News, 23 June 2004 (<http://news.bbc.co.uk/2/hi/health/3832333.stm>)

the clinical biobanks dominate completely in terms of number of samples, accounting for 95% of all samples. Nonetheless, there are in total more than 500 000 samples stored in various research biobanks at the region's hospitals. The situation in Stockholm is similar. That is, besides the large clinical collections, there are also many research collections.

Malmö Microbiology Biobank exemplifies a large clinical biobank located at Malmö University Hospital which, to a large extent, is also used for research. It contains, in total, 1.2 million samples from 454 000 individuals. Most of the samples stored are serum samples submitted since 1969 for diagnosis of blood-borne viral infections. Of particular importance, from an epidemiological research point of view, is a sub-collection of 120 000 samples resulting from a population-based screening for virus infections and rubella immunity during pregnancy²⁴. The **PKU Biobank** consists of blood samples from newborns originating from a national screening of certain metabolic diseases. Such blood samples, now amounting to more than 2.7 million, have been stored in a specific biobank at the Karolinska Hospital since 1974. It has been used for research only to a very limited extent. This is probably due to the organization and the fact that the biobank has not been positioned as a resource for research.

The three largest research biobanks in Sweden are located in Umeå and Malmö. The **Medical Biobank at Umeå University**, which started collecting samples in 1985, consists of three cohorts and contains samples from 90 000 unique individuals.. Besides its large size and long follow-up, the high value of this biobank comes from the attached database which contains rich information on environmental and life-style factors as well as results from previous analyses. Like other Swedish biobanks, its usefulness in scientific studies is further enhanced by the possibilities to link the biobank with reliable disease registries. This is also why the biobank has been used in a large number of epidemiological national and international studies. It has been used, for example, in international pooling projects such as MORGAM²⁵ and EPIC (the European Prospective Investigation into Cancer and Nutrition²⁶). As a result, it was concluded in an international evaluation of Swedish biobanks that “this is one of the best Swedish biobanks and can be utilized in various genetic and epidemiological studies in the future”.²⁷

Additionally, there is another population-based biobank in Umeå, namely the **Northern Sweden Maternity Cohort**, which contains serum and DNA samples from cervical screening. Samples have been taken from 85 000 unique individuals on 115 000 sampling occasions. The oldest samples date back to 1975.

Malmö Preventive Medicine (1974-2006) and **Malmö Diet and Cancer** (1991-96) are two other prospective observational population-based biobanks belonging to the Department of Medicine at Lund University but located at Malmö University Hospital. They comprise 33 000 and 30 000 individuals respectively. Like the Medical Biobank

²⁴ Another large mainly serum-based biobank exists at the Swedish Institute for Infectious Disease Control. Despite having a large number of samples from a 50-year period, which through the patient's personal registration number can be linked to other databases, this biobank has not been extensively used for scientific purposes.

²⁵ See www.ktl.fi/morgam/

²⁶ See www.iarc.fr/epic/

²⁷ International Evaluation of Swedish Biobanks, 18 March, 2005 (available on www.biobanks.se)

in Umeå, the Malmö Diet and Cancer biobank is an associated member of EPIC.²⁸ Both of the Malmö biobanks contain a comprehensive collection of phenotypic and environmental data. They have been used in several research projects leading to numerous publications (more than a hundred each). However, the need for continuing external collaboration was recognised as an important factor for harnessing the full benefit of the Malmö Diet and Cancer biobank for research²⁹.

Besides these relatively large population-based research biobanks there are, as already mentioned, many smaller biobanks, many of which are disease-specific. We can take the Southern Healthcare Region as an example to illustrate how these biobanks are organised. This is one of Sweden's six healthcare regions with some 1.6 million inhabitants. The ongoing work on a regional biobank register, imposed by the Biobanks Act, shows that there are in total 13 million samples, most of which have been taken for diagnostic purposes. But there are also many research biobanks. Besides the two large ones mentioned above, there are about 40 university departments at the region's two university hospitals, with at least one research collection each, often more. The samples are typically stored locally in the departments' own freezers. The number of samples or individuals typically ranges from 100 to 1 000, but some collections may be significantly larger. One example is the biobank related to the so-called **Botnia Study**, the aim of which is to elucidate the genetics of Type 2 diabetes. This study is carried out in the very north of Sweden and Finland (the Botnia area with some 120 000 inhabitants) by a research group at Lund University's Wallenberg Laboratory in Malmö. An original set of samples has been collected since 1990 from approximately 10 000 individuals and 1 400 families in both Sweden and Finland. Besides the biological material, researchers have also collected a comprehensive amount of environmental and clinical information. The Botnia study has resulted in a large number of scientific publications. Two years ago, a new population-based study called **PPP (Prevention, prediction and prevention of diabetes)** was started in Botnia. The aim was to collect samples and data from 5 000 individuals (reaching more than 10 percent of the population). At present, 3 000 individuals have been covered. That is why "**the Botnia biobank**" today contains samples and data from 13 000 individuals in total. Within a near future, a genome scan of these 3 000 individuals will be completed.

This research group also has a regional diabetes registry comprising samples from 8 000 individuals. This will now be transformed into a registry for all newly diagnosed diabetes cases in the Skåne Region. Besides these large biobanks, the group also has more than 10 smaller collections comprising 50 to 400 individuals. They have been established in connection to different research projects on obesity and other diabetes complications. One example is "**Biobank SC153**" consisting of DNA and serum samples collected in 2000 from 375 patients. The samples have been used by several research groups at the university, some of which are involved in international collaboration (i.e. samples have been sent for analysis to Norway and the USA³⁰).

It can be assumed that the situation is similar in other healthcare regions in Sweden. The above list includes a few research biobanks from other parts of the country: **ULSAM**

²⁸ While the samples collected through EPIC are normally stored in a centralized biobank at IARC in Lyon, the participating centres from Sweden, Denmark and Norway have chosen to store the samples in their own local biobanks.

²⁹ International Evaluation of Swedish Biobanks, 18 March, 2005 (available on www.biobanks.se)

³⁰ Remaining material is going to be returned to Sweden, as required by the Swedish Biobanks Act

(Uppsala), **ABIS** (Linköping) and the **Epidemiology Group**, Sahlgrenska University Hospital (Gothenburg). These are relatively well-known in the scientific community, but should be regarded mainly as examples. The last-mentioned biobank is established within the INTERGENE project, in which the genetic influence on the absolute risk for coronary disease is investigated.³¹ The study is a combined control and cohort study of 2 000 consecutive patients, with coronary artery disease from hospitals situated in western Sweden. The control group is selected from patients' relatives and approximately 10 000 healthy individuals randomly selected from the population. The study design provides possibilities for further analyses where the odds ratio, for a number of risk factors, can be estimated in relation to the genetic disposition.

One of the professors interviewed, with long experience in biobanking as well as in international research collaboration states that the picture in southern Sweden is probably quite typical for the whole Nordic region. He indicates that a policy to save original biological material was already established in these countries many decades ago, in some cases even a century ago. He also mentions that during the last decade or so, the previous policy to discard the oldest samples to make room for new ones has been abandoned and the sample collections are, therefore, nowadays growing continuously. However he is uncertain as to what extent the same patterns have developed in other parts of Europe.

The Karolinska Institutet (KI), in Stockholm, is Sweden's largest medical school and an internationally leading medical research institution. Many sample collections of varying size have been created over the years linked to various research projects. However, there are no large population-based biobanks similar to those in Umeå and Malmö. But since 2004, KI is heavily investing in building up a modern infrastructure for biobanking. A core facility called **KI Biobank** has been established with financial support from the Wallenberg Foundation. The aim is to build up a non-commercial resource for collection, handling and storage of human biosamples to be used in molecular and genetic research in Sweden. The biobank is, thus, positioned as a national resource. Another ambition is to increasingly use the biobank in international collaboration, for example, in the field of genetic epidemiology. Such collaborations have already started in some projects (e.g. GenomEUtwin and several studies funded by the National Institutes of Health in the USA).

The availability of donor information has been found to be a crucial precondition at KI for the effective use of collected biosamples in research. Therefore, in order to enhance the biobank's scientific usefulness, large resources are invested in building an advanced informatics structure. A central part of the biobank is, thus, the Biobank Information Management System (BIMS), which will facilitate linking samples and large databases containing phenotypic and genotypic information on the sample providers. This system, now under construction in cooperation with IBM, is argued to be unique in the world and is expected to significantly enhance the importance of the biobank. Other features of the KI Biobank are a strict quality control system, strong emphasis on ethical issues (e.g. existence of informed consent), and large-scale DNA extraction facilities.

The KI Biobank functions as host for several sample collections at the KI. There are today, in total, samples from around 15 000 individuals stored in this biobank. The

³¹ www2.sahlgrenska.gu.se/intergene/eng

Swedish Twin Registry (with phenotypic data from 140 000 twins) accounts for approximately half of these samples, including 5-6 000 samples collected in the late 1990s. The Twin Gene Project is an important ongoing biobanking activity aiming to transform the registry from a primarily epidemiology research into a strategic resource for functional genomics studies and gene-environmental interactions in complex genetic diseases. The goal is to create a collection of samples from 20 000 individuals. At present, samples are collected at a rate of approximately 250 twins per week, which means that the goal will be reached within less than two years. The updated twin registry, with its biological samples collection, will be used as an open-accessed resource for national and international scientists. Within the frame of the GenomEUtwin project, KI is already collaborating with twin registries in Finland, Denmark, Norway, the Netherlands and Italy.

The other half of the KI Biobank consists of smaller collections from approximately 10 different studies. All of these projects are new and begun after 2004 when this core facility was established. Outside the KI Biobank there are nearly 200 other collections stored at different departments around KI. Some of them may be integrated in the KI Biobank in the future. For example, there is an ongoing large study on prostate cancer with 6 000 samples that will be taken in [based on interview], but most of the existing collections will not be integrated, since they do not meet the quality standards applied by the KI Biobank. For example, samples may not have been stored at the right temperature, informed consent may be too narrow or missing, or the available data on the donors may be inadequate. As pointed out by the executive director, the role of the KI Biobank is to take care of those collections particularly valuable for future research. **LifeGene**³² is a new large-scale biobanking project at the KI, which is still in an up-start phase. It is a population-based prospective cohort study on lifestyle, health, and genomics. The goal is to collect samples and information from at least 500 000 Swedes, thereby, creating a large, open resource for research on disease aetiology and daily health problems, such as obesity, diabetes, allergies, psychiatric disorders, and infections. The project is still in a preparation phase, which means that collection of samples and data has not yet begun. In an initial phase, LifeGene intends to utilize existing resources such as the Twin Registry and start with all first-degree relatives of the twins in this registry.

An important feature of LifeGene, fully in line with the strategy of the KI Biobank, is to make maximum use of modern information and communications technologies. This means, for example, that following the initial use of existing databases, enrolment will be made through contact via mass e-mails and advertisements. Assessment of in-depth exposure information on research subjects will also be made by using electronic means, such as Internet, cell phones, digital papers and TV. The use of electronic questionnaires will enable frequent data collection and the building of a rich database. It is expected that the availability of this database will enhance the value of the biobank itself (in the past, the value of existing biobanks has often been limited by the lack of donor information).

National Biobank project

³² <http://lifegene.ki.se/>

The National Biobank Project (NBP) is a joint national program supported by the Wallenberg Foundation from 2002 to 2005 with a budget of approximately 5 million euros.³³ The background of this initiative was that Sweden, for a number of reasons (such as the existence of several large biobanks, the extensive use of unique personal identification number and high-quality health data registries), offers excellent conditions for carrying out population-based genetic studies of complex diseases. It was concluded that the bottlenecks preventing efficient use of biobanks were not due to the lack of samples or information, but rather to the downstream level. The aims of NBP, therefore, were to:

- enhance the overview and knowledge on the Swedish biobanking system;
- characterize and improve the quality of biobanks;
- increase the usefulness and accessibility of biobanks;
- raise the protection of integrity of individual donors, by using improved, formal quality standards for biobank-based studies and upgrade ethical awareness.

Among the various activities carried out within the NBP, are the funds used to support additional collections of samples (e.g. fresh-frozen tissue), delivery of samples and data for research, creation of new facilities for sample handling and analysis, training in ethics and law, and building of a pilot Regional Biobank Registry. One of the more important results is the creation of a common Quality Assurance manual for biobanking, called “Good Biobanking Practice” (GBP). This system has been recommended by the Swedish County Council Association and its implementation around the country is under way. Another result is the development of common standards for the protection of the donors’ integrity.

Biobanks in industry

There are many pharmaceutical and biotechnology firms carrying out R&D in Sweden. The multinational AstraZeneca has three of its largest R&D centres in Sweden. The biotechnology sector is the fourth largest in Europe³⁴. During the last ten years, well-characterized human biobanks have become an increasingly important resource for development of new drugs and diagnostics. First, biobanks were used in the companies’ early-phase of drug discovery activities to identify drug targets (which could then be taken, in the next step, as a starting point for product development). Second, pharmaceutical firms also collected and stored biosamples in connection to clinical trials, for example, for the purpose of pharmacogenomic studies. A study carried out a few years ago showed that pharmaceutical and biotechnology firms in Sweden had, with a few exceptions, chosen not to build up their own biobanks [7]. Instead, they established collaboration with academic researchers with access to biosamples and data (either collected by themselves or available in other public biobanks). Usually, the research was carried out by academic researchers, but in close cooperation with scientists from the sponsoring company. Sometimes, the biosamples were analysed by the industrial partner, but as a rule there was no transfer of biobank materials to the company. The latter was primarily interested in the research results and not the material *per se*.

³³ An evaluation report on Swedish biobanks written by an international evaluation committee is available on the NBP’s homepage (www.biobanks.se). The NBP is described in one of the appendices.

³⁴ Ernst and Young Refocus: The European Perspective 2004

From the industry's point of view, this mode of cooperation offered many advantages compared to in-house biobank research. Not least, researchers, in universities and hospitals, had contacts with patients who could be recruited as research subjects and donors, and also access to valuable information through various registers. Companies like AstraZeneca and Pharmacia & Upjohn (today Pfizer) had such projects of collaboration with many research groups both in Sweden and abroad. They also had research contracts with biotech companies, mainly foreign ones, that had access to samples and data either from proprietary or external biobanks.

It is worth mentioning that in the late 1990s, an attempt was made to commercialize the Medical Biobank in Umeå and, as inspired by deCode genetics in Iceland, UmanGenomics was established. The business idea was similar to deCode's, i.e. to carry out human genetic studies on behalf of the pharmaceutical industry. But the organizational set up was different (e.g. with regard to ownership, funding, and relationships with hospitals and universities). Unlike deCode, UmanGenomics would not have its own biobank. Instead, it was given exclusive rights to use the public Medical Biobank for commercial research. However, for several reasons this venture failed. Triggered by the establishment of UmanGenomics, a severe conflict regarding the disposal rights arose between researchers associated with the biobank on one side, and the university and the county council on the other. This made it impossible for the company to effectively use the biosamples to develop its business.

Sample collections

For the three large population-based biobanks the selection of participants is by definition random – in the case of the Medical Biobank also demographic-specific. The collection of samples has been carried out by specifically employed staff and, in the case of the Medical Biobank, also by primary care workers. For the other research biobanks, participant collection is disease-specific and/or random (often both). The sample collection is often made by using a combination of different channels: associated hospital staff, staff specifically employed for the project and primary care centres. For the Malmö Microbiology Cohort, participant selection is random and disease-specific. The sample collection is carried out by primary care workers. The Swedish Institute for Infectious Disease Control selects participants both, on the basis of diseases and other project-specific criteria. It has its own staff dealing with the sample collections. For all biobanks, public research is the principle reason for creating the biobank. In several cases, including clinical biobanks, clinical research diagnostics is another reason.

Access to and sharing of samples

Access to samples from the three population-based biobanks is free, in the sense that there is no fee to be paid, but access is restricted by scientific priority (e.g. in relation to main research questions in grant applications). For the Medical Biobank, decision on access is made by expert groups and a steering board. For the two Malmö biobanks, the decision is made by a scientific priority committee. Other research biobanks, in general, do not demand any payment for using samples.

An exception is the KI Biobank, which is using the self cost principle (this biobank has been created specifically as an infrastructure resource for biobanking at the Karolinska Institute). Even if there are no fees involved, access to samples and data from the

research biobanks is usually restricted in other ways. One factor is availability of DNA. Furthermore, research collaboration with the responsible organization is often required.

For all biobanks, cross-border sharing of samples and data is allowed, as long as samples are sent abroad only for analysis (according to the Swedish Biobanks Act). However, sharing of samples in international projects is associated with certain problems due to legal differences between countries. This is discussed in more detail in another section of this report [see section 3.1.2].

Consent

All three large population-based biobanks that replied to the survey use a broad consent to biomedical research. The other research biobanks usually use a more narrow consent, for a specific study or for research in a certain research area. The KI Biobank, which is hosting a number of individual collections, uses a set of different consent forms (these range from those used for a specific study, to those used for biomedical research on a broader scale). The Malmö Microbiology Cohort did not use any explicit consent before 2004 (when there was no specific law on biobanking). Since 2004, it uses a broad consent form to biomedical research.

As a rule, Swedish biobanks covered in this study do not refer back personal results to the donors. One exception is ABIS, which does if requested. Also, the KI Biobank reports that, in a few studies, clinical chemistry data is reported back to the study subjects.

In all biobanks, donors can withdraw their consent to the storing of samples.

Regulatory aspects

The Medical Care Act applying to Swedish biobanks entered into force on 1 January 2003, and will be revised in the near future. The present act only covers biobanks under the healthcare system. However, in reality many research biobanks are also concerned since sampling is often carried out by staff employed at hospitals and medical care centres. If sampling is made without involving healthcare providers the Medical Care Act will not apply. However, according to a proposal by the National Board for Health and Welfare, the revised Act will also cover all research biobanks.

The Swedish Biobanks Act, and its application has been heavily criticized by the research community, which complains about the increasing bureaucracy that it entails (also see section 3.1.2). Among other effects, some law elements make it more difficult to participate in international research cooperations – at least according to some leading biobank researchers. The current proposal to let the law cover all research biobanks, irrespective of who carries out the sampling, is not appreciated.

There seems to be a wide-spread opinion among leading Swedish biobank researchers that recent legislative changes, such as the new Biobanks Act and a new act on the ethical review of research involving humans (in force since 2004), have resulted in a transfer of powers from scientists to authorities (both at national and local level). For example, it used to be the individual scientist who applied for and received the ethical approval. Now, it is the employer (e.g. the university or the county council) who is the applicant and the possessor of the approval. In reality, in most cases, there have not yet been significant changes in the practical handling – since, in general, the authorities are

not interested in controlling research in detail. But there are exceptions. The Medical Biobank in Umeå is one case where the authorities have taken advantage of their power, and this has created severe conflict between the university and the county council on the one hand and the researchers who operate the biobank on the other. Even if this is an exceptional case, there is increasingly wide-spread concern among researchers regarding the harm this development will cause them. There are those who believe that “free research” is threatened and that Sweden’s leading position in biobanking and biobank-based research will be at risk. It remains to be seen whether this concern is justified.

Privacy/data protection

Like other Member States, Sweden has implemented the Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and to the free movement of such data. The Personal Data Act from 1998, has been complemented by the Personal Data Ordinance (1998). There are a number of other Swedish laws which have relevance to the protection of personal data in relation to biomedical research: the Medical Care Registers Act, the Health Data Registers Act, and the Act on Research Registers for Forensic Psychiatry, the Security Act, and the Archives Act [8].

In a public law study relevant to the use of biobank samples, it was concluded that it is not entirely clear how biobank materials are looked upon in the legislation on data protection.³⁵ In the *travaux préparatoires* of the Swedish Personal Data Act, the processing of biosamples is not even mentioned. However, the government has declared that DNA samples and other parts of the human body should, in principle, be considered as living persons. At the same time, the borderline between a biological sample and a document is not that sharp in legislation – “at a time where DNA can be digitalised and many other characteristics of human tissue and cells can be registered in enlarged photographs etc.” The study also concluded that the borderline between the scope of the Swedish Biobanks Act and that of the Personal Data Act is rather vague. For example, it is not clear which of the laws gives precedence in case of conflict.

Ethics discussion

A public debate on biobanks suddenly arose in Sweden in the late 1990s. The background was the increasing interest in biobanks and genomics research shown by the biotech and pharmaceutical industry. In the spring of 1999, one of the major tabloids, *Aftonbladet*, ran a series of articles on biobanks. Headlines such as “Your life is for sale”, “They make money on your cells” and “Swedish physician helped company to enter the biobanks” reveal a critical attitude towards the use of biobanks for research in general and industrial involvement in particular. It was, in fact, these articles that triggered the Swedish government to start an investigation into biobanks with a view to preparing new legislation. As a result, a Swedish Biobanks Act came into force in January 2003. Another reaction to this debate, was that academic research on ethical, legal and social aspects on biobanks was initiated. Since then, several research projects have been carried out by scientists from different disciplines (one example is the National Biobank Project mentioned above). Today, biobanks are one of the important research themes of the Centre of Bioethics at the Karolinska Institutet and Uppsala University. There is, thus, ongoing research and debate in the scientific community,

³⁵ *Ibid.*

among experts and professionals, but one cannot say that there are any public debates on biobanks ongoing today.³⁶

2.2.1.2 Biobanks in Norway

The following nine biobanks, in Norway, are covered in this study:

- ⇒ JANUS Serumbank (Cancer Registry of Norway)
- ⇒ HUBRO (Health Study of Oslo)
- ⇒ OPPHED (Health Study of Oppland and Hedmark)
- ⇒ **HUNT Biobank (Health Study of Nord-Trøndelag)**
- ⇒ Tromsø Health Survey
- ⇒ HUSK (Health Study of Hordaland)
- ⇒ MoBa (The Norwegian Mother and Child Cohort Study)
- ⇒ Sami Health Survey
- ⇒ Women and Cancer

There are many research biobanks in Norway at universities and research institutes. One of the oldest and best known is the so-called **Janus Serumbank**, which is owned and financed by the Norwegian Cancer Society. This biobank contains some 700 000 serum samples, collected from 1972 to 2005 from 330 000 donors. The purpose of the project is to search the material for changes that can help to discover the development of cancer at an early stage or indicate increasing risks for certain types of cancer. To date, the material has been used in more than 10 different studies, including in both national and international studies. For example, the Janus Biobank has been used in several EU-funded projects (such as ERICBSB, VIRASKIN and CCPRP).

Since the beginning of the 1970s, regional health surveys have periodically been carried out in different parts of Norway. For example, in Nord-Trøndelag surveys were conducted in 1984/86 and 1996/97, and a new one is planned for 2006/08. In more recent years, blood samples and data have, in some cases, been stored for research purposes. Today, biobanks built up linked to the following health studies constitute important resources for research: **HUNT** (Nord-Trøndelag), **HUSK** (Hordaland), **HUBRO** (Oslo), **OPPHED** (Oppland and Hedmark), and **Tromsø Health Survey**. Some of these biobanks (e.g. HUNT, owned by the Norwegian University for Science and Technology in Trondheim and comprising samples from 65 000 people) have already been used in a number of research projects. Other biobanks that started sampling later, have not yet come that far. Generally, these Norwegian biobanks have been positioned as resources for domestic researchers, but they are also available for use in international projects.

A few years ago, **CONOR** (Cohort of Norway) was established by the Norwegian Institute of Public Health (FHI) as a network/umbrella organization for these five regional health surveys.³⁷ The purpose is to achieve a national (population-based) high-quality collection of biological material, as well as responses to standardized

³⁶ A couple of years ago, a local debate took place in the County of Västerbotten regarding UmanGenomics and its right to commercialize the Medical Biobank in Umeå. The conflict, among the different parties involved, was covered by the local press and also, to some extent, by the national press.

³⁷ For more information on CONOR and the Norwegian health surveys, see www.fhi.no.

questionnaires. At present, CONOR has samples and data from approximately 185 000 adults.

CONOR is open to researchers, who can apply for data and samples from a central steering group. The data supplied to researchers, always collected with consent from the donors, are anonymized (although a key code is maintained by the FHI). If such data are to be combined with data from other registers or if analysis is to be carried out on the samples, permission from the Data Protection Agency is required.

MoBa (Mother and child study) is another large-scale project of interest from the biobank-based research point of view. In this ongoing study, carried out by FHI and includes collection of blood samples, the goal is to follow 100 000 mothers and children. The purpose is to enable research on factors causing diseases in mothers and children.

"The Sami Health Survey" and "Women and Cancer" are two relatively large research biobanks at the University of Tromsø. The former has so far been used only in domestic research projects, but the latter is part of EPIC³⁸.

With financial support from the Norwegian Functional Genomics Program, **BIOBANKS FOR HEALTH** (also called "Biohealth Norway") has been formed as a network, or technology platform, for genetic epidemiological research. The platform, hosted by FHI, is built upon the biobanks in CONOR and MoBa and also involves the universities in Oslo, Bergen, Trondheim and Tromsø. The aim is to create a biobank with samples and data from 450 000 Norwegians from different ages, that is, approximately 10% of the population. Biohealth Norway is one party in a new collaboration between Norway and Great Britain. In October 2005 a Memorandum of Understanding was signed between FHI, the University of Bristol (responsible for the so-called ALSPAC study) and UK Biobank. The basic idea is to pool samples and data from the different biobanks and thereby improving the efficiency of research.

Sample collections

The collection of samples for the regional health studies is made at random and demographic specific. The actual work for the collection of samples and data is carried out by specifically employed staff and, in some cases, also by associated hospital staff. In addition the MoBa biobank, currently with samples from 166 000 mothers and children, is also random. For "Women and Cancer" and the "Sami Health Survey", which are two studies carried out at Tromsø University, the participant selection is a combination of random, disease-specific and demographic. The large Janus Serumbank has recruited participants among blood donors and people undergoing public health surveys. For these biobanks, the collection has been carried out by associated hospital staff and/or specifically employed personnel.

Access availability and sharing of samples

The health survey biobanks are used by researchers at the collecting institutions as well as from other institutions in Norway. Several of them are also used in international collaborative projects. As a rule, access to biobank material is associated with payment and in all cases, the decision to grant access is made by a governing board. Some of

³⁸ <http://www.iarc.fr/epic/>

Biobanking activity

these biobanks allow cross-border sharing of both data and tissue but two of them (Tromsø Health Survey and HUSK) report that they only allow sharing of data.

Both the Janus Serumbank and MoBa allow both tissue and data sharing with foreign researchers.

Consent

The regional health surveys use a variety of consent types, ranging from specific studies to biomedical research. One study (Tromsø) provides donors, in all cases, feedback of their personal results, while two others (HUSK and HUNT) do not. In these two other cases, this remains to be decided. With one exception (HUBRO), donors can withdraw their consent.

The Janus Serumbank and MoBa use consent to research in certain areas and to biomedical research respectively. None of them give any feedback of personal results. Both the Sami Health Survey and Women and Cancer use different types of consent, again ranging from specific study to biomedical research. The former gives donors feedback of their personal results (in all cases), while the latter does not.

All these four biobanks allow donors to withdraw their consent.

Regulatory aspects

Like in Sweden, a new Biobanks Act entered in force Norway in July 2003 and a national biobanks register will also be established. This work is now under way and according to current plans, the register will be completed by mid-2006. In this context, new research biobanks will require evaluation of a regional committee for medical research ethics and the Social and Health Directorate. The Medical Use of Biotechnology Act (1994) is another law of relevance.

Privacy/Data protection

The Norwegian Personal Data Act is in effect from 2000.

2.2.1.3 Biobanks in Denmark

The following fifteen biobanks, in Denmark, are covered in this study:

- ⇒ The National Danish Birth Cohort
- ⇒ The National PKU Biobank
- ⇒ The Diet, Cancer and Health Biobank
- ⇒ The Copenhagen City Heart Study
- ⇒ The Copenhagen General Population Study
- ⇒ The Copenhagen Ischemic Heart Disease Study
- ⇒ The Copenhagen Carotid Stenosis Stroke Study
- ⇒ The Copenhagen Breast Cancer Study
- ⇒ The Danish Twin Registry
- ⇒ **NUGENOB**
- ⇒ **ORG/ADIGEN**
- ⇒ Pelvic Mass
- ⇒ HPV

Biobanking activity

- ⇒ The Danish Psychiatric Biobank
- ⇒ Research Centre for Prevention and Health (Copenhagen County)

It seems that the biobanking situation in Denmark is relatively similar to the one in Sweden. At large hospitals and universities there are many small research biobanks. The list above is not exhaustive but contains some of the more important biobanks, some of which are relatively large. One of them is the **Diet, Cancer and Health Biobank** (with samples from 57 000 individuals). This biobank constitutes the Danish part of the European Prospective Investigation into Cancer and Nutrition (EPIC). This biobank is owned by the Danish Cancer Society and used for epidemiological research, both in connection to EPIC and other national or international projects (e.g. the EU-funded DIOGenes).

NUGENOB is an example of a more recently created research biobank. It was established through the 3-year long project financed by FP5 and coordinated by a Danish institution (NUGENOB = Nutrient-gene interactions in human obesity: implications for dietary guidelines). There were 12 partners in 7 European countries. Samples and data have been collected from 890 individuals. Material is stored in three places: Copenhagen (buffy coat and extracted DNA), Maastricht (serum and plasma) and Toulouse (mRNA). Information is stored in an intranet database. Today, the three NUGENOB biobanks are used by members of the NUGENOB consortium in multiple ongoing projects addressing related research questions. In the future, the biobanks may be used in other collaborative projects, as there has been a considerable interest in collaboration with external users, both academics outside the NUGENOB group and the industry. There are for example ongoing negotiations on access with the FP6 Network of Excellence NUGO. An important issue for the consortium that owns the biobanks is to obtain financial resources to support their maintenance and exploitation.

The **Danish Psychiatric Biobank** is among several other valuable research biobanks.. This biobank, founded in 2001 and currently containing some 1200 samples, is located at St. Hans Hospital in Roskilde, where there is a research institute for biological psychiatry. However, recruitment of donors and sampling are carried out by several psychiatric departments and laboratories in greater Copenhagen. Thanks to this collaboration, individual studies can be based on larger sample sizes. Foreign researchers have shown a keen interest in this biobank. They can gain access to material by establishing collaboration with the Danish researchers. There are, today, collaborative projects with Brazil, Iceland, Canada, Norway and Sweden. Moreover, in collaboration with the Blood Bank at the hospital, the Psychiatric Biobank has established a collection of samples from 15 000 blood donors. These can be used as controls in the research. The use of anonymized DNA samples from these donors has been approved by the ethics committee. Access to this material can also be granted to researchers working outside the psychiatry.

Like in Sweden, Denmark has a **national PKU Biobank**, which is hosted by Statens Serum Institut. Neonatal screening for several diseases has been carried out in Denmark in the last twenty years. After analysis, blood samples are stored in a biobank mainly for medical care reasons. These screening samples can also be used for research. However, we have no information as to what extent this potential has been exploited.

In the medical research community in Denmark, biobanks are generally considered to be a key facility, both for current and future researchers.³⁹ One important reason is that Denmark, like for instance the other Nordic countries, has many high-quality registers covering the population (such as the national patient register, the cancer register, and the death cause register). This is believed to create excellent conditions for conducting biobank-based research – since it is possible to efficiently link the biological material to detailed and reliable information on the patient's disease and treatment. In this kind of environment the individual can be followed 'from womb to tomb'. It is also argued that the Danish population is interested in research and therefore it is possible for people to accept that biological material is stored and used for scientific purposes.

At the Copenhagen University Hospital ("Rigshospitalet"), Denmark's largest hospital, there are several existing clinical biobanks. Given the development of new molecular biological methods for diagnostics in recent years, there are now creating a central biobank function, called Rigshospitalet's Biobank. The primary purpose is to collect DNA, plasma and fresh-frozen tissue for diagnostics and optimisation of treatment (such as personalized medication). A secondary purpose is to use the biobank for research, in accordance with informed consent from donors and after approval of a special steering group. It is expected that DNA and plasma samples will be collected annually from 45 000 patients. Tissue samples will be taken from 5 000 patients per year. In 2008 the finishing touches were made and the biobank is now in operation⁴⁰.

Sample collections

Eight of the biobanks that replied to the survey make a random selection of participants. The other six are disease-specific biobanks. The former group of biobanks generally use several channels for sample collection, including associated hospital staff, specifically employed personnel and primary care workers. In addition, the Twin Registry uses self collection. The disease-specific biobanks use associated hospital staff with one exception – NUGENOB, which has specifically employed staff.

Access availability and sharing of samples

In the first group mentioned above, all but one biobank are open to researchers from Denmark as well as from other countries. The exception is the Danish HPV cohort which at least, so far, has been used only by the researchers who collected the samples. Four biobanks report that payment is a condition for access, at least in some cases. Access to the others is free. In most cases, access is restricted in some way, for example, to scientific relevance. One of the respondents writes: "anybody can submit proposals to the steering committee. If judged good science and we perceive no conflict of interest, usually even external researchers are given a go-ahead."

If we look at the disease-specific biobanks group, all of them are used both nationally and internationally (in some cases only in Europe). None of them require any payment, but like the former group, access is usually restricted, that is, requiring approval by a steering committee or similar body. For all the Danish biobanks in our study, decisions on access are usually made by either a governing board or a steering committee. In one case (The Danish HPV cohort) decisions are made by the principal investigator. Sharing of tissue as well as data is allowed in all cases.

³⁹ *Biobanker – fremtiden är begyndt* (Biobanks – the future has begun), special issue on research, Hovedstadens Sygehusfællesskab, November 2005.

⁴⁰ <http://www.rigshospitalet.dk/RHenglish/Menu/Diseases+and+Conditions/New+biobank/>

Consent

With a few exceptions, the type of consent used by the Danish biobanks is for research in a certain area and/or for biomedical research. One exception is NUGENOB, which asks the donors only to consent to the study. Some biobanks use blanket consent in combination with other broad types of consent (the Copenhagen General Population Study, the Copenhagen City Heart Study and the Danish Twin Registry). Moreover, half of the biobanks report that they send personal results back to the donors and the other half do not. All but one biobank (NUGENOB) allow donors to withdraw their consent.

Regulatory aspects

Denmark does not have a separate “biobanks act” in the same way as, for example, Sweden and Norway. Instead, biobanks are primarily regulated by the Processing of Personal Data Act. The Danish Data Inspection Agency has decided that biobanks are to be seen as manual registries (i.e. biobanks must be registered with the Authority).

However, new rules for biobanks became in force in Denmark in May 2004 through Law No. 312 adding certain provisions to the existing Danish Legal Status of Patients Act (No. 482 from 1998). In 2005, new provisions were added once more. The new rules affect the use of biobanks in several ways. For example, patients can now decide whether or not they wish stored samples to be used for research. This decision is then entered into the so-called Tissue Use Registry (*Vævsanvendelseregisteret*).

Also certain recent provisions to the Act on Research Ethics Committee System from 2003 are of importance for the use of biobanks. The Act allows, for example, the use of broad consent when establishing new research biobanks. That is, samples cannot only be used in specific projects but also for other studies on the same type of disease.⁴¹

To judge from comments made by interviewees, Denmark has the most “liberal” biobanks legislation in the Nordic countries, causing the least problems and bureaucracy from the researchers’ point of view.

Privacy/Data protection

In 2000, the EU Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data, was implemented to national law through the Act on Processing of Personal Data. As already mentioned, in Denmark this Act plays a particularly important role for the use of biobanks. In fact, Denmark is unique- in having clearly and officially declared that biobanks are subject to personal data legislation. This seems to be the main reason why Denmark has not introduced general biobank legislation [8].

2.2.1.4 Biobanks in Finland

The following five biobanks, in Finland, are covered in this study:

- ⇒ KTL Biobank
- ⇒ The Finnish Twin Cohort

⁴¹ For a short discussion on biobank legislation in Denmark, see *ibid*.

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- ⇒ Helsinki Sudden Death Study (Tampere University)
- ⇒ Tampere Coronary Study (TCT)
- ⇒ Tampere Acute Coronary Syndrome (TACOS) Study

In Finland, like in the other Nordic countries, there are many small research biobanks established by various researchers and research groups at the universities. Especially interesting about Finland is the role played by the National Public Health Institute (“KTL”) in the field of biobanking.⁴² KTL is a state-owned institute and expert body under the Ministry of Social Affairs and Health. It was established in its present form in 1982, but has its roots in the Serum Laboratory founded in 1911. The aim of KTL is to promote the population’s possibilities to live a healthy life, and it provides professionals and citizens with information needed to make choices. In the end of 2004, KTL had a staff of about 900, of which more than one third (approximately 350 employees) worked as researchers. The budget for 2004 amounted to 62 million euros, 63% of which was covered by the state. External co-financing of research projects amounted to 15% of the budget. 4% of the funding came from the EU.

Performing high-level research with broad international collaboration is one of the most important functions of KTL. Research is carried out at a number of various departments, such as Molecular Medicine and Epidemiology and Health Promotion.

Collection of biosamples has been carried in connection to several studies carried out by KTL, often in collaboration with other research centres in Finland or abroad. The largest cohorts with biological material have their origin in the following studies: ATBC Study, FINNRISK, Helsinki Heart Study, Health 2000, Finnish Mobile Clinic Health, NPHI psychiatric cohorts and Finnish Maternity Cohort.

To take one example, the ATBC study was a randomised, double-blind, placebo-controlled study on lung and other cancers. From 1985 to 1988, 29 000 smokers were recruited. All of them gave written informed consent, and the study was approved by the institutional review boards of KTL and the National Cancer Institute in the US, which was a co-funder. Today, DNA has been extracted from more than 2 000 participants, and blood for DNA extraction is collected from 22 000 participants altogether. Serum is available for analysis for all participants. The material has been used in several international collaborations such as the Harvard Cancer Pooling Project, the MORGAM project, which examines the gene-environment interactions for cardiovascular diseases, and the Nordic Biological Specimen Banks on Cancer Causes and Control.

All samples collected in **KTL projects** are stored in a centralized biobank, which today contains DNA and serum/plasma samples from 200 000 Finns (approximately 5% of the population). This biobank constitutes an important national resource, increasingly used in international research projects in which Finnish researchers from KTL and other institutions are involved in.

The list above includes some other large biobanks in Finland. The **Finnish Twin Cohort** was first established in 1974, to investigate genetic and environmental risk factors for chronic disorders. Several sub-studies concentrating on different phenotypes have been carried out at different universities. DNA collection and storage has been a

⁴² www.ktl.fi

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routine feature since the mid-1990s. Currently, the biobank contains samples from 55 000 twins recruited from 1974 to 1996. For the moment, there are no plans to expand the cohort.

The twin biobank has been used in many international projects several of which have been funded from the EU through FP5 or FP6. Other studies have been funded by the National Institutes of Health in the US. Normally, samples are not sent abroad, but there are some exceptional subprojects where the genotyping has been done by foreign partners. Both DNA and phenotype data were shared with a US partner in a project, but this was then specifically covered in the consent form.

Helsinki Sudden Death Study, Tampere Coronary Study and Tampere Acute Coronary Syndrome Study exemplify three smaller biobanks. The first one mentioned is a prospective consecutive autopsy study on acquired and genetic risk factors for sudden cardiac death and genetic factors for alcohol induced diseases.

Sample collections

The large KTL biobank contains samples which have been collected through both population-based and disease-based sampling. The institute has used its own personnel, specifically employed for different projects, as well as primary care workers. The individuals included in the twin cohort by definition are twins. Sampling is carried out by specifically employed staff. In the case of the Tampere biobanks, samples have been collected by the researchers themselves or other members of the study group.

Access availability and sharing of samples

The KTL biobank is used primarily by the researchers who have collected the samples stored in this biobank. These researchers may, however, be involved in collaboration with external research partners in Finland or abroad. The decision on access is made by a governing board at KTL. A research contract with KTL is required for external researchers to gain access to the material. International sharing of samples, as well as data, is currently difficult. There are problems with the interpretation of consents which are now being discussed in legal and advisory bodies. Until these uncertainties have been sorted out, no sharing of data or samples can take place.

The Finnish Twin Cohort is used extensively for research including collaboration with foreign researchers. Access to samples, on which decisions are made by an official manager, is restricted based on the need and availability of data. Sharing of data, but not tissue, is allowed if made anonymously.

The three disease-specific biobanks in Tampere are used not only by the researchers who collected the samples but, also by other Finnish and foreign researchers. Decisions on access are made by the researchers collecting samples. For two of these biobanks (TACOS and TCT), sharing of both tissue and data is allowed. For the third biobank (Helsinki Sudden Death Study) only data can be shared.

Consent

The samples in the KTL Biobank have been collected in connection to various studies for which study-specific consents have been obtained. No information on personal results is fed back to individuals. For the Twin Cohort, the type of consent varies from specific studies to biomedical research depending on the sub-study. Information is

reported back to donors, if consented to. The TACOS study uses the process of consent to research in a certain area or biomedical research. No personal information is fed back. For the other two biobanks in Tampere there is no need for consent procedures at all as the samples have been taken from dead persons. In all cases, except the two latter, donors can withdraw their consent.

Regulatory aspects

An Act on the Medical Use of Human Organs and Tissues (No 101/2001) came into force in Finland in 2001. However, this act is primarily concerned with the use of organs and tissue for transplant purposes. Importantly, in the same year another act (No 32/201) regulating the activities of the National Public Health Institute (KTL) came into effect in Finland. This law is of great relevance to biobanking, given the key role played by KTL in this kind of activity. For example, it gives KTL the possibility, under certain circumstances, to build and use biobanks without individual informed consent (e.g. archived samples from maternity screening). In Finland, KTL is in charge of many activities which in other countries are carried out by other actors (e.g. healthcare providers and universities). Therefore, other countries, in general, do not have the prerequisite for making the same type of legislation [9].

Privacy/Data protection

The EU Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data was implemented to national law through the Personal Data Act (1999). In 2000 the Act on the Amendment of the Personal Data Act came into effect.

2.2.1.5 Biobanks in Iceland

The following five biobanks, in Iceland, are covered in this study:

- ⇒ Icelandic Biobank (deCode)
- ⇒ UVS Biobank (decode)
- ⇒ The Icelandic Cancer Society Biological Specimen Collection
- ⇒ Reykjavik Heart Study
- ⇒ Tissue Archives, University Hospital

Iceland is an interesting country from a biobanking perspective. Its plan to create a national Health Sector Database (HSD) has attracted a great deal of attention far outside the country. One reason is that the right to build and run this database was licensed out to a private Icelandic company, **deCode** genetics⁴³. This is a biotech company founded in 1996. Based on certain unique characteristics of the Icelandic population and using a human genetics approach, deCode conducts research into the inherited causes of common diseases. At the beginning, deCode could be characterized as a “clinical genomics company” with the business idea to sell results from its genomics research (e.g. identified disease genes) to other companies, mainly in the pharmaceutical and diagnostics industry. Over the years, the business strategy has drifted, which means that deCode has now integrated forward to become a developer of new drugs and DNA-

⁴³ The parent company has its legal site in Delaware, USA, but most of the operations are carried out in Iceland by Icelandic employees. The company is also carrying out research in the US in acquired companies.

based diagnostic products. It also offers a range of related services to the pharmaceutical industry and the healthcare sector.⁴⁴

DeCode was founded on the assumption that Iceland offered unique opportunities to carry out clinical genomics research, thanks to the following four national characteristics:

- availability of genealogical records dating back, in some cases, to the settlement of the country in the ninth century.
- relative genetic homogeneity of the population, that is, clear “founder effects” facilitating the identification of disease genes.
- a centralized healthcare system since 1915.
- a well-educated population that tends to be cooperative when approached by physicians and medical researchers.

