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Final Version

# Symposium

## Biobanks and biomedical collections
## An ethical framework for future research

19-20 June 2012
Palais de l'Europe, Strasbourg, France

**Event organised by**
**the Committee on Bioethics (DH-BIO) of the Council of Europe**

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## The speakers: abstracts, full texts and biographical notes

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***Introduction***

## Dr Anne Forus (Norway)

Chair of the Coordination Group for the organisation of the Symposium


## Abstract

***Introduction***

The recommendation on research on biological materials of human origin was adopted by the Committee of Ministers in March 2006. The purpose of the Recommendation is to provide an ethical framework for use of biological material and tissue collections in medical research. The preamble mention important ethical principles; e.g. that the paramount concern should be the protection of the human being who has donated the biological material that is stored or used for research; that research on biological materials should be carried out freely and ensuring the protection of the human being; that the interests and welfare of the human being shall prevail over the sole interest of society or science; and that particular protection shall be given to human beings who may be vulnerable in the context of research. The Recommendation contains a set of articles that will help to ensure that these principles are met. According to the last article, the recommendation should be re-examined within five years after its adoption, and the primary objective of this symposium is to provide a basis for this re-examination by DH-BIO. The symposium will seek to identify new challenges caused by recent developments; both technological developments - such as the increasing use of genome wide genetic analyses; and other more "practical" developments - such as the increased level of international collaborations and exchange of biological materials between researchers and research institutions. Of equal importance; the symposium should help to identify challenges and difficulties encountered in the practical implementation of the principles, and the possible need for amendments.


## Full text

***Introduction***

The recommendation on research on biological materials of human origin was adopted by the Committee of Ministers in March 2006. The Recommendation is built on universal principles: Protection of the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms. These principles are embodied in the Convention on Human Rights and biomedicine, and the additional protocol on biomedical research.

The Protocol on biomedical research covers all biomedical research involving an intervention on a person. The intervention may be physical, such as the removal of biological material, or involve a risk to the psychological health of the person.

The recommendation is a supplement to the protocol, giving clear guidelines for research on biological material; such as material collected and stored in a diagnostic or therapeutic setting, or material in population biobanks. The Recommendation provides an ethical framework for use of biological material and tissue collections in medical research, and protects the rights and fundamental freedoms of those who donate the material. Thereby, it will contribute to facilitate biomedical research. I will come back to the main principles.

According to the last article, the recommendation should be re-examined within five years after its adoption. This re-examination is now in its first phase, starting out with this symposium, where the primary goal is to identify the elements that need to be considered in the re-examination. The type of elements we are referring to could be divided into (at least) two groups:

- new challenges caused by recent developments;
- both technological developments - such as the increasing use of genome technologies;
- and other more "practical" developments - such as the increased level of international collaborations and cross-border exchange of biological materials between researchers and research institutions.

And equally important

- elements related to challenges and difficulties encountered in the practical implementation of the principles, and the possible need for amendments.

I hope that this symposium will provide a broad perspective on research related to biobanks and biomedical collections, and thereby, provide a solid basis for the re-examination of the recommendation.

I would like to go back to the recommendation and the ethical principles on which it is built, as summarised in the preamble:
- the paramount concern should be the protection of the persons who have donated their biological material to be stored or used for research;
- research on biological materials should be carried out freely and ensuring the protection of those persons;
- the interests and welfare of the person shall prevail over the sole interest of society or science;
- particular protection shall be given to persons who may be vulnerable in the context of research.

It is clearly stated that every person has the right to accept or refuse contribution to biomedical research, and that no one should be forced to contribute. The right to give consent and the right to withdraw consent at any time is further elaborated in the different articles; as is the right to confidentiality and information.

The preamble stresses the importance of appropriate and transparent governance of biobanks, and that donations to biobanks are made in a spirit of solidarity and should not be monopolised by small groups of researchers. The importance of research on biological material as a significant contributor to progress in medical sciences and health care is clearly recognised.

I will reflect a bit on how recent developments may challenge some of the principles that are specified in the recommendation by referring to the main elements of the debates in Norway. I believe these examples also reflect elements of the international debate, since the issues at stake are universal:
Most of the debate in Norway is related to the increasing use of genome technologies in research. These technologies may have the potential to "transform the delivery of healthcare by providing vital insights to support more accurate diagnosis of disease and informed therapeutic decisions"; to cite a recent report. There is little doubt that genome technologies will give new insight in genetic mechanisms related to disease, the interaction between genes, and their interaction with the environment. But some challenges arise: An individual's genetic information is sensitive personal data, and a whole genome cannot be truly anonymised; meaning that there is a risk that the person who donated the material - "with reasonable efforts" - could be identified. Thus, there is a risk of the information being misused. If the ideal up to now has been to *anonymise* materials as far as appropriate in order to safeguard privacy and protection for the individual and the data, we may now look for other measures than anonymisation.

In large biobanks, where biological material will be stored for decades and used in different research projects, generic consents may be more practical than the specific consent used when recruiting participants for a specific research project. The discussion of generic versus specific consents may be an old one, but technological developments as well as increasing cross-border collaboration may challenge the concept of *informed* consent: The increasing use of genome technologies may reveal detailed information about a person's genetic makeup. It may be difficult to envisage the kind of results and information that can be revealed by using genome technologies in future research projects. It may also be difficult to foresee where the material will be stored and analysed, and to foresee which institutions or researchers that will have access to the personal data. Thus, it may be challenging to give adequate and sufficient information to the donors. It may also be challenging to ensure the right to withdraw the consent, and to have the biological material destroyed. Is it possible to establish a consent process that is "informed" and maintains the right to information and withdrawal when we are dealing with genome technologies and cross-border collaborations, or do we have to develop new concepts of consent?

Another challenge is the situation where research reveals information that has a potential impact on the health of the participant or his/ her family. The information revealed may be incidental to the research question. This is a well known situation not only related to projects using genome technologies – but the use of genome technologies seems to enhance the chances of incidentally revealing infor-

mation of potential relevance. What happens if the research incidentally reveals information about a condition that is serious or preventable? The recommendation refers to the protocol on biomedical research when dealing with the issue of information and feedback. I will cite from article 27 of the protocol: "*If research gives rise to information of relevance to the current or future health or quality of life of research participants, this information must be offered to them ...*(..)".
How should this be interpreted and related to our current situation? Is there a duty to give information to the patient/participant – even if he or she did not know about the particular research project – as may be the case in population biobanks? What criteria should be used to decide whether and when information should be given?

To summarise: It is important to maintain public confidence in how biobank material is stored and used. It is essential to develop biobank research within a robust ethical and legal framework that will respect the participants' autonomy, maximise potential health benefits and minimise potential harms such as information misuse, stigmatisation and discrimination. I think the main task for DH-BIO in the re-examination process will be to ensure that a future legal document for research on biological material maintains the core ethical principles, take the necessary measures to ensure the donors right to privacy and autonomy, and thereby, facilitating research.

## Biographical notes

I have a background in molecular biology, including a Ph.D. in molecular cancer research from the Norwegian Radium Hospital and the University of Oslo. After more than 10 years in research, I started to work as a senior advisor at the Norwegian Directorate of Health in 2003. My main field of work covers issues related to medicinal use of biotechnology, such as assisted reproduction technologies, prenatal diagnosis, genetic testing, gene therapy and stem cell research – all regulated by the Norwegian Biotechnology Act; and medical research and use of biological materials. I have been a delegate to the CDBI/DH-BIO since 2003, and was elected Vice Chair in June 2011. I am currently working for the Ministry of Health and Care Services, following up on the evaluation of our Biotechnology Act.

I am a member of the Programme Board for Stem Cell Research and observer and previous member of the Programme Board for ELSA Research at the Norwegian Research Council. I am also a freelance writer for the Journal of the Norwegian Medical Association.

***Session 1 - Biobanks: situation and expectations***


# Prof. Milan Macek (Czech Republic)

Head of the Department of Biology and Medical Genetics, Charles University Prague
Member of the European Commission Expert Group on biobanks


## Abstract


***Overview of the situation regarding research biobanks***

The field of biobanking is very heterogeneous. Although it is very difficult to exhaustively list all variable features of current biobank activities, these comprise for instance their size, character of the sample collection, disease type, research topic, approaches to coding or de-identification and the nature of the biological materials collection. All such variables influence the scope of their operations, recruitment, consent measures, the scale of informatics background, governance structures and the potential for commercial exploitation of stored samples and associated personal data. A recent European survey (Biobanks in Europe: Prospects for Harmonisation and Networking; 2010) substantiated the wealth of biobanking activities in Europe. Since then continuous updates are published at the BBMRI Portal website. Furthermore, clear evidence was presented for the creation of an international umbrella or network organisation that would foster harmonisation and standardisation of biobank practices. As in other areas of biomedicine, European national activities have the potential to act in concert and thus in aggregate set the stage at the world-wide perspective.

Biobanking will not lose its significance in the upcoming era of mainly informatics-based developments in medical research. On the contrary, high quality “template” biological material will increasingly be required for all high-throughput “omics” methodologies in order to render relevant biological correlates for modeling-based strategies. Consequently results generated by modeling will have to be validated through biobank-based research at the individual patient and tissue-specific levels.

Within the context of biobanking, and medical research in general, it will be necessary to a priori define which clinical endpoints of the new multimodal therapeutic approaches are considered to deliver optimal patient and societal value, given finite resources in health care. Realistic expectations should be put forward since there is a lot of hope for better future. However, the scale of biological complexity that has to be tackled and integrated for the provision of personalized / personal medicine also requires a prudent communication strategy which avoids hype and offers realistic expectations to the professionals and for the public. Proper communication of all such developments to the researchers, clinicians, public at large and policy makers will ensure trust and foster sustainable funding in upcoming economically difficult times.


## Full text

### The current context of biobanking

Biobanks collect biological samples and associated data for medical-scientific research and diagnostic purposes and organise these in a systematic way for use by others. The collection of samples and data for research purposes has a long history in the educational and medical systems. In the past, biorepositories were relatively uncontroversial, residing largely in the seclusion of pathology institutes. With recent technological advances, the potential to open up these existing collections for new uses is starting to be realized, but also new biobanks are being established. Innovations in information technology enable the systematic collection, linkage and tracking of samples and data but also provide the tools for analysis across vast sample and datasets. What distinguishes the present from the past is that the general scientific context has changed, and the scale of biobanking activities, both in terms of the quantity of samples and data, as well as the range of disease areas and institutions now involved in biobanking have increased considerably.[1] The other significant change is that these collections are being used by the scientific community.

[1] Knoppers B.M., Zawati, M.H., Kirby E.S. Sampling Populations of Humans Across the World:

Advances in bioinformatics and computing technology have enabled scientific research to be organised and carried out in new ways. Scientific practice 'has become increasingly interdisciplinary, with the rapid formation of flexible and dynamic research collaborations around the world'.[2] Research projects are frequently global in nature, involving teams with different types of expertise, such as clinicians, laboratory staff and researchers, bioinformaticians, statisticians and other data analysts. Biobanks are embedded in these complex networks of research collaborations that span regions, countries and the globe. As a result there are many different types of biobanks that have been built for a range of different purposes and reasons[3].

**The science of biobanking**

Contemporary medicine is moving from "reactive approaches" centered on disease therapy to personalized, predictive, preventive and participatory medicine ("P4 Medicine") which focuses on the maintenance of health[4,5]. This transition is fostered by advances derived from sequencing of the human genome and rapid improvements in bioinformatics and analytical laboratory technologies[7,6]. Biobanks have the potential to become important tools and instruments for helping to drive this change in healthcare.

Given the immense complexity of human biology, medical research has traditionally been utilizing a so called "reductionist strategy" [7,7]. This strategy, used in current medical research and practice, is based on the assumption that itemization of complex biological phenomena into smaller "research issues" makes them more easily amenable to our current technical possibilities and to human reason/logic-based examinations[7,10]. Although this research strategy has been very successful, it is now reaching its intangible limits. With few exceptions, it is becoming evident that complex diseases cannot be ascribed to disturbances of individual biological entities, e.g. merely mutated genes[2,9,8].

In order to address the substantial complexities of biology and medicine, interdisciplinary fields of systems biology/systems medicine have been established. In these young scientific disciplines interactions of individual biological elements are studied by advanced mathematical and statistics strategies. Systems biology can not only retrospectively analyses biological parameters, but also can model *in silico* different interactions. Thus, systems biology research combines "wet laboratory" experimentation with "dry laboratory" predictions of biological processes, and vice versa. All these developments, which started to accelerate approximately a decade ago, have led to the rapid establishment of organized biobanking [9,10].

The field of biobanking is, generally speaking, very heterogeneous[12,13,14,15]. Although it is difficult to exhaustively list all distinguishing characteristics of biobanks, there are some that can be used to characterize different types of biobanks. These are size, research design, the types of biological samples collected, the method of sample collection, processing and storage, and the disease/research

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ELSI Issues *Annu. Rev. Genomics Hum. Genet.* 2012. 13:1.1–1.19

[2] Kaye J, Heeney C, Hawkins N, de Vries J, Boddington P. Data sharing in genomics - re-shaping scientific practice´. *Nat. Rev. Gene.* 2009. Vol. 10, pp. 331-335

[3]Gottweis H, Petersen A. Biobanks. Governance in Comparative Perspective. 2008 London and New York, Routledge**.**

[4] Hood L, Rowen L, Galas DJ, Aitchison JD., Systems biology at the Institute for Systems Biology, *Briefings in Functional Genomics and Proteomics* 2008 ,Vol. 7, pp.239-248.

[5] Loscalzo J, Barabasi AL., ´Systems biology and the future of medicine´, *Wiley Interdisciplinary Review of Systems Biology Medicine*, 2011, Vol. 3, No. 6, pp.619-627.

[6] Ginsburg GS, Willard HF, Genomic and personalized medicine: foundations and applications. *Translational Research*, 2009, Vol.154, No. 6, pp. 277-287.

[7] Sobradillo P, Pozo F, Agustí A., P4 medicine: the future around the corner, *Archivos de Bronconeumologia.* 2011, Vol. 47, No. 1, pp.35-40.

[8] Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome, *Science*, 2001, Vol.291, pp. 1304-1351.

[9] Asslaber M, Zatloukal K., Biobanks: transnational, European and global networks, *Briefings in Functional Genomics and Proteomics.* 2007, Vol. 6, No. 3, p. 193-201.

[10] Riegman PH, Morente MM, Betsou F, de Blasio P, Geary P, Biobanking for better healthcare and the Marble Arch International Working Group on Biobanking for Biomedical Research, *Molecular Oncology.* 2008, Vol. 2, No. 3, pp.213-222.

focus. These characteristics will influence the scope of biobank activities, such as the recruitment of donors, the consent procedures, the scale of informatics support needed, the governance structures, and the potential for commercial exploitation. Until recently, terminology denoting organized collections in medicine has not been consistent. A number of terms such as "human genetic research databases (HGRDs)", "population genetic databases", "biorepositories", or "tissue banks" have been used to refer to activities involving biobanks/biobanking. However, "biobank" is now the over-arching term that is most commonly used. An example of a European legal definition of a biobank is found in the Recommendation on research on biological materials of human origin (2006) [11] which also refers explicitly to biobanks. This could also be applied to other types of biobanks. The key factor that distinguishes a biobank from a research collection is that a biobank has established governance mechanisms in place to allow access to the resource in a systematic way to outsiders.

Sample size is a characteristic that can be used to distinguish different kinds of biobanking activities. Large-scale biobanks are generally used for prospective and longitudinal molecular epidemiology research projects, while smaller scale biobanks are established for specific research projects, such as case-control studies[12,13,14]. Within the European context large-scale biobanks include the UK Biobank (BOX 3)[12], deCode-associated Icelandic Biobank[13], the Estonian Biobank[14], and the Genome Austria Tissue Bank (GATiB) projects[15]. While large-scale biobanks are relatively recent, small collections established for specific research projects have been more the norm. The majority of these biobanks comprise comparatively small collections of up to several thousand samples. Despite their different research foci and their often limited statistical power, these smaller scale projects represent an indispensable scientific resource complementary to large-scale biobanks[12,13,14]. All biobank formats are interlinked and to a certain degree represent a continuum within the infrastructure supporting all gradual steps of the biomedical research "pipeline" [12,13,14].

Issues related to population-based biobanks are compiled and analyzed by the Public Population Project in Genomics[16] (BOX 4) in its internet resources. Compared to population-based biobanking initiatives, disease-oriented biobanks store a much more heterogeneous collection of biological materials, which are mainly collected within the context of clinical care[12,13,14]. Tissue banks represent diverse collections of tissue specimens. These samples are associated with detailed information on the nature of the underlying disease for which these were sampled. A specific form of tissue banks is represented by formalin-fixed paraffin embedded (FFPE) specimen collections[12,13,14.]

Biobanking has been going on in tandem with many clinical trials[17] performed by various clinical research organizations and/or investigator-driven clinical trials in Europe, and elsewhere. During the time-line of a trial, these organizations compile not only complex clinical and laboratory monitoring data, but also examine samples (e.g. blood, urine of trial subjects/controls), which can in turn be integrated into a biobank and used for research. The major aim of clinical trial related biobanking is to identify disease/trial-associated biomarkers.

**(i) Biobanking in Europe**

In many European countries, high quality population-based and disease-oriented biobanks have been established. Major financial and scientific investments have been committed and millions of citizens have voluntarily contributed data and bio-specimens to such biobanks. These investments have permitted major progress in the comprehension of specific risk factors of complex diseases. The potential to further strengthen pan-European and global collaborations are now one way the research community can ensure the optimal leveraging of the scientific potential of current and future biobanks. Increas-

[11] https://wcd.coe.int/ViewDoc.jsp?id=977859 (This Recommendation is currently under re-examination)
[12] http://www.ukbiobank.ac.uk
[13] http://www.decode.com
[14] http://www.geenivaramu.ee/en/
[15] Asslaber M, Abuja PM, Stark K, Eder J, Gottweis H, Trauner M, Samonigg H, Mischinger HJ, Schippinger W, Berghold A, Denk H, Zatloukal K. The Genome Austria Tissue Bank (GATiB). *Pathobiology.* 2007, Vol. 74, No. 4, pp. 251-258.
[16] http://www.p3g.org
[17] Halim SA, Newby LK, Ohman EM. Biomarkers in cardiovascular clinical trials: past, present, future. *Clinical Chemistry.* 2012, Vol. 58, No. 1, pp.45-53.

ing data compatibility is crucial to enable valid comparison across countries or jurisdictions and to permit integration (or pooling) of data across biobanks. This integration is essential to obtain the large numbers of participants and samples necessary to conduct research investigating, for example, the interplay between genetic, lifestyle, environmental, and social factors that determine health and (complex) diseases. Nonetheless, cross-border biobank cooperation within the context of heterogeneous ethical and legal national and/or regional frameworks faces important challenges for the European Union[18].

In 2010, the European Institute for Prospective Technological studies (IPTS) of the European Commission´s Joint Research Centre[19] in collaboration with the European Science and Technology Observatory (ESTO)[20] published results from a comprehensive survey of biobanks (Biobanks in Europe: Prospects for Harmonisation and Networking; 2010)[21]. The main objectives of this project were to survey biobanking in Europe and identify challenges for networking and harmonisation. The overarching message from this survey was the variation and fragmentation of biobanking practices and activity within Europe. On the basis of this evidence, the report recommended the creation of an international umbrella or network organisation that would foster harmonisation and standardisation of biobank practices.

To answer to this need, a number of major international networking initiatives have emerged. These include the Biomedical Informatics Grid[22] and European Prospective Investigation into Cancer and Nutrition[23] (cancer); Public Population Project in Genomics (BOX 2); and PHOEBE[24] (population biobanks); EuroBioBank (rare diseases)[25]; GenomeEUtwin[26] (sibling and twin cohorts); TuBaFrost[27] (frozen human tissue bank); and NUGENOB[28] (nutrition and obesity). The European Commission has supported several collaborative projects within the last EU Framework 7 Programs. The Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)[29] preparatory phase project, the TISS.EU project (Evaluation of legislation and related guidelines on the procurement, storage and transfer of human tissues and cells in the European Union;[30]) and the BioSHARE-EU project (Biobank Standardization and Harmonization for Research Excellence in the European Union[31]) are examples of such EU-funded initiatives.

More than a decade ago the European Commission established the “European Strategy Forum on Research Infrastructures[32] (ESFRI), whose ultimate aim is to overcome fragmentation of European biomedical facilities by development of integrative policies (“Roadmaps”), which are continuously updated with new partners and scientific domains. The associated Community legal framework for a European Research Infrastructure Consortium (ERIC)[33] entered into force at the end of August 2009. This specific legal structure was designed to facilitate the establishment and joint operation of respective research infrastructures within ESFRI. This will allow biobanks across Europe to become part of the ERIC and operate under a common legal structure.

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[18] Yuille, M., van Ommen, G.J., Brechot, C., Cambon-Thomsen, A., Dagher, G., Landegren, U., Litton, J.E., Pasterk, M., Peltonen, L., Taussig, M., Wichmann, H.E., Zatloukal, K., ‘Biobanking for Europe‘. *Briefings in Bioinformatics.*, 2008, Vol. 9, pp. 14–24.

[19] http://ipts.jrc.ec.europa.eu

[20] http://ipts.jrc.ec.europa.eu/ataglance/networks.cfm

[21] Zika E, Paci D, Schulte in den Bäumen T, Braun A, RijKers-Defrasne S, Deschênes M, Fortier I, Laage-Hellman J, Scerri C.A., Ibarreta D., ‘Biobanks in Europe: Prospects for Harmonisation and Networking‘, European Commission Joint Research Centre, Institute for Prospective Technological Studies (EUR 24361 EN; ISBN 978-92-79-15783-7; ISSN 1018-5593)

[22] http://cabig.nci.nih.gov

[23] http://epic.iarc.fr/ centers/iarc.php

[24] http://www.phoebe-eu.org

[25] http://www.eurobiobank.org/

[26] http://www.genomeutwin.org/

[27] http://www.tubafrost.org

[28] http://www.nugenob.org

[29] http://www.bbmri.eu

[30] http:// www.tisseu.uni-hannover.de

[31] http://www.bioshare.eu

[32] http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri

[33] http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=eric

### (ii) Biobanking challenges in Europe

In addition to major harmonization issues, the current practice of biobanking and biomedical research in Europe faces a number of other important challenges. While networks and consortia are increasing, there are still serious issues that need to be addressed with regard to cross-border exchange of samples and data transfers. [34,35] In addition, informatics challenges in medical biobanking are immense. For instance, there are major challenges associated with the integration of various forms of data such as text (clinical information); numeric values (laboratory data, age); categorical (staging, grading, scoring); image (histology, röntgenology, magnetic resonance); array (genomic data); composite (DNA signatures, mutations, variants, transcription factor interactions); and/or hierarchic (pedigrees)[12,13,14]. Moreover, there exist a number of data security and confidentiality concerns related to the exchange of sensitive patient data[36].

There are also financial challenges associated with the long-term sustainability of individual biobanks as well as biobank networks and infrastructures. As ongoing financial support is uncertain, quite often biobanks must seek out multi-source financing whether they are based in the public or private sectors[37]. The biobanking business cycle is comparatively long and thus requires durable investment strategies[38]. In this respect networking grants or research grants, which are usually given to establish a biobank, do not assure long-term operational financing. Financial sustainability of biobanks strongly depends on background support from host partners such as academic hospitals (e.g. by offering free services and/or discounts for their own affiliates). For these reasons there have been calls to embed biobanks within healthcare structures so that they can fulfill a dual purpose of clinical care and research use[32,39,40]. One solution to the financial insecurity that biobanks face is to embed them within the healthcare structure. A model that embeds a biobank within clinical care is the CuraRata model[41], which has been recently developed at Leiden University in the Netherlands.

It must be noted that despite their size and strategic importance it is very difficult to gather information on biobanks collected by private pharmaceutical companies, which mostly operate at a transnational basis. Another important consideration is the fact that consent practices for biobank donors are not standardized, and in some instances (e.g. in Eastern Europe) even absent, which may present a "moral hazard" for the entire field of biobanking. The quality of sample annotation is also very heterogeneous and the industry mostly prefers targeted sample procurement under strict standard operating procedures necessary for final product certification.

There are also successful models of public–private collaborations in the area of biobanking, with several projects identified e.g. in Scandinavia[93]. The European survey provided evidence that intersectoral research was carried out primarily by academic scientists who had worked in close collaboration with their industrial partners. There were no accounts of intersectoral transfers of "academia-based" biological materials. The general notion coming out of the survey was that industry is mainly interested in collaboration, rather than in the biological materials themselves. However, development in the field

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[35] Bellazzi R, Diomidous M, Sarkar IN, Takabayashi K, et.al. Data analysis and data mining: current issues in biomedical informatics. *Methods Inf Med*. 2011 Vol. 50, No. 6, pp:536-544.

[36] Schwarz E, Leweke FM, Bahn S, Liò P. Clinical bioinformatics for complex disorders: a schizophrenia case study. *BMC Bioinformatics*. 2009, Vol. 10 Suppl 12, pp. S6.

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[38] Vaught J, Rogers J, Carolin T, Compton C. Biobankonomics: developing a sustainable business model approach for the formation of a human tissue biobank. *J Natl Cancer Inst Monogr*. 2011; Vol. 2011, No. 42, pp.24-31.

[39] Kaye J. Embedding biobanks as tools for personalised medicine. *Norsk Epidemiologi* 2012; Vol. 21, No. 2, pp. 169-175

[40] Murtagh MJ, Demir I, Harris JR, Burton P. Realizing the promise of population biobanks: a new model for translation, *Human Genetics* 2011; Vol. 130, pp. 333-345

[41] http://www.curarata.nl/uk/25/patients/about-us/curarata-the-basics.html

of “private” and “public” biobanking domains is rapid and such developments are monitored at the BBMRI Portal website[42].

**(iii) Summary and outlook for the future**

Biobanking will not lose its significance in the upcoming era of mainly informatics-based developments in medical research[43]. On the contrary, high quality “template” biospecimen material will increasingly be required for all high-throughput omics methodologies (e.g. genomics, mass spectrometry) in order to render relevant biological correlates for modeling-based strategies. Consequently results generated by modelling will have to be validated through biobank-based research at the individual patient and tissue-specific levels. A visionary project, which has already started to address such advanced strategies, is e.g. represented by the Austrian Gen-Au initiative[44].

Finally, it will be necessary to a priori define which clinical endpoints of the new multimodal therapeutic approaches are considered to deliver optimal patient and societal value, given finite resources in health care. Realistic expectations should be put forward since there is a lot of hope for better future. However, the scale of complexity that have to be tackled and integrated for the provision of personalized / personal medicine also requires a prudent strategy which avoids hype and offers realistic expectations to the professionals and the public. Proper communication of all such developments to the public and policy makers will ensure trust and foster sustainable funding in economically difficult times.

## Biographical notes

Professor Milan Macek Jr. MD, DSc is the chairman of the largest academic medical / molecular genetics institution in the Czech Republic at Charles Univeristy Prague-University Hospital Motol, which also comprises a research / diagnostics reproductive genetics centre (http://ublg.lf2.cuni.cz/). This department hosts a sizeable and unique, primarily disease-oriented biobank, comprising DNA and longitudinal personal data gathered from Czech patients with various rare diseases. He is also the Vice President of the European Society of Human Genetics (www.eshg.org), board member of the European Society for Human Reproduction and Embryology (ESHRE.com) and the European Cystic Fibrosis Society (ECFS.eu). His institute is a "clearing centre" for dissemination of knowledge in genetics gathered from various international European projects, such as CF Thematic Network, EuroGentest, EuroCareCF or Techgene, to central and eastern Europe. Prof. Macek obtained his first postdoctoral contract at the Institut of Human Genetics in Berlin, continued as a postdoctoral fellow at the McKusick-Nathans Centre for Genetic Medicine, Johns Hopkins University in Baltimore and during that time he was also a fellow at Harvard School of Medicine in Boston. He was the local host of the 1995 HUGO Mutation Detection Course in Brno, the 2005 European Society of Human Genetics conference and the 2008 European Cystic Fibrosis Conference, both held in Prague. He is national coordinator of Orphanet (www.orpha.net), active member of Eurogentest (www.eurogentest.org), national representative of EUCERD.eu and has been the chief advisor of the Czech EU Council Presidency (www.eu2009.cz) under which the EU Council Recommendation on an action in the field of rare diseases was adopted in June 2009. He has been involved in 26 domestic and international grants and currently has publication H-index - 23.

