

REVIEW

Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective

Béatrice Godard^{1,4}, Jörg Schmidtke², Jean-Jacques Cassiman³ and Ségolène Aymé*,¹

¹INSERM SC11, Hôpital Broussais, Paris, France; ²Institute of Human Genetics, Hannover Medical School, Hannover, Germany; ³Center for Human Genetics, Leuven, Belgium

The purpose of this paper is to formulate a professional and scientific view on the social, ethical, and legal issues that impact on data storage and DNA banking practices for biomedical research in Europe. Many aspects have been considered, such as the requirements for data storage and DNA banking in the public and private sectors in Europe and the issues relating to DNA banking, that is to say the consent requirements for the banking and further uses of DNA samples, their control and ownership, and the return of benefit derived from DNA exploitation to the community. The methods comprise primarily the review of the existing professional guidelines, legal frameworks and other documents related to the data storage and DNA banking practices in public and private sectors in Europe. Then, the issues related to DNA banking were examined during an international workshop organized by the European Society of Human Genetics Public and Professional Policy Committee in Paris, France, 07–08, April, 2000. A total of 50 experts from 12 European countries attended this workshop. It came out that DNA banking for medical and research purposes is indispensable. It facilitates the constitution of large collections, sharing of samples, multiple testing on the same samples, and repeating testing over the years. However, banking organization is complex, requires multiple actors, and concerns are expressed in various countries. International standardization of ethical requirements and policies with regard to DNA banking has been recommended. Such standardization would facilitate a greater protection of individuals as well as future international cooperation in biomedical research.

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Introduction

The last few years have witnessed an important expansion of human DNA sampling and data collecting in order to exploit and study the genetic information collected. The

strategic importance of this activity for genetic research and its applications is obvious. Human DNA, tissue or cell collections, Guthrie cards as well as databases which are attached to such biological resources are necessary for a wide range of purposes and these collections have been extensively exchanged for scientific purposes. However, the status of collections is not very well known and most laboratories that bank DNA have no written policies or agreements regarding this activity. Still, many DNA banks are concerned about how to obtain valid informed

*Correspondence: Prof S Aymé, Hôpital Broussais, INSERM SC11, 102 rue Didot, F-75014 Paris, France. Tel: +33 1 56 53 81 37; Fax: +33 1 56 53 81 38; E-mail: ayme@orpha.net

⁴Current address: Faculty of Law and Department of Social and Preventive Medicine, University of Montreal, Montreal, Canada.

consent, safeguard the privacy of samples and data, and avoid potential misunderstandings with depositors.¹⁻⁴ Regulations pertaining to the storage of human biological materials and genetic data are at their beginning stage in most European countries but the multiplicity of actors and of rules that regulate them (public *versus* private, hospitals, research centers, laboratories) make the situation increasingly difficult to comprehend. For instance, the rules that regulate access are still governed by practices that vary widely with the type of collection. The type of informed consent asked for at the time of constitution of the bank may be very different from collection to collection, and makes it even more difficult to understand the condition of their use. The rules for exchange and sharing of information and material are not clear. The notion of return of benefits to the communities, which recognizes their contribution, is fairly recent.

The purpose of this document is to formulate a professional and scientific view on the social, ethical, and legal issues that impact on data storage and human DNA banking practices for biomedical research in Europe. The use of human embryos in research as well as the use of human DNA for forensic purposes raise special ethical issues and are not addressed in this document. After the methods, the second section outlines the requirements for data storage and DNA banking in the public and private sectors in Europe. The third section addresses the issues relating to DNA banking, such as the consent requirements for the banking and further uses of DNA samples, their control and ownership, and the return of benefits derived from DNA exploitation to the community. The fourth section of the document presents a series of case studies involving the use of large DNA sample collections and personal medical information. Finally, the fifth section addresses the issues debated during an international workshop which aimed to compare the different approaches to DNA banking in Europe, and to come up with practical guidelines and recommendations.

Methods

The methods used for analyzing the professional and scientific views on the social, ethical and legal issues that impact on data storage and DNA banking for biomedical research was primarily the review of the existing professional guidelines, legal frameworks and other documents related to the data storage and DNA banking practices in public and private sectors in Europe. Then, with the help of the existing guidelines and a review of literature, the method was to examine questions which need debate, in particular the consent requirements for banking and further use of samples, the control of banked samples and quality issues, the ownership of banked samples and the return of benefits to the community. The following case studies were described: the ALSPAC study, deCODE

genetics and the Act on a Health Sector Database, and Guthrie cards. These questions and case studies were debated during an international workshop organized by the European Society of Human Genetics Public and Professional Policy Committee in Paris, France, April 07-08, 2000.

The purpose of the workshop was to identify, from a professional viewpoint, the most important/pressing/burning ethical issues relating to the data storage and DNA banking practices in public and private sectors in Europe. The formal workshop presentations covered the following themes: setting the scene (banking practices, policies, return of benefits to the community), point of view of data and DNA banks managers, analysis of practical examples and elaboration of statements and recommendations. Small multidisciplinary groups were convened to take these discussions further. Their initial task was to explore the practices and needs in the countries represented and to consider the extent to which these needs were currently being met. Following the small group sessions, conclusions were fed back to the whole group where there were opportunities for further discussion.

A group of 50 experts from 12 European countries was invited. These experts were representatives of the seven following sectors:

1. Medical Genetics;
2. Human Genetics Societies;
3. Ethical, Legal and Social Issues;
4. Support Groups;
5. Biotechnology/Pharmaceutics;
6. Insurance/Employment;
7. European Union Institutions.