Dr Kari Stefansson, who founded deCode together with Jeffrey Gulcher, had two objectives. One was to establish a commercial company to carry out research where genetic information, obtained by analysing human biosamples, would be linked with clinical information and genealogies. The second objective was to construct a large, computerized database containing genetic, genealogical and phenotype information on the Icelandic population.

In the context of its gene and drug target discovery programs on some fifty diseases, deCode has collected a large number of biosamples and related donor information, through collaboration with hundreds of Icelandic general and specialist physicians. These collections together make up deCode’s biobank, named “Icelandic Biobank”. In total, this biobank today contains samples from more than 100 000 persons (i.e. over half of the adult population; the response rate has been high, meaning that over 90% of individuals contacted have agreed to participate).

All stored samples and data have been obtained after receiving explicit consent from the donors (these can choose whether they wish their samples to be destroyed after the study’s completion or allow to store them for future use; a large majority of the participants choose the latter alternative). Collected samples and data, in combination with information from the genealogy database, are used by the company in its own research projects for which it has obtained approval from the National Bioethics Committee and the Data Protection Authority (DPA). To protect the integrity of the donors, deCode uses, in accordance with the regulation, an advanced third-party identity encryption system. It ensures that all information on individuals (genetic, medical and genealogical) employed in the research is “anonymized”, that is, only identified by an encrypted ID code generated and kept by the DPA.

The research projects carried out by deCode, either in-house or in collaboration with external scientific partners, have resulted in the identification of a large number of drug targets in many of the most common diseases, such as heart attacks, strokes,

⁴⁴ The text on deCode in this section partly builds on an unpublished research report written by Jens Laage-Hellman, Chalmers University of Technology (“Commercialization of biobanks: a study on biotech companies dedicated to human genetics”, 2003). Information on the company can be obtained from its website, www.decode.com.

hypertension, asthma, schizophrenia, type 2 diabetes and prostate cancer. Many of these targets now serve as the basis for deCode's drug discovery and development programs.

As to the second business objective mentioned above, deCode was awarded, in 2000, a 12-year exclusive licence by the Icelandic government to build, operate and commercialize a Health Sector Database (HSD). The basic idea of this database is to assemble encrypted data from medical records of the National Health Service and store it in high-security computer systems. Participation is based on the principle of presumed consent, but there is a possibility to opt-out for citizens who do not wish to participate. The intention is that the database should enable users, including deCode (the licensee) and others (e.g. Icelandic physicians), to conduct population-based analysis of longitudinal healthcare data and trends. In particular, it is thought that combining information from this database with genealogical data and genetic data, available in two other databases, would give valuable opportunities to study the impact of environmental and genetic factors in common diseases.

This project and the related legislation have triggered an intensive debate in the country and has attracted attention by the mass media, both in Iceland and abroad. There has been criticism regarding issues such as consent procedures, confidentiality and scientific openness. Partly resulting from the debate, the HSD Act underlying the licence requires a very high level of security, both with regard to the database itself and the combination of its content with other data. deCode, various government authorities (especially DPA) and the healthcare providers have been involved in long-lasting and complex discussions and negotiations regarding security and other issues related to the execution of the project. Still, many problems remain to be solved. This is why the actual work on the transfer of data to the HSD has not yet begun. It seems that the extremely strict security targets will make the database very expensive to operate and will also reduce its scientific usefulness. The question is to what extent deCode and others will be able to use it as an efficient research tool. Therefore, there seems to be an increasingly widespread belief that the project will never be undertaken, at least not in the intended form. deCode, though, still holds the licence. However, the company does not depend on the HSD for its development and growth. As described, it is already carrying out population-based genetic studies using data it has collected by its own means.

Outside Iceland, there is a common misunderstanding that there exists a national biobanking project in Iceland. However, as we have seen, the planned HSD is another type of database, although it is intended to be linked with genetic data originating from the analysis of biosamples. The biobank has been built separately by deCode through a number of disease-specific studies. Over the years, deCode has in this way collected such large number of samples that the biobank can now be described as being population-based.

Urdur Verdandi Skuld (UVS) is another, smaller clinical genomics company in Iceland founded in 1998. UVS is using a similar population-based research approach as deCode, but is entirely focused on cancer. UVS is carrying out the Icelandic Cancer Project together with some 50 clinicians, the two largest hospitals in the country and the Icelandic Cancer Society. With help from its clinical collaborators, UVS has collected blood samples and tissue. At present, the biobank contains material from 22 000 individuals, including 6 000 cancer patients. It has been used in several collaborative

projects both with pharmaceutical companies and academic institutions. UVS has, for example, received a grant from the EU (3 million euros) to study the genetics of breast and prostate cancer. In January 2006, deCode acquired UVS in order to enhance its own cancer program. This means that deCode, today, has two different biobanks for which they have separate licences from the Icelandic government.

There are, as indicated in the list above, a few other important biobanks in Iceland. **Reykjavik Heart Study** is a prospective health study of heart diseases carried out, since 1967, by the private Icelandic Heart Association (IHA), which has its own research institute. The study comprises 31 000 men and women, many of whom have supplied serum and DNA samples now stored in IHA's biobank. The biobank and the rich amount of clinical and lifestyle data collected are used in different studies, some of which are carried out together with foreign partners, such as the US National Institute on Aging. IHA is also one of deCode's domestic research partners.

Another large biobank, comprising 12 000 individuals, is owned by the **Icelandic Cancer Society**. This organization is one of UVS' partners, and it is also involved in several international projects some of which are funded by the EU (e.g. Breast Cancer Linkage Consortium and International BRCA1/2 Carrier Cohort Study).

The largest biobank in Iceland is the **Tissue Archives** at the Pathology Department of the University Hospital in Reykjavik. Since 1935 tissue specimens from approximately 200 000 individuals have been collected. This is a clinical biobank, but it is also used for research purposes (after approval by the National Bioethics Committee and DPA, and usually on the condition that informed consent is obtained from the patient). The biobank has been used in numerous academic studies, some of which have been carried out together with partners in Europe and the USA. deCode has also used tissue samples from this biobank in some projects.

Sample collections

The selection of donors for deCode's two biobanks as well as for the Icelandic Cancer Society's biobank is both random and disease-specific. The Tissue Archives consist of all histopathological specimens accessioned.

The Icelandic Cancer Society (like the Icelandic Heart Association) has its own staff that carrying out the sampling. Interestingly, deCode and UVS have created special centres which play an important role in the collection of samples and data. In accordance with requirements from the DPA, both of them have created service units to which the donors are invited. These service units are non-profit organizations, financed by the companies but physically and organizationally separated from the rest of the companies. The personnel of these units encode samples and information using methods approved by the DPA. The key code is kept by the DPA.

Access availability and sharing of samples

While the Icelandic biobank is used in deCode's own projects (sometimes undertaken together with others), the UVS biobank is used in several collaborative project, both in Iceland and with foreign partners. Both the Tissue Archive and the collection of the Icelandic Cancer Society are seen as national resources. The latter is also available to foreign researchers with active collaboration in the Society.

Biobanking activity

In all cases, access to samples is restricted. Approval is required by the DPA and the National Bioethics Committee. Sharing of samples takes place only within the context of collaboration, on a person-unidentifiable format and after approval of the authorities. According to deCode and UVS, samples are normally not shared with collaboration partners – it is more common that only results are shared. In the former case, informed consent is always required from donors.

Consent

Icelandic law requires people to give informed consent if samples are to be stored in a biobank. But if the biosample has been obtained for clinical reasons, tests or treatment, then presumed consent will be sufficient. In line with existing regulation, deCode asks donors to give consent to a specific study while UVS, as well as the Icelandic Cancer Society, use a broader consent procedure covering a whole research area (cancer). The Tissue Archive does not need explicit consent. Commenting on the different rules applying to research and clinical biobanks, an Icelandic ethics scholar states that this difference has been criticized and also affected people's willingness to give their consent. Except for the Tissue Archives, which is a clinical biobank used primarily for medical care purposes, personal information is not referred back to the donors. In all cases, it is possible for donors to withdraw their consent.

Regulatory aspects

In May 2000, the Icelandic parliament passed an Act on Biobanks whereby Iceland became the first country in the world to construct legal guidelines for scientific and clinical biobanks. In the following year, this law was complemented by Regulations on the Keeping and Utilization of Biological Samples in Biobanks. The Act on the Icelandic Health Sector Database (HSD) was passed in 1998. In 2000, the same year in which the licence was granted to deCode, the Government Regulation on a Health Sector Database came into effect.

Privacy/Data protection

In 2000, an Act on the protection of Privacy as Regards the Processing of Personal Data came into force in Iceland. This Act gives the Data Protection Authority an important role with regard to biobanks.

Ethics discussion

An ethics debate related to biobanks has primarily taken place in connection to the HSD project. The passing of the bill in 1998, which gave the government the possibility of granting an exclusive licence to a private company, was preceded by a 9-month intensive debate, both within the parliament and outside. Criticism put forward by the Icelandic Medical Association, among others, led to several changes in the bill compared to the original proposal. For example, an opt-out clause was included. However, despite these changes the whole HSD project, and related legislation, became subject to continued criticism and discussion, both domestically and internationally. Among other issues, concern has been raised regarding consent procedures, privacy and confidentiality, scientific openness and the appropriateness of monopolizing the database. A result of the debate is that the HSD Act demands very high level of security. There is no doubt that the delay in executing the project is related, *inter alia*, to the tough, cost-driving security targets and complex monitoring system to be put in place.

It is interesting to note that while the HSD project has caused such an intensive debate, there has not been much public discussion on the Icelandic Biobanks Act. It can be argued that biosamples contain more sensitive information on the individuals (e.g. genetic data) than the proposed database.

2.2.1.6 Biobanks in the Baltic countries

There are two particularly interesting biobanks in the Baltic countries created in connection to genome research initiatives:

- ⇒ Estonian Biobank
- ⇒ Latvian Genome Database

The best known of these initiatives is the Estonian Genome Project (EGP), which has been mentioned or described in several news and journal articles during the last years. This population-based research project was started in 2001, very much inspired by developments in Iceland. The goal is to create a database of health, genealogy and genetic data that would comprise a large part of the Estonian population. The database will be used for carrying out research on linkages between genes, environmental factors and common diseases – thereby making new discoveries in genomics and genetic epidemiology and contributing to improved healthcare. The project is run by the Estonian Genome Project Foundation, which is a non-profit government organization. The databank is available for research both in Estonia and outside.

A pilot study including collection of blood samples started in 2002. To date, samples and associated data of the donors from approximately 10 300 individuals have been collected. The target number is 100 000 individuals, to be achieved in 2010 at the latest. This means that the database will comprise nearly 10 % of the Estonian population.

DNA samples and data have been used for research since 2004. Up to now EGP has been involved in approximately ten studies, some of which are international.

A somewhat similar initiative to create a national genome database has been taken in Estonia's neighbour country Latvia. Sampling started in the same year (2002). However, the target number of participants seems to be more modest than in Estonia. The current size of the biobank and databank is 2 500 individuals. There is no specified limit on the size. Another difference is that the Latvian biobank is, primarily, intended for research carried out in Latvia. This means that, so far, none of the more than ten studies carried out have been carried out at international level.

Sample collections

While the Estonian Biobank collects samples randomly, the Latvian Biobank selects participants based on specific diseases or conditions. In both cases, the collection is carried out by primary care workers.

Access availability and sharing of samples

As already mentioned, the Latvian Genome Database is seen as a resource for domestic research while the Estonian Biobank is also open for international collaboration. Access to the latter is free for academic researchers. However, commercial companies have to pay a fee. The use of biosamples from the Latvian biobank is always free but every

project has to be approved by the Central Committee of Ethics and the Genetics Research Board., There is no legal barrier to cross-border sharing of samples or data in these countries.

Consent

The Estonian Biobank asks its donors to give broad consent to biomedical research. In Latvia, donors consent to a specific study or research in a certain area. Information of personal results is sent back to donors if consented to. Donors have the right to withdraw their consent if they wish.

Regulatory aspects

Estonia has not adopted a specific law governing all kinds of human research, as the ratification of the Biomedicine Convention 1997 is considered sufficient [10]. But Estonia, like Iceland, has enacted a special act to cover its genome project: Human Genes Research Act (2000). There is no special law regulating the use of human biological material in Latvia or in Lithuania. However, there is a Human Genome Research Act (2003) in Latvia

Privacy/Data protection

There is a Personal Data Protection Act (1996) and a Databases Act (1997) in Estonia. Similarly, Latvia has a Personal Protection Law (2000) and Lithuania has an Act on Legal Protection of Personal Data (2003).

Ethics discussion

As already mentioned, the Estonian Genome Project (EGP) started with inspiration from developments in Iceland – with deCode and plans for a national Health Sector Database. But in designing the project, people and organizations behind EGP have tried to learn from the Icelandic case to avoid creating the same type of controversy. Developing a good relationship with the public and others concerned has, therefore, been given high priority. The aim is to be an active party and give as much information as possible to all target groups. EGP also includes a strong educational component, i.e. informing the public on genetics and developments in the field of gene technology and biotechnology in general.

Ever since 1999, Estonian as well as the foreign media has expressed considerable interest in EGP. This has resulted in hundreds of articles both in newspapers and science magazines.⁴⁵ In general, it seems that the attitude of both Estonian and the foreign media towards the project has been positive. But there have also been some critical analyses. It has, for example, been questioned why millions of Estonian crowns are poured into EGP at the expense of the overall health care. Independence of the ethical committee has also been called into question.

Several investigations have been carried out in order to establish awareness levels and opinions of the Estonian population regarding EGP. According to information available on EGP's homepage, a study carried out in March 2003 showed that 65% of the population was well-informed. Only 2% of the inhabitants in the counties where the pilot study took place said they were against the project.

⁴⁵ Many articles can be accessed through EGP's own website, www.geenivaramu.ee.

2.2.1.7 Biobanks in the UK

The following twelve biobanks, in the UK, are covered in this study:

- ⇒ Generation Scotland: Genetic Health in the 21st Century
- ⇒ Generation Scotland: Scottish Family Health Study
- ⇒ EPIC Oxford
- ⇒ UK Women's Heart Study
- ⇒ Twin Research Unit Laboratory
- ⇒ National study of colorectal cancer
- ⇒ International familial CLL consortium
- ⇒ Liverpool Lung Project
- ⇒ **EUELC (Early lung cancer)**
- ⇒ UK DNA Banking Network
- ⇒ UK Cord Blood Bank Ltd
- ⇒ Oxagen Ltd⁴⁶

The UK has an advanced publicly funded healthcare system and many prominent universities. Large public and private resources are invested in medical and biotechnology research, and it can, therefore, be assumed that there are many collections of human biosamples built by various academic research groups. Like in other countries, most of these biobanks are relatively small, but there are also some large ones. The most important research biobanks are presented in this report (although the list is non-exhaustive).

Undoubtedly, there is a large and increasing interest in biobanking in the British research community. Such activities have, for many years now, been actively supported in different ways by e.g. the Medical Research Council (MRC), the largest public financier of medical research in the UK. For example, following the mapping of the human genome in 2000, the MRC identified genetic epidemiology as a strategically important research area. Among other initiatives, the MRC made awards to enable collection of large numbers of samples in 13 common diseases. As will be described below, these samples are now stored and managed centrally as national resources.

Other relatively large population-based biobanking projects under way is **Generation Scotland**. Sampling for the main study (Scottish Family Health Study) has recently begun (the current size of the repository is 24 individuals!). The aim is to have achieved by 2011 a family-based cohort comprising 50 000 individuals and approximately 10 000 families. The biobank will be used for studying the genetics of health areas of current and projected public health importance, such as heart and mental diseases. Samples and data will be made available anonymously to Scottish researchers. It is envisaged that these will use the resource in collaborative projects with colleagues from other countries around the world. In a separate study Generation Scotland will build a “random population biobank” with samples from 2 500 individuals. The objective is to establish the genetic profile of a control population of people living in Scotland. It is a family-

⁴⁶ We have not received a questionnaire from this company but, have useful information on the company's biobank activities thanks to previous research.

based study, those registering interest are then asked to determine the interest of other adult family members.⁴⁷

Two English universities, Cambridge and Oxford, are participating in the international **EPIC project on cancer and nutrition**. The two UK cohorts, recruited from the general population, consist of 30 000 and 57 000 participants respectively (recruited from 1993 to 1999). The Oxford centre has collected blood samples from 20 000 individuals. These are stored in several locations in the country.⁴⁸

The **UK Women's Heart Study** and the **Twin Research Unit Laboratory** at St Thomas Hospital are two other relatively large research biobanks in the UK. The former, located at the University of Manchester's Cardiovascular Research Group Division, comprises samples from 20 000+ individuals. The participants are female employees of Marks' and Spencer's shops throughout the country. The sampling took place from 1988/1991. The database, which is of the stand-alone type, contains a broad set of data (medical, demographic, environmental, and socio-economic and ethnicity). So far, the biobank has only been used by the researchers who collected the samples, which has produced around ten publications. The research group is now seeking funding for DNA extraction, the creation of a permanent biobank and for the collection of follow-up data (lifestyle and health questionnaires; checking death certificates etc.) and data entry to convert this into a prospective study.

The list above includes some independent disease-specific biobanks. These should be seen mainly as examples, since there are many others not covered by our mapping.

The **UK DNA Banking Network (UDBN)**⁴⁹ is an interesting biobanking venture. This is not a research project in itself but, a biobanking infrastructure set up in collaboration between scientists and funded by the Medical Research Council (MRC). The basic idea is to offer scientists, carrying out case-control or family studies on particular diseases, a modern and efficient infrastructure for management of samples and data. The studies are carried out by 13 independent groups of clinical scientists who collect blood samples and data from their research subjects (in a given disease area). The UDBN has been given the task to manage samples, as well as data, so as to ensure that these are kept uniformly and safely and used in an efficient way. DNA samples are managed at UDBN's archive in the University of Manchester's Centre for Integrated Genomic Medical Research (CIGMR). Cell samples are managed at the Health Protection Agency's European Cell and Culture Collection in Salisbury (ECACC). The responsibility for data management means creating links between databases holding clinical, sample and experimental data. The custodianship (ownership) of both samples and data remains with the collectors (clinicians).

UDBN's archive was set up in 2003. The DNA extraction is carried out either by the sample collector or by the archive. At present, the archive stores samples from 25 000 individuals. The target size is 40 000 individuals, but the total capacity of existing facilities is over 100 000 samples. The samples and data stored by UDBN can be accessed by other researchers in the UK or abroad who want to establish collaboration

⁴⁷ www.generationscotland.org

⁴⁸ We have not managed to get the corresponding information regarding the Cambridge cohort.

⁴⁹ www.dna-network.ac.uk

with collectors. Access requires registration as a network user, technical, scientific and ethical approval and the payment of a fee for labour and consumables.⁵⁰

The **UK Biobank** project⁵¹, a national prospective study of genes, environment and health proposed in the late 1990s, has received much publicity during the last 5-6 years. It is probably the world's largest project of this kind and aims to create a unique and powerful resource for genetic epidemiological research. Following two years of planning, the original three partners – the Wellcome Trust, the MRC and the Department of Health – agreed in April 2002, to establish the biobank at an estimated cost of £63 million⁵². Using information from DNA samples and medical records of 500 000 volunteers, aged 45-69, the study would capitalize on the sequencing of the human genome accomplished by the Human Genome Project.

The aim of this long-term project is, thus, to build a comprehensive resource for medical research on susceptibility genes, gene-environment interaction, disease pathways and genetic markers. It is expected that the biobank project will provide healthcare providers and government with information, helping them to improve the health service for future generations.

Having completed a pilot study comprising 318 individuals, the recruitment of volunteers through general practitioners throughout the country began in 2006. It is expected that the full recruitment of the 500 000 participants will be completed by 2011. In addition to physical examination and blood samples, taken after having obtained a written consent, information on the donors' lifestyle will be collected through questionnaires and interviews. Medical information will be obtained by links to medical records and other databases in the public sector. The recruitment of volunteers and collection of samples and data are managed by 6 regional collaborating centres, each consisting of a network of academic and research institutions. In total, 22 universities will be involved in these centres. It is envisaged that the biobank, during the coming decade, will be used in many different research projects dealing with various diseases. However, only studies that are scientifically and ethically fully approved, will be allowed to use the biobank.

With regards to the organization and governance of the project, the UK Biobank is hosted by the University of Manchester but it is centrally managed by a charitable company, UK Biobank Ltd, which coordinates the activities of the 6 collaborating centres. The headquarters, based in Cheadle, is responsible for delivering the project, including data management and quality assurance, computing, financial management and formal custodianship of samples and data. Overall responsibility for the direction, management and control of the project lies with a board of directors accountable to the MRC and The Wellcome Trust. The board also receives advice from a science committee and the Ethics and Governance Council (EGC). The creation of such an oversight body, entirely separated from the management structure of the biobank, is a unique feature of this project. The role of EGC is to act as an independent guardian of the UK Biobank, to safeguard the interests of the participants and the wider public and, to ensure good ethical practice. The funders are well aware of the fact that this type of

⁵⁰ <http://www.dna-network.ac.uk/From+registration+to+access/>.

⁵¹ www.ukbiobank.ac.uk

⁵² Besides the three founding organizations, the UK Biobank is currently also funded by Scottish Executive and the Northwest Regional Development Agency.

study, to be carried out over a long period of time, raises many ethical concerns. Therefore, to set a high ethical standard they have committed to developing a public Ethics and Government Framework (EGF). A description of the EGF can be found on UK Biobank's homepage.⁵³

Biobanks in the pharmaceutical and biotech industry

There are several large pharmaceutical companies with major R&D units in the UK. As already mentioned, due to "the genetic revolution", human biobanks have become important resources for drug discovery and pharmacogenomic studies. It is well-known that large pharmaceutical firms collect samples and data in connection to clinical trials and other projects. Since these collections are regarded as proprietary assets, it is in general difficult to get information about them. Therefore, we have not even tried to include such biobanks in our mapping. As described in the above section on Swedish biobanks, it is common that pharmaceutical firms collaborate with academic researchers having access to publicly owned biobanks at universities and hospitals. It can be assumed that this mode of industrial biobank use is frequently used also in the UK.

Oxagen Ltd⁵⁴ is a genomics and drug discovery company using an interesting approach to biobanks [11].⁵⁵ This company, originally a spin off from Oxford University and the Wellcome Trust Centre for Human Genetics, has established collaboration with some 30 academic groups in the UK and other European countries. The clinical partners collect samples and data locally and carry out research in collaboration with Oxagen and, sometimes, with other industrial partners. Although the researchers retain the custodianship of the samples, these are physically stored in Oxagen's biobank. Oxagen has invested in state-of-the-art facilities for biobanking and carry out high-throughput genotyping on the material. All together, the collections managed by Oxagen in 2003 comprised samples taken from some 34 000 individuals in different countries.

PROCARDIS can be mentioned as an example of a project where Oxagen has worked with multiple centres, namely from the UK, Germany, Italy and Sweden. The international project group, also supported by AstraZeneca, has collected and genotyped samples from 4 000 families (15 000 individuals) with the purpose of studying the genetic factors behind coronary artery disease. In accordance with the company's policy, the samples were collected with appropriate informed consent from the donors. The samples were coded by the collecting institutions before being sent to Oxagen for storage and analysis.

Cord blood banking

The list of biobanks includes one cord blood bank: UK Cord Blood Bank Ltd (UKCBB).⁵⁶ It is part of the New England Cryogenic Center founded in Boston, USA in 1982. This company expanded its cryogenic storage services to include cord blood stem cells in 1995 by establishing the New England Cord Blood Bank, Inc. UKCBB was the first private cord blood bank in the UK and has provided cord blood processing and storage services to clients throughout Europe since 2000.

⁵³ www.ukbiobank.ac.uk/ethics/efg.php

⁵⁴ www.oxagen.com.

⁵⁵ Laage-Hellman, J., "Commercialization of biobanks: a study on biotech companies dedicated to human genetics", Chalmers University of Technology, 2003 (unpublished research report).

⁵⁶ www.cordbloodbank.co.uk.

Biobanking activity

UKCBB currently utilises the 45 000 square foot laboratory and cryogenic facility in Boston. This facility is accredited by the American Association of Blood Banks (AABB), registered with the US Food and Drug Administration (FDA) and licensed by the states of Massachusetts and New York, signifying adherence to the highest international standards of quality and excellence.

UKCBB is in the process of setting up a dedicated processing and storage laboratory which is part of The University of Manchester's Core Technology Facility. While the company does not currently undertake any research (the cord blood stem cells are stored on behalf of parents who retain full ownership of them), it intends to participate in research, once its facility is fully established. The company collects blood from clients in different European countries. It does not experience any problems *per se* in this regard. However, it is mindful of the regulations in place in various EU countries (e.g. Italy) governing the transport of cord blood samples.

Sample collections

We can identify two main groups of biobanks. The following biobanks select participants randomly: Generation Scotland (both biobanks), EPIC Oxford, Liverpool Lung Project (LLP) and the UK Cord Blood Bank. The following ones are disease-specific: UDBN, EUELC, International familial CLL consortium, National study of colorectal cancer and Oxagen. The Twin Research Unit and UK Women's Heart Study use other criteria, as explained above.

Most biobanks use a combination of several channels to collect samples, typically including hospital staff, primary care workers and staff specifically employed for the project.

Access availability and sharing of samples

There are five biobanks presently only used by the researchers who collected the samples: EPIC Oxford, UK Women's Heart Study, EUELC, CLL consortium and National study of colorectal cancer. The others are used also in domestic or international collaborative projects (except for the UK Cord Blood Bank currently not used for research).

Besides the UK Cord Blood Bank, which is a commercial biobank, only Generation Scotland reports that access to samples may be associated with payment. However, for most biobanks there are other restrictions for access, such as collaboration with the responsible organization. Decision on access is usually made by a governing board or an official manager but, in some cases, it is the principal investigator who is in charge. In the case of UK Cord Blood Bank, the Chief Scientific Officer is the decision maker. It should be noted, though, that stem cell samples are wholly owned by the parents, who are able to arrange access to their samples at any time.

Most biobanks report that they are allowed to share samples, as well as data, with other researchers outside the country. An exception is Generation Scotland that only allows sharing of data.

Consent

About half of the UK biobanks ask for consent to a specific study or a certain research area (e.g. lung cancer). Both EPIC Oxford and the Twin Research Unit, apply a broader

type of consent procedure. Interestingly, three biobanks use blanket consent. With the exception of Generation Scotland, which gives feedback of personal results in all cases, other biobanks do not. With the exception of the Twin Research Unit, in all other biobanks surveyed donors can withdraw their consent to store samples in the biobanks.

Regulatory aspects

On 15 November 2004, the Human Tissue Act obtained Royal Assent. The background was that the previous law on removal, retention, and use of human tissue contained many uncertainties (e.g. proved in connection to several organ retention scandals in the country, such as the one at the Alder Hey Hospital). The government's response was to draft an entirely new bill. In the subsequent debate, this bill was criticized by the research community fearing that the proposed bill would compromise medical research. For example, scientists were concerned that it would outlaw the use of any human tissue for research without the patient's explicit consent. Modifications to the bill meant that patients could be presumed to have given consent unless explicitly having stated the opposite. But such tissue samples would only be possible to use on the condition that the patient's identity is protected and that the study has been officially approved.

The new Act deals broadly with the removal, storage and use of human organs and tissue, which means that it also has important implications for the use of biobanks in research. An important result of the Act is the establishment of the Human Tissue Authority (HTA).⁵⁷ This is a new public body the role of which is to regulate the removal, storage, use and disposal of human bodies, organs and tissue for a number of "scheduled purposes" set out in the Human Tissue Act and in regulations. As part of this, the HTA issues Codes of Practice to ensure that best practice is adhered to. Moreover, the HTA is responsible for licensing a number of activities (including all forms of transplants from living donors) and carrying out inspections, to ensure licence conditions are met. These licensable activities are:

- the storage of human bodies for anatomical examination and related research.
- the carrying out of post mortem examinations, including removal and storage of human tissue.
- the removal of tissue from the body of a deceased person for scheduled purposes except transplants.
- the storage and use of human bodies or parts for public display.
- the storage of human tissue for other scheduled purposes, for example, for research.

From 7 April 2006, anyone storing human tissue or cells for human application must be in possession of a licence from the HTA. Other activities under the HTA's remit, will become licensable in September 2006.

Also of great importance to biobank-based research in the UK is the MRC guidelines on human tissue and biological samples for use in research issued in 2001 [12]. In 2005, following the passage of the Human Tissue Act, the MRC issued a clarification. These guidelines, recognizing the crucial importance of human tissue for medical research, emphasize the need for patient confidentiality, consent and information. It states that the public and research participants must be confident that such material has been obtained

⁵⁷ www.hta.gov.uk

lawfully and with appropriate consent, and will be handled and used sensitively and responsibly by scientists.

Privacy/Data protection

The EU Directive 95/46/EC on the protection of individuals, with regard to the processing of personal data and on the free movement of such data, was implemented to national law through the Data Protection Act (1998). A number of Statutory Instruments have been developed to implement this Act. In 2003, the MRC issued specific guidelines on Personal Information in Medical Research.

Ethics discussion

The ethics debate on biobanks has primarily taken place in relation to the UK Biobank project in the UK. The two initiators, the Wellcome Trust and the MRC, early realized that such a project would raise a number of important social and ethical issues, such as “ownership” and accessibility of data. The project has been not unexpectedly criticized by various individuals and groups since its inception. Public concern has been caused, for example, by questions related to data storage and use and the role of commercial interests (e.g. the pharmaceutical industry).⁵⁸ Much of the criticism has been channelled through GeneWatch UK, an independent stakeholder group monitoring the use of genetic technology. In 2002, GeneWatch called for the project to be frozen until the law was changed to guarantee that individuals’ genetic information remained private and protected from commercial control.⁵⁹ GeneWatch has identified 5 questions that potential volunteers should ask before agreeing to take part:⁶⁰

- What type of research is going to be carried out on my sample?
- What are the benefits and dangers of this research?
- Will my sample ever be used for research I do not agree with?
- Will any of my genes be patented and if so, when will I be informed about this?
- Can I change my mind?

The funders of UK Biobank have responded to the criticism and debate by initiating research on ethical issues and engaging the public and professionals in consultations. Over the years, a number of consultations and workshops have been carried out both with the general public and with special groups in society (such as scientists, primary health care workers and industry representatives). This consultation process, undertaken to ensure that all interested stakeholders have been given the opportunity to comment, has affected the design of the project in different ways, including the development of the Ethics and Governance Framework (EGF). The intention is that the EGF will continue to evolve, adapting to scientific, ethical, legal and other developments, with advice from the previously mentioned Ethics and Governance Council, the Science Committee and other parties concerned.

Despite this extensive consultation process, the UK Biobank project is still subject to public criticism. Many scientists have accused the project of being badly designed and likely to give misleading results.⁶¹ The question has been raised as to whether the

⁵⁸ See e.g. *Guardian*, “Fury at plan to sell off DNA”, 23 September 2001.

⁵⁹ *Guardian*, “Safeguards fail at gene bank says watchdog”, 14 January 2002.

⁶⁰ “BioBank UK: A Question of Trust: A consultation exploring and addressing questions of public trust”, Report prepared for The Medical Research Council & The Wellcome Trust, People Science & Policy Ltd, March 2002.

⁶¹ *Guardian*, “Critics’ U-turn as the world’s biggest medical project begins”, 15 March 2006.

project should be straight epidemiological or focus on genetics. According to a recent statement from GeneWatch: “*UK Biobank is based on false assumptions about the role of genes in the major killer diseases today*”. GeneWatch is also concerned about the lack of legal safeguards to protect participants and others from future misuse of their genetic information. For example, there are no laws to prevent discrimination by insurers or employers and inadequate controls on access by the police or by commercial companies.⁶²

2.2.2 Biobanks in Eastern Europe

In the context of this study, Eastern Europe comprises the countries: Bulgaria, the Czech Republic, Slovak Republic, Poland, Hungary and Romania. No large-scale biobank for research purposes was identified in Bulgaria. Although it can be assumed that some small-scale biobanks for research exist in many hospitals but it was only possible to retrieve one of them: the Laboratory of Molecular Pathology⁶³ which houses the National DNA Bank of the Republic of Bulgaria, founded in 1990 and storing DNA, serum and tissues (7000 samples) paired with demographic, ethnic, medical and genetic information on the donors for public research and clinical research diagnostics. This biobank is not connected to other biobanks and is used for research only by those scientists who collected the samples. Furthermore, the access availability to the samples is restricted through a Material Transfer Agreement. However, this biobank was already involved in international projects, like BIOMED-2, Concerted Actions for CF Research and Therapy, MDA-USA. The shipment of the DNA samples stored is deemed to be an impediment for international collaboration.⁶⁴ Similarly, relevant biobank activities were difficult to identify in Poland, Slovakia and the Czech Republic (for more details on these countries see ESTO report).

2.2.2.1 Biobanks in Hungary

14 public biobanks devoted to public research and/or clinical research diagnostics were explored in Hungary:

- the NEPSYBANK collecting DNA, tissues, fibroblast stored in a -80°C freezer;
- the biobank at the Uzsoki Teaching Hospital, collecting DNA, serum, whole blood and tissues stored in liquid nitrogen;
- the Preterm infants and full-term neonates, collecting whole blood, dried on filter paper and stored at room temperature;
- and 11 Biobanks all at the same institution, the Department of Medical Genetics and Child Development, each storing DNA in -20°C freezer and devoted to a specific disease or a specific population.⁶⁵

Beyond this, the survey identified 1 commercial biobank (KRIO Institut⁶⁶); 1 private biobank for public research and clinical research diagnostics (the “Prof. Korányi András” Dunántúli Génbank⁶⁷)⁶⁸, and the Danubian Biobank Consortium.

⁶² www.genewatch.org/Press/Releases/pr86.htm

⁶³ <http://ivo.medfac.acad.bg/>

⁶⁴ Cf. returned questionnaire.

⁶⁵ Mitochondrial disease, roma, szizofrenia, stroke, metabolic syndrome, huntington, heart attack, familiar deaf, crohn, asthma, adult coeliacia.

The identification of public Hungarian biobanks for research was mostly based on the analysis of, a database listing all biobanks in Hungary (and also the research methods employed and the facilities of the laboratories) which was set up by a group of scientists and is accessible through the website www.biobank.hu.⁶⁹

The Department of Genetics, Cell- and Immunobiology of the Semmelweis University in Budapest, is the coordinator of this project and has the following aims:

- to establish a register of biologic specimen collections in Hungary;
- to provide a possibility to search for opportunities for collaboration for registered users, such as sharing of specimen collections and methodology;
- to establish a forum for research groups using molecular biological techniques;
- to provide information on genomic research.

Most biobanks cited above - except the KRIO Institute - are public biobanks set up for the purpose of public research or clinical research diagnostics. They are affiliated to hospitals or clinics and store DNA, tissues, umbilical cord blood, etc., together with demographic, ethnic, medical and lifestyle data on the donors depending on the diseases targeted. These biobanks are small (less than 5000 samples) and are either stand-alone or networked. Most of these biobanks seem to be only accessible to Hungarian researchers and have not been involved in international studies yet. Furthermore, the consent conditions are very heterogeneous: either the donors have to give their consent to a specific study or to biomedical research in general, either they even have (can?) to give any consent.⁷⁰

Sample collections

The selection of donors for the public biobanks and also for “Prof. Korányi András” Dunántúli Génbank is made on the basis on whether they have a specific disease or whether they belong to a specific demographic group or random selection. There is no selection of participants at the KRIO-Institute. Apart from the “Prof. Korányi András” Dunántúli Génbank, where also Centres/Staff specifically employed for the project are involved, the samples have been collected by the associated hospital staff and/or primary care workers.

The size of the biobanks which perform public research, varies considerably: some have less than 50 samples, although they have been collecting some for several years, and some have ca. 3000 samples. Apart from the Preterm infants and full-term neonates, which collects demographic information and environmental/lifestyle information and genetic data about the data, all the research biobanks collect medical/phenotype information on the donors, sometimes also demographic, ethnicity and environmental/lifestyle information and genetic data. The KRIO Institute is the only biobank which collects samples not only in Hungary but also from other countries.

⁶⁶ The KRIO Institute stores, against payment, sperm, egg and umbilical cord blood bank in liquid nitrogen. However, the KRIO Institute also carries out commercial research.

⁶⁷ Collecting DNA, serum, mononuclear cells and storing them in a -80°C freezer and in liquid nitrogen

⁶⁸ In contrast to other private/commercial institutions the KRIO Institute, as well as the “Prof. Korányi András” Dunántúli Génbank, answered the questionnaire openly and completely.

⁶⁹ Iso the “Genomic investigation for Human Health” Consortium (GKEE), founded in 2001, registers all Hungarian human biobanks. However, no more information in English language about this project was available.

⁷⁰ Cf. returned questionnaires.

Access availability and sharing of samples

Most of the biobanks for research stand-alone. Only the NEPSYBANK is networked and on the internet, but with restricted access, and the KRIO Institute and the biobank at the Uzsoki Teaching Hospital both have an intranet system.

The “Prof. Korányi András” Dunántúli Génbank, the NEPSYBANK and the biobank at the Uzsoki Teaching Hospital are used by researchers in the same country or, even in other countries. The other biobanks are only used by researchers at the same institution. The access to samples and data is free for all biobanks dedicated only to Public research. However, access to the samples of the biobank at the Uzsoki Teaching Hospital is restricted depending on specific, individual agreement. For the rest, access is only possible against payment.

The current consent form and legal framework allow sharing tissues and samples data with researchers outside country. Only the KRIO Institute *cannot* share tissues with researchers outside country, but only data. This is not very surprising, since the samples collected from this biobank are partly devoted to subsequent, autologous uses. Though sharing of samples and data is possible for almost all biobanks (apart from the KRIO Institute), none of them has already been involved in international projects. For all biobanks, researchers using the samples are always required to feed back results to the biobank.

Consent

The handling of consent is not homogenous. Almost all biobanks devoted to public research require consent to biomedical research in general, or to a specific study. However, the Preterm infants and full-term neonates biobank, as well as the “Prof. Korányi András” Dunántúli Génbank, both working on research do *not* require any specific consent. Moreover, in these two cases, information arising from biobank studies cannot be sent back to individuals (personal results). Yet, in all other cases, it can indeed if donors have consented to it. The KRIO Institute handles consent issues in a completely different manner but did not specify how.

The Preterm infants and full-term neonates biobank and the biobank at the Uzsoki Teaching Hospital are the only biobanks for which it is *not* possible for donors to withdraw their consent to store samples in the biobank. For the “Prof. Korányi András” Dunántúli Génbank, the privacy of donors is protected through anonymization but without any key code, whereas for all other biobanks a key code is used to anonymize the samples.

Privacy/data protection

Data Protection found itself on the Hungarian agenda, following the political and economic changes of 1989. Data Protection, and the ability of citizens to be able to monitor information collected, was seen as an important element of the rule of law and human rights. Act LXIII of 1992 on the Protection of Personal Data quickly followed (“Act LXIII of 1992 on the Protection of Personal Data and Public Access to Data of Public Interest”). On 26 July 2000, the European Commission decided that Hungarian law ensured an adequate level of protection of personal data within the meaning of Article 25(6) of Directive 95/46/EC. Act LXIII of 1992 was later amended by Act No XLVIII of 2003.

⁷¹ The EU Directive 2002/58/EC concerning the processing of personal data and the protection of privacy in the electronic communications sector was translated to national law in the Act of 2003 on Electronic Communications adopted by Parliament at its session of 24 November 2003⁷².

2.2.2.2 Biobanks in Romania

Given most of the Romanian internet sites are only in Romanian language, it was very difficult to retrieve information regarding the biobanking situation in Romania by desk research. Requests for information sent to scientists and to the Romanian Ministry of Health or to the Romanian Academy remained unanswered. However, 12 questionnaires were received from the Agentia de Transplant Romania⁷³, corresponding to 12 biobanks, all of them apparently public ones, inasmuch as the answers to the questionnaires allow this conclusion⁷⁴.

There are 10 medical centres allowed to carry out organ and tissue transplants (3 for kidney transplants, 3 for liver transplants, 4 for heart transplants, 1 for spinal cord transplants and 1 for skin transplants).⁷⁵ Furthermore, it might be assumed that some small (tissue, blood, etc.) biobanks are established in hospitals, designed for diagnostic or therapy purposes. Also, a first commercial umbilical cord blood bank has been founded in Romania.

Four biobanks are devoted to research purposes and/or clinical research diagnostics:

- The **Skin Bank of the Center of Excellence for Scientific and Technological Research** in the Domain of Tissue Transplant and Skin Grafts, collecting skin tissues stored in liquid nitrogen.
- The **Human Skin Liquid Nitrogen Storage Service**, also collecting tissues stored in liquid nitrogen.
- The **Biobank at the M. G. - International Center RUA**, collecting human tissues stored at room temperature.
- The **Biobank at the IVF Center “Victor Babes”** of the University of Medicine and Pharmacy in Timisoara, also collecting human tissues stored at room temperature.

Six biobanks are devoted to Public Research and/or Clinical Research Diagnostics as well as for transplant purposes or, in the case of the biobank at the University Hospital “Panait Sarbu” in Bucharest for IVF purposes:

⁷¹ <http://www.privereal.org/content/dp/hungary.php>

⁷² http://en.ihm.gov.hu/data/25087/eht_eng.pdf

⁷³ The National Transplant Agency, subordinated to the Ministry of Health, was created in 2004 with the aim a. o. to coordinate and control transplant activities (organs and tissues) in Romania, in accordance with the European Directive. The National Transplant Agency was specially mandated to set up a “National Transplantation Register” including available human organs and tissues for transplants to facilitate their allocation. The questionnaires received may correspond to biobanks monitored in this scope. http://www.cdep.ro/proiecte/2004/600/70/3/leg_pl673_04.pdf.

⁷⁴ It has been realized after having set up and sent the questionnaire that therein only the reason for the creation of the Biobank has been asked for but not whether the biobank is a public or a private one. As some biobanks investigators, in other countries indeed ticked both of the responses on “Public research” and on “Private Commercial Research”, it seems important to make a distinction between the stated purpose of creation of one biobank and its funding/administrative status.

⁷⁵ <http://assembly.coe.int/Mainf.asp?link=/Documents/WorkingDocs/Doc04/FDOC10260.htm>

- the **Colentina Biobank**, collecting tissues stored in liquid nitrogen. The stored bones and ligaments are also used for allograft transplants in orthopaedic surgery.
- the **Marburg Bone Bank Lobator SD-2**, collecting tissues and bones, stored in a -80°C freezer. This Biobank is also a Bone Bank for Transplant purposes.
- the **Heart Valve Bank in Timisoara**, collecting tissues stored in a 4°C refrigerator or in liquid nitrogen. This biobank also provides allografts for heart valve replacements.
- the **Biobank at the University Hospital “Panait Sarbu”** in Bucharest is settled in the Department for Assisted Reproduction Department. The sperm samples and embryos collected are stored in liquid nitrogen and used for research as well as for treatment of infertility.
- the **Biobank at the Medsana Bucharest Medical Center** and the **Med New Life Biobank** are biobanks storing embryos and sperm for IVF purposes.
- the **Bone Bank** stores bones and the **“Corneas Bank”** stores corneas, both for transplantation purposes.