[42] https://www.bbmriportal.eu
[43] http://www.itfom.eu
[44] http://www.gen-au.at/projekt.jsp?projektId=34&lang=en

*Session 1 - Biobanks: situation and expectations*


# Dr Jane Kaye (United Kingdom)

Rapporteur of the European Commission Expert Group on biobanks


## Abstract


***Public understanding and expectation regarding biobanking***

How publics perceive biobank projects is of significant importance for their development. In my presentation I will examine the public perception towards biobanks in Europe using quantitative and qualitative data. I will argue that e-authors show that public support for biobanks in Europe is characterized by striking heterogeneity and is dependent on a range of interconnected variables: 1) the public's engagement with biobanks; 2) views about privacy and data security issues; 3) trust in the socio-political system, key actors and institutions involved in biobanks; and 4) the issue of benefit sharing. I argue that biobank developers and operators will have to acknowledge the impacts of these issues in order to successfully integrate biobanks at a pan-European level.


## Full text

***Public understanding and expectation regarding biobanking***

Europe is one of the key investors in the development of biobanking infrastructure in the world. Therefore, it is increasingly important to understand the public understanding and expectations of biobanking. I will present some of the findings of the the Eurobarometer survey EB 73.1, 'Life Sciences and Biotechnology' that took place in 2010. I will also discuss the findings of an international study on public opinion regarding biobanks that analysed qualitative data from focus groups conducted by Herbert Gottwies and his colleagues.

In this talk I will discuss three things (Slide 2):

1. The importance of public engagement
2. Report on the findings of recent research on public attitudes to biobanking
3. Recommendations of the Expert Group Report

**1. The importance of public engagement**

Biobanks rely on people. They are dependent upon individuals to donate samples and data but also the continued success of the biobanking infrastructure strategy and the vision for personalized medicine is strongly dependent upon public support to provide the long-term funding for such endeavors (Slide 4).

Controversial projects, such as the Icelandic and Tongan population biobanks have shown that not all biobank projects are warmly received by all groups in society. Biobanks are dependent not only on donors but also on continued societal and political support to remain operational. There is also the possibility that ambitious projects such as these may fail due to political pressure. Therefore, public attitudes towards biobanks are of great importance and will considerably influence the development and future success of biobanks. In this respect, the political-cultural context of any biobank project is essential and needs to be carefully considered. It is evident that public attitudes will have a major influence on the success of biobanks (Slides 5,6,7,8).

**2. What does the public think about biobanks? What are their concerns? (Slide 9)**

But what do Europeans expect from biobanks? What do they know about them, and how do they want biobanks to operate? Where are the public sensitivities, fears and hopes?
The Eurobarometer survey EB 73.1, 'Life Sciences and Biotechnology' that took place in 2010. This large-scale survey, conducted in 32 European countries contained 8 questions on biobanks. The Eurobarometer is a series of surveys commissioned regularly by the European Commission. The findings

on biobanks were written up in a report by **G. Gaskell et al., Europeans and Biotechnology in 2010: Winds of change? (2010)** (Slides 10 – 13).

### 2.1. People's Awareness of Biobanks (Slide14)

One of the most remarkable findings of current public opinion research on biobanks is the limited awareness of Europeans concerning biobanks (see Figure). More than two thirds of all Europeans said they have never heard of biobanks, and only 17 % answered that they had actively talked about or searched for information about biobanks in the past. Those who are better informed are concentrated in Northern Europe – in Sweden, Finland, and Iceland.

### 2.2. People' Willingness to Participate (Slide 15)

The percentage of people willing to participate in a biobank varies across Europe. This situation points to a critical knowledge deficit in Europe when it comes to biobank research. In terms of participation, we can observe wide variation in attitudes across Europe. There is a strong concentration of people in Northern European countries who say that they will 'definitely' or 'probably' participate in biobank research, whereas the publics in other countries in Europe are much more reluctant. There is a greater willingness in Northern Europe where there has been a long history of collection. But also willingness to participate is strongly related to trust in national governments and institutions.

### 2.3. People's attitudes to giving Broad Consent (Slide 17, 18)

One of the controversial aspects of biobanking has been the use of broad consent for participants enrolling in a biobank, rather than seeking the more conventional informed consent. While this has been seen as a practical solution to the fact that all research uses of the biobank cannot be determined when participants are enrolled, this approach appears not to be supported by the general public. This is one of the most troubling aspects of this research, considering how biobanking is progressing, as it suggests that the people who do not know about biobanks, do not think that a broad consent is appropriate for these kinds of studies. The striking feature of the findings presented in this graph is that across Europe, the majority of respondents agree that permission must be asked for every new kind of research done on a biobank. It was a minority of people who thought it appropriate not be asked for permission to have their details and samples entered into a biobank. (Slide 18). Interestingly, attitudes in Europe towards broad consent are also shaped by levels of information: the more people know about biobanks, the more they are ready to give broad forms of consent, whereas the less they know the less likely are they to participate (Slide 19). Citizens want to know about research aims and about the actors involved. They call for transparency in the governance of biobanks (Slide 20).

### 2.4. What are people concerned about? (Slide 20)

When people participate in biobank research, questions of privacy and data protection are the uppermost concerns. For people who have little or no engagement with biobanks, unwillingness to participate may be not so much a rejection of biobanks per se, but rather a reasonable hesitation to divulge personal information to a little-understood endeavour and purpose. The international study involving focus groups showed that people in all countries of Europe seem to have serious concerns about data abuse by insurance companies or employers. They expect biobanks to have the best possible security protections and oversight mechanism to prevent misuse of their personal information. Data security is an issue even in countries where people expressed broad support for biobanking (Slides 22- 25). When people donate to a biobank, many think that this is not a free gift they participate with the expectation of getting something in return. Supporting science and medicine is a strong incentive across Europe. At the same time, many people assume that they will receive insights into their health status, and they look forward to the possibility of regular health checks with the opportunity of meetings with medical experts (Slide 26).

## 3. In summary (Slide 28)

- Public knowledge and understanding of biobanks is limited across Europe
- The biggest concern is about privacy and access by employers and insurers
- Use of a broad consent is not considered appropriate

- People want to receive information that will be important for their health care
  G. Gaskell H. Gottweis, J, Starkbaum, M. Gerber M. et.al. Publics and Biobanks: Pan-European Diversity and the Challenge of Responsible Innovation *Eur. J. Hum. Gene.* (in press)

**4. The Importance of Trust (Slide 29)**

Trust is an essential societal precondition of biobank research. This raises the question of the organizational set-up of biobanks. Embedding biobanks in well-known and long-trusted structures will increase people's trust because of such institutions' commitment to advancing scientific knowledge and serving the public interest. Publicly funded research in universities, national research institutes, and hospitals are widely regarded as trustworthy. People are certainly not ignorant of what might happen with their data, but they trust these institutions to handle data with care. Transparent structures and the feedback of findings are likely to improve public support. Confronted by the novelty of biobanks, and in the absence of a culture of trust, people may well opt for a precautionary approach. Those hesitating to sign up for and participate in biobanks have lower trust in key actors and have greater concerns about data privacy and security. Such concerns will only be allayed by building trust and transparency and by engaging the public as partners in the biobank project.

**5. Recommendations for Ways Forward (Slide 35)**

To address some of these concerns an Expert Committee made some recommendations in their report Biobanks for Europe - A challenge for governance http://www.coe.int/t/dg3/healthbioethic/Activities/10_Biobanks/biobanks_for_Europe.pdf to address these concerns.

To address the publics' concern about protecting privacy we recommended:
***Recommendation 1:***
Member states and European institutions should develop a consistent and coherent legal framework for biobanking that should protect participants' fundamental rights, in particular in the areas of privacy, data protection and the use of human tissue in research (Slide 36).

To address the need to develop public trust we recommended:
***Recommendation 3:***
For European biobanks to operate successfully there need to be sustainable governance mechanisms to involve and engage the public, and in doing so ensure their continual participation, trust and support (Slide 39).

To address the public's perception that they should receive something in return for participation we recommended:
***Recommendation 4:***
Sustainable governance mechanisms for creating a relationship of reciprocity between biobanks and European society need to be encouraged so that Europeans can understand and obtain the benefits from biobank research (Slide 41).

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

**6. In conclusion**

There is considerable investment in biobanking within Europe. This research suggests that care should be taken to address the concerns of the public to ensure that biobanking is well supported and resourced in the years to come. A public engagement strategy is needed to inform the general public about the public benefits in biobanking and to actively involve them in this endeavour. Transparent and accountable governance structures are needed that encourage public trust and address the concerns that are raised by the public.

## Biographical notes

Jane Kaye is Director of the Centre for Law, Health and Emerging Technologies at Oxford (HeLEX) based in the Department of Public Health at the University of Oxford. She obtained her degrees from the Australian National University (BA); University of Melbourne (LLB); and University of Oxford (DPhil). She was admitted to practice as a solicitor/barrister in 1997. She is advisor to a number of F7 projects and on the Sample and Ethics Committee of the 1000 Genomes Project; International Scientific Advisory Board Canadians for Tomorrow Project; UK10K Ethics Advisory Group and Chair of the CARTaGENE International Scientific Advisory Board, Canada. She is also a member of the Ethics and Confidentiality Committee of the UK National Information Governance Board. She is also on the editorial boards of Law, Innovation and Technology, Journal of Law and Information Science, and Genomics, Policy and Society.

Her research involves investigating the relationships between law, ethics, and practice in the area of emerging technologies in health. The main focus is on genomics with an emphasis on biobanks, privacy, data-sharing frameworks, global governance and translational research.

Her book 'Principles and Practice in Biobank Governance', co-edited with Mark Stranger is now available.

***Session 2 - Information and consent as a process***


## Prof. Bartha Knoppers (Canada)

Director of the Centre of Genomics and Policy, Faculty of Medicine, McGill University



## Abstract

***Main Challenges***

There are several ongoing and systemic challenges in the area of informed consent in biobanking. Foremost is the persistent and ongoing failure to distinguish consent for populational, longitudinal biobanks organized as resources for future research from clinical or residual tissue biobanks. Second, while this misunderstanding continues to color biobanking opinion polls and research due to the lack of nuanced questions reflecting this typology, the population biobanks themselves have continued their emphasis on governance including oversight, heightened data security and ongoing recontact and communication with their participants. Third, the emergence or extension of new rights such as the right to be forgotten, the right to results, and the right not to know, adds further ambiguity as the exercise of such choices needs to be validated over time since personal values and contexts change. Finally, the overriding issue crossing the wide range of biobanks is that of ensuring transparency as to data, confidentiality and personal privacy – perhaps soon to be an illusion considering emerging sequencing and IT technologies? In short, do we need to turn consent on its head and reframe current approaches?


## Full text

***Main Challenges***

Introduction:

There are several ongoing and systematic challenges in the area of informed consent to biobanking. Foremost is the persistent and ongoing failure to distinguish consent for population longitudinal biobanks organized as resources for future research from consent to clinical trials. Second, while this misunderstanding continues to color biobanking opinion polls and research due to the lack of nuanced questions, the population biobanks using a broad consent have continued their emphasis on governance including oversight, heightened data security and ongoing recontact and communication with their participants. Third, the emergence or extension of new rights such as the right to be forgotten, the right to results, and the right not to know adds further ambiguity as the exercise of such choices needs to be validated over time since personal values and contexts change. Finally, the overriding issue crossing the wide range of biobanks is that of ensuring transparency as to data, confidentiality and personal privacy- perhaps soon to be an illusion considering emerging sequencing and IT technologies? In short, do we need to turn consent on its head and reframe current approaches? While consent is a *sine quo non* it should not be either a panacea (one size fits all) or a "Thermopylae". To that end, perhaps we should consider realizing, reviving, ratifying and reforming consent in biobanking.

A. Realizing Consent

Much as been made of the nature and scope of consent in the context of biobanking.[45] Flawed comparisons of the open nature of consent for ongoing population biobanks with the highly specific consent required for interventionist research such as clinical drug trials or disease-specific research have led to much confusion.[46] Paradoxically, the broad consent for population biobanks with their frequent recontact mechanisms, heightened security, constant oversight and ongoing communication,

[45] Caulfield,T., Knoppers, B.M. (2012) Consent, Privacy and Research Biobanks. Policy Brief No.1. *GELS Series Genome Canada*: 1-10.

[46] Solberg, B., Solum-Steinsbekk, K. (2012) Managing incidental findings in population based biobank research. *Norsk Epidemiologi*.21(2): 195-201.

actually constitute an opportunity for the validation of altruistic and open participation,[47] an approach currently lacking in one-time, detailed specific "clinical" consent.

Indeed, the recontact for updates, the public engagement strategies, the ethics review of each future project seeking to access the biobank, and, the ongoing communication strategies (e.g. notice of which researchers access biobanks and for what) trump any "specific" one-time detailed consent in terms of ethical propriety. These governance strategies that counter-balance the trust inherent in broad consent constitute "a movement from legal-transactional to a communications model". … "What potential biobank donors genuinely can be asked for is not consent for research but rather permission for the biobank to make future research decisions on their behalf".[48] In reality then, broad consent is realized over time by offering an ongoing possibility of renewal during real-time participation. This strategy for realizing consent also constitutes a reminder of the opportunity to withdraw, again absent from one time specific consent.

While devices or clinical drug trials in disease domains are not the subject of this analysis, it should be noted that clinical researchers are also creating disease specific biobanks. For example, the International Cancer Genome Consortium that crosses all cancer genomes promotes consents not only to cancer research but to research in "related conditions" or even for "future unspecified research" provided there is ethics approval.[49]

Another form of biobanking involves residual tissues that would otherwise be destroyed leftover following medical care. Here approaches vary from requiring an explicit opt-in from patients, to a presumed opt-in albeit with proper notification to all patients of the existence of such biobanks for ethically approved biomedical research.[50]

In short, realizing consent in biobanking is dependant on the mechanisms of public engagement and notification as well as ongoing communication so as to recognize the important role altruistic citizens play in creating a resource for future research. The public role of these infrastructures will only become increasingly important as we move from population mapping via gene-environment studies to stratification into at-risk/healthy sub-populations for health promotion and protection. Indeed, the sustainability of universal health care programmes may well become dependant on State access to such infrastructures for resource allocation planning and prevention purposes.

B. Reviving Consent

Even if population biobanks are leading the way in realizing consent via communication and recontact strategies, the impact of social media networks and of access to the web is revolutionizing consent generally. In particular, more dynamic modes of communication are being developed by researchers [51] and patients advocacy groups.[52] If successful, research consent will be more consensual and participatory. Again, it should be mentioned that the full gamut of options and choices offered to patients-participants in clinical research may however not be possible in fundamental or populational research. This is because the primary mission of research is to seek generalizeable knowledge and as such its goal is social and public not individual. In this sense, basic research and the creation of public resources such as population biobanks cannot offer individual benefits or a menu of individualized preferences since the data they provide has to be without bias and representative of the population as a whole in order to be useful.

Also crucial to meaningful consent is the security of data and samples. It could be said that personal privacy is determined by the degree of the free and autonomous expression of consent to the use of data and samples. In that sense, autonomy and privacy go hand in hand. The trust of participants in the privacy, security and oversight mechanisms of a biobank is crucial. Since their physical integrity is not at stake nor at risk, their consent is largely to the informational security, access and use

[47] Mongoven, A.M., Solomon, S. (2012)Biobanking: shifting the analogy from consent to surrogacy. *Genetics in Medicine*: 14(2):183-187.
[48] Ibid, p.185
[49] www.ICGC.org (Policies and Guidelines)
[50] Reigman, P., Van Veen E.B. (2011) Biobanking residual tisssues. _____ .130(3): 357-68.
[51] Kaye,J. (2012) Embedding Biobanks as tools for personalized medicine. *Norsk Epidemiologi* .21(2):169-175.
[52] www.patients like me.com

aspects. Thus, this is where a revived approach to consent should concentrate, rather than only the initial consent and one time IRB review upon recruitment.

Moreover, it should be noted that in the specific context of paediatric research, parents cannot refuse to receive clinically significant incidental findings that are actionable (i.e. preventable or treatable) during childhood. This is because parents are duty bound to act in the best interests of their children.[53] For conditions of onset during adulthood or for reproductive information (e.g. carrier status) the same does not hold. Indeed, in such cases it is for the minor to decide upon reaching legal majority what information to receive – hence, the importance of ratification.

C. Ratifying Consent

If the emphasis then is less on turning the consent process and form into a notarial deed and more on nuancing and distinguishing between different contexts and biobanks with different levels of risks and benefits, then the "reviving" process just described provides the opportunity to ratify participation. It is here that the initial choices made concerning the right to know or not to know are validated over time since personal values and circumstances change. For example, personal and familial circumstances may influence individuals who chose to not receive, or, to receive eventual clinically significant incidental findings. Recontact provides the opportunity for them to indicate a change of mind. Opportunities for ratification also concerns the initial choices made by participants concerning the destruction of samples or data upon death.

It is however in paediatric research that such ratification holds the greatest promise. Indeed, in biobanking studies that are not longitudinal, the inclusion of children and adolescents in clinical trials or even disease-specific biobanking for a particular and related conditions, often avoids (for practical feasibility reasons) the issue of recontact upon the age of majority. Should children now adults ratify their ongoing inclusion and use of samples and data as consented to by their parents? To date, only longitudinal biobanking studies are able to recontact and consent children when they reach maturity.

Conclusion: Reforming Consent

It has become commonplace to say that "Privacy is Dead". Perhaps we should say "Consent is Dead". Obviously, neither are dead but only their reified forms. While consent and privacy are foundational, overemphasis creates and fosters a disproportionate approach often fuelled by hypothetical "What if one day …" scenarios. Ethics guidelines and review of biobanking have become paternalistic to say nothing of "infantilizing" participants. Legal protectionism plays a role here as well. There is little or no physical danger in biobanking research other than the needleprick. Yet often the same boiler plate physical risk language is used as well as the psycho-social stigmatization and discrimination warning paragraphs originally conceived for hereditary, single gene research. Trying to cover all eventualities real or imagined has made consent an artefact.

Reforming consent then involves remembering the goal of biobanking – the creation of a resource for future research for future generations. It involves realizing consent with transparency as to this goal, a goal that is both social and public from a health systems point of view.

Longitudinal, disease-specific, or, residual biobanks while distinct in their relationship between the researcher and participant and in their recruitment share this social goal. Reformed consent should concentrate on creating ongoing communication strategies (where desired and appropriate) so as to revive consent. Recontact, newsletters, websites and personalized and dynamic electronic consents are but a few possibilities. In this way, consents are validated and ratified over time and not frozen and reified in the ominous and overwhelming initial consent FORM. Reforming consent in biobanks means moving out of research consent based on a "Nuremberg model" presuming that research is always potentially dangerous and harmful. The scientific viability and sustainability of biobanks and their integration in health care systems and programmes depend on such a change of perspective and accompanying reforms.

[53] Kaye,J. (2012) Embedding Biobanks as tools for personalized medicine. *Norsk Epidemiologi* .21(2):169-175.

## Biographical notes

Bartha Maria Knoppers, Ph.D., holds the Canada Research Chair in Law and Medicine (Tier 1: 2001-). She is Director of the Centre of Genomics and Policy, Faculty of Medicine, Department of Human Genetics, McGill University. In 2007, she founded the international Population Project in Genomics and Society (P3G) and CARTaGENE Quebec's population biobank (20,000 indiv.). Former holder of the Chair d'excellence Pierre Fermat (France: 2006-2008), she was named Distinguished Visiting Scientist (Netherlands Genomics Initiative) (2009 - 2012) and received the ACFAS prize for multidisciplinarity (2011). She is Chair of the Ethics Working Party of the International Stem Cell Forum (2006 - ), Co-Chair of the Sampling/ELSI Committee of the 1000 Genomes Project (2008 - ) and a member of the Scientific Steering Committee of the International Cancer Genome Consortium (ICGC) (2009- ). She holds four Doctorates *Honoris Causa*, is *Fellow* of the American Association for the Advancement of Science, of The Hastings Center (Bioethics), the Canadian Academy of Health Sciences (CAHS), and *Officer* of the Order of Canada.

***Session 2 - Information and consent as a process***


## Prof. Christian Chabannon (France)

Director of the Cancer Biobank, Institute Paoli-Calmettes, Marseille



## Abstract

***Information process (quantity, quality, dynamics)***

For more than a decade, discussions and controversies surrounding the operations of human biobanks have mostly focused on samples as physical entities. As a consequence, biobank curators, regulators, patients' representatives and associations have been mostly concerned with issues relating to cell or tissue procurement, the secure and prolonged storage of ever increasing series of samples, or the protection of confidentiality and privacy, since the very presence of one or several samples in a biobank was an identifier of an individual and his/her disease. However, the value of a biological sample resides in the latent information that scientists will eventually reveal through the conduct of increasingly powerful and high-throughput biological analyses. It is also well recognised that the scientific value of a sample of human origin is greatly increased by its association with abundant and updated clinical and biological information ("dynamic annotations"). By confronting this already available information with newly produced information, new knowledge can be generated with collective value as well as individual significance. To fully exploit human biobanks and their biological resources will require significant improvements in the deployment of information technologies in hospitals and translational research facilities, the design of tools for data mining and the definition of procedures to facilitate patients' perception of these issues and appropriately return newly produced information.


## Full text

Since the Organization for Economic Cooperation and Development (OECD) identified "bioresource" as a key factor for the success of life sciences and biotechnologies in a landmark report published in 2001, a lot of attention and financial resource were devoted to the creation, restructuring or upgrading of infrastructures that allow for the safe storage of primary samples and derivatives. Technical, biological and logistical aspects have been primarily addressed. These include specimen procurement, with the definition of minimal requirements such as the amount/quantity of biological material, the delay and conditions in which it is transferred to the biobank; for human biobanks, education and interactions with surgeons, physicians, nurses and other categories of healthcare personnel or investigators involved in tissue or cell procurement is of utmost importance to eventually obtain valuable samples. Tailored processing of collected specimen pursues two major goals. The first one is adequate preservation of biological samples for future analyses and studies. The second one is the optimization of their use in view of the growing demand for biological resource that has to be confronted with the increasing difficulty of obtaining large amounts of primary biological material, that cannot be replicated in many situations such as tissues derived from humans; the derivation of sub-cellular species such as DNA, RNA, proteins, organelles, the immortalization of cell lines or micro-organisms, are of special interest, especially when it results in replicable material.

Biobanks are as diverse as biological research, and include environmental, microbiological, vegetal, animal and of course human biobanks. A common theme for all types of biobanks is that increasing quantity and variety in associated information ("annotations") is seen as an important asset, thus leading to the implementation of policies that aim at collecting and storing large volumes of information, and to the design and deployment of large digitalized and searchable inventories and catalogues. The need for ever more efficient and powerful information technology is a high priority for biobank curators and stakeholders; the pressure is growing with the need to network biobanks that distribute comparable biological material, some of them on a worldwide scale (e.g. The International Cancer Genome Consortium, ICGC (1)) in order to fulfil the requests of scientists who design more complex and multiparametric experimental plans, focusing on more accurately defined and thus more restricted groups or subsets of individuals. As an example drawn from research in oncology, no sound and modern scientific project would address a question on "Breast cancer" in general, but will rather focus on molecularly defined subtypes of the disease, such as Her-2 positive or triple-negative breast cancers, thus

restricting the population of interest. Similarly, no haematologist would nowadays design a project on "Leukemia", but will rather concentrate his or her attention on a molecularly defined subset of these haematological diseases. All groups of cancers are currently undergoing the same process, with the addition of morphological, immunological and molecular criteria resulting in the dissection of what was once thought of as a unique disease, in an aggregate of quite different diseases. The fact that some diseases that belong to different groups but share molecular alterations may actually behave similarly, particularly in terms of response to targeted therapies, is only apparently paradoxical.

Indeed, one can argue that biobanking is all about information, its production, storage and use.
Samples are only interesting for the information that they conceal, "latent" information that can be revealed through the use of low to high-throughput novel analytical technologies, the latter including the "omics" technologies that produce large amount of new information. The technical challenges that biobank face are to design and master the pre-analytical steps so that stored samples will meet the expectations and requirements for these future analyses , the nature, principles and modalities of which may not be known at the time of the procurement of the primary specimen. This is the addition and confrontation of the newly produced information with already existing information - whatever its nature - that will result in new knowledge, which in turn will generate new-hypothesis driven research.

Thus biobanks should not be seen as "stocks", but rather as "living organisms" that change shape as information flows in and out.

In the case of biobanks that collect, store and distribute samples of human origin, the collection, storage, and distribution of associated information raises critical issues. This is because the environmental, behavioural, medical and biological information not only describes the sample, but also the individual from whom it was obtained. It is thus paradoxical that such sensitive information must at the same time be disseminated for the benefit of the scientific community (and expectedly of our global society) and concealed for the benefit of privacy and confidentiality of an individual (2). Technical measures such as anonymization cannot entirely resolve this contradiction, nor can one-time donor information and consent. One reason is because biological information – especially genomic information – is now generated on a large and extensive scale, up to the point where "genome wide" analysis is produced and can thus itself become an identifier; another reason is the already mentioned changing with time nature of the collected and stored information, and of scientific projects that will arise from this changing knowledge. As an example, follow-up of patients and update on disease progression, disease response to first-line and subsequent lines of various types of treatments (surgery, radiation therapy, systemic therapy, physical therapy ...) are of utmost interest for disease-oriented biobanks such as tumour banks. Clinical and biological information must also be formatted in an easily-exchangeable format such as provided by nomenclatures; this is especially true of information produced by pathologists: although now "challenged" by genetic and molecular information, the morphological examination of tissues and cells remains an important criterion for disease classification. Pathology provides an example of a highly-specialized medical practice, in which several nomenclatures co-exist that pursue the same goal but in different forms, depending on the linguistic and professional background (i.e. ICD-O and ADICAP classifications that both provide a morphological and topographical information on neoplastic diseases, the first one being international in essence and thus in English, the second one being elaborated among the French-speaking community of pathologists). Because nomenclatures change over time (to more accurately reflect the understanding of physiology and diseases), previously collected information must be re-evaluated, and eventually recoded to remain of interest for future projects. The generalization of electronic health records in hospitals still has a long way to go, but should provide investigators with an advantage over currently existing paper medical files by allowing easier and wider access to large amounts of updated and exchangeable medical information (3); this will require that these IT systems can efficiently communicate across different institutions and countries and can evolve quickly enough to integrate novel practices and new diagnostic tools such as biomarkers.

To fully deliver the promise of biobanking through access to this wealth of personal information will likely request and induce further and profound changes in the interactions of biobank curators and personnel with all categories of stakeholders, and especially with patients and citizens. Because patients and citizens are the very source of most information, they may well become increasingly involved in the delivery of such information, including behavioural as well as environmental aspects, in addition to the medical information that is accessible through healthcare professionals. Active participation of patients and citizens in reporting and updating their personal information and in consenting

for newly designed scientific projects – such as recently proposed through the deployment of a unique biological identifier: the BioPin (4) – however represents a tremendous challenge, and will require a much improved and broad education. As an example of such needs for education, a recent study conducted at our institution (5), a comprehensive cancer centre serving a large geographical area in south-eastern France, revealed the insufficient understanding of patients when asked to consent for donating “their” samples to the institutional tumour bank; in addition to poor remembrance of the conditions in which they had answered this solicitation and of their response, the study revealed that few individuals had understood that they were also granting access to their medical file and medical data (the consent form explicitly states this request). Thus patient perception of risks to their privacy and confidentiality is probably quite low (daily practice and individual responses suggest that most patients are mainly concerned with the consequences of sample donation on their physical status and treatment plan). Similarly one can hypothesize that few patients realize that return of newly generated information to them – when deemed useful for their health or safety, or those of their relatives – represents a tremendous challenge in terms of counselling (reviewed elsewhere during this symposium). The same individuals were however concerned that profit could be made through access to their samples, particularly if private partners were to be involved in the conduct of a scientific project; whether such concern would be increased through the understanding that access to personal data may also generate profit deserves further explorations (6).