A first background document was discussed during the workshop. A second document, including discussions of the workshop, was sent for comments to representatives of the human genetic societies and European experts in the field of DNA banking for biomedical research, as well as to all ESHG members. This document was also put on the ESHG website (www.eshg.org) for public consultation and discussion. The final document was approved by the ESHG board.

Data storage and DNA banking practices in public and private sectors in Europe

In 1988, The American Society of Human Genetics (ASHG) statement on DNA Banking and DNA Analysis defined a DNA bank as 'a facility that stores DNA for future analysis', whereas a DNA diagnostic laboratory was 'a facility that analyzes DNA to provide information about the diagnosis of a disease state or susceptibility thereto, about the diagnosis of a carrier state, or for identification purposes'. In 1989, the British Clinical Genetics Society stated that the purpose of a DNA bank is 'to provide for the future

requirements of families affected by serious single gene disorders and who require DNA analysis for the purpose of: (1) confirmation of diagnosis at the molecular level; (2) presymptomatic diagnosis; and (3) carrier detection'. After 10 years, the American National Bioethics Advisory Commission⁵ defined a DNA bank as 'a facility that stores extracted DNA, transformed cell lines, frozen blood or other tissue, or biological materials, for future DNA analysis'. The same Commission defined a DNA databank as 'a repository of genetic information obtained from the analysis of DNA, sometimes referred to as 'DNA profiles'. The genetic information is usually stored in computerized form with individual identifiers'.

Ethical principles for the prospective use of human genetic material and data have been introduced in several European countries. The British Clinical Genetics Society⁶ and the Danish Council of Ethics⁷ emphasized the quality assurance of banked tissue samples and consequently the origin of samples that may be banked. In Denmark, a Data Surveillance Authority, which has jurisdiction over biobanks, was created in 1996. The Health Council of the Netherlands⁸ issued the recommendation that human material cannot be stored 'without a good reason' (1994). In France, a 1996 ordinance pursuant to the 1994 Bioethics Laws mandated that 'no person may take samples with a view to constituting a collection of human biological specimens, or use, to this same end, samples already taken or derivatives thereof if they have not notified the competent administrative authority of the proposed collection'. In Iceland, the Biobanks Act (2000) states that 'the interest of science and of the community shall never be given priority over the interests of the donor of a biological sample' (Article 1). The Estonian Human Genes Research Act (2000) also insists on 'the voluntary nature of gene donation and the confidentiality of the identity of gene donors'. Recently, the British Human Genetics commission⁹ suggested 'the establishment of independent oversight bodies for all large genetic databases'.

Conditions of data storage and DNA banking

Under what conditions may samples be banked? In its statement on informed consent for genetic research (1996), the ASHG distinguished between retrospective and prospective studies: 'Retrospective research studies utilize previously obtained samples collected for a purpose that is different from that of the project under study; prospective research studies are those in which the collection of the new samples is part of the study design'. Whatever the study, the ASHG defined four types of identification that may be employed to store the samples as the following:

- *Anonymous*: 'Biological materials that were originally collected without identifiers and are impossible to link with their sources'.

- *Anonymized*: 'Biological materials that were originally identified, but have been irreversibly stripped of all identifiers and are impossible to link to their sources'.
- *Identifiable*: 'Biological materials that are unidentified for research purposes, but can be linked to their sources through the use of a code. Decoding can only be done by the investigator or another member of the research team'.
- *Identified*: 'Biological materials to which identifiers, such as a name, patient number, or clear pedigree location, are attached and available to the researchers'.

The extent to which a research sample can be linked with the identity of its source is a significant determinant in assessing the risks and potential benefits to human subjects.⁵ The American Commission defined the different types of research samples as follows:

- *Unidentified*: 'Sometimes termed 'anonymous', these samples are supplied by repositories to investigators from a collection of unidentified human biological specimens'.
- *Unlinked*: 'Sometimes termed 'anonymized', these samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being. Typically, repositories send unlinked samples from identified human biological specimens to investigators without identifiers or codes so that identifying particular individuals through the clinical or demographic information that is supplied with the sample or biological information derived from the research would be extremely difficult for the investigator, the repository, or a third party.'
- *Coded*: 'Sometimes termed 'linked' or 'identifiable', these samples are supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information, such as a name or Social Security number'.
- *Identified*: 'These samples are supplied by repositories from identified specimens with a personal identifier (such as a name or patient number) that would allow the researcher to link the biological information derived from the research directly to the individual from whom the material was obtained'.

A great variability exists in the identification of the samples used, depending upon the source of the material and the purpose of the research. In some studies where individuals just serve as the sources of the samples, identifying them is not necessary. For other studies in which extensive information on diagnosis, family history, and demographics is crucial, the ability to identify the source of the sample is essential. But whatever the type of sample identification, with modern – DNA – identification techniques, it is possible even in anonymized collections to link a sample with an individual if one wishes to spend the

effort and if the individual provides a fresh sample for matching.¹⁰

The consent requirements for the banking and further use of samples will be explored in the third section.

