Belgian Advisory Committee on Bioethics

Opinion No. 45 of 19 January 2009
on human biological material banks intended for research

Request for an opinion of 20 June 2005
from a human genetics centre
on the use of DNA banks

Content of the opinion

The question put to the Committee

I. Introduction

II. The history of biobanks

III. Examples of current biobanks

IV. Description of biobanks

V. Legal provisions

V.1. At the European level
V.2. At the Belgian level
V.3. In some European Union countries

VI. The ethical issues

VI.1. Informed consent
VI.1.1. Samples taken specifically for research
VI.1.2. Residual parts of materials taken for a diagnostic or therapeutic purpose
VI.1.3. Information to be given to the patient
VI.1.4. Samples taken at the community level
VI.1.5. Samples taken from an incapable person

VI.2. Protection of privacy – confidentiality

VI.3. Property right to samples
VI.3.1. The question of who the owner is
VI.3.2. Sample storage and transfer
VI. 3.3. The right to know or not to know

VI.4. The biobank manager-custodian

VI.5. Access to biobank samples and data

VI.6. Biobank recognition

VI.7. Biobank financing

VII. Recommendations

The question put to the Committee

On 20 June 2005, the Advisory Committee received a request from two medical geneticists, expressing concerns about "commercial deviations as to the use of genetic tests in general and of DNA (desoxyribonucleic acid) tests in particular, as well as to the use of DNA banks (biobanks), which, in the domain of constitutional diseases,[1] are comprised of samples from patients suffering from rare or even very rare (orphan) diseases."

The Committee decided to take this request into consideration and entrusted to the 2006/2 bis commission a more general consideration of the ethical issues raised by banks (commonly called "biobanks") of tissues and by-products taken as samples and stored for research purposes.

I. Introduction

In this Opinion, the term "biobank" is taken to mean a structure which stores and provides human bodily (biological) material exclusively for fundamental scientific, clinical or applied research.

A recent Belgian law of 19 December 2008 on obtaining and using human biological material intended for human medical applications or for scientific research purposes[2] defines human biological material as any biological material, including tissues, cells, gametes, embryos and foetuses as well as substances which are extracted from them - in particular DNA - and regardless of their degree of transformation (see Article 2.1). Personal identification data (age, sex, date on and place in which the sample was taken) and/health data (diagnosis, treatment, developments) are usually stored in association with these human biological material samples.

This Opinion is only concerned with the collection of human biological material intended for academic research or applied research for commercial purposes. It does not deal with banks storing organs, cells or tissues built up for autografts or xenografts within the framework of a therapeutic application. Likewise, this Opinion is not concerned with collections of gametes or reproductive tissues intended for medically assisted procreation, or with banks of blood or constituents thereof intended for a therapeutic purpose. These other collections are the subject of specific legislative texts as well as of previous Opinions of the Advisory Committee.[3] Moreover, this Opinion is not concerned with the ethical issues raised by DNA banks set up and used for juridicial purposes.

---

[1] A "constitutional disease" is a disease or an anomaly due to a germinal mutation present as of fertilisation in all cells as opposed to diseases, such as for example most cancers, caused by somatic mutations occurring later in life and not affecting all cells. These constitutional disease-generating germinal mutations are in general - but there are exceptions - transmitted by one or both parents and are therefore hereditary.

[2] This law results from the proposal of Messrs Vankrunkelsven, Mahoux and Beke, Mrs Defraigne, Mrs Delvaux, Mrs Lanjri and Mrs Brotchi, adopted in the Senate on 18 July 2008 and sent to the Belgian House of Representatives in the form of a bill on 25 July 2008 (Doc. 52 1409/001). This bill was adopted in the Public Health Commission on 10 November 2008 and in plenary session of the House on 4 December 2008. The law finally adopted on 19 December 2008 (Belgian Official Gazette 30 December 2008) only differs very slightly and on formal details from the initial bill.

[3] See in particular the Opinion of the Committee No. 11 of 20 December 1999 on organ and tissues procurement in healthy living donors with a view to transplantation and the Opinion of the Committee No. 42 of 16 April 2007 on umbilical cord blood banks.

II. The history of biobanks

Biobanks have existed for a long time, in particular in the anatomical pathology and anatomy departments of hospitals, but also in natural history museums.
In the 19th century and in the first part of the 20th century, these collections were encouraged by the authorities. In this respect we can cite the edict of the Austrian authorities in 1813 encouraging the collection of tissues and anatomical parts.
These collections, comprised of autopsy parts and leftovers from biopsies taken for diagnostic examination, are sometimes very large. As an example, we can cite that of the School of Medicine of the University of Graz in Austria which has over 3 million samples, corresponding to some 800,000 patients. For its part, the collection of the Pitié Salpetrière Hospital in Paris contains approximately 10,000 brains collected post mortem over one hundred and fifty years, and the collection of the Bunge Institute in Antwerp (Belgium) has 3,000 collected since 1935.

Up until recent years, these samples, mostly fixed and encased in paraffin or another medium, were generally used for teaching and quality control, or to apply new techniques to confirm a diagnosis.

These collections have played a considerable role in the progress of medical science. A major part of the classification of diseases and, more specifically, the identification and classification of cancers, has been achieved thanks to the use of collections of tissues stored in anatomical pathology institutes.

In the last twenty years, progress in molecular biology and more specifically in genetics and proteomics,[4] has changed the nature of these collections. Current techniques, albeit within certain limits, allow the studying of fixed tissues, DNA, RNA and, to a lesser extent, proteins. The difficulties of this approach, however, have rapidly revealed the need for collections of fresh tissues, frozen shortly after they have been taken as a sample, in order to assure as perfect storage as possible. The evolution of these collections is impressive, but nevertheless they do not fully respond to the current needs of research and industry.

In the oldest tissue banks, anonymised samples[5] are most often only associated with a minimum of clinical data - age, sex, date on which the sample was taken, diagnosis - which limits their utility. One should not however deny their interest. The collections of skeletons, mummies and other human materials stored in natural science museums have enabled the living conditions of extinct populations to be determined and have advanced our knowledge of the history of mankind. These old collections have also enabled us to study not only the changes in the incidence of some pathologies over time (plague and syphilis for example), but also their presentation due to the development of effective treatments. More recently, analysis has enabled the detection of the presence of HIV (human immunodeficiency virus) in a sample collected in 1959 in Kinshasa, i.e. almost 20 years before the description of the disease in 1980, thus providing invaluable information as to the origin of the disease. Most of the time, however, samples are identified by a coding number. A coding key enables the donor patient to be recontacted, either so that the patient can benefit from progress in diagnostics or to enhance the database with new information requested by a researcher.

[4] Proteomics is the study of the proteins present in a cell or a tissue, with a view to identifying those which are specific to a pathology.
[5] To see what this notion of anonymised samples covers, see below point IV. Description of biobanks, last paragraph.

Besides such banks of tissues and cells, desoxyribonucleic acid (DNA) banks have been developed, initially comprised for the most part of samples taken from patients having disorders caused by one or a small number of genetic anomalies (Mendelian transmitted disorders), in order to obtain the material necessary for identifying the anomalies responsible for the disorder and with an essentially diagnostic or physiopathological objective.
These samples pose particular problems of confidentiality since they contain information concerning, *inter alia*, the state of health and the family or ethnic origin of the donor patient, and also data concerning the patient's close family or the social group to which he or she belongs. They are generally the subject of a coding procedure which ensures that the researcher who receives the sample does not know the identity of the patient.

III. Examples of current biobanks

Progress made in molecular biology has changed the very nature of biobanks. The samples accumulated have gained considerable value - on the one hand for the researcher and on the other for industry. For the researcher, these materials - tissues, cells, DNA - can enable the identification not only of the anomalies that are the basis of Mendelian hereditary diseases, but also of acquired (somatic) anomalies which play a role in numerous non-hereditary diseases, such as cancers, dementia and other degenerative disorders. These researches should enable more effective diagnostic tools and tests enabling the early detection of subjects at risk or even high specificity treatment tools to be developed.

The drug and health products industry cannot ignore this progress. As of now, diagnostic tests and treatment methods have been developed and have contributed to significant progress in the treatment of certain diseases, for example breast cancer and some forms of leukaemia.

These research studies require huge biobanks. This is why, alongside the scientific collections focused on pathology and often built up by one researcher or by a team of researchers, huge biobanks have been developed. The example of the 3 million samples of the Graz School of Medicine has already been cited above. In France, the Genethon biobank has 46,000 samples, in 2002 the biobank of the School for the Study of Human Polymorphism had 20,000, and in 2000 the biobank of the Lille Institute of Biology had 15,000. These collections are constantly being added to.

Moreover, we cannot ignore the DNA collections built up and managed by the legal authorities and the police. In the United Kingdom the "Police National DNA database" already has 4 million samples.