Citizen education on the benefits and risks of science, including the science of biobanking, together with transparency in governance, will be key factors to raise trust and active participation of patients in improving current and future biobanks. An important issue will be to identify efficient and likely tailored means to convey information from the medical and scientific community to patients and citizens, in order to help them sort out the different categories of risks raised by their participation or their absence of participation in biomedical research: many individuals remain confused as to the delineation between risks to their physical integrity (when they undergo a more or less invasive procedure) and risks to their privacy. While the former may be significant when patients agree to participate in clinical trials testing new drugs, new strategies, new devices, it is usually much lower when consenting to donate samples, especially when these are residual material after a medical procedure. Conversely, the latter increases with the increasing amount of information extracted and associated with biological samples.

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## Biographical notes

Christian Chabannon received medical training at Lyon University School of Medicine in France, and then trained as a resident in Haematology at Grenoble University School of Medicine. He later moved to the Fred Hutchinson Cancer Research Centre in Seattle, WA, USA where he worked as a research associate in the Clinical Research Division, focusing his attention on human haematopoietic stem cell biology and transplantation. He returned to Grenoble University Hospital as an assistant professor in Clinical Haematology, and later moved to Institut Paoli-Calmettes, the Comprehensive Cancer Centre in Marseilles, France to join the cell therapy program. For many years, he has been the head of the cell therapy facility that includes the cell collection and cell processing facilities, and serves the adult and paediatric hematopoietic stem cell programs in the Marseilles metropolitan area; the facility hosts an allogeneic cord blood bank. Since 2000, Dr. Chabannon has run the tumour bank that collects, stores and distributes biological samples of human origin to support research programs in oncology.

Dr. Chabannon is a professor of medicine in cell biology at Aix-Marseille University School of Medicine. He currently serves as the Director of Cancéropôle PACA, the Provence-Alpes-Côte d'Azur network that fosters multidisciplinary exchanges between local scientists involved in the conduct of scientific projects in oncology.

***Session 2 - Information and consent as a process***


## Prof. Christian Scerri (Malta)

Associate Professor, Department of Physiology and Biochemistry, University of Malta



## Abstract

***Recontacting – Consenting again***

The use of biological samples and data outside the scope of the research to which consent was given, is considered a 'secondary use' and thus outside the original consent. Obtaining specific consent for each separate research project requesting the use of samples stored in a biobank, is frequently not feasible. The consensus is for a broad consent approach that has been the accepted practice for most of the newer biobanks. In contrast the broad consent approach is not applicable to already existing biobanks such as samples collected for specific research (with a research specific consent), clinical pathological collections or collected as part of population screening (clinical intervention consent). The main ethical issue in the use of these collections is the lack of specific informed consent for the new research project and the possible requirement for individual re-consent. The alternative view is that if the reviewing ethics committee considers the proposed research as being: (i) of significant ***scientific importance,*** (ii) that the collection of new material cannot be ***reasonably achieved*** and (iii) that consent is not obtainable after ***reasonable efforts***, then samples can be used without seeking a new consent. The third alternative is unlinked anonymisation of the samples, so that no re-consent is necessary.

None of the three alternatives are ideal solutions. Re-contacting subjects for re-consent is time consuming, costly and frequently impossible. Regarding the second scenario a possible dilemma that is faced by both the researcher and the reviewing ethics board is the scale of measurement by which one could quantify the extent of effort reflected in terms such as 'reasonable effort and /or achievement' and the importance of the science. In an age where multicentre collaboration is the norm and thus sample and data transfer are a requirement, an effort should be made to define these measurements so that a level-playing field across all ethics committees and countries is obtained.

Though at first sight, unlinked anonymisation seems to solve these problems for both researchers and ethics committees, it poses other ethical issues such as no consent for anonymisation and inability to re-contact if important medical information concerning the donor arises from the research.

A renewed discussion should take place so that the envisaged actions that deal with these issues are fine-tuned, so as to decrease the risk of reducing the autonomy of the research participant as well as the risk of possibly hindering lifesaving research that would benefit both the individual and society as a whole.


## Full text

***Are re-contact and re-consent always necessary for new research on archival material?***

Human biobanks can be defined as collections of human tissues together with the related phenotypical (and possibly demographical) data from which genetic data can be derived. Biobanks form a major pillar in the identification of disease causing genes and as such, they constitute a major research resource.

As expected, a number of varied ethical issues have surrounded biobanks, mostly depending on the design and research methods of each particular biobank. These varied methods can be grouped depending on the sampling methodology (left over clinical samples versus new sample collections), subject recruitment (population based, broad medical conditions or specific medical condition), subject recruitment process (opt in versus opt out) and the temporal aspect of the medical information collection (cross sectional design in contrast to prospective, long term, re-access of medical information

It should be clear that biobanks are not discrete research projects, but are research platforms that can be used by:

- a number of researchers,
- for various, possibly trans-border, research initiatives,
- and over many decades.

A common ethical issue that is encountered in all the various types of biobanks is that of consent including re-consent and re-contact.

**The Informed Consent**

The concept of the informed consent arose from the Nuremburg Trials and was further amplified in the Declaration of Helsinki. If biobanks are considered as clinical research, then the consent process should be divided into three distinct types:

1. Consent to collect data/sample;
2. Consent for research to be performed on the data/sample;
3. Consent to use data(+/- sample) that was collected for other purposes;

In consenting to the collection of data and sample, the subject is required to understand relatively easy concepts such as the actual questions that would be asked, any physical examination and tests to be performed at the moment of sampling and the actual sampling procedure. The participant can thus decide, with relative ease, whether to participate or not in the recruitment, whether to be informed of any conditions identified, information on how this shall be imparted to him/her and that they can withdraw participation at any moment during the recruitment phase. So this type of consent can be described to be fully "**informed consent**".

The second consent that the participant to a biobank recruitment project is asked to give, concerns the possible research that could potentially be performed on the donated sample and data. Though as has already been described, the "immediate" research can be known and thus this information can be passed on to the participant, a major feature of biobanks is the possibility of performing as yet unknown future research on the sample or data. At best, one can have a general framework of the possible research, but details would be lacking. These details would include the purpose, methods, risks and benefits. Thus, such a consent cannot be truly informed.

To be effective biobanks need to rely on the availability of data collected for other purposes, e.g., medical records. Giving one's consent for one's medical records to be accessed is ethically even more problematic as it concerns future, as yet unknown information. This again puts serious questions on the "informed" phrase within the informed consent concept.

While there is no doubt that, some type of consent is required and usually requested prior to collecting samples/data, any type of consent for the collection of samples and data in a biobank, shall fall short of a fully informed consent as:

1. There is uncertainty on the potential benefit to individual and public;
2. There is an apparent potential risk of lack of privacy and misuse;
3. It cannot be ascertained at the time of recruitment whether future research might violate the participants religious or cultural beliefs.
4. The choice to know or not to know has been taken in a relative vacuum of information.

In addition, differences in the requests and interpretation by different ethics boards of phrases such as "reasonable efforts", "best efforts", "all efforts", produce a real potential of seriously limiting multicentre studies, where biobanks play an important role. There is also the risk for ethical boards to take a mechanical approach to informed consent rather than consider the potential risks against potential benefits to participants and society in general.

So if one had to accept the fact that though in every biobank project, some kind of consent is obtained for the collection of tissue samples and use of data, this is hardly ever fully informed, does this mean that one requires a new informed consent for every new research use of the samples and data? Is re-consent a feasible proposal? Does re-contact and re-consent pose any ethical dilemmas on the part of the participant? Can there be better alternatives to the informed consent?

**What are the alternatives to informed consent?**

At present, four clear alternative types of consent have been utilised in biobanking activities. These are the presumed, graduated, extended and broad (and its variations) type of consents.

**Presumed Consent**
Presumed consent has been adopted for the use of health data in conjunction with biobanks. In most cases an "opt-out" possibility is available. The Icelandic Population Database is a prime example of such a type of consent. Certain countries, for example Western Australia, have gone a step further in that they have enacted legislation that authorises the use of medical data for research purposes without the need for consent but without an "opt-out" possibility. Sweden and Denmark utilise a similar system for archival pathological samples, where a presumed consent for use in scientific research is assumed unless the individual expresses otherwise. In such cases, there is no clear evidence that the subject has engaged in an act of self-determination and should be better considered as a waiver rather than consent. Such waivers require strict conditions and limitations to reduce the risk of actual or perceived abuse.

**Graduated Consent**
In the graduated or authorization model of consent, participants are invited to consent for a range of options. Thus the consent form might include consent for the type of research, wish for re-contact and whether the participants or their families wish to receive relevant medical information that could arise from the study. Thus, the initial consent operates as an advance directive. This places heavy administrative burdens on the management of the consent and many times requires particular interpretation of the directive depending on the prevailing circumstances.

**Extended Consent**
Apart from consenting for the particular research for which the sample is collected, in the extended consent model, participants are asked to to show their preferences whether to participate or not in other research related to the original project. This increases the "informed" part of the informed consent for the collection and use of biobank samples and data. Obviously, questions can arise on the relatedness of the secondary research to the primary one.

**Broad Consent**
The broad consent is a type of unspecified consent where participants give consent for the use of samples and data in future unrelated research. Withdrawal of sample and data is still possible at any point of the research. This type of consent has become the most common type in most of the newer biobanks (Estonia, UKBiobank,[54] and the HUNT biobank in the Norwegian HUNT study[55]). One basic requirement is the need of participants to have readily available and up-to-date data so that participants can be free to withdraw consent. Such a need has produced a novel variant of the broad consent, the **dynamic consent.**

In the dynamic consent model, there is a continuous two way interaction between the donors and the researchers. This is achieved through an IT interface where participants can show preferences on the use of both samples and data, depending on the choices that are presented. Thus participants can withdraw from the particular study at will as well as choose when and how to be contacted. Such a consent has the obvious benefit that it reduces the bureaucratic burden of re-contact and re-consent while at the same time, enabling the participants to exercise their autonomy by giving informed consent for new research. On the other hand, it assumes that all participants have access to the IT infrastructure and are knowledgeable in its use. Thus there is a real danger that such collections could have a strong bias towards individuals of a higher social as well as educational level.

[54]Knoppers BM. Biobanking: international norms.J Law Med Ethics. 2005 Spring;33(1):7-14.Biobanking: international norms.
[55] Ministry of Health and Care Services. (2006). Ot.prp.nr.74 Proposition from the Norwegian Parliament on medical and health research (The Health Research Act)

**CoE recommendation on Biobank Sample Consent**

Article 10:2 of the CoE recommendation (2006)4 states "Information and consent or authorisation to obtain such materials should be **as specific as possible** with regard to **any foreseen research uses** and the choices available in that respect." Additionally, if samples for a research project are **"not within the scope of prior consent"**, the researcher should make **"reasonable efforts" to re-contact the subject**

From the above, the CoE recommendation seems to rule out broad consent as a viable option. The explanatory memorandum to this article seems to favour a graduated type of consent, by offering participants a number of available options. One of these options is that of re-contact with a view of re-consent. While re-contact and re-consent seem to be a solution to uphold the individual's autonomy, it does pose a number of problems both from the practical as well as from the ethical point of view.

Re-contact with a view to re-consent, results in a **wastage of time and resources** to trace participants, inform them of the new research and obtain their consent. This could discourage researchers from utilising the resources in hand to the maximum benefit for the participants, their families and society in general. By increasing the number of times that a particular participant is re-contacted and asked for a re-consent, there is a real risk of **"consent fatigue"** and could result in an increase in the number of consent withdrawals. Even though participants could have consented for re-contact and re-consent, re-contact could put **undue psychological stress** leaving them wondering why they have been re-contacted and whether something wrong has been identified in "their" sample. Similarly, **unnecessary distress could be caused to the relatives** of participants deceased since the submission of the sample/data. Lastly, but of similar importance to the rest, physicians might be reluctant to participate in the biobanking activity if they know that they shall need to re-contact and ask for re-consent a number of times during the lifetime of the biobank, basically suffering from **"physicians fatigue."**

The value of an informed consent is its "role as a practical manifestation of a right of self determination."[56] An act of self determination can only be considered so, if one has the competence, voluntariness and the necessary understanding of the material information that is presented. Though voluntariness and competence can be relatively easily assessed, the understanding of the material presented is most cases rudimentary. This has been shown in various studies[57] where participants were assessed on their knowledge, following an informed consent process. On the purposes of the research, information beyond the superficial was considered not to be relevant to participation decision and most had difficulty to recall whether a sample was to be stored for an indefinite period. On being questioned about the benefits and risk of the study, participants had a hazy hope that the biobank research could produce future cures with some holding the misbelief that they would receive personal health benefit even though the documentation had clearly stated otherwise. On the other hand, very few expressed concern in view of potential risks and opted out. On the issues of rights and responsibilities, almost all understood the general role of the consent, knew that they had a right to withdraw as well as being aware of the responsibilities of the researchers.

Thus even when consent was of the fully informed type and dealing with one particular research project, it was actually at best "**adequately informed",** but participants were usually satisfied that their actions were self determined, under control and free to withdraw their consent.[58]

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[56] McNamara AJ, Reconsidering the value of consent in biobank research. B.Bioethics. 2011 Mar;25(3):155-66

[57] Skolbekken, J. *et al*, (2005). Not worth the paper it is written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15 (4), 335-347; Höeyer K. (2003) "Science is really needed - that's all I know". Informed consent and the non-verbal practices of collecting blood for genetic research in Sweden. New Genetics and Society, Vol. 22, 198-212; Höeyer K & Lynöe N. (2006)Motivating donors to genetic research? Anthropological reasons to rethink the role of informed consent. Medicine, Health Care and Philosophy 9:81-86

[58] Skolbekken, J. *et al*, (2005) *op. cit.* note 4; Höeyer K. & Lynöe N. (2006), *op. cit.* note 4; Allen, J. and McNamara, B. (2011) *op. cit.* note 3; Helgesson G, Ludvigsson J, Gustafsson Stolt U. (2005) How to handle informed consent in longitudinal studies when participants have a limited understanding of the study. J Med Ethics; 31: 670-673 Johnsson, L. *et al,* (2008) Opt-out from biobanks better respects patients' autonomy. BMJ, 337(a1580).

So while the CoE recommendations favour a graduated consent with its inherent problems of re-contact and re-consent, most of the participants in limited and thus specific studies seem to be satisfied with a broader consent. A compromise between these apparently two extremes could be reached through the adoption of a proposal by Steinsbekk and Solberg (2011)[59] to adopt a consent to a framework of research. In particular Steinsbekk and Solberg propose that:

> "in order to make informed decisions, participants should concentrate on ***what matters***. Decision making is not about processing as much information as possible, but rather to be able to pick out the most relevant and decisive information. To be able to make an autonomous choice, you need to know the pieces of information that could make a difference in your decision of whether to participate or not."

Such a consent to a framework is based on "what *should* people have in mind when consenting (or not) to medical research"[60] A list of issues that should naturally matter would include whether:

- a **medical intervention** is a part of the research;
- research can cause **physical or psychological harm;**
- project can identify **potentially disturbing information** that is planned to be returned;
- research is **directly on participant** or his/her DNA;
- research shall lead to **public benefit or private profit;**
- performed for **common and general public health** purposes or for **controversial causes** such as human cloning;
- there is and what type of **institutional control;**
- focus is on the **community (group) or on the individual**
- samples collected for research can be used for **other purposes apart from research;**
- **data** appears to researchers as **anonymous or not**

By answering these issues, one can build a framework that includes aims, conditions, use of the resources, governance and what is at stake for the participants. Thus the informed consent would be for a framework and only if the framework changes then re-contact and re-consent would be required. Though innovative, interesting and on face value practical, such a consent is void of potential ethical challenges.

The consent for a framework is given on the premise that the framework does not change and hence participants have a right to know of potential changes in the framework. So who should decide when the framework changes? On deciding this issue, one has to keep in mind that the aim of consent to a framework is to limit the need for re-contact and re-consent of participants. Another important aspect is the fact that participants should not be asked to decide on ethical issues of whether a framework has changed or not. It should be the role of ethical committees to decide such issues.

On the other hand, participants should be kept fully informed of the activities of the biobank both by traditional (post) as well as by electronic means (e-newsletter, website), without the need of asking specific consent for each new project. The latter aspect, i.e., no need to obtain a new specific consent, is the major difference between consenting to a framework and a dynamic consent model.

The next aspect that should be examined is whether existing collections could utilise the consent to a framework as an extension of any existing consent. If the biobank was set up as a research tool, and thus with an initial broad consent, it should be possible to transform the original consent into a framework to reduce the need to re-contact. If the original consent was specific, transformation might still be possible but a formal ethics committee decision should be sought. If the biobank is composed of residual tissues with an original consent that would not have included research, it would seem very improbable that a retrospective consent to a framework could be applied. Thus for the latter two examples, the need for re-contact and re-consent, with their inherent problems, still exists. In this context article 22 of the CoE recommendation, could result in a potential hurdle towards international co-operation and multicentre studies.

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[59] Steinsbekk , K.S. and Solberg , B. Biobanks—When is Re-consent Necessary? (2011) Public Health Ethics, 4 (3): p 237

[60] Steinsbekk & Solberg, *op. ci. note 6*

Article 22 proposes that the researcher should make "**reasonable efforts**" to contact the participant and if this is not possible "**with reasonable**" efforts, then the material could be used, if it fulfils three conditions, namely:

a. the **research addresses an important scientific interest**;
b. the aims of the research **could not reasonably** be achieved using biological materials for which consent can be obtained; and
c. there is no evidence that the person concerned has expressly opposed such research use.

Most of this article is based on a very subjective notion of "**reasonable effort**" and the **importance of the research.** There is no clear definition or objective benchmarks upon which to judge the reasonableness of a reasonable effort. In contrast, the literature is full of legal contentions on what constitute "reasonable effort". In common law, the term "reasonable":

- involves an element of judgement
- depends upon the facts of the case
- depends upon the environment in which the issue is examined.

As multicenter research projects would normally require ethics committee approval in each of the participating centres, there is the real risk of different subjective interpretation of this relevant article. Such major differences can potentially hinder multicenter studies. As it is difficult if not impossible to objectively describe the "reasonableness" aspect, an alternative approach is required

A possible solution (Table 1) was proposed by Hellgeson et al. (2007)[61] from the Centre for Bioethics at Karolinska Institute, Sweden.

Table 1

| **Type of collection** | **Special Consideration** | **Utilisation** |
|---|---|---|
| No explicit consent for Research | • research interests,<br>• strict coding<br>• secrecy laws | • May be used without consent<br>• Opt-out when feasible |
| Consent limited to specific study | None | |
| Consent restricted to specific use | None | • Not to be used for the excluded kinds of research |
| Consent specifies that research results reported back to donor | Results aimed at general question not sufficient as a basis for medical treatment – might cause unjustified concern and harm | • If re-contact consent is given only for a specific study, then it can be used for other studies but results not reported back.<br>• Opt-out when feasible.<br>• If results to be reported included future studies, new consent is required. |

[61] Hellgeson *et al* (2007) Ethical framework for previously collected biobank samples, Nature Biotechnology Volume 25 September Number 9

**Conclusion**

Broad consent has become the norm in new biobank projects. The use of broad consent offers the possibility of future, yet unknown research, on the collected samples and data. As it lacks the necessary details, a broad consent cannot be fully informed and as such seems to fall foul of article 10 of the CoE recommendations. On the other hand, if the broad consent includes details that really matter to the participants, then it becomes an informed consent to a framework. Re-contact and re-consent would only be required if the proposed research is deemed to fall outside the boundaries of the framework.

In an attempt to reduce the need to re-contact in regard to already existing biobank collections, the existing biobanks should be divided into four groups. If no explicit consent for research was given at the time of collection e.g., pathological samples, then both sample and data can be used if the samples and data are coded or anonymised. If a consent had been given for a specific study, then samples could be used through the extrapolation of the original consent to a consent to a framework type. If the original consent was restricted to a specific use only, then re-contact and re-consent would be necessary if the new research involves any of the originally excluded group. If the donor consented to having the results reported back, then re-contact is necessary to obtain a new consent.

While keeping the need for consent as a crucial part of any research, the points outlined above offer an objective way to offer an informed consent and reduce subjectivity on the use of collected tissues and data for further and novel research while reducing the need for re-contact and re-consent.

## Biographical notes

Christian Scerri has been active in the field of molecular and clinical genetics for the past 23 years. Following his qualification as a Medical Doctor from the University of Malta and following 5 years of clinical work, he read for a Ph.D. at the University of Malta. His work involved the molecular characterisation of a number of genetic conditions in Malta. In addition, he has published in international peer-reviewed journals on a number of multi factorial disorders. Christian has held various public and private managerial appointments. He was also assigned the role of coordinator in the preparation and submission of the University of Malta Structural Funds projects. He was a member of the team that worked on a report for the European Science and Technology Observatory on Biobanks in Europe: Prospects for coordination and networking - Implementation Plan, external consultant to the Luxembourg National Research Fund (FNR) foresight exercise in identification of research areas for 2020 and member of the European Task Force for Rare Diseases. He is presently a member of the Maltese National Bioethics Consultative Committee, member of the National Task Force on Rare Disorders, Consultant to the Malta Council for Science and Technology on Health Research, Chairman of the Association of European Coeliac Societies and a Governor of The BioMalta Foundation.

# Prof. Martina Cornel (Netherlands)

Professor of Community Genetics and Public Health Genomics, VU University Medical Center, Amsterdam

## Abstract

***Protection of vulnerable persons: the case of children***

Blood samples of newborn children have been collected for newborn screening (NBS) programmes in many countries, including most European countries. The goal of NBS is the identification of treatable conditions to avoid irreparable health damage. Once the dried blood spots have been collected, a wealth of data may become available for secondary use in research. The procedures to inform parents on NBS, to ask for consent for storage and use for research purposes show major differences between EU countries.

When considering the special position of infants and children in biobanking and biobank research, several issues need attention. These consider the protection of individual rights of infants and children, but also the collective protection of minors, by promoting pediatric public health:

1) Informed consent for the storage of dried blood spots is not always asked for. Parents sometimes consent on behalf of minors (or decide whether or not to opt out). When reaching majority, children may want to have the possibility to reconsent or opt-out.

2) Incidental findings, especially when highly predictive of treatable conditions, have to be treated differently when a minor is involved. If a biobank uses material of vulnerable persons, a stronger duty to inform the participant of relevant information may be applicable.

3) Research has often included only adult males as study participants. To study conditions of childhood, especially rare disorders, biobanks of children may be urgently needed. Priorities in medical research related to vulnerable persons may require biobanks of infants and children.

## Full text

Mr. Chairman, ladies and gentleman,

Thanks for the opportunity to contribute to this symposium with a presentation on “protection of vulnerable persons: the case of children.” My name is Martina Cornel, I am chair of the Netherlands Programme Committee Neonatal Heelprick Screening.

Every infant can undergo neonatal screening for treatable disorders in the Netherlands. In the neonatal screening program, early diagnosis and treatment can prevent irreversible health damage. In the programme committee, four times per year all parties involved in the programme meet for attunement: coordinators at the national center for public health, screening laboratories, metabolic pediatricians, endocrine pediatricians, hematologic and lung pediatricians, obstetricians and gynaecologists, child health care organisations, etc.

In the Netherlands, when an infant is (at least) 5 days old, some blood is taken on a dried blood spot card for laboratory investigation. At the same time hearing screening is performed. Information on child, pregnancy, general practitioner etc is written on the card. Parents can refuse participation to the program, which happens in a few per thousand. The main reason for refusal is that the child was born in Belgium, and participated to neonatal screening there. Parents can opt out of use of the dried blood spot for research. Also, there is an opt out possibility for receiving carrier status information. In the laboratory test for sickle cell disease, carrier status is automatically seen, as an unsolicited finding. As it can be relevant for the parents, because of an increased risk of homozygous sickle cell disease in the next child, this information is communicated to parents, unless they opt out.

In 1974 the neonatal screening started in the Netherlands with PKU. A diet can avoid mental retardation. Later congenital hypothyroidism and congenital adrenal hyperplasia were added. Here, medication can avoid respectively mental retardation and sudden death.
In 2007 the program was extended with 14 disorders. This dynamics of major extensions is seen in many countries in recent years.

Extension of the neonatal screening program is driven by two forces: more diseases becoming treatable and more tests becoming available for high throughput screening: cheap, sensitive and specific. The extension in 2007 was mainly driven by tandem mass spectrometry, where two mass spectrometers are put behind one another (in tandem) to allow a computer to report on many metabolites.
Recent genomics, proteomics, metabolomics research promises many more such possibilities.

Intuitively, we feel that early diagnosis is always an advantage. However, as Sir Muir Gray, for many years director of the national screening program in the United Kingdom said: All screening programs do harm. Only some do more good that harm at reasonable cost. We have to follow the advise of this wise man, especially when it concerns vulnerable persons: children, and continuously balance the pros and cons.

The **primary** goal of neonatal screening is to protect children: to identify infants with disease in whom timely treatment can prevent irreversible health damage.
If all dried blood spot cards are stored, in a sort of a biobank, this does generate many possibilities for **secondary** use in research. Some of the secondary uses are linked very much to further improvements of the heelprick program. I will discuss SCID, the development of high troughput testing for Pompe disease from diagnostics to screening in the laboratory, and a prevalence study on MCADD.
Some of the secondary uses are further away from the neonatal screening program, such as an epidemiological study on the frequency of HIV in newborns, that I will discuss.
I will NOT discuss secondary uses **in the interest of the individual infant or family**. If a child is several years of age, and suffers from hearing problems and developmental delay, the question may be raised whether the child has a congenital CMV infection. In the heelprick card the DNA of the virus CMV may be investigated to confirm the individual diagnosis.
If a child has died suddenly, sometimes a suspected cause of death can be confirmed in DNA. This may help to inform parents of diagnosis and recurrence risk.
In forensics, the identification of children that are victims of disasters may be performed with the help of heelprick cards.
I will not come back to these individual uses of heelprick cards.

In the Netherlands in 2007 the neonatal screening was extended to 17 disorders, but I told you that many countries are discussing further extensions. In the United States of America, up to 60 conditions can be screened. As an example, I will discuss SCID: Severe Combined Immuno Deficiency.

You may know this disorder as “the boy in the bubble”. Because of a deficient immune system, these patients do not respond adequately to infections. Haematological stem cells may help them to make blood cells, including T cells, that function normally. A laboratory test is available to investigate TRECs: T-Cell Receptor Excision Circles: small pieces of DNA which are a by-product of normally functioning T cells, that are NOT present in SCID patients, as can be seen in the lower right figure.

SCID could be the first condition in the neonatal screening program where not only treatment is available, but cure! After stem cell transplant, the child would have a normal life and be cured from SCID. Here we see the first potentially curable condition for newborn screening. Obviously, if countries would consider to include this and other “new” conditions in the neonatal screening program, research is needed to accompany the implementation from bench to population screening.

I come back to the need for research on potential new newborn screening conditions. If a test is developed in the clinic for diagnostic purposes, it is often performed for one patient only. To develop it for screening purposes, hundreds of samples must be tested simultaneously, and an extremely high sensitivity and specificity are needed. If in NL the specificity would be only 99% for example, this would mean that 2000 infants per year would be referred to the hospital, most of which are healthy. Instead, the specificity has to be close to 99.99%. The slides I show you here are from a Rotterdam study, where dried blood spot cards are used to develop a screening test for Pompe disease. Only if the par-

ents had **not** opted out for secondary use of the dried blood spot card for research purposes, could the card be used for this anonymous study.