Confidentiality issues

Studies that maintain identified or identifiable specimens must maintain subjects' confidentiality, that is 'information from these samples should not be provided to anyone other than the subjects and persons designated by the subjects in writing'.¹¹ However, the American Society recommends that investigators inform individuals that they cannot guarantee absolute confidentiality. The ASHG ethics committee recommended¹² that researchers 'consider a way of coding samples by a third, independent party, who would keep the codes inaccessible unless there are specific circumstances in which the code needs to be broken'. In other instances, the only way to protect the confidentiality of identified and identifiable samples is to code them^{5,7,9,13,14} The Health Council of the Netherlands⁸ considers that wherever possible, anonymous samples be used; identifiable samples should be limited to studies that could not otherwise be performed. For the Swedish Medical Research Council,¹⁵ 'if biobanks are to fulfill important purposes for future biomedical research, the identity of the samples must be preserved. It is essential for biological material to be coded, and for the code key to be stored separately. The code must be kept within public institutions. Strict rules for storage and the use for the code key must be established, preferably in consultation with the local personal data representative'. In the United Kingdom, the Human Genetics Commission⁹ considers that one-off consent should be sufficient if identifiers are encrypted and recommends that the Government support research into robust methods for encryption for use in situations where the encryption needs to be reversible.

Requests for DNA banking

Who may request that DNA samples be stored? In 1988, the ASHG stated that 'a DNA bank or a DNA diagnostic laboratory should accept samples only in response to requests from health-care professionals and not in response to requests from individuals or families without the mediation of health-care professionals. (...) If an individual should bank DNA without a genetic evaluation, such an evaluation is desirable before the DNA is analyzed'. In order to avoid misunderstandings between the depositor and the DNA bank, it has been recommended that the depositor be informed about the following issues: (1) the services to be provided; (2) the duration of storage; (3) the disposition of the DNA at the end of the agreed-upon term of storage or upon the death of the depositor; (4) the conditions under which DNA can be used for purposes not requested by the depositor; (5) a discussion of risks

associated with DNA banking, such as loss of samples; and 6) an agreed-upon method of maintaining contact between the depositor and the bank.^{15,16}

Security of banking facilities

What are the security mechanisms for DNA banking? HUGO's 1996 Statement on the Principled Conduct of Genetic Research recognized privacy and the need to protect against unauthorized access by putting in place mechanisms to ensure the confidentiality of genetic information. It advocated that information and samples be coded, that procedures be put in place to control access, and that policies be developed for the transfer and conservation of samples. The Council of Europe's Recommendations on the Protection of Medical Data (1997) included new provisions applicable to the collection and automatic processing of medical data, including genetic data. Article 9.1 states that 'appropriate technical and organizational measures shall be taken to protect personal data – processed in accordance with this recommendation – against accidental or illegal destruction, accidental loss, as well as against unauthorized access, alteration, communication or any other form of processing. Such measures shall ensure an appropriate level of security, taking account, on the one hand, of the technical state of the art and, on the other hand, of the sensitive nature of medical data and the evaluation of potential risks'. At the national level, most countries would subject genetic information to the security mechanisms in place for nominative and medical data generally^(7,17); French Bioethics Law, 1994;⁸; Swedish Act Concerning the Use of Gene Technology on Human Beings, 1991). Austria (1994), Estonia (2000) and Iceland (2000) have specifically adopted a law to ensure that appropriate measures are applied to the storage and use of genetic information.

Quality assurance for banking

As with the principle of quality assurance, it has been argued that the implementation of security mechanisms to ensure the confidentiality of genetic information and long-term conservation of genetic material should be a *sine qua non* condition of banking.^{18,19} These mechanisms should be in place before sampling is done. Very strict guidelines should be designed concerning the practical aspects of data storage and DNA banking, which imply coordination by experienced researchers, analysis by qualified personnel as well as modern storage facilities. Evaluation of the validity of the obtained results should also be included. The Swedish MRC¹⁵ recommends that 'all biobanks containing both biological material as well as associated information about individuals must have an organization with explicit procedures for quality assurance, including systems for storage, coding, and registration'.

Regulation of banking facilities

What are the regulatory mechanisms for banking facilities? A first type of regulatory mechanism relates to the accountability and oversight of these facilities.²⁰ Some policy statements recommend that DNA banks be covered by institutional regulations, such as Institutional Review Boards (British Clinical Genetics Society 1989, Health Council of the Netherlands 1994).^{9,15} Means of ensuring the oversight of banking facilities vary from accreditation of banking facilities²¹ to their voluntary certification.^{2,16} A second class of regulation relates to the quality assurance of the techniques used by the banks and the competence of technicians.²⁰ Proposed requirements to ensure maintenance of high standards include the training and certification of personnel and the listing of bankers' responsibilities (Health Council of the Netherlands 1994).¹⁶ A third type of regulation relates to safety measures for banks, such as storage conditions or means of protection from hazards including unauthorized access, loss of samples, computer breakdowns, etc.⁹

Self-regulation is another approach to ensuring that DNA banks conduct their activities in a way which is ethically and legally sound.² McEwen & Reilly² argued that DNA banking could be responsibly managed if professionals developed and adhered to a code of conduct and developed and used written agreements that describe the rights and obligations of all parties with respect to storage. Because of the differences in orientation between academically based and commercial DNA banks, the authors recommended two different approaches: in the case of academically based banks, they recommend that governmental agencies, like the NIH Office of Protection from Research Risks in the USA, advise local institutional review boards to follow specified guidelines to ensure that DNA banks adhere to uniform standards. As for commercial DNA banks, voluntary agreement should be sought on a core set of rules for DNA banking to which all banks should adhere (a code of professional conduct) (*ibid*). A professional body, such as the American College of Medical Genetics in the USA, should play an oversight role to ensure compliance by the DNA banks that adopt the code of conduct. To a voluntary code of conduct, McEwen and Reilly² added the use of a depositor's agreement that delineate the rights and obligations of both those who provide samples for storage and those who bank them. This may indicate one way in which academic and commercial DNA banks can conduct their activities in an ethically sound manner. More specifically, the Swedish Medical Research Council¹⁵ considered that 'rules on research ethics review should apply in the same manner for biobanks maintained by industry. Such biobanks should only include coded material. A code key should be stored with a suitable public authority such as a university or county council'.