Other collections, mostly DNA ones, have been developed from particular populations.

A first example is provided by the "Icelandic Health Sector Database" the aim of which is to collect blood samples and medical data (which have been stored since 1915) from the entire population of Iceland, namely 270,000 people, mostly descendants of the Vikings who settled on the island in the 9^{th} and 10^{th} centuries. The isolation of this population and its highly homogeneous nature make it interesting for genetic studies. The objective is to increase knowledge about the respective roles of genetic predisposition and environmental factors in the pathogenesis of common diseases, e.g. cancer, cardiovascular disease, diabetes, etc. "The Act of Health Sector Database" defines the conditions according to which all medical files are entered on the database, unless the subject concerned has opted out.

The company "deCode Genetics" has obtained the exclusive use of this database for a period of 12 years. This company has entered into a research agreement with the pharmaceutical company Roche concerning the study of twelve common diseases. As part of this agreement, the resultant progress in treatment or diagnosis which is made will be offered free of charge to the Icelandic population.
The project has aroused criticism both from the Icelandic population and from the scientific community concerning the protection of privacy and the lack of formal consent (opting in). The risk of invasion of privacy by computer technology has also raised fears. The Icelandic authorities, however, feel that formal consent is not necessary since the data collected is seen as anonymous, or at least non-identifiable without major effort, and it is used in the interest of the community as a whole. In order to protect privacy, Article 14 of the agreement prohibits the provision of data concerning individuals. Only data concerning groups of subjects can be collected.[6]
Another concern raised by the Icelandic population and the scientific world was the freedom to access the data. The agreement between deCode and Roche constitutes an obstacle to the possibility of other researchers accessing the information on the database. Whilst the Icelandic authorities exercise control over deCode, they have not done so over the indirect users.

Within a similar study, namely the study of an isolated population whose genealogical tree is known, in 2000 an Australian scientific company initiated the collection of information and blood samples of 900 inhabitants of Norfolk Island in the Pacific Ocean. Two thirds of the inhabitants of this small volcanic island are descendants of Fletcher Christian, of his eight Mutiny-of-the-Bounty companions and of their Polynesian wives, exiled in 1856 to the island by the British government. Studying this highly genetically homogeneous population, scientists hope to identify the genes which play a role in the development of hypertension. The island's government refused an initial study proposal asking questions about the ownership of the information obtained, its control, the respect for privacy and the fear that the inhabitants might be considered to be guinea pigs. Their subsequent change in attitude was based on general interest, and more specifically the interest of the population to be studied, in terms of health.[7]

Other studies of populations are either in progress or being planned.[8]

As an example we may cite the Estonian Genome Foundation Human Genes Research Act 2000 the objective of which is to regulate the creation and operation of a biobank comprising the medical files and DNA samples of a portion of the Estonian population. The DNA is donated voluntarily and the confidentiality of the data is assured by the law so as to prevent infringement of privacy. To date, over 10,000 volunteers have been recruited. The Estonian authorities consider these databases to be a resource to be marketed.

The UK Biobank hopes to store data and blood and urine samples for 500,000 subjects, to be selected from the age range of 40-69 and monitored for 30 years, in order to study the impact on health of environmental, lifestyle and hereditary factors. This public initiative started in 2006 under the control of an independent ethics committee and an Ethics and Governance Council.

---

[6] B. Godart, J. Schmidtke, J.J. Cassiman and S. Ayme, "Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits - A professional perspective", *European J. of human genetics* 2003, suppl 2, S88-S122.

[7] F. Manni, "A qui appartient votre DNA? ", *Le Monde Diplomatique* June 2008, pages 1, 18-19.

[8] For an overview see B. Godart et al., footnote no. 6.

In Belgium, the Flemish government has announced its intention to allocate funds to the setting up of a clinical data and human biological materials bank called "BioBank Vlaanderen". This biobank will be made available for academic and industrial research (Belga - 23/09/2008).

This enormous mass of material is obviously arousing the interest of researchers and also of industry. The latter has no direct contact either with patients or with the population, except perhaps through the pharmacogenetics parts of clinical trials. Hence it is keen to have access to these biobanks for its research programmes. An example is provided by the interest in the deCode Genetics' database which groups together the samples and the data for the Icelandic population.

If we are not careful these huge collections could become tools of power. They are, in any event, of great intellectual value, capable of being exploited and potentially the source of financial value.[9] A collection of human biological material, even a modest one, taken from subjects suffering from rare diseases, may elicit commercial interest, and the danger of a transfer or a sale on the national and international markets at the expense of disinterested scientific research is not negligible. At the ideological level, one can envisage the risk of biobanks being built up from samples taken from subjects characterised not by their state of health but by certain behaviours or lifestyles, with the possible consequences of this material and the related data being used for abusive or discriminatory purposes. Finally, internationally, the use of the genetic data of the population of a country could appear to be an exploitation of the donor subjects with a zero or modest return for the country or research, as this seems to be the case for the Icelandic biobank.

Furthermore, we must emphasise the interest which such data can represent for insurance companies and police investigation departments.

IV. Description of biobanks

The collections of biobanks differ depending on the *nature of the materials* from the human body which are collected, on the *procedures* used to guarantee privacy, and on the personal data associated with the samples.

The samples, formerly organs, are today most often coated or frozen tissues, frozen or cultured cells, blood samples, urine samples or other liquids from the human body, or DNA samples taken from these different materials. DNA has the advantage of requiring a simple preservation procedure by refrigeration which is available in all laboratories. However, the storage of tissues and cells requires expertise and appropriate equipment.

In the past, for example thirty years ago, patients who died in the major hospitals were autopsied almost automatically. Samples of some of their organs were taken and kept, generally for teaching purposes. The change in opinion, formalised by laws concerning the protection of privacy and resulting from some scandals which have been widely covered by the media, have altered this situation. We recall, amongst others, the collection of foetuses of the Saint Vincent de Paul Hospital in Paris kept in formaldehyde jars. More recently, six

[9] See Opinion No. 77 of the French CCNE: "Problèmes éthiques posés par les collections de matériel biologique et les données d'information associées: "biobanques" "biothèques"", available on http://www.ccne-ethique.fr/

hundred children's organs, collected without consent from and even without the knowledge of the parents, were discovered in an anatomy laboratory in Great Britain.[10]

At present, the materials collected come mostly from tissues sent for diagnostic tests or from tissues resected during a surgical procedure. A part of these materials is *used for the diagnostic examinations for which they were taken*. The surplus is kept for the purpose of enabling additional examinations if the initial diagnosis is not certain or if it is questioned on the basis of new factors. It is these tissues which today constitute the basis of the biobanks developed in the anatomical pathology institutes. *Their secondary use* is to constitute a reservoir of human body materials intended for researchers. If a researcher wishes to have samples of colon cancer, for example, he or she can, by using the biobank, obtain them quite quickly. However, if the researcher has to collect this sample *de novo*, this can take time and make his or her research project difficult.

Until recent years, these collections were made without the knowledge of the parents, or even of the community. Protection of privacy was routinely guaranteed. The samples and their related data were essentially identified by a number, generally a sequential number following the order in which they were received by the laboratory. In addition there was a concordance list enabling the connection to be made between the number of a sample and the identity of the patient. This concordance list is not generally directly accessible to the researcher who receives a sample.

In the meantime, the sociological context has changed considerably. The inviolable nature of the human body and the rights of privacy and to autonomy have become essential values of our societies. They have been formalised in a series of international and national laws, declarations and directives. It emerges from these that the patient should be informed of what will happen to the samples taken and how the residual portions of samples will be used for research purposes. This use is conditional upon either the lack of opposition (opting out) by the patient or by the obtention of formal consent (opting in) from the patient.
This point is discussed further below.

It is important to distinguish clearly between the following categories of samples:

1. Human biological material or organs which are taken as samples for treatment purposes, such as umbilical cord blood stem cells, red bone marrow, some peripheral blood cells and organs for transplantation. This category is not dealt with by this Opinion.

2. Surplus tissue or other materials taken as samples for diagnosis. In this category, we can distinguish between samples stored in anatomy and anatomical pathology departments essentially for teaching purposes and the samples intended for research. This category also includes blood samples taken at birth for diagnosing metabolic disorders and stored in genetics centres (see Opinion No. 25 of 17 November 2003 of the Belgian Advisory Committee on Bioethics on the storage

[10] D. Sicard, *Le Monde* of 26 February 2008. For the report from the inquiry commission put in place further to this scandal see "Royal Liverpool Children's Inquiry Report". London: Stationery Office, 2001, available on: www.rlcinquiry.org.uk/. See also J.L. Burton & M. Wells, "The Alder Hey Affair: Implications for pathology practice", *J. Clin. Pathol.* 2001, 54, pages 820-823.

period for blood cards and the confidentiality of data concerning the screening of congenital metabolic anomalies).