Sample collections

Among the 10 biobanks for research purposes, the selection of donors is not homogenous, even among those which are devoted only to research and not to transplant. 3 biobanks select the donors on basis of whether they have a specific disease: the Human Skin Liquid Nitrogen Storage Service, the Colentina Biobank and the Marburg Bone Bank Lobator SD-2. In addition to this condition, the Skin Bank of the Center of Excellence for Scientific and Technological Research also collects samples from random population and the biobank at the University Hospital “Panait Sarbu” from specific demographic groups. The Biobank at the MG - International Center RUA and the Biobank at the IVF Center “Victor Babes” select donors from demographic specific groups. The Heart Valve Bank in Timisoara selects donors from random population without further restriction. For all biobanks, the samples have been collected either by the associated Hospital Staff, Primary Care Workers (including Hospital Staff) or by Centres/Staff specifically employed for the Project. The Marburg Bone Bank Lobator SD-2 additionally collects samples left over after surgery.

The Colentina Biobank is the biggest of the 8 biobanks with samples from 248 individuals. The Marburg Bone Bank Lobator SD-2, the Heart Valve Bank and the Biobank at the University Hospital “Panait Sarbu” have between 20 and 87 samples. Concerning the size of their sample collection, the Skin Bank of the Center of Excellence for Scientific and Technological Research, the Biobank at the M. G. - International Center RUA and the Biobank at the IVF Center

The type of data stored, in combination with the samples, also varies. The Marburg Bone Bank Lobator SD-2 only collects demographic data. The Biobank at the M. G. - International Center RUA and the Biobank at the IVF Center “Victor Babes” only collect “IVF data”. The other 5 Biobanks all collect demographic data, in addition to medical/phenotype data and/or genetic data and/or environmental/lifestyle data and/or ethnicity. The biobank at the University Hospital “Panait Sarbu” also keeps track of the quality of the samples and embryos collected. It might be supposed that this corresponds to the “IVF data” stored by the 2 other biobanks active in the IVF field.

Access availability and sharing of samples

Except for the Skin Bank of the Center of Excellence for Scientific and Technological Research, all biobanks are stand-alone. However, the Heart Valve Bank in Timisoara states it is stand-alone, and provides restricted access to its collection through the internet.

Samples and data from the Heart Valve Bank in Timisoara, the IVF Center “Victor Babes”, the biobank at the M. G. - International Center and the Skin Bank of the Center of Excellence for Scientific and Technological Research are used by the researchers who have collected the samples, and by other researchers at the same institution or elsewhere in the country. For the other biobanks, samples and data are only used at the institution where they have been collected. No biobank samples and data are used by researchers from other countries and no biobank has already been involved in international research projects.

Only one biobank provides access to samples and data against payment: the biobank at the University Hospital “Panait Sarbu”. In the other cases, access is free although sometimes restricted (IVF for the Biobank at the M. G. - International Center RUA and the Biobank at the IVF Center “Victor Babes” and limited number of samples for the Marburg Bone Bank Lobator SD-2). It is interesting to notice that all the biobanks considered are regulated by a Research Ethics Board approval. According to the answers to the questionnaire, the current consent form and legal framework seems to allow biobanks to share tissue and sample with researchers outside the country.

Consent

The Biobank at the University Hospital “Panait Sarbu” is the only one which requires informed consent from the donors. Apart from the 2 other IVF Biobanks, which require specific IVF consent, the other 5 biobanks do not require any consent or require only a blanket consent. In almost all biobanks considered, information arising from biobank studies cannot be sent back to individuals (personal results Personal communication?). Only at the Colentina Biobank and at the Heart Valve Bank in Timisoara, this information can be sent back to donors if they have consented to it. In the case of the Biobank at the University Hospital “Panait Sarbu”, information is reported back to patients even without consent it is even so in all cases. For half of the biobanks, donors can withdraw their consent to store samples in the biobank.

Finally, For the Human Skin Liquid Nitrogen Storage Service, the Biobank at the M. G. - International Center RUA and the Biobank at the IVF Center “Victor Babes”, privacy of donors is protected through an anonymous procedure but without any key code. All the other biobanks use coding with a coding key.

Regulatory aspects

The procedures related to organ transplants in Romania, are regulated through the following laws:

- Law n° 2/1998 related to the utilisation of human organs and tissues;
- Law n° 104/2003 related to dealing with dead bodies and organ removal from dead bodies for transplant purposes.

Privacy/Data Protection

Data Privacy is regulated through law No. 677/2001 for the Protection of Persons Concerning the Processing of Personal Data and Free Circulation of Such Data (2001), enacted in November 2001 by the Romanian Parliament⁷⁶. The law closely follows Directive 95/46/EC.

2.2.3 Biobanks in Central Europe

2.2.3.1 Biobanks in Austria

Biobanking in Austria is very much linked to universities and public hospitals. Here, the comparison with Germany is important, as the Austrian system of pathology and also the applicable legal regulations allow the collection of tissue from diseased persons and human corpses, in the course of the diagnostic procedure. This favours, to a certain extent, the emergence of biobanks. In general, biobanks are not deliberately established. In most cases, pathological archives were the basis and starting point for the biobanks. Most of the collections in Austria are tissue biobanks.

Two public biobanks were found affiliated to hospitals or non-profit making firms, devoted to diagnostic, therapeutic and research purposes, and three private and profit-making cord blood banks.

The Austrian Tissue Bank is a non-profit making organization, specialized in the nationwide supply of tissue grafts, especially of allogenic bone grafts.⁷⁷

BioResource-Med is a biobank specifically designed to support the needs of systems biology approaches to human diseases, drug discovery, and public health. BioResource-Med is an interdisciplinary research platform of the Medical University Graz, which mainly builds on one of the world's largest collection of diseased human tissues of the Institute of Pathology at the Medical University Graz (approx. 2.9 mio samples from 888000 patients). In the context of the Austrian Genome Program **GEN-AU I**,⁷⁸ tissue collection has been developed into a biobank, by establishing the logistics and technologies for coordinated and standardized collection of various human biological samples, medical and experimental data as well as human disease-associated animal models. Furthermore, high-throughput genomics (cDNA-arrays) and proteomics (tissue microarrays) analysis platforms, and an IT-infrastructure, which enables proper access and usage of biological samples, as well as associated data, have been established. The further development of BioResource-Med focuses, on the one hand, on extensive annotation of already existing archival tissues with medical data and, on the other hand, on the prospective collection of human tissues, blood samples and patient-related data in an internationally standardized manner.⁷⁹

Regulatory aspects

⁷⁶ <http://www.avp.ro/leg677en.html>

⁷⁷ Bärwald, H., "Biologische Selbstorganisation und Möglichkeiten ihrer technischen Nutzung", Kurzstudie im Auftrag des isw - Institut für Strukturpolitik und Wirtschaftsförderung, Gemeinnützige Gesellschaft mbH, Halle, 2005.

⁷⁸ The Austrian Genome Program GEN-AU, financed and organised by the Federal Ministry for Education, Science and Culture, covers a widespread variety of research activities. GEN-AU's focus is medical biotechnology, but there are also projects in agricultural and animal genomics. The GEN-AU program, strongly supports biobanking, as an instrument for GENome Research in Austria, as well as in cooperation with foreign Genome Projects. The anticipated benefit of biobanking is to understand disease processes and the development of more efficient diagnostics and therapies. www.gen-au.at

⁷⁹ www.bioresource-med.com

For human biobanks, general regulations concerning medical purposes are valid. The processing of medicines is regulated in the Austrian Pharmaceuticals Act (AMG) and the regulations on blood safety. If human biologic material is used for genetic testing, the regulations of the Austrian Gene Technology Act provides special conditions to be considered: purpose of testing, handling of samples, institution, equipment, qualification of staff, protection of data and genetic counselling are regulated.⁸⁰ By Austrian legislation, existing human tissue collections, containing tissues from patients that have died, can be used for scientific investigation without specific informed consent as long as patient confidentiality is maintained and approved by the local ethical committee. This is in accordance with the emerging opinion in most European countries⁸¹. For newly collected samples, specific informed consent is obtained. Informed consent is also in line with the recommendations of the German Ethics Council and other international guidelines.

Privacy/Data Protection

The EU Directive 95/46/EC on the protection of individuals, with regard to the processing of personal data and on the free movement of such data, has been translated to national law in the “Data Protection Act” 2000 (“Bundesgesetz über den Schutz personenbezogener Daten, Datenschutzgesetz 2000 - DSG 2000”).⁸² The EU Directive 2002/58/EC, concerning the processing of personal data and the protection of privacy in the electronic communications sector was translated to national law through the Telecommunications Law of 20 August 2003 (“Telekommunikationsgesetz”, *Stammfassung: BGBl. I Nr. 70/2003*).⁸³

Ethics Discussion

Until 2004, no public debate on human biobanks took place in Austria.⁸⁴ In 2005, the (Austrian) Bioethics Commission⁸⁵ cooperated with experts from the German National Ethics council⁸⁶ regarding an opinion on biobanks for research purposes.⁸⁷ Yet, biobanking has not caused any broad public discussion in the media.

2.2.3.2 Biobanks in Belgium

According to the results of our survey, there are several biobanks in Belgium affiliated to hospitals, designed for local research or therapeutic purposes and devoted to the treatment of specific diseases but, no large-scale biobank for research purposes. Among

⁸⁰ European Commission Research Directorate-General, Directorate E Biotechnology, Agriculture and Food, “Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human biobanks”, edited by Line Matthiessen and Kimmo Pitkänen, Update October 2004.

⁸¹ For review, see the Opinion of the German Ethics Council and the Report from the EU Working Group on Biobanks for Health: “Optimising the Use of European Biobanks and Health Registries for Research Relevant to Public Health and Combating Disease”, workshop, Oslo, 21-23 Jan 2003.

⁸² <http://www.dsk.gv.at/dsg2000d.htm>

⁸³ http://www.rtr.at/web.nsf/deutsch/Telekommunikation_Telekommunikationsrecht_TKG+2003#p1

⁸⁴ “Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human biobanks”, European Commission Research Directorate-General, Directorate E Biotechnology, Agriculture and Food, Edited by Line Matthiessen and Kimmo Pitkänen, Update October 2004

⁸⁵ Established at the Federal Chancellery in 2001:

<http://www.bundeskanzleramt.at/DesktopDefault.aspx?TabID=3455&Alias=BKA>

⁸⁶ www.ethikrat.org

⁸⁷ http://www.ethikrat.org/english/publications/Opinion_Biobanks-for-research.pdf

the tissue banks, cord blood banking is well-established in Belgium, with the banks at Leuven and Liege as members of NetCord⁸⁸.

The **Biobank of the University Hospital of Liege** contains Hematopoietic Stem Cells, Umbilical Blood and also plans to store tissues like cornea, bones, arteries, etc. in the future.⁸⁹ No English information could be retrieved regarding the DNA Bank, at the Renal unit of the Faculté de médecine/Département de médecine interne of the Université catholique de Louvain, the DNA Bank, Service de Chirurgie digestive, Cliniques Universitaires de Bruxelles, Hôpital Erasme, the PSY-GEN Biobank or the De Leuven Navelstrengbloedbank.

The **DNA Bank of the Renal Unit of the Catholic University of Louvain** is a member of the European Renal Genome Project, an interdisciplinary research program, integrates European excellence in research on renal development and pathogenesis. Their goal is to discover genes responsible for renal development and disease, their proteins and their actions.⁹⁰

The University of Liege is a parent member of the **Belgian Cord Blood Bank**, which also includes the Free University of Brussels (ULB) and the Catholic University of Louvain (UCL). This bank was established in 1993, with funds obtained through the fund raising operation TELEVIE. More recently, an additional storage facility has been added at the Institut Bordet, a cancer institute situated in Brussels with funds from la Fédération Belge contre le Cancer, Fonds Ariane and les Amis de l'Institut Bordet. In April 2003 Netcord and BMDW recorded 7484 and 7581 Belgian Cord Blood Units respectively.

The **Tissue Bank of the University Hospital Saint-Luc** in Brussels was founded in 1983 and is specialized in tissue supply for allogenic grafts. Additionally, scientists at the Tissue Bank have developed therapies for autologous grafts since 2001.⁹¹

The **Global Allergy & Asthma European Network (GA²LEN)** is a network of centres with high clinical and experimental research competence across Europe, conducting and providing platforms for clinical, translational, intradisciplinary and multidisciplinary research. The overall objective of GA²LEN is to establish an internationally competitive network, to enhance the quality and relevance of research, address all aspects of the disease and eventually decrease the burden of allergy and asthma throughout Europe. The network brings together epidemiological, basic and clinical researchers carefully considering ethical and gender issues. It investigates allergy and asthma across the life course, including intra-uterine life and foeto-maternal interface, interaction between genetic and environmental factors in early life, translation of allergic sensitisation into disease and persistence of the disease.

Cryo-Save is a private firm specialized in the isolation and storage of (adult) stem cells. Stem cells can be harvested from umbilical cord blood and also from mature bone

⁸⁸ The "NetCord Virtual Office" is an online search system for unrelated cord blood of the 14 leading cord blood banks world-wide (www.netcord.org).

⁸⁹ <http://www.chuliege.be/sm/78.html#activities>

⁹⁰ "Stem Cells - European Research Projects Involving Stem Cells in the 6th Framework Programme", ed. by Joliff-Botrel, G. and Perrin, P., EC, Dec. 2005.

⁹¹ <http://www.saintluc.be/hospitalisation/dpts-serv/banque-tissus/>

marrow. In contrast to embryonic stem cells, ethically disputed, these cells are an excellent alternative for transplants. Cryo-Save is a member of the Life-Sciences Group N.V., a Dutch holding with affiliates and partnerships in 20 countries and a nominal capital of more than 5 million Euros. Cryo-Save has a central laboratory in Brussels and a cooperation partner in Germany, and is one of the largest service providers in the world in the field of stem cell storage with more than 30000 stem cells samples.⁹² Cryo-Save is currently the only private cord blood bank in Belgium.

Regulatory aspects

The legislation on human tissue use and human tissue banks in Belgium is currently based on two principal texts: the *Crown Order of 13 June 1986* and the *Crown Order in Council of 15 April 1988*.

- the *Crown Order of 13 June 1986* regulates the retrieval and grafting of organs and tissues, with a limited scope to therapeutic uses.
- the *Crown Order in Council of 15 April 1988* regarding human tissue banking, addresses the care and storage of human tissue from the time of donation until transplant in the recipient. Its goal is to promote tissue quality and safety in non-profit human tissue banks through tissue bank accreditation and activity supervision. Under the Royal Order, a Human Tissue Bank (HTB) is defined as “a technical unit in a hospital, with the assignment guaranteeing quality of the tissues from the moment they are retrieved, to the moment they are used as an allograft, more particularly during the preparation, storage, distribution, transportation, and delivery.” Establishment of an HTB requires prior approval by the Minister of Health (in conjunction with certain other specified criteria), authorization for the HTB granted for a limited duration and HTB activities are subject to strict monitoring. Accordingly, the Royal Order requires clinical, biological, microbiological, and immunological donor and donor tissue testing. The Royal Order also mandates the keeping of detailed records, tracking the origin, processing, and handling of human tissue, thereby ensuring traceability of the tissue implant [13].

The *Crown Order in Council of 15 April 1988*, was actually revised in 2002 and replaced by the *Crown Order in Council of 23 December 2002*. According to this Crown Order and an opinion given by the Belgian Health Council on 7 December 2001 on tissue banks’ legislation⁹³, the therapeutic autologous uses of human tissues for deferred preventive intentions is prohibited, as well as advertising and profit-making of commercial blood banks.⁹⁴ However, this Crown Order was suspended by the Council

⁹² <http://www.cryo-save.com/>

⁹³ The Belgian Health Council on 7 December 2001 gave an opinion on the revision of tissue banks’ legislation. In particular it recommends for the cord, cord blood and derived cells that:

- “The cord and cord blood cells are part of the legislation regulating tissues and cells;
- Quality standards for cord blood banks have to be worked out;
- The therapeutic autologous uses for deferred preventive intentions have to be prohibited.”

The Health Council, in its Annex II, lists the conditions of approval and authorisation of the activities relating to cell and tissue banks. It stipulates, in particular, that “each cell or tissue bank has to be approved by the Minister after a report of the relevant service and after the opinion of the Health Council and that this approval can only be granted for (...) non-profit-making organisms”. Cf. Opinion n° 19 : “*Ethical aspects of umbilical cord blood banking*”, The European Group on Ethics in Science and New Technologies to the European Commission, 2004.

⁹⁴ Demande d’explications de Mme Clotilde Nyssens au ministre des Affaires sociales et de la Santé publique sur «les banques de sang de cordon ombilical» (n° 3-1384), Annales, Sénat de Belgique, 16 Feb 2006.

on 24 February 2005 after the legal proceedings, initiated by the private cord blood bank Cryo-Cell Europe⁹⁵, established in Malines.

A Royal Decree is under preparation by the Ministry of Public Health in order to have a clearer legislation regarding human tissues and particularly, umbilical cord blood banks. The draft Decree provides that all tissue banks will have to be accredited by the Ministry of Health. The Royal Decree proposes that the accreditation will be granted to non-profit organizations only. The draft Decree also clearly forbids the use of umbilical cord blood cells for deferred preventive intentions, as well as all discrimination aiming at favouring a person's access to therapeutic possibilities linked to tissues of human origin, any form of publicity and the research of profit. This preliminary draft was planned to be submitted to the Council of Ministers in March 2006⁹⁴.

Privacy/Data Protection

The EU Directive 95/46/EC on the protection of individuals, with regard to the processing of personal data and on the free movement of such data, was implemented to national law on 11 December 1998, and came into force on 1 September 2001.

2.2.3.3 Biobanks in Germany

In Germany there are many public, more or less small-scale biobanks affiliated to hospitals and designed for research. These biobanks are mostly devoted to the research of treatment of specific diseases. They are stand-alone or networked and accessible to researchers on site or available for international research groups.

Five public biobanks are devoted to research and/or clinical research diagnostics:

- the Jose Carreras Cord Blood Bank Düsseldorf, collects neonates cord blood DNA, serum of the mother, whole blood (cord blood) and plasma of cord blood units. Serum and plasma are stored in a -80°C freezer, cord blood units in liquid nitrogen.
- the European Searchable Tumour Line Database (ESTDAB) collects cancer cell lines stored in liquid nitrogen.
- the KORA-gen biobank collects DNA, Serum, Whole Blood, urine and EBV immortalized cell lines stored in a -80°C freezer and in liquid nitrogen.
- the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft "Eurocroyo SAAR" collects serum and tissues stored in liquid nitrogen. This biobank is also devoted to technology development, automation and demonstration.
- the Patient DNA collection at Institute of Human Genetics Heidelberg, collects DNA stored in a -20°C freezer.
- One public biobank devoted to allogeneous grafts for transplants: the Tissue Bank at the Charité – Universitätsmedizin Berlin, collects tissues stored at room temperature or in a -80°C freezer.

⁹⁵ Cryo-Cell Europe is an affiliate of the American company Cryo-Cell International. It is represented, so far, in Austria, Belgium, Germany, Luxemburg, the Netherlands, Switzerland and the UK but aims to collect and store blood from 18 European countries. Cryo-Cell has recently acquired the German biotechnology company MainGen in Frankfurt, with interests in cell expansion and cell therapy. Cryo-Cell Europe currently holds over 5,000 CBU stored for autologous and family use. Cf. Opinion n° 19 : "*Ethical aspects of umbilical cord blood banking*", The European Group on Ethics in Science and New Technologies to the European Commission, 2004.

http://www.europa.eu.int/comm/european_group_ethics/publications_en.htm

Biobanking activity

- Two biobanks devoted to public research and clinical research diagnostics, as well as to private commercial research:
 - the ITI DNA-Bank, collects DNA and whole blood stored in a -80°C freezer;
 - the Human Melanoma Biobank, collects DNA, serum, whole blood and tissues in -20°C freezer, -80°C freezer and in liquid nitrogen.

The breast and colorectal biobank of Germany, the European Searchable Tumour Line Database (ESTDAB), the International German Melanoma Tissue bank, the AUTOROME biobank, the Tissue Bank of the university hospital in Heidelberg (devoted to the study of cancer diseases) and KORA-gen cited above, are representative of biobanks affiliated to hospitals and designed for research purposes. They are designed only for public research and clinical diagnostics research but, sometimes also for commercial research (e.g. the Human Melanoma Biobank). These biobanks store DNA, serum, whole blood, and tissues, mostly combined with demographic, genetic, ethnicity or lifestyle data. They can be networked or stand-alone but, mostly allow international researchers to use their samples and data in their studies. Furthermore, some of these biobanks have already been involved in some international research studies.⁹⁶

The Bayerische Stammzellbank GmbH and the José Carreras Stammzellbank Düsseldorf are representative of public tissues and blood banks. There are five non-profit cord blood banks in Germany. These are situated in Düsseldorf, Dresden, Mannheim, Dresden, Düsseldorf, Freiburg, Mannheim und München⁹⁷. The José Carreras Cord Blood Bank in Düsseldorf, is the longest established blood bank, having been opened for family donation in 1992 and then for unrelated donors in 1993. The Düsseldorf bank is a founder member of NetCord⁹⁸, an online search system for unrelated cord blood of the 14 leading cord blood banks world-wide, and is also a partner in the EUROCORD III project. The bank aims to preserve a broad ethnic mix of CBU. It also stores DNA and cord blood plasma. The Düsseldorf bank is devoted to public research, clinical research diagnostics.

Besides these five public cord blood banks, the following private cord blood banks have been identified: Basic Cell GmbH, Cryo-Care GmbH, Cryostore Deutschland GmbH, Lifecord.de GmbH, Vita 34 AG Deutschland, eticur) GmbH. VITA 34, established in 1997, was the first private cord bank to be set up in Europe. On 1 January 2003, VITA 34 held 12,000 CBU of which >99% were stored for autologous/family use and <1% were donated for research. Patients are recruited through the VITA 34 web site and through advertising in the press. In its publicity material, VITA 34 recommends that prospective parents, who do not wish to bank cord blood privately, should consider donating their baby's cord blood to a public bank for unrelated use. The bank ran at a loss between 1997 and 2001 when it reached break even point. In 2003, the bank moved to new laboratories at Leipzig Bio City, a biotechnology and biomedical centre being established by the State of Saxony in association with the University of Leipzig. VITA

⁹⁶ For instance: the Human Melanoma Biobank in the EU OISTER project (5th framework program) and ENACT (6th framework program) or KORA-gen in P3G - Public Population Project in Genomics, International meta analyses, International replication studies, e.g. with US Framingham Heart Study.

⁹⁷ http://9monate.qualimedic.de/Nabelschnurblut_einlagerung.html

⁹⁸ www.netcord.org

34, has also established a research base and collaborates with: the Institut für Immunologie und Transfusionsmedizin at the University of Leipzig on cell expansion and stem cell differentiation into neural tissue; the University of Rostock, on the development of cell therapy for the treatment of cardiac infarct using cord blood stem cells and with the Ruhr University Bochum, on the development of cell therapy for Alzheimer's disease using cord blood stem cells.

The Cytonet Group is active in the field of medicine and biotechnology and develops new pharmaceuticals for cell therapy until they are marketable. Cytonet GmbH & Co. KG partners are internationally leading university clinics. Cytonet is currently developing an entirely new liver cell product to be used in the treatment of severe liver diseases and metabolic liver defects in newborns and small children. EU marketing authorization by the European Medicines Agency (EMA) is expected in approximately the next two years. Today, Cytonet is Germany's largest company involved with cell therapy. The city of Weinheim is home to the management, administration and marketing organization of the Cytonet Group, established in April 2000 by spinning off the Cell Therapy division of Roche Diagnostics GmbH. The operative production and development activities take place at Cytonet's locations in Hannover, Heidelberg and Sofia. The Hannover location was established as the first site, for collaboration between Cytonet and a university clinic. The Center for Cell Therapy was opened jointly with the Hannover Medical School (Medizinische Hochschule Hannover – MHH) in 1997, by the company formerly known as Boehringer Mannheim GmbH, now Roche Diagnostics GmbH. The establishment of the Hannover subsidiary was additionally supported by the Investment Promotion Agency of the state of Lower Saxony. As a result, the Cytonet Group has been operating the most modern German center for cell therapy in Hannover since January 2002. Since May 2000, Cytonet has been collaborating with the University of Heidelberg in the form of a joint company, Cytonet Heidelberg GmbH. Like the Hannover subsidiary, this branch also manufactures blood stem cell and bone marrow transplants for oncology and hematology departments. Pursuant to Section 13 of the German Medicines Act, the company was granted a manufacturing permit for the new premises for blood stem cell products, T-cell preparations and bone marrow transplants in July 2003. This manufacturing permit was extended to the production of stem cell products from bone marrow, for the treatment of acute cardiac infarction in the spring of 2004. The corresponding clinical validation studies with the departments of Professor Katus, Heidelberg University Clinic, and Professor Drexler, Hannover Medical School, have already begun. Apart from the Heidelberg University Clinic, Cytonet collaborates with the German Cancer Research Center (DKFZ) and supports the implementation of research projects in clinical applications, in compliance with all applicable guidelines of the state and federal authorities for cell therapy products.

Sample collections

Even among the biobanks devoted to research, the selection of donors is not homogenous: for the European Searchable Tumour Line Database (ESTDAB), the Patient DNA collection at Institute of Human Genetics Heidelberg, and the ITI DNA-Bank, the selection of donors is made on the basis of whether they have a specific disease. In contrast to this, the selection at José Carreras Cord Blood Bank Düsseldorf and at the KORA-gen biobank is random. The participant selection for the Tissue Bank Charité is also random: this is not very surprising insofar as this biobank was founded to provide musculoskeletal transplants (allografts). For the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft "Eurocroyo SAAR", the selection is random as well as based on a specific disease or based on stem cells. For all biobanks, the samples have been collected either by the associated hospital staff, primary care workers (including Hospital Staff) or by centres/staff specifically employed for the Project.

Apart from the European Searchable Tumour Line Database (ESTDAB biobank) which has only samples from 200 individuals, the biobanks devoted to research are quite large and have at least 5000 samples. However, we have no information on the size of the Tissue Bank, Charité – Universitätsmedizin Berlin and of the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft “Eurocroyo SAAR”.

The only information the Tissue Bank, Charité–Universitätsmedizin Berlin collects from the donors, is the tissue bank-ID. This is not surprising, as this biobank is a provider of musculoskeletal transplants (allografts). All the other biobanks are devoted to research and collect at least medical/phenotype information from the donors and often also demographic, ethnicity, genetic information and information on the environment/lifestyle of the donors. The KORA-gen biobank also collects medication, physical investigations and Laboratory parameters. The European Searchable Tumour Line Database (ESTDAB) collects medical/phenotype information and genetic data indeed and additionally immunological parameters.

The Patient DNA collection at Institute of Human Genetics Heidelberg, the European Searchable Tumour Line Database (ESTDAB), the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft “Eurocroyo SAAR” and the Human Melanoma Biobank all collect samples from different countries. No problems have been reported thereby.

Access availability and sharing of samples

Most of the surveyed biobanks are stand-alone or provide only a restricted access through intranet or internet to their data and samples. However, some of the biobanks mention they were stand-alone as well as providing a restricted access through internet: for instance, the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft “Eurocroyo SAAR”, the José Carreras Cord Blood Bank Düsseldorf and the Human Melanoma Biobank.

Many of the biobanks considered are used from researchers from European countries or even from the rest of the world: the José Carreras Cord Blood Bank Düsseldorf, the KORA-gen biobank, the ESTDAB Biobank, the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft “Eurocroyo SAAR” and the Human Melanoma Biobank. All these biobanks have been already involved in international projects. Only the José Carreras Cord Blood Bank Düsseldorf mentioned the sampling size as a problem when sharing samples/data with international partners. The other biobanks are used by either only researchers in Germany (the ITI DNA-Bank) or by researchers on site (the Tissue Bank Charité and the Patient DNA collection at Institute of Human Genetics Heidelberg) and have, therefore, no experience of sharing samples in the scope of an international research project.

The Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft “Eurocroyo SAAR”, the Human Melanoma Biobank are the only biobanks which provide partly free access to their samples and data: the Human Melanoma Biobank provides indeed free access for non-commercial users - whereas commercial users have to pay. We have no information regarding the conditions associated with either a free access or access against payment at the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft “Eurocroyo SAAR”. All other biobanks provide access to their

samples/data only against payment - the ITI DNABank provides access against a fee for each sample that just covers some of the costs for DNA isolation. In addition, a co-authorship of the DNA-Bank manager on publications based on the DNA-bank is arranged - or under specific conditions:

- the Patient DNA collection at Institute of Human Genetics Heidelberg provides access to samples only on a collaborative research basis;
- the KORA-gen biobank only provides access to samples after the KORA-gen steering committee has decided on the scientific relevance of the study planned with the samples/data;
- also the Tissue Bank Charité provides access after research groups asking for the samples/data have been approved by the local ethics committees.

Only the ITI DNA-Bank and the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft “Eurocroyo SAAR” are not regulated by a Research Ethics Board approval. According to the survey, the DNA-Bank has been approved by the local Ethics Board and based on the strict anonymous procedures of the samples no further consent is needed.

The current consent form and legal framework allow the following biobanks to share samples and data with researchers outside Germany: the ITI DNA-Bank, the ESTDAB Biobank, the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft “Eurocroyo SAAR” and the Human Melanoma Biobank. According to its questionnaire, the Patient DNA collection at the Institute of Human Genetics Heidelberg allows sharing DNA samples with researchers outside the country. For the Patient DNA collection at the Institute of Human Genetics Heidelberg, the ITI DNA-Bank and the ESTDAB Biobank, an impediment to a potential networking on European level might be the fact that researchers using the samples are not required to feed back results to the biobank.

Consent

The handling of consent is not homogenous. The answers received are not easy to understand because several answers have been ticked to one question, and no precision added. For the ITI DNA-Bank, the KORA-gen biobank and the Human Melanoma Biobank, the donors have to consent to biomedical research. According to the questionnaire answers, it can be assumed that there are some trial settings where the Patient DNA collection at Institute of Human Genetics Heidelberg, the European Searchable Tumour Line Database (ESTDAB) and partly the José Carreras Cord Blood Bank Düsseldorf do not need any form of consent from the donors. In addition, consent only for a specific study might be requested: this is the case for CB transplant at the José Carreras Cord Blood Bank Düsseldorf. As expected, at the Tissue Bank Charité, consent is requested for multi-organ donation. We have no information on the consent requested from the donors by the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft “Eurocroyo SAAR”.

In almost all biobanks considered, information arising from biobank studies *cannot* be referred sent back to individuals (personal results). Only at the José Carreras Cord Blood Bank Düsseldorf, unusual testing results can be referred back to individuals. For half of the biobanks, it is possible for donors to withdraw their consent to store samples in the biobank. For the others, it is not. This handling seems to be quite heterogeneous

and *cannot* be associated with whether a biobank is devoted to a specific aim. For the ITI DNA-Bank and the ESTDAB biobanks, privacy of donors is protected through anonymization but without any type of key code (not surprising, as we already know that these biobanks do not refer any results from their studies to the donors). Also the Human Melanoma Biobank and the Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft “Eurocroyo SAAR” use either anonymization or coding..

Regulatory aspects

There is no explicit law up to now exclusively referring to human biobanks. The Federal Data Protection Law (“Bundesdatenschutzgesetz”) is, of course, relevant.⁹⁹ Also, the following laws are in force:

- the Embryo Protection Act (Embryonenschutzgesetz) of 13 December 1990;
- the Gesetz zur Regelung des Transfusionswesens (Transfusionsgesetz) on 1 July 1998;
- the Stem Cell Act (Stammzellgesetz) of 28 June 2002;
- the Federal Data Protection Law of 14 January 2003;
- the Federal Law on Human Genetic Examinations (GenDG) of 24 April 2009;
- the Law on legal protection of biotechnological inventions of 21 January 2005.¹⁰⁰

There is no specific legislation in Germany on the retention, storage or use of umbilical cord blood or cells and little discussion on related ethical questions. However, umbilical cord cell banks in Germany are licensed under the terms of the German Drug Law (Arzneimittelgesetz). Where Cord Blood Units (CBU) are stored, solely for autologous use, a licence can be granted by a Local Authority or Regional Council but where CBU are stored for related or unrelated third party use, then rigorous cGMP standards have to be met and a licence obtained from the Paul Ehrlich Institute, the relevant Federal statutory licensing body. In 1999, The German Federal Medical Society issued guidelines for the production, storage and use of stem cells from umbilical cord blood. The German Government (German Ministry of Health and Social Security) had announced to bring a first draft of the long planned law on genetic testing/diagnosis (Gendiagnostik-Gesetz) before parliament in June 2004. All relevant ethical issues, concerning informed consent, the storage and further use of biomaterials and personal data linked to it should be dealt with.¹⁰¹ However, due to political wrangling, the law has not been released yet, but announced for 2006.¹⁰² Finally the law was enacted in Spring 2009 but it does not contain provisions on research anymore. In the first drafts research was seen as a key area of regulation but in the later stage of the legislation

⁹⁹ “Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human biobanks”, European Commission Research Directorate-General, Directorate E Biotechnology, Agriculture and Food, edited by Line Matthiessen and Kimmo Pitkänen, update October 2004.

¹⁰⁰ Martin Uranga, A., Martin-Arribas, M.C., de Donato, J-H, and de la Paz, M.P., “Outstanding legal and ethical issues on biobanks: an overview on the regulation of member states of the EuroBioBank project”, EuroBioBank, 2006.

¹⁰¹ “Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human biobanks”, European Commission Research Directorate-General, Directorate E Biotechnology, Agriculture and Food, edited by Line Matthiessen and Kimmo Pitkänen, update October 2004

¹⁰² <http://www.gesundheitpro.de/Genetische-Untersuchungen-Gendiagnostik-Gesetz-Forschung-A050805ANOND018530.html>

project research was dropped as the legislation was influenced by several constitutional rights including the freedom of researchers.

Privacy/Data Protection

The EU Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data, was implemented to national law in the “Data Protection Act” of 18 May 2001, and entered into force on May 23 2001 (“Bundesdatenschutzgesetz (BDSG) in der Fassung des Gesetzes zur Änderung des Bundesdatenschutzgesetzes (BDSG)*) vom 18. Mai 2001 (BGBl. I S. 904)”) ¹⁰³.

Ethics Discussion

There has been a debate in Germany on human biobanks for years:

- the National Ethics Council began debating the issue of human biobanks in May 2002. A joint debate with the French National Consultative Ethics Committee (Comité Consultatif National d’Éthique) began in late June 2002, in Berlin and led to a common declaration on the subject in October 2003. An opinion on human biobanks was published by the German National Ethics Council in March 2004;
- the Central Ethics Commission of the Federal Chamber of Medical Doctors (Bundesaerztekammer) published its opinion on the (further) use of human body materials for medical research. This opinion refers to the systematic storage of biological materials;
- the Enquete Commission Ethics and Law in modern medicine of the German Parliament (Enquete-Kommission Ethik und Recht der modernen Medizin des Deutschen Bundestages) has issued a statement at its 8th session on November 11, 2003 concerning the adoption of a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (Interinstitutional Dossier 2002/0128). Within this statement, the Enquete Commission deals with ethical questions concerning access and benefit sharing which it recommends for commercial biobanks. Ethical questions concerning informed consent are also dealt with;
- on March 27, 2003 the Senate Commission on Genetic Research of the Deutsche Forschungsgemeinschaft (DFG, German Research Organisation) formulated a new statement on predictive genetic diagnostics. It takes the place of the statement "Humangenomforschung und prädiktive genetische Diagnostik: Möglichkeiten - Grenzen - Konsequenzen", made in 1999, and reaches beyond the latter's content. Regarding genetic samples and data banks, the DFG recommends that procuring, storing and processing samples and data has to go hand in hand with a reliable protection of the respective donors from any abusive use. In addition, the donor has to give his self-determined consent to the use of his/hers samples and data. Under these conditions, the DFG also holds that a donation of samples or data, with a right of usufruct, formulated in broad terms and without being tied to any concrete research projects is ethically and legally justified. The emphasis has to be made on striking an appropriate balance between the legal protection of the donor's personality and the protection of confidence for the researcher ¹⁰⁴.

¹⁰³ http://www.berlin.de/datenschutz/infomat/dateien/bdsg/bdsg_01.pdf

¹⁰⁴ http://www.dfg.de/aktuelles_presse/reden_stellungnahmen/2003/download/praediktive_genetische_diagnostik.pdf

There was also a public debate on human biobanks as the German National Ethics Council held a public conference on this issue on 24 October, 2002. The conference papers and discussion received considerable attention in the general media and in specialised publications. The opinion on human biobanks, published in March 2004, has also drawn considerable attention from the media and other interested parties [ref??].

2.2.3.4 Biobanks in the Netherlands

In the Netherlands 14 biobanks were identified of which 7 public biobanks are devoted to public and/or clinical research (the Erasmus MC Tissue Bank, the EORTC VTB biobank, the TuBaFrost biobank, the BioBank Maastricht, the LifeLines biobank, the Netherlands Brain Bank and the EuroBoNeT biobank); 4 public biobanks not necessarily with research purposes (the CONCOR, ECARUCA, the Genomos project, The Chronic Kidney Diseases project); 1 public biobank devoted only to clinical therapeutic use (the Sanquin Bloodbank), 1 private, commercial cord blood bank (Cryo-Save); and 1 private stem cell biobank (Cells4Health).

There are many public biobanks for research and also many private biobanks in the Netherlands. The first public cord blood bank in the Netherlands was established in Leiden by **Sanquin** (the Netherlands Red Cross) which runs the Dutch blood services. Subsequently, three other banks have been established at Groningen, Nijmegen and Amsterdam. Leiden acts as the hub for all haematopoietic stem cell activities in the Netherlands and is the home of the Europdonor Foundation (the Stem Cell Donor Registry of the Netherlands) which acts for **EuroCord** Nederland, the Dutch Registry of Cord Blood Units. The aim of EuroCord Nederland is to collect 5,000 CBU. Europdonor is also co-ordinating the STEMNET project which aims to link donor registries and stem cell banks in Central Europe with networks and registries in Western Europe such as NetCord and BMDW. In this way, the project aims to contribute to better therapy in Central Europe and, through the introduction of new ethnic groups, better chances for patients world-wide. Bone Marrow Donors World-wide also has its headquarters in Leiden. The Leiden Cord Blood Bank is a member of NetCord and a partner in EUROCORD. In April 2003, Leiden registered 1,535 CBU with NetCord.

Among the seven public research biobanks, three are devoted to tissue banking: the Erasmus MC Tissue Bank is collecting tissues; the **EORTC VTB Biobank** is collecting tissues frozen and paraffin embedded and xenografts, and cell lines derived from bone tumours; the **TuBaFrost** biobank is collecting tissues.

The other four public research biobanks are the **BioBank Maastricht**, which is collecting DNA, serum, whole blood and also urine, CSF, breastmilk, buccal cells, faeces, intra ocular fluid; the **LifeLines Biobank** is collecting DNA, serum, whole blood; the **Netherlands Brain Bank** is collecting serum, whole blood, tissues, and also CSF; and also the **EuroBoNeT Biobank** whose development has just started and is collecting DNA, serum, whole blood, tissues and also xenografts, cell lines all derived from bone tumors.

In the following, a biobank of each category will be presented as an example.

Public biobanks with research purposes

The overall aim of the **LifeLines Biobank** is to provide a state-of-the-art infrastructure for the study of universal risk factors and their modifiers for multifactorial diseases, by means of a common bank for DNA, serum, and other patient-derived samples, medical information, and modern and ultra fast ICT solutions to query these data. The biobank will be a nation-wide facility, ensuring Dutch collaborating centres and institutes a permanent resource for standardised isolation and storage of DNA, serum, plasma and urine from large cohorts of healthy volunteers and patients. It provides continued long-term availability in optimal quality, easy and uniform access to the biological material, on an appropriate basis for genotyping and sample analysis, by a network-based bioinformatics system accessible from the different participating centres in the medical and biological research communities. The facility will incorporate equipment for low- and medium-throughput genomics and proteomics, whereas high-throughput genome screening will take place in Utrecht and Leiden. It secures a linkage of these human tissue samples to high quality medical records and phenotypic databases, with adequate protection of patients' confidentiality, lower costs by requiring less staff, hardware and facility space than for individual cohorts. It guarantees higher quality and lower error rate by automation, cross-cohort analyses with other European cohorts, by standardised genotyping and biochemical sample analysis, enabling independent confirmation as well as large-scale studies.

There will be special attention for standardisation of methodology and techniques. This will be achieved, in close collaboration, with several existing (European) partners, such as ICT companies (LIMS), UK Biobank and companies supplying cryofacility, and infrastructure for sample isolation, storage and retrieval, as well as other research initiatives such as the P3G consortium (as an associate member in the latter: questionnaires and related methodology).¹⁰⁵ The biobank will be of strategic importance to the identification of genes, vital to the development of health-related biotechnologies, diagnostic applications and the quest for new therapeutic targets and drugs.

The **LifeLines Cohort** will be the first study using the LifeLines Biobank. It investigates a representative sample of 165.000 participants from the three northern provinces of the Netherlands in a unique three-generation design. LifeLines is 'hypothesis-driven', i.e. all data collection and analyses are performed on the premise of specific research questions. The central hypothesis is that interaction between universal, generic risk factors and specific modifiers, e.g. genetic, environmental and complex factors, accounts for the development of specific single disorders versus the clustering of multiple disorders in individuals.

The **TUBAFROST** and **EORTC VTB** projects are central European databases collecting the information of frozen tumor tissues with the goal of centralizing the tumor tissues information to facilitate the search of doctors/researchers for tumor tissues which they need for their cancer research. So far, it is a virtual tissue bank with central database and local collection. The goal of these projects is to facilitate cancer research.¹⁰⁶ Per se, these projects are international and the database information is networked. According to the biobanks investigators, it is very difficult to cope with the

¹⁰⁵ www.lifelines.nl

¹⁰⁶ www.tubafrost.org

various legislations in European countries. In the scope of these two projects, a European code of conduct was developed describing how to deal with this.¹⁰⁷

Public biobanks with no necessarily research purposes

The **CONCOR** registry was initiated in 2002 to make an inventory of the epidemiology and specific morbidity of adult congenital heart disease at national level. A rough estimate of the current number of adults, with congenital heart disease in the Netherlands is between 20,000 to 25,000 patients. This number is growing steadily at a yearly rate of approximately 5%, thanks to the development of new operation techniques for children with a congenital heart defect who, therefore, have a better prognosis and life expectancy. Since it concerns a new, rapidly growing, patient population with often substantial (post-operative) morbidity, it is important that comprehensive knowledge regarding the specific problems of this category of patients is available. Rapid progress is being made in studying the genetic causes of congenital heart disease and in identifying which genes are involved in the development of the heart. Genetic changes may give rise to congenital cardiac defects and the knowledge of the genetics of heart defects is likely to increase strongly in future years. Furthermore, most of the patients with congenital heart disease now live into their reproductive age. These considerations emphasize the urgent need for intensive genetic research, which requires large numbers of patients. The first goal of the registry was to include adult patients under treatment at one of the eight academic hospitals in the Netherlands. Data entry of patients under treatment at non-academic hospitals was started in 2004. At present (January 2006), more than 6,050 patients from 83 hospitals have been included. Blood samples for DNA analysis have been collected from 3,000 of these patients.