When a country considers to extend the programme, some may suggest that a condition is too rare. In the Netherlands the frequency of MCADD was studied before this was included in the neonatal screening. MCADD can hardly be considered a disease, it is rather a condition needing life style advice. These children need frequent feeding. If they are between half a year and 1 ½ year of age, and sleep from 7 in the evening till 7 in the morning, finally allowing their parents to rest at night, they may not be able to mobilize their energy stored in fat. Especially when growing fast and suffering at the same time from a flu, they may die suddenly. All they need is regular feeding, for instance by extra milk at 11 in the evening before parents go to sleep.
In a Dutch study in Guthrie cards (dried blood spot cards) the prevalence of carriers of the most frequent MCADD mutation was 1:55. The allele frequency is half of that, say 1:100 and the disease frequency the square, say 1:10.000. This implies that some 20 infants are born each year in the Netherlands with MCADD. We started the program for PKU, which has a similar frequency! So adding MCADD, just looking into its frequency, could be worthwhile.

The previous examples of research were linked to the goal of neonatal screening. We now turn to an epidemiological study.

When HIV/AIDS was recognised as a potential problem for mother and child, a question was whether this had occurred already decades ago, but had not been recognized, or was really a new problem. In a survey, the frequency amongst pregnant women over a period of more than 10 years indeed showed an increase. Dried blood spots were also used to confirm this trend in newborns. Over a five year period, indeed a significant increasing trend was found. In anonymous samples, some 80% of HIV positive newborns turned out to have mothers born in Sub-Saharan Africa. For mother & child health policy making this has clear implications.

I have shown you that research with dried blood spots can be useful for infants without doubt.
However, research is not the primary goal of neonatal screening, so informed consent is needed. As a collection of dried blood spots contains biological material, including DNA, of the infants, as well as names and some medical information, the collection can be considered a biobank. Important issues to be discussed are the governance: who decides for which purposes the cards can be used? Researchers, medical ethical committees, program committees with representatives of all parties involved, patients, parents?
A separate issue is whether patient organisations, that are often well informed on the issue and convinced of the relevance of biobanks for “their disease”, represent the voice of parents of healthy children. False positives, recalls to the hospital that were, in retrospect, not needed, may have a different meaning for parents vs. patients. Privacy issues and the prioritisation of use for different goals may differ as well, e.g. should some dried blood be kept in the interest of child or family? Finally, for some purposes long term storage beyond a few years may be useful, as in the HIV example I showed. Should children be asked for consent when they reach the age or maturity? Should they be allowed to withdraw their sample from the age of 12? 16? 18?

When starting to discuss ethical issues in neonatal screening, we have to consider what to do with unsolicited findings, as the information on carrier status for sickle cell disease that I mentioned in the beginning, or the diagnosis of a condition that was not the goal of our screening but is the result from the MS/MS testing.
In research, as a standard procedure no information on individual results is provided to participants, mainly because research findings have to be confirmed in other studies first. Furthermore, the funding is available for research, often not for the counselling of individual participants afterwards.
However, when parents, researchers, third parties decide to use the dried blood spot of a vulnerable person, the “right to know” may need a different equilibrium. If a better test for neonatal screening is developed, and a (still anonymous) child is diagnosed with a treatable condition, it may be in the interest of child and family to recontact.
As a very concrete example, if whole genome sequencing for research purposes would lead to the diagnosis of cardiogenetic or oncogenetic conditions, where a high risk of serious disorders exists, but at the same time preventive options are available, there is a duty to inform!

As a more general question we can reflect on the question whether research on dried blood spots of vulnerable persons should be allowed. Because pediatric conditions often can only be studied in infants or children, this should not a priori be dismissed. I mentioned the example of CMV testing for an individual child with hearing problems and developmental delay. Nowadays, some researchers consider that CMV testing might be added to the neonatal screening program. The evaluation of effects of early diagnosis and treatment can only be done in the population of newborns and children.
Especially in pharmacological studies, the preferred volunteers are adult males. Priorities in research in general have to take into account the needs of women and children.
In the EU many countries are preparing national plans for rare diseases. The fact that a condition is rare, does not necessarily mean that it should not be a priority in research. Many EU citizens suffer from a rare condition. The laboratory methods and programmatic approach of neonatal screening are suitable to target several rare conditions at once.

In conclusion I have shown you that, under certain conditions, vulnerable persons may profit from use of their biological materials.
Parents represent the interests of their children and thus need to be involved in the informed consent and governance of the collections of dried blood spot cards, that can be considered biobanks.
There is an ethical duty to inform parents on treatable conditions in their children, if these are diagnosed in research with dried blood spots, and finally:
Rare diseases in infants deserve priority in research programmes, as many quality adjusted life years can be gained with interventions from the start of life onwards.

## Biographical notes

Martina C Cornel, M.D, Ph.D. (♀, 1959) is professor of community genetics and public health genomics at the VU University Medical Center in Amsterdam. She is a physician and epidemiologist. In recent years she was involved in research on genetic screening criteria, a pilot on preconception screening for cystic fibrosis and hemoglobinopathy, research on genetic education and the international database for rare diseases (Orphanet). She teaches medical students and health science students in the areas of health promotion and large scale applications of genetics and genomics and is involved in postgraduate training in these areas.

She was a member of the Netherlands Health Council Committees on Neonatal Screening (2005), “Screening between hope and hype” (2008) and Neonatal Screening for Cystic Fibrosis (2010). She is chair of the Public and Professional Policy Committee (PPPC) of the European Society for Human Genetics (ESHG) (www.eshg.org), chair of the Dutch Programme committee Neonatal Heelprick Screening (www.rivm.nl/pns/hielprik), chair of the working party on societal aspects of genomics, CMSB, Leiden (www.cmsb.nl), principal investigator of the Centre for Society and Life Sciences, CSG, Nijmegen (www.society-lifesciences.nl) and chair of the scientific advisory board of Orphanet-Netherlands (www.orpha.net).

Some relevant publications:
European Society of Human Genetics. Cornel MC, Evers-Kiebooms G, Aymé S, et al. Genetic testing in asymptomatic minors. Eur J Hum Genet. 2009;17(6):720-1.

Cornel M, Rigter T, Weinreich S, Burgard P, Hoffmann GF, Linder M, Loeber JG, Rupp K, Taruscio D, Vitozzi L (2011) Newborn Screening in Europe; Expert opinion document.
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*Session 3 - Privacy and data protection*


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## Abstract


***Main challenges***

In the light of the effects produced on the legal systems of some European countries by the principles set forth in the Council of Europe's Recommendation Rec(2006)4, this paper will highlight shared views and also pinpoint the differences at national level – which in some cases may hinder the performance of (especially cross-border) research.

As regards, in particular, the protection of participants' private life and personal data – which are fundamental rights under Article 8 of the ECHR and Articles 7 and 8 of the EU Charter of Fundamental rights, respectively – the relevant criticalities will be pointed out by having regard to the latest research methods along with the growing internationalisation of research. The criticalities have to do on the one hand with confidentiality of the personal information used for research purposes – including that extracted from biological samples – on account of the limitations applying to its (possible) anonymisation and/or pseudonymisation, which may impact in turn on participants' right to private life as also applying to their family members. On the other hand, emphasis will be put on the risk that participants' right to informational self-determination may also be jeopardized if the use of biological samples and the processing of personal data are authorized or consented to for multiple future researches serving purposes that may be unknown beforehand, which may ultimately result in losing control over the participants' data (and samples).

In order to provide the highest possible level of protection of participants' fundamental rights and accordingly ensure active participation in biobanks-based research, integrated protection strategies should be developed. They should consist in enabling uninterrupted information flows for participants based on full-fledged use of ICTs; enhancing transparency and accountability requirements applying to the entities that manage biobanks and carry out researches; introducing appropriate risk assessment tools as also related to the massive deployment of ICTs; setting up appropriate, non-redundant co-ordination mechanisms between the supervisory functions vested in data protection authorities and other bodies (such as ethics committees) tasked with monitoring biobanks-based research.


## Full text

***Privacy, Data Protection and Biobanks-Based Research: Main Challenges*** (*)

1. *Foreword*

I firmly believe we were not convened here merely to address (perhaps in detail) the issue of privacy and data protection in biobanks-based research. I do not think we are supposed to take stock of the specific conditions applying to this new approach to medical and scientific research, maybe by highlighting the (more or less significant) adjustments required as compared to other, more traditional types of bio-medical research on humans.

Whilst these issues are important and will be addressed in detail by other contributors, let me first of all ask the following question: should we re-affirm the individual's pivotal role, primacy and dignity also in this biomedical research sector – which might be regarded as "new" to the extent this research relies on new ICTs? Or should we regard the individual whose biological data and samples are collected and made available via biobanks – on the most diverse grounds of a scientific, technological, social, economic or organizational nature – as a sort of book, which - valuable though it may be be-

(*) The opinions and the views expressed are the Author's only. The Author would like to thank Mr. Antonio Caselli for translating the text.

cause of its being unique – is ultimately just a "book" placed on a peculiar "shelf" we now call a "biobank"? And could this "book" be browsed and borrowed by any entity that can access this new "library" irrespective of any geographic borders?

The library I am thinking of is a "virtual" as well as "dynamic" one, being made up not only by an individual bio-bank but by networked bio-banks existing all over the world, which in a not too remote future will be interlinked with longitudinal (electronic) health records containing (all) the information (medical and non-medical alike) relating to a given individual.

Faced with this impressive vista of a pool of biological information and samples that can be related (directly or indirectly) to individuals, we are called upon to gauge whether the objective set out in the Recommendation on research on biological materials of human origin pursuant to Article 1 of the Convention on Human Rights and Biomedicine (ETS No. 164) as well as to its Additional Protocol concerning biomedical research (CETS No. 195) – i.e. "to protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine" as per its Preamble – can be considered to be still topical or is merely becoming a rhetorical statement.

In my view, this is the key challenge to be taken up in revising the Recommendation.

This is so because sticking to language that is now current in literature concerning these issues (such as "donors", "data (and samples) sharing", or even alleged "ownership rights" on biological samples and biobanks data used for research purposes) without carefully considering the relevant implications may ultimately pave the way to a legal framework grounded in property rights as opposed to the framework that has been (and in my view should be) prevalent in this sector – at least in Europe's legal tradition – i.e., the legal framework based on personal rights as a tool to turn respect for the individual's dignity into reality.

I believe that answering this fundamental question, which is key in terms of law policies as it has to do with the relationship between research, society and individuals, is a precondition to work out specific solutions to the multifarious issues raised by biobanks-based research.

On a more general level, let me just point out that the issue coming up is (once again) whether the law – seen as a tool to regulate social relationships – and rights – seen as apportionments of powers and obligations in the societal context – can "cope with" technical and scientific innovations or one should surrender to the "domination of science" evoked by Emanuele Severino and thus join the scores of supporters of Scott McNealy – who in 1999, when he was CEO of Sun Microsystems, stated quite bluntly that "you have zero privacy anyway. Get over it" ([62]).

2. *On the Impossibility of Doing Without Biobanks-Based Research*

I will get back to these issues in a moment. Let me however do away with any doubts or misunderstandings: as far as I am concerned, I am absolutely convinced that one cannot go without effective biomedical researches performed by the scientific community with the help of data and biological samples kept in biobanks.

This statement is past discussion per se, even though one might want to check factually whether these researches can actually meet the expectations they raised on the basis of their current methodologies, or whether some additional standardization measures are needed urgently.

One might quote Dante's Comedy and the well-known words spoken by Ulysses to describe the quest for knowledge that is an ever-lasting feature of man: "*Ye were not made to live like unto brutes, But for pursuit of virtue and of knowledge*"; more simply, let me just recall that the constitutional charters of all countries protect freedom of expression and research.

2.2. *On the Impact on Fundamental Rights*

On the other hand, biobanks based research is liable to impinge on some of the most intimate features of a person's (i.e. participants' and relatives') life and may sometimes impact considerably on personal choices as well as on the key values that inform a person's life. It should be highlighted in this regard that biobanks-based and genetic research has attained unprecedented dimensions in terms of both the number of individuals potentially involved and of the amount and quality of personal information that can be processed – at times over a considerable time span. The latter developments

[62] See Wired News, 11 March 1999.

can be accounted for in the light of the massive introduction of electronically managed health records in European health care systems.

This is why one can easily grasp that there is a possible conflict between the interest in carrying out these researches and the right to private life and the protection of personal data (seen in a broader perspective) as applying to any individual that is the subject of such researches – which may actually be the case for that individual's family members, especially if genetic data are processed.

The conflict in question may only be coped with by way of the "praktische Konkordanz" technique - that is to say, one should seek to strike the balance between conflicting fundamental rights (and public interests) – i.e. find the right momentum between autonomy and solidarity – [63] based on what is termed the "balancing technique".

This is meant not just to implement an interpretive standard applying to the principles contained in constitutional charters; in fact, it is an approach grounded in the belief – also supported by the findings of surveys concerning samples of the European population, as Herbert Gottweis has explained to us – [64] that societal trust in research can only be achieved by ensuring respect for fundamental personal values (among them, private life and data protection), this being a prerequisite for research to be carried out [65].

2.3. (Contd.) As regards, in particular, confidentiality and & informational privacy

This is not the time for dwelling on how "privacy" has been construed also in the case law of higher / supreme courts( [66]). Indeed, the word privacy is to be found basically everywhere and has often been compared to a sort of "black box" ([67]) because of its wide-ranging scope of application ([68]). The ECHR has also found repeatedly that «*la notion de "vie privée" est une notion large non susceptible d'une définition exhaustive*» (*Pretty v. U.K*., 25 April 2002, § 61) whilst it is «*ni possibile ni nécessaire de chercher à définir de manière exhaustive la notion de "vie privée"*» (*Niemitz v. Germany*, 16 December 1992).

For our purposes, there are nevertheless two areas of interest that are mainly involved – on which we should accordingly focus. The former has to do with confidentiality of the information (and samples); traditionally, this has been achieved by way of more or less sophisticated anonymization and (more frequently) pseudonymization techniques applied to data (and samples). The interest at stake is the right to private life as vested in the individual the information relates to. I am not saying anything more on this because Pilar will be addressing the issue in detail. Let me just highlight the ever-increasing criticalities it is fraught with – even though this is not just a feature of biomedical research – if one considers the research methods deployed and the wealth of data to be processed, which make it easier to re-identify (under certain circumstances) the individuals concerned. This is a risk participants should be made aware of. Given this context, one should not take for granted that the research

[63]. In this perspective, regarding the relation between the fundamental right to data protection and other rights/interests, see ECJ (Grand Chambre), 9 November 2010, *Schecke e Eifert c. Land Hessen* (joint cases C-92/09 e C-93/09), in part. points 76 e 77 (regarding the publication of personal data in the internet by a public body in order to satisfy transparency requirements); see also ECJ (C-465/00, C-138/01 e C-139/01), 20 May 2003, *Rechnungshof c. Österreichischer Rundfunk e a*.; *Neukomm e Lauermann c. Österreichischer Rundfunk*, points 88-90. The assumption made in the text results clearly from **art. 8, par. 2 EHRC** and is widely accepted (even if this is often forgotten in literature) in the constitutional case law: e.g., for the BverfGe 1983, the right to data protection «würde nicht nur die individuellen Entfaltungschancen des Einzelnen beeinträchtigen, sondern auch das Gemeinwohl, weil Selbstbestimmung eine elementare Funktionsbedingung eines auf Handlungsfähigkeit und Mitwirkungsfähigkeit seiner Bürger begründeten freiheitlichen demokratischen Gemeinwesens ist» (BVerfG, 15 dicembre 1983, *BVerfGE* 65, 43).

[64] See Eurobarometer, *Biotechnology Report*, October 2010, Special Eurobarometer 341/Wave 73.1 – TNS Opinion & Social, p. 137 ss.; G. Gaskell, S. Stares, A. Allansdottir, N. Allum, P. Castro, Y. Esmer, C. Fischler, J. Jackson, N. Kronberger, J. Hampel, N. Mejlgaard, A. Quintanilha, A. Rammer, G. Revuelta, P. Stoneman, H. Torgersen and W. Wagner, *Europeans and biotechnology 2010. Winds of Change?*, A report to the European Commission's Directorate-General for Research, October 2010, in http://ec.europa.eu/public_opinion/archives/ebs/ebs_341_winds_en.pdf

[65] It should be noted that this is actually the guiding principle of all European researches: Decision 1982/2006/EC of the European Parliament and of the Council (Recital 30 and Article 6), "All the research activities carried out under the 7th Framework Programme shall be carried out in compliance with fundamental ethical principles".

in question entails a “minimal risk” to data subjects although it does not impact immediately on data subjects’ private sphere and health.

The latter area of interest targeted by biobanks-based research consists in the right to informational self-determination (*informationelles Selbstbestimmungsrecht*, or informational privacy) as relating to any data that is used jointly with biological samples. This is a key feature of European legal tradition and was enshrined initially in CoE’s Convention 108/1981 to be subsequently taken up into EU’s law, firstly via directive 95/46/EC and thereafter through Article 8 of the EU Charter of Fundamental Rights as part of the Lisbon Treaty. Drawing upon its definition as laid down originally in the US by Alan Westin, this right empowers each individual basically to "*control, edit, manage, and delete information*" about himself, and to "*decide when, how, and to what extent information is communicated to others*" ([69]).

In this context, the participant’s fundamental rights may be breached not only at the time his/her personal data (or the biological samples his/her personal data may be extracted from) are disclosed or disseminated, but also if such data (or samples) are used without any authorization to do so – which holds true in some cases even after anonymizing the data in question, as per Article 23(1) of the Recommendation.

Let me point out that I am referring to personal data – to the extent they allow tracing back the participant’s identity whether directly or indirectly – and biological samples alike, because the principles underlying the regulations that should apply to data and biological samples (which are considered here as information carriers) should not diverge significantly in this context. This is an issue that has already been addressed by some data protection authorities as well as by the ECHR in the Marper v. UK case ([70]) – as aptly recalled in the Expert Group’s Report([71]). Indeed, the link between data and samples can be traced back to the Recommendation, which refers repeatedly to “biological materials and associated personal data” and envisages safeguards (see Article 16) for the transfer of biological samples outside CoE’s Member States that are clearly modeled after those to be found in personal data protection legislation.

3. *Private Life and Data Protection in the 2006 Recommendation*

3.1. The Recommendation already considers both the participant’s confidentiality and privacy as for both data and samples (see Articles 3, 8, 23, 24(3) and 25, the latter referring to the relevant provisions as contained in the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research - Strasbourg, 25.1.2005) and the issues related to informational self-determination – including what one might term “bio-informationelles Selbstbestimmungsrecht” with particular regard to the participant’s informed consent and right to at any time withdraw from a research (the latter issue will be tackled by Elisabeth in depth).

3.2. Whilst the contents of the Recommendation are largely to be supported and retained, they might be supplemented and enhanced somewhat ambitiously (as well as in a forward-looking perspective) by taking account of some features that mark a turning point compared to the past. I am referring here to the effects produced by technical and scientific developments and the new methodologies used for biobanks-based research, which brought about a shift from the conventional model (i.e. “one-researcher, one-project, one-jurisdiction” as described quite convincingly by Jane Kaye) ([72]) to a model based on the supra-national networking of bio-banks for multiple future research projects (which is actually already envisaged by Article 17(1) of the Recommendation).

This innovation is far from transient and is actually bound to consolidate over time and extend to future generations. More importantly, it is producing effects on participants’ fundamental rights. Let me focus on some basic issues – the information to be provided to participants; the (extended) consent participants are empowered to give (and withdraw, in whole or in part) to one or multiple researches; and the inherently transnational dimension of these researches.

3.3. The information to be provided to participants cannot be given once and for all, since both data and samples can be used for several researches over an extended time span - contrary to conventional clinical trials, and in spite of the fact that the regulations devised for clinical trials have influenced those for biobanks-based research because research ethics committees have a role to play also in the latter sector. In fact, the provision of information will have to be “continual” and take account of the

[69] A. Westin, Privacy and Freedom, New York, 1967.

options that were submitted initially to and accepted by the participant. Against this backdrop, a fundamental help will come from ICT in order to update participants on any new research without significantly impacting on organizational arrangements and costs in the long run. Participants will thus turn ever more into partners in the research, especially if more general awareness-raising initiatives are deployed to enhance the transparency of biobanks-based activities among the public.

3.4. The above issue is closely related to what is still the most controversial feature of these researches by also having regard to the regulatory solutions in place, i.e. the one concerning the participant's "strict" or "broad" consent. If consent is regarded as possibly the most meaningful as well as genuine expression of an individual's right to self-determination, and if one considers the multifarious features of bio-banks, all options should be accommodated – ranging from the least to the most "liberal" in allowing the use of samples and data. Only think, for instance, of those researches participants may wish to be closely linked to specific geographic areas and communities and/or specific diseases as opposed to researches that are much broader in scope (e.g. in accordance with the design outlined by UK Biobank or with initiatives such as "23 and Me"). All the options, including the full gamut of possible positions, should be accommodated in a truly "participant-centric" perspective that could thus be truly free from whatever paternalistic undercurrent. What is more, all these options should be safeguarded effectively against possible breaches.

From this standpoint one should go beyond all excessively narrow-minded approaches as typified by the "strict consent" vs. "broad consent" supporters and welcome the proposal put forward by the Irish Council for Bioethics, whereby "consent forms should be developed to provide potential research participants with options relating to future unspecified use, storage and disposal of their biological material"([73]). As well as mirroring a pragmatic approach, this proposal is really focused on respect for individuals' self-determination and dignity.

3.5. Allowing for multiple choices to be made by (truly) "informed" participants requires an appropriate IT-supported infrastructure along with the appropriate governance mechanisms.

This is why the expert group decided to rely on a model that is quite widespread in the personal data protection world and has long been known as "privacy by design. It is a model for the governance of biobanks that, daunting (and ambitious) as it might be in terms of implementing measures, should consist in "ELSI by design". ([74]) Based on this model, the impact of research infrastructures on participants' rights should be assessed beforehand; given the substantial use of personal data, such assessment should be performed by specialized staff – and I am thinking here of data protection officers as part of the broader biobanks governance mechanisms. Let me recall that DPOs are currently being considered in the context of the proposals for the new EU data protection framework.

3.6. Regarding the transnational dimension of biobanks-based researches, this issue has been timely taken care of by Article 16 of the Recommendation – which requires an adequate level of protection as a precondition to transfer data to "third countries" according to a model imported from data protection legislation.

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[73] Human Biological Material: Recommendations for Collection, Use and Storage in Research 2005, http://www.bioethics.ie/uploads/docs/BiologicalMaterial.pdf. "Such options might include:
(a) Refusing storage and coded or identified use of their biological material for future unspecified research
*Or*
(b) Permitting storage and coded or identified use of their biological materials for any study relating to the condition for which the sample was originally collected, *provided they are contacted and their consent is obtained at the time of the research* and subject to the research being approved by a Research Ethics Committee
*Or*
(c) Permitting storage and coded or identified use of their biological materials for any study relating to the condition for which the sample was originally collected, *without further consent being required* and subject to the research being approved by a Research Ethics Committee
*Or*
(d) Permitting storage and coded or identified use of their biological materials for any future unspecified research, *provided they are contacted and their consent is obtained at the time* of the research and the research is approved by a Research Ethics Committee
*Or*
(e) Permitting storage and coded or identified use of their biological materials for any future unspecified research, *without further consent being required* and subject to the research being approved by a Research Ethics Committee".

Still, there is an additional facet to the transnational dimension of these researches, and this is highlighted in the Expert Group's Report – namely, the desirability of homogeneous regulatory provisions applying to such researches in the individual jurisdictions as also related to the entities tasked with their supervision (including data protection authorities). From this standpoint, a sound as well as consistent legal framework should be set up in order to overcome the current differences – at least at European level. To do so, one could usefully start from the all but scarce shared elements (clearly marked up in the Report) ([75]) and leverage new proposals and ideas as introduced into the individual legal systems – which are modeled, more often than not, after the Recommendation. Indeed, diversity of regulations is not just a limitation: it is actually a stronghold of Europe, being a repository one can draw upon to devise effective as well as innovative solutions. Let me only refer to the Spanish experience, where consent to the performance of researches based on biological samples is not to be obtained by the physician treating the patient, as it is up to another health care professional working as part of a biobank. This is clearly a solution that is aimed at affording greater freedom to give one's consent.

3.7. A final issue to be considered in connection with revising the Recommendation has to do, in my view, with determining which entities should be allowed to access data and samples under what conditions. This issue does not usually come up in other types of biomedical research, whereas it is likely to be inherently a feature of biobanks-based research because biobanks entail the substantial pooling of data and information over an extended time span.

The latter features are fundamental with a view to carrying out researches; however, respect for the purpose limitation principle – which is a pillar of data protection laws – makes it necessary to prevent personal data from being processed in a manner that is incompatible with the initial purposes. In this connection, clear-cut guidance would be necessary apart from and beyond statements of principle that may leave room for interpretive ambiguity. This means, for instance, that third parties such as employers or insurance companies should not be allowed to access data and samples; however, it also means that data and samples may not be used for law enforcement purposes. Such issues were highlighted by the German report of the Nationaler Ethikrat chaired by Spiros Simitis ([76]) and proven to be far from theoretical in nature. Indeed, they surfaced in the course of the ongoing discussion in Sweden following the request made by the police during the investigations into the murder of Foreign Minister Anna Lindh – to get access to a neonatal database in order to compare some traces with the blood samples of a suspect – as well as in the Norwegian legislation – where § 27 of the Medical and Health Research Act (2008-06-20 no. 44) provides somewhat ambiguously that: "Human biological material from research biobanks may not be surrendered for insurance purposes, to employers, to the prosecuting authorities or to a court of law even if the person the material originates from consents to this" but "the King may by regulations decide that human biological material may be surrendered to the prosecuting authorities or to a court of law *in very exceptional cases justified by extraordinarily compelling private or public interests*."

As for family members, one should point out that the boundaries of a "family" are rather blurred if genetic data are involved; still, if accessing the participant's information proves indispensable with a view to reproductive choices and/or to make treatment-related decisions, such access should be allowed. This is the stance taken in the past by the Italian data protection authority under similar circumstances. Significantly, Section 18(7) of the Portuguese Act on Personal Genetic Information and Information Regarding Health (Act no. 12/2005 of 26 January) provides that some family members may access stored samples relating to their relative providing this is aimed exclusively at getting information on "their genetic status" rather than on that of the individual the sample relates to ([77]).

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[76] Nationaler Ethikrat, *Biobanken für die Forschung,* Stellungnahme, 2004, p. 109, at http://www.ethikrat.org/dateien/pdf/NER_Stellungnahme_Biobanken.pdf: "sollten die Proben und Informationen, die im Rahmen eines medizinischen Forschungsprojektes gesammelt wurden, nicht der Polizei, der Justiz, dem Arbeitgeber oder den Versicherungsgesellschaften zur Verfügung gestellt werden".

[77] Art. 18 (7) — "Todos os parentes em linha directa e do segundo grau da linha colateral podem ter acesso a uma amostra armazenada, desde que necessário para conhecer melhor o seu próprio estatuto genético, mas não para conhecer o estatuto da pessoa a quem a amostra pertence ou de outros familiares".

4. Conclusions

To conclude, one should never forget that the pooling of personal information – at times including highly sensitive data - is bound to increase to an unprecedented extent in future, whether this information is hosted in biological samples or channeled via information systems.

It is fundamental for this to occur within the framework of a set of rules to be discussed by society at large and shared democratically. These rules should be legally binding and subject to regular review; being grounded in the protection of fundamental rights, they should lay the foundations for a modern governance approach that could afford the best conditions to carry out biomedical research and enable "a human use of human beings" – to quote Norbert Wiener ([78]).

The issues we are now tackling cannot be addressed in a merely domestic dimension; difficult though this may be, a multi-sectoral approach is needed.

Mindful of the European values and legal traditions, we should look with interest at the many initiatives undertaken in other parts of the world. Scientific co-operation will not be limited to continents: I am thinking, for instance, of the ongoing discussions within the U.S. Presidential Commission for the Study of Bioethical Issues.