3. Samples of human biological material taken specifically for research.

4. Collections of human body materials, mainly DNA, built up for juridical reasons. This category is also not dealt with in this Opinion.

The stored human bodily materials are further distinguished by the nature and the form of the related personal data. The objectives of research implicitly require information concerning the donor and his or her pathology.

In this respect, three situations may be considered:

1. Where the sample of human tissue is only associated with basic data which does not allow the patient to be identified and therefore additional information concerning him or her cannot be obtained later on. This will frequently be the case for samples associated with a minimum amount of data, such as age, sex and the pathology of the donor. In this case we can speak of ***anonymous*** or more precisely ***anonymised samples.***
2. Where the samples are identified by a code. The identity of the subject and his or her personal details are accessible to the person who has the concordance list showing the code and the name of the patient. This is a case of ***coded samples.*** This is the method that is used most frequently today. Indeed, when collecting samples, it is difficult to predict what use will be made of them and, hence, what personal data will be necessary for the research to be undertaken. The researcher wishes to have the possibility of being able to return to the patient's file if he or she needs to supplement a database, depending on his or her needs. In some cases, in particular in genetic studies, double coding is used. The sample then bears a code which refers to a second code kept by a third party who, in turn, can give access to the identity of the donor or to his or her personal data.
3. Where the researcher who has access to the tissues can identify the donor subject and access his or her personal data directly we speak of ***identifiable samples***.

V. Legal provisions

Until recently there was no Belgian legislation or European Directive that dealt specifically with banks of human biological materials intended for scientific research. However, some legal provisions dealt with collections of human biological material taken as samples for the purposes of transplantation or human treatment.

V.1. At the European level

At the European level, we must cite:

European Directive 2004/23/EC of 31 March 2004 on the setting of standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and

distribution of human tissues and cells. In Article 12(2), paragraph 2, this Directive recommends that:

> "Member States shall endeavour to ensure that the procurement of tissues and cells as such is carried out on a non-profit basis".

European Directive 2006/17/EC of 8 February 2006 which implements the aforementioned Directive as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

Finally, European Directive 2006/86/EC of 24 October 2006 which concerns traceability requirements, notification of serious adverse reactions and events, and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

However, these three directives are essentially concerned with tissues and cells intended for *treatment purposes.*

V.2. At the Belgian level

At the Belgian level, other than the Law of 13 June 1986 on the sampling and transplantation of organs and its implementing decrees,[11] we must cite the Royal Decree of 23 December 2002 on the procurement, preservation, preparation, importing, transport, distribution, and delivery of human tissues as well as on human tissue banks. With a content very similar to that of the aforementioned European Directive 2004/23/EC, this Decree lists the recognition criteria and the quality requirements for human tissue banks. This Decree was voided by Decree No. 141137 of 24 February 2005 of the Council of State for lack of legal basis.[12]

It is appropriate now to examine in detail the Belgian Law of 19 December 2008 *on the procurement and use of human biological material intended for human medical applications or for scientific research purposes* since, once it enters into force, this Law will constitute the basis for the new regulatory corpus on this subject.[13]

This Law reproduces most of the elements of European Directive 2004/23/EC. As with the French law on this subject, ***the Belgian Law applies*** to the donation, sampling, procurement, control, processing, preservation, storage, distribution and use of human biological material intended for diagnostic or therapeutic applications in humans and also for scientific research purposes, including the sampling of stem cells and all operations carried out on bone marrow, peripheral blood, umbilical cord blood, embryonic cells, etc., regardless of their origin. The only samples and actions excluded from the scope of this Law are the samples of organs taken with a view to transplantation (as provided for by the Belgian Law of 13 June 1986 on the sampling and transplantation of organs), the operations carried out with blood and blood by-products (as provided for by the Belgian Law of 5 July 1994 on blood and human blood by-products), the sampling and the operations carried out with

[11] The Royal Decree of 15 April 1988 on tissue banks and the procurement, preservation, processing, importing, transport, distribution and delivery of tissues.

[12] Further to this cancelation, the Royal Decree of 15 April 1988 has been reapplied. As this Decree essentially targeted organs, tissues and cells collected for treatment purposes, the status of these bodily materials, if stored for research purposes, remains in a legal haze.

[13] For the Law of 19 December 2008, see footnote 2 *supra*.

human biological materials with a view to autologous use within the framework of one and the same procedure, and donations and operations carried out with an exclusively diagnostic objective to benefit the person from whom the material has been taken (see Article 3).

The text of the Law provides that ***any sample of human biological material*** intended for human or research application must be ***taken under the responsibility of a doctor*** in an approved hospital (see Article 4). No material advantage or compensation for costs or loss of income may be offered in exchange for the donation of human biological material. All of the operations must be carried out on a non-profit basis (see Article 6).

The human material bank must be used by an approved hospital as stipulated by the Belgian Law on Hospitals of 7 August 1987 ***or by*** a hospital run by National Defence ***or by*** a university with a fully operating faculty of medicine which uses a university hospital (see Article 7.1).

The human biological material banks and the intermediary structures (namely the organisations which carry out processing, preservation, storage and distribution of human biological material in collaboration with a human biological material bank - see Article 2.25) must be the subject of an ***approval*** by the Minister of Public Health. The King lays down the recognition criteria, the quality and security standards as well as the operating methods to which the said banks must conform (see Article 7.2 and 7.3).

Article 8.1 of the Law prohibits ***sampling*** and any operation on human biological material which is not carried out ***for a specific,*** scientifically founded, ***preventative, diagnostic or therapeutic purpose*** or for a specific and relevant scientific purpose which has been specified.

In these different provisions, the Law makes no distinction between banks for therapeutic purposes and ones set up exclusively for research purposes.

However, as regards the ***consent of the donor****, the legislator has laid down different rules*. Indeed, Article 20.1 provides that: "for any secondary use of human biological material, i.e. a use other than the one for which the material has been taken as a sample, explicit consent must be obtained beforehand by the manager of the bank whereas point 2 of this Article specifies that "for the use of residual human biological material for scientific research purposes, the consent is deemed to have been given as long as the donor or a person competent to give his or her consent has not communicated prior to any operation carried out with this residual human biological material, their refusal to the doctor who has taken the sample or to the head doctor of the hospital. " Moreover, Article 21 provides that: "Any form of secondary use of the human biological material, as well as the specific objectives of this, must be the subject of a prior favourable opinion from an ethics committee which fulfils the provisions of Article 2.4 of the Law of 7 May 2004 on experiments on humans ".

Chapter VI of the Law, in Article 2.27, specifically concerns the provisions related to ***"biobanks"*** which are defined as ***"the structures which assure the storage and the provision of human biological material, exclusively for scientific research and which is not intended for any human application"***. The objectives, purposes and activities of each biobank must be the subject of a favourable opinion from an ethics committee as stipulated by Article 11.3.2 of the Law of 7 May 2004, i.e. in practice one of the ethics committees authorised to hand down an opinion concerning a human research protocol. The same applies each time human biological material is made available by a biobank, unless the material is intended for *in vitro* research or research into animal

experiment models (see Article 22.1). Finally, Article 22.2 requires the biobank to keep a register on the nature of the human biological material the storage and provision of which it assures, as well as on its origin and its destination.

Under Article 22.3, it is the responsibility of the King to lay down "the list of articles of the Law which are applicable to biobanks intended for scientific research purposes and to the human biological material the storage and/or provision of which they assure. He may stipulate a modified system which caters for the specific features of biobanks".

Some aspects of the ***creation and operation of biobanks must meet the requirements of other legal provisions***, such as the Law of 8 December 1992 on the protection of privacy in respect of the processing of personal data and its implementing Royal Decree of 13 February 2001, the Law of 22 August 2002 on patients' rights in respect of information and consent and, finally, the Law of 7 May 2004 on human experiments.

V.3. Some other European Union countries

Some other European countries have legislative texts or recommendations on tissue banks intended for research purposes. This is the case, *inter alia*, of the United Kingdom and France.

A few years ago, *the United Kingdom* was faced with the discovery in anatomical pathology departments of collections of children's organs and tissues, stored after autopsies without the knowledge of the parents.[14] These practices, considered acceptable by most pathologists, justified the adoption of the "Human Tissue Act"[15] in 2004 in England and the "Human Tissue (Scotland) Act"[16] in 2006 in Scotland and the putting into place of the "Human Tissue Authority".[17] The mission of this authority is the recognition of tissue banks and the control of their operating practices. Its activity covers a very wide domain including the use of tissues and cells for transplants, teaching, clinical audit and research as well as the practising of autopsies and anatomical examinations.

The "Human Tissue Act" stresses the necessity for consent before the storage of tissues and their related personal data, whether the tissues are taken from a living or a deceased subject. It also stresses the importance of confidentiality, particularly in the case of genetic studies. So as not to create difficulties for existing collections, particularly those of anatomy departments, these rules are not applicable if the samples are taken from subjects that have been deceased for more than 100 years.