ECARUCA (“European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations”) a European database initiated by the European Cytogeneticists Association (ECA)¹⁰⁸ and supported by the European Union, collects cytogenetic, molecular and clinical data¹⁰⁹ of rare unbalanced chromosomal aberrations from all (cyto) genetic centres that are member of the ECA¹¹⁰. ECARUCA aims to improve patient care and collaboration between genetic centres in the field of clinical cytogenetics.¹¹¹

The aim of the **Genomos** project is to identify by prospective meta-analysis of association studies, susceptibility alleles for parameters of osteoporosis, i.e. BMD and fracture risk. Also, to look for the influence of gene-gene and gene-environment interaction on the effect of these risk alleles. Over the course of three years, the consortium has grown from 18.000 samples to now over 40.000 DNA samples of which about 50% is kept and genotyped centrally (at ErasmusMC). Procedures for both genotyping (using a reference DNA plate) and phenotyping have been standardized. The samples are from well characterized epidemiological study cohorts across Europe, as well as from Canada and the USA. The Genomos global consortium is part of the

¹⁰⁷ To avoid inter-institutional variability or intrinsic bias in specimen quality in multi center studies, TuBaFrost has developed Standard Operating Procedures for sample quality. These Standard Operating Procedures and Quality Assurance measures must be implemented in each collecting institute in order to become a collector.

¹⁰⁸ <http://www.biologia.uniba.it/eca/>

¹⁰⁹ ECARUCA collects the cytogenetic research *results* and the accompanying clinical features, but does not collect the patient material used for the analysis itself.

¹¹⁰ <http://www.biologia.uniba.it/eca/>

¹¹¹ www.ecaruca.net

HuGENET Network of Networks^{112 113} [14]. The **Chronic Kidney Diseases project**, the Netherlands Twin Register and the Netherlands Brain Bank are further public biobanks for research.

Public biobank devoted only to clinical therapeutic use

The **Sanquin** Bloodbank of rare bloodgroups of the Council of Europe at the Sanquin Blood Bank¹¹⁴ is a public biobank devoted only to clinical therapeutic use, collecting red cell concentrates of rare bloodgroups. Sanquin is a nationwide organisation with four blood banks, a division R&D, a Fractination Institute and a Diagnostic Lab for hospitals. It has some HLA typed donors for bone marrow transplant and or platelet transplant. The organisation of searching is done by Europdonor in Leiden. The Sanquin Blood Banks in Nijmegen and Rotterdam collect cord blood and keep them in storage. All data are sent to EuroCord in Leiden, which organises the matching of the cord blood from the donor with the patient. Sanquin has a Blood Bank for rare Blood Groups. The bank consists of about 1500 red cell concentrates kept in storage. If blood banks cannot find the correct red cell concentrate for a patient with cross matching problems, they can look in that blood bank. Since the last 20 years, the Blood Bank in Amsterdam has stored samples of all donations, and can go back to donor-identification number, donation, date of donation etc. This “serothek” is organised for research reasons. For example, a few years ago a research project on rheumatoid arthritis (RA) used this serothek. The samples of blood donors, who developed RA after a few years, were used to search for markers of the disease in their blood. The goal was to see whether certain markers could predict the development of RA, a few years before the donor had complaints about his health. No typing of the samples has been done.

Commercial biobanks

Cells4health BV is a Dutch holding, with affiliates in various European and Asiatic countries, specialized in the collection, processing and storage of stem cells derived from cord blood. Furthermore, Cells4health is working on advanced cellular therapy strategies to achieve effective medical treatments in the fields of vascular repair and regeneration, spinal cord injury and regeneration, stroke and regeneration. Partner laboratories of Cells4health BV are located in Freiburg (Germany) and Plymouth (United Kingdom).¹¹⁵ **Cryo-Save** is carrying out private commercial research and collecting whole blood. It is specialized in the isolation and storage of (adult) stem cells. Cryo-Save is a member of the Life-Sciences Group N.V., a Dutch holding with affiliates and partnerships in 20 countries and a nominal capital of more than five million Euros. Cryo-Save has a central laboratory in Brussels and a cooperation partner in Germany, and is one of the largest service providers in the world in the field of stem cell storage with more than 30,000 stem cell samples.¹¹⁶

Sample collections

¹¹² <http://www.hugenet.org.uk/networks/list.html> Human Genome Epidemiology Network, or HuGENet™ is a global collaboration of individuals and organizations committed to the assessment of the impact of human genome variation on population health and how genetic information can be used to improve health and prevent diseases.

¹¹³ Private communication from André Uitterlinden, coordinator of the GENOMOS Project.

¹¹⁴ http://www.sanquin.nl/Sanquin-eng/sqn_DiagnosticServices.nsf/p-WebFSSstart!OpenPage&h=0&body=9350EB325EBA2F97C12568AB00445FD9

¹¹⁵ www.cells4health.nl

¹¹⁶ <http://www.cryo-save.com/>

At the EuroBoNeT Biobank, the Erasmus MC Tissue Bank, the EORTC VTB Biobank and the TuBaFrost biobank, the selection of donors is made on the basis of whether they have a specific disease. At the BioBank Maastricht, the selection of donors is random as well as based on whether they have a specific disease or fulfil a specific condition. As this biobank is devoted to clinical research diagnostics, it can be assumed that the donors selected at random build the control group in the trial settings.

The donors at the LifeLines Biobank and at the Netherlands Brain Bank are selected on a random basis. This is also the case for the Cryo-Save Biobank, which is not surprising, as this biobank is a private company and profit oriented, storing whole blood against payment. At the BioBank Maastricht, the LifeLines Biobank and the Netherlands Brain Bank, samples are collected by primary care workers and also by services and staff especially employed for this purpose. At all other biobanks, samples are collected by associated hospital staff or primary care workers.

The Erasmus MC Tissue Bank, the LifeLines Biobank and the Netherlands Brain Bank are the only biobanks which do not collect any samples from different countries, whereas the others do. The EuroBoNeT Biobank, the EORTC VTB Biobank and the TuBaFrost biobank, which are all settled at the same institution¹¹⁷, argued that the various regulations in different countries are an impediment to collecting samples from different countries; therefore, a **European code of conduct** was developed for these biobanks, describing how to deal with this¹¹⁸. The biobanks considered can be divided into two groups of sample size: the Sanquin Bloodbank of rare bloodgroups of the Council of Europe, the EORTC VTB Biobank, the TuBaFrost biobank and the Netherlands Brain Bank with more than 1000 samples, but less than 5000. In contrast, the other biobanks have a large samples collection with more than 5000 samples. The Cryo-Save Biobank even mentioned 38,000 samples, but it cannot be ruled out, that this number refers to Cryo-Save's samples in all European countries where Cryo-Save has activities and not only in the Netherlands¹¹⁹.

All biobanks have in common that they also collect medical/phenotype information about the donors. Some biobanks collect additionally demographic information and/or ethnicity information and/or environmental/lifestyle information and/or genetic data. The Sanquin Bloodbank of rare blood groups of the Council of Europe also collects red cell antigens and the LifeLines Biobank information about the medication used.

Access availability and sharing of samples

The Erasmus MC Tissue Bank, the BioBank Maastricht and the Netherlands Brain Bank are all stand-alone biobanks. No biobank provides open public access to its samples/data through internet. In case of existent networking with other biobanks, access to samples and data is always restricted¹²⁰. Samples and data of the BioBank

¹¹⁷ University Medical Center Erasmus MC established in the city of Rotterdam: www.erasmusmc.nl

¹¹⁸ www.tubafrost.org

¹¹⁹ This might be underpinned by the fact that, although the Cryo-Save Biobank in the Netherlands was addressed, the questionnaire returned came from Belgium.

¹²⁰ Interpretation of the answers to the question on the database connectivity is quite difficult because the definition of the "stand-alone" and "networked-intranet concepts" are not consistent for all. For instance, if one supposes that "stand-alone" means that the biobank is not networking with any other team in the institution where it is settled, the answer "stand-alone" and "networked-intranet" does not make sense. In contrast, one can suppose that "stand-alone" means "not networking with any other institution". Due to this inconsistency, we cannot be sure that the respondents understood the question in the same way and, therefore, the answers must be interpreted very carefully.

Maastricht, a stand-alone biobank, are only used by researchers on-site. In contrast, samples and data from the Erasmus MC Tissue Bank and the Netherlands Brain Bank are mentioned to be used also by researchers from other institutions in the same country, by researchers from different European countries and even from the rest of the world. It may be assumed that these biobanks can indeed send their samples to other researchers from outside countries that need them for research but cannot send any data through an internet connection¹²¹. Indeed, the Netherlands Brain Bank has already been involved in some international projects. All others biobanks, not cited yet, are used by researchers on-site and also by researchers in the same countries, in other European countries and even in the rest of the world (LifeLines Biobank). However, among them, only the EORTC VTB Biobank and the TuBaFrost Biobank have been already involved in international research projects. The reason why the Erasmus MC Tissue Bank has not been involved in international projects already might be the problem mentioned from the investigators of the biobank as occurring when cooperating with researchers in other countries: the legislations in the European countries are too various. The Cryo-Save Biobank though not having been involved in international projects already mentions the fact that “non commercial samples” is a problem thereby. Although this answer is not quite clear, one can assume that this private for-profit biobank would not cooperate with biobanks only using “non-commercial samples” for their research. Finally, samples and data of rare bloodgroups of the Sanquin Bloodbank of the Council of Europe are used by other therapeutical medical doctors in other European countries.

According to the Cryo-Save’s questionnaire, samples and data collected are only used by other researchers in other European countries. (However, this questionnaire was returned from Belgium, where the legislative situation is not clear, e.g. it is unclear whether private cord blood banks are allowed or forbidden, which might be the reason for Cryo-Save samples and data not being used currently in Belgium.).

No biobank surveyed provides free access to its samples and data. The following biobanks provide access only against payment: the Sanquin Bloodbank of rare bloodgroups of the Council of Europe, the Cryo-Save Biobank, the BioBank Maastricht and the Netherlands Brain Bank. The others only provide restricted access to their samples and data: the EuroBoNeT Biobank, the Erasmus MC Tissue Bank and the TuBaFrost Biobank after negotiating reimbursement of costs, cooperation and co-publication; the EORTC VTB Biobank only provides access to trial related institutes and the LifeLines Biobank provides access to samples/data only to approved research projects. By whom these projects have to be approved is not mentioned. The Cryo-Save Biobank is the only biobank which indeed performs research *not* regulated by a Research Ethics Board approval.

The current consent forms and legal frameworks allow most of the biobanks to share samples and data with researchers outside the country, but only data are allowed to be shared at the Lifelines Biobank. The LifeLines Biobank and the Netherlands Brain Bank are the only biobanks devoted to research to which researchers using the samples are required to feed back results of their research to the biobank., This is not the case for all other biobanks.

¹²¹ It is also possible that this apparent contradiction can be put down to the lack of definition of the “stand-alone biobank” concept.

Consent

The handling of consent is not homogenous, even among all public biobanks devoted to research. The EuroBoNeT Biobank, the EORTC VTB Biobank and the TuBaFrost biobank from the Erasmus Medical Center request a special consent procedure defined in their code of conduct. The Erasmus MC Tissue Bank uses blanket consent with an opt-out option i.e. donors can object the use of their tissues for medical research purposes. They have also developed a code of conduct for secondary use of residual tissue¹²². Cryo-Save, the private cord blood bank, requests informed consent as specified in the contracts signed with the donors/clients.

Information arising from biobank studies can be referred back to individuals (personal results) if they have given their consent at the Cryo-Save Biobank, the EuroBoNeT Biobank and at the BioBank Maastricht. The LifeLines Biobank may also refer information, arising from studies, back to individuals, even if the donors did not give their consent. At other biobanks, information arising from biobank studies cannot be referred back to individuals (personal results). However, at the Erasmus MC Tissue Bank, if this information is “beneficial the proper medical treatment routes will be found, if findings are of influence on diagnosis it will be told to the treating physician who has the best judgement how to deal with the information.”

For all biobanks considered, it is possible for donors to withdraw their consent to store samples in the biobank. Also, a common feature to all biobanks: privacy of donors is protected through coding with a key code.

Regulatory aspects

The following laws are relevant for human biobanks in the Netherlands:

- in February 2004, a new law was passed on “Safety and quality of human tissues”, in force since 1 July 2004. The law states that, in principle, all human material that becomes available to a medical professional must be offered to an ‘Organ Bank’. The bank then decides whether to accept it or to dispose of it as medical waste. When the relevant parts of the Act come into force, the Organ Banks will only be able to operate with a Government permit and will be inspected regularly. This means that all cord blood banks, whether public or private, will have to apply for a permit to operate as an Organ Bank. It has been specifically stipulated that no-one may profit from the storage of cord blood for later personal use. This means that, as long as profits are invested in the bank, there will be no problem and the law allows commercial corporations to apply for an Organ Bank permit as long as they keep their cord blood storage activities administratively and financially separate from their other (e.g. pharmaceutical) activities and within the intentions of the law.
- the “Decree concerning Requirements for the handling of Human Tissue” in force since 1 July 2004, specifies requirements for Organ Centers (under the Organ Donation Act) and Organ banks (under the Safety and Quality of Human Tissue Act).
- still in preparation is the Bill on the right of determination concerning human tissue.

¹²² www.fmww.nl

Privacy/Data Protection

The EU Directive 95/46/EC on the protection of individuals, with regard to the processing of personal data and on the free movement of such data, was implemented to national law **in the law from July 2000** which entered into force on 1 September 2001.

2.2.4 Biobanks in Southern Europe

In the context of this study, Southern Europe comprises the countries: Cyprus, France, Greece, Italy, Malta, Portugal and Spain. The search for biobanks in this region of Europe turned out to be difficult, mainly due to the lack of publicly available information. However, several small university based collections which are disease-specific do exist. Some of these were identified through Eurobiobank, a consortium of European Rare Diseases Biobanks, and are discussed in the following sections. Biobanking activities in Cyprus, Portugal, Greece and Malta were scarce (or difficult to identify), and are thus not discussed in this report .

2.2.4.1 Biobanks in Italy

Eight biobanks and one consortium of biobanks were identified in Italy. Although it can be assumed that some small scale biobanks for research exist in many hospitals, it was only possible to retrieve a few of them, for which information was available. Though an initiative to set up a large scale biobank was announced in June 2003, it was only set up in December 2005 and has been constituted within the Center of Transfusion Medicine, Cellular Therapy and Cryobiology, in Milan. The following biobanks were identified:

- ⇒ GEHA
- ⇒ GENESKIN
- ⇒ IMPROVE
- ⇒ Istituto Nazionale Neurologico Carlo Besta
- ⇒ NHMGB - Naples Human Mutation Bank of the Cardiomyology and Medical Genetics
- ⇒ Ospedale Maggiore Policlinico,
- ⇒ University of Milano,
- ⇒ University of Padova, Department of Neurosciences
- ⇒ CNRB - Centro Nazionale per le Risorse Biologiche
- ⇒ European IgA nephropathy Biobank
- ⇒ Center of Transfusion Medicine, Cellular Therapy and Cryobiology

At the **University of Padova, Neurosciences¹²³ Department** a neuromuscular bank, was started in 1980 and collects most muscle pathologies. The bank was first officially approved by Telethon in 1994. The neuromuscular bank contains more than 6000 tissue samples stored frozen (5600 muscle, 240 nerve, 122 thymus, 18 heart, 54 skin, 9 chorion villi) and about 400 new samples are collected every year. The bank stores the slides of stained sections of about 6500 muscle biopsies, and 2300 muscle specimens embedded in epoxy resin for electron microscopy. About 1950 DNA samples from patients and relatives with inherited neuromuscular disorders are stored. A standard protocol for collection of biopsies is followed: at the arrival in the laboratory, each sample is subdivided in several fragments, stored both in a bank of frozen tissues for morphological and biochemical studies, and in a bank for tissue culture, where more than 2300 muscle biopsy samples are kept in liquid nitrogen. An informatic database records the clinical data, diagnosis, muscle biopsy code number and location of each sample. The Bioethical Committee of University of Padova, approved the consent form for

¹²³ <http://telethon.bio.unipd.it/NMTB>

Biobanking activity

patients muscle biopsy and DNA sample collection, analysis and storing. The "Neuromuscular Tissue Bank" is supported by Telethon Italian Foundation¹²⁴ since 1996. The bank is part of Eurobiobank.

The **Neuromuscular Biobank of the Dpt. di Scienze Neurologiche, Ospedale Maggiore, Milan**¹²⁵ has been operative for 27 years and received the ISO 9001 Certification in 2002 by DNV. It consists of four different laboratories (morphology, biochemistry, genetics, tissue cultures) with two specifically equipped storage rooms, all related to a Department for the clinical evaluation of patients and their follow-up. The laboratories examine biological specimens obtained from hospital patients, or sent by other hospitals/laboratories after signing a legal agreement with the Unit. All specimens are obtained from patients, affected with neuromuscular disorders, after informed consent –.This bioank is also part of the Eurobiobank Consortium.

The **Integrated Project (IP) GEHA** has been instituted to identify genes involved in healthy ageing. The plan of this project is to: (i) collect 2650 long-lived (90+) sibpairs from 11 European countries; (ii) perform a genome scan by microsatellites in all the sibpairs (a total of 5300 individuals) (iii) case studies (i.e. the 2650 probands of the sibpairs) and controls (2650 young people), the three genomic regions (chromosome 4, D4S1564, chromosome 11, 11.p15.5, and chromosome 19, around APOE) which were identified in previous studies to be involved in ageing and life longevity.

The **Naples Human Mutation Gene Bank (NHMGB)**¹²⁶ was established in 1994. Its main aim is to collect samples from patients with neuromuscular diseases and primary cardiomyopathies, showing the Mendelian mode of inheritance. Each sample set in the bank includes the DNA sample from the affected individual, a sample from his/her first-degree relatives where necessary (depending on the mode of inheritance) and the result of the molecular investigations. A comprehensive pedigree and a clinical profile are also recorded. The bank also contains DNA samples from normal people, useful in the study of polymorphisms in the population. The "Naples Human Mutation Gene Bank" has been supported by Telethon Italian Foundation since 1996; it is a member of the Eurobiobank consortium.

The **National Biological Resource Centre (Centro Nazionale per le Risorse Biologiche-CNRB)**¹²⁷ is a non profit consortium, which groups a network of biotechnological Italian Institutes of excellence that are strongly representative at local and national level within the field. The CNRB's legal seat is the Italian Institute for Industrial Promotion (Italian Ministry of the Productive Activities) The CNRB is a network, aiming at fostering and coordinating the best operative programs linked to technology transfer and innovation policies. It also thrives at creating stable links between research and industry, within the national and international biotechnological, bionanotechnological and bioinformatics research and production circuits.

The **Center of Transfusion Medicine, Cellular Therapy and Cryobiology**¹²⁸ is composed of two banking Units. The first, is the **Milan Cord Blood Bank** operational since 1993 which stores and supplies placental cord blood from and to the whole world. The second, is the newly set up (December 2005) **Biobanca Italiana**, an Italian biobank. This bank has been set up with the intention of collecting random biological samples of the Italian population. In addition it also holds disease specific samples.

¹²⁴ <http://www.telethon.it/>

¹²⁵ http://www.centrodinoferrari.com/sito/en/servizi/diagnostica_banca.html

¹²⁶ <http://cardiomiologia.it>

¹²⁷ <http://www.cnr.it/index.htm>

¹²⁸ <http://www.policlinico.mi.it/>

Regulatory aspects

The Constitution of the Republic of Italy (Art. 32 par 2) set the ethical basis, upon which informed consent for the deposition of biological samples is based. In addition, amendments to the Italian Medical Code (art 38) of the Italian Medical Federation and the European Charter of Fundamental Rights (2000/ C354/01) have reaffirmed the need for proper informed consent. More specifically, the Italian Society of Human Genetics and the Telethon Foundation have set up guidelines for the proper running of Human Biobanks. The local ethics committees within the health facilities or authorised research institutes were given legal status in 1992 by a Ministerial Decree and, subsequently by another Decree in 1997. The EC Directive 2001/20/EC was implemented by the Legislative Decree No. 211 of 23 June 2003¹²⁹. Regional Bioethics Committees (REC) were created in 2000 and act as co-ordinators for local research ethical committees, as well as providing a link between them and the National Bioethics Committee. In regions where only a regional REC exists, they review research proposals. The National Bioethics Committee was established in 1990 by a Prime Minister's Decree. It acts as a consultative body of the Council of Ministers. The National Ethics Committee for Research and Clinical Trials established 1992, advises the Ministry of Health on ethical and scientific issues and is in charge of co-ordinating ethical and scientific review of multi-centre clinical trials of substantial national interest.

Privacy/Data Protection

The Italian Data Protection Act was enacted in 1996¹³⁰ and fully implements the EU Data Protection Directive. The act covers both electronic and manual files, for both government agencies and the private sector. As a member of the Council of Europe, Italy has signed and ratified the Convention for the Protection of Individuals, with Regard to Automatic Processing of Personal Data (ETS No. 108) and the European Convention for the Protection of Human Rights and Fundamental Freedoms. The OECD Guidelines on the Protection of Privacy and Transborder Flows of Personal Data have also been adopted.

2.2.4.2 Biobanks in France

Similar to the Italian situation, though small/medium scale biobanks for research should exist in many centres, very little information was publicly available (in English). However, two biobanks were identified in France: **Généthon DNA and Cell Bank**¹³¹ was created in 1990 and its main aim is to promote progress in genetic research, in the interest of patients and their families, by making high quality cells and human products available to the scientific community; Généthon's DNA and cell bank is devoted, primarily, to genetic research on rare genetic diseases. The relationship between the DNA and cell bank, and those using its services is regulated by a charter. The bank's relationship between donors and users is regulated by ethical principles governing the receipt of human products, its removal, processing, storage and any associated information. Every project intending to use the DNA and cell bank, must be requested to the arbitration committee of the Bank and formerly the Collection Department in writing. This arbitration committee is assisted by experts if necessary. On acceptance of the project, a contract is prepared specifying the rights and obligations of the parties. This bank is part of the EuroBiobank Consortium.

¹²⁹ https://oss-sper-clin.agenziafarmaco.it/normativa/decreto_24062003_inglese.pdf?

¹³⁰ http://www.dataprotection.it/codice_privacy_english.htm

¹³¹ <http://www.genethon.fr/?id=82>

In 1990, the Picardie Regional Council and the Somme General Council launched the **Biobanque de Picardie**¹³². Both Councils invested in the project by providing grants for the construction, functioning and equipment of the biobank. The biobank accepts cellular tissues, DNA, RNA and serum. The DNA and cell bank collects and conserves biological samples in accordance to the protocols requested by the partners.

Both biobanks are certified Biological Resource Centres (BRCs) thus carrying out activities in accordance with the BRC definition of the OCDE working group: "*specialized resource centres that acquire, validate, study and distribute collections of cultivable organisms (micro-organisms, plants, animals, or human cells), replicable parts of these organisms (genomes, plasmids, DNA libraries) and viable but not cultivable organisms*". In France, official BRCs have to be certified by the AFNOR normalization body.

In addition, some cohort studies are also storing biological elements for long term research and should be considered as biobanks, such as the “Elfe” cohort involving 20.000 children or the “Constance” cohort involving more than 200.000 adults.

Regulatory aspects

In France, there is a specific law applicable to collections of Human biological material, from their removal to their storage, including their transformation and their distribution (“Décret n°2007-1220 du 10 août 2007”¹³³ and “Arrêté du 16 Août 2007” introducing the new articles L. 1243-3 and L. 1243-4 of the Public Health Code). If samples are being processed for internal use only, a notification to the French Ministry of Research of the existence of such sample collection is sufficient; an authorization will be needed if the samples are to be distributed to other institutions. It is interesting to notice that this regulation shall not apply on sample collections hosted outside of France. Nevertheless, an authorisation to export or import Human samples is required to allow samples to cross the French borders (Public Health Code article R.673-22).

In addition, a complex legal framework is applicable in relation to issues on data protection, medical research and informed consent¹³³. Here, the protection of the person and his/her personal data, in case of medical research, is regulated by different authorities with different roles:

- the Committees for the Protection of Persons (CPPs): the committee issues an opinion to the biomedical research investigator, for the protection of individuals and for any subsequent amendments to the research protocol; the CPP can also issue an opinion about a collection of biological samples, especially when Human biological material is planned to be used for purposes different from those described in the initial clinical research protocol or for scientific research projects not requiring the approval of a protocol;
- the French Health Products Safety Agency (AFSSAPS, “Agence Française de Sécurité Sanitaires des Produits de Santé”)^{aaa} must be consulted before starting a clinical trial in order to authorize the protocol and the sites;

¹³² <http://www.biobanque-picardie.com/>

¹³³ <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000829163&dateTexte=>

- the CNIL (Data Protection Supervisory Authority)¹³⁴ is responsible for the supervision of any use of personal data including biomedical research data and its authorisation is required prior to the collection or the processing of health personal data;
- the CNIL (Data Protection Supervisory Authority) is responsible for the supervision of any use of personal data including biomedical research data and its authorisation is required prior to the collection or the processing of health personal data;
- the CCTIRS (consultative committee on health data processing in research)¹³⁵ must be consulted prior to the CNIL in order to provide the CNIL with an opinion on the lawfulness of the processing of personal health data;
- the French medical board (“Conseil de l'Ordre des Médecins”) reviews each contract engaging a doctor in a clinical trial in order to verify that the conditions settled in the contract are aligned with the reality of the study; both the protocol and the case report form (CRF) must be included in the submission dossier to allow this evaluation;
- the CCNE (National Consultative Ethics Committee)¹³⁴ is an independent committee which missions are defined in the Bioethics law of August 6, 2004; it gives general opinions on ethical issues related to biology, research or health but do not review research protocols (*e.g.*, see CCNE Opinion n°77 on Ethical problems raised by biological material collections and biobanks issued on March 20, 2003)¹³⁶;
- additional local and institutional Ethics Committees exist within some institutions such as hospitals; they issue specific and general decisions on ethical issues but rarely review research protocols; their opinion is not required by the law but they contribute to the definition of ethical best practice.

The approval for biomedical research requires various procedures. If the research involves personal data processing, then full approval requires both an approval for the research protocol and a separate legal procedure for data processing.

While CPP considers the patients protection within the research protocol, the French Health Products Safety Agency is focusing on the patient safety (AFSSAPS)¹³⁷ and the French medical board checks if the relation binding the doctors to the sponsors are ethically acceptable, especially regarding the financial agreements. Approval of the protocol by the AFSSAPS, the CPP and the French medical board is compulsory, except if the study does not involve patients (only data), in which case the CPP opinion is not needed. AFSSAPS approval is not needed so far for studies which are not considered as biomedical research (which do not involve the use of a drug, *e.g.*, epidemiological studies) but the new law proposition called “Jardé” might change this in the near future. Research projects involving samples from embryos or deceased

¹³⁴ <http://www.cnil.fr/>

¹³⁵ <http://www.enseignementsup-recherche.gouv.fr/cid20537/cctirs.html>

¹³⁶ <http://www.ccne-ethique.fr/docs/fr/avis077.pdf>

¹³⁷ <http://www.afssaps.fr/>

persons are subject to specific regulations (*e.g.*, an authorization issued by the “Agence de la biomédecine”¹³⁸ is needed when banking or conducting research projects on embryos or embryonic stem cells);

The legal procedure regarding the data processing depends on the type of study. If the study is in the scope of the CNIL guideline for biomedical research (MR-001)¹³⁹, then a unique declaration to the CNIL is sufficient and covers all other future studies which are in the scope of this guideline. If the study is not in the scope of MR-001 (*e.g.*, epidemiologic studies or studies in which samples are collected for purposes not defined in the study protocol), then a specific authorization should be gathered from the CNIL for each study. In such case, the CCTIRS should be contacted first to issue an opinion and then refers to the Data Protection Supervisory Authority (CNIL) for approval (if the study does not aim to improve scientific knowledge the CCTIRS opinion is not needed and the CNIL should be notified directly). It is important to notice that data that have been anonymized (for which the link between the subject and the data has been permanently broken) are not subject to personal data protection regulations anymore, thus the CNIL does not need to be involved.

2.2.4.3 Biobanks in Spain

Two biobanks were identified in Spain:

- the **Instituto de Investigación de Enfermedades Raras IIER** is located inside an institute, namely "Instituto de Salud Carlos III", with more than 10 centres dedicated to Health Research, including basic research, epidemiological research and applied clinical research. The IIER (former CISATER) was designated by the World Health Organization Regional Office for Europe, as a Collaborating Centre for the Epidemiology of Environmental related Diseases. A number of rare diseases are included within this framework. It is a foundation member of the International Society for Biological Environmental Repositories (ISBER), created by large American and European research agencies. Following this Society instructions and collaborative agreement with CDC, the CISATER created a DNA and biological samples bank for the Toxic Oil Syndrome cohort and is now establishing the Spanish bank of biological samples for Rare Diseases. As it is a partner of Eurobiobank, IIER collections and methods are published in the EBB website
- the **Banco Nacional de ADN**¹⁴⁰ is a service of the University of Salamanca. It receives, processes and stores samples of DNA, plasma and cells of voluntary donors, as well as basic information on the health and socio-demographic data of the donors. One of the bank's objectives is to try and obtain a representative sample of the resident population in Spain, and more than 1,000 voluntary donors have already provided blood for this bank. These samples are at the disposal of the scientific community, in order to facilitate, promote and develop national and international scientific investigation on human evolution and the genetic diversity in relation to the health and genesis of the disease. The bank was officially inaugurated in 2004, by a contract between the Foundation Genome Spain, the Department of Health of the region of Castilla and Leon, and

¹³⁸ <http://www.agence-biomedecine.fr/professionnels/recherches-sur-l-embryon-et-les-cellules-souches-embryonnaires.html>

¹³⁹ <http://www.cnil.fr/en-savoir-plus/fiches-pratiques/fiche/article/une-procedure-simplifiee-de-declaration-pour-les-recherches-biomedicales>

¹⁴⁰ www.bancoadn.org

the University of Salamanca. Recently, a new call for tenders has been published to create four new banks for high prevalence diseases. These four new banks will be nodes of the DNA National Bank network and they are focusing on neuropsychiatric, metabolic, cardiovascular and oncologic diseases¹⁴¹.

Regulatory aspects

Biobanks in Spain are regulated under the law 14/2007 on biomedical research. Every health centre that intends carrying out research and clinical trials must have an REC. The health authority of each autonomous community authorises these REC's. As a member of the EU, the Spanish data protection law is in conformity with the EU directive. The 41/2002, of 14 November law, regulates the autonomy of the patient, the rights and duties of providing information and clinical documentation. The Royal Decree of 65/2006, of 30 January regulates the activities relating the import/export of human tissues. The Royal Decree 65/2006 regulates international circulation of samples for use in vivo, no in vitro. The international circulation of samples for in vitro use is going to be regulated by the government, as a development of the law 14/2007. In Spain, data protection is guaranteed in the Constitution. Organic Law 15/1999 of 13 December on the Protection of Personal Data¹⁴² and the Royal Decree 994/1999, of 11 June, on Safety Measurements Rules for Computerized Personnel Data, constitute the most updated regulation in this issue. More important than the Royal Decree 944/1999, is the Royal Decree 1720/2007, that approves the Reglament that develops this Organic Law.

2.2.5 Biobanks beyond Europe

Some major biobanking initiatives outside Europe are discussed in this section. Due to the challenging geographical area to cover, the main focus of this section focusses at the first level of large biobanks. However, a more diverse sample of biobanks was gathered for the United States showing different models of biobanking activities¹⁴³.

2.2.5.1 United States of America

In a report prepared by the RAND organization, following an extensive mapping of human biobanks in the United States in 1999, the conservative estimate number of tissue collections was a staggering 307 million tissue specimen, accumulating at a rate of more than 20 million samples per year [15]. Given the frantic race towards scientific developments and improvement of health, we can only imagine today's actual numbers. Thus, this section does not pretend to provide an exhaustive mapping of all biobanks. It will focus on the range of tissue banks which can be used for research and that provides a potential for collaboration or interesting models of biobanking.

¹⁴¹ http://www.bancoadn.org/imagenes/noticias_web/samples_of_prevalent_diseases_in_the_spanish_population.pdf

¹⁴² https://www.agpd.es/upload/Ley%20Org%Ednica%2015-99_ingles.pdf

¹⁴³ P³G is a not-for-profit (shouldn't this be "profit-making") organization aimed at facilitating collaboration in the field of population genomics. P³G maintains a website with descriptive information on population based research. For this section, information made available through the P³G Observatory (www.p3gobservatory.org) was used to complete the information collected through the ESTO questionnaire. The HUMGEN website was used to identify applicable legislation and guidelines (www.humgen.qc.ca).

Biobanks identified

The tissue banks vary according to purpose, size, and nature of the tissues collected. For the purpose of this section, we have classified the biobanks identified according to the following categories:

- nature of the material collected: tissue (pathology, brain, heart tissue, etc); stem cell; blood;
- purpose of the collection: specifically for research, clinical, or transplant purposes;
- funding: private, public/non-profit, hybrid.

Tissue Banks

- Penn State Cancer Institute (PSCI) Tissue Bank
- TARPS Tissue and Research Pathology Services (University of Pittsburgh)
- Pediatric Rheumatology Tissue Repository (PRTR) is a national resource
- Early Detection Research Network Exchange (EDRN) -NCI
- Cooperative Family Registry for Breast and Colorectal Cancer (NCI)
- Tissue Bank Shared Service/Greenbaum Cancer Center/Maryland
- Children Oncology Group (NCI funded)
- Armed Force Institute of Pathology-National Pathology Repository
National Institute of Child Health and Development (NICHD), Brain and Tissue Bank for Developmental Disorders
- Kathleen Price Bryan Brain Bank
- Stanley Foundation Brain Collection
- Harvard Brain Tissue Resources Center
- New York Brain Bank
- National Parkinson Foundation Brain Endowment Bank
- Human Brain and Spinal Fluid Resource Center
- McKnight Brain Institute Brain Bank
- National Alzheimer Coordinating Center

Pathologists in the hospitals and health Institutions are collecting human tissue for clinical diagnostic purposes. By law, they are required to keep these tissues for validation for a period of time ranging from 2 to 10 years¹⁴⁴. These collections or the leftovers from clinical procedures have an important potential for research purposes, however, their use for research must comply with legal and ethical requirements (including a proper consent process). For instance, the **National Pathology Repository** housed at the *Armed Force Institute of Pathology* (AFIP) currently stores: ‘over 50 million microscopic slides, 30 million paraffin tissue blocks, and 12 million preserved wet tissue specimens’¹⁴⁵. According to their website, this resource is currently ‘under utilized’ and collaboration with AFIP is encouraged. Moreover, many hospitals have organized their own local tissue bank/registry, ranging from a relatively modest to a large scale.

The NIH is the main Federal focal point for medical research in the United States. It is composed of 27 research institutions and centers. The NIH is supporting various

¹⁴⁴ CLIA Regulation, sub-part J: tissue retention (493.1105 Standard: Retention requirements).

¹⁴⁵ <http://www.afip.org/Departments/repository/npr.html>. Date Accessed: April 1st 2006

infrastructures for tissue banking across the United States. In the field of Cancer Research, the NIH National Cancer Institute is the lead organization for funding and coordinating research efforts to find a cure for cancer. The availability of high quality, well annotated tissue is pivotal to the success of such research, thus the NCI is one of the key players in the development of biobanking research tools. The pooling of biological resources is an important strategic asset in a highly decentralized collection model. Various strategies to virtually or concretely pool biobank resources together have been put in place and are supported by the NCI. The pooling of these resources can take various forms:

"There are three main models of collection and storage operations: decentralized collection with centralized storage, centralized collection and storage, and decentralized collection and storage " [16]

An example of decentralized collection and storage of tissue is the **Cooperative Human Tissue Network**. Through a management system, the CHTN can coordinate the procurement and distribution of tissues from routine surgical resections and autopsies.

*"CHTN provides biomedical researchers with access to human tissues. Six member institutions coordinate the collection and distribution of tissues across the United States and Canada in six regional divisions. The CHTN specializes in the prospective procurement, preservation, and distribution of human tissues for research. In addition to normal, benign, and malignant tissues, tissues from patients with specific diseases such as ulcerative colitis, a premalignant state, are provided"*¹⁴⁶

CHTN was established in 1987 and claim to have provided 'more than 500,000 high quality specimens from a wide variety of organ sites to over a thousand investigators'. Tissue is offered, in priority, to peer-reviewed funded investigators, including investigators from Federal and National laboratories. However, the priorities list goes all the way down to include private funded research. Access to tissue is conditional upon IRB review and other requirements set by the Network. Canada is the only foreign country for which tissues are provided (via the Midwestern Division)¹⁴⁷.

The NIH-NCI **Early Detection Research Network** is another example of an effective collaboration, where research centers can virtually pull together the specimen collected in a decentralized way. The EDNR members seem to be all American. The EDNR claims to have access to almost 92 000 samples.¹⁴⁸

The NIH-NCI Clinical Trial Cooperative Group Program funds various research platforms collecting tissue for research. For instance, the **Cooperative Oncology Groups** (COG) collects tissue from paediatric clinical trials. It maintains a tumour bank and cell lines for research. It is a joint effort from Canada and USA, however, applications for membership from the international community are also considered.

¹⁴⁶ National Biospecimen Network Blueprint, (2003) appendix N.

¹⁴⁷ <http://www-chn.ims.nci.nih.gov/require.html>

¹⁴⁸ <http://edrn.nci.nih.gov/resources/erne-specimen-summary>

TARP is an example where tissues are collected in various hospitals but are centrally banked at one location, namely the University of Pittsburgh. In operation since 1991, TARPS 'serves as the central support for UPCI research programs needing tissue materials from patients seen at the University of Pittsburgh Medical Center (UPMC)',¹⁴⁹. It collects neck cancer tissue and is being broadened to include gastrointestinal and pancreatic cancers, haematological malignancies, and melanomas. Specimen distribution is based on a defined priority order of usage for investigators involved in a particular research field. The Tissue Utilization Committee (TUC) establishes priorities and handles any conflicts. Based on a similar approach, the **PennState Cancer Institute (PSCI)** is collecting tissue within the hospital for the primary use of researchers within their Research Center or affiliated institutions¹⁵⁰. As of 2006, the bank contains 2855 fresh frozen 278 OCT embedded and 2246 paraffin fixed normal, tumour and non-tumour samples. The **Tissue Bank Shared Service/Greenbaum Cancer Center/Maryland** has a similar 'in-house' service for its members and affiliates.

Besides cancer research which is an important area of activity when it comes to tissue banking, other disease-focused sectors of research are establishing similar organized resources at a small or large scale. Brain, heart, bone and other tissues collected in local hospitals, can be used for research purposes. These biobanks can be supported by private foundations, dedicated to fighting a particular disease or through public research funds in research centers. They are usually housed in hospitals and other health institutions. We have focussed our attention, for this project on brain banks. Our research revealed more than 20 brain banks throughout the country. For instance, the **Kathleen Price Bryan Brain Bank** located at Duke University, contains 1200 brains for research. These brains are collected by pathologist in a local institution: the Memory Disorders Clinic (North Carolina). It is a member of the *International Brain Banking Network* whose goal is to improve the acquisition and distribution of quality neurospecimens to qualified neuroscientists from anywhere in the world. The **Stanley Foundation Brain Collection** is located at the Uniformed Services University of the Health Sciences (USUHS) in Bethesda, Maryland. It collected around 600 brains from 1994 to 2005. This biobank will ship tissues to foreign countries.

NCI is leading a large-scale initiative to improve what has been identified as the most difficult problems that will drive 21st century cancer research: the limited availability of carefully collected and controlled, high-quality human biospecimens annotated with essential clinical data and properly consented for broad investigational use:

'Although many existing tissue repositories in the United States collect and store millions of specimens for many types of scientific investigations, the contents of these repositories are frequently collected and stored under varying conditions, making it difficult for scientists to compare or pool genomic and proteomic results from biospecimens across institutions. Because many of these samples were initially collected for a broad range of uses, the amount of clinical information associated with these biospecimens also varies widely, and is rarely detailed or longitudinal. In addition, many of these biospecimens may not have appropriate donor authorization for genetic studies. Finally, current access to existing specimens is often uneven, further

¹⁴⁹ <http://www.upci.upmc.edu/facilities/tarps/index.html>

¹⁵⁰ <http://www.hmc.psu.edu/cancer/research/tissue/allocation.htm>

*impeding scientific progress. The heterogeneity among existing repositories poses a challenge to support genomic and proteomic research, particularly concerning the ability to conduct and compare large numbers of biospecimens to capitalize on genomic and proteomic technologies.*¹⁵¹

To change this situation, the NCI has created the Office of Biorepository and Biospecimen Research in 2005. The OBBR serves as the coordinating and management center for overarching biospecimen-related policies, practices and other related issues across the NCI's biorepositories. One of the key initiatives of the OBBR is the creation of the National Biospecimen Network.

National Biospecimen Network Blueprint¹⁵² lays the foundation to provide a solution to this situation. The solution lies not in the creation of a mega biobank but rather a solid network of high quality biobanks, in the pure tradition of NCI cooperation. :

*'The NBN (<http://biospecimens.cancer.gov/nbn/blueprint.asp>) is a concept for a common biospecimen collection and biorepository infrastructure that promotes resource building and sharing for team science. Such an infrastructure would harness the potential of new technologies for cancer research, while ensuring that the privacy interests of biospecimen donors are preserved. The NBN would support a comprehensive framework of policies and technology to increase the number and quality of biospecimens available for research. It would include deployment of a robust, flexible, scalable, and secure bioinformatics system that supports the collection, processing, storage, annotation, and distribution of biospecimens and data using standard operating procedures based on best practices.'*¹⁵³

Such a National Biospecimen Network could change the landscape of biobanking in the United States currently faced with multiple parallel efforts to create networks of virtual or real tissue repositories.

The BRN has active collaborations with other NCI programs such as The Cancer Genome Atlas and Clinical Proteomic Technologies for Cancer. Through these partnerships, the BRN serves as a resource for project grantees and presents new opportunities for biospecimen research.

Stem Cells

- ⇒ University of California, Human Embryonic Stem Cell Line
- ⇒ WiCell Research Institute

Human Stem Cell research is a leading field of research. In 2001, the Bush Administration limited research using public funding to a limited number of authorized cell lines already collected. Stem Cell Research conducted on other lines or for purposes prohibited by legislation can only be funded privately. The **University of California** and **WiCell Research Institute** are amongst the 'authorized' Federal Government cell lines eligible for public research funds¹⁵⁴. It should be noted that Stem Cell lines are also used for research in the private sector.

¹⁵¹<http://biospecimens.cancer.gov/nbn/blueprint.asp>

¹⁵²National Cancer Institute (NCI) - National Dialogue on Cancer (NDC), National Biospecimen Network Blueprint, Washington, September 2003.