Use of DNA sample collections by academia and industry

There are a number of potential sources of DNA samples, including the military, teaching hospitals, new-born screening, pathology or research labs, commercial laboratories, pharmaceutical or biotechnology companies, patient associations, forensic services, and various blood, cell and tissue banks. DNA sample collections vary considerably in size, ranging from large collections formally designated as repositories to samples informally stored in a researcher's lab freezer. It is difficult to quantify the scale of existing sample collections or to describe the use of such collections. An inventory of stored tissue specimens in the United States revealed that a conservative estimate of the number of specimens held in the country was in excess of 282 million (National Bioethics Advisory Commission 1999).²² New samples are being collected in the US at the rate of 20 million a year and the NIH spent some \$53 million in 1996 alone supporting extramural tissue repositories.²²

DNA sample collections are used for various purposes, namely for clinical, research, and industrial uses.^{23,24} This tends to legitimate different institutional and legal frameworks (profit or nonprofit organizations, private or public). It may be necessary, however, to bring institutions operating in the same domain closer when it comes to defining the conditions of exchange of biological material or information. Different conditions and prices could create a distortion among various institutions maintaining the same material. Further information is also missing if the contractor wants to evaluate the structure and the regulations that govern the observed collection or database in the light of its objectives and social and economic context. Gathering information on the main issues related to the constitution and the maintenance of collections as well as on research, the clinical or the industrial purposes they are to be subjected to and the expected results appears crucial in order to provide an exact picture of the diversity, role and importance of banking institutions (either public or private). The type of information to be gathered can be described as follows:

- How are collections constituted?
What kinds of samples are collected and are they subject to transformation? Under which criteria is genetic material included in the collection and how is it documented? How is the information linked with the material managed?
- How are collections maintained?
Are there standards of conservation, regeneration, distribution and if so, how are they established? What are the safety provisions?
- What is the scientific work done on these collections?
Content of the scientific activity: evaluation, characterization, gene mapping, genetics of diseases, etc.

Organization of research: modalities of cooperation, further uses of samples.

- How are scientific results made available to the scientific community and what are the conditions of access to such results for private as well as public institutions?

The analysis of the structure of the existing collections and databases and the way they operate appears to be the only way to provide regulators with the information and analyses that will help them make necessary choices.

The biotechnology and pharmaceutical industries are also developing DNA banking and it is highly relevant to understand their objectives in this respect.²⁵ The majority of biotechnology companies are primarily concerned with generating and selling information about the relationship between specific genetic sequences and particular diseases, rather than developing drugs themselves. However, it has been reported that some firms are planning to develop diagnostic tests based on this data, a number are offering contract genotyping services, and others are looking to develop drugs in partnership with large pharmaceutical companies (*ibid*). As to pharmaceutical companies, many of them have major interests in the collection of biological samples. There has been a rapid growth in pharmacogenetics research in recent years, with companies increasingly taking samples from participants in clinical trials to support their work in three main ways: (1) to analyze the molecular basis of disease; (2) to understand disease stratification and (3) to analyze drug response, including dosage and adverse events. Pharmaceutical companies also obtain DNA samples from patients via agreements with academic researchers in order to have additional material for points 1 and 2. Relatively little seems to be known about the scale of these collections by large pharmaceutical companies, but industry reports suggest that this is now a routine activity (*ibid*). It should also be noted that research is international in scope, with companies working in many countries across different continents.

In other respects, private sector activities depend heavily on both publicly funded research and widespread public participation. It is therefore difficult to draw a line between public and private research, as researchers from both sectors are often involved in supporting the same project. Very close academic-industry links are a general feature of research in genetics. While this enables effective technology transfer, it also gives rise to concerns about academic conflicts of interest (*ibid*).

Issues

Consent requirements for the banking and further use of samples

For research use of human biological materials, two basic protections for individuals usually come into play: (1) informed consent is required, and (2) Institutional

Review Board (IRB) or ethical committee oversight is required to ensure an acceptable balance between risks and benefits. However, there are variations that are pertinent to research using human biological materials.

Most countries explicitly mention that (1) consent should be written, and (2) specific protections should be provided for vulnerable populations. The majority mention the possibility of anonymous studies as an exception to an express consent. There is some debate as to whether the principle of consent can be met in every research situation. Consent requirements can depend on the study (prospective or retrospective) to be conducted and on the category (identified, identifiable, anonymized, anonymous) of samples to be banked.^{1,11,26}

Nonanonymous samples At the time that new collections are created it is difficult to foresee all the potential research applications that the collection may be used for. It can be argued that different consents should be required for the physical taking of the sample, its use in a specific research study, its use by third parties, its subsequent use for other research purposes, and its use in a commercial application. Or rather than providing choices, participants may simply be informed of institutional policies concerning, for instance, the length of time of storage, approaches to discarding, or conditions of access by others.¹⁹