This Act also permits the use of samples collected before the "Human Tissue Act" came into force, namely on 1 September 2006, if they are anonymised.

Some literature however does stress the difficulty of applying these recommendations and, more specifically, the difficulty of obtaining consent and of informing donors of the possible uses of the materials already collected. We will return to this point in the next section "The ethical issues".

---

[14] See footnote 10 *supra*.
[15] Available at http://www.opsi.gov.uk/ACTS/acts2004/ukpga_20040030_en_1
[16] See http://www.opsi.gov.uk/legislation/scotland/acts2006/asp_20060004_en_1
[17] See http://www.hta.gov.uk

In France, from 1996 to 2004 there was legislation on collections of tissues and derived substances, with a restrictive definition of these terms, namely a set of samples taken for genetic research purposes from a group of persons selected in accordance with clinical or biological characteristics. There were also other provisions concerning other types of collections. The Law of 6 August 2004 on Bioethics[18] unifies the different requirements referring to human bodily materials without making further reference to collections and without making specific rules for genetics. It regulates use for research, transplantation, medically assisted procreation, and genetics.

These legal provisions provide for the notification as regards the action of collecting, the authorisation for the act of transferring collected bodily materials, and the authorisation for the import or export of human bodily materials. The notification of collection is required to be renewed every 5 years.

[18] Since this Law of 6 August 2004, the general principles relating to the donation and use of human body materials are set out in Articles L.1211-1 to L.1211-9 of the Public Health Code. See the website: http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000441469&dateTexte=

VI. The ethical issues

The ethical issues raised by biobanks are based on the very nature of these collections which associate on the one hand human body materials, some of which might permit genetic studies, and on the other hand personal data, including data relating to health, such as is defined in the law on the protection of privacy. These aspects have already been partially considered above when describing the different types of biobanks.

VI.1. Informed consent

In this respect we need to distinguish between materials collected specifically for research and the residual parts of samples taken for diagnostic or therapeutic purposes.

VI.1.1. Samples taken specifically for research

If samples are taken specifically for research, **formal written consent** is required for the collection and storage of the human materials and the related personal data, especially since these materials are not collected with a therapeutic or diagnostic purpose which is in the direct interests of the patient. This obligation results from the fundamental ethical principles concerning the rights of subjects participating in research, rights which are summarised in Article 11 of the Declaration of Helsinki:

> "It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy and confidentiality of personal information of research subjects. ".

Identical provisions are found in European Directive 2001/20/EC of 4 April 2001 on the adjustment of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use and in the Belgian Law of 7 May 2007 on human experiments.

The consent must be informed. The subject must be informed fully of the conditions in which the samples and the data will be collected. He or she must know the nature of the associated personal information and the storage period. He or she must be informed of the use which will be made of his or her samples and personal information.

The British, Swiss and Swedish regulations provide that the subject has the right to stipulate a specific or extended use of his or her samples, for example, for research into breast cancer, into cancer in general, or medical research in the widest sense. He or she may record his or her opposition to certain uses, for example, genetic studies dealing with behaviour or with the psyche, or even to commercial use of the samples.

Whilst the Committee stresses the importance of defining these terms and conditions at the time of the initial consent, it also appreciates the difficulty of listing them exhaustively at that time. Indeed, the life cycle of samples, particularly of DNA, is long and it is difficult to predict today the studies which could be of interest tomorrow, or in 10 or 20 years. Experience also teaches us how difficult it is to re-contact the donor subjects. Accordingly, some members of the Committee propose, where the donor does not respond or is dead, that tacit agreement ("presumed consent") be assumed, by analogy with the law on organ donation, as long as the subject has not previously opposed a wider use than the one initially specified of his or

her samples and personal information; in these circumstances however a new opinion from an Ethics Committee concerning this research would be necessary. Whilst this position simplifies the work of researchers, other members of the Committee favour protection of privacy and an obligation to obtain formal consent from the donor, at the time the sample is taken, to the different possible uses of his or her samples and personal information. Failing this, a new agreement seems necessary to them for any research project not initially specified. Finally, other members advocate the possibility of the use without consent of very old samples, for example those dating back more than one hundred years, as provided for in the British regulations.

VI.1.2. Samples of residual parts of materials taken for the purpose of diagnosis or treatment

If the samples collected are the residual parts of materials taken initially for a diagnostic or therapeutic purpose, the necessity and the form of consent are influenced by whether or not the materials and their related data are identifiable.

VI.1.2. A. *The details of the donor are identifiable: formal consent*

If the details of the donor are identifiable, formal consent, within the terms and conditions described above, seems to be recommended both from the ethical and from the legal standpoints.[19] This necessity for consent exists, whether identification is direct or indirect and whether it is limited or not to an easily identifiable and small group, such as an ethnic minority, certain districts of a town, etc. This is even more to be recommended when the subject of the research and the nature of the group studied could lead to the stigmatisation of the donor.

For the Committee, the use of identifiable samples for research purposes must remain the exception.

VI.1.2.B. *The samples and data are anonymous or anonymised: potential use without opposition at the time the sample is taken or even without condition*

Where the samples and data are anonymous, or anonymised when collected, the literature is divided on the necessity or not of formal consent. Some defend the idea that these are materials which, if they were not introduced into a biobank, would be destroyed as waste. In this situation, some members of the Committee defend the idea of the possible unconditional use of these samples. However, the Advisory Committee stresses the fact that there is a difference between the potential destruction of material that has become useless and its use for reasons other than those for which it was taken as a sample. Hence, other members of the Committee recommend that, at the time the sample is taken, the subject must at least be warned of other potential uses of the sample that he or she may oppose.[20]

Anonymisation or irreversible coding, if it meets the concerns for confidentiality, deprives the donor subject of the possibility of withdrawing his or her consent and requesting the destruction of his or her samples, or even of checking and potentially correcting the personal data collected (as provided for by the Law on the protection of privacy). There is hence a

[19] By virtue of the Law of 8 December 1992 on the protection of privacy in respect of the processing of personal data.

[20] See L. Glantz, P. Roche and G. Annas, "Rules for the donations to tissue banks – what next?", *New Eng. J. Med.* 2008, 358, 298-303.

loss of the individual's right of control over the samples taken from his or her body and over the related data.

Anonymisation which does not enable a connection to be established between samples and the data collected at different times or in different places from the same individual can lead to a biobank being contaminated by duplications. This is why the materials in the biobanks are rarely anonymous, with the exception perhaps of the oldest collections. Anonymisation in fact limits the related data and prevents any monitoring, thus considerably restricting the possible studies.

VI.1.2.C. *The materials in the biobank are coded: formal consent versus unconditional use, deferred consent, or right to oppose*

Most of the time, *the materials in a biobank are coded*, according to the methods described previously. As coding, as strict as it may be, always entails a risk of the subject , in this case most often a patient, being identified, **formal written consent** obtained following the same rules as those described above for samples taken specifically for research seems to be justified. Some authors stress the fact that it is easier to obtain consent and to inform the patient of the possible faults of data protection than to guarantee absolute security, if that is at all possible.

However, practice shows the difficulty of obtaining such consent. The patient's information concerning diagnosis, treatment options and resulting treatment plans is a priority. The doctor must obtain consent on these different points, including the performance of a biopsy and the taking of samples. Hence, there is very little time during the consultation to obtain consent concerning the collection of samples and data for a biobank. The circumstances are hardly favourable at a time when the patient is concerned about his or her health problems. Moreover, in the minds of patients, the notion of biopsy is strongly associated with that of cancer.

This is why, on the basis in particular of the Swedish experiment reported by M.G. Hansson, [21] we can consider several possibilities:

First option: deferred consent. Samples are taken and the patient is given two months to give his or her approval. If the response is negative, the samples are destroyed.

Second option: in some circumstances, the hospital's ethics committee could authorise the use of samples and of some data without consent. The justification, according to the author, would be the security of the patient, a therapeutic exception in some way, when the patient's information would incur a serious risk for him or her.

Third option: **the right of opposition**. The information concerning the collection of samples for a biobank, its objectives and the operating mode would be widely disseminated. Similar to the rules stipulated for organ donation in Belgium, patients who had not expressed their opposition would be considered as having given their consent to the use of their samples and personal data for research. This procedure is based on the repeated observation, both in Sweden and in the United Kingdom, that almost all patients (over 80%) agree and that negative responses are exceptional.

[21] M.G. Hansson, "For the Safety and Benefit of Current and Future Patients", *Pathobiology* 2007, 74, 198-205.

These indirect procedures have the disadvantage, *inter alia*, of not requesting the patient's consent as to the use which may be made of his or her samples. In such an approach, the donor is no longer treated as a fully fledged partner in the research programme.
Note, however, that the British "Human Tissue Act" requires formal written consent in genetic studies which are likely to have repercussions not only for the donor subject but also for his or her family circle or even the social group to which he or she belongs.