Once again, the challenge to be taken up by scientists, policymakers and lawmakers is first and foremost an intellectual one as well as a daunting one. All of us, whatever our jurisdictions, are being asked the question Stefano Rodotà referred to on many occasions – namely, whether "all that is technically feasible is also ethically permitted, politically and socially acceptable, and legally admissible" ([79]).

This is why, once again, we have great expectations of the wisdom harboured by the Council of Europe as the guardian of the values that are enshrined in the European Human Rights Convention.

This is why I was deeply honoured as well as pleased to be here, today, with you and give my modest contribution to a pressing as well as important issue that is ultimately social rather than merely scientific in nature.

## Biographical notes

Roberto Lattanzi, Ph.D., is the Head of the "Unit on Public and Private Work" at the Italian Data Protection Authority (*Garante per la protezione dei dati personali*). Admitted to the Bar of Piacenza, he has been Assistant Professor of Private Law at the Catholic University of Piacenza and served as seconded national expert at the European Data Protection Supervisor. He has authored scientific articles, especially in the data protection field, and was appointed as «*Marie Curie Fellow*» under the European Commission Training and Mobility of Researchers Programme, doing comparative studies at the *Albert-Ludwigs-Universität* Freiburg, *Institut für ausländisches und internationales Privatrecht* (directed by Prof. dr. R. Frank) on «*Package Tours and Contract Law*» and regarding «*Information Society and Private Law*». He participated in PRIVIREAL ("*Privacy in Research Ethics and Law*") and PRIVILEGED Projects ("*Determining the Ethical and Legal Interests in Privacy and Data Protection for Research Involving the Use of Genetic Databases and Bio-banks*"), funded by the European Commission, and was awarded the «Lauro Chiazzese» national prize by the University of Palermo for leading studies in "Computer Law" (with a thesis entitled «Privacy and Databanks»).

[78] N. Wiener, *The Human Use of Human Beings: Cybernetics and Society*, 1950.
[79] Speech given by Stefano Rodotà, President of the Italian data protection authority, when submitting the 1997 Activity Report to the Italian Parliament. Rome, 30 April 1998.

***Session 3 - Privacy and data protection***


## Dr Pilar Nicolàs (Spain)

Research projects co-ordinator, Inter-University Chair in Law and the Human Genome, University of Deusto, University of the Basque Country[80]



## Abstract

***Limits of anonymisation***

Taking into account that the genome is unique for each human being, potentially the subject from whom a sample comes could be identified by comparing a sample whose origin is unknown with a sample with a known origin. Therefore, it can be said that it is not possible to anonymise a human sample.
If it is stated that a sample or genetic data are anonymous only if the possibility of identifying the subject source does not exist at all, we must conclude that anonymous sample or genetic data do not exist.

The consequence of this position is that the principles of protection of sensitive personal data must be applied to any treatment of any genetic data or human sample. This would make the flow of the data and/or samples become extremely complex and would hinder a fluid circulation of information and material in the context of scientific research.

To reconcile the legitimate rights and interests that arise in this situation, two mechanisms can be described: limiting the concept of personal data or making the rules on personal data protection more flexible. In the first case, efforts have been made to clarify the meaning of the "possibility of identification". In the second, the concept of express and specific consent as a requirement to use or transfer the sample or data could be softened taking into account the protection of other interests and the implementation of additional safeguards (proposal for a Regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data).

Recommendation Rec(2006)4 distinguishes two categories of personal samples but makes no distinction in the regimen of these two categories. It would be very positive to examine in greater depth the meaning of this distinction and its implications.


## Full text

***Limits of anonymisation***

1. Limits of anonymisation of human samples / data. 2. Limits of the legal concept of personal data / anonymous data. 3. Limiting the requirements for the management of the data. 4. Anonymisation in Rec (2006). 5. Anonymisation “limits identification” and excludes the exercise of rights and the implementation of security measures. Conclusions.

In the following pages I will **bring up some points for discussion** regarding the revision of the Recommendation Rec(2006)4 on research on biological materials of human origin in relation with **anonymisation.** All the issues related to data anonymisation are applicable to the management of human samples with research purposes as the sources of all genetic information of a person. Anonymisation and de-identification have been considered as useful tools to manage data in scientific research[81], but the meaning of the terms and the feasibility of their implementation have created confusion in the


[80] This research was supported by the Department of Education, Universities and Research of the Basque Country Government (Promotion of Research Groups of the Basque Universities. Reference IT-360-07).
The author thanks Sofía Zubiria for the English revision.


[81] A. Cavoukian, K. El Emam (2011) Dispelling the Myths Surrounding De-identification: Anonymization Remains a Strong Tool for Protecting Privacy. Information & Privacy Commissioner. Ontario. Canada. 2011. p. 1.

field[82]. Since the adoption of Recommendation Rec (2006)4 there are controversial points still remaining and new technical and legal scenarios have arisen.

**1. Limits of anonymisation of human samples /data**

The starting point of the discussion about the limits of anonymisation could be seen from a biological perspective: taking into account that the genome is unique for each human being, the subject from whom a sample or a genetic sequence comes could be identified potentially by comparing the information whose origin is unknown with a sample or a sequence with a known origin. Therefore, it could be said that it is not possible to anonymise a human sample.

**If it is stated that a sample or genetic data are anonymous only if the possibility of identifying the subject source does not exist at all, we must conclude that anonymous sample or genetic data do not exist[83]** (except for genetic sequences shared by the human species or a large population group).

The consequence of this statement would be that the principles of protection of personal data must be applied to the processing of any genetic data or human sample. Genetic data is sensitive information and one of the conditions of the applicable regime is the requirement of an express and specific consent for obtaining the data as well as for each transfer of these data or sample[84].

The direct implementation of those rules would make the flow of the data and/or samples become extremely complex and would prevent the fluid circulation of information and material. This could represent an important burden for the internationalisation of scientific research and an unfair obstacle for the collaboration between institutions, that could be justified when there is a risk to the violation of the fundamental rights of subjects.

**2. Limits of the legal concept of personal data / anonymous data**

From another perspective, **in legal and ethical terms**, **the concept of personal data in Europe is not as broad as described above (so the object of the rights of the subject is limited as well)**.

As is known, the concept was limited in the Directive 95/46/EC in the terms below:

> Article 2 (a): "personal data shall mean any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity".
> Recital 26 "(...) to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person".

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[82] B. M. Knoppers, M. Saginur (2005) The Babel of genetic data terminology. Nature Biotechnology; 23: 925 - 927.

[83] This opinion is held by S Elger & L Caplan (2006) Consent and anonymization in research involving biobanks: Differing terms and norms. EMBO Rep; 7(7): 661–666. Instead, it has been critized, among others, by P$^3$G Consortium, G. Church, C. Heeney, N. Hawkins N, J. de Vries, et al. (2009) Public Access to Genome-Wide Data: Five Views on Balancing Research with Privacy and Protection. PLoS Genet; 5(10).

[84] Article 29 Data Protection Working Party, Opinion 15/2011 on the definition of consent, p.25: "*In contrast to the provisions of Article 7 of the Directive, consent in the case of sensitive personal data (…) must be explicit. Opt-out solutions will not meet the requirement of being explicit.*"*(…) "*A patient who is informed by a clinic that his medical file will be transferred to a researcher unless he objects (by calling a number), will not meet the requirement of explicit consent". "A 'general agreement' of the data subject - e.g. to the collection of his medical data for an EHR and to any future transfers of these medical data to health professionals involved in treatment - would not constitute consent in the terms of Article 2(h) of the Directive".

Texts of different nature and from different institutions follow this criteria.

> E.g. R (97) 5 on the Protection of Medical Data: "An individual shall not be regarded as 'identifiable', if identification requires an unreasonable amount of time and manpower. In cases where the individual is not identifiable, the data are referred to as anonymous".

The Proposal for a Regulation on the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (25/1/2012) gathers the same idea as well:

> 'data subject' means "an identified natural person or a natural person who can be identified, directly or indirectly, **by means reasonably likely to be used by the controller or by any other natural or legal person,** in particular by reference to an identification number, location data, online identifier or to one or more factors specific to the physical, physiological, **genetic**, mental, economic, cultural or social identity of that person" (Art. 4.1)

Therefore, the key question is: **What does constitute an unreasonable amount of time and manpower regarding identification?** The process of identification is only feasible if certain parameters exist that allow the linking between the information and the code. These parameters are called identifiers. The effort regarding identification means the effort to access these parameters.

> "Identification is normally achieved through particular pieces of information which we may call "identifiers" and which hold a particularly privileged and close relationship with the particular individual" (Opinion 4/2007 on the concept of personal data of the Article 29 Data Protection Working Party).

The Opinion 4/2007 goes through this issue and states that identifiers are certain parameters that allow the identification of a person in a concrete situation, so the concept of identificability is a relative one that **has to be evaluated in a specific context taking into account among others, some circumstances.**

> "The **cost** of conducting identification is one factor, but not the only one. The intended purpose, the **way the processing** is structured, the **advantage expected** by the controller, the **interests at stake** for the individuals, as well as the **risk of organisational dysfunctions** (e.g. breaches of confidentiality duties) and **technical failures** should all be taken into account".
>
> The Spanish Authority on Data Protection has studied the applicability of the principles of data protection to the collection of samples with the purpose to search for persons. According to this Institution, even if the subject of the samples or data is not identified, because they are kept to identify persons, the principles of protection of personal data must be applied. Thus, **the purpose of the processing is of extreme importance to evaluate this issue**.
>
> http://www.agpd.es/portalwebAGPD/canaldocumentacion/informes_juridicos/datos_esp_protegidos/common/pdfs/2000-0000_Tratamiento-de-datos-gen-ee-ticos-para-la-localizaci-oo-n-de-personas-desaparecidas-o-en-investigaci-oo-n-criminal.pdf

**This test should be dynamic** and should consider the state of the art technology at the time. The system should be able to adapt to these developments as they happen, and to incorporate the appropriate technical and organisational measures in due course:

> "this test is a dynamic one and should consider the state of the art in technology at the time of the processing and the possibilities for development during the period for which the data will be processed. Identification may not be possible today with all the means likely reasonably to be used today. If the data are intended to be stored for one month, identification may not be anticipated to be possible during the 'lifetime' of the information, and they should not be considered as personal data. However, it they are intended to be kept for 10 years, the controller should consider the possibility of identification that may occur also in the ninth year of their lifetime, and which may make them personal data at that moment. The system should be able to adapt to these developments as they happen, and to incorporate then the appropriate technical and organisational measures in due course".
>
> (http://ec.europa.eu/justice/policies/privacy/docs/wpdocs/2007/wp136_en.pdf)

In 2008 Homer et al. published a paper that could be relevant to this test in the framework of genetic data[85] (other papers have been published recently describing different possibilities of identification[86]). A review of the situation in 2009 can be found in P$^3$G Consortium, Church G, Heeney C, Hawkins N, de Vries J, et al. (2009):

> "The privacy concerns raised in the recent paper by Homer et al. have had a significant impact on international open-access genomic databases. Although in hindsight it is clear that basic statistical theory would predict this to be the case, the reality is that it had previously gone completely unrecognised".
>
> "Reactions to this decision span the full breadth of opinion, from "too little, too late—the public trust has been breached" to "a heavy-handed bureaucratic response to a practically minimal risk that will unnecessarily inhibit scientific research." Scientific concerns have also been raised over the conditions under which individual identity can truly be accurately determined from GWAS data".
>
> "The implications of the Homer paper were discussed by the international Public Population Project in Genomics (P$^3$G) (http://www.p3g.org). The consensus was that any scientist seeking to work with genomic data be required to adhere to an internationally agreed code of conduct and to provide proof of institutional status as a bona fide researcher".

**Although the discussion about the consideration of a genetic sequence as an identifier by itself is not closed, it has shown that the new state of the art technology allows for the possibility of this analysis, or at least, raises the need to be aware of the increasing risks of identification. The implementation of measures that avoid or minimise the risk of identification are absolutely relevant for the legal requirements in the processing of the data or samples.**

In the evaluation of the degree of identificability of the data, the increasing number of genetic databases and GWAS[87] are important factors to take into account as well as the kind of genetic data included in a database (e.g. the population frequency of genetic sequences). The higher amount of information and more individualised, the bigger risk of identification of a subject.

**The policy and governance of the data processing are a fundamental factor in evaluating the possibility of identifying a person through genetic data, as such policies can imply an unreasonable effort for the identification in the processing of the samples and data.**

As a matter of fact, the potential risk of identifying a person while processing a huge amount of genetic information (even with no other identifiers) has led to the introduction of new policies in this framework in order to avoid this possibility.

> The National Institutes of Health (NIH) have implemented new data sharing policy in their genome-wide association studies (GWAS): "Access to the genotype and phenotype datasets submitted and stored in the NIH GWAS data repository (…) will be provided for research purposes through an NIH Data Access Committee (DAC)". "Investigators and institutions seeking data from the NIH GWAS data repository will be expected to meet data security measures (…) and

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**85** N. Homer, S. Szelinger, M. Redman, D. Duggan, W. Tembe, et al. (2008) Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex Mixtures Using High-Density SNP Genotyping Microarrays. PLoS Genet; 4(8).

86 E. Schadt, W. Sangsoon, H. Ke (2012) Bayesian method to predict individual SNP genotypes from gene expression data. Nature Genetics; 44(5): 603-8.
H. Kyung Im, E. R. Gamazon, D. L. Nicolae, N. J. Cox (2012) On Sharing Quantitative Trait GWAS Results in an Era of Multiple-omics Data and the Limits of Genomic Privacy. The American Journal of Human Genetics; 90 (4): 591-598.

87 A GWAS (Genome Wide Association Study) is defined "as any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition. Whole genome information, when combined with clinical and other phenotype data, offers the potential for increased understanding of basic biological processes affecting human health, improvement in the prediction of disease and patient care, and ultimately the realization of the promise of personalized medicine. In addition, rapid advances in understanding the patterns of human genetic variation and maturing high-throughput, cost-effective methods for genotyping are providing powerful research tools for identifying genetic variants that contribute to health and disease". (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html#protection).

will be asked to submit a data access request, including a Data Use Certification that is co-signed by the investigator and the designated Institutional Official(s)"[88].

**3. Limiting the requirements for the management of the data**

With the aim of establishing an adequate protection of the subject rights taking into account the real dimension of the infringement risks, two mechanisms can be described: **limiting the concept of personal data or making the rules on personal data protection more flexible**. In the first case, efforts have been made to clarify the meaning of the "possibility of identification", and who can identify (the user of the data or other person) is crucial[89]. In the second, the concept of express and specific consent as a requirement to use or transfer the sample or data could be softened taking into account the protection of other interests and the implementation of additional safeguards. The conceptual approach of these two options is not the same: the first one refers to confidentiality; the second one refers to the subject control of the information and material in a broader sense (see epigraph 5). **In Europe, the trend is the second one: to consider a broad concept of personal data, but to allow flexible rules for the applicable regime depending on the context.**

This trend is contained in Articles 4.1, 9.2 (i), and 83 of the **Proposal for a Regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data** (25/1/2012). These articles take into account the reasonability of the possibility of linking information and subject when considering the data as personal. However, **if a reasonable possibility exists for any given person, even if this person is not the user of the data, this information is considered personal. At the end, in certain circumstances, the interest of scientific research justifies the application of specific rules[90].**

"Art. 9. Processing of special categories of personal data

[88] Data access requests should include a brief description of the proposed research use of the requested GWAS dataset(s). Within a Data Use Certification investigators will agree, among other things, to: Use the data only for the approved research; Protect data confidentiality; Follow appropriate data security protections; Follow all applicable laws, regulations and local institutional policies and procedures for handling GWAS data; Not attempt to identify individual participants from whom data within a dataset were obtained; Not sell any of the data elements from datasets obtained from the NIH GWAS data repository; Not share with individuals other than those listed in the request any of the data elements from datasets obtained from the NIH GWAS data repository; Agree to the listing of a summary of approved research uses within the NIH GWAS data repository along with his or her name and organizational affiliation; Agree to report, in real time, violations of the GWAS policy to the appropriate DAC; Acknowledge the GWAS policy with regard to publication and intellectual property; and Provide annual progress reports on research using the GWAS dataset". "Data Access Committees or their designees will review requests for access to determine whether the proposed use of the dataset is scientifically and ethically appropriate and does not conflict with constraints or informed consent limitations identified by the institutions that submitted the dataset to the NIH GWAS data repository. In the event that requests raise concerns related to privacy and confidentiality, risks to populations or groups, or other concerns, the DAC will consult with other experts as appropriate". (http://grants.nih.gov/grants/guide/notice-files/NOT-HG-10-006.html).

[89] The OHRP (US Office for Human Research Protections) Guidance on Research Involving Coded Private Information or Biological Specimens considers "private information or specimens to be individually identifiable as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems". Mark A. Rothstein critizes this strategy: M. Rothstein (2010). Is Deidentification Sufficient to Protect Health Privacy in Research?. Am J Bioeth; 10(9): 3-11:4.

[90] The possibility of applying these exceptions to the sensitive data are now expressly recognized. The need to introduce changes in the Directive concerning anonymisation and the regime of de-coded data was underlined by C. Romeo Casabona (2004) Anonymization and pseudonymization: the legal framework at a European level, in The Data Protection Directive and medical research across Europe (D.Beyleveld D. Townend, S. Rouillé-Mirza and J. Wright, Eds.). Ashgate. pp. 40 and 49.

1. The processing of personal data, revealing race or ethnic origin, political opinions, religion or beliefs, trade-union membership, and the processing of **genetic data** or data concerning health or sex life or criminal convictions or related security measures shall be prohibited.
2. Paragraph 1 shall not apply where:
(a) the data subject has given consent to the processing of those personal data (…)
(…)
(i) **processing is necessary for historical, statistical or scientific research purposes subject to the conditions and safeguards referred to in Article 83**
(…)"
"Article 83. Processing for historical, statistical and **scientific research purposes**
1. Within the limits of this Regulation, personal data may be processed for historical, statistical or scientific research purposes only if:
(a) these purposes **cannot be otherwise fulfilled** by processing data which does not permit or not any longer permit the identification of the data subject;
(b) **data enabling the attribution of information to an identified or identifiable data subject is kept separately from the other information as long as these purposes can be fulfilled in this manner**".

**4. Anonymisation in Rec (2006)**

Recommendation Rec (2006)4 **distinguishes two categories of personal samples** (or identifiable biological material):

"i. *Identifiable biological materials* are those biological materials which, alone or in combination with associated data, allow the identification of the persons concerned either directly or through the use of a code.
In the latter case, the user of the biological materials may either:
*a.* have access to the code: the materials are hereafter referred to as 'coded materials'; or
*b.* not have access to the code, which is under the control of a third party: the material are hereafter referred to as 'linked anonymised materials'".

**Although the Recommendation recognises different categories of personal samples, it makes no distinction in their regimen**[91]. The following articles refer to the management of samples only considering if they are non identifiable or just identifiable:

"Article 8 – Justification of identifiability
1. Biological materials and associated data should be anonymised as far as appropriate to the research activities concerned.
2. Any use of biological materials and associated data in an identified, coded, or linked anonymised form should be justified by the researcher".

"Article 15 – Right to change the scope of, or to withdraw, consent or authorisation
1. When a person has provided consent to storage of identifiable biological materials for research purposes, the person should retain the right to withdraw or alter the scope of that consent. (...)
When identifiable biological materials are stored for research purposes only, the person who has withdrawn consent should have the right to have, in the manner foreseen by national law, the materials either destroyed or rendered unlinked anonymised".

[91] This is the same perspective as the one in the UNESCO International Declaration on Human Genetic Data, 16 October 2003. This document distinguishes three categories, but makes no differences in the regime of the two first.
Article 2 (…) "(ix) Data linked to an identifiable person: Data that contain information, such as name, birth date and address, by which the person from whom the data were derived can be identified;
(x) Data unlinked to an identifiable person: Data that are not linked to an identifiable person, through the replacement of, or separation from, all identifying information about that person by use of a code;
(xi) Data irretrievably unlinked to an identifiable person: Data that cannot be linked to an identifiable person, through destruction of the link to any identifying information about the person who provided the sample".

> "Article 23 – Unlinked anonymised biological materials
> 1. Unlinked anonymised biological materials may be used in research provided that such use does not violate any restrictions placed by the person concerned prior to the anonymisation of the materials.
> 2. Anonymisation should be verified by an appropriate review procedure".

The Guide for Research Ethics Committee Members (Strasbourg, 7th February 2011 CDBI/INF(2011)2) of the Steering Committee on Bioethics does not make any express changes, although it includes also the reference to "subcategories":

> Identifiable data are "Data that allow the identification of the persons concerned either directly or through the use of a code. Identifiable data are subcategorised as coded data and linked anonymised data. Coded data are "Data that allow identification of the persons concerned through the use of a code to which the user of the data has access". Linked-anonymised data are "data that allow the identification of the persons concerned through the use of a code which is inaccessible to the user of the data and controlled by a third party".

It would be very positive to **examine in greater depth the meaning of this distinction and its implications for the evaluation by the Ethics committees, taking also into account the perspectives in the new European regulation on personal data** (article 83 cited above).

**5. Anonymisation "limits identification" and excludes the exercise of rights and the implementation of security measures**

When data or samples are considered anonymous, the subject no longer has rights over the information or the material. The reason is that the object of the right (personal data) does not exist anymore, and that, in practice, the absence of traceability makes the exercise of rights impossible. When traceability is still possible but data are considered anonymous, a paradoxical situation emerges and several conflicts could arise. A broad concept of personal data that finds its limits in the possibility of traceability with the development of a flexible regime of processing seems to be a good option.

Considering a broad concept of personal genetic data allows a broad consent for future transfers if some measures are implemented. However, taking into account that the data continue to be included in the category of personal data, these mechanisms have to be consistent enough, and other rights have to be respected. This is to say that the control of the subject over his/her personal information has to be guaranteed somehow, for example, through an authorised institution that would be considered as a "bridge" between the subject and the researchers. Authorised biobanks could have an important role in this sense (table 2).

The other option (to consider the need to implement mechanisms for the exclusion of the genetic data from the category of personal one) should consider two main factors: the possible risk of identification in the future, and the subsequent impossibility of the exercise of any right concerning this information (table 1). Although, the existence of anonymous genetic data or human samples should not be discarded definitely.

**Conclusions**

● Defining the subject of a genetic sequence or of a biological sample as identifiable or not identifiable is difficult and controversial in practice and should be analysed case by case. The existence of anonymous genetic data or human samples should not be discarded definitely, but the categorisation should be subject to revisions and, if adequate, to modifications.
● The categorisation determines whether the existent legal regime should be applied or not but specific provisions could be implemented depending on the context of the processing.
● This specific provisions in the legal regime of personal data should include rules that consider, among other factors, the possibility that the user of the data can access the code and the interest of the processing. In certain circumstances a broad consent for the transfer of data, even abroad the EU could be allowed.
● The lack of harmonisation in this field difficults international research. New perspectives in the EU seem to appear. Efforts should be done in different geographical and binding regulatory levels in this direction.

● Guarantees for the rights of the subjects should be implemented taking into account the characteristics of the genetic data.
● There are three pillars that could hold a system that would allow a fair and agile processing of genetic data and biological samples with research purposes: a general and harmonised regulatory framework; the requirement that only authorised institutions with adequate policies should be involved in the management of data and samples; and the control of the processing of samples and data by ethics committees. Authorised Biobanks could play an important role within this system.
● The revision of the Recommendation is an opportunity to take steps toward the development of this system. It would describe the status of human samples as well as the genetic data obtained distinguishing different scenarios and the consequences of this distinction, and it would establish the general policies for their fair processing. Efforts should be made for the harmonisation with countries abroad the Council of Europe through different forums and mechanisms.

Table 1

| | Identified /coded | Linked anonymised | Anonymised |
|---|---|---|---|
| Identification of the subject | | | |
| Information and consent for the obtaining (specific or broad) | | | |
| Consent to each transfer | | | |
| Limits on the use | | | |
| Return of results | | | |
| Right to withdraw | | | |
| Security measures | | | |

**Implementable / Difficult / Impossible**

Table 2

| | Identified /coded | Linked anonymised (under an standarised control) | Anonymised |
|---|---|---|---|
| Identification of the subject | | | |
| Information and consent for the obtaining (specific or broad ) | | | |
| Consent to each transfer | | Control of each transfer | |
| Limits on the use | | Control of the use | |
| Return of results | | Mechanisms stablished | |
| Right to withdraw | | Mechanisms stablished | |
| Security measures | | | |

**Implementable / Difficult / Impossible**

## Biographical notes

Degree in Law (University Complutense of Madrid), Ph.D. (University of Deusto, Bilbao). Doctoral thesis: “La protección jurídica de los datos genéticos personales” (Legal protection of personal genetic data).

She is the research projects co-ordinator for the Inter-University Chair Provincial Government of Biscay in Law and the Human Genome, University of Deusto, University of the Basque Country. She teaches the course on “Human Genetics, Bioethics and Law” in the Faculty of Law of the University of the Basque Country, and participates in several Masters in Medicine and Law. She teaches also Criminal Law.

She has participated in several research projects at the local, national and international levels on matters such as the legal protection of genetic information, genetic counselling, the implementation of the Directive on the protection of data, the legal implications of the use of human biological samples and biobanks in scientific research and the fundamental rights and new settings of biomedicine. She is now a member of the Ethics and Policy Committee and of the International Data Access Committee in the International Cancer Genome Consortium; she collaborates as Spanish expert in the hSERN and participates in ENERCA project. She has also participated as external reviewer in the 7th Framework Programme of the European Commission.

She has participated in numerous conferences and workshops in national and international fora as speaker and she has published articles and chapters in monographs on diverse matters related to law and the biomedical sciences. She has collaborated with the Spanish Ministry of Science and Innovation in the preparation of the Spanish Law 14/2007 on Biomedical Research (in particular in the Title devoted to genetic analysis, human samples and biobanks) and the Royal Decree on biobanks approved on 18 November 2011.

***Session 3 - Privacy and data protection***


## Prof. Kurt Zatloukal (Austria)

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## Abstract


***Transborder flows of samples and accompanying data***

Human biological samples, such as blood, tissues or DNA including associated medical data are key resources in unraveling genetic and environmental factors causing diseases and influencing their outcome. Furthermore these resources are required for development of new solutions to improve prevention, diagnosis and treatment of diseases. The ageing population is resulting in an increase in certain diseases, increased health care expenditure for people in old age that place pressure on the sustainability and viability of healthcare systems. These challenges can only be addressed efficiently in an internationally coordinated and on scientific evidence-based approaches. Therefore international collaboration in medical research that relies on efficient transborder exchange of biological samples and associated data will become more important than ever.

The OECD Global Biological Resource Centres Network (GBRCN) should provide an international framework to sustainably provide access to biological samples and biomolecular resources in a quality controlled and secure manner. In Europe, the pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) implements the OECD best practice guidelines for biological resource centres and will become the European part of a human-domain GBRCN. The planning phase of BBMRI has been completed in 2011 and involved more that 270 institutions from 33 countries (for details see www.bbmri.eu). BBMRI will now be implemented by EU Member States under the international ERIC legal entity and should start its operation in 2013. BBMRI-ERIC will comprise existing and newly established collections of all types of human biological samples including associated data, biomolecular resources (e.g., antibodies, gene clone collections, cell lines and model organisms), biobanking and analytical technologies, data management solutions as well as ethical and legal services. BBMRI-ERIC is designed to improve efficacy and reduced costs of high quality research collaborations in all fields of medical research. In order to facilitate international collaboration BBMRI developed the concept of expert centres that are linked to biobanks and perform the sample analysis under internationally standardized conditions. BBMRI expert centres commit to implementation of common quality management schemes, share reference materials, and participate in proficiency testing. This facilitates data integration from multinational studies thereby allowing sample analysis in the country of origin and avoiding the need of transnational sample shipment. Furthermore, expert centres can be established as public-private-partnerships in the field of pre-competitive research to improve innovation.