The British Medical Research Council Working Group²⁷ suggested that at the time of the collection of the sample, broad consent should be obtained for the future unforeseeable uses of the sample in research, without the need to recontact individuals. As for the British Royal College of Physicians,²⁸ it regarded that the secondary use of human material samples does not require the express consent of the individual. The concerns of the College are that requiring consent may bring to a halt all research on existing, archived material. It has been reported that this would be similar to the approach that has been used in epidemiological research, where the practice has been that consent need not be obtained for noninvasive research as long as approval has been obtained from an ethics board.²⁵ Finally, it is also recommended that researchers provide subjects with choices concerning subsequent use of a sample.²⁹ For instance, it would be reasonable to give the individual the option to refuse permission for any secondary use, permit any use but only if the sample is rendered anonymous, permit only research involving a certain disease or diseases, or permit any use without anonymization at the discretion of the investigator.

In the case of existing collections it may be impractical to gain consent for new research uses from the donors of the samples. Concerning already-collected, coded and identified samples, many bodies have agreed that they may be stored and used for other purposes than those originally intended if informed consent for banking and subsequent use has been obtained.^{4,7,8,14,15,30} The Ethics

Committee of HUGO^{13,31} states that 'research samples obtained with consent and stored may be used for other research if there is general notification of such a policy, the participant has not yet objected, and the sample to be used by the researcher has been coded or anonymized'. An exception to the principle of consent has been proposed for prospective statistical and epidemiological purposes¹³ The ASHG¹¹ considers that 'investigators should be required to recontact the subjects to obtain consent for new studies'. The National Bioethics Advisory Commission⁵ states that for research samples that are identified or coded, the possibility that the investigator will contact the source or the source's physician for additional information should be discussed during the consent process. In other respects, the Commission considers that research on existing samples that are identifiable does not require informed consent and may receive IRB review, provided that it does not exceed 'minimal risk' to the donor. Minimal risk is defined as any risk exceeding those encountered in daily living or during routine medical visits.

Anonymous samples Regarding already-stored anonymous samples, several bodies have agreed that they may be stored and used for other purposes than those originally intended.^{5,7,8,11,26,32} In 1993, the Danish Council of Ethics recommended specific legislation to this effect.

Concerning anonymized samples, a number of statements consider anonymizing samples acceptable in order that they be banked and subsequently used in retrospective and prospective studies without obtaining an explicit consent. The advantage is that there is no possibility of breach of confidentiality, of duty to communicate results, of risks of stigmatization or of discrimination.⁵ Others consider that this approach is unacceptable since researchers have an opportunity to seek consent on whether the samples may be anonymized or not but do not use it.²⁰ According to the NIH guidelines, when samples are obtained in a research setting, consent of the 'source' should be obtained for the stripping of identifiers and for prospective research.³³ As for the ASHG,¹¹ 'investigators should consider the appropriateness of anonymizing samples, especially when there is available medical intervention for the disorder being tested'. The HUGO Ethics Committee³¹ mentions that while necessary demographic and clinical data may accompany the anonymized sample, careful consideration should be given before proceeding to strip samples of identifiers since other unknown, future uses may thereby be precluded as well as the subsequent validation of results.

Scope of informed consent When consent is required, what is the scope of informed consent? In obtaining consent for the banking of identifiable or identified samples and subsequent use, policy statements recommend that several elements be disclosed, such as the purpose of

the research, its limitations and outcomes, its risks and benefits, the types of information that could result from genetic research, communication of results, or means of maintaining confidentiality.^{7,8,11,13-16,21,26,27,34,35} Individuals should be given options with respect to the types of research that can be carried out, the access to or sharing of stored samples, the duration of storage as well as the right to withdraw samples. ASHG¹⁶ considers that unless immortalized cell lines have been established, patient DNA is exhaustible and the patient's needs should take priority.^{3,36} Individuals should also be informed if the sample will be stored for later study as well as the possibility of storage failure. For the ASHG,¹⁶ 'it is inappropriate to ask a subject to grant blanket consent for all future unspecified genetic research projects on any disease or in any area if the samples are identifiable in those subsequent studies'. Individuals whose samples are stored should also receive general information pertaining to the institutional policy with respect to banking (Health Council of the Netherlands 1994).¹⁶ Documents now focus on what constitutes appropriate disclosure during the consent process and on the documentation thereof in consent forms. Most assert that the potential subject must be told about the investigator's intent to retain samples and the scope of intended subsequent use. They have also asserted that the subject has the right to decline to permit secondary use of his or her sample or to limit it in general terms.²⁹

The Health Council of the Netherlands⁸ and The Nuffield Council of Bioethics³⁵ set out special rules for the storage and subsequent uses of samples procured from vulnerable persons. According to the Nuffield Council on Bioethics, when the patient is lucid his or her consent should be required and sought, and when the patient is in no position to give that consent the guiding principle must be that what is in his or her best interests should be determined by family members and/or physicians.

Concerning postmortem uses of samples, a policy of unrestricted access cannot be justified on the grounds that no ethical issues are at stake.³⁷ In cases in which research using samples from deceased individuals involves identifiable private information about their living relatives, the research may pose risks for them.³⁸ When they are still alive, individuals may want to establish policies to ensure that some of these outcomes do not occur. According to the National Bioethics Advisory Commission,⁵ if individuals restrict use of their samples when they are still alive, those restrictions should also apply after their deaths.