As a result, some members of the Committee recommend the third option, namely the right of opposition after wide dissemination of the objectives of and the ways in which the biobank operates. The argument according to which surplus body materials are donated with the aim of contributing to progress in research and to the welfare of society, underlies this position.

Incidentally, this was the solution taken in *the Belgian Law of 19 December 2008* (see footnote 2 *supra*) which provides for the right of opposition only when a secondary use is to be made of human biological materials taken initially as samples for diagnostic purposes (see Article 20).

On the other hand, other members of the Committee think that a "right of opposition" is not sufficient and that informed consent regarding the use of biological material for a diagnostic and/or therapeutic purpose *cannot* be interpreted as an implicit authorisation to use that material for research purposes. These members are of the opinion that the authorisation to use material for research cannot be implicit but, to the contrary, must *be given explicitly* by the person from whom the material is taken. Consequently the person concerned must receive clear, exhaustive and comprehensible information on the reasons why it might perhaps be desirable for his or her material to be used for research purposes. On the basis of this information, and after having the opportunity to ask questions, the interested party must be able to decide whether or not to agree to the use of his or her material for research, with the option potentially being available to distinguish between, on the one hand, use for research purposes concerning the disease or diseases from which the donor suffers (if any) and, on the other hand, use for scientific research in general. If the person concerned is also being treated - with medical treatment and scientific research therefore being able to be combined - it is appropriate to explain clearly that a potential opposition to the use of the material for research purposes will have absolutely no influence on the treatment to be given to the person. Thus one may avoid giving the impression that the scientific research is being disguised in the form of medical treatment in order to obtain the agreement of the person concerned.

These members feel that the arguments according to which the asking for consent for use of material for research requires too much time, is too challenging from a logistics point of view or poses other practical problems, are not justified, given that *in all cases where the biological material sample is taken for diagnosis and/or treatment, at the moment when informed consent is requested for sampling for this purpose, consent may also be explicitly requested for use of the material for research purposes* (provided that the interested party is advised that use for research is possible or may in future be considered).

In this way, each sample can be assigned a code when it is taken, which clearly shows if the interested party:

- has not given his or her consent for the use of the material for scientific research (for example a code starting with or ending in A); or
- has given his or her consent for the use of the material for scientific research in general (for example a code starting with or ending in B);

Admittedly, we note that in some countries a large majority of the persons concerned are not, when asked, opposed to giving their authorisation to use material for research. However, one cannot assume that everyone will agree.

The argument according to which the refusal of some will compromise scientific progress is also not convincing, just as with the point of view according to which all potential morality - based reservations are no longer convincing when we ensure anonymity or coding of the material so as to offer solid guarantees in terms of respect for privacy.

Indeed, none of the three aforementioned arguments takes account of the ethical basis for the requirement for informed consent: respect for autonomy. Each person has values which translate into aspirations and life plans. These values may conflict with the working methods and/or the objectives of certain types of scientific research. When scientists think that they have valid reasons to use biological material for research, they are fully entitled to explain to the person concerned just why the research is crucial and why his or her contribution (via the provision of the material in question) is of the utmost importance. However, this does not give scientists the right, in place of the interested party, to take the decision to use the material. *The person concerned must have the possibility of checking whether the proposed use of the material for research is contrary to his or her moral values.* If this possibility is taken away from him or her in order to take the decision in his or her place, "in the interests of science", the material is being used to achieve an objective which is not his or her own and, consequently, the decision violates his or her dignity.

Another argument is that failure to respect the requirement for informed consent, as described above, is likely to damage very seriously the trust of the population, both in medicine and in medical research.

For these members*, it is therefore perhaps legitimate to expect that citizens wish to contribute to progress in research, but one should not force this contribution by assuming consent instead of asking for it*. It is fitting to inform citizens of the value of research and encourage them to contribute - but this does not authorise using biological material for research "in the name of science" without the person concerned having been informed or his or her explicit consent having been obtained.

VI.1.3. Information to be given to the patient

Finally, as regards the **extent of the information** to be given to the patient, the Committee shares the concerns discussed below expressed in the judgment handed down in the case of "Moore v Regents of the University of California" by the Supreme Court of the State of California. This judgement held that "physicians have a fiduciary duty to patients". This duty implies in particular that a physician must communicate all the important factual elements for the patient's decision (e.g. the decision to have a biopsy performed), because the personal interests of the physician may influence his or her professional judgment.

Consequently, the Court held as follows: (1) a physician must disclose personal interests unrelated to the patient's health, *whether research or economic*, that may affect the physician's professional judgment; and (2) a physician's failure to disclose such interests may give rise to a cause of action for performing medical procedures without *informed consent* or breach of *fiduciary duty*.

A physician who *treats* a patient in whom he also has a *research interest* has potentially conflicting loyalties: according to the Court, he must then provide the patient with information concerning this research.[22]

VI. 1.4. Samples taken at community level

When a biobank processes samples and/or data collected within a community, or even when the subject of the research is likely to have repercussions for this entire community, the researcher and the manager of the biobank must obtain the consent of the community, in addition to the individual consent of the tissue donors. This consent could be informal, for example by assuring that the projects have widespread publicity in the media, thus giving the population the possibility to express its reserves. It could also be requested from the political authorities. In the studies undertaken in Iceland, in Estonia and in Norfolk Island, it was actually the political authorities that gave their agreement and also their support to the realisation of the projects, whilst assuring widespread dissemination of information for the population. These authorities thus authorised the researchers, often private organisations as in the case of Iceland, to hold medical and genetic information concerning persons. This data gained the status of a form of collective property which the authorities believed they were authorised to manage in the interests of the community and of medical science more generally.[23] It should be remembered too that precautions were taken in the contracts with the researchers to assure the protection of the privacy of individuals.

VI.1.5. Samples taken from an incapable person

If health problems justify research into genetics or proteomics in the foetus, a child or a *de facto* incapable person, particularly one with dementia, the members of the Committee consider that consent must be obtained from the legal representative, as defined in the Belgian Law on Patients' Rights of 22 August 2002. Given the particularly sensitive nature of the data collected and the research carried out, some members would like the consent of the legal representative to be confirmed if the donor subject becomes capable, for example when a child donor reaches the age of 18. Others insist that the collection of materials and data from those patients incapable of giving informed consent be limited to research into diseases which are not found in capable subjects or which cannot be carried out on materials provided by capable subjects. This is in particular the case for research carried out on foetal tissues. In this case, however, the material and the data could most often be anonymised.

VI.2. Protection of privacy - confidentiality

The size of the biobanks, the sensitive nature of the personal data collected, and the very nature of the samples are all features which justify as absolute protection as possible in relation to access to the biobanks' data. Biobanks which are based on large samples from the population, as is the case in Iceland and Estonia, can be interesting to the police, insurance companies and even large employers. They are tools for the epidemiological study of the genetics of populations. The samples and the data may also be used for purposes unfavourable to the subjects, for example, paternity tests carried out purely out of curiosity

[22] Moore v Regents of University of California, 51 Cal. 3d 120, 134 (1990). See also *infra* point VI.3.1.
[23] F. Manni, op cit. footnote 7 *supra*.

and without the agreement of the different parties concerned and sometimes against the interests of the child.[24]

The infringement of confidentiality of his or her privacy is a major risk for a donor. On the one hand, the data associated with a sample may include specific information on his or her lifestyle, his or her race, profession, health, etc. and, on the other hand, DNA analysis may also provide information of which the patient is not necessarily aware. This risk today remains mostly theoretical. The relationship between genetic anomalies and polymorphism and the risk of disease is, indeed, only clearly established in Mendelian hereditary disorders. In other situations such as atherosclerosis, multiple sclerosis and diabetes, anomalies most often relate to several genes and are associated with an increased risk and not a causal relationship.

The progress made in analysing the human genome and the use of available data banks lead us to believe that in the near future there will be a more precise definition of which subjects are at risk of cardiovascular disease, diabetes or dementia, to only mention a few of the diseases most frequently found. We can also envisage on this basis identifying a greater or lesser susceptibility to certain toxins and drugs. We might thus detect the subjects at risk of occupational diseases and select the applicants for a job, thus interfering with the right to work.

Confidentiality is a major concern, addressed in the Swedish and English regulations, as well as encountered in the experience of already operational large biobanks.

The anonymisation of data has ethical implications: the impossibility of going back to the patient to let him or her benefit from potential progress in diagnostics, to assure monitoring of the development of his or her disease and his or her response to treatment, to enable the patient to exercise his or her right to withdraw his or her consent, and to request the destruction of samples or to correct his or her personal data.