## Full text

***Transborder flows of samples and accompanying data***

There is a major need for transnational collaboration in biomedical research. Firstly, the only way to develop a scientific basis to address the grand healthcare challenges related to aging societies and to cope with increasing healthcare costs is a multinational collaborative effort. Furthermore, transnational collaboration is required to integrate resources. This is particularly evident in the case of rare diseases where individual countries do not have an adequate number of cases to achieve sufficient statistical power. Furthermore, in the context of precision medicine, in which large disease entities split up into smaller disease subgroups, transnational collaboration is essential. Finally, transnational collaboration should avoid unnecessary duplication of effort, which currently results in significant waste of resources, but also in a fragmentation of the scientific community.

Key elements with respect to transnational collaboration in the field of biomedical research are biological resources comprising living organisms, cells, genes and related information, which was considered by the OECD as the essential raw material for the advancement of biotechnology, human health and research and development in the life sciences. Consequently, in 2001 the OECD already proposed a

global biological resource center network (GBRCN) with the aim to provide a framework for transnational exchange of biological samples and data in a secure und quality controlled manner. In March 2007 the OECD also endorsed best practice guidelines for biological resource centers in order to facilitate implementation. However, to establish such a global framework several hurdles and roadblocks have to be overcome, such as the lack of common quality criteria for biological samples and data. Furthermore, diseases are described typically in plain text and local languages which make multinational research collaboration difficult. Another challenge is that criteria and ontologies that are used to describe certain diseases are developing in the course of time and these developments need to be carefully tracked and documented. With regard to disease ontologies also another challenge emerges: Current disease ontologies are not appropriate for precision medicine since they are not suitable to characterise the feature of a disease of an individual patient in sufficient detail. This has recently been addressed by the United States Academy of Sciences that proposed a paradigm shift in disease taxonomy foreseeing a change from a mainly organ-based to a mechanism-based disease definition. Another challenge is that biological samples and associated information on diseases are collected in a context of healthcare systems and have to be compliant with local or national ethical and legal frameworks which are very heterogeneous within the European research area. Finally there are societal issues that may prevent international exchange of samples and data. For instance, clear and transparent rules are required concerning the sharing of finite resources and collaborations should lead to balanced win-win scenarios.

In Europe the ESFRI research infrastructure for Biobanking and Biomolecular Resources (BBMRI) was designed to create a new European framework that should accurately facilitate transnational exchange of samples and data for the advancement of biomedical research. ESFRI research infrastructures are characterised by the following criteria: i) scientific excellence, ii) pan-European scope that foresees only one type of a specific infrastructure for a certain scientific field for Europe, iii) providing access to resources and services, and iv) long term sustainability (20 to 30 years or even longer). The planning of BBMRI was funded within the framework programme 7 from the years 2008 to 2011 and involved more than 270 institutions from 33 countries. BBMRI should now be implemented under the ERIC legal framework in early 2013 and member states have already committed approximately 160 million Euros for the implementation of BBMRI at the national levels. BBMRI-ERIC will become a distributed infrastructure owned by member states with one common headquarter based in Austria. The members of the infrastructures are the member states and - on the member state level - universities, hospitals and resource centres are going to be associated to BBMRI-ERIC. In this context it is important to emphasize that BBMRI-ERIC is not the owner of samples and data but just provides a framework to facilitate top level research collaboration. To exert this role BBMRI-ERIC provides a common access portal for academic and industry users with enough flexibility to integrate existing and developing resources of member states.

A big challenge for enabling this integration is a current lack of quality criteria for the integration of biological resources and data collected and stored in different member states. The importance of evidence-based quality criteria for biological samples used in biomedical research becomes particularly important in the context of the rapidly developing analytical technologies. It is now increasingly recognised that even the most advanced analytical technologies cannot generate better results than the quality of the biological material analysed. Consequently, the performance of diagnostic assays that rely on the analysis of bio-molecules cannot only be defined on the basis of the analytical technology used but also has to comprise all the pre-analytical parameters that may impact on a biological sample quality. To address this issue a European funded large integrated project (SPIDIA) frames in huge collaborative effort the generation of evidence-based European standards and norms for pre-analytics in molecular diagnostics. One of the major conclusions drawn from this European effort was that certain bio-molecules are unstable, and that there are major patient to patient variations affecting sample quality. Furthermore, combined effects of ischemia and underlying diseases were found, which makes it very difficult to define a general quality standard for biological samples. Consequently, a careful evaluation is required of the quality criteria for each bio-molecule to be analysed. Based on the findings generated by SPIDIA a three-layer concept for standardisation and improved interoperability for transnational research is proposed by BBMRI. Laboratories and biological research centres have to implement common standards and guidelines. The internationally best established common basis among these lines is the OECD best practice guideline for biological resource centres. The advantage of referring to these OECD-guidelines is that they have already been accepted by OECD member states and therefore provide an internationally acknowledged common basis. The next level is formed by standard operating procedures (SOPs). In this case BBMRI recommends referring to standards

published by the International Agency for Research on Cancer (a WHO unit) which already published consensus protocols of several guidelines and protocols from different organisations. The third layer is the evaluation for the fit-for-purpose requiring a careful documentation of all pre-analytical parameters that may have impact on sample quality, and the assessment of the stability of the bio-molecule of interest.

A specific challenge in structuring transnational access to biological samples and data is the collaboration of academia and industry. In the context of the planning of BBMRI a new model for academia and industry collaborations was developed in order to improve access for industry. The challenge to be addressed is the fact that on the one hand human biological samples and medical data are considered as a common good that is established in a public non-for-profit environment. On the other hand, industry requires access to these resources to manufacture diagnostics and drugs that are needed to secure better healthcare, and industry has to make profit. One problem that emerges from these different scenarios is the following: Biological samples and medical data that were donated and further processed by using public funding cannot be provided for free to the industry. On the other hand, it is illegal to make any profit from providing access to medical data and samples, and the border between cost recovery and profit making is hardly defined. Even if there was a clear cost recovery setting the public acceptance is questionable and the difficulties in designing a transparent and fair financial stream to the public may be a cause for concerns and controversies that finally result in roadblocks for industry to access public resources. In order to avoid such scenarios a new model was developed in collaboration with academia and industry, and by involving patient organisations. This model foresees to avoid a direct shipment of samples and data to the industry as well as financial reimbursement for such a shipment by setting up joint public private partnerships that are positioned in the pre-competitive, not-for-profit domain. In this new structure complementary expertise from academia and industry can be integrated to analyse biological samples by using latest knowhow and technologies. This results in high quality primary data that can then be commonly used by the public and private sectors. The results generated in such a high quality framework lead to a growing and common knowledge base on human diseases. However the building of this unprecedented knowledge base which provides a major competitive advantage for industry would also require that intellectual property rights are not applied to primary data but only in the context of a specific product development.

The concept of transforming biological samples into data and knowledge by using advanced and highly standardised analytical technologies would not only be a solution for academia and industry collaboration but also for international collaboration in a broader context. One of the challenges of international research collaboration in the field of biomedical research is that several countries have legal restrictions for export of biological samples. These restrictions are based on negative experience with research projects where samples were exported to a third country and all the knowledge and value was generated outside of the country where the resource was established. To avoid such a situation a global network of expert centres is proposed that perform the analysis of biological samples under internationally standardised conditions in the country. Such expert centres that are established within the environment of biobanks and biological resource centres would create a new framework for international research collaboration. This would avoid the transnational shipment of samples by transforming natural resources to knowledge and stimulate regional development and innovation in the country of origin of the resources.

BBMRI-ERIC is designed to eventually become the European part of the OECD GBRCN by implementing OECD best practice guidelines and by taking advantage of the expert centres' concept to minimise the requirement of global sample shipment. Furthermore, the model of expert centres has been discussed as a new opportunity to structure collaboration with the United States, China, the Arabian Emirates and the African Union.

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## Biographical notes

Kurt Zatloukal, M.D. is professor of Pathology at the Medical University of Graz, Austria. He coordinated the preparatory phase of the European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) within the 7th EU framework programme. In this context it was crucial to establish Europe-wide harmonised processes and quality criteria that facilitate transnational research collaboration and are compliant with the requirements of latest -omics technologies as well as with ethical and legal regulations. Furthermore, he leads in the FP7-funded large integrated project SPIDIA the development of new European standards and norms for pre-analytical processing of tissue samples.

Kurt Zatloukal was member of the OECD task force on biological resource centres and the Roadmap Working Group of the European Strategy Forum on Research Infrastructures. Moreover, he contributed to the OECD best practice guidelines for biological resource centres, the regulations for genetic testing of the Austrian Gene Technology Law, and was member of the Bioethics Commission at the Austrian Federal Chancellery. He has published more than 150 scientific papers and was co-inventor of 15 patent applications.

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## Abstract


***Right to withdraw consent – right to be forgotten***

The right to change one's mind about the storage and future use of biological material, that may carry endless amounts of sensitive personal information as well as the potential for many different types of use, does of course clearly concern the right to protection of private life, under Article 8 of the ECHR. Recommendation Rec(2006)4 includes two articles specifically addressing this issue. Article 15.1 thus stipulates that there should be a right to withdraw or alter the scope of the consent to storage of identifiable biological materials, and – if they are stored for research purposes only – have the materials either destroyed or rendered unlinked anonymous, in accordance with domestic law. This means that national legislators are allowed a certain flexibility, bearing in mind that the rights of the person concerned may only be restricted to the extent this is necessary in a democratic society, in the interest of public safety, for the protection of public health or for the protection of the rights and freedoms of others (cf. Article 26 of the Oviedo Convention). Under Article 22.2, the person concerned may freely, at any time, withdraw consent for the use in a research project of his or her identifiable biological materials.

The balancing of interests related to biomedical research and future public health, against the right to protection of private life in a rapidly changing society, naturally gives rise to many questions. For instance, how adequate is the protection offered by "anonymisation" as an alternative to destruction, considering for example the increasing possibilities of re-identification by way of genetic analysis and/or the use of personal data available from other sources? To what extent would a stronger right of withdrawal and destruction constitute a threat to research? Should holders of biological materials even be required to offer services aimed at facilitating withdrawal of consent? Given the close link between human biological material and sensitive personal data, are the present rules on withdrawal consistent with "the right to be forgotten", for example, under Article 17 of the proposed EU General Data Protection Regulation? The re-examination of the appropriate scope of the right to withdraw consent to storage and use of biological materials will involve all these issues, and more.


## Full text

***Right to withdraw consent – right to be forgotten***

### 1 Consent and Withdrawal – Two Parts of a Packaget

The right to withdraw consent is in several ways closely linked to the well established requirement of a free and informed consent to the participation in research. Consent and withdrawal could even be considered as inseparable parts of the same package.[92]

If participation in research and related activities is to be truly voluntary, the persons participating should do so willingly, throughout the activity. This presupposes that the research subjects are also allowed to withdraw their consent and stop participating at any time. Any restrictions of this right will affect the voluntariness and constitute an infringement of the participants' autonomy.

Even in the ideal – but rather unrealistic – situation where full information concerning all relevant aspects of the specific research project has been provided and understood, some research subjects may still change their mind at a later stage, due to e.g. altered external circumstances or merely a change of heart. If the consent has been based only on more general information – a so-called broad consent,

[92] Holm, S. Withdrawing from Research: A Rethink in the Context of Research Biobanks, Health Care Anal (2011) 19:269–281, at 273.

which has become the standard model in research biobanking[93] – it is of course all the more likely that some participants later will want to withdraw from the project, based on new information or improved understanding. If an opt-out system is applied, consent is presumed and those who do not wish to participate will have to actively declare this. In this case, it would perhaps seem a bit misleading to talk about withdrawal of consent, since no consent has actually been given, but the focus is still on the subject's wish not to participate in an activity that may already be under way. Just like consent, any true right of withdrawal or opting-out is largely dependent on the research subject's access to adequate information. It must therefore be considered to what extent researchers and biobank principals should be required to provide information throughout the relevant activity, even by direct re-contacting or similar means. More recently, it has been argued that in certain contexts, consent should be viewed as an on-going process or dialogue, rather than a one-off event.[94] One example of such a model, based on the use of modern information technology, is the so-called dynamic consent advocated by the EnCoRe project.[95]

It seems clear that the right to withdraw must also have an impact on the willingness to participate in research. If there was no possibility to withdraw, potential research participants would arguably be more hesitant to give their consent, or would at least require more detailed information before doing so.[96] This could of course prove counter productive to the goal of facilitating important research.

Additionally, the right to withdraw consent may serve as an incentive for good research practices,[97] and would also in other ways seem important for the preservation of public trust in research, thereby securing long term preconditions rather than constituting a threat to research.

However, allowing or even facilitating withdrawal could also have negative effects for research. [98] If a sufficient number of participants withdraw from a project, the remaining materials may loose their value and resources will have been wasted if the planned research cannot be carried out, or the results no longer will be significant. Cost for administration of the withdrawals as such, not to mention any re-contacting of participants, may also be considered burdensome. Not only the researchers and biobank holder could suffer from these negative effects, but also remaining participants whose efforts become less valuable, and of course the general public who may loose the potential for better future health care. It is easy to agree with Holm, that "if some of the components of the right to withdraw can be modified to ameliorate the problems caused by withdrawal, without incurring important moral costs, there is good reason to make such modifications."[99]

Although the right to withdraw from research constitutes an important – even inseparable – part of the "consent package", the more precise implications of this right would seem to have attracted far less attention than the requirements for different types of consent, in literature as well as in guidelines and laws.

In research biobanking, consent as well as withdrawal must be considered with regard to two different situations, i.e. *storage* of samples and data for future research and the actual *use* in a research project. It should be clear that consent to the collection and storage of biological materials, for future use in more or less unspecified research projects, is not the same as consent to the participation in a specified research project. Likewise, withdrawal of consent to a particular research project need not necessarily imply complete withdrawal from the biobank where the samples are stored, for use in different future projects.

The issues of consent and withdrawal in research biobanking thus require a more refined discussion, than the one needed in the context of clinical research. The need for guidelines and minimum stan-

[93] Biobanks for Europe: A challenge for governance. Report of the Expert Group on Dealing with Ethical and Regulatory Challenges of International Biobank Research. European Commission 2012, p. 51.
[94] Kaye, J. et al. From patients to partners: participant-centric initiatives in biomedical research, Nature Reviews Genetics 13, 371-376 (May 2012).
[95] Ib. id.
[96] Holm (2011) p. 273.
[97] Ib id.
[98] See e.g. Holm (2011) p. 272 and Helgesson, G & Johnsson, L. The right to withdraw consent to research on biobank samples, Medicine, Health Care and Philosophy (2005) 8:315–321 at 317.
[99] Holm (2011) p. 277.

dards in this particular field was of course one reason for the development of the Council of Europe Recommendation (2006)4 on research on biological materials of human origin. The right to withdraw consent is made explicit in the Recommendation, with regard to storage as well as participation in individual research projects.[100] Although certain implications of the right to withdrawal are mentioned in the Recommendation, however, there still remains some issues to discuss and clarify.

Due to restrictions of time and space, this paper will not specifically address the specific aspects ensuring the right to withdraw when the original consent or authorization has been provided by a proxy. In situations where samples and data have been collected for example from a small child or a temporarily incapacitated adult, maybe even based on broad consent/authorisation from the proxy, the right to withdraw at a later stage becomes all the more important.[101] Article 15.3 of Rec (2006)4 states that where a person on whose behalf authorisation has been given attains the capacity to give consent, that person should have the right to withdraw as described in the Recommendation. No further guidelines explain what this might entail with regard to the duties of researchers or biobank principals, and the issue is not even mentioned in the Explanatory Memorandum.[102] This is definitely an area where further guidance is called for, for example regarding the appropriate time and means for providing the persons concerned with the information necessary to ensure their right of withdrawal.

## 2 Withdrawal of Consent as a Human Right

Is the right to withdraw consent a legally protected fundamental human right? The wish to change one's mind about the storage and use of human biological material carrying endless amounts of sensitive personal information as well as the potential for many different types of use, undoubtedly concerns the right to protection of private life, under Article 8.1 of the European Convention on Human Rights.[103] The protection required by this Article covers not only the informational privacy and bodily integrity of individuals, but also their right to self-determination.

However, the right to protection of private life is not absolute, but may be restricted by law, in accordance with Article 8.2, where this is necessary e.g. in the interest of public safety, for the prevention of crime, for the protection of public health or for the protection of the rights and freedoms of others. A balancing of the interests concerned must thus be performed by the national legislator.

In the context of more traditional clinical research and medical experiments, the right to withdraw consent has been described as absolute, unconditional, immediate, complete and inalienable.[104] This means that the right to withdraw can never be overridden by other interests or made dependent on certain criteria being met, nor must the withdrawal be delayed or limited to certain aspects of the participation, or even waived by the research participant himself or herself. The right to withdraw consent at any time during the research is laid down both in the legally non-binding Helsinki Declaration[105] and the Oviedo Convention.[106] The 2005 Additional Protocol to the Convention, concerning Biomedical Research, reaffirms in Article 14.1 that consent may be freely withdrawn at any phase of the research.[107] Under Article 14.2, the withdrawal of consent shall not lead to any form of discrimination against the person concerned. Article 3 of the Protocol also reaffirms the primacy of the human being,

[100] Articles 15.1 and 22.2, discussed in section 3 below.
[101] Holm, S. Informed Consent and the Bio-banking of Material from Children. Genomics, Society and Policy, Vol.1 No.1 (2005) p. 16-26, at 22. See also Hens, K. et.al. Developing a policy for paediatric biobanks: principles for good practice, European Journal of Human Genetics (2012), 1–6 at 3.
[102] Explanatory Memorandum to the Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin.
[103] European Convention for the Protection of Human Rights and Fundamental Freedoms (1950, CETS 005).
[104] Holm (2011) p. 270.
[105] World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 (last revised 2008), Principle 24.
[106] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (1997, CETS 164), Article 16.v.
[107] Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (2005, CETS 195)

previously prescribed in Article 2 of the Oviedo Convention, by stating that the interests and welfare of the human being participating in research shall prevail over the sole interest of society or science. An older document often referred to in research ethics is the Nuremberg Code of Ethics from 1947, where it says in Principle 9 that during the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

When it is argued that the right to withdraw consent to biobank storage and research should perhaps be more limited, this is normally based on the fact that research on data or biological materials involves considerably fewer potential harms to the bodily integrity, health and safety of the research subject, compared to clinical research and medical experiments on human beings.[108]

The risks related to infringements of autonomy and other aspects of privacy, however, would seem to be similar, if not higher. Whereas research subjects in clinical research are in one way or another *present* when the research takes place and at least to some extent can be expected to be aware of what is going on, this is not the case with donors of biological material.[109] Samples and data may have been collected based on a broad consent, and even materials collected for a specific project may later be used for other projects that the donors have not explicitly consented to. Accordingly, they would seem to run a higher risk of participating in research projects or procedures they are unaware of and thus do not have the opportunity to refuse.

If it was to be agreed that the overall risk of harm must be considered lower in biobank storage and research, would this then justify a more limited right of withdrawal; a right that might be negotiable, conditional, delayed, incomplete and waivable? In order to be lawful, such an infringement of the donor's right to protection of his or her private life must meet the requirements laid down in ECHR Article 8.2. This involves a balancing of the interests concerned, in accordance with the principle of proportionality. As stated above, the right to privacy may be restricted only where this is *necessary* for the protection of certain other important interests, such as public health or the rights and freedoms of others. One relevant question is thus if an unrestricted right of withdrawal would constitute any substantial threat to valuable research and thereby public health, or maybe to the rights of biobank holders and researchers. It should also be kept in mind that the restriction must constitute an adequate means to protect these interests, and that this result could not be achieved by means involving lesser infringements.

### 3 The Right to Withdraw Consent under CoE Rec (2006) 4

Recommendation Rec (2006)4 includes two articles specifically addressing the issue of withdrawal. Article 15.1 thus stipulates that there should be a right to withdraw or alter the scope of the consent to storage of identifiable biological materials, and – if they are stored for research purposes only – have the materials *either* destroyed *or* rendered unlinked anonymous, in accordance with domestic law. This means that national legislators are allowed a certain flexibility, bearing in mind that the rights of the person concerned may only be restricted to the extent this is necessary in a democratic society, in the interest of public safety, for the protection of public health or for the protection of the rights and freedoms of others (cf Article 26 of the Oviedo Convention).[110] Under Article 22.2, the person concerned may freely, at any time, withdraw consent to use in a research project, of his or her identifiable biological materials.

It is clear that the right to withdraw consent to *storage* under the Recommendation is not complete, since it is accepted that domestic law may stipulate restrictions on the donor's possibility to have the materials destroyed, see Article 15.1. This restriction is motivated by the fact that "in certain cases, the destruction of the biological materials could affect the value of the aggregate of stored materials, for

[108] See e.g. Eriksson, S. & Helgesson, G. Potential harms, anonymization, and the right to withdraw consent to biobank research, European Journal of Human Genetics (2005) 13, 1071–1076.
[109] Silvola, S. Biobank Regulation in Finland and the Nordic Countries. Nordic Health Law in a European
Context – Welfare State Perspectives on Patients' Rights and Biomedicine (eds. Rynning, E. & Hartlev, M.) Liber & Brill 2011, pp.277-291, at 281.
[110] Explanatory Memorandum para 52-53.

example in case of small collections, containing rare biological materials."[111] The donor may thus have to be content with having the materials rendered unlinked anonymous.

With regard to withdrawal from participation in actual *research* projects, Article 22.2 of the Recommendation does not explicitly mention any right to have the biological materials or data destroyed, but it is clear from the Explanatory Memorandum that the right to withdraw consent is understood to include such a right of destruction.[112] If the research has already generated findings, it is stated that these should be rendered unlinked anonymous, unless they have already been published or it is otherwise impossible to withdraw them from the research. A number of aspects should therefore be considered, such as the degree of identifiablility, the nature of the research, the need for feedback and the risks to group privacy.

For the outcome of the balancing of interests – bearing in mind the principle of proportionality – it is necessary to consider to what extent anonymisation could really be an adequate means to protect the interests of donors and research.

## 4 Anonymisation as an Alternative to Destruction

A key concern of people participating in biobank research would seem to be privacy issues and data protection, If complete and durable anonymisation were considered possible, this measure could serve to protect the part of privacy that concerns control of spreading and disclosure of information about the donor, but an increasingly relevant objection concerns the risk for re-identification of anonymised data or samples, by way of cross-referencing with available sets of identifiable personal data and/or genetic analysis.[113]

Disregarding this risk, anonymisation would still be insufficient to adequately protect donor autonomy if the donor objects to any form of further participation in the research.[114] Such objections could for example be based on moral concerns or just a general mistrust in the Neither will anonymisation protect group interests in not having the research carried out, for example due to a risk of stigmatization and discrimination.[115] It is furthermore important to remember that the donor loses the possibility to decide over the material once it has been anonymised, and no feedback will be possible. There may also be practical difficulties, for example reaching all secondary or tertiary etc. holders of data and/or samples, but this problem would seem to be the same whether the materials are to be anonymised or destroyed.

As regards the interests of the research society, some of these might of course be protected by the alternative anonymisation, rather than having the samples or data destroyed, Even so, many research projects require access to linked samples and data. The original research plan thus might not be feasible with anonymised materials. Just as the case of destruction, anonymisation might also affect the value of the remaining materials.

All in all, the alternative of anonymisation clearly has its limitations, both as a means of protecting the privacy rights of participants in research biobanking and as a way to protect resources for research. This in turn leads to the question if anonymisation really constitutes a proportionate and adequate means of protecting conflicting rights and interests in research biobanking.

## 5 Restrictions Suggested in the Scientific Debate

[111] Explanatory Memorandum para 52.
[112] Para 71.
[113] See for example Porter, C.C. De-Identified Data and Third Party Data Mining: The Risk of Re-Identification of Personal Information, 5 Shidler J.L. Com. & Tech. 3 (Sep. 23, 2008),
[114] See for example Eriksson & Helgesson (2005) pp 1074. See also Rynning, E. Legal Challenges and Strategies in the Regulation of Research Biobanking. In The Ethics of Reseach Biobanking (eds. Solbakk, Holm & Hoffmann) New York: Springer 2009, pp. 277-313, at 289-290; and Rynning, E. Public law aspects on the use of biobank samples – Privacy versus the interests of research. In Biobanks as Resources for Health (eds. Hansson, M & Levin, M.) Uppsala 2003, pp 91-128, at 109-110.
[115] Eriksson & Helgesson (2005) p. 1074.

What other restrictions have then been suggested, with regard to withdrawal of consent to biobank storage and research, and how are these restrictions justified?

a) One idea that has been put forward is to make the withdrawal conditional, by the *requirement of an acceptable explanation*. It has been argued that since the right to withdraw consent in the Nuremberg Code is subject to the condition that "continuation of the experiment seems to [the research subject] to be impossible", it would be reasonable to introduce a similar requirement for the withdrawal of consent to biobank research.[116] Eriksson and Helgesson thus "suggest that the current view on withdrawal from research,
supported by the Declaration of Helsinki and subsequent ethical guidelines, be abandoned in the context of biobank research and be replaced by an approach inspired by the Nuremberg Code", which "requires those wishing to withdraw their samples from research to present sufficient reason for doing so." The authors aim to underline "that we all share a responsibility for health research and that no one should take withdrawal from biobank research lightly", while their definition of sufficient reason include "all those involving genuine, deeply felt concerns that are not based on misconceptions." They also state, however, that the reasons presented by the person wishing to withdraw "should be judged primarily by the researchers or biobank holders" although a research ethics committee should be consulted if the reasons are believed to be insufficient.
ethics committee is recommended.

b) The proposal of Eriksson and Helgesson has been quite severely critisised by Holm, who declares that their "suggestion that withdrawal should only be allowed if the
participant can present 'sufficient reason' and that the researchers should be the
judges of whether the reasons given are sufficient seems either naive or dangerous
(or possibly both)."[117] This does not mean that Holm is negative to all forms of discussion regarding the reasonableness of the withdrawal. Quite the opposite, he believes that while it would be considered wrong in traditional clinical research also to *inform the participants about the wider implications of their withdrawal*, there is no reason why this principle should apply generally in the biobank context, where the risks and relationships are different.[118] On the contrary, Holm argues that "we are usually justified in explaining the consequences of their actions to people if we think their actions have problematic consequences, and we believe that they are ignorant of these consequences."

c) Several authors have argued that it could be justifiable to restrict the inalienability of the right to withdraw consent, by sometimes *allowing binding waivers* of this right.[119] It is for example argued that such waivers respect our autonomy and allow us to make beneficial agreements.[120] Nevertheless, some authors underline that this kind of waivers must be handled with care, for the sake of public trust in medical research.[121] The use of such contracts should thus "be restricted to cases where it is particularly motivated
to allow them in order to avoid more than minimal drop-out rates" and that "researchers and ethical review committees must act to ensure that the interests of the sample
providers are protected" in cases where "the right to withdraw becomes of major importance to the lives of the sample providers involved." This would seem to bring us back to the dubious discussion above, on the proposed requirement of sufficient reasons for the withdrawal.

d) While the traditional right to withdraw consent to research should be immediate, it has been argued that it could be justifiable to *delay the right to completely withdraw* from a research biobank.[122] According to Holm, what is presumably important to the individual concerned, is that the researchers stop using the samples and data, not that they destroy them. One possibility could therefore be to introduce a "cooling off period" during which the "withdrawn samples and data could be parked in 'limbo', or be dead-locked for a period of time (say 3 months) and only destroyed/erased at the end of that period if the person withdrawing has not changed her mind." Holm argues that this model would only minimally

[116] Eriksson & Helgesson (2005) p. 1076.
[117] Holm (2011) p. 275.
[118] Holm (2011) p. 279.
[119] E.g. Helgesson & Johnsson (2005) and Chwang, E. Against the Inalienable Right to Withdraw from Research *Bioethics*; *Volume 22 Number 7 2008* pp 370–378.
[120] Chwang (2008).
[121] Helgesson & Johnsson (2005) p. 320.
[122] Holm (2011) p. 278.

infringe autonomy, and reduce the risk of hasty and ill-advised decisions with negative consequenses not only for the research interests but sometimes also to the donor himself or herself, should he or she later regret the withdrawal.

e) Holm also seems to be in favour of a model with incomplete withdrawal, *allowing certain further use of data already collected*.[123] He discusses different variations of this model, and believes that anonymisation of data and samples, as well as certain other restrictions on their use, could provide adequate protection of the privacy rights of the individuals concerned. As stated above, however, it has become increasingly obvious that anonymisation has many shortcomings as a tool for the protection of conflicting interests in biobank research.