¹⁵³<http://biospecimens.cancer.gov/nbn/blueprint.asp>

¹⁵⁴ <http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp>

Blood Specimens and DNA Research Banks

Research collecting blood and DNA

- ⇒ Healthy Aging in Neighbourhoods of Diversity across the Life Span study
- ⇒ Nun Study
- ⇒ Bogalusa Heart Study, (NHLBI)
- ⇒ National Health and Nutrition Examination Survey (NHANES) (CDC)
- ⇒ Women's Interagency HIV Study.
- ⇒ Framingham study (NHLBI)
- ⇒ Jackson Heart Study (NHLBI)
- ⇒ ARIC study (NHLBI)
- ⇒ **Physicians' Health Study, (NIH)**
- ⇒ Nurses' Health Study (Original cohort) (NIH)
- ⇒ Nurses' Health Study II (NIH)
- ⇒ Women's Health Initiative - Observational study (NHLBI)
- ⇒ Iowa Women's Health Study
- ⇒ Cancer Prevention Study - 3 (CPS-3) (American Cancer Society)
- ⇒ Cancer Prevention Study - II Nutrition Cohort (CPS)
- ⇒ **Marshfield Clinic Personalized Medicine Research**
- ⇒ Study of Women Across the Nation (SWAN)
- ⇒ Cardiovascular Heart Study (CHS) (NHLBI)
- ⇒ National Children Study
- ⇒ Genomic Medicine Program
- ⇒ **GAIN** (Genetic Association Information Network)¹⁵⁵ NIH

Blood collected specifically for research purposes is mainly collected during clinical trials, or longitudinal studies. The number of biobanks collecting blood for research purposes is staggering. In the post Human Genome era, the need for well characterized DNA banks seems almost inexhaustible. Any given research initiative is susceptible of creating a small biobank for research purposes, stored in a public or private research center. We did not attempt to retrieve all these studies and focussed our attention on large biorepositories. However, we have identified a few representative ones to show the diversity of such biobanks.

NHLBI supports many of these clinical research initiatives and longitudinal studies. **Framingham Heart Study**, funded by the NIH-NHLBI, collects blood samples and data since 1948. Three generations of participants (for a total of almost 15 000 participants) contributed to the Framingham Heart study, with continued monitoring of participants over a long period of time. Researchers can apply to the Framingham Heart Study, through a well defined process, to obtain material and data for research. The philosophy seems to be one of openness towards collaboration; however, no specific mention is made on the sharing policy with respect to international collaborators¹⁵⁶.

¹⁵⁵ http://www.fnih.org/GAIN/GAIN_home.shtml

¹⁵⁶ 'The NHLBI and Boston University seek to encourage use of these data and materials by investigators not affiliated with the Framingham Study or Boston University, to foster collaborative relationships where appropriate, and to ensure that the Framingham investigators are appropriately acknowledged. Collaboration with Framingham investigators (past or present) is not required as a condition of receiving DNA and/or genetic data. The NHLBI and Boston University further seek to promote the development of valuable discoveries and inventions beneficial to the

NHLBI supports other large scale projects around the United States. Often, these tissue banks are hosted in hospital centers or affiliated research centers. The **ARIC Study** includes a Cohort Component which began in 1987 and includes a cohort sample of approximately 4 000 individuals between the ages of 45 and 64 from a defined population in their community. A total of 15792 participants received extensive examination, including medical, social, and demographic data every 3 years. While use of the resource is well organized and seems almost encouraged, the Material Distribution Agreement (available online) seems to limit distribution within the United States.

"Promoting use on a national scale of such a resource will require a large and concerted effort which may involve investigators not currently part of the ARIC Study. The NHLBI and the researchers it supports have a responsibility to the public and the scientific community to encourage as rapid scientific progress as possible using these resources, subject to appropriate terms and conditions".¹⁵⁷

The use of such material is well regulated in the MDA. Among the topics covered, it includes the need for IRB approval, the duty of the researcher not to share or use the tissues for other research purposes, not to try to identify participants and to return to ARIC the data generated from his study to benefit the biobank.

The **Jackson Heart Study** is an expansion of one of the study sites of the ARIC project. The JHS 'plans to include up to 6 500 African-American men and women between the ages of 35 and 84 and will invite all previous ARIC participants (approximately 59 to 78 years of age in 2000) along with younger and older men and women from a larger geographic area'¹⁵⁸. The process and forms for requesting material is available on the website.

The **NHLBI Biologic Specimen Repository** maintains a blood bank for research on blood donor and blood recipient. Since the mid-1970s, the Institute's Blood Division has established and supported several large blood specimen repositories to perform prospective and retrospective studies of blood donors and recipients. 'From 1991-2004, a total of 148 667 specimens from the NHLBI Biological Specimen Repository were sent to various investigators.'¹⁵⁹ Other important NHLBI studies include: **Bogalusa Heart Study**, Women's Health Initiative - Observational study, etc.

The **Nurse Study** collected more than 51 000 blood samples in phase I and 30 000 in phase II. The **SWAN study** collected an important repository of blood samples. 'The repository includes approximately 510 000 samples from the first 7 years of specimen collection. This included more than 300 000 samples from the annual visits and 206 000 samples from the Daily Hormone Sub-study (DHS)'¹⁶⁰. The Swan study has a detailed policy and process for accessing the resources for further research. Contrary to

public health based upon use of this Framingham Study repository of valuable materials and data.' Framingham DNA and Genetic Data distribution policy available on NHLBI website:

¹⁵⁷ <http://www.nhlbi.nih.gov/about/framingham/policies/index.htm#purp>.

¹⁵⁸ <http://www.csc.unc.edu/ARIC/datadist/download/UNLICOMM>.

ExternalDataDistributionAgreementForMaterialsAloneorforMaterialsandDataCombined06012005.doc

¹⁵⁹ <http://www.nhlbi.nih.gov/about/jackson/2ndpg.htm>

¹⁶⁰ <http://www.nhlbi.nih.gov/resources/medres/reposit/reposit.htm>.

¹⁶⁰ <http://www.swanrepository.com/>

the Framingham study where participation of an ‘in-house’ investigator is encouraged, here it is mandatory. We could not come to a firm confirmation about the potential for international collaboration from reading the policy available on the web. Other important studies include: **Healthy Aging in Neighbourhoods of Diversity across the Life Span study**, **Nun Study**, etc.

The Center for Disease Control’s (CDC) mandate is to protect the health and safety of the population. It supports the **National Health and Nutrition Examination Survey (NHANES)** program. Since 1960, the National Center for Health Statistics has been conducting NHANES surveys, nationally representative survey of the population. Since 1999, it is a permanent program of the CDC. The **NHANES III** Study led to the creation of an important DNA bank resource (about 7000 specimens from participants¹⁶¹) at the Division of Laboratory Sciences (DLS) at the National Center for Environmental Health (CDC)¹⁶² that is made available for research purposes. More precisely, 7500 cell lines and about 17000 samples are stored in the laboratory. CDC is also leading many other research initiatives entailing the collection of biological samples, including the National Birth Defect Prevention Study. It also serves as a reference laboratory and thus collects various biological samples, cells, bacteria and other biological agents.

Marshfield Clinic Personalized Medicine Research Project is a new ambitious longitudinal research initiative. This is a 20-year project that hopes to recruit 40 000 participants. Started in 2002, the project has so far collected over 18 000 samples. Nothing seems to preclude International collaboration with the Marshfield Clinic project. The resource has already been used for Alzheimer and glaucoma research projects.

Physicians’ Health Study II of the Brigham and Women’s Hospital is the second phase of a study that started in 1981. This NIH funded research is aimed at testing the effect of supplements in the primary prevention of cardiovascular disease, cancer, and age-related eye disease--vitamin E, vitamin C, and a multivitamin. The physicians were asked to provide blood samples for research. Seventy-six percent (76%) of the participants accepted and thus the sample size is around 12 000 samples. This project indicated its interest for international collaboration. As it is increasingly the case with repositories, researchers who use the resource are required to return data back to the resources once the research is completed.

In 2000, the US Congress authorized the planning and implementation of the **National Children Study**¹⁶³. This study is a coordinated effort between the National Institute of Child Health and Human Development and the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, and the Environmental Protection Agency. This study will ‘*examine the effects of environmental influences on the health and development of more than 100 000 children across the United States, following them from before birth until age 21*’¹⁶⁴. Children will be followed throughout the different stages of their development and growth, with in-person visits with the research team and questionnaires. Collection of samples began in January 2009.

¹⁶¹ <http://www.cdc.gov/genomics/activities/ogdp/2003/chap01.htm>

¹⁶² http://www.cdc.gov/nceh/dls/dna_bank.htm: 17 000 specimen and 7500 cell lines

¹⁶³ Children’s Health Act of 2000 (Public Law 106-310 Sec. 1004

¹⁶⁴ <http://nationalchildrensstudy.gov/>

The Department of Veterans' Affairs announced in March 2006 the launch of a Genomic Medicine Program that could lead to the creation of large-scale research program¹⁶⁵. The NIH is also considering creating a large scale project. A compelling case for such a large-scale population project was made by Francis Collins in *Nature* in 2004¹⁶⁶.

The **GAIN** (Genetic Association Information Network)¹⁶⁷ is an NIH initiative aimed at providing research resources for the scientific community. On March 15, 2006, this public-private partnership invited investigators at Universities and research centers world-wide to submit applications to have existing disease-specific samples from case-control (or similar) studies genotyped at no cost¹⁶⁸. In exchange, the data will be made available to the research community in general. In 2008 the Genetic Association Information Network (GAIN) completed its work, posting genotypes and phenotypes from the 18,000 samples it mapped to a National Library of Medicine database (dbGaP) that was also funded by the program.

Tissue Bank/Blood Bank Resources

- ⇒ Angioma Alliance
- ⇒ AIDS and Cancer Specimen Resource (ACSR) -NCI
- ⇒ Division of the Acquired Immunodeficiency Syndrome (DAIDS), Specimen repositories
- ⇒ **Coriell Institute for Medical Research (NIH)**
- ⇒ National Disease Research Interchange
- ⇒ PathServe Autopsy and Tissue Bank Inc.
- ⇒ SeraCare Life Science Inc. /BBI Biotech
- ⇒ Asterand
- ⇒ US Biomax Inc.
- ⇒ LifeSpan Biosciences
- ⇒ NHLBI Biologic Specimen Repository

The main purpose of some biobank is to offer easy access to tissues as a resource per se. They are centered more around a research infrastructure than a project per se. They specialize in the procurement, preservation and distribution of tissue samples. These banks could be privately funded or supported by national organizations. **Asterand, or PathServe** are good examples of private companies offering these types of services. They all offer a range of human tissue and researchers can order their tissue even through internet¹⁶⁹. Privately funded tissue resources are usually opened for international collaboration.

Other repositories are publicly funded resources for researchers. We have already mentioned various collaborative initiatives earlier in the section on Tissue bank (NCI-

¹⁶⁵News Release, 'VA Forms Committee to Advice on Genomic Medicine' March 16, 2006:

<http://www1.va.gov/opa/pressrel/docs/GenomicMedCmte.doc>

¹⁶⁶ *The Case for a US Prospective Cohort Study of Genes and Environment, Nature* 2004, 429, 475-477.

¹⁶⁷ http://www.fnih.org/GAIN/GAIN_home.shtml

¹⁶⁸ http://www.fnih.org/GAIN/Solicitation_press_release.shtml

¹⁶⁹ See the Arda's online submission process at Harvard University:

<http://www.research.bidmc.harvard.edu/Corelabs/BIGRDetails.asp>

related initiatives). These biobanks resources can serve a single hospital or offer a nation-wide or world-wide service. In addition to be a leading research center, the **Coriell Cell repository** holds the world's largest collection of cell cultures. This NIH funded institution, offers a human genetic cell repository, an Aging cell repository, privately funded diabetes collection and cancer collection. It offers services to private or public institution, in the USA or abroad.

The National Allergy and Infectious disease (NIAID) of the NIH supports multiple repositories for research and reference purposes. DAIDS, a division of the NIAID, supports research initiatives on HIV. Researchers supported by DAIDS are clearly encouraged to establish collaboration and shared the resources with the larger scientific community. The NIAID National Disease Research Interchange offers a catalogue of human cells, tissues and organs for research. Finally, the **AIDS and Cancer Resource** is a multi-site repository source for 'well documented tissue and biological samples serving investigators working in the fields of HIV/AIDS and related cancer, virology, immunology, pathology, epidemiology, tumour biology, assay development, as well as others'¹⁷⁰. ACSR is coordinated at University of California but has collaborators throughout the US and internationally.

Finally, repositories can be constituted by a given disease foundation to support and stimulate research on this specific disease. For instance, the **Angioma Alliance** (a volunteer network created in 2002) recently centralized its tissue and DNA bank to facilitate research in cavernous angiomas.

Regulatory Aspects

The legal framework for biobanking activities is a complex one. In the United States of America, there is no single legislation governing biobank at the Federal level. However, a web of legislations governing research activities, privacy and human tissues form the basis of the regulatory framework. Also, many health-related activities are governed by States legislation: offering a patchwork of different approaches.

Federal Regulation applies to research funded by a federal agency. Title 45 CFR 46: 'Protection of human subjects' regulates all aspects of research with human subjects including IRB review of research and consent process. The NBAC report recommended that anonymized tissue NOT be considered research with human subject and thus be excluded from the application of the legislation. However, all other types of research with human tissues are covered by this legislation. Other articles of the Common rule could apply to human tissue banking depending on the context in which it takes place.

Stem cell research and banking is subject to a specific legislation: United States House of Representatives, Stem Cell Therapeutic and Research Act of 2005¹⁷¹. Also the recent DHHS Health Insurance Portability and Accountability Act of 1996 (and regulation: 45 CFR Parts 160, 162, and 164) have brought profound changes to the research activities (including biobanking). In contrast, there are quite a significant number of guidelines for biobanks and repositories. For Instance, the International Society for Biological and Environmental Repositories (ISBER), a United States-based international organization

¹⁷⁰<http://acsr.ucsf.edu/aboutUs.aspx>

¹⁷¹H.R. 2520, 109th Congress, 1st Session, December 20, 2005

has recently adopted: *Best Practices for Repositories I: Collection, Storage, and Retrieval of Human Biological Materials for Research*¹⁷². This document covers all aspects from record management, facility, quality assurance, and safety.

In view of a certain lack of clear legislative guidance in the field, various professional organizations have sought to offer guidance to their members with respect to research with human tissue and banking activities. For example, the College of American Pathologists also have a policy on the use of human tissue,¹⁷³ and is almost entirely dedicated to research with human tissue. The American College of Medical Genetics adopted guidance on the storage of human tissues some time ago¹⁷⁴. More recently (2002), the American Medical Association adopted a policy on the Safeguards in the Use of DNA Databanks in Genomic Research¹⁷⁵. Private corporation in the field of banking have also adopted code of ethics (for instance Arda's Code of ethics). Over the course of the HapMap project, Coriell has adopted its own policy for the Responsible Collection, Storage, and Research Use of Samples from Named Populations for the NIGMS Human Genetic Cell Repository¹⁷⁶.

Finally, the Office of Human Research Protections (OHRP) has adopted a '*Guidance on Research Involving Coded Private Information or Biological Specimens*'¹⁷⁷. This document clarifies the application of the federal code of regulation and reiterates the application of principles elaborated in the 1997 *Guidance Repositories, Tissues Storage Activities and Data Banks*.

Privacy / Data Protection

The Health Insurance Portability and Accountability Act (1996)¹⁷⁸ and the *Standards for Privacy of Individually Identifiable Health Information* (designated as the 'Privacy Rule')¹⁷⁹ govern the protection of individually identifiable health information that is held or maintained by an entity designated in the legislation. The Privacy Rule generally requires authorization from the person to use their protected health information for research purposes. However, the Privacy Rule provides for some exceptions.

Privacy Act of 1974 applies to certain personally identifiable information held by federal agencies in a "system of records" and thus applies to any research record held by HHS. Under this law, an agency must provide an individual access to his or her record. Still the legal situation in the USA is influenced by the federal system. Important privacy regulations differ from state to state.

Ethics Discussion

¹⁷² CELL PRESERVATION TECHNOLOGY, Volume 3, Number 1, 2005
<http://www.isber.org/Pubs/BestPractices.pdf>

¹⁷³ College of American Pathologists, Use of Human Tissue, August 1996,
http://cap.medical.org/Ethical_Use_of_Human_Tissues_guideline.pdf

¹⁷⁴ Statement on Storage and Use of Genetic Materials, 1995, <http://genetics.faseb.org/genetics/acmg/pol-17.htm>

¹⁷⁵ American Medical Association (AMA), E-2.079 Safeguards in the Use of DNA Databanks in Genomic Research, Chicago, June 2002, <http://www.ama-assn.org/ama/pub/category/print/11989.html>

¹⁷⁶ <http://ccr.coriell.org/nigms/comm/submit/collpolicy.html>

¹⁷⁷ Department of Health and Human Services (DHHS) - Office for Human Research Protections (OHRP), Guidance on Research Involving Coded Private Information or Biological Specimens, Rockville, August 8 2004

¹⁷⁸ Public Law 104-91, August 21, 1996

¹⁷⁹ 45 CFR Part 160 and Subparts A and E of Part 164

In 1999, the National Bioethics Advisory Commission of the United States of America published a report on *Research Involving Human Biological Material: Ethical Issues and Policy Guidance*¹⁸⁰. This report examines quite extensively the situation with respect to biobanking in the United States, including the RAND report, which is a comprehensive mapping of biobanks in the United States. It also offers 23 recommendations on ethical issues and policy guidance with respect to biobanking activities.

Given that many actors have showed expressed their interest, the question of the creation of a large-scale population-based project is being debated in the United States. Investments have already been committed to develop the National Children Study. However, there are discussions about the need for other large scale project(s), and debates about the format such a project should take and how ELSI issues could be appropriately addressed before a final decision is made. Hearings in front of the *Secretariat Advisory Committee on Genetic Health and Society* suggested different avenues for such a large scale project¹⁸¹. Representatives from the CDC, Department of Veteran's Affairs, NHGRI, P³G and National Institute of Child Health and Human Development suggested were among the organization who testified. The *Draft Report on Policy Issues Associated with Undertaking a Large US Population Cohort Project on Genes, Environment and Disease*¹⁸², is currently available for comments. ELSI questions such as public engagement and legal framework for such projects are being examined.

2.2.5.2 Canada

Tissue collection

- ⇒ Procure Cancer
- ⇒ **Cancer Research Network of the FRSQ/ Réseau de recherche sur le cancer (FRSQ)**
- ⇒ Alberta Research Tumor Bank
- ⇒ British Columbia Cancer Agency Tumour Tissue Repository
- ⇒ Manitoba Breast Tumor Bank
- ⇒ **Ontario Cancer Research Network**
- ⇒ Children's Oncology Group
- ⇒ **Tissue Bank of the Respiratory Health Network of the FRSQ**
- ⇒ The Brain Tumour Tissue Bank
- ⇒ **Douglas Hospital Brain Bank**
- ⇒ LIFE Banc/Arthur and Sonia Labatt BTRC
- ⇒ **Capital Health/Regional Tissue Bank**

Pathologists in all hospitals and health Institutions are collecting human tissues for clinical diagnostic purposes. The Canadian Association of Pathologists (CAP)

¹⁸⁰It should be mentioned that all the legislative research was made possible through the help of the HUMGEN research tool. NBAC Report, Rockville, Maryland, August 1999, http://www.bioethics.gov/reports/past_commissions/nbac_biological1.pdf

¹⁸¹<http://www4.od.nih.gov/oba/SACGHS/meetings/Feb2005/SACGHSFeb2005postmeeting.htm>, March 1st, 2005.

¹⁸²http://www4.od.nih.gov/oba/SACGHS/public_comments.htm

recommends various periods of retention for validation (up to 20 years)¹⁸³. However, their use for research purpose requires a proper consent.

Cancer registries are present in all provinces and regulated provincially. Some provinces created not only registries but also tumour banks (with consent). For instance, the **Ontario Cancer Research Network** coordinates the collection, storage, analysis, annotation, and distribution of tumour and blood samples obtained from hospitals across Ontario¹⁸⁴. In Quebec, the **Cancer Research Network of the FRSQ** can count on 4 major health institutions in the province to collect tumour and blood for research purposes. Recently, **Alberta** has set up a centralized tumour and blood bank available for research¹⁸⁵. All these organizations are open for collaboration. These initiatives offer many scientific advantages including fair and equitable access to high quality and well annotated tissue samples.

To coordinate and pool resources procurement for research throughout Canada, the **Canadian Tumour Repository Network (CTRnet)** was formed in 2004 with the financial assistance of the Canadian Institutes of Health Research (CIHR) under the direction of the Canadian Association of Provincial Cancer Agencies (CAPCA). Through this innovative network, tissues are collected and kept under the authority of their local institutions. Decisions to share tissues rest solely with such institution. Through this alliance, researchers have access to more than 7000 samples¹⁸⁶.

‘CTRNet operates as a not-for-profit consortium of leading provincial tumour banks and programs that furthers Canadian health research. CTRNet provides interested researchers with a streamlined process to obtain quality human tissue and human tissue products from member tumour banks.’¹⁸⁷

In other fields of research, similar efforts are being put into place to pool locally collected research material together. At a provincial scale, other networks are being organized to link local biobanks for research purposes. For instance, a virtual network, the **Tissue Bank of the Respiratory Health Network of the FRSQ**, facilitates the procurement of tissue for research in respiratory diseases. This virtual bank stores the sample information on a central server, while the samples are preserved in each respective centre. **ProCURE** is a not-for-profit organization whose mission is to fund and structure over time a bank of biological materials and data on men with prostate cancer as well as those at risk of developing the disease. This Alliance is currently under development. Once fully operational it will collect prostate tissue and blood from patients in four hospitals across the province of Quebec. This project is also funded by the FRSQ.

Any tissues collected for clinical diagnosis or following surgery can potentially be used for research (with appropriate consent). Tissues can also be collected post mortem, for research purposes. The **Brain Tumour Tissue Bank of London Ontario** collects

¹⁸³The Retention and Use of Human Biologic Material (2005). http://cap.medical.org/guide_retention-human-biologic-material.htm

¹⁸⁴<http://www.ontariotumourbank.ca/public/about.jsp>

¹⁸⁵http://www.cancerboard.ab.ca/pdf/media_desk/05-09-19_tumour_bank.pdf

¹⁸⁶ Press release: Le Québec participe à la création d'un nouvel outil de recherche dans la lutte contre le cancer à l'échelle canadienne, March 15 2006 ; <https://fqc.qc.ca/infopro2.asp?id=755>

¹⁸⁷ <https://www.ctrnet.ca/index.php?pid=11000>

leftovers from pathology analysis in local hospitals (with appropriate consent). The **Douglas Brain Bank** actively recruit post-mortem brain donor for research purposes¹⁸⁸.

Blood Specimens and DNA Research Banks

- ⇒ Canadian Study on Health and Aging
- ⇒ Genizon BioSciences
- ⇒ Interheart
- ⇒ Healthy Aging Study

The Canadian Institute of Health Research, Genome Canada, provincial public funding agencies and private funds support many biobanks created in the specific context of research projects. These biobanks vary in size from the traditional small individual research purpose to longitudinal large scale repositories, and are kept in hospitals, university research centers and various health institutions. There is no formal and centralized registration process for biobanks created for research purposes. Thus, it is difficult to assess the number of such banks. Also, not all biobanks created in the context of a research project can be used for other research purposes, either because of lack of proper consent or lack of research infrastructure and funding. When multiple research use is possible, the decision to collaborate is at the discretion of the investigator.

Major research centers across Canada hold multiple biobanks created for research purposes. For instance, Michael Smith Genome Science Center runs many of these research projects, including the **Healthy Aging Study** which collects blood from participants 85 years old or older. Another good example is the **InterHeart Study**, a Canadian led research project, which has enrolled 14 000 cases of acute myocardial infarction and 16 000 matched controls from 55 countries. Blood collected during this study was centralized in the Canadian laboratory at McMaster University. Finally, genetic/genomics research is thriving, stimulated by a dedicated funding organization: Genome Canada, and although we could not formally assess the number of DNA banks, we suspect it is quite impressive.

Private pharmaceutical companies also collect tissue and blood samples during clinical trials. However, the existence and size of these biobanks are difficult to track. It is perhaps seen as commercial privileged information. **Genizon Bioscience** is a private corporation leading various types of research in the field of genomics¹⁸⁹. Their website indicates the creation of a biobank for research purposes which is maintained by the company.

Longitudinal studies are of increasing interest in the context of human genome research. The **Canadian Study on Health and Aging** is one of the important population-based studies performed in Canada. The data collection is now ended and blood samples have been collected for more than 9 000 participants of 65 years of age and more. Regular follow-ups of the participants have been completed between 1991 and 2001. The Public Health Agency of Canada has built and maintains a level 4 security laboratory in Winnipeg, responsible for identification, control and prevention of infectious disease. This facility serves as a reference center for infectious disease and various research

¹⁸⁸ <http://www.douglasrecherche.qc.ca/brainBank/about.asp>

¹⁸⁹ <http://www.genizon.com/html/content.asp?node=22>

projects are on Genetic, bacteriology or virology. The genetic laboratory has a capacity of 250 000 samples. The samples of the third phase of the longitudinal study of risk factors for dementia in elderly Canadians (Canadian Study of Health and Aging)¹⁹⁰ are currently stored there.

The Canadian Institute of Health Research has recently launched a **Canadian Longitudinal Study on Aging (CLSA)**. This study would follow 50 000 men and women 40 years and older for 20 years and collect blood from every participants.¹⁹¹ CLSA will collect information on the changing biological, medical, psychological, social, and economic aspects of their lives. These factors will be studied in order to understand how they have an impact on aging. The recruitment of the first 20,000 participants in collaboration with Statistics Canada began in January 2009.

A few important population-based studies are emerging in Canada and are creating research infrastructures open to multiple future research uses. Statistics Canada, Canada's central statistical agency, is responsible for the national census. It is currently planning the realization of a study including extensive physiological measures and biological sampling among a random sample of 5 000 Canadians. **Canadian Health Measurement Survey** involves Canadians from 6 to 79 years old¹⁹². The survey includes two phases: an interview at the household to administer questionnaires about health and lifestyle, and a visit to a nearby health clinic to collect blood and urine samples and to perform various physical measurements. A pilot survey took place in Calgary in 2004. The full collection began in spring 2007.

The **CARTaGENE** project targets the recruitment and follow-up of 1% of the Quebec province population aged between 24 and 75 (50 000 participants). All participants will be asked to provide a blood samples for DNA research and basic clinical analysis. Health, lifestyle and genealogical information will also be collected. The blood and DNA samples will be kept for future researches¹⁹³. The recruitment of participants began in 2008.¹⁹⁴

Genome Canada is the primary funding and information resource relating to genomics and proteomics in Canada. Together with the 5 genome centers across Canada, Genome Canada funds and manages large-scale projects and platforms. For instance, multiple research platforms are funded through Genome Canada and its centers such as the Genome Quebec and McGill University Innovation Center who played a key role in the HapMap project. Genome Canada recently funded another population-based initiative in the Atlantic Region: the Atlantic Medical Genomic and Genetic Initiative, but this project is only in very early stages of preparation.

Regulatory Aspects

There is no specific legislation governing biobanking activities specifically. However, recently, the Federal Government adopted the *Assisted Human Reproduction Act* (2004, c. 2) which governs the collection and research with reproductive material.

¹⁹⁰ http://www.nlm-lnm.ca/english/hostgenResearch_e.htm

¹⁹¹ <http://www.cihr-irsc.gc.ca/e/22982.html>

¹⁹² <http://www.statcan.gc.ca/pub/82-003-s/2007000/article/10363-eng.pdf>

¹⁹³ www.cartagene.qc.ca

¹⁹⁴ http://www.cartagene.qc.ca/images/stories/pdf_en/pressrelease-06-01-2008.pdf

The 3 major Canadian Funding Agencies, the Canadian Institutes of Health Research (formerly, the Medical Research Council of Canada), the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada, have adopted a common guidance document for research with human subjects and human tissues: the Tri-Council Policy Statement — Ethical Conduct for Research Involving Humans.¹⁹⁵ All federally funded research as well as the institutions that hope to receive Federal funds must be in compliance with the principle therein described. Section 10 of this document is about human tissue collection. It stresses the importance of a free and informed consent process as well as respect for privacy in any biobanking activity.

Health is a matter of provincial competence. Provinces have specific and different legislations on many aspects of health activities but there is no specific legislation on biobanking activities for research purposes *per se*. However, there are multiple guidelines that can be applied. For instance, in the province of Quebec, the main research funding agency has adopted guidelines on research with human subjects and human tissues¹⁹⁶.

Privacy / Data Protection

The *Personal Information Protection and Electronic Documents Act* (PIPEDA) was adopted in 2000¹⁹⁷ but came into full effect in 2004. The legislation set rule for how the private sector organizations may collect, use or disclose personal information in the course of commercial activities. The law gives individuals the right to access and request correction of the personal information these organizations may have collected about them. It also governs the protection of personal information and exchange or disclosure outside a province. It should be mentioned that provinces that have enacted equivalent legislation will not be subject to PIPEDA (Quebec, Alberta, British Columbia). Health legislations and other privacy legislations have been adopted at the level of provinces.

The *Privacy Act* took effect on July 1, 1983. This Act imposes obligations on federal government departments and agencies to respect privacy rights by limiting the collection, use and disclosure of personal information. The *Privacy Act* gives individuals the right to access and request correction of personal information about themselves held by these federal government organizations.

Ethics Discussion

The CARTaGENE project, in preparation for several years, stimulated public debate about population-based biological resources. Over the course of the preparation phase, CARTaGENE initiated various activities of public consultation and public information and discussion. The reports are available on their website.

Ethics is developed on a decentralized model in Canada. There is no national bioethics committee. The Province of Quebec, *Commission on Ethics, Science and Technology*,

¹⁹⁵Interagency Advisory Panel on Research Ethics (PRE): 1998 (with 2000, 2002, 2005 amendments), Ottawa, October 2005. http://www.pre.ethics.gc.ca/english/pdf/TCPS%20October%202005_E.pdf

¹⁹⁶FRSQ, Guide d'éthique de la recherche et d'intégrité scientifique, 2003.

<http://www.frsq.gouv.qc.ca/en/ethique/ethique.shtml>

¹⁹⁷PIPEDA, 2000, c. 5

published a position paper in 2003 about Genetic DNA databases.¹⁹⁸ The *Canadian Biotechnology Advisory Committee*, who provides expert advice on ELSI to the Federal Government, commissioned several research papers on biobanks and population-based research in 2003¹⁹⁹. The *Interagency Advisory Panel on Research Ethics* is a body of experts to ensure the evolution of the ethics policy statement of the funding agencies (Tri-Council Policy Statement). Although the Interagency did not publish a position paper on this topic, it is part of the mandate of the group. Finally, Canadian Biotechnology Secretariat of Industry Canada (Government of Canada) has funded several survey of public opinion research into biotechnology issues. The 2005: 'A Canada - US Public Opinion Research Study on Emerging Technologies - Report of Findings' provides a picture of Canadian opinion on several issues including gene bank²⁰⁰.

It should also be mentioned that Canada hosts several internationally recognized research center on ELSI. The vitality of academic discussion about population-based biobanks has stimulated several academic published papers and forums of discussion.

2.2.5.3 Asia

The geographical area of Asia is wide and the organizational structure for research is not easy to map. More importantly, given that one key component of the methodology for this research was desk research and internet contact, the language barrier proved to be a real challenge. Even once a biobank was identified; trying to find contact information proved to be difficult. Some websites are translated (or partially translated) in English, but not all.

Even direct communication was complicated by the time zones (phone calls had to be made late in the evening or night time, Montreal time). All these elements constituted a challenge for this survey, but they assuredly could also constitute a challenge for plans towards collaboration.

For this part of the survey we kept the research at the first level (large biobanks) or key components of the biobanking network.

Many countries in Asia have launched or are about to launch ambitious population biobanks. In fact, some of the biggest projects (in terms of number of samples) can be found in Asia.

However, there are important ELSI challenges that must be examined taking into account the different cultural context than the European or North American approaches.

JAPAN

- ⇒ **Health Science Research Resources Bank/Japan Health Science Foundation**
- ⇒ Biobank Japan - Riken Institute
- ⇒ Japanese collection of research bioresources (JCRB Genebank)
- ⇒ Japan National Cancer Center

¹⁹⁸Commission d'Éthique du Québec, *Les enjeux éthiques des banques d'information génétique: pour un encadrement démocratique et responsable* (2003). <http://www.ethique.gouv.qc.ca/eng/publications.html>

¹⁹⁹http://cbac-cccb.ca/epic/internet/incbac-cccb.nsf/en/h_ah00128e.html. See CBAC (2004), Protecting Privacy in the Age of Genetic Information, ; CBAC (2005) Human Genetic Materials: Making Canada's Intellectual Property Regime Work for the Health of Canadians .

²⁰⁰<http://www.biostrategy.gc.ca/english/View.asp?pmiid=720&x=721>

Biobanking activity

⇒ Brain Bank Project

SINGAPORE

⇒ National University of Singapore Tissue Repository

⇒ Singapore Consortium of Cohort Studies

⇒ ES Cell International Inc.

⇒ **Singapore Tissue Network**

CHINA

⇒ Kadoorie Study of Chronic Disease in China (KSCDC)

KOREA

⇒ MizMedi Women Hospital Research Center

⇒ Biobank for Health Sciences

TAIWAN

⇒ Taiwan Biobank

Japan

Japan has currently many large-scale biobanking initiatives. This dynamic development is the result of a planned and concerted effort, deployed by the Japanese Government to stimulate the growth of the biotechnology industry. In 1999, the Government announced massive investments in various sectors of activities including the biotechnology to stimulate the economy²⁰¹. Sixty-four (64) Billion ¥ were allocated to genome analysis and various research projects.

One of the most ambitious projects is ‘**Biobank Japan Project on the Implementation of Personalized Medicine**’ which aims to create a large-scale DNA repository, with blood samples from some 300,000 individuals linked to a database containing clinical information [17]. This initiative started in 2003 and is funded by the Government’s Ministry of Education, Culture, Sports, Science and Technology. It is a collaborative effort from the Human Genome Center, the Institute of Medical Sciences (Tokyo University)-IMST- and the Japan Science and Technology Agency (JST). The project is collecting samples from 66 hospital centers across Japan. In 2005, 150 000 DNA samples and clinical data had been collected²⁰². The team is led by Dr. Nakamura of RIKEN (the Institute of Physical and Chemical Research). It is not clear whether this biobank is opened for international collaboration.

In addition to high-profile Japan Biobank, it is estimated that there are large numbers of State sponsored bioinformatics and biobank projects in an estimated 40-50 research institutions²⁰³. However, as noted in a report to the UK Parliament Select Committee on Science and Technology, these ‘private collection’ tend not to distribute their samples beyond their groups or institutes²⁰⁴. An example is the Bio-sample bank set up in 2002 by the Clinical Laboratory Division of the **National Cancer Center**. This

²⁰¹ National Science Foundation, ‘The Government of Japan Special Millenium Project Budgetary Framework’ Jan. 26, 2000 Tokyo Regional Office, <http://www.nsftokyo.org/rm00-03.html>

²⁰² Press Release: RIKEN and Perlegen Begin Collaboration to Conduct High-Resolution, Whole Genome Studies of up to 47 Common Diseases

http://www.perlegen.com/newsroom/pr/2005/2005_07_21_Riken_Press_Release.pdf

²⁰³ Gerard Porter, ‘Regulation of Human Genetic Databases in Japan’ Report prepared for the AHRB research Center for Studies in Intellectual Property and Technology Law, Sept. 2004, p. 497.

²⁰⁴ C. Stuart, ‘Human Genetic Databases in Japan’ Memorandum by the Science and Technology Section of the British Embassy, Tokyo, tabled UK Parliament Select Committee on Science and Technology (2000)

resource is aimed at in-house doctors and researchers from the Research Institution of NCC (as mentioned in their annual report)²⁰⁵.

Providing appropriate material for research is a concern that is addressed by a web of organizations supported by the Government. The **Japanese Collection of Research Bioresources** (JCRB) is an example of such biorepository. In 2005 the JCRB, created under the auspices of the National Institute of Infectious Diseases was transferred under the responsibility of National Institute of Biomedical Innovation (NiBio), Osaka, Japan. JCRB collects samples from a number of cell and gene banks. However, the distribution of the material to researchers is entrusted to a public research resource bank: the **Human Science Research Resource Bank (HSRRB)**. The HSRRB was created in 1995 and is managed by the Japan Health Sciences Foundation, and funded by the Ministry of Health and Welfare. Genes and cells are made available to researchers both locally and internationally. The use of the samples is subject to strict ELSI conditions and procedures established by HSRRB.

Singapore

The biomedical science industry has been identified as one of the four pillars of Singapore's economy and it is thriving.

In 2002, the Singapore Bioethics Advisory Committee prepared a report on Tissue Banking for Research. According to the report, a significant portion of tissue bank consists of tissues taken for clinical purposes and held in hospitals, health institutions or even doctors' offices. The SBAC took the position that tissue collected by private individual should not be encouraged and that biobanks should be held by institutions (whether private or public) and be subject to statutory supervision and appropriate governance. This translated into the implementation of a well coordinated system for tissues supply for research.

National initiatives for coordinated tissue collection began with the establishment of the Singapore Tissue Network (STN) in 2002. The Singapore Tissue Network is a not-for-profit organization housed at Biopolis, the nation's biomedical hub established by the Agency for Science and Technology and Research (A*Star), which also funds the project.

The Singapore Tissue Network is a nation-wide network repository for clinicians in Singapore to archive tissue, sera, and DNA, RNA and other derivative products of both normal and disease origins for research purposes.

'These samples collected by the Singapore Tissue Network under strict informed consent and confidentiality ethical processes, will be used by public research efforts to further the advance of the medical sciences while ensuring strictest standards for maintaining donors' privacy.'

Such coordinated program offers multiples advantages including: ensuring standardized ethics procedures, proper funding for biobank resource, and equitable distribution of

²⁰⁵ See 2003 annual report of the NCC Clinical Laboratory Division: www.ncc.go.jp/en/ncc/annrep/2003/clin.pdf

Biobanking activity

high quality tissues available. On the topic of collaboration, one of the benefits underscored by the organization is:

‘Active participation between clinicians and researchers will promote multi-center research collaborations and serves as a nucleating force for attracting overseas collaborations from academia and industries R&D.’

One example of collaboration is the STN’s collaboration with the National University of Singapore/National University Hospital Tissue Repository which is a hospital-based central collection system aimed at collected tissue leftover from surgical procedure and assures a coordinated and high quality supply of tissue for researchers. This tissue repository is the result of collaboration between three departments: the NUH Office of Biomedical Research (OBR), the NUH/NUS Department of Pathology and the NUS Office of Life Sciences. Funding comes from NUH and NUS, as well as the Singapore Cancer Syndi-cate. The tissues are intended for researchers of the NUH/NUS Center.

Another example is STN’s collaboration with the Singapore Consortium of Cohort Studies. In 2005, the A*Star Institute has proposed 4 research consortium to pool and focus the re-search efforts and resources. One of these consortiums is the ‘Singapore Consortium of Cohort Studies’. This project consists of a prospective cohort of 10 000 diabetic patients and an amalgamated cohort of 12 000 participants.

Stem Cell research is also very active in Singapore. Funded by A*STAR, The Singapore Stem Cell Consortium (SSCC) will serve as the primary coordinating body for stem cell-related research activities in Singapore with the aim to build strong linkages between basic science and clinical research groups.

Activities

The SSCC plans to focus its efforts in three areas:

- R&D: Basic stem cell biology research will encompass the characterization, validation, differentiation and expansion of stem cells. Translational & clinical research will include the derivation of clinically-compliant stem cell lines, the differentiation and modulation of stem cells into various tissue types, and the development of cell-based therapies.
- Resources & Infrastructure: Two examples include a cell processing facility to produce cGMP-grade cells, and an SSCC core lab that will focus on the derivation, characterization and expansion of stem cell lines.
- Training and Education: The SSCC plans to increase the pool of local stem cell scientists by organizing training courses and workshops, as well as stem cell-related conferences and journal clubs. Public education will also be an important function of the SSCC, to improve public knowledge and understanding of stem cell research.

China

In China we were able to identify 1 major biobank: the **Kadoorie Study of Chronic Disease in China (KSCDC)**. KSCDC is a collaborative project between the Clinical Trial Service Unit of Oxford University and the Chinese National Centre for Disease

Control. The project is funded by the Kadoorie Charitable Foundation in Hong Kong and is aimed at collecting blood samples and various lifestyle and medical data from 500 000 adults from 10 geographic areas of China²⁰⁶. However, we anticipate this is just the tip of the Iceberg. There are important research centers, in Beijing, Shanghai (National Human Gene Research Center, Shanghai) and in Hong Kong, but unfortunately, we had difficulty finding the appropriate information.

Taiwan

Taiwan has launched the '**Taiwan Biobank**' initiative. So far, the leading group from Academia Sinica has collected 3 000 samples. Funding announcement by the highest authority in the Government, on April 2005 (15 million NT), confirmed the expansion of the pilot study into a large-scale DNA bank²⁰⁷. The group plans to collect blood plasma samples and genetic information from 200 000 participants between the ages of 40 and 60²⁰⁸. However, apparently, the Taiwan Biobank raises criticisms in the literature for lack of transparency and public consultation.

So far, a Feasibility Study has been concluded²⁰⁹. It is expected that an on-going pilot research plan will provide a solid foundation for its biobank development [18]

South Korea

In South Korea, we found a biobank resource under the responsibility of the **Korea Center for Disease Control and Prevention**: *'The BioBank for Health Sciences preserves biological resources including cells, sera, plasma, urine, tissues, DNA, lymphocytes, peripheral blood as well as BAC clones of human and microorganisms that have been collected by various national projects such as the Korean Health and Genome Study (KoHGES), the National Survey of Health and Nutrition, and Genome Research Centers for 12 disease groups'*²¹⁰. Our research indicates this biobank is of an important size, but we were unable to confirm the number of tissue collected.

Stem Cell research in South Korea caught the media attention in unfortunate circumstances recently. However, South Korea remains a key player in the field of stem cell research. In fact, there are 3 institutions from Korea that can provide cell lines for research eligible for Federal funding in the United States²¹¹. These include the **Miz-Medi Women Hospital** which is amongst the Stem Cell banks. This center provides human embryonic stem (hES) cells to researchers in academic and industrial science all around the world.

²⁰⁶ <http://www.ctsu.ox.ac.uk/~kadoorie/public/>

²⁰⁷ Chiu Yu Tzu, 'Biomedical project aims to establish a top research center' Taipei Time, April 7, 2005. <http://www.taipeitimes.com/News/taiwan/archives/2005/04/07/2003249445>

²⁰⁸ Basic information for the project can be found on the official Taiwan Biobank website but no translation is available in English: <http://www.ibms.sinica.edu.tw/biobank/biobank.htm>. Through secondary sources we were able to collect basic information. Chou Kuei-Tien, 'Risk Governance of Biobank' August 8th 2005 power point presentation. Liu Ching-Yi, 'Explain database plan to the public', Taipei Time, Jan. 11, 2006. <http://www.taipeitimes.com/News/editorials/archives/2006/01/11/2003288507>

²⁰⁹ www.twbiobank.org.tw/nsc/

²¹⁰ <http://www.cdc.go.kr/webcdc/english/en09/dbhs.jsp>

²¹¹ <http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp>

2.2.5.4 Other Large Scale Biobanks Initiatives

- ⇒ Howard's Genomic Research in the African Diaspora (GRAD)
- ⇒ The Western Australian Genome Health Project (WAGHP)
- ⇒ Melbourne Collaborative Cohort Study (HEALTH 2000)
- ⇒ Indian Genome Variation Consortium
- ⇒ Prospective blood-based study of 200,000 individuals in Mexico
- ⇒ Genomic variability and haplotype map of the Mexican population
- ⇒ **National Laboratory for the Genetics of Israeli Populations (NLGIP)**

There is an international enthusiasm towards the creation of large-scale biobanks. We have surveyed a few selected large-scale biobanks from other countries outside EU and not covered so far in this report²¹². All these large scale initiatives are more repositories for multiple research uses than research projects per se. Large scale biobanking initiatives are underway in several countries (Australia, India, New Zealand, Mexico, etc.), including blood and tissues banking for research as well as non-research purposes.