The solution agreed on almost unanimously is coding. For maximum security, some propose that the coding of samples and that of the associated personal data be distinct so that the data can only be matched with the samples via a trustworthy third party who can enable the relationship between the patient's identity and the samples to be established. This triple coding enables almost absolute confidentiality to be assured, as long as the coding keys are not kept by one and the same person. In this regard, the Committee does not consider it desirable for the third party to be the manager-custodian of the biobank and recommends that the management of samples of human cells and tissues be by persons who are independent of each other.

The medical ethics Committee of the institution which manages a biobank has a major role to play in controlling this coding procedure, and one could consider that it alone can define the circumstances, which must remain the exception, where the identity of the patient can be matched directly or indirectly with the samples and define clearly the limits of this relationship, such as for example by enabling specific data to be extracted from the medical file. It is also appropriate to define which researchers can benefit from this exemption - researchers who must be bound by professional secrecy. The Belgian National Medical

[24] On this point, see the Opinion of the Committee No. 37 of 13 November 2006 on the use of DNA tests to determine parentage.

Association, commenting on the law on patients' rights, is of the opinion that only a doctor should have access to a medical file.[25]

This problem concerning confidentiality and the quality of coding assumes even more importance since biobanks are increasingly frequently associated together through an electronic network and pooled together in a common database. This is the case in Spain and particularly in France. There are pooling projects in Belgium. This collaboration enables researchers to have access to a greater quantity of samples of a larger number of patients. It sometimes also implies cross-border exchanges of tissues and cells. However, the countries do not have the same requirements as regards the protection of privacy. Some members of the Committee suggest that it is the rules of the country where the sample has been taken which should be applied by the different partners in the exchanges. This would avoid depriving a researcher from one country where the rules are strict - Switzerland or Austria for example - of samples taken in countries where the requirements are not as strict. However one can only approve cross-border transfer if the recipient laboratory offers sufficient guarantees of confidentiality and quality. Other members of the Committee, making reference to an opinion of the E.U. European Group on Ethics, consider that it is those regulations which best protect the rights of the individual which should be applied.[26]

VI.3. Property right to samples

VI.3.1. The question of knowing ***who owns the samples*** *stored in a biobank is posed.*

It is useful to recall that, in law, the ownership of something is defined as the ability or the right to possess or control a thing in the most sovereign manner, excluding those uses prohibited by law.

One will not therefore be surprised of the existence of a lively debate on whether property right devolves upon the researcher who has collected the materials, upon the institution which runs a biobank, upon the custodian of this institution, or even upon the subject who has given the samples.

This question can be discussed in the light of three examples of case law in the United States, with the case law being exclusively American to our knowledge.[27]

1. The case of "Moore v Regents of the University of California"[28]

In 1976, suffering from a specific form of leukaemia, John Moore underwent a splenectomy. Without the patient being informed, fragments of it were sent to a research laboratory, as well as blood samples taken at various times. From these materials, a cell line was developed producing a lymphokine, GMCsf (granulocyte macrophage colony stimulating factor). This molecule was deemed to be one of the most useful for treating a reduction in the leukocytes caused by

[25] Belgian National Medical Association, Opinion on the law on patients' rights (26.07.2003), *Bulletin Conseil National* 2003, 101, p 6.
[26] EGE, Opinion No. 17 of 4 February 2003 "Ethical Aspects of Clinical Research in Developing Countries".
[27] This case law is summarised in a recent article "Rules for Donation to Tissue Banks – What next?", op cit. footnote 20 *supra*.
[28] Moore v Regents of University of California, 51 Cal. 3d 120, 134 (1990).

chemotherapy. A patent was filed by the University of California. The product was the subject of major commercial development. The patient, informed at a late stage, asked to be able to share in the profits. After several legal debates, the Supreme Court of California (SCC) dismissed his case by invoking the argument according to which the cell line was, in fact and at law, different from the cells provided by Moore and argued, consequently, that Moore could not claim a property right. According to the SCC, the cell line could be patented by virtue of the fact that it was the product of the human ingenuity of its inventors.
The SCC recognised that the tissues taken could be the subject of a property right in certain circumstances but dismissed Moore's claim, according to which the cells belonged to him, considering that it was important to avoid the possibility of threatening "innocent parties who are engaged in socially useful activities, such as researchers who have no reason to believe that their use of a particular cell sample is or may be against a donor's wishes." One of the main arguments of the Court concerning illegal appropriation was that a judgment ruling that Moore had a property right would have implied that there would no longer be a distinction between the innocent and fraudulent holders of Moore's cells and that consequently clinical research in this critical domain would be constrained. According to the SCC, accepting that a patient had a property right over his cells after they had been extracted from his body would imply that he could claim "a proprietary interest in each of the products that any of the defendants might ever have created from his cells or the patented cell line. " The Court felt that this was not desirable given that it "[...] would affect medical research of importance to all of society [...]. "

The position of the Supreme Court of California is similar to the European position on this matter, namely that human body materials as such - i.e. as long as they are in the human body - cannot be patented, unlike isolated parts of the human body or those obtained by technical means and processes used for obtaining them.[29] However, the arguments concerning society's interest and that an end justifies the means used seem debatable.

2. The second case is similar.

The family of a patient suffering from a rare disease, Canavan's Disease, a degenerative disease of the central nervous system, persuaded a neurologist to collect samples of brain tissue in order to identify the gene or genes responsible for this disease. From this collection, the neurologist developed a highly sensitive diagnostic test, and patented and marketed it. The family, which initiated the research, also claimed a portion of the profits made from the commercialisation of this test. It based its case partly on the argument that the samples of brain tissue were used for a purpose different from the one for which they had been taken. The Disctrict Court of the Southern District of Florida rejected this argument, concluding that the samples had been used for research in the widest sense and based its decision on the law of the State of Florida which states that:
"The property right in blood and tissue samples […] evaporates once the sample is voluntarily given to a third party".

[29] Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions, Official Journal L 213 of 30/07/98.

On the basis of this conclusion, a donor has no right to control the subsequent use of a tissue sample given for research.

3. A last example

A last example illustrates the case law in the USA.

> A researcher working in the field of prostate cancer decided to leave the University of Washington for another institution. He wished to take a collection of prostate tissues, taken from patients who had given consent to the storage and use of these samples for research. Without the agreement of the University of Washington, the researcher sent 10,000 letters to these patients, asking them to confirm that they had personally entrusted to him the fragments of cancerous material and that they wished for him to make use of them. Although 6,000 of them responded agreeing, the State Court concluded that the tissues had been given unconditionally to the University. That the consent was drawn up on the letter-headed paper of this institution was proof. It was this institution which assured and controlled the storage conditions as well as the conditions of use of the samples. By this fact, the patients had transferred control to the university.

This last example attributes a property right to the institution which hosts the biobank and not to the researcher who has taken the samples. Once again, this decision limits the right of a donor over the use made of his or her samples.

If we accept the aforementioned legal definition of the property right - the right to possess or control a thing in the most sovereign manner, with the exception of those uses prohibited by law - the patient is not the owner of parts removed from his or her body. He or she cannot commercialise them: this rule of non-commercialisation, which is found in all the legal provisions concerning the donation of samples of the human body, whether for diagnostic or treatment purposes or for scientific research, is not unanimously accepted within the Committee. This debate is discussed at more length in Opinion No. 43 of 10 December 2007 on the problem of the commercialisation of human body parts.[30]

After the introduction of a tissue into a biobank with the agreement of the donor, this latter, according to the opinion of the Committee, retains a right to decide on the use made of it and the right to request its destruction. These patient rights imply that neither the manager-custodian of a biobank nor the institution which hosts it are the owners of the samples in the full meaning of the term. The patient's rights do not in fact enable the manager-custodian or the institution to make free use of the materials stored. The manager-custodian appears more to be like the guardian of the biobank: the guarantor that the materials are collected and used in accordance with the rules established and the wishes of the donor patients.
Some members of the Committee draw attention to the fact that, after anonymisation, the donor loses this right of decision.

[30] See Opinion of the Belgian Advisory Committee on Bioethics No. 43 of 10 December 2007 on the problem of the commercialisation of human body parts.

The responsibilities of the researcher who collects the samples, of the manager and of the institution also constitute a question of importance.

VI.3.2. Sample storage and transfer

The samples in these biobanks have a prolonged storage duration which can exceed the life expectancy of the donor subjects, often that of the manager of the biobank, and unfortunately that of the funding used by the researchers.

Hence the question arises as to how to transfer, over time, the custodianship of and responsibility for storing the samples.
Directive 2004/23/EC on tissue and cell banks intended for of transplantation provides in its Article 21,§5:

> "Member States shall ensure that tissue establishments have agreements and procedures in place to ensure that, in the event of termination of activities for whatever reason, stored tissues and cells shall be transferred to one or more other accredited, designated, authorised or licensed tissue establishments [...]. ".

It would be desirable that similar precautions be taken when biobanks intended for research are set up. As has already been highlighted above, samples patiently collected over the years can be of great value for research. Furthermore, their destruction constitutes a lack of respect for the donations made by the patients providing the samples.