Generic consent The ASHG¹⁰ considers that a blanket consent for all future unspecified genetic research projects is inappropriate if samples are identifiable. On the contrary, the American Society for Investigative Pathology³⁹ as well as the Association of American Medical Colleges⁴⁰ believe that specific requirements for informed

consent will discourage patients from participating in biomedical research, and that researchers will be unable to pursue such studies without additional financial resources to support such an administrative burden. The Pathology Societies agreed that for research with identifiable specimens, the Institutional Review Board approval remains the norm but add that such research should be possible with a general consent procedure. The AAMC recommends that research on archival patient materials, whether linkable or not, should be permitted under a general informed consent mechanism. This mechanism should protect genetic information from unauthorized disclosure and misuse. WHO¹⁴ also proposed that existing stored samples 'should not be subject to new rules for consent or recontact that may be established in the future': (...) 'a blanket informed consent that would allow use of a sample for genetic research in general, including future, as yet unspecified projects, appears to be the most efficient and economical approach, avoiding costly recontact before each new research project'.

Two complications with individual informed consent must be noted: (1) Sometimes informed consent is not possible; in those circumstances, a carefully circumscribed use of community consent or 'permission' may be allowed if the potential benefits are sufficiently great and particular ethical care is taken (CIOMS 1991). (2) Informed consent by and for vulnerable subjects raises serious ethical problems; if it is absolutely necessary to sample such individuals, it should be done only after an explicit review and approval by an Institutional Review Board (*ibid*).

Consent at the population level: group consent For populations, if a such population is to be the subject of research, then there is a case for saying that consent may be required at a group level.⁴¹ This requirement has been recognized by the Tri-Council of Canada⁴² and by the Human Genome Diversity Project,⁴³ which supports the principle that population consent, as well as individual consent, should be sought for genetic research. Researchers should obtain the informed consent of the population, through its culturally appropriate authorities, before they begin sampling. Some may argue that the refusal by a population may violate the rights of an individual who wants to participate.

What form should group consent take? For some populations, that will be individual signed consent forms as well as a group consent form or agreement signed by the population's authorities.⁴⁴ In other populations, written documents may not be appropriate. The precise form of the consent must take these differences into account. Nevertheless, there is a possible conflict between this form of consent and the law of some sponsoring countries. Many countries require signed consent forms from all individuals participating in funded research and affected researchers may have to abandon plans to work with that community.

Use of samples banked prior to collection of informed consent A few clinical laboratories have formal policies for the use of stored specimens which has been obtained in the past without consent or without specific consent to their use in research and from which genetic inferences can be made.⁴⁵ It is also not known how many clinical laboratories have a fully informed understanding of the way consent was obtained for specimens they are testing as part of their involvement in scientific or clinical research.⁴⁶

A variety of scientific groups, including the British Medical Research Council Working Group²⁷ the American Society of Human Genetics,¹¹ the American College of Medical Genetics,²⁶ the National Bioethics Advisory Commission,⁵ HUGO,³¹ and WHO,¹⁴ issued position papers that address the use of archived specimens. Although everyone recognizes that the consent process under which many samples were acquired does not meet today's standards, they recognize that there are many valuable archived specimens that could be used and that it would be prohibitively expensive to try to obtain a new consent from each donor for reuse.²⁹ For ASHG,¹¹ making samples anonymous will eliminate the need to recontact to obtain informed consent. This will also reduce the chance of introducing bias due to inability to recontact some, or the possible refusal of others to participate. Or if the samples are identifiable, new consent would have to be sought. In NBAC's judgment (1999), where the research uses identified or coded samples from previously collected specimens, such uses usually are not justified without the source's consent; the use of unidentified or unlinked samples for research could be justified in some cases if other appropriate protections were in place, despite the lack of consent. The HUGO Ethics Committee³¹ considers that routine samples obtained during medical care and stored before the notification of using such samples for research and with the patient's consent may be used for research if the sample has been anonymized prior to use. The British Medical Research Council Working Group's position²⁷ is that for old collections, samples should be regarded as abandoned and therefore are able to be used for new research purposes as long as ethics committee approval is obtained.

Use of samples from archived pathology materials -

Most researchers using human biological samples have relied on specimens from archived pathology materials. Some studies require samples with specific biological, clinical, or demographic characteristics. The creation of such collections can be of great value to researchers.

As noted in the previous section, some specimens are gathered during clinical procedures for which no informed consent was obtained. However, even when informed consent was given for the medical procedures that produced the specimens, the individuals may not have consented to possible future research uses of the material

or may not be aware that their specimens might be used for various research purposes by a number of investigators. Even when individuals are asked to provide samples for possible use in future research and even though an approved research protocol does not yet exist, the question is whether individuals can give specific, informed consent today to the use of their materials at some time in the future. For the American Pathology Societies³⁹ and the Association of American Medical Colleges⁴⁰ research on archival patient materials should be permitted under a general informed consent mechanism. In a report on 'research involving persons with mental disorders that may affect decision-making capacity', the National Bioethics Advisory Commission⁴⁷ considered that, within limits and with appropriate protections, individuals, while competent, could give prospective authorization to a particular class of research if its risks, potential direct and indirect benefits, and other pertinent conditions were explained. Perhaps more than for other samples, it seems appropriate to ask a subject in the setting of a clinical biopsy or a surgery to grant a blanket consent for future unspecified genetic research projects on the disease this person suffers from. Indeed, it is by no means possible at any given moment to predict exactly which further studies will be undertaken. As stated by the HUGO Ethics Committee³¹ while necessary demographic and clinical data may accompany the anonymized sample, careful consideration should be given before proceeding to strip samples of identifiers since other unknown, future uses may thereby be precluded as well as may the eventual validation of results. As to old collections, according to the British Medical Research Council Working Group's position²⁷ samples could be regarded as abandoned and therefore be used for new research purposes as long as ethics committee approval is obtained.