A different type of suggestion made by Holm is that participants should be allowed to withdraw the broad consent they may previously have given, but still agree to the storage of samples and data for potential future use in research, on the condition that they will then be re-contacted for further information and consent.[124] This ambition to facilitate more individualised consent and withdrawal options is well in line with the dynamic consent procedures that have been advocated by e.g. the EnCoRe project.[125]

## 6 A Right to be Forgotten?

Since research biobanking is so intimately linked to the processing of sensitive personal data, it also seems relevant to briefly mention some recent developments in the field of personal data protection. A draft for a General Data Protection Regulation, planned to replace the Data Protection Directive 95/46/EC was thus presented by the European Commission in January 2012.[126] Article 17 of the proposed Regulation has the headline “Right to be forgotten and to erasure”, and deals with the right of data subjects to have their personal data erased when they are no longer necessary for the original purposes, or consent on which the processing is based is withdrawn. A similar, albeit less developed, requirement of erasure or blocking of personal data is already laid down in Article 12 (b) of the Data Protection Directive. In the proposed Regulation, however, the duties of Data Controllers have been extended, but there are still exemptions for situations where the retention of data is necessary e.g. for reasons of public interest in the area of public health or for research purposes, see Article 17.3 (3) and Article 83. This means that the continued use of already collected data, for research purposed, after consent has been withdrawn, could still be lawful under the new Data Protection Regulation.

The terminology of a “right to be forgotten” in the context of data processing has been critisised, on the grounds that it could cause misunderstandings and unnecessary negative reactions, and that the justifiable idea of a right to delete is both nominally and qualitatively different from the original concept of right to be forgotten, which in certain situations may restrict the freedom of speech.[127] It would thus seem wiser just to speak of a right to have data erased or deleted – and samples destroyed – than to introduce a “right to be forgotten” in this particular context.

## 7 Summing up

This paper does not aim to provide solutions to the problematic issues related to withdrawal of consent in research biobanking, but rather to draw attention to shortcomings in the present guidelines and discuss some of the requirements for justifiable infringements of the fundamental human right to protection of private life.

Although the right to withdraw consent to storage and research use of biological materials can certainly be described as a fundamental human right, the implications and justifiable restrictions of this right are insufficiently discussed and defined. The right to withdraw consent to participation in research biobanking may not be equal to the more firmly established right to withdraw from clinical research or

[123] Ib. id.
[124] Holm (2011) p. 279.
[125] Kaye, J. et. Al. (2012).
[126] Proposal for a Regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation), COM(2012) 11 final.
[127] Bernal, P.A., 'A Right to Delete?', European Journal of Law and Technology, Vol. 2, No.2, 2011.

medical experimentation, but even so, more attention should be paid to the need for a thorough analysis, based on the principle of proportionality, in order to decide *what* restrictions of the right to withdraw consent can really be considered adequate and necessary to protect other interests concerned. It could for example be questioned whether anonymisation, as an alternative to destruction of samples and erasure of data, meet the requirements. The particularly vulnerable position of minors and incapacitated adults in research biobanking also requires further consideration, in order to ensure their right to withdraw once they have attained the capacity to consent.

The close link between consent and withdrawal has become increasingly obvious in the context of research biobanking, and the new approaches to consent as an individually tailored ongoing process – facilitated by modern information and communication technology – should be reflected in the revision. As a part of this process, the duties of researchers, biobank holders and responsible agencies at different levels must also be redefined.

## Biographical notes

Elisabeth Rynning, LL.D., is Professor of Medical Law at Uppsala University, www.jur.uu.se (chair jointly financed by the Faculty of Law and the Faculties of Medicine and Pharmacy). Her research interests include issues of privacy, autonomy and the use of new technology in health care and biomedical research. She has participated in a number of multi-disciplinary European research projects on biobanking and/or privacy in biomedical research, and has published widely in this field. Elisabeth Rynning coordinates the Nordic Network for Research in Biomedical Law (www.nordicnetwork.org) and is a member of the editorial boards of the European Journal of Health Law and the Medical Law International. She has been the legal expert of the Swedish National Council on Medical Ethics (1997-2008) and has worked on a number of Swedish law commissions in the areas of health care and research, including the commission preparing a revised Act on Biobanking (2008-2010).

***Session 4 - Responsible governance and use***


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## Abstract


***Mechanisms for internal biobank governance – oversight bodies and independent ethics bodies***

The challenges of governance of biobanks have revealed important questions about the nature and role of many long-established concepts such as consent and privacy and have called into question their long-term utility. Additionally, the governance conundrum has led us to question the function and authority of ethics bodies in overseeing research and whether pre-existing mechanisms are fit-for-purpose. The three features of biobanks which drive this inquiry are:

(iv) Diversity – dealing with heterogeneity on biobanks
(v) Uncertainty – dealing with the unknown future uses of biobanks
(vi) Temporality - dealing with the long-term nature of biobanks

This paper takes these three challenging features as its starting point to assess the role of oversight bodies and independent ethics bodies in contemporary biobanking. It will be argued that there is a need to establish clarity of function with respect to those bodies performing an approval function and those performing an oversight function throughout the lifetime of a biobank.

The paper will propose a good governance framework for biobanking which allows for adaptive and responsive oversight and ethical input and which can compensate for limitations in the role of more traditional ethico-legal devices such as consent and privacy. A model of *reflexive governance* will be advanced as the optimal basis for law and policy development in the biobanking context.


## Full text

***Mechanisms for internal biobank governance:oversight and independent ethics bodies– a role for reflexive governance****128*

**Introduction**

This paper is concerned with the governance sections of Recommendation 2006(4) and with the role of oversight and independent ethics bodies in delivering responsible governance. It is argued that a more holistic approach to governance is required compared to what is found in the current version of the Recommendation. In particular, the central thesis is that biobanks and other biomedical collections require robust ethical input throughout their life cycle and that the optimal way to deliver this is through mechanisms of reflexive governance. The paper explains this concept and how it can add considerable value to governance frameworks and other devices used to protect participants' interests such as consent or information security measures.

**Asking the right questions**

Ethics bodies and independent oversight groups are now a common feature of biobank and biomedical governance. Indeed, their input is mandated by Recommendation 2006(4). The crucial question to ask at this time of revision of the Recommendation is, however: what are the kinds of ethical input that contribute *best* to good biobanking practice?

[128] Elements of this paper draw directly on my publication G Laurie, 'Reflexive Governance in Biobanking: On the Value of Policy Led Approaches and the Need to Recognise the Limits of Law' (2011) 130 Human Genetics 347-356.

In order to answer this question, it is important first to be clear about what we consider to be good biobanking practice. This is a moveable feast, but there are certain common features that few could dispute are essential to the process. These include governance mechanisms that are:

•**Effective and efficient** ✓

•**Transparent and accessible** ✓

•**Procedurally robust** ✓

•**Understandable and navigable** ✓

•**Proportionate to risks and benefits** ✓

•**Legal and ethical** ✓

To this, however, there are other features of governance that are less obvious and less well explored. These include questions about how far governance and the practices of ethics and oversight bodies should be:

- **principled** – in the sense that conduct is guided by an agreed set of principles and that decisions are transparent and objectively justifiable by reference to those principles;

- **adaptive** – in the sense that governance mechanisms are capable of accommodating changing circumstances, including ethical, legal, social or economic;

- **reflexive** – in the sense that governance mechanisms and the ethics and oversight bodies are committed to reflection on how best to proceed, open to dialogue on such matters and receptive to various inputs along the decision-making process.

As this paper will go on to argue, the very nature of biobanks and other biomedical collections requires that good governance mechanisms include these last three features. Thus, when we ask, what are the kinds of ethical input that contribute *best* to good biobanking practice?, we would expect the answer to point towards input that deliver this kind of support, especially the reflexive element.

**Important differences in ethical input**

In surveying the conduct of ethical and oversight bodies it is possible to discern two broad categories of approach.

1. **Compliance** – many ethical bodies operate in a quasi-regulatory fashion to ensure that the rules of the game are being adhered to. Often this kind of ethical input comes at the beginning of a biobanking project to approve the protocol and to ensure that participants' interests are sufficiently well protected (as far as they can be accurately established at this point in time). Failure to comply will lead to refusal of an application; downstream failures might also result in sanction, such as withdrawal of approval. On-going monitoring, if it exists, will often be in the form of receiving regular reports or updates in the form of audits. Most ethical reflection will occur only at an early stage in the process. Some ethics bodies are even required to consider compliance with the relevant legal framework, re-enforcing the quasi-regulatory role.

2. **Assistance** – the above approach is to be contrasted with a role for ethics bodies to assist in the resolution of ethical dilemmas. In this context the deliberation is not about whether requirement X or Y has been met, but rather it is concerned with critical consideration of the ethical issues raised and a search for ethical ways to proceed. There is no expectation of compliance because many of the issues are unresolved and/or it is not clear how to move forward. As such, this kind of assistance is concerned with genuine dilemmas where there might be two or more justifiable options. Ethical input here can be invaluable for the robust analysis that it can provide and the opportunity to think issues through in a deep manner. Deliberations might rely on ethical and other principles as starting points for deliberation and action; ultimately, however, many decisions might be a question of judgment about how best to proceed.

The importance of appreciating this distinction between compliance approaches and assistance ap-

proaches lies in form and content of ethical and oversight bodies and in being clear about what they are asked to do in governance processes. This has implications for any revision of the Council of Europe Recommendation because prescriptive measures can only take us so far in achieving good governance in biobanking.

It is the case in practice that many judgments are needed where discretion must be exercised. Ethically robust dialogue and input would be invaluable in such instances. A biobank project might be perfectly legal but its decision-makers might be unclear about how best to proceed with respect to a range of issues such as feedback policies, access arrangements, pricing and benefit sharing requirements, public and stakeholder engagement etc.

**Recommendation 2006(4)**

Two key provisions of Recommendation 2006(4) address governance and the role of ethics and oversight bodies. The above analysis suggests that these currently embody a view of ethical input that is more concerned with compliance than with providing ethical assistance. Consider:

Article 24 –

" …research should only be undertaken if the research project has been subject to an independent examination of its scientific merit...and verification of its ethical acceptability."

There are two principal ways to interpret this provision, each of which raises troubling issues. First, is this Article satisfied by a one-off, up-front approval by an ethics committee at the start of a biobanking project? If so, how can we ensure on-going compliance for research resource-type projects that might have a duration of decades? Conversely, if the expectation is that ethical approval be sought each time that a research resource is accessed, how does this satisfy governance commitments to proportionality and what are the associated regulatory-type burdens that would ensue? Is this effective and proportionate governance for a resource that has been established specifically for research and when requests for access are in keeping with original purposes? This Article does not seem to take sufficient account of the long-term nature of biobanking and biomedical collections. This is discussed further below.

Article 19 – deals with oversight of population biobanks and states:

"Each poplulation biobank should be subject to independent oversight, [especially] to safeguard participant interests; …regular audits required on access and use; …reports on activities should be published."

These considerations, while very important, also largely reflect a compliance role for ethics bodies. Accordingly, we must consider whether the Recommendation currently only offers half of the full governance picture. In particular, we must contemplate whether there are serious unmet ethical needs for assistance, input and support especially for long-term (population) biobanks on a range of issues from re-contact to feedback, and from access to sustainable use, etc.

The remainder of this paper will proceed to argue for the kinds of factors that should be of central importance in any biobanking governance regime in terms of core objectives; moreover, it will posit an approach of *reflexive* governance that will not only help to deliver on these objectives but that will also contribute to addressing the unmet ethical needs identified above.

**What are the key governance challenges and objectives?**

It is trite to confirm that a vast array of biobanks and biomedical collections exists that necessitates, in turn, a wide range of governance responses. Notwithstanding, it is submitted that there are three common challenges to collective and individualised biobanking efforts that should be recognised for what they demand of governance responses. These are common challenges that should shape policy and regulatory agenda because of the common goal of improving human health and well-being. The commonality of concern is further revealed by the simple truth that the full potential of biobanks and biomedical collections can only be realised through international and extensive cooperation and exchange. Quite simply, good governance must deliver this.

*Common challenge I: Diversity*

The heterogenous nature of biobanks and biomedical collections is important in two fundamental senses: first, the resources in and of themselves differ considerably in terms of size, nature, purpose, scope and likely contribution to human health and well-being. Secondly, the diversity of associated governance arrangements poses real challenges for realising the goal of international and extensive cooperation and exchange.

The heterogeneous nature of biobanks is both a benefit and a challenge. Heterogeneity is key to both the promise and the problems for science and science policy. These coalesce around one stark fact about the importance of these collections with respect to the overarching objective of improving human health: the said objective cannot be realised if diversity of approaches—towards the conduct of the science and its governance—is too great. The irony is that while the diversity of the samples and data within collections is potentially enriching of our understandings of human health and disease, diversity of scientific methods or governance arrangements between collections will stand to thwart this understanding if biobanks cannot link up and learn from each other, ideally on a global scale. There are, therefore, dual elements to the diversity challenge:

(1) designing-in interoperability both with respect to scientific and governance approaches, and

(2) designing-out approaches that are restrictive of sharing, cooperation, flexibility and mutuality.

*Common challenge II: Uncertainty*

Many biobanks and biomedical collections are set up explicitly with an open-ended purpose, for example to foster health-related research. Even those that are established to investigate a particular disease or condition do not, and often cannot, specify how the resource will be used. Moreover, given that these resources are normally set up to promote important and, as yet ill-defined public interests such as the improvement of human health, it is often unclear how they will be (best) exploited to such ends. All of these factors mean that considerable uncertainty surrounds the management of biobanks and biomedical collections, not least with respect to who will have access, for which purposes, at which times and for what ends.

This gives rise to an immediate tension between, on the one hand,

(3) establishing policies and procedures to protect adequately the interests of participants who have contributed to the establishment of the resource,

and, on the other hand,

(4) establishing policies and procedures which promote the use of the resource as widely as possible.

Mechanisms that can effectively secure the dual elements of the uncertainty challenge are not readily available. Most notably, while laws exist, or can be created, to protect individuals' rights and interests—and indeed to protect against harm to the public interest—law as a social tool has a far less salubrious record in promoting public interest as such. Thus, while these governance goals might seem self-evident, the means to achieve them is far less so.

*Common challenge III: Temporality*

The third challenge is inherently linked to the first two. This is the temporal challenge of establishing resources the benefits of which might not be realised for a considerable time, and which most probably will only be enjoyed by generations to come. The temporal challenge arises both because of scientific and natural restraints—the time needed to generate sufficient data on instances of disease and/ or through overcoming the diversity challenge—and because many biobanks are purposefully designed as long-term endeavours, generating uncertainties such as those outlined above. As with the other challenges, the temporal challenge as two potentially competing elements:

(5) ensuring the longevity of the biobank, e.g., through care- fully managed access policies and arran-

gements and stewardship of depletable elements of the resource, and

(6) ensuring that governance policies and mechanisms remain fit for purpose over time with respect to both the private and public interests that are—or might be—at stake.

Taken together, it is submitted that these six objectives ought to form the core concerns of any good governance regime.

To reiterate, these are:

1. Design-in interoperability
2. Design-out approaches that restrict sharing, cooperation, mutuality
3. Establish policies and practices to protect participants' interests
4. Establish policies and practices to promote use as widely as possible
5. Ensure longevity of the resource
6. Ensure policies remain fit for purpose (private *and* public interests)

Importantly, there are elements here that cannot be addressed by law or technical means alone. Thus, while interoperability might be seen as a matter of scientific or technical import, policies to promote sharing, access, wide-spread use and longevity will require serious (ethical) judgment and discretion. As such, the governance question is the central one of this paper, viz, how best to secure this. In terms of Recommendation 2006(4) the related question is whether its terms recognise and promote this end. It is suggested here that they do not and, moreover, what is required is a commitment to reflexive governance, as defined and explained below.

**Reflexive governance**

Reflexive governance is defined here as: "a system of in-parallel development and partnership in governance typified by arrangements which facilitate mutual learning over time".

It is characterised by a rejection of the compliance culture approach to ethical input, and instead the focus is on providing mechanisms for helpful ethical input during the entire life cycle of a biobank or biomedical collection.

Reflexive governance accepts, and indeed embraces the reality that many decisions about good biobanking practice come down to (ethical) judgment when there might be a plurality of possible paths to take on any given decision. Examples might be whether a biobank resource can now be used for a once-controversial research end that might have been unacceptable several decades ago but times have changed. Another example is the need to continually reflect on policies with respect to participants. Thus, while it was once thought to be entirely acceptable to adopt a no-feedback policy for population collections, attitudes on this have also changed necessitating, at least, reflection on the justifiability of original policies.

The precise manner or arrangement for reflexive governance can adapt to local needs of a particular collection. Notwithstanding, it is suggested that there are three key considerations to bear in mind to help to ensure that the process of reflexivity works.

a. **Guiding principles**

Given that reflexive governance is about engaging in open dialogue when genuine ethical questions arise to which there is no immediately obvious answer, the importance of guiding principles comes to the fore. Principles can be seen as starting points for deliberation and action; they provide a common language for dialogue and also a set of parameters within which the discussion should take place. Important guiding principles in this context might include:

i*. the principle of integrity of purpose*

This principle suggests that the resource will be managed to bring about the core objectives for which it was establish, for example—as a disease register or to promote the health of future generations. Furthermore, this principle can help to promote trust and to set realistic expectations for all stakehol-

ders in the biobanking enterprise, and particularly the participants. Importantly, the principle of integrity of purpose does not dictate any particular approach to any particular aspect of the operation of a biobank, for example by mandating informed consent or by requiring absolute anonymity of personal data. Rather, the principle focuses on the relationship between those with responsibility for the biobank and those who have contributed to it or might expect to benefit from it, which could include society at large.

ii. *the principle of proportionality of action*

This principle speaks to the imperative both to protect participants' interests and to promote public interests and recognises that this can give rise to conflict and tension (albeit that this is by no means inevitable). It should not be forgotten, e.g., that the protection of individual rights and interests is equally an important public interest. Moreover, the principle of proportionality of action can serve to militate against arriving at stalemate because it requires that conduct that might impact negatively on a countervailing set of interests should only occur to further the legitimate purposes of the resource, as above, and when it is effective, necessary and proportionate to so act. Thus, risks to privacy—while always present and undoubtedly increased by sharing of data—can be seen as acceptable so long as the imperative to share is demonstrated, the benefits to the public interest are articulated, and the relative risks to privacy are minimised.

iii. *the principle of reflexivity of approach*

The principle of reflexivity of approach requires that we devise mechanisms to allow biobanks to proceed in the face of uncertainty and that we learn from experience along the way to deliver effective governance that meets the six objectives outlined above. This is a non-trivial task. We simply do not know what is in store for these resources and their participants, nor can we effectively second-guess what value might be realised from their operation, nor what further challenges might be generated by their continued existence. This approach is about the governed and the governing being reflective, receptive and responsive in the framing of challenges and their possible solutions. Put otherwise, it is about a partnership arrangement between the governed and governing that is based on dialogue when faced with genuine dilemmas and admits the possibility of discretion and judgment in deciding how best to proceed.

**b. Governor and stakeholder engagement**

Reflexive governance is premised on mutual learning, which can only occur through dialogue and engagement with relevant parties. Self-evidently, this will focus on the biobank personnel and any ethics entity charged with the reflexive role. More than this, however, it admits the possibility of engagement with participants and publics as part of the on-going commitment to these stakeholders in the research enterprise. Engagement would be more than mere education and communication; it would require efforts to take account of responses received (which is not the same as slavishly doing what stakeholders think they want). Equally, such on-going engagement, especially with participants, allows for other governance mechanisms to perform adequately. An obvious example of this is the role of broad consent. This mechanism is now common in biobank practice, but it should not be confused with blanket consent. This last mentioned form of consent is a carte blanche permission to deal with tissue samples and data. Broad consent is, rather, evidence of agreement to the proposition to participate in an open-ended project when the precise consequences of this cannot be explained *at the time of recruitment*. Arguably, there is an attendant obligation on the recruiters to inform participants of developments *as and when these happen*. Reflexive governance not only promotes this but also permits opportunities to respond to feedback from participants and others about the management of the biobank and its resources.

c. **Complementarity**

Finally, reflexive governance must be about providing complementary governance input to biobanking practice. If it simply adds to procedural burden it undermines the central importance of proportionate governance. For these reasons, it is imperative that reflexive governance is seen as voluntary partnership and not as some quasi-regulatory function. Ethics bodies in this mode act as a "critical friend" throughout the life of the project. The previous section has indicated ways in which reflexive governance can complement other mechanisms, such as consent. Equally, it can do so with respect to the

protection of other interests, such as privacy, by providing responsive advice as technological and other developments happen in the life of the biobank (as they inevitably will).

**Reflexive governance in action: an example**

UK Biobank has been established as a major research resource containing genetic, health and life-style information, as well as samples, from over 500,000 people in the United Kingdom, aged between 40 and 69 at the time of recruitment.[129] The purpose of UK Biobank is to support a diverse range of health-related research intended to improve the prevention, diagnosis, and treatment of illness, as well as to promote health throughout society. It is envisaged that the resource will be maintained as openly as possible to encourage wide-ranging applications from around the globe; the project will be blind to whether applicants come from a commercial or a public sector background; the sole consideration about pedigree will relate to the calibre of the research to be conducted and the trustworthiness of applicants to provide safe systems to protect participants' interests and to conduct science in keeping with the original broad purposes of the endeavour, i.e., health-related research in the public interest.

UK Biobank is subject to a plethora of existing legal provisions protecting participants' interests and has not required any legislative intervention in this regard. The real challenge has been in designing internal governance mechanisms to promote the core purposes of the resource, and in this respect the project has been ground-breaking in two respects: (1) its Ethics and Governance Framework and (2) its Ethics and Governance Council.

The Ethics and Governance Framework (EGF) is a publicly-available living instrument from UK Biobank which makes explicit the core undertakings of UK Biobank to its participants, researchers, and wider society. As such, this document directly embraces both the principle of integrity of purpose and the principle of reflexivity of approach advocated in this paper. The former is engaged by articulating—deliberately and very broadly—the purposes in pursuit of which the resource will be run. The latter is invoked by envisioning the EGF as an organic policy device that will be revisited and revised over time as the project progresses and as new or unforeseen circumstances develop. The EGF will remain throughout as a publicly-facing expression of what UK Biobank can be said to stand for.

UK Biobank's critical friend is the independent and permanent Ethics and Governance Council (EGC). This was established in 2004 in the set-up phase of UK Biobank. Since its inception the work of the EGC has been evolving, reflecting the necessarily organic nature of its role. For example, in the early stages before recruitment the EGC's role was primarily advisory and related to associated recruitment policies and procedures, the content of information leaflets and consent forms etc. As recruitment got underway, the EGC also assumed a monitoring role pertaining to complaints and enquiries, information security provisions, proposals for follow-up and implementation of the project's plans for ongoing engagement with participants. Latterly, the EGC has also taken on a foresight and development role with respect to the UK Biobank access and intellectual property procedures, working with UK Biobank through an EGC sub-group. The practice throughout has been to facilitate and foster an open dialogue with UK Biobank through regular meetings, sub-groups, public meetings and the publication of minutes.

A number of examples of reflexivity as defined above can be identified as arising from this governance mechanism. These can be found in the public minutes of the EGC. Two examples are particularly pertinent:

(a) Revision of the EGF

The original version of the EGF contained the following option for participants to withdraw at any time and for any reason:

''No further use'': In addition to no longer contacting the participant or obtaining further information, UK Biobank will destroy all of their health-related information and samples collected previously (although

[129] The author of this paper served as the Chair of the UK Biobank Ethics and Governance Council from 2006-2010. Nothing contained in this paper should, however, be taken to represent the views of UK Biobank, its funders or any entities associated with the initiative. All views as personal to the author, who takes full responsibility for what is contained here.

the participant would be told that it may not be possible to trace and destroy all distributed anonymised sample remnants) (emphasis added).

Over time, and as UK Biobank began to develop its IT systems, it became clear that it would not be possible to destroy all data held. System designs were such that some data had to be retained for the integrity of audit systems and to demonstrate that the systems themselves worked effectively. After discussion with the EGC, the following revision was made to the EGF:

‘‘No further use’’: ...in addition to no longer contacting you or obtaining further information about you, any information and samples collected previously would no longer be available to researchers. UK Biobank would destroy your samples (although it may not be possible to trace all distributed sample remnants) and would only hold your information for archival audit purposes. (emphasis added).

The Council also recommended that the information leaflet to new participants be revised and that these changes be brought to public attention via the UK Biobank and EGC web pages. The question also arose as to whether persons already recruited should be approached directly and informed. After joint consideration and reflection, it was agreed that this was not necessary. The justification was that the integrity of the original promise to participants—that their data and samples would not be used for further research—had not been compromised; nor was the absolute right to withdraw affected in any way. The course of action agreed upon was agreed to be proportionate to the new circumstances that had arisen.

(b) Future use of the resource

The purposes of UK Biobank are potentially very wide. It is not unusual for the EGC or UK Biobank to receive queries about possible future uses of the resource. One such query arose in 2009 concerning applications to access the resource to carry out research into somatic-cell nuclear transfer. The query which was raised was why the EGC did not take a stand on the hypothetical possibility of such an application arising, given the current climate of concern surrounding this particular branch of science.

The EGC responded by re-iterating the broad purposes of the project and the robust governance mechanisms that are in place to oversee all future applications. It confirmed that the breadth of purpose would not automatically rule out such an application (which is not the same as saying that such an application would ever be granted access). The EGC pointed out further that, as an independent body, it is not in a position to control access to the UK Biobank resource. Moreover, it would not be appropriate for the Council to second-guess future social mores. Notwithstanding, the Council did note that if ever such an application were to arise then the UK Biobank system of governance would ensure that appropriate dialogue would arise at the appropriate time. Furthermore, a core objective of the Council is to monitor that the original consent of participants—to participate in UK Biobank—is being respected. Any concern that this was not the case would result in a recommendation that further, more specific consent be sought. Other options might include recommendations for public engagement activities to test the moral waters of the time. In this way, the principles of integrity of purpose and reflexivity of approach can be seen to be in operation here. This is a paradigm example of what reflexive governance can provide.

Another advantage of a reflexive governance approach is that it can serve to engender healthy institutionalised distrust as a means to foster trust in the enterprise as a whole. For example, it has been suggested in the wider literature that mechanisms which are internally regarding and self-critical of policies and procedures can help to assure outsiders, or in the context of biobanks—participants themselves, of the robustness of the checks and balances that are in place. Supportive critical engagement lies at the heart of reflexive governance.

This having been said, reflexivity—or reflectiveness— might not come easily to some actors, especially those whose acts are under scrutiny. This is a capability that must be learned, for otherwise it might result in ‘defensive strategies’. For some, this learning can arise merely from inherent capacity and an attitudinal openness to reflection. For others, more is required of the reflexive governance approach, for example, a positive engagement by each actor with the form of relationship that its identity has taken in the past and that which it might take in the future. This enables a necessary transformation towards an ‘ability-to-do’ what is required of the actor in its future capability.

It must also be recognised that trust between the relevant actors is not merely a matter of transparency as is so often claimed in other contexts. Trust here stems from the common commitment to the principle of integrity of purpose while the principle of reflexivity provides a means to realise this and to found a relationship for moving forward.

Finally, and as this author has argued elsewhere:

'...an obligation to express clearly one's value-stance necessitates reflexivity, that is, self-reflection on what exactly it means to hold such a value and where its limits lie. It is in the territory between value positions that effective, reasonable, legitimate and legitimated policy is to be found.'