In the same vein, experience with current large biobanks shows that the donor subject, or the family of a deceased donor, frequently expresses the wish, if not to know the use made of his or her samples then at least to know if these have been used. Knowing that the donation has been useful may be a reason for personal satisfaction. However, not all samples are used immediately and this does not detract from their interest or their value. The patient must be informed from the offset of the availability or not of this right to information. With most currently operational biobanks, the patient does not enjoy this right.

VI.3.3. The right to know or not to know

Biobanks do not usually communicate to donors the data obtained as a result of the research carried out on their samples. Indeed, in a research context, the results obtained from a sample must generally be validated using other samples. However, the experiments of fundamental research are carried out in conditions which differ from those under which standard laboratory tests are performed. It would not therefore be appropriate for the doctor of the donor patient to use these results within the framework of medical monitoring. Furthermore, the anonymisation or coding of the samples and data makes it difficult to go back to the patient.

However, some members of the Committee feel that, if the research carried out on human biological material provides information which would be useful for the donor subject or his or her family, he or she must be informed of this information. He or she must also, at the time consent is given, be allowed to express his or her wish to receive such potential information, and also the opportunity to express his or her right not to know. If feedback is envisaged, these members consider that high quality support and assistance is needed; they recommend that this be provided through the physician or doctor taking the sample, to

ensure that the information is provided in terms understandable to the patient, the relevance of the information is explained, and appropriate psychological support is provided. The researcher who has been provided with the sample seems less suited to provide this. Not being a member of the team responsible for the patient's treatment, he or she will not have the necessary knowledge of the patient to complete this mission.

VI. 4. The manager-custodian of the biobank

In these different areas, the role of the **manager of the biobank** seems critical.

It is the responsibility of the manager to check whether the conditions required prior to collecting the samples are satisfied, whether the personal data relating to the samples are limited to those required for research, and whether this data is coded or anonymised in the most effective way. It is also the responsibility of the manager to determine the rules regarding access to the biobank, with the support of an independent Ethics Committee which must rule on the merits of the research, on the information provided to donors, on the content of the informed consent, but also on the internal rules of the biobank. These internal rules must clearly establish the responsibilities of each party involved.

Directive 2004/23/EC, as well as the Belgian legal provisions on tissue and cell banks intended for transplantation, provide that the management of these banks must be guaranteed by a doctor with the necessary competence to ensure the required quality criteria are met. This is also the case for the management of genetic centres in Belgium.

Given the sensitive nature of the data collected in biobanks and the nature of the research which requires access to the samples and data, the same requirements should be made of the manager-custodian of a biobank. This should be for a doctor with the necessary competence not only to ensure that the required ethical rules are respected, but also to guarantee the correct storage of the samples and to develop the techniques required for the optimum use of the samples and to evaluate the requests of the users.

The Belgian law of 19 December 2008 provides that samples must be taken by a doctor, but does not define the requirements regarding the responsibility of the biobank. Numerous biologists also have the necessary competence to assume most of the responsibilities placed on the custodian. Furthermore, France, as with a lot of other countries, does not require that this role of guardian-manager has to be filled by a doctor. The biobank must then separately ensure the collaboration of a doctor to control access to the personal clinical data of the patients and to extract from the biobank any additional information required by the researcher.

The need for tissues and cells for research, whether academic or economic, are not fully met by the biobanks as they exist at present. As a result, cell line cultures developed from the tissue samples taken, micro-dissection techniques and other technological approaches have been developed to enable a maximum amount of information to be obtained from the minimum amount of tissues. The supervision of these sample storage and preparation techniques requires specific competencies in the manager-custodian.

For these reasons, it is also the responsibility of the manager-custodian to develop collaborations with other centres within the country and at the international level. Some research studies require the availability of a large number of samples and, for specific research projects, recruitment from a large population may be deemed necessary. This is the

experience of the Austrian and Spanish biobanks which have quickly felt the need for pooling into a common data bank.

It is also the responsibility of the manager-custodian to keep a list of the samples available and a **register** recording the transfers made, as well as to trace the samples distributed so as to check that they are used in accordance with the established criteria.

Finally, it is the manager-custodian who is responsible for the management of the biobank, the application of security instructions, and the observation of professional directives or of international conventions and codes. It is also his or her responsibility, as a last resort, to respond to the supervisory authorities and to the management committee of the biobank in relation to infringements of the rules.

It would be dangerous for the manager-custodian not to be subject to any control. A **management committee** should be put in place to exercise the two-fold role of assisting him or her in his or her mission and to ensure that he or she is supervised. This committee should include independent people from the biobank and representatives of the institution which hosts it. Given the diversity of the biobank's activities - collection, preparation, storage, and distribution of samples and data - and the financial responsibilitiess entailed, the people involved in the supervision must come from various fields of expertise - scientific, of course, but also legal and ethical.

VI.5. Access to biobank samples and data

The material stored in the biobanks is limited in volume and number. The use made of it must hence be optimal and prudent.
It is therefore necessary to define criteria and priorities for access to the samples. The first rule is to reserve a preferential right to the purpose for which the sample was taken. If diagnostic or therapeutic progress were to be made, it would be regrettable if the samples were no longer available to allow the patient to benefit, or, for example in the case of some genetic diseases, if not the patient then at least the members of his or her family.

The Medical Ethics Committee (MEC), such as established by Article 70b of the Law on hospitals and the role of which has been amplified by the Law of 7 May 2004 on experiments on human beings, has an essential role to play in the creation and operation of a biobank. When a biobank is created, it will be the responsibility of an MEC to ensure that the biobank has the technical means and infrastructure to ensure the appropriate processing and the storage under the best conditions of the materials entrusted to it, in the same way that the Law of 7 May 2004 confers on the MEC the mission of checking the competence of the researcher and of his or her collaborators and the quality of the facilities involved in a research protocol.

It is in the evaluation of the access requests, of their interest and their scientific value that the role of the independent ethics committee seems to be most important.

Samples of tissues, cells and DNA are taken from a patient or a healthy volunteer with the objective of providing material necessary for research concerning the diagnosis, the physiopathology and the treatment of diseases. The great majority, if not all, of these studies fall within the remit of the aforementioned Law of 7 May 2004.

In the opinion of the Advisory Committee, biobanks should preferably be developed within academic institutions which have the financial resources and qualified personnel for diversified treatment of patients so as to enable their effective development and lasting operation. The sustainability of the collections could be assured by means of successions of academic chairs.

Within this framework, it is the medical ethics committees of the university hospitals which must be referred to. It is probably within these committees - to which the law confers a specific role - that the necessary experience is built up that is required to judge in total independence the protocols relating to the biobank.

The quality of a protocol is in itself insufficient to justify access to the collections. It is also important for the proposed research to fall within the objectives of the biobank. The access conditions must be defined in the internal rules. Among the criteria for the recognition of a biobank in France is the accessibility of the samples. This must not be unlimited, but equally it would not acceptable if restrictions on access were to be used to favour one research team at the expense of another.

To avoid any risk of commercialisation of the materials in a collection or of a breach of confidentiality, the rules applicable to the biobank must be applied *mutatis mutandis* to the researchers who receive samples from it. The access contract should include a prohibition on supplying onwards the materials obtained. In order to assure control over the samples where not all the material transferred to a researcher is used, it seems preferable that any residual part be returned to the biobank. The transfer contract should include a prohibition on the recipient supplying on the materials obtained to a third party, and more importantly on commercialising them. In most countries, such a prohibition exists in the legal provisions or regulations concerning collections of human biological material. As regards biopsy fragments collected in clinical trials, it is sometimes left up to the patients or to the researchers to decide to relinquish to the study promoter residual parts which will be anonymised or to have such parts returned to the original institution.

The medical ethics committee must also decide on the **internal rules of the biobank** defining the rights, duties and responsibilities of each of the players involved in the operation of the biobank, and in particular of its manager-custodian whose specific importance has been underscored above.

These internal rules must also clearly define the conditions under which samples are collected and stored, and how the access of researchers is governed.

The MEC should give particular attention to the information given to the patient or the volunteer on the way in which samples will be collected, where and for how long they will be stored and, above all, for what research projects they are intended.

The donor must clearly be able to decide on the different eventualities:

a) the sample will be used in order to make progress in the knowledge of the disease or group of diseases from which the patient is suffering, or even other diseases or medical research in the widest sense;

b) the sample is associated with a certain set of personal data collected in the medical file. This data set must be defined. If the data is coded or anonymised, the coding and anonymisation procedures must be described. Double coding seems

necessary given the number of persons who may have access to this data, in particular for genetic research. The patient must know the identity or the function of the person responsible for the coding key;

c) the patient must decide on any potential extended usage. It would be useful to ask the patient about the possible use to be made of the sample if he or she died or if contacting him or her became impossible;

d) the sample and the associated data may be transferred to another laboratory working on the same subject, in this country or abroad.