The British recommendation may be particularly relevant for pathology samples. In fact, good clinical practice in pathology requires long-term storage of tissue samples for different reasons. First, initial results may need validation by additional techniques that were not yet available at the time the biopsy was taken. Alternatively, important progress made in the understanding of certain pathologies may demand re-evaluation of the material in view of current insights. Finally, the prognostic impact of certain evolutions in the patient's disease process often strongly depends on the pathologic findings at diagnosis that frequently cannot be adequately judged by means of the pathology report only. Electronically stored pictures will not solve this problem.

Control of banked samples and quality issues

Access to samples and sharing Worldwide research endeavors have raised the issue of access to and sharing of banked samples. While protecting confidentiality, the free circulation and the availability of genetic information

and samples for research has been promoted by many instances.^{13,14,48,49} At the international level, HUGO (1996) and UNESCO (1997) mandated that DNA samples should be openly available to the scientific community: 'collaboration between individuals, populations, and researchers and between programs in the free flow, access, and exchange of information is essential not only to scientific progress but also for the present or future benefits of all participants. Cooperation and coordination between industrialized and developing countries should be facilitated'. WHO¹⁴ adopted the same position: 'qualified researchers should have access to samples, provided that strict confidentiality is observed or that identifying characteristics are removed'. Concerning access by relatives, HUGO³¹ stated that 'Where there is a high risk of having or transmitting a serious disorder and prevention or treatment is available, immediate relatives should have access to stored DNA for the purpose of learning their own status. These exceptional circumstances should be made generally known at both the institutional level and in the research relationship'. WHO¹⁴ went further and recommended that 'control of DNA should be familial, not individual. All blood relatives should have access to stored DNA for purposes of learning their own genetic status, but not for learning the donor's status'.

At the regional level, in 1991, the Council of Europe proposed that 'standard research contracts have a clause to the effect that the sharing of all knowledge and distribution of materials will be obligatory. (...) Data and materials as much as possible should be free of charge or available at a nominal cost or to cover distribution costs'. In 1997, the same instance adopted the Recommendation on the Protection of Medical Data which provided that 'Medical data can be used by health professionals for their own medical research as long as the data subject has been informed of this possibility and has not objected'.

At the national level, access to medical records or to samples for genetic research is normally restricted to qualified investigators and subject to institutional oversight, be it legislative or via ethics committees.^{19,50} Generally, consent of the patient is also required.^{11,15,21,51,52} Ethics committees or legislative provisions may also grant access to records or samples without consent for research purposes, mainly if the data are anonymized (French Law No. 94-548 1994).^{7,32}

In most international and national legislation and protocols, individuals are considered to have an absolute right to give or to withhold information about their genetic status, and equally an absolute right to prevent their stored genetic data being transmitted to a third party for whatever purpose. However, one of those purposes might be further research in which individuals' genetic data might assist in securing health benefits for a large number of other people. Some people wonder if in such a case should such individuals be able to exercise a right to

withhold their genetic information, particularly if it is encrypted or anonymized, when it might play a part in establishing links and patterns with genetic defects in members of their families or some wider social grouping and thus contribute significantly to their well being.⁵³ It has been argued that the principle of inalienable individual rights that lies at the heart of much of the legislation about data protection may not be in the best interests of the population's health (*ibid*).

Duration of storage Several policy statements recommend that samples be stored for limited periods to be specified at the time of collection or only for the time needed to complete the purpose pursued in banking the samples.^{7,8,16,26} A prolongation of storage must be justified by a good reason, such as research or an absolute need,^{7,8} or when the original consent to collection and storage did not prohibit the use of anonymized samples for research.⁷ WHO¹⁴ recommends that DNA be stored as long as it can be of benefit to living or future relatives, while the British Clinical Genetics Society⁶ recommended an open-ended duration for the storage of DNA.

Concerning the destruction of stored samples, a few guidelines state that individuals who withdraw from a study may request destruction of their sample.^{26,33,54} For the HUGO Ethics Committee³¹ in the absence of need for access by immediate relatives, stored samples may be destroyed at the specific request of the person. The Committee recognizes that the destruction of samples is not possible for samples already provided to other researchers or if already entered into a research protocol or used for diagnostic purposes. Some authors point out that given certain techniques used in genetic research, such as the immortalization of cell lines, doubt may be raised as to the realism of offering individuals the possibility of having their samples destroyed upon withdrawal from a study.^{1,20} By their nature, anonymized samples cannot be withdrawn by their donors.

Responsibility of the diagnosis of stored samples Most researchers believe that findings from research should not be communicated to subjects unless they are confirmed and reliable and constitute clinically significant or scientifically relevant information. Revealing unconfirmed findings may place subjects at risk of harm. However, it has been argued that the principle of autonomy dictates that subjects have a right to know what has been learned about them and that interim results should be shared with subjects.⁵⁵ In 1996, the ASHG recommended that 'all genetic research studies involving identified or identifiable samples in which disclosure of results is planned have medical geneticists or genetic counselors involved to ensure that the results are communicated to the subjects accurately and appropriately. In other respects, it is the obligation of the subjects to keep the investigator informed

of how they may be contacted'. In 1999, the National Bioethics Advisory Commission considered that disclosure of research results to subjects should occur only when all of the following apply: '(1) the findings are scientifically valid and confirmed; (2) the findings have significant implications for the subject's health concerns; and (3) a course of action to ameliorate or treat these concerns is readily available'. (...) 'When research results are disclosed to a subject, appropriate medical advice or referral should be provided'.