In developing countries some projects are present, like the African Center for health and population, and often focus investigation of HIV or infectious diseases. However, major population-based or cases-controls studies including blood banking for genetic research are more rare, possibly due to scarce resources.

The **National Laboratory for the Genetics of Israeli Populations (NLGIP)** is a population-based biobank in Tel Aviv University that is collecting over 4000 samples. DNA and cell lines are being collected for future uses. This biobank is opened for international collaboration. The fact that the tissues are collected with a blanket consent certainly makes such collaboration more easy, which tends to be the case in most of the population based project (unless prohibited by law).

GRAD study is hosted at the Howard University. Researchers plans to gather blood samples or cheek swabs from 25,000 African-Americans to create the Genomic Research in the African Diaspora (GRAD) Biobank, the largest repository of DNA from Blacks.

World-wide, the **Western Australian Genetic Health Project (WAGHP)** of the Western Australia Institute for Medical Research is probably one of the most ambitious population-based initiatives. Efforts to build this project started in 2004 and it targets the recruitment of 2 000 000 participants.

The **Indian Genome Variation Consortium**, initiated in 2003 [19] aims to provide data on validated SNPs and repeats, both novel and reported, along with gene duplications, in over a thousand genes, in 15,000 individuals drawn from Indian subpopulations. DNA will be collected following the Indian Council of Medical Research Guidelines²¹³.

²¹² In addition to the ESTO Questionnaire, we referred to the P3G Observatory as a source of information for this section.

²¹³ Ethical Guidelines for Biomedical Research on Human Subjects (2000), <http://icmr.nic.in/ethical.pdf>

In South America, Mexico has just created an important pole of genomic research with the Institute of Genomic Medicine of Mexico (INMGEM). The Center is currently conducting a Genomic Mapping of the populations of Mexico. Mexico has been the place for previous large scale projects such as the prospective blood-based study of 200 000 individuals in **Mexico** (1999-2001). However, this biobank is kept with CTSU of Oxford University. Several of those projects could be open to potential collaboration. However, collaboration will be limited by the difficulty to harmonize the data collected through various tools, study designs and cultural contexts.

To achieve such harmonization and create opportunities for future collaboration, the P³G Consortium²¹⁴, a not-for-profit organization, is committed to facilitate the sharing of expertise and catalyze efforts to develop research strategies and tools for a meaningful collaboration between biobanks and population projects. Many population-based projects around the world are active members of P³G. P³G also disseminates this knowledge in the public domain so as to support the international scientific community in improving the health of populations through its web-based Observatory.

Regulatory aspects

In Asia, some countries have a different perspective on some ELSI questions, including the consent process, than the traditional, more individual centered perspective prevalent in North America and Europe. The discussions level varies from one country to another, and from an external point of view, the governance of human research seems uneven from one country to another.

Singapore and Japan have deployed extensive efforts towards the development of an ELSI framework for biomedical research. The 'Human Tissue Research Report' of the Bioethics Advisory Committee (Appointed in 2000 by the Government) is extremely useful to map the current legal and ethical landscape in Singapore²¹⁵. In fact, the committee concluded that there was very little guidance on tissue banking activity outside of the Human Organ Transplant Act. However, the report offers general guidance on the conduct of biobanking activities.

In Japan, two sets of guidelines have been adopted to offer a timely framework for the current increase in biobanks and biomedical research activities. The 'Fundamental Principles of Research on the Human Genome'²¹⁶ (2000) proposed by the Bioethics Committee of the Council for Science and Technology is Japan and the 'Ethical Guidelines for Analytical Research on the Human Genome/Genes'²¹⁷ (2001) Issued by the Japanese Ministry of Health, Labour and Welfare, the Ministry of Education, Culture, Sports and Technology and the Ministry of Economy, Trade and Industry. Both documents stress the importance of privacy and informed consent.

In South Korea, the Government adopted the 'Bioethics and Biosafety Act' in January 2005²¹⁸. This legislation covers many aspects of biomedical research, including

²¹⁴ www.p3gconsortium.org

²¹⁵ Report of the Singapore Bioethics Advisory Committee, Human Tissue Research, 2002, <http://www.bioethics-singapore.org/resources/reports2.html>

²¹⁶ http://www.mext.go.jp/a_menu/shinkou/shisaku/principles.htm

²¹⁷ <http://zobell.biol.tsukuba.ac.jp/~macer/eghgr.htm>

²¹⁸ <http://www.ruhr-uni-bochum.de/kbe/Bioethics&BiosafetyAct-SouthKorea-v1.0.pdf>

biobanking activities. It creates a National Bioethics Committee and includes principles such as free and informed consent for biomedical research.

Our research did not enable us to find legislation in China or Taiwan. However, this does not mean that bioethics is not the subject of discussion [20]. The only relevant document we could find was prepared by the Ethics Committee of the Chinese National Human Genome Center of Shanghai [21].

Privacy / Data Protection

China has limited protection on Privacy. Article 40 of the Constitution of the People's Republic of China provides for the freedom and privacy of correspondence of citizens of China. However, HongKong has adopted a Personal Data Ordinance (Chapter 486). The implementation of the ordinance is under the authority of a Privacy Commissioner for Personal Data. This legislation is into force since 1996, in response to the EU directive, in order to maintain the free flow of information with countries that have equivalent legislation. Taiwan has adopted the Computer-Processed Personal Data Protection Law, enacted in August 1995²¹⁹. The Act governs the collection and use of personally identifiable information by government agencies and many areas of the private sector. The constitution also provides for a limited right of privacy (similar to the article 40 of the People's Republic of China).

South Korea offers a contrasting legislative picture than the Chinese situation. The privacy is protected both in the Constitution and in privacy legislations. Article 17 of the Constitution clearly states that the 'Privacy of no citizen may be infringed'²²⁰. We found two legislations of relevance: the 1994 *Act on the Protection of Personal Information Managed by Public Agencies* and the 1996 *Act on Disclosure of Information by Public Agencies*.

We could not find privacy legislation in Singapore. However, there are 'satellite' legislations such as the Electronic Transactions Act 1998, which offer some limited protection over personal information.

Japan has adopted the *Law on the Protection of Personal Information* in 2003. The law applies to personal information handling enterprises that constitute databases. It sets rule for the collection, storage and use of personal information. It came in full effect in 2005.²²¹ However, the law only applies to data collectors that store data on 5000 individuals or more.

Ethical Discussion

The creation of population biobank resources are accompanied by ethical discussions:

- Israel's Bioethics Advisory Committee, *Population-Based Large-Scale Collections of DNA Samples and Databases of Genetic Information* (2002)
- Australia Law Reform Commission, *Essentially Yours*, Part E: Human Genetic Databases (2003)

International Regulatory Initiatives

²¹⁹ <http://www.privacyexchange.org/legal/nat/omni/taiwan.html>

²²⁰ Article 17, Constitution of South Korea, http://www.oefre.unibe.ch/law/icl/ks00000_.html

²²¹ For information about the legislation see: <http://www.bakernet.com/ecommerce/japaneseprivacylaw.pdf>

Given the global enthusiasm for population based biobanks and for biorepositories, many international organizations have recently examined questions related to biorepositories or large-scale databases, and issued guidelines or discussion papers:

- Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002);
- World Medical Association (WMA), *Declaration on Ethical Considerations regarding Health Databases* (October 2002);
- Human Genome Organization (HUGO), *Statement on Human Genomic Databases* (December 2002);
- UNESCO – General Conference, *International Declaration on Human Genetic Data*, Geneva (2003);
- World Health Organization (WHO), *Genetic Databases – Assessing the Benefits and the Impact on Human Rights and Patient Rights* (2003).

Currently, other initiatives are underway. WHO is conducting a project called: Human Genetic Database: towards a global ethical framework:

‘With the support of the Geneva International Academic Network (GIAN), the Ethics and Health Unit of the World Health Organization (WHO/DGO/ETH) and the Bioethics Unit of the Medical Faculty of Geneva University (Unité de recherche et d’enseignement en bioéthique) have joined together to study the conditions under which genetic databases can be established, kept, and made use of in an ethically acceptable way.’²²²

The team will be looking into the current scientific literature and conduct interviews. The ultimate goal is to produce draft practice guidelines.

OECD is also working on Human Genetic Research Databases.

‘An expert working group of delegates from the OECD’s Working Party on Biotechnology and the Working Party on Information Security and Privacy has been established to study the challenges raised by the interactions between genomics and informatics. The group will review how well existing privacy and data security rules and practices, including the [OECD Privacy and Security Guidelines](http://www.oecd.org/dataoecd/6/0/2340_en_2649_34537_1911942_1_1_1_1,00.html), might be applied to data from genetic testing. It will also consider the social dimensions raised by the growth in availability and use of individuals’ genomic data.’²²³

It was hoped to complete the research by May 2006 and that a final document would be submitted to OECD members in 2008. Finally in 2009 the OECD Guidelines on Human Biobanks and Genetic Research Databases were finalised and published. A background report on the issues addressed in the guidelines has also been published. Within the guidelines the OECD defines top- and mid-level principles and endorses best practices which are aiming to translate the principles into practice. The document covers also the highly contested areas such as consent, benefit sharing and return of information procedures.

²²² <http://www.who.int/ethics/topics/hgdb/en/>

²²³ http://www.oecd.org/document/6/0,2340,en_2649_34537_1911942_1_1_1_1,00.html

Biobanking activity

OECD is leading another initiative related to biorepositories including cells and material from micro-organism, plant, animal and human: ‘the Global Network of Biological Resources’.

A global BRC would:

‘... Connect national BRCs and provide the framework within which co-ordination, harmonisation and quality assurance could be provided. This would enhance the services provided to the global community by BRCs beyond what the existing international frameworks could achieve.’²²⁴

Global Biological Resource Center Network would help face the challenges of maintaining and exchanging biological resources. According to the OECD website, efforts to establish a Global Biological Resources Network have been endorsed by OECD Science and Technology Ministers.

²²⁴ Biological Resources Centers, Underpinning the Future of Life Science and Biotechnology, OECD, <http://www.oecd.org/dataoecd/55/48/2487422.pdf>

3 BIOBANK NETWORKING IN EUROPE: CHALLENGES AND OPPORTUNITIES

The study has identified several biobanks across Europe and world-wide which range from small disease-based to large population-based collections. Undoubtedly these offer a great resource for research on disease mechanisms and for the development of appropriate therapies and diagnostics. In this context, the sharing of samples and data gains immense significance but also implies a need for better interaction and networking among existing and emerging biobanks.

Several initiatives towards this direction already exist or are currently emerging including EU-funded projects such as BBMRI, PHOEBE and DanuBiobank, and international projects such as P3G which have been discussed in the study. In addition, some of the survey's findings point to the potential opportunities provided by existing biobanks for improved networking at least at the EU level. Firstly, the surveyed biobanks have already a strong tradition of collaboration (over 88% collaborate with at least another group) and the majority of them have been involved in international projects. Moreover, a large number of repositories exist across Europe and some infrastructure (e.g. labs and personnel) is already in place. However, many challenges also exist due to the different biobanking practices on data collection, processing and storage. An additional barrier to harnessing the full benefit of biobanks may be presented by the different legal, regulatory and ethical frameworks that are applied across MS.

This chapter discusses these challenges (as identified by the survey and our desk research) and identifies the options for improving biobank networking. In this context, the prospects for developing a potential European Biobank Networking Platform, the potential for funding of such activities, the insurance of appropriate benefit sharing and public engagement in biobanking activities and the promotion of legal and technical harmonization (samples, data, etc) are also discussed.

3.1 Challenges

3.1.1 Technological challenges

IT infrastructure and bioinformatics: data comparability and standardisation

The collection of various biological samples and associated information is central to biobanking. Bioinformatics and IT have become critical tools in life-sciences research allowing data acquisition, processing, analysis, management and reporting. However, these approaches vary widely in the different biobanks examined. For example, the way one repository collects, processes, and stores its specimens may be very different from that of another repository, which may complicate comparisons of research results obtained using biospecimens from different repositories. The quality and the extent and type of clinical information collected with the specimens also vary from repository to repository. In addition, the type of informed consent obtained from many of the tissue sources of these specimens is not always sufficiently robust to allow the use of these specimens in research that requires long-term follow-up of clinically relevant data. Such

variability is likely impeding comprehensive data analysis, and could potentially pose a greater challenge for data sharing and networking among biobanks.

One of the biobank managers interviewed in the course of this project said:

"One of the main barriers which really hampers large scale multicenter transnational research and sharing of tissues is the lack of freely available safe coupling standard operating procedures or applications of databases with safeguards approved by juridical and IT specialists on privacy issues. It would be ideal to couple data of tissue specimen of population banks with systematic disease banks; so both could access each other's samples if needed. Moreover, including registry data would allow a better view on the donor's history. Also it is crucial for the outcome of experiments to offer means to acquire follow up data and add these data to the sample record in a way that the privacy of the donor is not compromised just by extracting anonymously the data from existing clinical databases, of course only in those cases it is experimentally needed. Furthermore, it is in everybody's interest (patient (donor and patients to come), treating physician, health lawyers and scientists) to find ways to improve the balance between all stakeholders".

Data associated with research samples and donors must be structured in a comparable way. Yet, in today's healthcare environment, the relevant clinical data are rarely in such a form and practices for data collection depend on the mission of the repository. Collections of biospecimens used primarily by basic researchers may only require minimal associated clinical data, such as demographic data and pathology reports. Biospecimens collected for translational research (e.g., target identification or validation) may require more in-depth associated clinical data, such as medical and family histories, treatment, and clinical outcomes data [16]. Inconsistencies of format, depth, and vocabulary are significant challenges even within one single site.-

Comparability of specimens and of the associated clinical and biomedical data should be a key feature on next generation biobanks and will be critical for the development of a European biobank. Specifically, researchers will require the ability to utilize specimens and the associated annotation collected within a multi-site network to build data sets of sufficient statistical power. This creates a need for a collection process management and a quality assurance system. Moreover, the informatics infrastructure for biobanking will have to include standardized software²²⁵.

Standardization of biobanking procedures as well as adherence to these practices by all participating organizations is necessary to ensure the scientific quality of data generated downstream. One of the ways to achieve this is through the establishment of biobanking good laboratory practice (GLP) and good clinical practice (GCP) that could be enforced by regulatory authorities²²⁶. Some biobanks, such as TubaFrost, which are already based on the association of several local biosamples collections in different European countries made available through a central database have chosen to develop such "Code

²²⁵ IBM Releases Six Critical Issues for the Success of Biobanks:
<http://www.ibm.com/news/be/en/2005/06/14.html>

²²⁶ IBM Releases Six Critical Issues for the Success of Biobanks:
<http://www.ibm.com/news/be/en/2005/06/14.html>

of Conduct”²²⁷ on their own. A similar approach may be applied across Europe. In this context, a proposal recently funded by the EU for developing a Biobanking and Biomolecular Resources Infrastructure (BMRI), is putting emphasis on providing best practice-based standard protocols for different types of sample and data collections with a view to facilitating their long-term use [22].

In the USA, the National Biospecimen Network (NBN) Design Team, a subset of the Tissue Access Working Group (TAWG) convened by the National Dialogue on Cancer (NDC) to address “access to appropriately collected, consented, and annotated tissue,” drafted in 2002 a blueprint for a national biospecimen network. The NBN Design Team envisioned a network of geographically dispersed tissue repositories to collect, process, store, and distribute appropriately consented diseased and normal tissue and other biological specimens with associated clinical data supported and coordinated by an accessible, user-friendly bioinformatics system networked across the country. The biospecimens would be collected, processed, annotated, stored, and distributed in a highly standardized manner to minimize experimental variability and accelerate scientific progress [16].

However, the challenge remaining would be to devise internationally approved criteria, standards, laws, regulations, systems, and professional practices for controlling physical and computerised access to data, managing personal identifiability, and securing informed consent - while at the same time, facilitating justified access for research purposes.

The conclusions from the meeting of the EU-funded biobanking projects stressed once again the need for “federated databases with robust IT communication for secure and effective data integration, storing and sharing (data submission, data integration searching standards for getting data in and out ” [23].

3.1.2 Legal, Regulatory and Ethical Requirements

The conditions for biobanking and scientific use of biobanks are affected by laws and regulations in different ways. First, there are a number of important *issues*, more or less associated with each other. Many of them are of an ethical nature or somehow related to ethical considerations such as: consent, autonomy and personal integrity; privacy protection and safety; access to stored samples and data; transfer of samples and data across national border; “ownerships” and disposition of samples and data; intellectual property rights; commercialization; feedback of results to sample providers; information to the public/public engagement. Second, there are different types of *legal and regulatory mechanisms* used by policy-makers. On the one hand, there are “hard instruments” such as specific biobanks or human tissue acts and other relevant laws that apply to biobanks and medical research in general. On the other hand, the use of biobanks is also affected by “soft instruments” such as joint standards and guidelines, used for example by various monitoring bodies, or even softer governing mechanisms like incentives or sanctions.

Yet, currently, there is no uniform regulatory system applying to human biobanks used for genetic research purposes and the way existing regulations and guidelines are interpreted and

²²⁷ Cf. Tubafröst Biobank.

implemented extremely varies across biobanks in different countries which might create an impediment to research collaboration and coordination [24]. The main question dealt with here is to what extent, and how, these national differences actually influence the establishment of joint research projects where different national biobank resources are effectively pooled²²⁸. The analysis is based on desk research and interviews with biobank researchers and law/ethics specialists, as well as on data collected through the survey, and discussions at the two meetings with experts organized in the context of the study.

In this context, IPTS (in collaboration with Dr. Jane Kaye from the University of Oxford and the Public Health Genomics European Network PHGEN²²⁹), organised a workshop in March 2007 with experts from academia and industry, lawyers, national data protection authorities, and representatives from the European Commission and the European Data Protection Supervisor. The main objective of the meeting was to take an in-depth view at the existing legal bottlenecks and future needs of biobanking with special regard to the collection, exchange and linkage of samples and data in Europe. The scope of the workshop captured the linkage of data and samples, both the internal linkage of data and samples stored in a biobank and the external linkage of biobanks and secondary information resources such as cancer registries. The need for standard terminology but also the increasing role of ethics committees in the interpretation of existing regulation and guidelines were seen as some of the most important factors influencing global collaboration in biobanks-based research [60].

In January 2010, experts from academia, industry and the European Commission convened in Sevilla again to discuss the development of the field in the last 3 years. In the meantime, both biobanking and the basic sciences which use biobanks have made substantial progress. New disease-specific and population based biobanks are set up in Europe and around the globe. While the need for biobanks was still debated in 2007 there is now an overall mutual agreement in the research community that biobanks are important tools for modern health research. This research in the field of genomics and systems biology is by nature a global enterprise which needs a global research infrastructure.

Privacy protection and security issues

Biobank legislation seeks to balance the interests of individuals (especially sample donors and their families) and the research interest. Therefore, it is logical that privacy and security issues are addressed by biobank-related legislation and regulation. An important aim of the regulation is to protect the donors against harm that can arise due to the handling of sensitive information. Much of the focus, both in the debate and in the actual regulation, has been directed at DNA analysis – although unauthorised diffusion of other type of medical information can be as harmful.

Data protection requirements in Europe are laid down by the Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data²³⁰. However, currently, significant variability still exists with

²²⁸ It should be noted that collaboration usually takes place between researchers or research groups, not between biobanks. That is, researchers may engage in international collaborative projects where different teams contribute samples and data stored in their own biobanks (or in joint biobanks).

²²⁹ www.phgen.eu

²³⁰ 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. Official Journal L 281, 23/11/1995 P. 0031 - 0050

regards to privacy and data protection requirements for biobanks. Experts suggest that such differences may be partly attributed to the varied interpretation and implementation of the Directive covering aspects of biobanking by national authorities, and its translation into administrative procedures. As a market directive the directive 95/46/EC is by definition fully harmonising; still the Art. 8 (3) and 8 (4) which cover Public Health issues are allowing exemptions from this harmonisation. According to Art 8 (4) of the Directive, Member States “may, for reasons of substantial interest, lay down exemptions in addition to those laid down in paragraph 2”. The design of Art 8 of the Directive gives Member States substantial discretion in the field of Public Health. Still, Member States shall set up national regulations which are not in conflict with the overall aim of the Directive to facilitate the exchange and flow of data in the EU Member States. The existing information does not allow the conclusion that the Member States have explicitly used the exemption of Art. 8 (4) to develop divergent regulations for biobanks. Within the transposition of the Directive Member States may have rather focused on the national Public Health setting, such as monitoring and surveillance systems, as they transformed the discretion of Art. 8 (4) into policies.

One of the main complications being that although the field of data protection is harmonised through the EC directive on data protection, the collection, storage and sharing of samples for research purposes is not [42]. Furthermore, in countries that have enacted special biobanks acts it is not always clear where the borderline goes between the scope of these acts and that of the Directive. For example, how biobank materials are looked upon in various jurisdictions is not always the same. Furthermore, in countries that have enacted special biobanks acts it is not always clear where the borderline goes between the scope of these acts and that of the personal data acts [8]. There may, for instance, be uncertainty regarding which law should give precedence in case the rules differ.

Different demands on coding or anonymizing of data are often used by the authorities as a complement to requirements on consent. For example, research on biosamples without informed consent can sometimes be permitted if the identity of research subjects is protected by high-security data-handling systems. In this context, there seems to be a broad agreement among researchers that biobank-based research should be carried out on samples and data that are coded (or double-coded), and that the code should be broken only in exceptional cases (this is in line with requirements from UNESCO). It can be in the following types of situation: cases where there is suspicion about cheating; when there is need for new data; when carrying out longitudinal studies; and in the context of metaanalysis (in order to avoid counting individuals twice). This means that generally researchers do not want samples and data to be anonymized in the sense that there exists no code key that can be used to break the code, if necessary.

As discussed in a recent publication, coding has major advantages over anonymization in the context of using research samples for secondary purposes: “... Anonymization, while often ethically and legally expedient, undermines the scientific usefulness of the samples over time since no further clinical data can be added to the database because tracing the sample back is impossible. Likewise, the individual can never benefit from any results. International bodies have yet to support the obvious personal and scientific advantages of double-coding.” [43]

It should be noted that anonymization here means that samples or data contain no information whatsoever that could reasonably be used by anyone to identify the individuals who donated the samples [43]. This is what the Medical Research Council (MRC) in the UK calls “unlinked anonymisation”²³¹. MRC in its ethical guidelines also uses the term “linked anonymized samples or data”, meaning that samples and data are fully anonymous to the people who receive and use them but contain information or codes that would allow others (e.g., the biobank operator) to link them back to identifiable individuals. There are others who would describe these samples as being coded [8]. Thus, there is no consensus on the terminology used in this field. This lack of clarity “undermines possible harmonization due to the resulting complexity, especially when new concepts such as reasonable or proportional anonymity are introduced” [27]. However, some biobanks have already taken initiatives to improve this lacking²³² and the EMEA has published a note for guidance on definitions on genomic data and sample coding categories which came in operation from May 2008²³³.

In the biobanks acts and the guidelines adopted by various countries a common provision is that coding is recommended or even prescribed. The answers that were received through the questionnaire also show that a large majority of biobanks apply coding (including “linked anonymization” according to the terminology of MRC). Thus, such a practice seems to be spreading in Europe, whether imposed by regulation or not. The development of such a standard in Europe should facilitate international collaboration where biobanks are involved. There are of course many ways in which the coding/decoding can be carried out technically. There is also the possibility of involving a third party responsible for holding the key. However, the regulatory authorities rarely specify which solution to use. It is up to the biobank operators to decide how to do the coding so that the authorities’ requirements can be met. In the context of individual research projects, it may then be a task for the research ethics committee to judge if the methods applied are appropriate, given other circumstances at hand (e.g., what type of consent the researchers have obtained).

The handling of privacy protection and data security in accordance with emerging standards, which usually means some kind of coding, makes biobank-based research more complicated and costly. There is no indication that differing regulation between countries *per se*, in this particular regard, would constitute an obstacle to international research collaboration, even when there is a need to share samples across borders. There are well-established techniques that can be used. However, lack of agreement on the nomenclature can be an obstacle. When collaborating biobanks use different types of techniques and security standards this may of course complicate the pooling of samples and data. One possible solution to facilitate harmonisation and collaboration would be the creation of a “safe” and “trusted” third party to be used for all researchers as a trustee for the names and identity of participants. Moreover, in the absence of a uniform standard level, commercial biobanking activities may potentially flock to countries setting the lowest requirements on privacy protection. The European Medicines Agency (EMA) proposed specific terminology in pharmacogenetics through a position paper

²³¹ Medical Research Council (in the UK), “Human tissue and biological samples for use in research: operational and ethical guidelines”, *MRC Ethics Series*, 2001 (p. 2).

²³² In Sweden, the KI Biobank has developed a Biobank Lexicon with the purpose of paving the way for consensus on terms within the field of biobanks.

²³³ Note for guidance on definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data, and sample coding categories (EMA/CHMP/ICH/437986/2006)
<http://www.emea.europa.eu/pdfs/human/ich/43798606en.pdf>

in 2002²³⁴. This nomenclature could fit the needs for current research practice and is line with different harmonising efforts to optimise privacy [36]. Nevertheless a deeper international understanding of these issues still needs to be reached.

Access to stored samples and data

Small collections of biosamples are often used only by the local researchers who collected the samples. Larger biobanks are often open to be used also by other researchers in the same country or from other countries. However, this does not mean that these external researchers have unconditional access to samples and data. The access is almost invariably restricted and is normally controlled by the biobank operator itself (no national regulation exists for access, but rather for transport)²³⁵. Typically, there must be collaboration with researchers linked to the biobank in some way. Furthermore, it is very common that the planned research project, besides the ethical review carried out by appropriate authority, must be approved also by a steering committee or similar body that has responsibility for the biobank (in extreme cases only one person, such as the principal investigator). This type of review is usually based on scientific principles aiming at making the best use of stored samples. Finally, it varies greatly whether researchers using the biobank need to pay or not, although it seems that payment is becoming more common. This is understandable since running biobanks as an infrastructural resource is costly, and such costs can rarely be covered by normal research grants²³⁶.

Transfer of samples and data across national borders

Sending samples abroad may in some countries require a special consent from the donors. With the principal aim of protecting donors, the biobanks acts in Sweden and Norway, for example, only permit samples to be analysed abroad, not stored for a longer period of time²³⁷. The Swedish Biobanks Act also requires that samples be coded or anonymized before shipping. Moreover, to get the approval for sending samples is in these countries associated with some bureaucracy, which the researchers perceive to be irritating and constituting an obstacle to international cooperation. However in most European countries, as it seems, apart from the time-consuming ethics review process researchers do not experience any legal barriers to sending biobank material abroad. A large majority of the researchers who answered our questionnaire state that they face no problem in this regard – provided that appropriate permission for the projects has been obtained from the research ethics committee and others concerned (such as the board or steering group of the biobank).

If biobank legislation is to be harmonized within Europe, the barrier to sending samples abroad that obviously exists in some countries is one of the more important aspects to deal with. To effectively carry out research projects it may often be advantageous to centralize the handling and analysis of samples. While the requirements for sharing of data is pretty much harmonized in Europe, thanks to the implementation of the Directive 94/46/EC on data protection, the legal situation with regard to biosamples is

²³⁴ <http://www.emea.europa.eu/pdfs/human/press/pp/307001en.pdf>

²³⁵ Following the HAPMAP project, there is a whole trend towards the sharing of data in a pre-competitive fashion. This is supported by funding agencies for publicly funded research.

²³⁶ Previous research on biobanks in Sweden showed that it was often relatively easy to get project funding for collection of samples and data. But it was more difficult for the researchers to finance the operation of the biobank itself.

²³⁷ This means that researchers from these countries cannot participate in projects where samples are to be stored in a central biobank located abroad.

far from being clear. Therefore, it was suggested that legal experts from different countries should make an analysis. For example, by making a legal observatory or clearing-house they could help the researchers to deal with the regulatory uncertainties. Such an observatory is needed to facilitate bilateral and trilateral contracts between researchers and biobanks. An increasing number of stakeholders seem to favour an analogous application of the Data Protection Directive to achieve an equivalent level of harmonisation for both domains, data and samples. It also needs to be further investigated whether the regulations as such are posing problems or whether the interpretation and application through ethics committees and IRBs is causing adverse effects due to the heterogeneity. These committees may also set standards which are stricter than the law; in this case the role of ethics committees and the rule of law need to be studied. So far there is no literature or evidence available which explores the field. Further research needs to be launched in this field.

To enhance the legal certainty for researchers and to reduce the administrative complexity a permanent European hub for the exchange of samples and data might be considered. Information on particular countries are increasingly accessible on the internet, e.g. through the work of BBMRI. Still, the national rules need to be tailored for international multi-centre studies and consortia and a facilitator is needed to streamline this process.

The issue of consent

Human bodily substances and, to a minor extent, the personal data are proprietary in many EU Member States and can only be processed with the explicit and informed consent of the data subject concerned. The existence of informed consent is a standard ethical requirement in all kinds of medical research, and therefore applies also to biobank-based research. In such a context, informed consent concerns the process in which a potential sample donor receives the relevant information and decides whether or not to authorize storage and various uses of the sample, based on that information and his or her own values [25]. In this sense the informed consent of the donor consists of different ethical and legal layers. In practice the consent process is often seen as one domain and the different subsections of the consent process are not clearly defined. The consent encompasses the (invasive) retrieval of the sample, in some countries the transfer of property rights regarding the sample, the processing of sample and secondary personal data and the consent to the research which is carried out in a later stage. The different layers of consent need to be reflected in the information and disclosure duties of the biobank as the consent would be invalid otherwise.

Although the basic principle of informed consent for approval of biobank-based research is applied in most countries, there are national differences regarding the strictness and the procedures, as imposed by national laws and guidelines. Such discrepancies in the regulation of biobanks may create problems for international collaborative projects. In this context, one interviewee expresses the following concern: *“the interpretation of the consents is currently discussed in the legal and ethics advisory bodies. Until those questions have been sorted out, no wider sharing of samples and data can take place”*.

The «informed consent» requirement could, additionally constitute a problem if a pre-existing data collection is being used, or if a research project moves in a different direction from the one originally assumed. Thus, whenever data and biological samples

are introduced into a biobank for the first time, the question arises of how precise the consent of the data subject should be²³⁸. Especially, for an optimum use of European biobanks, it may be appropriate to link data and information from a variety of sources. With modern electronic techniques and the internet, biobank data can be exchanged and pooled across networks. This may yield information of a quantity and quality beyond those envisaged when the donors gave their consent. Consideration must be given to the rules for limiting the arbitrary transfer and linkage of samples and data collected for biobanks²³⁹.

A number of different solutions have been proposed, and some are already being applied. Traditionally, in research, the object of consent must be quite precise and the participant must be informed of all potential procedures and risks. However, some are questioning whether this traditional view is applicable in biobanking activities. Depending on the focus, these solutions give priority to either the autonomy of the donor (in the sense of the right to informational self-determination) or the research interests for practicality and implementability of the research projects. Like the UK Biobank, the German National Ethics Council and the Swiss Academy of Medical Sciences (SAMS) have indicated their support for a blanket consent system for biobanks, and do not have any ethical reservations provided that consent can be withdrawn at any time^{240, 241}.

One can distinguish two types of situation, which put different demands on the handling of the consent issue. The first is when a study is going to *use existing biobanks* containing samples that have been collected previously for some purpose (e.g., diagnostics, a clinical trial or a specific research project). The second situation is when *building new research biobanks* from scratch, for the purpose of a particular study or with other more far-reaching aims – such as creating repositories that can be used for a number of different studies.

The first situation is probably the most problematic one. Before starting an international collaborative project where samples and data stored in different countries are to be used, each research group needs to obtain an ethical approval from concerned authorities in the respective country (irrespective if biological material is to be transferred or not). So far there seems to be no mutual recognition process for ethical approvals from third institutions. The authorities have to review, *inter alia*, the existing consents and decide if these are sufficient or if there is need for some kind of action (such as getting renewed informed consent from the donors or applying some kind of opt-out solution).

For international projects, there are two types of problems. First, there may be differences between the biobanks in terms of what kind of consent that exists for the stored material. When it comes to old biobanks it is common that the donors' original consents, if there are any, do not coincide with the purpose of the planned research. Very often samples stored in clinical biobanks have been collected without any explicit consent for research from the patients. Second, the review carried out in each country

²³⁸ Claudia Mund, Biobanks – Data Sources without Limits?, in: Jusletter 3. Oktober 2005
<http://www.weblaw.ch/jusletter/Artikel.asp?ArticleNr=4211>,
http://www.privacyconference2005.org/fileadmin/PDF/mund_e.pdf

²³⁹ "Biobanks for Research", Opinion of the German National Ethics Council, Berlin, 2004

²⁴⁰ Cf. German National Ethics Council, Biobanks for Research, opinion of 17 March 2004, Berlin 2004, p. 55 ff., especially p. 61 f. (www.ethikrat.org/_english/publications/Opinion_Biobanks-for-research.pdf).

²⁴¹ The guidelines can be found at www.samw.ch/docs/Richtlinien/d_RLBiobanken.pdf (in German).

will of course be carried out based upon each country's domestic laws and rules. The current provisions of existing regulations concerning information and consent may vary from country to country. Depending on these circumstances the review process may thus take shorter or longer time, and the outcome in terms of the requirements may vary.

Further complication may be added when considering the requirements for sample transfer. As the survey brought about, in practice, different handlings exist with regards to the sharing of samples. For example, researchers asking for DNA samples at the National Laboratory for the Genetics of Israeli Populations (NLGIP) need to declare they would *not* be transferred to others. In contrast, the EORTC VTB Biobank can share its samples (tissues and data) with researchers in the other countries, as soon as the donors and patients have expressly permitted it²⁴². Another barrier to an unproblematic transfer of samples is also the fact that the consent obtained from the donors might depend on the clinical trial setting and not be universally valid, as it is the case for the EORTC VTB Biobank.

With regard to archived medical care samples, there is a trend where ethically approved research on such material is permitted without re-consent. The condition is that samples are either anonymized or exceptionally coded, provided there are important health interests, there is notification of such practice, no objection, and research ethics approval [26].

Although informed consent is the norm in medical research, an opt-out solution is sometimes regarded as acceptable in biobank research, since there is no physical risk to the subjects. But this requires that strict security measures are taken in order to safeguard the privacy of donors and that there is widespread support of medical research in the population. In Iceland, for example, according to the law on the Health Sector Database, people will have the possibility to opt out from the database [27]. Opting-out is considered by some as detrimental to research without real benefits for the autonomy of the donors [28].

The observation that the routines used for obtaining consent may vary greatly between existing biobanks involved in international projects has been taken as starting point for a study carried out at the Centre for Bioethics at Karolinska Institutet and Uppsala University. It addresses the selection of appropriate information and consent procedures when previously collected samples are used in international collaboration. The researchers behind the study argue that although informed consent is a standard requirement in the ethics literature, the circumstances for research on existing biobanks are sufficiently different to motivate a special practice. Moreover, they present a special ethical framework that can be used to solve the problems and challenges that international biobank researchers encounter with regard to the consent issue [[26].

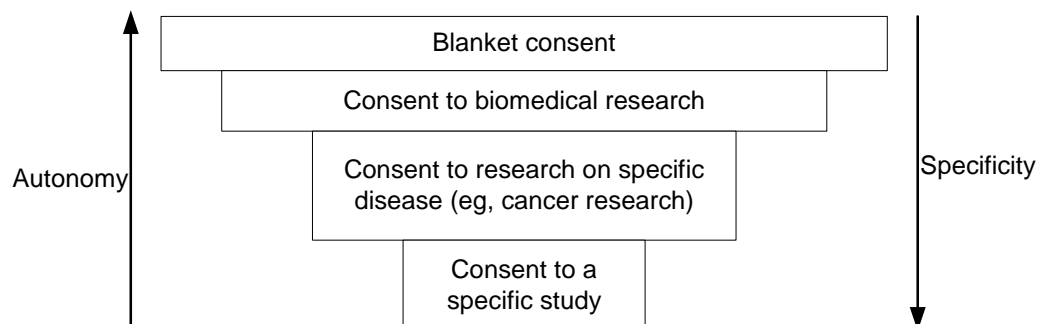
In the second situation (i.e. creation of new research biobanks), new samples are going to be collected in different countries for the purpose of a new international research project or the creation of new infrastructures for future collaborative research. Obviously, there are strong incentives to use, if possible, the same type of consent in all participating countries – since this would enable flexible uses in the future as it is often impossible to know in advance how the researchers will like to use the material. It

²⁴² Cf. returned Questionnaire.

would be a great advantage if common grounds for review of consent, and other ethical aspects on biobank research, could be established in different countries.

As illustrated in Figure 3-1, consent procedures can be thought of as a continuum from highly specific consent to blanket consent [29]. A much debated topic is whether broad consent to future biobank research can be acceptable, or if a renewed consent must be asked for each new study. Broad consent means that donors give permission to use samples and data for multiple purposes of future biomedical research. Several arguments against broad consent have been put forward. For example, the Icelandic ethics professor Vilhjalmur Arnason, referring to the principle that consent should be based on information relevant to an assessment of benefits and risks associated with the research, argues that “the more general the consent is, the less informed it becomes” [30]. He means that the standard meaning of informed consent cannot accommodate broad consent (sometimes also called “authorization”).

Figure 3-1: Categories of consent



Source: Hansson, et al. [29]

The question of what is appropriate information has been raised, considering that blanket consent can indeed provide all relevant information if the risks and benefits are appropriately informed. For research that involves less risks for research participants, less-strict information and procedures are appropriate [29]. In the same way, if these risks and benefits are common to several studies, then general information on these studies might be sufficient [29]. Of course, in assessing risks and benefits associated with a proposed study the ethics review boards must take into consideration how personal data is handled and other potential risks for the donors. They might also consider to what extent donors are willing to take the risk of being not fully informed on all aspects of the future use of a biobank.

It has been suggested that *the* key to broad consent is that participants are not consenting to a specific study, but a specific process and a given governance structure that ensures that future uses are within acceptable and agreed parameters. In other words, the donors should be offered a whole package that includes a number of procedures for handling of samples and data. By having good procedures and structures in place people will feel confident that their integrity will not be violated. In this context, a recent study concludes that (“well-informed generalized”) consent to future research has not yet become the norm in international regulation [27]. But for certain types of research there is a gradual move towards allowing biobanks to obtain a broad

consent for future research using either anonymized or, preferably, coded samples and data. Especially for large-scale longitudinal studies on genomic variation such a practice may be accepted provided it is justified both scientifically and ethically.

It seems that scientists involved in large population-based biobank projects, such as the UK Biobank and the Estonian Biobank, favour a solution with an *explicit* broad consent, which is documented through the donor's signature on a special consent form. The existence of such a clear consent undoubtedly makes it easier to use such biobanks for various scientific purposes.

As commented by a clinical researcher working in a hospital, *such a practice is convenient for this type of research biobanks, but it is not a good solution for healthcare-based biobanks. To require a practice where a written consent has to be obtained from patients is impractical and costly.* Thus should be enough to inform the patients on notice boards – and that the research ethics committee should have the right to permit research without consent. Such a practice is already applied in several countries. It also needs to be noted that the existence of a consent document does not per se prove the validity of the consent. From a legal perspective rather the appropriate information of the patients/donors should be stressed and not necessarily the sheet of paper which is finally signed.

The view of actual and potential donors in various countries has been examined in a number of studies. Although there is no consensus of opinion among these studies, most actual donors seem to favour a procedure of broad consent given on the occasion of recruitment. Blanket consent was amongst the "persistent disagreement" issues in a public deliberation group exercise carried in 2007 [41]. Some of the public's alternative as an alternative to the blanket consent was, as an example, a consent form with specified preferences for different research uses. By giving the right to withdraw the consent later, regretful donors can be protected²⁴³. It can be added, though, that the right to withdraw necessarily requires some kind of public accessible information about the uses. Therefore, many are arguing that uses of biosamples should be publicly known in some sort of registries.

While there are those defending both explicit and specific consent [30, 31] or a multi-layered more specific consent which allows for prospective research [32-34] many experts seem to be in favour of a well-informed blanket consent [18, 35-40]. Their arguments are mainly economical feasibility (to create a large biobank for to study just one particular issue would have a tremendous cost and would make it impracticable). Moreover, from a scientific point of view, if the informed consent is too strict, future research may be hindered because most of the studies will not be planned or even conceptualised when the consent is given. This however should not suggest a policy where anything goes. Even the Council of Europe seems to be more open to a broader consent for future research²⁴⁴. A working group at UNESCO concluded in 2002 that blanket consent might be more appropriate to allow future research in biobanks²⁴⁵.

²⁴³ Our questionnaire data shows that the right to withdraw previous consent is almost invariably practised in European biobank research.

²⁴⁴ CM(2006)21 Addendum, Council of Europe, Steering Committee on Bioethics (CDBI): Draft Recommendation Rec(2006) of the Committee of Ministers to member states on research on biological materials of human origin Draft explanatory memorandum . <https://wcd.coe.int/ViewDoc.jsp?id=961137>

²⁴⁵ UNESCO SHS-503/01/CIB-8/3 (Rev.2): Human Genetic Data: Preliminary Study by the IBC on its Collection, Processing, Storage and Use, May 2002
http://portal.unesco.org/shs/en/files/2138/10563744931Rapfinal_gendata_en.pdf/Rapfinal_gendata_en.pdf

Those defending the use of blanket consent also stress the importance of the right to opt-out or withdraw consent. Maintaining the right to withdraw consent preserves personal integrity and autonomy of the donors [19]. In addition, consent for future secondary research, requires public notification of such research and ongoing ethics reviews [27].

The role of Ethics Review Boards

It has been argued that broad consent for use of human blood and tissue samples in future biobank research in epidemiology is legitimate. The arguments include the great value of such research, the respect for the autonomy of the donors, and the current regulatory practice in many countries. It is concluded, *inter alia*, that provided the security level is high and donors and families are protected from harm, no limitation on autonomy is necessary²⁴⁶. The third argument (on the regulatory practices) is of particular interest in the context of the present study. According to current practice in the UK, Estonia and Sweden, ethics review boards have a mandate to approve a biobank study without requiring informed consent. In Iceland, the National Bioethics Committee can do the same. Furthermore, Germany, Norway, the Netherlands, and the USA, existing regulations permit biobank research without consent provided that the samples are not identifiable (furthermore, there must be a consent for taking the sample, and the anonymization must be assessed by an IRB). It is concluded that if ethics review boards might grant permission to carry out research without consent, there is no reason why the participants themselves should not be allowed to give broad consent if they are clearly informed about the underlying factors which determine the need for a broad consent.