The way in which written consent is solicited must also be the subject of the opinion of the MEC.

Subsequently, the MEC must rule on the scientific value and the terms and conditions for performance of all the projects which make use of the biobank. It should ensure that samples are transferred to researchers under the conditions for which the donor has given his or her consent. This opinion must consider the potential financial agreements in the event the samples are to be transferred to commercial organisations. In the operation of the biobanks, as with that of tissue banks and cell banks for transplantation purposes, the Law of 19 December 2008 provides, in its Article 6, §3, 2, that the procedures be carried out on a non-profit basis.

All the national directives consulted provide for the absence of remuneration of the donors for their participation in the biobank. Reasonable expenses related to their participation are however generally accepted. The amount of this must not influence the free nature of the consent given by the donors.

VI.6. Biobank recognition

The "Human Tissue Act" in Great Britain requires authorisation to create a biobank to be given. This authorisation is granted by the "Human Tissue Authority" and may be withdrawn in case of breaches of the relevant rules: informed consent, quality of the storage, availability of the samples, lack of marketing. These provisions are very similar to those provided for by Directive 2004/23/EC and by the Belgian Law creating tissue and cell banks. The latter also provides for the approval of human biological material banks by the competent Minister for Public Health.

France provides for a simple notification of the intention to collect, a declaration renewable every 5 years and whose renewal depends on the activity of the biobank in terms of the material stored and the research projects involved.

The Committee is also favourable to the authorisation or at least to the notification of biobanks. This authorisation or notification would have the advantage of avoiding the multiplication of initiatives, whose consequence would be the dispersal of means in terms of infrastructures, but also and above all the quantity of the material stored. However, as the purpose of a biobank is above all that of research, one must avoid legislation which is too restrictive and which would not enable the institution to adapt to the needs of research which, by definition, change over time.

VI.7. Biobank financing

The collection, preparation and distribution of samples, and the management of databases, require personnel and a technical infrastructure the cost of which is not negligible. The sustainable financing of a biobank is one of the major elements of the long term storage of samples entrusted by patients to an institution.

In some cases, in particular with rare hereditary diseases, the samples are extremely valuable. Their loss or their accidental destruction would constitute real damage to scientific research. In this respect, the UK Biobank provides for a division of the material so that it is not processed in its entirety upon each request and thus to avoid its deterioration. These samples as well as the associated data are stored at two geographically different sites so as to avoid a catastrophic event, such as a prolonged electricity cut occurring on one of these sites, leading to the loss of a major part of the collection.[31]

The human body materials are provided free of charge by the patients. The bank does not modify, nor does it invent or produce new materials - it is an essentially passive intermediary, not adding any commercial value to the samples. It would be contradictory and indecent for a bank that receives tissues free of charge to benefit from these donations as its exclusive mission is to manage them in the interests of science, through research and according to the wishes expressed by the donors.

However, from these collections, commercial applications have been or will be developed - diagnostic tests, treatments, etc. - from which the drugs or health products industry would benefit. It would be abnormal for a portion of the profits so made not to be returned to the biobank, which could thus find a part of its financing and means to ensure its development. Whilst recognising the operating cost of biobanks, the Swedish and British regulations stress the fact that one cannot accept the sale of samples to researchers or to industry. Only the necessary costs related to the storage and preparation of the samples and the personal data may be invoiced. This way of proceeding, whilst it poses the problem of financing the biobanks, has the advantage of avoiding commercial pressures detrimental to the interests of research.

However, it is less clear that the individual patient is entitled to benefit from the financial gains of a commercial development deriving from his or her samples. Legal decisions in the USA have confirmed the absence of rights of the patient to the discoveries made from samples taken from his or her body. This has relied on the widely accepted prohibition on the sale of the human body, a problem discussed in detail in Opinion No. 43 of the Belgian Advisory Committee on Bioethics mentioned above.[32] Further, these commercial developments are not usually made from an individual sample, but from a large group of tissues taken from a selected population. The meaning of certain polymorphisms requires the studying of several thousands of samples. This explains the interest of the drugs industry in the biobanks developed from significant portions of the population of a country.

Apart from the contribution of these potential profits to the operation of biobanks, one could consider their use to finance research into the disease concerned or to provide help to patient associations. It seems however ethically unacceptable for those in charge of the biobank to gain profit other than a fair salary for the work accomplished, a salary which

[31] *Lab. Times* Feb 2008, no. 1, p. 46-47.
[32] See supra, no. VI.3.1.

cannot be conditional on the potential financial profit of the institution or upon the increase in the number of samples held.

VII. Recommendations

Collections of human tissues and fluids, although in existence for a long time, have in recent years become of renewed interest and gained new importance due to the development of research into genetics and more widely into molecular biology.
The association between tissue samples and personal and health data poses problems of confidentiality and the protection of privacy.

Just like the Belgian and European political authorities, the members of the Advisory Committee agree on the need for strict regulations.

The biobanks must be the subject of an authorisation (by the responsible authorities) or at least a notification (by the biobank itself). Their numbers should be limited, so as to allow development of sufficiently important collections to respond to the needs of researchers. The limitation of their number and a sufficient size should, on the one hand, reduce their cost and, on the other, increase their security conditions. The value of these collections is not limited over time. It is therefore important to ensure that the samples and the associated data are stored under the best conditions. It would be desirable for the institutions managing biobanks to be academic and for a management committee as well as an ethics committee to supervise the activities of the manager-custodian.

Given the risks concerning the privacy of donors, free and informed consent seems essential. This is particularly important when the samples are taken specifically for research. When, and this is most frequently the case, the materials are the residual parts of samples taken for a diagnostic or therapeutic purpose, some members of the Committee feel that merely informing the patient about the use which is made of his or her samples and of his or her right to oppose this, could be acceptable, in particular when samples and data are the subject of coding. Other members, however, think that formal consent is necessary, in particular in the case of genetic research, thus enabling the donors to exercise the rights conferred on them by the principle of autonomy.

This consent must be informed by providing the donor with detailed information concerning:

- the objectives of the biobank and the importance of participation,
- the nature of the biological materials and data collected,
- the planned use of the samples and data collected,
- the measures taken to protect the privacy of the donor and potentially of his or her family circle and the socio-cultural environment to which he or she belongs,
- the policy followed in terms of sharing the potential benefits,
- any potential collaboration with commercial firms and other research teams,
- the identity of the manager in charge of the biobank and the means of contacting him or her.

It is the responsibility of the manager-custodian of the biobank, in collaboration with the ethics committee, to check that these rules are respected.

The interest of a biobank is essentially to ensure the optimum availability of the samples to researchers and to ensure that the samples are used in accordance with the consent given by the donors.

Access agreements must define:

- the basic objectives of the biobank. Some will be more specifically orientated towards genetic diseases, others towards cancers and others still towards degenerative diseases,
- the access conditions, the quantity and the nature of the material available, the cost of the distribution, etc.,
- the intellectual property rights (e.g. requiring mention of the source of the material and data in publications),
- the requirement for submission of a research project to an ethics committee,
- the requirement to ensure protection of confidentiality and privacy to a level at least equal to the one exercised by the biobank,
- the limits imposed on the transfer of data and materials to third parties, in particular abroad,
- the potential return to the biobank of the residual samples at the end of the project,
- the procedure for accessing additional personal or clinical data.

Finally, even though there may be room for debate regarding the legal situation of the institution hosting the biobank - owner of the samples, custodian, etc. -, in any event the institution has a responsibility for storing the samples and the associated data. It must also ensure the optimum use thereof. Its operating and financing must hence be the subject of measures necessary for ensuring its sustainability.

The opinion was prepared in select commission 2006/2 - Bis – consisting of:

Joint chairpersons	***Joint reporters***	***Members***	***Member of the Bureau***
E. Heinen E. De Groot	G. Rorive P. Cras	L. Michel J.-N. Missa S. Sterckx G. Verdonk	J.-A. Stiennon

Member of the Secretariat: M. Bosson

Experts interviewed

- Yves Gillerot, Doctor, Emeritus Director of the Loverval Genetics Centre
- Lionel Van Maldergem, Doctor of Genetics, Loverval Genetics Centre and subsequently Human Genetics Department, University Hospital CHU-Sart Tilman-Liège
- Anne Cambon Thomsen, Doctor of Biology, Director of Research at the CNRS, Member of the EU EGE
- Nicole Van Regemorter, Doctor, Erasme-ULB Genetics Centre
- Eric Legius, Doctor, UZ-KULeuven Genetics Centre

The working documents of select commission 2006/2 - Bis - questions, personal contributions of the members, minutes of meetings, documents consulted - are stored as Annexes 2006/2 - Bis at the Committee's documentation centre, where they may be consulted and copied.