**Conclusion**

This paper has offered an argument that ethical input to biobanking and biomedical collections must go beyond quasi-regulatory attempts to confirm compliance with legal rules or extant guidance. It suggests that there are real unmet needs for ethical input to biobanking endeavours that allow ethics bodies and independent oversight groups to act as critical friends in facing genuine ethical dilemmas where neither law nor technical fixes provide appropriate answers. A model of reflexive governance is proposed to achieve this.

To be clear, reflexive governance is not about (i) policing compliance, (ii) carrying out mere risk-benefit assessments, or (iii) a tick-box top-down control mentality akin to quasi-regulatory oversight. Rather, reflexive governance is about:

(i) facilitating mechanisms of mutual learning faced with genuine dilemmas;
(ii) understanding and working together to meet challenges over time; and
(iii) developing and applying principles and policies that remain fit for purpose over time

By these means, biobanking and biomedical collections governance can be responsive to both scientific and ethical developments in the field. It is suggested that Recommendation 2006(4) be revised to take account of this need in biobank governance for responsiveness and reflexivity.

## Biographical notes

Graeme Laurie is Professor of Medical Jurisprudence at the University of Edinburgh and Co-Director of the Arts and Humanities Research Council (AHRC) Research Centre for Studies in Intellectual Property and Technology Law. He served as Director of the Centre from 2007-2011 until he took up the position of Director of Research for the School of Law. His own research interests include the role of law in promoting and regulating science, medicine and technology. He was the Chair of the permanent Ethics and Governance Council of UK Biobank from 2006-2010 and is currently the Chair of the Privacy Advisory Committee in Scotland. He is a member of the Nuffield Council on Bioethics and the BMA's Medical Ethics Committee. He currently serves on a Royal Society Working Group on Science as a Public Enterprise. He is a member of the editorial teams of the European Journal of Health Law, Medical Law International, Law, Innovation & Technology and the AHRC Centre's own online journal *SCRIPT-ed*.

***Session 4 - Responsible governance and use***


## Prof. Kristian Hveem (Norway)

Director of the HUNT Biobank / leader of Biobank Norway



## Abstract

***Access (fairness of access, transparency, criteria, Biobank network)***

In our efforts to reveal new disease mechanisms and treatment strategies for both rare and common, complex diseases, research biobanks have proven to be increasingly important. Sample size, large infrastructure investments and high running costs are critical issues promoting the establishment of both national and international biobank networks. The FP 7-funded biobank infrastructure project, BBMRI (Biobanks and Biomolecular resources Research Infrastructure) and national research councils have promoted the formation of a number of national biobank nodes in Europe (for example, BBMRI.se, BBMRI.nl, BBMRI.fi, Biobank Norway, Danish National Biobank).

Large biobank research infrastructures are most likely to be publicly funded, with a natural focus on a transparent and fair access policy. Most commonly, both data access committees and ethical review boards will evaluate the scientific strength and public value of a research application as well as the ethical issues involved. The biobank donors will also have their established rights, based on consent forms and national legislation. To meet these requirements, good research governance is critical and must be based on an open, proactive information policy to ensure trust and transparency between researchers and research participants. In principal, both publicly and privately funded research projects should have access to biobanks as research resources.


## Full text

The significance of biobank research and networks

Modern, state-of-the-art biobanking is a major prerequisite to remain competitive within medical research for the development of new drugs and the validation of biomarkers.

Comprehensive biobank networks require large sustainable resources that involve advanced and expensive technologies. Though the user group may be heterogeneous, the main interest has so far come from the university sector and biobanks are still mostly publicly funded. Based on the ESFRI Roadmap, there is a strong international focus on biobank-based research and interdisciplinary collaboration. The FP 7 funded European biobank infrastructure, BBMRI.eu (Biobanks and Bio-Molecular resources Research Infrastructure) was established in 2009 with successors as BioSHaRE.eu and BBMRI.LPC (2012). A legal entity, the BBMRI ERIC (European Research Infrastructure Consortium), has recently also been approved. Some of the major achievements by BBMRI.eu, have been to promote excellence, efficacy and internationally competitive European research, but most importantly, to stimulate the establishment of strong national biobank hubs such as BBMRI.se, BBMRI.nl, Biobank Norway (BBMRI.no) and BBMRI.fi. These are national networks with a similar work package structure, enabling an extensive collaboration across work packages internationally.The basis for the larger European biobank establishments has been an altruistic contribution from the donors, providing researchers with extensive health information and biological samples. An increasing number of the general population in Europe has donated samples for biobank storage with a growing complementary collection of phenotypic information, clinical data and analytic results.

Access

The international community has put some vast resources into biobank establishments and networks and biobank access rules and procedures must be based on sound principles such as fairness, uniform and simple criteria, transparency and ethical awareness.

Generic Access Agreements have been developed for many prospective, longitudinal population-based genomics studies (Knoppers et al, Genome Medicine 46, (2011). The applicant must respect the policies of the biobank including consent forms, biobank access, Material Transfer Agreements and IP and publication policies. A major purpose of access procedures is to encourage the extensive and appropriate use of the biobank resource for health-related research that is in the interest of the public. Access by researchers may also create added value to the biobank by funding/providing analysis to be returned to the biobank as part of its future resources.

Fairness of access

Fairness of access means equal rights to access, not only for researchers and research groups in the public domain or nationally, but also across national borders and for representatives from the industry. Fairness also includes providing informed consent from donors, the logistics of data disclosure to participants, the right to ownership of intellectual property and the privacy and security of donors who participate.

Access criteria, security and governance

Access criteria should be kept simple and be uniformed and harmonised across studies and nations. They must ensure the rights and integrity of the study participant and comply with existing laws and regulations. Access attempts by the police or other agencies must be strongly restricted.

The participant's confidentiality and anonymity must be properly protected by having a robust security system in place. Data sets may be shared by several researchers, but data access committees must counteract conflicting or overlapping publications. Any kind of discrimination or violation of the rights of the study participants must be avoided.

Study participants must be given insight into the exploitation of their samples and clinical data. A web site or other sources should give updated information on researchers being granted access and subsequent publications. Regardless of the level of detailed information in the consent form, openness and transparency must always be ensured.

Ethical challenges

Some of the most essential issues are the national legislation, the role of Ethical Review Boards, specific or broad informed consent and how to handle comprehensive genetic studies. Reduced costs and advanced technologies have given rise to large scale population-based whole genome sequencing studies where ordinary routines related to genetic testing may not apply. Is this to be considered predictive testing, how may one address the individual study participant's right to insight and the communication of incidental findings?

Data sharing of anonymized data sets is encouraged, e.g. in international data bases such as dbGaP that may increase the risk of backwards identification. Should results be reported back on an individual level, and how can we ensure that correct results are retrieved in data sets involving tens of thousands of participants?
These both important and complicated questions call for careful handling and constructive discussions.

Conclusion

We have only seen the beginning of a rapidly-growing international biobanking activity. Biobank research has fostered a close and productive international collaboration where interdisciplinary research activity has increased, including ethicists. New discoveries will have significant impact on the development of better biomarkers, new treatment strategies and tailored medical treatment.

The whole research community must have a fair access to these valuable resources where also transparency, strong governance and ethical awareness is essential.

## Biographical notes

Kristian Hveem, MD, Ph.D., is a Professor in Clinical Epidemiology, at the Faculty of Medicine, the Norwegian University of Science and Technology (NTNU), Norway. He acts as Director of HUNT Biobank, NTNU and the National CONOR (Cohorts of Norway) biobank. Since 2011, he has been leading the Norwegian Biobank Infrastructure, Biobank Norway, comprising all major population based and clinical biobanks in Norway.

Since 2010, he has been instrumental in the establishment of the newly opened Danish National Biobank at Statens Serum Institut, Copenhagen, Denmark, and holds the position as its first Director.

He has served as a member of the Biobank Infrastructure Committee (BISC) of the Swedish Research Council (2008-09) and lead the work on a national report on “Potential for commercial use of population based biobank” (2009), initiated by the Research Council of Norway. His major research interest is genetic epidemiology, with a special focus on cardiovascular disease, diabetes and other metabolic syndrome related traits.

***Session 4 - Responsible governance and use***


## Prof. Andres Metspalu (Estonia)

Head of the Estonian Genome Center of the University of Tartu



## Abstract

***Feedback – rights, obligations, and the mechanism***

As new technologies allow fast generation of data, the topic providing feedback is becoming increasingly pertinent. In general, the questions are whether, when and how to inform research participants about findings? The emphasis in the Estonian case is placed on the last, as according to Human Genes Research Act (HGRA), legislation which regulates the Estonian Genome Center of the University of Tartu (EGCUT), gene donors have the right to receive feedback on their genetic information. The HGRA also states that the feedback should be accompanied by genetic counselling. This implies that the medical field is prepared to do so and the necessary IT solutions have been developed. Steps have been taken in both these areas. The goal for the EGCUT is to set up a central national health database that would be accessible to all physicians in Estonia. This database would contain genomic data along with all other medically relevant information on the patient. The information and communication technology would utilise this database and facilitate the genetic counselling process. Once the health care system is prepared for integrating genomic information into medical care, genetic risk estimates will be able to be taken into account together with the rest of a patient's health information, rather than being considered in isolation.


## Full text

***Feedback – rights, obligations, and the mechanism***

### Introduction

The Estonian Genome Center is a research institute at the University of Tartu which has maintained the Estonian Biobank since April 2007. Before that, the Estonian Genome Project was conducted by the Estonian Genome Project Foundation from 2000 to 2007. Recruitment was conducted in years 2002-2010. The Estonian Biobank is a longitudinal, prospective population based biobank with nearly 52,000 gene donors which is approximately 5% of the adult population (81.2% Estonians and 15.4% Russians). As of May 2012, the total population of Estonia was 1,294,336 people from which 693,884 were woman and 600,363 were men. 68.7% were Estonians, 24.8% were Russians. Hence, the Biobank is slightly enriched for more Estonian nationals. The cohort of gene donors follows quite closly the age and gender of the general population of the Estonia (Fig.1). There is a slight overrepresentation of women between 18 to 65 years and underrepresentation of women over 65 years and men in all age groups above 23 years of age. The first follow-up has recently started (www.biobank.ee).

We have followed the public opinion and awarness from 2001 until 2011 using the professional polling company TNS EMOR. The results demonsrate that the overall support ("yes" to the question "I am in favor of the Estonian Biobank idea") has increased from 18% to 55% during the past 10 years, whereas 2% to 4% were always against the idea of a biobank. The is relatively high proportion of the population (from 38% to 33% during 2001-2011) who answered that "they had never heard of the Estonian Biobank". Estonian Biobank had been publicisized by radio and TV broadcasts, mentioned in over 1000 news articles , and we held public lectures during this 10 year period. The lack of awareness despite procative publicity is important to keep in mind when planning to translate the results of the genome medicine to the health care practice as an important part of it involves educating the public.

### Rights and obligations

According to the Estonian HGRA ("Human Genes Research Act," 2000; Riigikogu, 2000) the EGCUT who is the chief processor of the Gene Bank (the Estonian Biobank) is to use the results of the

research conducted towards improving the public health. The HGRA stipulates the objectives of the Estonian Biobank (Table 1.).

Furthermore, the HGRA states that the gene donors have the right to know what information we have on them in the biobank. And if we deliver something it has to be accompanied by counseling as provided in §11 of the HGRA (Table 1.).

Therefore, the Estonian Genome Center is legally obliged to return and/or release results to the gene donors interested and ensure that counseling will be offered.

**What to return and how – this is the question?**

Over the past decade, the EGCUT has collected and generated a lot of data on the gene donors. This includes both non-genetic data from the questionaires as well as genetic data (30% have high density SNP array data used in GWAS analysis, 4% have gene expression data, close to 100 gene donors have full genome sequenced).

*Non-genetic data*

The latest version of the EGCUT questionnaire consists of 320 questions, and the data collected includes personal information, genealogy, health behavior, information on diseases and treatments, as well as anthropometrical measures. There are also some subgroups with clinical chemistry analysis (on 4% of the gene donors), NMR and MS/MS metabolomic tests (25% of the gene donors), 80% have filled the Munich Short Chronotype Questionaire, and 6% have filled the personality questionnaire NEO-Pi-3 the results of which can be explain and commented.

For example by performing a cluster analysis on the nutrition data we found that there is a cluster of gene donors who eat mainly sausages with a little bread and drink lots of soda. This group has the highest cardiovascular mortality (K. Fischer, personal communication). Another example would be from the clinical chemistry data where some relatively young gene donors have particular measurements of lipids or triclycerines and are close to the upper boundary of the reference value, but formally still within the “normal” range. However, if we look into the family history and there are early CAD events and the physical exersise load is neglible and diet is “caffeteria type“ then we could give an early warning signal based on the combination of the laboratory data, environmental and health behavioral information, and family history. This part is not very different from what physicians do today. However, what the donors seem to be most interested in, and possibly the reason they have joined the biobank in the first place, is genetic information. The EGCUT receives emails inquiring about genetic information available weekly.

*Genetic data*

What are the types of genetic data that can be returned today? The choices can roughly be classified into three groups: risk and predictive alleles, pharmacogenomics, and ancestry.

The **i**ntegrative **P**ersonal **O**mics **P**rofile (iPOP) approach taken by Chen et al. (Chen et al., 2012) is an extensive study demonstrating the capabilities of the omics approach. However, the data that the Estonian Biobank has is far less comprehensive, which limits our capabilities to use it for disease prediction. Nevertheless, using GWAS data one can find some alleles with much higher risk compared to the population average. For instance for glaucoma, there is a SNP indicating up to 10 fold increased risk for the individual with a certain genotype (Thorleifsson et al., 2007). It will not be difficult to check the intraocular pressure once per year and it could save the eyesight for a certain number of people. There are more examples like this, but genetic counseling must clarify, what these risks mean, that all is still based on probability, and some caution is necessary.

At this early phase of implementation of genetic medicine there exists substantial resistance from the clinicians with the argument that in many cases (e.g. hypercholesterolemia) clinical chemistry (glycose, lipids, triglycerides) and other nongenetic factors (age and gender) can tell as much as the genetic analysis. ROC analysis may have similar curves, but it is not challenging to predict rain when

the first drops are already falling. Whereas genetic testing could have predicted the same 25 years in advance, allowing for possible prevention or proactive monitoring.

Pharmacogenetics is probably the most potent field to benefit from the genomics data. There are several good examples where genomic information could be used and for many cases the FDA reccomendations are in place (FDA, n.d.). For instance, statin induced myopathy is relatively common, and has an odds ratio of 4.7 per copy of C - allele (noncoding SNP rs4363657) (Link et al., 2008). Polymorphisms in VKORC1 and CYP2C9 genes cause reduced metabolism of warfarin (Epstein et al., 2010).

Ancestry information is facinating the people more and more. Place like Estonia which has seen many conquerors during the last 1000 years hides most probably alleles from many current neighbours and people from more disctant places.

People are interested to know about their roots. “Am I related to someone from the *Knights of the Sword*?” and many variation of the theme are quite common questions we receive. Through principal component analysis the genetic map of Europe shows can separate sufficiently european populations to answer basic questions about ancestry (Nelis et al., 2009). However, although it might seem quite favourable to provide such information, one should be cautious in presenting results and not involve politics to promote racism, like it happened recently in Hungary (Abbott, 2012).

**Feedback mechanisms**

Besides the question of what to provide back to the participants, the question remains what mechanism or combination of mechanisms is the most appropriate for feedback of genomic information. Some of the options that have been mentioned include primary care practitioners, hospitals and specialists, or will the feedback of genomic information move beyond the medical community and be reachable to the public through alternative solutions similar to the Illumina application “MyGenome” for i-Pads. The latter option might be inevitable because the EGCUT is required to release genomic data if the participants express the wish for it. The participants could then upload the genotypic or sequence data on “MyGenome” or related applications, and they are free to explore the meaning of the data received. However, the law also stipulates a duty to offer counseling together with the genotypic data. If the analysis of the genotypic data leaves the hands of the EGCUT it will be increasingly hard to prepare the necessary members of the medical community who the gene donors might turn to.

EGCUT recruited gene donors through primary care practitioners. A unique network of 640 recruiters covering all 15 counties of Estonia was established specifically for that purpose. The network included 454 family physicians and 186 senior nurses or nurses. This means over half (56%) of the family physicians in Estonia have collaborated with the EGCUT through recruitment. This means that there is a group of family physicians who have shown interest in the project. Since the EGCUT is a research institution and not a medical institute, the EGCUT cannot start translating genomic information into clinical practice directly nor can the EGCUT start making referrals to specialists. The option for translating genomic information into practice is through the unique network of primary care practitioners who have collaborated with the EGCUT.

The EGCUT investigated the knowledge base as well as the perspectives and opinions of the recruiters regarding the use of genomic information in their practice (Leitsalu, Hercher, & Metspalu, 2011). Anonymous survey was sent to 130 family physicians collaborating with the EGCUT, 65 responded. Three themes emerged from the survey – eagerness to apply genomic information, disparity between the enthusiasm of using genomic information and preparedness to do so, and willingness to improve that knowledge base (96.3% - agree that a training program in genetics and genomics is necessary). Overall, a large majority of the respondents (96.4%) believe that predictive genetic testing will improve health care. This means that the EGCUT has a group of collaborating family physicians who can participate in a pilot project run by the EGCUT.

**What are others doing?**

Navigenics takes a cautionary route, where tests are ordered through physicians, whereas 23andMe interacts directly with the consumer (Pollack, 2010a). In the Coriell Personalized Medicine Collaborative, donors access their results through the Internet, and can also request genetic counseling, either

face-to-face or through the telephone. Approximately 15% of the donors have used the genetic counseling resources (Stack et al., 2011). There may be limits to accessibility: in the United States, an attempt to distribute genomic tests through the nationwide pharmacy chain Walgreens was stopped by the FDA (Pollack, 2010b).

Studies with large cohorts such as Decode project or Kaiser Premanente have hundreds of thousands of patients along with their health records. However, their primary focus is to find disease genes and improve drug treatments, rather than provide disease risks at an individual level. The Scripps Translational Science Institute provided subsidized Navigenics tests to over 3000 subjects (Bloss, Schork, & Topol, 2011), and found that although the subjects tend not to have test-related stress, there was limited value of the disease predictions when family history was available (Bloss, Topol, & Schork, 2011). However, a substantial proportion of the participants were employees of Scripps Health, and would be presumably more aware of their health histories, whereas a more general population may not have such knowledge or dialogue with their families. The Coriell Personalized Medicine Collaborative is another large-scale study that returns predictions for actionable diseases and drug responses (http://www.cpmc.coriell.org CPMC also work in medical profession (Gollust et al., 2012). In contrast, the Estonian Biobank is representative of the Estonian population because general practitioners recruited their patients. Therefore, EGCUT does not have the health-profession bias of other studies and may be closer to the true reactions/and realities of a general population.

**Future plans**

Currently, when calculating disease risks, we take published risk SNPs and build a model based on the EGCUT donors' phenotypes. We keep only those SNPs that fit our model on the Estonian population, thus the predictions have gone through a second layer of testing. We have enough donors and phenotypes to do so.

EGCUT plans to start providing results with a more conservative approach, by distributing results through general practitioners throughout the country. The situation in Estonia has several unique factors that can be taken advantage of when introducing genotypic data into health care system. Previously mentioned network of family physicians collaborating with the EGCUT is just one of them. Another factor is the existing infrastructure including the Estonian National Health Information System with electronic health records and electronic prescriptions, as well as the X-road, a platform for secure data exchange between all public databases. The goal for the EGCUT is to implement a central national health database that would be accessible to all physicians in Estonia.

This database would contain genomic data along with all other medically relevant information on the patient and could be used in medical counseling. When considering the translation of genomic risk predictions, the family physicians in Estonia will be like the gatekeepers to the Estonian health care system. This database, together with the risk predictions, could be used by them to be able to stratify patients and make necessary referrals in more of a proactive way (moving towards 4P medicine).

For these plans to succeed, not only are further developments necessary in the arena of research and the IT sector, but also the physicians as well as the public need to be more educated about genetics and genomics and the future of medicine (4P medicine). Some steps have already been taken by including the training of recruiters and a specific session on personalized medicine in the continuing education program for physicians. Again, there is a unique factor about Estonia – there is a single medical school. This means, that all physicians would receive the same education.

The vision for 2020 is to have 5000 individuals sequenced to develop a chip for genome based predictions specifically for the Estonian population – this will be used in clinical care like any other test currently used (MRI, ELISA test, clinical chemistry, X-ray etc.). There is a need to create a system where high-risk patients are being followed. Currently it is only possible to determine groups at high risk or groups who are highly protected for a disease, the large part of the population however still remains in the middle with a very heterogeneous genetic component that is currently too difficult to interpret.

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## Figures and Tables

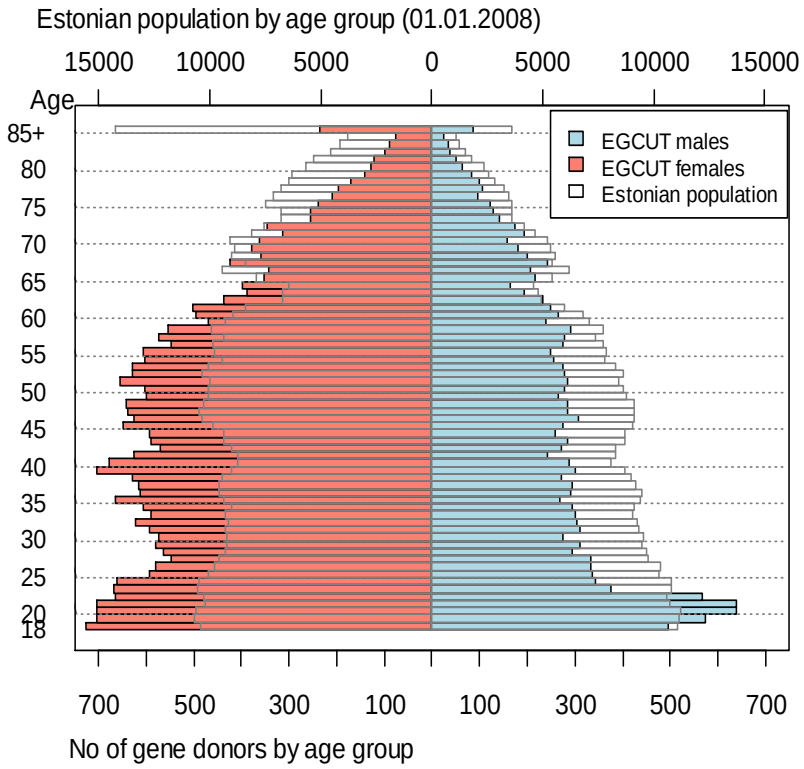


**Fig.1. Age and gender distribution of the participants at recruitment in comparison with the adult population of Estonia.**

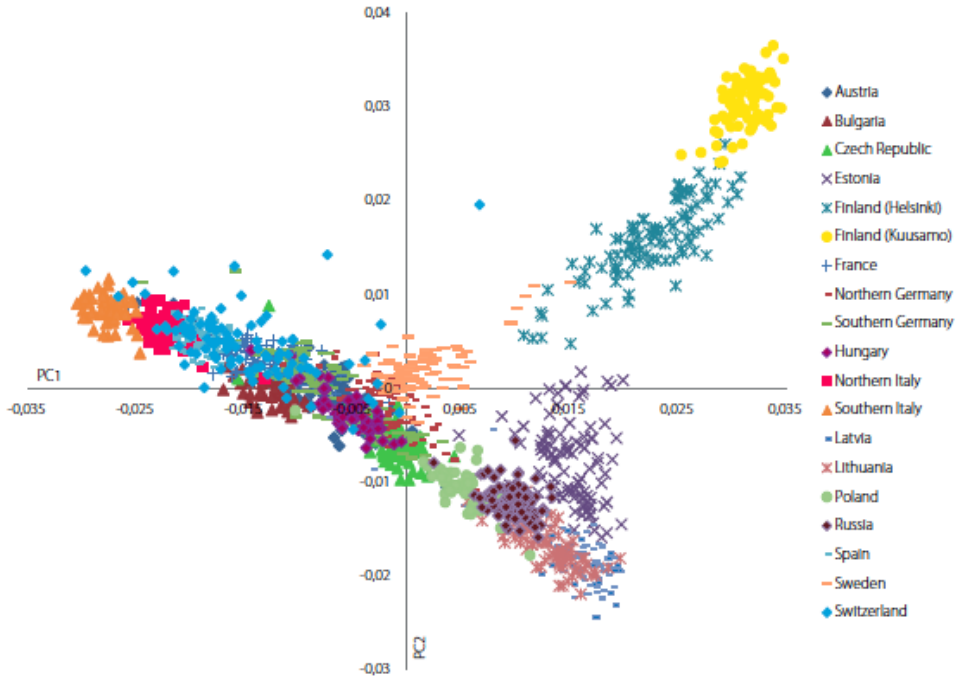


**Fig 2. European genetic map based on principal component (PC) analysis of the genetic distances between 19 European populations.**

Table 1. §3 and §11 of the Estonian Human Genes Research Act.

| | |
|---|---|
| **Chapter 1 General Provisions**<br><br>**§ 3. Chief processor of Gene Bank** | (1) The chief processor of the Gene Bank is the University of Tartu, whose objectives as the chief processor are to:<br><br>1) promote the development of genetic research;<br>2) collect information on the health of the Estonian population and genetic information concerning the Estonian population;<br>3) use the results of genetic research to improve public health. |
| **Chapter 2 Rights of Gene Donors**<br><br>**§ 11. Other rights of gene donors** | (1) Gene donors have the right not to know their genetic data.<br><br>(2) Gene donors have the right to access personally their data stored in the Gene Bank. Gene donors do not have the right to access their genealogies.<br><br>(3) Gene donors shall not be charged for accessing their data stored in the Gene Bank.<br><br>(4) Gene donors have the right to genetic counselling upon accessing their data stored in the Gene Bank.<br><br>(5) Gene donors have the right to submit additional information on themselves to the chief processor.<br><br>(6) Gene donors have the right to prohibit the supplementation, renewal and verification of descriptions of their state of health stored in the Gene bank. |

## Biographical notes

Professor of biotechnology at the University of Tartu, Estonia, and Director of the Estonian Genome Centre of the University of Tartu, graduated from the University of Tartu in 1976 as a physician, and was awarded a Ph.D. in 1980 on ribosome structure and function. He carried out postdoctoral studies (IREX fellow) at Colombia University (yeast mtDNA) and Yale University (snRNAs) in 1981-1982.

His main scientific interests are genetics of complex diseases, biobanking and microarray technology applications in research and diagnostics. He has published and co-authored over 180 papers and chapters in international peer review journals and books. His main contributions are in the field of the microarrays (APEX) and population-based biobanks (The Estonian Biobank www.biobank.ee), and human genomics including GWAS studies.

From 1986, he was Scientific Director and head of the laboratory of gene expression at the Estonian Biocentre of the University of the Tartu. He worked at EMBL, Heidelberg (1985 as a FEBS fellow), at MPI Molecular Genetics in West Berlin (1988 as an EMBO fellow) and at the University of Hamburg (1990-1991) as a DAAD fellow with the support of the EC. In 1993-1994, he was at Baylor College of Medicine, Houston, Texas, as a visiting faculty (Dept. of human genetics with Dr. T. Caskey) and 2000 at IARC (Lyon) as a recipient of the International Visiting Senior Scientist Award (genetic epidemiology). From 1996 to 2008, Andres Metspalu was also the head (and founder) of the Molecular Diagnostic Center of the Tartu University Hospital. He is the past (2006) president of the European Society of Human Genetics (ESHG) and current president of the EstSHG. He is one of the founders and directors (2002-2007) of the P3G consortium of biobanks. Since 2007 he is a member of the ScanBalt academy and was elected to the Estonian Academy of Sciences in 2010.

He is serving in several national and international committees, editorial boards and has received among other awards and honors the Order of the Estonian Red Cross 3rd Class and L'Ordre des Palmes Academiques from the Republic of France. (www.biotech.ebc.ee)