The view of Ethics Review Boards can be challenged from the perspective of the European Data Protection Directive. According to Art. 8 (2 a) of the Directive the processing of sensitive data is not prohibited if the data subject has given his or her “explicit consent to the processing of those data”. Member States are even empowered to put further restrictions on the right to consent. Biobanks and ethicists may rightfully argue that this regulation is paternalistic but it fits into the overall regulatory rationale of the Directive. It is the explicit aim of the Directive to prevent mass data preservation as the Directive has a rather narrow understanding of the concept of purpose. In Art. 2 (h) of the Directive the informed consent is defined as “the data subject’s consent shall mean any freely given specific and informed indication of his wishes by which the data subject signifies his agreement to personal data relating to him being processed”. In line with the argument of Arnason and open or broad consent may not be in line with the definition of the Directive as the data subject seems not to have the right to take a risk. The wording of the Directive has been influenced by a decision of the German constitutional court which ruled that the German law on population’s censuses was partly unconstitutional as it infringed the “right to informational self-determination”²⁴⁷. This fundamental right includes a right to know who is processing what kind of personal information for which purpose. Due to the political situation at the time of the decision, the fundamental right does not include a right not to know or a right to take a risk. Following this rationale an “uninformed” or partially informed consent can be seen as invalid as the data subject is not empowered to assess the long-term consequences of his or her consent.

²⁴⁶ It can be questioned though whether the current regulatory frameworks are efficient enough to enable broad consent.

²⁴⁷ BVerfGE 65, 1, Decision from the 15 December 1983 1BvR 209, 269, 362, 420, 440, 484 / 83

Feedback of personal results to sample providers

Analyses carried out on samples in the course of research may reveal information that has implications for the donors' future health or healthcare, or affect their interests in other ways. This raises the question whether such information should be reported back to the donors. This question is often addressed in ethical guidelines for biobank research. The Medical Research Council (MRC) in the UK, for example, states that "researchers should assume that participants have a right to know information that may affect their interests, but that they might choose not to exercise this right" [12]. MRC advises researchers to decide in advance what their strategy will be regarding the feedback and whether any linkage of research results to individuals will be possible. This must be set out in their submission to the ethics committee and the chosen policy must be explained clearly to the donors before they consent to take part in the study.

In the UK Biobank, participants have access to general information about the project's progress, but are not to be given any individual information relating to the project's findings. This is in contrast to the proposed US Biobank project whose volunteers will be given the option of being told about findings that could affect their health, such as whether they are developing cancer [45].

Maybe, this is an issue that is of higher relevance to individual research projects than to biobanks as infrastructure. But biobanks can of course have a policy regarding this issue. A general feedback policy may also have implications on the communications infrastructure of the biobank as the biobank might have to handle a large set of complicated data. Therefore, a question on this was included in the questionnaire. The results show that approximately 40 percent of the biobanks surveyed state that they give such feedback, but on the condition that the donors have consented to it. The two genome projects in Estonia and Latvia are two examples. However, the option to give feedback in *all* cases is rarely used. One exception is Generation Scotland.

General information about research results of a biobank study is made available through publication in scientific journals. However, giving specific information to individual donors is discouraged by some because of the high levels of responsibility assumed by the researcher [36]. If clinically relevant information is expected from the study, collaboration with clinical experts is then advised [32].

Giving feedback of analysis results is only possible if the data is coded (i.e. not anonymized in a strict sense). But, in line with the researchers' reluctance to use the key to break the code, there is a preference not to report back any individual results. In this context, one professor says that "if there is a proposed partner for a new project who has such a requirement, that partner's biobank would not be regarded to be useful. At the same time he says that such requirements are unusual in Europe. It is mainly when discussing collaboration with American researchers that ethics committees sometimes come up with this kind of demand". It should be noted though that according to our questionnaire data feedback of personal analysis results is not so uncommon in Europe (Figure 2-16).

"Ownership" and right of disposal over samples and data

The issue of who "owns" biosamples, or biobanks, and has the right of disposal over them is very complex. In a study on intellectual property (IP) and biobanks carried out a few years ago it was concluded that in an IP context, biobanks are regarded as

protectable compilations, that is, databases [46]. This means that biobanks may be protected by intellectual property in the form of copyright or *sui generis* protection. The study recommends that the intellectual property rights be regulated by contracts among the various actors involved in creating the biobank. These IP rights do not infringe the IP rights of researchers who use the materials of the biobank to create their own inventory step which enables them to seek, e.g., patent protection. The commercial exploitation of biobanks might be a huge ethical and political issue as it also affects the public trust in the biobank. In contrast the commercial exploitation does not affect the legal framework for biobanks to the same extent. Property and Intellectual Property rights regimes are in place to structure the process. The existing international framework seems to be appropriate to govern the domain. It seems to be rather a political question to ensure the equitable access to biobanks and to organize a fair distribution of financial gains which have been achieved by using the (public) infrastructure of a biobank.

There is a trend to consider samples and data in a biobank as a public or community good so that donors cannot claim any property rights [18, 47, 48]. The business value derived from the biobank would then belong to those conducting the research, not the individual donors [18]. In terms of property rights, the open source model as well as the benefit-sharing proposed by UNESCO²⁴⁸ have been claimed by some [48].

There is no doubt that the issue of ownership and disposal is important for effective use of biobanks, generally. There are at least a few cases where long-lasting disputes concerning the ownership have had negative effects on the use of specific biobanks for research. One such case, which has got a fair amount of publicity, concerns the Medical Biobank in Umeå where some of the researchers involved are opposing the university's and the county council's attempts to take control over the biobank. Especially, this dispute effectively hindered the use of this biobank in commercial research [49]. The case revealed that at least in Sweden the legal situation is not entirely clear. However, it remains to be seen how this issue will be handled in other countries. In Singapore, for example, the National Ethics Committee suggests that biobanks should be owned by "institutions" and not private individuals. The situation is even more complex in legal systems which do not use the property rights regime for samples obtained from donors. Still, the collection of the samples (the bank) constitutes a substantial value and may need to be protected by property rights. The economic value of a biobank may also constitute a legal problem if the biobank or the institution behind the biobank goes bankrupt. There is no clear position yet how the rights of donors shall be fully protected in such a case.

In the present study we have not come across any case where international collaboration has been hindered by IP-related factors. However, it cannot be excluded that such problems have occurred or will occur in the future. This is an issue that needs to be further investigated.

Benefit sharing

²⁴⁸UNESCO International Declaration on Human Genetic Data, 16 October 2003 http://portal.unesco.org/en/ev.phpURL_ID=17720&URL_DO=DO_TOPIC&URL_SECTION=201.html

The individual participant in a biobank study will not typically benefit by participating [50]. The outcomes of the research on these data bases improve our knowledge of the genetic and non-genetic factors contributing to disease and therefore facilitating treatment or prevention strategies. Therefore, biobanks are established base on the altruism of individual donors. Inevitably, this good-will is based on trust [40].

With the argument of public benefits, even the right to withdrawal has been questioned based on the notion of solidarity [51].

3.1.3 Funding and Financial Maintenance

While it is desirable that biobanks eventually become financially self-sufficient, in the short-term they will require a substantial infusion of capital for the establishment, development and maintenance of the necessary infrastructure²⁴⁹. In private biobanks the costs are typically borne by the depositor; in public biobanks the costs are charged to the user and paid either through medical insurance (principally in the USA) or by public health services. However, sample storage is rarely a fully recognised activity, except in some pharmaceutical groups or biotechnology companies. Even for bigger banks, continuity of funding is not always assured. For those involved, regrouping of the biobanking activity could enable economies of scale and cut costs. However, it has to be compatible with simplicity of use [52].

There are different kinds of funding actors involved in biobanks (Figure 3-2). While health care-based biobanks are formally financed internally by the county councils, special funding is in most cases needed in order to build, administer, and use research-based biobanks. Obviously, funding provided by public entities are usually short term where the funding for biobanks infrastructures would need to be on a long term - hence, there seems to be a need to shift from funding projects to funding long term infrastructures.

Return-on-investment models or a sustainable public funding will be critical for the successful funding and development of a biobank approach on EU level. Biobanks that make their samples available to other researchers might want to participate at the profit. This has been confirmed by a survey respondent who “would be willing to share samples with other biobanks provided that a system for fair revenue sharing is set”²⁵⁰. Furthermore, a critical attribute of a shared resource is that the distributed resource be what it is supposed to be²⁵¹. The issues of quality control and quality assurance for shared samples or sample repositories are of major concern, because these activities might be a major contributor to the costs of some public research institutions. Commercial competitors willing to employ less stringent measures on a smaller selection of resources can and do offer apparently similar products at cut-rate prices. High-quality research depends on high-quality materials, and the scientific community will have to recognize that it must pay for quality control, through subsidy if not

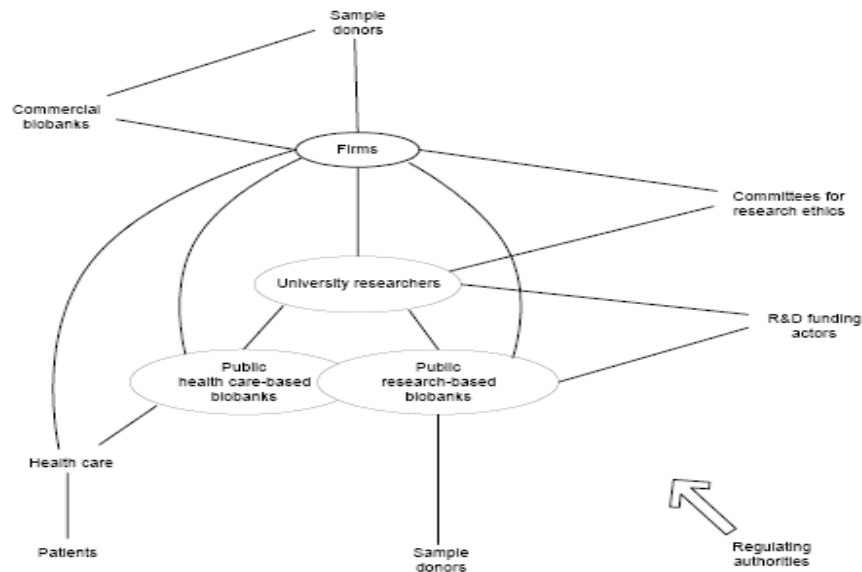
²⁴⁹ IBM Releases Six Critical Issues for the Success of Biobanks: <http://www.ibm.com/news/be/en/2005/06/14.html>

²⁵⁰ Cf. returned Questionnaire.

²⁵¹ Resource Sharing in Biomedical Research, Committee on Resource Sharing in Biomedical Research, Division of Health Sciences Policy, Institute of Medicine, 1996.
<http://bob.nap.edu/html/biomed/#contents>.

through user fees. Precise handlings might be necessary to state that has to defray these costs.

Figure 3-2: Different types of actors involved in biobanks



Adapted from: Laage-Hellman, J., “The industrial use of Biobanks in Sweden: an overview” [7]

However, the mode of sample allocation between biobanks is not guided by market relations. In the language of welfare economics, there are “externalities”, benefits and costs transmitted among individuals for which compensation in price terms is not and perhaps cannot be obtained. In the dynamics of scientific production, biological samples are research intermediary products when final products are publications or patents. Even if the research material is a critical resource, the necessity to corroborate results by other teams using the same biological material or to reach a critical mass of samples can partly explain the importance of the sample flows between laboratories [52].

When developing a European biobanking structure, handlings must be set up for sharing samples among several biobanks which take the costs of transport and quality control into account. Otherwise, this point might be an impediment to the willingness of biobanks to cooperate. The questionnaires returned from the Erasmus MC Tissue Bank, the TubaFrost Biobank and the just-started EuroBoNeT biobank have confirmed that these biobanks are indeed willing to share their samples with others, but only after a negotiation on reimbursement of costs²⁵².

3.1.4 Public involvement, information, acceptance

The success of any research project has a direct relation with the trust of participants that will voluntarily accept to provide samples and, usually, private information about their health and living habits. To secure the trust of all partners, including participants and the larger community to which they belong, public information, consultation and public participation seems one of the most important factors influencing success [53].

²⁵² Cf. returned Questionnaires

The more recent literature goes one step beyond and states that trust is earned through the establishment of an ongoing relationship with the participants [54] .

Most available data on public trust in relation to the use of genetic information suggest that individuals do have some confidence in the privacy and confidentiality of the use of their data and are willing to allow to the use of this information [55]. However, any single violation can easily break this trust and lower the support.

While all biobanking projects can raise concerns because of the pooling of sensitive information from a group of individuals, large-scale projects raise issues and concerns in an acute way and, the question of public participation has recently received of attention in this context. There is now general recognition that large-scale projects need to engage the public, at the stage of its conception and on an ongoing basis, in order to draft and implement a project that will be viewed as legitimate and as an overall a positive scientific initiative. Engaging the public supposes first that it be informed. It also requires a dialogue about all aspects of the research project. Finally, the object of discussion should not only be the project itself. When making a decision about participation in a project, potential participants must understand the overall context. They must have trust not only in the project itself by in the overall process and regulatory system governing biotechnology and research activities in general. For example, even if donors might be willing to accept blanket consent, such a practice might jeopardize public trust in biobanking and make it more difficult to collect samples. Second, the application of broad consent on the sampling occasion is not the same thing as letting research ethics review boards, and other authorities involved, grant once-and-for-all permission for broad research proposals.

A meta-analysis of more than 30 studies of research participants from around the world was published in 2006. The researchers concluded that of the 20 studies that assessed willingness to donate samples for research purposes, 17 found that at least 80% of respondents would donate a sample if asked [38]. However, the limits of these apparent positive findings must be acknowledged. The polls show a range of various responses and we can anticipate these responses are intrinsically linked to the cultural, scientific and political context. For instance, in a pool of Singapore population, 49% were willing to donate samples of blood for genetic research [56]. A group of Canadians and Americans were asked if they would donate a genetic sample and health history information to a genebank to be used for health research, provided that their identity would be stripped. ‘Three in ten Canadians and a third of Americans would be very willing to do so, while four in ten would be somewhat willing’²⁵³.

This general willingness to donate blood samples for research must be put in contrast with some of the concerns raised by participants. There is a range of concerns that have been identified in the literature especially in the context of DNA banking: appropriate consent, confidentiality, future uses, nature of the research, etc²⁵⁴. These concerns must be identified and addressed by the scientific community and policy-makers in order to create a positive climate for blood and tissues donation for research.

²⁵³Report prepared for the Canadian Biotechnology Secretariat, ‘First Impression Understanding Public Views on Emerging Technologies’ (2005) p. 18 http://www.biportal.gc.ca/CMFiles/CBS_Report_FINAL_ENGLISH249SFD-9222005-5696.pdf

²⁵⁴See for instance: Voss, Report to the Human Genetic Commission on the Public Attitudes to the Use of Genetic Information (2000) p. 11-12.

Having a better understanding of the public's opinion about biobanks in general is especially important in the context of rapid scientific changes and capacity. In 2003, the French National Consultative Bioethics Committee (CCNE) recommended that a large consultation of the public take place on the question of pooling of databases and biobanks to understand their views on the question²⁵⁵. It is certainly a good practice to have an independent and credible organization to conduct polls to better understand publics' views about biobanking. Public education program to address the fear and concerns, and to raise awareness about the need for biobanks in the research process and improvement of health, is also a good objective towards building and maintaining trust with the public.

Faced with such challenging issues, almost all the emerging large-scale population-based biobank projects have invested time, energy and efforts towards public communication and consultation. Various models to approach the public have been experimented by these large-scale projects. *'The Iceland Health sector database and Estonian Genome Project have followed a 'communication approach' in order to address public concerns, whereas UK biobank and Quebec CARTaGENE have chosen a 'partnership approach to involve the public in decision-making processes' [57].* Any public consultation must be a well-integrated process that will really feed, influence and shape the research proposal rather than a parallel process. The House of Common Select Committee on Science and Technology criticized the UK Biobank project for having 'bolted-on' the public consultation process. It was strongly suggested that establishing a dialogue with the public should be an integral part of the science process. It is suggested that public consultation should aim to: (1) Enhance protection, (2) enhance benefits, (3) legitimacy, (4) shared responsibility [58].

Wellcome Trust and the MRC have funded many public consultation processes and various experts' papers on the development of UK Biobank²⁵⁶. The most recent round, in 2003, covered most aspects of the proposed project, from recruitment, consent, to financial gains²⁵⁷. Generation Scotland has also developed an extensive public consultation program. A reflection on defining an appropriate model was initiated early in the process²⁵⁸. Ten focus group discussions formed the basis of a 'Preliminary Consultation Exercise' in 2003-2004²⁵⁹. This consultation covered topics such as: participation, recruitment, withdrawal, access, consent, feedback, public engagement, and confidentiality and participants were also encouraged to raise issues. CARTaGENE (Canada) also conducted focus groups about the project²⁶⁰. These focus groups were informed about the proposed project and were invited to express their willingness to participate in such project or not, and to discuss about various topics from the protocol, to consent, confidentiality, future uses, etc.

²⁵⁵Comité consultatif national d'éthique pour les sciences de la vie, (CCNE), 'Problèmes éthiques posées par les collections de matériels biologiques et les données d'information associées : 'biobanques', 'biothèques'. Avis no 77, p. 7.

²⁵⁶See the UK Biobank website for a complete list of consultation.

²⁵⁷People, Science and Policy Ltd, 'UK Biobank Framework for the Consultation of the Ethics and Governance Framework', (2003), <http://www.ukbiobank.ac.uk/docs/people-science-policy.pdf>

²⁵⁸T. Wakerford, F. Hale, 'Generation Scotland: Towards Participatory Models for consultation' <http://129.215.140.49/gs/Documents/Consultation.pdf>

²⁵⁹G. Haddow and al., October 2004. <http://www.generationscotland.org/>

²⁶⁰CROP, 'Project Cartagene: Faits saillants des rencontres du groupe' (2003), <http://www.cartagene.qc.ca/focus.cfm>

There is an increasing recognition that participants should not only be consulted, they should partake in the implementation and long-term development of the project. Finding an appropriate way to involve the public in such a project is quite a challenge. Establishing a long-term dialogue with the public is an essential component of this partnership [54]. A reflection, already initiated by the projects mentioned above and others should be pursued to define the parameters of appropriate models such a long-term involvement should take in Europe. Funding agencies should also recognize the need to hold such consultations and fund public engagement activities as integral part of any large-scale initiative funded in the future.

The right to withdraw consent is considered important for the public trust in research and consequently to people's willingness to participate and to consent to research [19].

3.2 Options for a European Biobank Networking Platform

In the current era of genomics based medicine, large-scale genetic epidemiological studies have become a key tool in elucidating disease and designing improved and more personalised therapies. However, such studies require large numbers of cases and controls so that statistical significance of results is ensured²⁶¹. In this context, biobanks constitute a critical resource. Yet, the existing collections vary widely in several aspects which maybe in turn hindering their collaboration and effective use in research. There is a recognised need for increasing networking and harmonisation among biobanks in Europe (and world-wide).

In the following sections, we address first the issue of networking large population-based biobanks and then focus on smaller, disease-specific biobanks and the need for pooling such resources within Europe.

In several European countries, initiatives have already been taken to build national population-based biobanks (e.g. decode, EPIC, Estonian Genome Project, IBBL Luxembourg) (Chapter 2.2). Given these ongoing or planned biobanking activities, creating a completely new European biobank project would be a costly and not very efficient operation (e.g. it would take years to reach the number of cases needed for the prospective research). In this context, one expert from the UK explains why there is a need to network and “harmonize” biobanks internationally:

“For example, it would take UK Biobank 17 years to achieve 10 000 cases of breast cancer, which would be needed in order to effectively study the genetic effects on this disease. In order to reduce this time lag, the expert pointed to the need of 4-6 “UK Biobank equivalents” around the world. By pooling samples and data from these biobanks, which would thus be based upon 2-3 million recruits, the researchers would

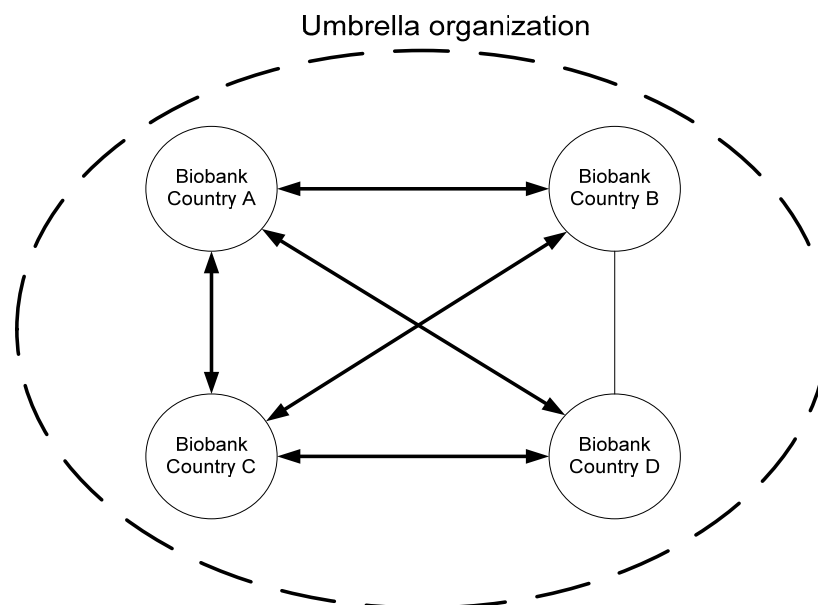
²⁶¹ However, it should be recognised that the fact that many diseases are dependent on coinciding abnormalities or disturbances in multiple pathways, and therefore non-replicated findings may not at all be a rejection of the first finding: the context of other causes may be so different that the association found in the first disappears in the next. On the top of that, replication may in fact mean replication of the same confounding or bias. Hence, until a more comprehensive knowledge about the multiple pathways is available that lead to the disease, it will be difficult to definitely verify or refuse gene-disease associations for the more common complex diseases. These are also the problems that make the population sample size requirements so huge and – in spite of the obvious advantages – a bit problematic, because there may be many other reasons for moderately strong but very precisely estimated association (say odds ratios of 1.2-1.5).

more rapidly gain access to the necessary material to work on. Such pooling would be especially important for research on “less common but not rare diseases”. For example, it would take UK Biobank 29 years to get 2 500 cases of stomach cancer. With six UK Biobank equivalents 10 000 cases could be achieved in 20 years. Besides enabling earlier analyses, this kind of pooling would facilitate the study of events at younger ages and a broad range of environmental exposures”.

Therefore, it would be better to build on and strengthen existing national initiatives. Interviews conducted with other biobank experts support the idea of facilitating pooling among national biobanks rather than creating a huge single European Biobank. However, the creation of a “virtual biobank” is likely more feasible and efficient, although the way to achieve this is not entirely clear.

As an expert suggested, the establishment of some kind of **international umbrella (or network) organization** could facilitate in various ways collaboration between different biobanks, as several ongoing parallel coordination initiatives, all working on harmonization issues already exist. The most important task of this organization would be to facilitate the creation of a well-functioning network among independent population-based biobanks/studies (Figure 3-3). These should retain the control over samples and data. Thus, the merger of samples and data should take place at the level of individual studies, which may involve all or a subset of the “partner banks”. If the integration of the national resources should go further in the future remains to be seen.

Figure 3-3: International umbrella organization supporting networking among independent population-based biobanks.



The network to be supported by the umbrella organization should probably not be open to everyone who wants to join. It should be a dynamic network for selected biobanks and the criteria for “membership” would need to be further discussed. But it is assumed that candidate biobanks should have a certain target size (e.g., 50 000 or 100 000 individuals). They must also be willing to share their own resources with others in an

open and cooperative atmosphere. How commercial population-based biobanks would be involved in such a network would require further investigation.

There are many issues that need to be addressed in order to facilitate large-scale studies where samples and data are pooled and used effectively. There is a need to jointly investigate how common operating procedures can be established for practices such as genotyping and phenotyping, quality assurance, information management. Related legal and ethical issues (type of consent, privacy protection, feedback of information to donors, etc) must also be considered. In particular, harmonization of data collection and management methods is of crucial importance in order to guarantee an even and high quality of the data stored in the databases. If the reliability and error frequency of data varies too much among participating biobanks, this will have undesirable effects on research findings. For example, false associations might be identified due to quality differences. Thus, pooling of data can even lead to “dangerous results”, as one interviewee put it.

Based on previous collaborative research projects there is already a great deal of experience which should be used as an input to this work. For example, the European Commission has funded “Population Biobanks”, which is a Coordination Action under FP6 addressing the need for very large sample sizes. The project has been running from 2006 to 2008 and involved institutions in 13 countries. The Norwegian Institute for Public Health is coordinating the project, the aim of which is to help ensure that Europe makes the best use of its rich array of population-based biobanks and longitudinal cohort studies²⁶². This project was preceded by another initiative called COGENE.

The Cogene project aimed at strengthening the foundation of European biomedical science in the post-genome era. The project aims to establish a collaborative research network that will identify and explore some of the key issues that will help ensure that Europe is able to make best use of its rich array of population-based biobanks and longitudinal cohort studies. These include world-leading cohorts that already exist and new initiatives that are just beginning. The ultimate long-term aim is to harmonise those features that are common to many biobanks and cohort studies and that, when implemented in a complementary manner, can act to: (1) promote communication between major biobanking initiatives; (2) enhance the effective sharing and synthesis of information; and (3) avoid the expensive mistakes and inefficiencies that can arise when individual initiatives repeatedly “re-invent the wheel”.

Other examples include GenomEUtwin²⁶³, the Danubian Biobank Consortium²⁶⁴ and the Cancer Control using Population based Registries and Biobanks (CCPRB)²⁶⁵. This is a network of excellence project within FP6, aiming at improved control of cancer by facilitating research linking biobanks and cancer registries. One of the goals is to define and implement a “European Quality Standard for Biobanking”. The network consists of 19 partners from 9 European countries. It includes 7 cancer registries, 20 biobank projects, and a number of platforms for advanced technological analysis of biosamples. Other models for the creation of a European Population Biobank are represented by the

²⁶² http://www.p3gconsortium.org/events/2003Manchester/LifeSciHealth-Population_Biobanks.pdf

²⁶³ www.genomeutwin.org

²⁶⁴ <http://www.danubianbiobank.de/DanubPublic/misc/mscHome.jsp>

²⁶⁵ www.cancerbiobank.org

CEPH repository in Paris²⁶⁶ or the TuBaFrost Network²⁶⁷, characterised by the low invasiveness on implementation and incentives for the collecting institutes (single biobanks keep the collection and the custodianship over their samples). The possibility to make a very large scale biobank on the basis of the same principles as the PKU biobanks are made in Denmark and Sweden (health service routine drawing of drops of blood on filter paper that dry and can be kept in envelopes under normal room temperature) may also be considered. The efforts in the field of biobanking have been continued under the FP 7 program. In addition to the continuous funding of research projects and networking activities, the European Commission has also agreed to fund projects which aim to establish a new infrastructure for the life sciences. BBMRI²⁶⁸ is the project which addresses the biobanking domain in Europe. The continuation of the enterprise can only be reached if the Member States and affiliated countries make a long-term commitment for a strong European hub in the field of biobanking.

However, a key question is whether this type of networking and harmonization should take place only at the European level or more globally. Samples and information are routinely moved across the globe and research processes are increasingly complex. In addition, there are many companies whose activities cross national boundaries, as headquarters may be in one country whilst the research is carried out in another. A clear message from the experts, participating in the workshops organised in the context of the study, was that the biobank network or umbrella organization should be established at the global level – not just the European. It was suggested that the EU should be able to invest in such an international organization even if it would work with non-European biobanks. In this context, it was proposed that the Public Population Project in Genomics (P³G) could possibly play the role as umbrella organization for collaboration among large population-based biobanks – if it is agreed that such an organization should work globally²⁶⁹. However, this is one of several important questions that need to be addressed in future studies on European biobank networking. It also needs to be ensured through substantial European initiatives that Europe plays a leading role in the international biobanking arena.

3.2.1 Networking among “smaller” biobanks

The scenarios presented thus far for networking have largely focused on large-scale populations based repositories. However, the value of small or medium-sized disease-specific biobanks for research should not be disregarded. Experience shows that by picking up a small number of informative families in isolate populations one can identify loci and subsequently genes in multifactorial disorders. These genes could then be searched for in larger cohorts, and also other genes within the pathways could be analyzed. Ensuring improved collaboration and networking among such collections is therefore just as critical.

²⁶⁶ <http://www.cephb.fr/>

²⁶⁷ www.tubafrost.org

²⁶⁸ www.bbmri.eu

²⁶⁹ P³G (www.p3gconsortium.org) is an initiative whose mission is to facilitate harmonization between population-based biobanks and open the way for future international collaboration. Its main objective consists in the creation of an open, public and accessible knowledge database. The consortium is international and its members include leading public organizations partaking in large-scale genetic epidemiological projects and biobanks. There are several regular members from Europe (e.g. UK Biobank, the Estonian Genome Project, LifeGene, KORAGene, The Danubian Group, GenomEUtwin).

There are already many ongoing collaborative projects involving European scientists working with disease-specific biobanks. Some of these projects are small-scale in the sense that they involve only few partners. In other cases, projects may bring together ten or more different research centres several of which may be contributing biological materials collected in their own countries. A typical case is that a number of academic groups/centres have a joint research interest related to a particular disease (e.g. colorectal cancer, Type 2 diabetes). The efficiency and effectiveness of the research can be enhanced by joining forces implying that biobank resources may need to be shared. Besides exchanging ideas, knowledge, data and analysis results, samples may sometimes (but not always) be transferred from one place to another for the purpose of analysis. Sometimes, the researchers come to an agreement that all samples and/or data for practical reasons should be stored in one place. Normally, we can assume, this kind of “distributed collaboration” is not dependent on large infrastructure investments at the European level as the ones discussed above.²⁷⁰

Obviously, all collaboration activities involving biobanks cannot be coordinated through one Europe-wide network or one single model. However, in certain research areas, for example centred on a specific type of disease, it should be possible to achieve substantial benefits by establishing joint network-based infrastructures. Examples of such organisation already exist. The EuroBioBank, which is dedicated to research on rare diseases, is a case in point. It should be further investigated if this interesting organizational concept can be used a model for other research groups around Europe. The UK DNA Biobanking Network is another possible model.

The case of EuroBioBank²⁷¹

This is a network of biobanks providing human biological material (DNA, tissue, cell) for research on rare diseases. The establishment of the network was financed by the EU through FP5 from January 2003 to March 2006 (including 3 months extension). The consortium presently consists of 15 partners. There are 12 academic and private biobanks (Biological Resource Centres, BRCs) which together store a total of 155 000 documented samples collected in the following eight countries: France, Italy, Spain, Belgium, Slovenia, Malta, Germany, and Hungary. At present a total of 65 000 DNA samples and 15 000 tissue samples are available from existing collections:

	Cells	DNA	Tissue
No of collections	145	546	282
No of persons	5 038	40 981	8 952

Besides these biobanks, the consortium also includes two information technology partners, one academic and one commercial. Both are French. The project is coordinated by the European Organization for Rare Diseases (EURORDIS). From the

²⁷⁰ However, each group may, of course, benefit from the availability of a local core facility for biobanking. That is why Karolinska Institutet in Stockholm has established KI Biobank, which is hosting collections coming from different departments. Such a core facility has advanced equipment for handling of both samples and data. By storing samples in the KI Biobank, for example, the researchers who collected the samples gain access not only to state-of-the-art physical facilities and systems but also specialized biobanking competencies.

²⁷¹ This section is mainly based on EuroBioBank's website (<http://morgan.imag.fr:9443/eurobiobank/index.htm>) and Fabrizia Bigniami's presentation at the present ESTO project's kick off meeting in Seville on 20 January 2006.

beginning there was also a biotech company involved, but it left the consortium because of bankruptcy.

The overall aim of EuroBioBank is to help scientists to gain access to a critical mass of collections thereby accelerating research on rare diseases. By creating this project the partners are trying to achieve four objectives:

1. Promote the EuroBioBank network in order to improve the links between existing biobanks (in the field of rare diseases).
2. Harmonize and spread quality banking practices with regard to collection, preparation, transport, storage, and distribution of samples, adapted to each type of material; this is done through a Network Charter and Standard Operating Procedures (SOPs) adopted by all partners.
3. Distribute quality material and associated data through a dynamic updated database.
4. Disseminate knowledge and know-how through a dedicated website and specialized training sessions.

An important effect of the network is that it facilitates identification and localisation of available samples throughout these countries, thereby optimising the scientific use of existing collections. To make this possible the partners have set up a dedicated website through which the researchers can access a centralized database. The latter contains information on each sample. Appropriate information has been imported from local databases using a secured shared data protocol. The website represents the very core of the network and also displays other information on the network's activities. The network is open also to external stakeholders through several communication means. To further boost the creation of new collections and the exchange of material new partners from other European countries are welcome. On EuroBioBank's website it is explained how a researcher at one of the partner institutions can gain access to samples he or she would like to use for at certain study:

“When a researcher needs biological material, he only has to access the EuroBioBank website and use the search engine to find the samples required. One click on the biobank's e-mail address next to the desired sample and a form appears. The researcher simply fills the form out and sends it to the biobank to obtain the samples necessary for his research project. This way, the biological material is exchanged much more quickly, thus speeding up rare disease research.”

So far, thousands of samples have been exchanged in this way between the partners (approximately 6 800 in 2004, according to the website).

As to the promotion of quality banking practices, the partners have jointly developed harmonized SOPs and a Material Transfer Agreement that comply with the OECD's recommendations for BRCs²⁷². In this context, one expert made the following statement:

²⁷² OECD Best Practice Guidelines for Biological Resource Centres, 2007, OECD, Paris (<http://www.oecd.org/dataoecd/7/13/38777417.pdf>).

"Harmonisation as the key word in EU: Both at the legislative and scientific level, to reach high quality standards. Standard definition of «Biological Ressources Centre»: OECD recommendations as a starting point. Networking BioBanks to optimise resources and boost research more efficiently. A need for structural funds for the coordination and networking activities and the recognition of Biobanks public health value and as fundamental infrastructures -Reflection on public BioBanks' long term sustainability. Wide and coordinated communication to the general public and all interested parties".

The SOPs developed by EuroBioBank, have been published on the website and are now available to the scientific community. The network has also worked on ethical and legal issues related to these banking practices. For example, the partners have conducted a survey which is giving an overview of current legislation in the different member states represented at EuroBioBank.²⁷³

The EuroBioBank argues that it has been instrumental in increasing research on rare diseases. The partners have now worked together for more than three years, and it seems that they have succeeded to create a well functioning network where biosamples and related data are effectively exchanged. Researchers working on rare diseases in other European countries are now invited to become members. Assuming that long-term funding can be secured, the EuroBioBank will have a good chance to expand and play an even more important role for rare disease research in Europe.

The case of UK DNA Banking Network

The UK DNA Banking Network (UDBN) is an interesting example of biobanking infrastructure²⁷⁴ (see also chapter 2.2.1.7) The UDBN is managing samples and data on behalf of thirteen independent research groups ("collectors") working on different diseases. Today, the archive contains samples from 25 000 individuals (the target is 40 000, but the total capacity of existing facilities is over 100 000 samples).

The experience of using this model for managing samples and data is very positive. The UDBN has therefore proposed to scale up the network to the European level. The key idea behind this initiative, called European BioBanking Union (UBBU) is to create an EU research infrastructure to underpin investigative research in sample-based epidemiology. The focus would be solely on logistics and cooperation – not on investigation. UBBU would be a nodal network. The nodes could be either national or regional. The initial focus would be on linking disease-based collections existing in various European countries. By generating hypotheses on gene-environment interactions, in a second wave of genome-wide association studies, a case can be made for new population-based studies. UBBU cooperation and logistics should thus be designed to support future population-based studies.

Other examples of disease specific biobank networks

NUGENOB (Nutrient-gene interactions in human obesity: implications for dietary guidelines) is a randomised study of high vs. low fat content in a hypoenergetic diet for weight loss in 771 obese subjects. It was completed FP5 3-year project with 12 partners

²⁷³ Martin Uranga, A., Martin-Arribas, M.C., de Donato, J-H, and de la Paz, M.P., "Outstanding legal and ethical issues on biobanks: an overview on the regulation of member states of the EuroBioBank project", EuroBioBank, 2006 (www.eurobiobank.org).

²⁷⁴ www.dna-network.ac.uk

in 7 European countries, and delivered an analysis of effects on weight loss of a panel of SNPs in selected obesity-related candidate genes.

DIOGENES (Diet, obesity and genes) is an ongoing FP6 5-year integrated project with 29 partners in 14 European countries, which started in January 2005 (coordinator: University of Maastricht). Its main objective is to assess if high protein content and low glycemic index (post-meal rise in blood glucose) of the diet can prevent weight regain in obese after successful weight loss, and weight gain in the general population - and thereby prevent obesity and its co-morbidities.

HEPADIP (Hepatic and adipose tissue functions in the metabolic syndrome) is a FP6 5-year integrated multidisciplinary project with 27 partners in 11 European countries, starting November 1, 2005. Its main objective is to investigate the role of – and thereby search for possible diagnostic markers and therapeutic or preventive targets in – the liver and the adipose tissue in development of central components of the metabolic syndrome: the disturbed insulin signaling, glucose homeostasis and lipid metabolism. The HEPADIP planned biobanking activities consist in the exploitation of pre-existing biobanks associated with participating centres for genotyping of multiple SNPs in selected pertinent candidate genes, the collection of human liver biopsy material for genomic and proteomic analysis, storage of residual material and the testing of the predictive value of identified novel biomarkers of the hepatic and adipose tissue dysfunction related to metabolic syndrome components in associated and external biobanks as suitable and available, for example via GenomeEUhealth.

4 CONCLUSIONS

4.1 Biobanking in Europe

Based on the survey conducted, there is an acceleration in biobanking activities in recent years in Europe. While a few of the biobanks identified started collection in the 70's, they have been built up relatively recently (during the 90s) with 37% of the surveyed biobanks starting their activity after 2000, obviously reflecting the burst of genome-wide association studies and the search for disease susceptibility genes and diagnostic biomarkers after the completion of the human genome sequencing project.. The majority of the biobanks do not foresee an end to their sampling activities and indicate a high potential for growth, showing the dynamic nature of biobanking and an increasing role in research.

Significant variability emerged with regards to privacy and data protection requirements among biobanks in Europe. Although informed consent for approval of biobank-based research is almost ubiquitously required, the actual consent requirements and related procedures vary widely among biobanks, depending on the national laws and guidelines applied. The present survey demonstrates that the majority of biobanks have at least one type of consent form that allows tissue and data sharing. Yet, a significant proportion of them utilise more than one type of consent depending on the sample. The use of samples defined in the consent form is also highly varied, ranging from research on specific diseases to blanket (as practiced for example in the case of the UK biobank). Importantly, 13 respondents indicated that they do not apply consent at all. Six of them belong to Eastern European Countries with the rest based in Western Europe.

The role of research ethics committees is, in this context, gaining increasing importance, as shown by the large majority of the biobanks surveyed which are governed by an ethics board.

Although differences amongst practices could hamper collaborative research, our survey suggests that this may not yet be the case as more than half of the sampled biobanks had been involved in international collaborations and reported no major problems in sample sharing. This seems to be in line also with previous findings where "gift and exchange relations" were found to be the rule in biobanking interactions [Hirtzlin, 2003 #29]. As a consequence of that most of the respondents represented stand-alone (rather than networked) collections.

As one measure of the effectiveness of this biobanks in generating knowledge, only 16% of biobanks have not produced any scientific publication, a positive sign of the contribution of biobanks to medical research

4.2 Networking and Harmonisation

Experts widely recognised the need to improve collaboration and networking among the numerous existing biobanks, as well as new initiatives in Europe (and world-wide). Efficient organisation of these resources through the development, for example, of an infrastructure would potentially facilitate financial sustainability and greatly contribute to the rapid progress of research and development of better diagnostic and therapeutic

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approaches. The model most favoured involved the development of a **virtual biobank** that would allow networking of biobanks across different countries and centralisation of data rather than samples. However, several organisational challenges (wide variation in biospecimen collection, processing, storage techniques, data comparability, definitions) may hamper such an effort. The lack of uniform regulatory and ethical requirements and/or practices may pose an additional barrier.

It should be noted that some of the experts considered the virtual biobank as difficult, very resource demanding. A web-based meta-database on European biobanks (possible in collaboration on a world-wide basis with P3G) is seen as a cost-effective first step, promoting international collaboration by providing access to biobanks world-wide. The European Commission recognised the importance of international biobank projects and many of them have been funded and established in the context of the EU Framework Programmes (e.g. GenomEUtwin²⁷⁵, EuroBioBank²⁷⁶, NUGENOB²⁷⁷, PHOEBE²⁷⁸ and BBMRI²⁷⁹, among others). The European Commission, DG Research in partnership with two EU-supported biobanking projects, PHOEBE and BBMRI, has recently organised a "Networking Meeting for EU-Funded Biobanking Projects", gathering the coordinators or senior investigators of 28 EU-funded projects with a significant biobanking component. The meeting identified challenges and critical issues to be addressed for the development, success and sustainability of biobanks. Among the recommendations formulated, the adoption of measures in favour of harmonisation was considered one of the most important [59].

It has been widely recognised by all stakeholders that in order to accelerate scientific discovery it will be critical to improve biobank quality, interoperability and sustainability. The report from the aforementioned "Networking Meeting for EU-Funded Biobanking Projects" [59], also pinpoints this issue raised by the responsible investigators of these projects, and there is a general call for harmonisation of sample and data storage practices (standard operating procedures for both) but also clear procedures for ethical reviews and clarification of legal international requirements for data and sample sharing between different countries. Harmonization was also indicated as the critical process to stimulate and accelerate scientific discovery in a recent workshop jointly organized by P³G, PHOEBE, and BBMRI and sponsored by the European Science Foundation [59].

Based on the analysis thus far, it is evident that there is a need for creating an umbrella organisation which would aim at networking biobanks thus also helping to improve their collaboration. Such an organisation should have an international focus and could be a web-based (virtual) network with a physical hub. Some models for such networking have been discussed earlier. However, several barriers must be overcome to ensure the success of such an endeavour.

²⁷⁵ <http://www.genomeutwin.org>

²⁷⁶ European Network of DNA, cells and tissue banks for Rare Diseases (<http://www.eurobiobank.org>)

²⁷⁷ Nutrient-Gene Interactions in Human Obesity (<http://www.nugenob.com>)

²⁷⁸ Promoting Harmonisation of Epidemiological Biobanks in Europe (<http://www.phoebe-eu.org/>)

²⁷⁹ Biobanking and Biomolecular Resources Research Infrastructure (<http://www.bbmri.eu>)

4.2.1 *Regulatory aspects*

Bomedical research in Europe still faces substantial problems when it comes to the exchange of samples and in particular data. The **sample/data** dichotomy (are they the same or should they be treated as one?) still poses a problem. While the Data Protection Directive serves as a benchmark for the exchange and flow of data, there seems to be no competence of the EU to govern the exchange of samples as this part of regulation falls under property law in many Member States. Interestingly, the problems in practice are rather observed in the field of data protection. To some extent this situation is owed to the fact that the field of Public Health is not harmonized in the Data Protection Directive.

The current discussion stresses the protection of individuals adequately but it should not be neglected that the Directive aims to enable a free flow of information in a common European zone. Data protection issues in biobanking need to be seen in the wider context of health information, which includes cancer registries, e-health, and communicable disease prevention to name just a few. The current Data Protection Directive to some extent facilitates a different interpretation, in particular through the wording of Art 8 (4). Thus, a interpretation which uses Art 8 (3) would be favorable to achieve a better harmonization in Europe. Finally it was stressed that such an open research space should not hamper the protection of citizens per se as better barriers and the application of new privacy-enhancing technologies can protect the data of citizens. A high level of data protection is essential ensure the necessary public trust in Public Health institutions an medical research.

Recently, several countries have set up specific regulations for biobanking, biomedical research and the use of genome-based information. For the EU Member States these new regulations also have to be interpreted and assessed by applying the principles of the existing Data Protection Directive. Problems are raised by the differences in regulatory frameworks across Member States:

- Many researchers who share samples and data across jurisdictional boundaries may be operating unlawfully because of the differences between the legal requirements in Europe [24].
- It is difficult to ascertain what the law is in different member states and it is also time consuming and expensive for researchers to find out.
- This is ultimately detrimental to the development of genomic research, which is increasingly dependent upon large sample sizes and the networking of collections.
- It is possible that not all participants in research have the same protections across the different member states of Europe.
- It is also possible that research is not equally competitive across all member states as different standards apply across Europe.

Other major challenges for setting up an EU-biobank connected globally are hampering national regulations and rules that prohibit the transfer / export of DNA samples. Here, international agreement should be reached on the transfer of human DNA samples for research purposes (UNESCO, WHO, etc) for removing these barriers. The focus should be on open global (rather than European) transfer of DNA samples for research.

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A further barrier to European networking is the differences in data protection measures in the Member States (differences in definitions and in the wording of domestic legal documents that implement Directive 95/46/EC.) The reasons for such differences are due to:

- The ‘margin of appreciation’ that is given to Member States when implementing directives.
- The lack of a binding legal instrument for biobanks at a European or international level, or an international regulatory structure that applies specifically to biobanks. In the Explanatory Memorandum to the Recommendation of Council of Ministers Recommendation (2006) 4 that was passed on the 15th of March 2006, it was stated that:- *“There is a need for a common international framework, especially in view of increasing border flow of biological material of human origin and data and in the light of important third party interests (e.g. the pharmaceutical and biotechnology industries).”*
- The fact that the Convention on Human Rights and Biomedicine is voluntary and has not been signed by, inter alia, the UK and Germany.

In order to fulfil this legal vacuum specific guidelines have been drafted in member states by parliaments and National Ethics Committees. For example, the Nationaler Ethikrat and the French Comité Consultatif National d’Ethique have both written specific national guidelines for biobanks²⁸⁰. In countries, such as Estonia and Iceland, which have undertaken to establish national population biobanks or health-related databases, specialist legislation has been drafted to deal with the complexity of the issues that surround such activities. In several countries in Northern Europe specialist biobank legislation has been developed. However these measures have led to diversity rather than uniformity of practice.

The general law of the European Union and the Member States does not apply readily to biobanks that are used for genomic research. For example, there can also be different requirements that apply for biosamples and information, which can be problematic in the case of genomic research where it is difficult to make a clear distinction between the samples and the information contained in the sample. In practice, principles of data protection are often applied to samples in order to ensure a coherent regulation of the field.

A prerequisite to building networks for biobanks across Europe is the better understanding of the current legal framework and the nature of the legal obstacles and incentives.

Consent issues - Informed consent is a standard ethical requirement in medical research, and thus applies also to biobank-based research. In this context, informed consent is the process in which a potential sample donor receives the relevant information and decides whether or not to authorize storage and various uses of the sample, based on that information and his or her own values. Although informed consent for approval of biobank-based research is almost ubiquitously required, the actual **consent requirements** and related procedures vary widely among biobanks,

²⁸⁰ Nationaler Ethikrat 2004 ‘Biobanks for Research – Opinion’ and Comité Consultatif National d’Ethique 2003 Opinion No.77.

Conclusions

depending on the national laws and guidelines applied, which may pose difficulties for collaborative research. The present survey demonstrates that the majority of biobanks have at least one type of consent form that allows tissue (63.5%) and data (69%) sharing. Yet, a significant proportion of them utilise more than one type of consent depending on the sample. The **use of samples** defined in the consent form is also highly varied, ranging from specific to blanket. Importantly, 13 respondents indicated they don't apply consent at all.

Seeking reconsent from participants, while often viewed as burdensome, is nevertheless explicitly required in many cases. In France, for instance, researchers have a legal obligation to renew consent before reusing donors' samples for a new purpose, and an effort in Canada to advance population genomics research must renew consent for participants every 5 years.

Generally, public preferences for consent depend on the context, including the country or region, the tissue type (e.g., cancer, brain), and the situation (treatment versus death), to name only a few.

Two issues of critical concern in biobanking are recontacting study participants with research results and getting participants' reconsent to use their specimens in further studies, including for previously unforeseen purposes. Both of these issues highlight the importance of balancing the needs of patients with those of scientists. The changing landscape with respect to these and other ethical and legal considerations can have long-term implications for health care and disease. Further, differences between countries in handling these issues can pose challenges for international harmonisation.

While some studies recontact participants in cases of abnormal results, most do not provide participants with specific information but instead may offer aggregate feedback on the progress of the study via Web sites and newsletters. This presents both ethical and legal concerns in known cases of serious, treatable conditions and thus has been a topic of ongoing discussion. Some contend that recontacting participants with individual results would promote public trust while offering meaningful return for individuals' participation.

Further analysis as to whether an open consent is permissible under the existing data protection legislation is also required. Informed consent is a standard ethical requirement in medical research, and thus applies also to biobank-based research. The consent requirements and related procedures vary widely among biobanks, depending on the national laws and guidelines applied, which may pose difficulties for collaborative research.

Purpose - A related observation is that any collection of samples (a biobank for reasons other than research) could transform into a biobank for research or, at least could be used for biobank research purposes, wholly or partially, permanently or temporarily. For example, the blood stored in the Dutch Sanguin transfusion bloodbank has been used (with full consent) by researchers to find biomarkers for RA (section 2.2.3.4. Biobanks in the Netherlands). A similar phenomenon may occur if cancer registries change into biobanks. Does this potential for conversion mean that these potential 'incidental convertibles' should be governed by the proposed harmonisation initiatives and be covered by the proposed virtual biobank and umbrella organisation? In

accordance with the Data Protection Directive one might argue that such a change of purpose requires certain legal safeguards.

4.2.2 Funding sustainability

On EU Commission level a virtual, dynamic international networking platform could help consolidate and illustrate the available (European) biobank activities, even though networking and capacity building strategies for different biobank clusters require different ways of coordination. A distinction has to be made between “networking principles” and “capacity building principles”.

There is need for assuring sustainability of biobanks. Most funding resources do not accept requests for funding of project for periods exceeding 3 to 5 years. However, biobanks by definition are projects that must be run for at least 20 years, or even without a preset closing date. For an EU-wide biobank, whether physical (population collection) or virtual (a network of biobanks), there must be a funding structure assuring sustainability over long (>20 years) periods.

Some experts claims a need for a 'salvation fund' for saving local European collections (either private or public) that are about to be lost due to lack of funding. Surely, scientific criteria must be applied for eligibility to be saved by such a fund. But the necessity is real – it already happened and valuable collections were lost due to lack of funding. (An example from Israel was mentioned: is IDgene Pharmaceuticals Ltd., a private company which ceased activities in 2004, and the fate of its collection is uncertain at the moment²⁸¹). Whatever model will be realized, e.g. a “virtual biobank” (networking among existing biobanks) or an International Umbrella Organization (network of population-based biobanks) on global level, the EC could become active in the biobank field through future EU Research activities (FP8 and beyond) for the clarification of various open questions, such as:

- ⇒ Establish biobanking as a new area of research;
- ⇒ Develop biobank operation guidelines (data-driven-public comments);
- ⇒ Promote professional oversight of biospecimen standards;
- ⇒ Develop new technologies for biobank operations;
- ⇒ Carry out studies on the whole array of patient derived material ranging from tissues to body fluids, blood cell lines xenografts useful for translational cancer research;
- ⇒ Carry out feasibility study on the development of a European biorepository accreditation program
- ⇒ Encouraging networking and self-governance
- ⇒ Encourage better data-sharing from the private sector – mostly from the pharmaceutical industry
- ⇒ Support the protection of citizens by EU-wide legislation (or at least regulations) prohibiting the use of genomic or proteomic data collected during research for employment or insurance reasons (see separate mail with the Israeli Genetic Information Law 2000)

²⁸¹ <http://www.biotechcareercenter.com/IDGene.html>

Conclusions

- ⇒ Develop EU-wide oversight mechanism to see that benefit sharing from research using genomics databases and leading to marketed products (drugs, devices and diagnostics) really takes place. This would be essential for building public trust in large genetic databases.
- ⇒ Develop training activities across and outside the EU Virtual Biobank should also represent one major element for development of biobanks and of the research with human biological samples.

In this context, there is an increasing mobility of samples and data across national borders, in particular within Europe. In some cases, such as the European Prospective Investigation into Cancer and Nutrition (EPIC)²⁸², samples collected in different countries, and associated data about the donors, are stored in a central biobank. But in other cases, samples are sent abroad for being analysed at one of the participating research centres, which is specializing in carrying out this particular task. It may also be that no samples are sent at all. Instead, data and information obtained through the research is exchanged among participating centres. Sometimes a “virtual biobank” is created where data is kept in a central database, while the collected samples are stored locally. TuBaFrost and EuroBoNet are two examples of such partnerships managed by the Organization of European Cancer Institutes. Samples are here stored in 9 and 25 locations respectively.

4.2.3 Appropriate benefit sharing and public engagement in biobanking activities

On the question of insurance of appropriate benefit sharing and public engagement in biobanking activities, it is clear that research results will be more valid given the possibility of making inferences to large populations (European population). There is need for the private sector to collaborate with public databases, and the strong need for better biomedical data-sharing from pharma companies, which displays a key policy issue. Such data would be invaluable in the long term for improving drug safety and efficacy.

Clearly, an EU Biobank Networking Structure/Platform must include some mechanism for benefit sharing back to the community, for building public trust and reducing public fears from large genetic databases. One way could be to include representatives from patient groups in a body which oversees sharing of benefits from companies who received samples or data from the biobank (medicines / diagnostics at reduced costs to communities were the DNA samples were donated). The same representative individuals should also take part in on-going consultation process on biobank policies (collection of samples and data; sample distribution and data access; networking on a global scale; feedback from researchers; etc.). It needs to be clearly communicated how Europe, and in this sense each citizen in Europe, profits from a strong infrastructure for medical research. Donors may be more likely to see the positive impact of research on future generations in disease specific biobanks. Communication tools are needed which help citizens to understand the long-term fruits of biobanking and which demonstrate that they support the common good by sharing samples and data with researchers.

²⁸² <http://www.iarc.fr/epic/>

4.3 Ways forward

It seems evident and widely recognised the recognition that biobank quality, networking, and sustainability are critical to accelerating scientific discovery. Building and sustaining biobanking infrastructures and ways to maximise their scientific value and international usage have become immediate goals.

To help promote networking of biobanks and thus maximising the public health benefits to be harnessed at least some degree of harmonisation must be achieved. Whether this should be achieved solely at level of legal/regulatory requirements and practices and/or by technical standardisation requires further investigation. Experts suggested the establishment of an **international** (rather than just European) **umbrella (or network) organization**, which would establish common operating procedures in e.g. genotyping and phenotyping, quality assurance, information management, and common approaches to ethical and legal requirements such as consent, data protection and privacy, feedback of information to donors, etc. In this context, already existing initiatives with similar objectives [examples] should be taken into consideration. On a global level p3g and ISBER have been working in this domain and in Europe the recently established BBMRI has shown great efforts to take Europe to the next level of networking in biobanking.

On basis of the knowledge gathered in this report one might conclude the European Commission to be the ideal platform for the creation of a European framework for biobank networking through a robust, flexible, scalable, and secure bioinformatics system that supports the collection, processing, storage, annotation, and distribution of biospecimens for research purpose and data using standard operating procedures based on best practices, while ensuring that the privacy interests of biospecimen donors are preserved. The current development rather envisages having an independent, community driven approach. While BBMRI has proven to become a successful enterprise for the networking of biobanks in Europe and beyond, a sustainable financing and non-discriminatory access to services and tools has to be guaranteed. Apparently a long-term commitment from both the Member States and the European Commission would be needed to stimulate these activities. Thus, both options require a strategic decision on the side of the European Commission.

If a European Biobank Networking Platform were successful in facilitating cooperation and creating a European biobanking logistics system,

“then it would, de facto, create or increase the long term security of existing national biobanks and biobanking infrastructures (the distinction is between an investigative project and a pure logistics operation). Such long term security is essential if the full value to molecular epidemiology of population-based and case-based studies is to be realised. If the.... concept is developed through cooperation between existing biobanks and biobanking infrastructures, then that cooperation will itself help to lay the basis for a successful union that also can engage successfully with others in the biomedical community and will strengthen (rather than detract from) those existing organisations.”
(European Biobanking Union: Flyer, MartinYuille, 2006).

Conclusions

Today 2010	Tomorrow 2025
Wide variation in biospecimen collection, processing, and storage techniques, and difficulty obtaining sufficient samples for large-scale genomic and proteomic studies	Single, European/nationally coordinated biospecimen collections, employing standardized procedures for storage and distribution, as well as collection of associated clinical data.
No uniform bioinformatics system existing that is capable of remote searching and data entry	European coordinated and centralized bioinformatics system for all aspects of specimen and data collection and dissemination
Restricted access to researchers outside institution at which specimens are collected	Extensive, external specimen-sharing of “EU biobank platform” affiliated collection centres
Consent procedures that are variable and may be insufficient for future genomics/ proteomics research	Standardized consent for all specimens tailored to genomic and proteomic studies while respecting the local and cultural differences/values.

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ANNEX 1: SURVEY QUESTIONNAIRE

1. Name of the biobank:	
2. Contact person:	
3. Contact person Email:	
4. Contact person Phone (include prefixes):	
5. Does the Biobank consist of a partnership of banks?	Yes <input type="checkbox"/> No <input type="checkbox"/>
6. Does the Biobank consist of several geographical locations:	Yes <input type="checkbox"/> No <input type="checkbox"/> If Yes how many
7. Is it "owned" or is there a responsible organisation	Yes <input type="checkbox"/> No <input type="checkbox"/>
8. Name of "owner"/organisation	
9. Principal reason for the creation of the Biobank (Mark all that apply)	<input type="checkbox"/> Public Research <input type="checkbox"/> Private commercial research <input type="checkbox"/> Clinical Research diagnostics <input type="checkbox"/> Others, please specify
10. Participant Selection (Mark all that apply)	<input type="checkbox"/> Random, population <input type="checkbox"/> Disease/condition specific <input type="checkbox"/> Demographic specific (e.g. isolates) <input type="checkbox"/> Others, please specify

Annex 1

11. Collection of samples done by:	<input type="checkbox"/> Associated Hospital staff <input type="checkbox"/> Centres/Staff specifically employed for the Project <input type="checkbox"/> Primary care workers (including hospital staff) <input type="checkbox"/> Patient interest groups <input type="checkbox"/> Others, please specify
12. Current size of the repository	Number of individuals: Number of families:
13. Targeted size of repository	Number of individuals: Number of families: <input type="checkbox"/> Open, no target size
14. Sampling period	Year start of sampling Year end of sampling (if applicable)
15. Type of material in the biobank	<input type="checkbox"/> DNA <input type="checkbox"/> Serum <input type="checkbox"/> Whole Blood <input type="checkbox"/> Tissues <input type="checkbox"/> Others, Please specify:
16. Storage of Samples	<input type="checkbox"/> Samples room temperature <input type="checkbox"/> 4°C refrigerator <input type="checkbox"/> -20°C freezer <input type="checkbox"/> -80°C freezer <input type="checkbox"/> liquid nitrogen

Annex 1

17. Type of Data kept	<input type="checkbox"/> Demographic <input type="checkbox"/> Ethnicity <input type="checkbox"/> Medical/Phenotype <input type="checkbox"/> Environmental/lifestyle <input type="checkbox"/> Genetic data <input type="checkbox"/> Others, Please specify:
18. Database connectivity	<input type="checkbox"/> Stand-alone <input type="checkbox"/> Networked – intranet <input type="checkbox"/> Networked – internet – restricted access <input type="checkbox"/> Networked – internet – open public access <input type="checkbox"/> Others, Please specify:
19. By whom is the biobank used for research?	<input type="checkbox"/> The researchers who collected the samples <input type="checkbox"/> Other researchers at the same institution <input type="checkbox"/> Other researchers in the same country <input type="checkbox"/> Other researchers in other European countries <input type="checkbox"/> Other researchers from other parts of the world
20. Access availability:	<input type="checkbox"/> Payment <input type="checkbox"/> Free <input type="checkbox"/> Restricted if yes please specify how:
21. Decision on Access	<input type="checkbox"/> Curator/Official manager <input type="checkbox"/> Governing board <input type="checkbox"/> Others, Please specify:

Annex 1

22. Is the Biobank regulated by an Research Ethics Board approval	<input type="checkbox"/> Yes <input type="checkbox"/> No
23. Does your current consent form /legal framework allow sharing of : (i) tissues (ii) data with other researchers outside country? yes no	Tissues: <input type="checkbox"/> Yes <input type="checkbox"/> No Data: <input type="checkbox"/> Yes <input type="checkbox"/> No
24. Is it possible for donors to withdraw their consent to store samples in the biobank?	<input type="checkbox"/> Yes <input type="checkbox"/> No
25. Type of consent (Please mark all that are relevant):	<input type="checkbox"/> No explicit consent <input type="checkbox"/> Consent to a specific study <input type="checkbox"/> Consent to research in a certain research area <input type="checkbox"/> Consent to biomedical research <input type="checkbox"/> Blanket consent <input type="checkbox"/> Others, Please specify:
26. Is any information arising from biobank studies referred back to individual (personal results)	<input type="checkbox"/> Yes (if consented to) <input type="checkbox"/> Yes (in all cases) <input type="checkbox"/> No
27. How is privacy of the donors protected?	<input type="checkbox"/> Anonymization (no code key) <input type="checkbox"/> Coding (code key) <input type="checkbox"/> Others, Please specify:
28. Are researchers required to feed back results to the biobank?	<input type="checkbox"/> Yes <input type="checkbox"/> No
29. Is publication of research results monitored?	<input type="checkbox"/> Yes <input type="checkbox"/> No

Annex 1

<p>30. How many collaborations have been carried out so far utilising the Biobank resource?</p>	<p><input type="checkbox"/> none</p> <p><input type="checkbox"/> one</p> <p><input type="checkbox"/> 2-10</p> <p><input type="checkbox"/> more than 10</p>
<p>31. How many publications are based on the biobank?</p>	<p><input type="checkbox"/> none</p> <p><input type="checkbox"/> 1- 10</p> <p><input type="checkbox"/> 11-100</p> <p><input type="checkbox"/> more than 100</p>
<p>32. Has the biobank been used in international projects?</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If Yes give examples:</p> <div style="height: 150px; border: 1px solid black;"></div>

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Additional Comments:

ANNEX 2: EU FUNDED PROJECTS

Biobank	Contact/Website
ADDNET	harry.holthofer@helsinki.fi
Autorome	hans-juergen.thiesen@med.uni-rostock.de
Brainnet, Brainnet II	http://www.brainnet-europe.org/
CCPRB	joakim.dillner@mikrobiol.mas.lu.se
COGENE	eero.vuorio@utu.fi
DIOGENES	http://www.diogenes-eu.org/WeightLossStudy/NL/Default.asp
Early Lung Cancer	http://www.euelc.com/partnerships.htm
ECARUCA	http://agserver01.azn.nl:8080/ecaruca/ecaruca.jsp
ELSAGEN	http://www.elsagen.net/
EMBIC	http://www.embic.org/
EMUMITOCOMBAT	j.smeitink@cukz.umcn.nl
EPI-HPV-UV-CA	J.N.Bouwes_Bavinck@lumc.nl
ERICBSB	joakim.dillner@mikrobiol.mas.lu.se
ERSPC	http://www.erspc.org/
EUGENE2	http://www.eugene2.com/
EUGINDAT	http://www.ub.es/eugindat/
EUHealthGen	http://www.wellcome.ac.uk/doc_WTX026759.html
EURAPS	http://www.euraps.org/home.htm
EuroBioBank	www.eurobiobank.org
EUROCLOT	http://www.twin-research.ac.uk/euroclot.html
EuroGentest	www.eurogentest.org
EUROSCA	www.euroasca.org
EUROSPAN	http://www.chs.med.ed.ac.uk/phs/staffprofile.cfm?profile=hcampbel
EUROWILSON	http://www.eurowilson.org/
EVGN	http://www.evgn.org/
EXGENESIS	http://gnp8.polestar.demo.eibs.co.uk/projects/exgenesis
GALEN	paul.vancauwenberge@UGent.be
GEHA	http://www.geha.unibo.it/
GENADDICT	i.kitchen@surrey.ac.uk

GENESKIN	g.zambruno@idi.it
GenomEUtwin	http://www.genomeutwin.org/
Genomos	uitterlinden@endov.fgg.eur.nl
GenOSept	http://www.esicm.org/PAGE_genosept
HUMGERI	fesus@indi.biochem.dote.hu (EU-funded, FP6)
IMPROVE	rodolfo.paoletti@unimi.it
MITOCIRCLE	http://mitocircle.unimaas.nl/
MOLPAGE	http://www.ocdem.com/composite-108.htm
MOLTOOLS	http://www.moltools.org/default.asp
NUGO	http://www.nugo.org/everyone
OISTER	http://www.dkfz.de/oister/OISTERnav.html
PHGEN	www.phgen.eu
P-MARK	http://www.p-mark.org/
POLYGENE	www.uvs.is ; eirikur@uvs.is ; oddny@uvs.is ; thorunnr@uvs.is
Population Biobanks	camilla.stoltenberg@fhi.no
PRIVIREAL	http://www.privireal.org/
PWS	http://pwsa.co.uk/main.php?catagory=14&sub_catagory=62
UBIGENES	pnavas@dex.upo.es
VIRASKIN	ola.forslund@mikrobiol.mas.lu.se
VIRDIAB	http://www.uta.fi/laitokset/laaket/VIRDIAB/

ANNEX 3: BIOBANKS IDENTIFIED IN EUROPE

Name of Biobank	Contact/Website
<i>Austria</i>	
BioResource-Med	http://www.bioresource-med.com/
Cells and Tissue Bank Austria	http://www.ctba.at/
The Austrian Tissue Bank, Österreichische Gewebebank GmbH	http://www.tissuebank.at/
Lifecord	www.lifecord.at
VITA 34 GmbH Österreich	www.vita34.at
Vitacord, Gesellschaft für Stammzellenlagerung m.b.H	www.vitacord.at
<i>Belgium</i>	
Biobank of the University Hospital of Liege	
DNA Bank of the Renal Unit of the Catholic University of Leuven	
Tissue Bank of the University Hospital Saint-Luc	http://rch.sia.ucl.ac.be:8820/unit_to_printer?unit=ORTO&newlang=fr
Belgian Cord Blood Bank	
Cryo-Save	www.cryo-save.com
<i>Bulgaria</i>	
National DNA Bank of the Republic of Bulgaria	http://ivo.medfac.acad.bg/
Tissue Bank Pirogov	http://www.pirogov.net/
<i>Denmark</i>	
The National Danish Birth Cohort	http://www.ssi.dk/sw9314.asp
The National PKU Biobank	
The Diet, Cancer and Health Biobank	http://www.cancer.dk/epi/afdelinger/kkh/undersogelsen/diet,+cancer+and+health.asp
The Copenhagen City Heart Study	http://healthsciences.ku.dk/
The Copenhagen General Population Study	http://healthsciences.ku.dk/
The Copenhagen Ischemic Heart Disease Study	http://healthsciences.ku.dk/
The Copenhagen Carotid Stenosis Stroke Study	http://healthsciences.ku.dk/
The Copenhagen Breast Cancer Study	http://healthsciences.ku.dk/
The Danish Twin Registry	http://www.dtr.sdu.dk/?sprog=eng , http://www.sdu.dk/health/
NUGENOB	www.nugenob.com
ORG/ADIGEN	http://www.ipm.hosp.dk/
Pelvic Mass	hogdall@dadlnet.dk
Danish HPV Cohort	www.cancer.dk
The Danish Psychiatric Biobank	http://www.ribp.dk/page/page.php?page=5&tid=7&sid
Research Centre for Prevention and Health	allin01@glostruphosp.dk
<i>Estonia</i>	
Estonian Biobank	http://www.ebc.ee/EBC/

	http://www.geenivaramu.ee/
Finland	
KTL Biobank	http://www.ktl.fi/portal/english/
The Finnish Twin Cohort	http://www.twinstudy.helsinki.fi/ , http://www.kttl.helsinki.fi/content_english.asp?route=4.835.838
Helsinki Sudden Death Study (Tampere University)	http://www.uta.fi/laitokset/laaket/bio/research/forensicmedicine.html
Tampere Coronary Study (TCT)	http://www.uta.fi/laitokset/laaket/bio/research/forensicmedicine.html
Tampere Acute Coronary Syndrome (TACOS) Study	http://www.uta.fi/laitokset/laaket/bio/research/forensicmedicine.html
France	
Généthon DNA and Cell Bank	www.genethon.fr
Biobanque de Picardie	www.biobanque-picardie.com
Germany	
Jose Carreras Cord Blood Bank Düsseldorf	http://www.stammzellbank.de/
European Searchable Tumour Line Database (ESTDAB)	http://www.medizin.uni-tuebingen.de/estdab/
KORA-gen biobank collecting DNA	http://www0.gsf.de/kora-gen/index_e.html
Kryoforschungs- & Demonstrationsbank der Fraunhofer Gesellschaft "Eurocroyo SAAR"	www.ibmt.fraunhofer.de
Patient DNA collection at Institute of Human Genetics Heidelberg	http://www.klinikum.uni-heidelberg.de/Humangenetik.5035.0.html http://www.klinikum.uni-heidelberg.de/Mitarbeiter.6978.0.html?&L=0
Danubian Biobank Consortium	http://www.uni-regensburg.de/Fakultaeten/Medizin/Klinische_Chemie/englstart.html
Human Melanoma Biobank	http://www.klinikum.uni-heidelberg.de/index.php?id=6969
ITI DNA-Bank	http://www.iti-ma.blutspende.de/
Regiscar	www.regiscar.uni-freiburg.de/
Tissue Bank, Charité – Universitätsmedizin Berlin	http://www.charite.de/itm/Gewebebank/Gewebebank.html
Greece	
Hellenic Cord Blood Bank	cstav@ath.forthnet.gr
Hungary	
NEPSYBANK	www.biobank.hu
ASTHMA	www.biobank.hu
Uzsoki Teaching Hospital	www.biobank.hu
Preterm infants and full-term neonates	www.biobank.hu
"Prof. Korányi András" Dunántúli Transdanubian Génbank	www.biobank.hu
ADULT COELIACIA	www.biobank.hu
Biobank of the Cardiovascular Research Group of the Hungarian Academy of Sciences-	www.biobank.hu

Semmelweis University	
CROHN	www.biobank.hu
FAMILIAR DEAF	www.biobank.hu
HEART ATTACK	www.biobank.hu
HUNTINGTON	www.biobank.hu
METABOLIC SYNDROME	www.biobank.hu
MITOCHONDRIAL DISEASE	www.biobank.hu
ROMA	www.biobank.hu
SHIZOFRENIA	www.biobank.hu
STROKE	www.biobank.hu
KRIO Institut	www.krio.hu
<i>Iceland</i>	
Icelandic Biobank (deCode)	www.decode.com
UVS Biobank (decode)	www.decode.com
The Icelandic Cancer Society Biological Specimen Collection	http://www.krabb.is/?PageID=196
Reykjavik Heart Study	
Tissue Archives, University Hospital in Reykjavik	http://www4.landspitali.is/lsh_ytri.nsf/htmlpages/index.html
<i>Italy</i>	
Istituto Nazionale Neurologico Carlo Besta	http://www.besta-miopatologia.it/moralab_italiano/morabancadati.htm
Naples Human Mutation Bank of the Cardiomyology and Medical Genetics (NHGMB)	http://www.cardiomiologia.it/cardiomiologia/FILES/ednabank.html
Centre of Transfusion Medicine, Cellular Therapy and Cryobiology	http://www.policlinico.mi.it/
The Neuromuscular biobank, Department of Neurological Science, University of Milano	
Bank of DNA cell line and nerve-muscle-cardiac disease	http://www.centrodinoferrari.com/sito/servizi/diagnostica_banca.html
University of Padova, Department of Neurosciences Neuromuscular bank	www.unipd.it
CNRB - Centro Nazionale per le Risorse Biologiche	http://www.cnr.it/
European IgA nephropathy Biobank	http://www.igan.net/
Center of Transfusion Medicine, Cellular Therapy and Cryobiology	http://www.policlinico.mi.it/
<i>Latvia</i>	
Latvian Genome Database	bmc.biomed.lu.lv/gene , www.lu.lv
<i>Luxembourg</i>	
Integrated BioBank of Luxembourg	www.ibbl.lu
<i>Malta</i>	
Biobank Laboratory of Molecular Genetics	http://www.biotech.um.edu.mt/
<i>The Netherlands</i>	
Erasmus MC Tissue Bank	http://www2.eur.nl/fgg/pathol/vtb/index.htm

EORTC VTB Biobank	http://www.erasmusmc.nl/
TuBaFrost	http://www.tubafrost.org/
BioBank Maastricht	http://www.biobank.unimaas.nl/index.html
LifeLines Biobank	www.lifelines.nl
Netherlands Brain Bank	http://www.nih.knaw.nl/
EuroBoNeT Biobank	http://www.eurobonet.eu/
The Chronic Kidney Diseases project	m.r.daha@lumc.nl
Bloodbank of rare bloodgroups of the Council of Europe	www.sanquin.nl
Cells4Health	http://www.cells4health.com/
Cryo-Save	www.cryo-save.com
Norway	
JANUS Serumbank (Cancer Registry of Norway)	http://www.kreftregisteret.no/ramme.htm?start.htm
HUBRO (Health Study of Oslo)	http://www.fhi.no/
OPPHED (Health Study of Oppland and Hedmark)	http://www.fhi.no/
HUNT Biobank (Health Study of Nord-Trøndelag)	www.ntnu.no
Tromsø Health Survey	http://uit.no/samfmed
HUSK (Health Study of Hordaland)	www.helse-bergen.no
MoBa (The Norwegian Mother and Child Cohort Study)	http://www.fhi.no/
Sami Health Survey	http://uit.no/samfmed
Women and Cancer	http://uit.no/samfmed
Poland	
Family Stem Cells Bank ActiVision Life SA	
Department of Transplantology and Central Tissue Bank/Research Tissue Bank	
Collection of DNA	
Romania	
Skin Bank of the Center of Excellence for Scientific and Technological Research	ENESCUDR@hotmail.com
Bone bank	http://domino.kappa.ro/telemed/ortopedia.nsf/Home/Page?OpenDocument
COLENTINA	http://www.spitalul-colentina.ro/
Heart Valve Bank Timisoar	http://www.umft.ro/en/r_index.html
HUMAN SKIN LIQUID NITROGEN STORAGE DEVICE	ileana.florin@webline.ro
IVF Center, „Victor Babes” University of Medicine and Pharmacy, Timisoara	http://www.umft.ro/en/r_index.html
Marburg Bone Bank Lobator SD-2	http://www.foisor.ro/index.php?lang=en
MED NEW LIFE	http://www.med-new-life.ro/
MEDSANA BUCHAREST MEDICAL CENTER	http://www.medsana.ro/

M.G. – Internatioanal Center RUA	gina.munteanu@yahoo.com
University Hospital “Panait Sarbu” Bucharest Assisted Reproduction Departmen, Sperm Bank, Embryo Bank	http://www.psarbu-fiv.ro/
Oftalmologie - Spitalul clinic de urgenta militar central	
<i>Slovak Republic</i>	
Eurocord Slovakia	http://www.eurocord.sk/
<i>Slovenia</i>	
Neuromuscular Biobank of University of Ljubljana, Medical Faculty	http://www.mf.uni-lj.si/
<i>Spain</i>	
National DNA Bank	http://www.bancoadn.org/
Spanish bank of biological samples from Rare Diseases (IIER)	http://www.isciii.es/htdocs/index.jsp
<i>Sweden</i>	
Medical Biobank	http://www.umu.se/phmed/naringsforskning/forforskning/Medical_Biobank/indexB.htm
Northern Sweden Maternity Cohort	
Malmö Preventive Medicine	http://www.med.lu.se/english
Malmö Diet & Cancer	http://www.med.lu.se/english
Malmö Microbiology Biobank	http://www.med.lu.se/english
Botnia Study	http://www.botnia-study.org
”Biobank SC153”	http://www.med.lu.se/english
Karolinska Instiutet Biobank	http://www.meb.ki.se/biobank/about.php
Swedish Institute for Infectious Disease Control Biobank	http://www.biobanks.se/swedishinstitute.htm
PKU Biobank	
ULSAM	
ABIS (All babies in Southeast Sweden)	http://www.liu.se/hu/ihm/abis/index.htm
Epidemiology Group, Sahlgrenska University Hospital	http://www.sahlgrenska.se/vgrtemplates/Page_27536.aspx
LifeGene	http://lifegene.ki.se/
<i>UK</i>	
Generation Scotland: Genetic Health in the 21 st Century	www.generationscotland.org
Generation Scotland: Scottish Family Health Study	www.generationscotland.org
EPIC Oxford	http://www.epic-oxford.org/
UK Women’s Heart Study	http://www.mhs.manchester.ac.uk/research/facilities_institutes
Twin Research Unit Laboratory	http://www.gstt.nhs.uk/
National study of colorectal cancer	http://www.icr.ac.uk/
International familial CLL consortium	http://www.icr.ac.uk/
Liverpool Lung Project	www.liv.ac.uk

EUELC (Early lung cancer)	http://www.euelc.com/
UK DNA Banking Network	http://www.medicine.manchester.ac.uk/cigmr/Newsarchive/dnabank
UK Cord Blood Bank Ltd	http://www.cordbloodbank.com/
Oxagen Ltd	http://www.oxagen.co.uk/

ANNEX 4: BIOBANKS IDENTIFIED BEYOND EUROPE

Name of Biobank	Contact/Website
USA	
Penn State Cancer Institute (PSCI) Tissue Bank	http://www.hmc.psu.edu/cancer/tissue_bank/allocation.htm
TARPS Tissue and Research Pathology Services (University of Pittsburgh)	http://www.upci.upmc.edu/facilities/tarps/service.html
Pediatric Rheumatology Tissue Repository (PRTR)	http://www.cincinnatichildrens.org/research/project/rheum-cores/prtp.htm
Early Detection Research Network Exchange (EDRN) -NCI	http://edrn.nci.nih.gov/
Cooperative Family Registry for Breast and Colorectal Cancer (NCI)	
Tissue Bank Shared Service/Greenbaum Cancer Center/Maryland	
Children Oncology Group (NCI funded)	http://www.childrensoncologygroup.org/
Armed Force Institute of Pathology-National Pathology Repository	
National Institute of Child Health and Development (NICHD), Brain and Tissue Bank for Developmental Disorders	http://medschool.umaryland.edu/BTBank/
Kathleen Price Bryan Brain Bank	http://adrc.mc.duke.edu/BB.htm
Stanley Foundation Brain Collection	http://www.stanleyresearch.org/programs/brain_collection.asp
Harvard Brain Tissue Resources Center	http://www.brainbank.mclean.org/
New York Brain Bank	http://nybb.hs.columbia.edu/
National Parkinson Foundation Brain Endowment Bank	http://www.parkinson.org/NETCOMMUNITY/Page.aspx?pid=265&srcid=465
Human Brain and Spinal Fluid Resource Center	http://www.loni.ucla.edu/uclabrainbank/index.html
McKnight Brain Institute Brain Bank	http://www.mbi.ufl.edu/facilities/brainbank/about.php
National Alzheimer Coordinating Center	http://www.alz.washington.edu/
University of California Human Embryonic Stem Cell Line	http://escells.ucsf.edu/main/home.asp
WiCell Research Institute	http://www.wicell.org/
Healthy Aging in Neighbourhoods of Diversity across the Life Span study	
Nun Study	http://www.mc.uky.edu/nunnet/
Bogalusa Heart Study, (NHLBI)	http://www.nhlbi.nih.gov/resources/deca/descriptions/bhs.htm
National Health and Nutrition Examination Survey (NHANES) (CDC)	http://www.cdc.gov/nchs/nhanes.htm
Women's Interagency HIV Study	http://statepiaps.jhsph.edu/wihs/
Framingham study (NHLBI)	http://www.nhlbi.nih.gov/about/framingham/
Jackson Heart Study (NHLBI)	http://www.nhlbi.nih.gov/about/jackson/index.htm
ARIC study (NHLBI)	

Annex 4

Physicians' Health Study, (NIH)	
Nurses' Health Study (Original cohort) (NIH)	http://clinicaltrials.gov/show/NCT00005152
Nurses' Health Study II (NIH)	
Women's Health Initiative - Observational study (NHLBI)	http://www.nhlbi.nih.gov/whi/
Iowa Women's Health Study	
Cancer Prevention Study - 3 (CPS-3) (American Cancer Society)	http://www.cancer.org/docroot/RES/RES_6_6.asp
Cancer Prevention Study - II Nutrition Cohort (CPS)	
Marshfield Clinic Personalized Medicine Research	http://www.marshfieldclinic.org/chg/pages/default.aspx?page=chg_pers_med_res_prj
Study of Women Across the Nation (SWAN)	http://www.edc.gsph.pitt.edu/swan/
Cardiovascular Heart Study (CHS) (NHLBI)	http://www.nhlbi.nih.gov/resources/deca/descriptions/chs.htm
Canada	
Procure Cancer	http://www.procure.ca/
Cancer Research Network of the FRSQ/ Réseau de recherche sur le cancer (FRSQ)	
Alberta Research Tumor Bank	http://www.abtumorbank.com/
British Columbia Cancer Agency Tumour Tissue Repository	http://www.bccancer.bc.ca/RES/TTR/default.htm
Manitoba Breast Tumor Bank	http://www.umanitoba.ca/institutes/manitoba_institute_cell_biology/MBTB/MBTB_Overview.htm
Ontario Cancer Research Network	Ontario Cancer Research Network
Children's Oncology Group	
Tissue Bank of the Respiratory Health Network of the FRSQ	http://www.frsq.gouv.qc.ca/en/publications/frsq_actualites/octobre_2006/banque.shtml
The Brain Tumour Tissue Bank	http://www.braintumour.ca/braintumour.nsf/eng/BTTB
Douglas Hospital Brain Bank	http://www.douglasrecherche.qc.ca/brain-banks/general-bank.asp
LIFEBANC/Arthur and Sonia Labatt BTRC	
Capital Health/Regional Tissue Bank	http://www.capitalhealth.ca/NewsAndEvents/NewsReleases/2006/CH_Comprehensive_Tissue_Centre_receives_Medical_Device_Licence_from_Health_Canada.htm
Canadian Study on Health and Aging	http://www.csha.ca/
Genizon BioSciences	http://www.genizon.com/
Interheart	http://www.cihr-irsc.gc.ca/e/26489.html
Healthy Aging Study	http://www.bcgsc.ca/project/healthy-aging-study/aging_summary
China	
Kadoorie Study of Chronic Disease in China (KSCDC)	http://www.ctsu.ox.ac.uk/~kadoorie/public/
Japan	
Health Science Research Resources Bank/Japan Health Science Foundation	
Biobank Japan - Riken Institute	

Annex 4

Japanese collection of research bioresources (JCRB Genebank)	
Japan National Cancer Center	
Brain Bank Project	
<i>Korea</i>	
MizMedi Women Hospital Research Center	
Biobank for Health Sciences	
<i>Singapore</i>	
National University of Singapore Tissue Repository	http://medicine.nus.edu.sg/tissue/
Singapore Consortium of Cohort Studies	http://www.a-star.edu.sg/astar/biomed/action/biomed_strategic_initiatives.do#scs
ES Cell International Inc.	http://www.escellinternational.com/
Singapore Tissue Network	http://www.stn.org.sg/
<i>Taiwan</i>	
Taiwan Biobank	
<i>Other</i>	
Howard's Genomic Research in the African Diaspora (GRAD)	
The Western Australian Genome Health Project (WAGHP)	http://www.genepi.org.au/waghp
Melbourne Collaborative Cohort Study (HEALTH 2000)	http://www.med.monash.edu.au/epidemiology/cardiores/echidnas.html
Indian Genome Variation Consortium	
Prospective blood-based study of 200,000 individuals in Mexico	
Genomic variability and haplotype map of the Mexican population	
National Laboratory for the Genetics of Israeli Populations (NLGIP)	http://www.tau.ac.il/medicine/NLGIP/nlgip.htm

European Commission

EUR 24361 EN – Joint Research Centre – Institute for Prospective Technological Studies

Title: Biobanks in Europe: Prospects for Harmonisation and Networking

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Luxembourg: Publications Office of the European Union

2010

EUR – Scientific and Technical Research series – ISSN 1018-5593

ISBN 978-92-79-15783-7

doi:10.2791/41701

Abstract

Biobanks (i.e. the organised collections consisting of biological samples and associated data, have gained great significance for research and personalised medicine) are increasingly recognised as a crucial infrastructure for research. However, at the same time the widely varied practices in biobanking regarding for example collection, storage and consent procedures may also pose a barrier to cross-border research and collaboration by limiting access to samples and data. In this context the limited sharing and linkage of samples is a key barrier for research, such as pharmacogenetics. Wide variation is observed in the implementation of relevant existing regulation, which may add further burden to harnessing the public health benefit of these collections. It has been suggested that there is a strong need for a harmonised approach on biobanking practices and improved networking of existing and new collections.

The Report shows information on the extent of biobanking in Europe, collected through a survey of existing European biobanks regarding both technical aspects (e.g. storage conditions) and aspects of governance and ethics (e.g. sample and data sharing, consent procedures, collaborations etc.). In total, 126 biobanks from 23 countries in Europe were surveyed.

Significant lack of harmonisation has been found, especially in the legal aspects (e.g. data protection, consent). This may be partly attributed to the varied interpretation and implementation of EC directives covering aspects of biobanking by national authorities. One of the main complications is that, although the field of data protection is harmonised through the EC directive on data protection, the collection, storage, and sharing of samples is not. Furthermore, in countries that have introduced special biobanks acts it is not always clear where the borderline lies between the scope of these acts and that of the Directive. Indeed, according to the survey, biobanks within the same country reported different practices, suggesting that the problems of harmonization might be higher than expected and claimed. Not only are there different national laws, but apparently within EU member states biobanks do not implement homogenous practices on privacy and data protection issues.

Experts interviews confirmed the need to improve collaboration and networking among the numerous existing biobanks. Efficient organisation of these resources through the development, for example, of an infrastructure would potentially facilitate financial sustainability and greatly contribute to the rapid progress of research and development of better diagnostic and therapeutic approaches. The most favoured model involved the development of a virtual biobank that would allow networking of biobanks across different countries and centralisation of data rather than samples. However, several organisational challenges (wide variation in biospecimen collection, storage techniques, data comparability, etc.) may hamper such an effort.

The European Commission has already recognised the importance of international biobank projects and many of them have been funded and established in the context of the EU Framework Programmes. To help promote networking of biobanks and thus maximise public health benefits, at least some degree of harmonisation must be achieved.

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