Ownership of banked samples

Many of the agreements about ownership of banked samples and access to biological material and information are determined by multiparty contracts and are not regulated by legislation.^{25,56} The general practice is that information belongs to the researcher or team that creates it and the individual who may have been a subject of the research has no legal entitlements to that research. The claim that subjects should own their sample even while it is entered into research is the minority view.²⁹ In 1988, the ASHG statement established that 'banked DNA is the property of the depositor unless otherwise stipulated'. On the other hand, the British MRC Working Group on Collections of Human Tissue and Biological Samples for Use in Research^{4,27} considered that the funding body retains ownership of the collection while the researcher is the custodian of the collection. The custodian has the responsibility of control over the access to the collection and ensuring that standards of confidentiality are maintained. Funding bodies need to determine the purpose of the collection and if it is available to both commercial ventures and academic researchers. It has been suggested that potential subjects should decide whether they are willing to participate only after they have been informed about who will own the sample (as it is for tissue) and whether or not there is a plan for subsequent use of sample. Subjects should have the right to decide to donate their tissue to the research team. As with other aspects of life, competent individuals have the right to make gifts and these gifts are owned by those who receive them.²⁹

The issue of ownership arises primarily because of the possibility that DNA samples could have some commercial value. This issue is most controversial in connection with the patentability of 'inventions' derived from the scientific analysis of human material. This patentability remains contested in various nations and within particular groups. At the international level, HUGO has maintained a consistent position on the unpatentability of human DNA sequences.^{57,58} At the regional level, in 1994, the Council of Europe's recommendation on the Protection and Patentability of Material of Human Origin stated that 'human beings are subjects – not objects – of law'. After 3 years, in its Convention on Human Rights and Biomedicine, the Council of Europe insisted that 'the human body

and its parts shall not, as such, give rise to financial gain'. Finally, in 1998, the European Commission Directive concerning the Legal Protection of Biotechnology Inventions intended to complement international intellectual property provisions. By distinguishing between inventions and discoveries (the latter being unpatentable), the Directive responds to concerns that the human body or parts thereof could be patentable. According to the Article 3, 'an element of the human body in its natural environment or even a sequence or partial sequence is unpatentable', while Article 9 states that 'even a patentable invention – according to the European patent law – can be excluded if contrary to public order and morality'.

At the national level, the status of human genetic material is not so clear: some countries have not taken any position on the issue of status, or among the few that do, the position is often through an indirect reference. Whatever the country, any inventions even if patentable are still subject to the public order and morality filter of European patent law.¹⁹ Finally, while a property position may allow for actual or potential financial return, the personality approach avoids individual returns but not the possibility of commercialization by the researcher, through traditional intellectual property rules. Thus, irrespective of the qualification, ultimately, patenting is still possible but the locus of the financial benefits is different (*ibid*). There are important questions which remain unanswered about the social acceptability of the private ownership of gene patents, and the impact this might have on scientific research, innovation and the costs of new medical technologies.

Return of benefits to the community

In the case of research using donated samples, it is generally assumed that the individual donor is giving his biological material to further the collective good of the community, rather than his personal profit or the private profit of a company.^{41,59} Simultaneously, while some policies aim to encourage the commercial exploitation of publicly funded research, there is also a recognition that this must be matched by a suitable social return, either in the form of technology transfer, local training, joint ventures, provision of health care or information infrastructures, reimbursement of costs, or the possible use of a percentage of royalties for humanitarian purposes.^{13,25,60} As we noted it, some consider that research teams, whether they be situated in academe or industry, should disclose that they may someday benefit economically from the research and that the subjects will not.^{2,29} Potential subjects will then be free to decide whether they are willing to participate regardless of this stricture. According to the Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, if an invention is based on biological material of human origin or if it uses such

material, and where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law (Recital 26).

The remuneration of participants in genetic research is widely proscribed, irrespective of the fact that its use may ultimately lead to financial rewards for the researcher or industry. Although commodification (reification) and commercialization of the human body and its elements is not considered ethically sound,^{13,49,61} there is an emerging concern for a more equitable approach that provides some return of benefits to the community.^{13,14,60,62} Many new products, including vaccines and drugs for common diseases, are now based on genetic research. Much government or nonprofit research will eventually be commercialized and companies involved in human health may have special moral obligations.

The North American Regional Committee of the Human Genome Diversity Project⁶³ has proposed guidelines for providing benefits to sampled populations. Three basic principles should govern researchers in this connection: (1) Honesty, that is any benefits that are promised must be both deliverable and delivered. If the sampling is a part of research aimed at studying a disease, the community must be told so, but it should also be warned that the research may not lead to any useful knowledge and that even useful knowledge may not lead to treatments. (2) Legality, that is national and local laws in the areas where research is being conducted must be consulted to see what kinds of benefits may legally be given to whom. The researchers' national laws, or the conditions of any financial support for their specific project, may also affect what benefits can be legally given. (3) *Appropriateness*: the benefits must be appropriate in their nature, in their scale, and in their distribution within the community. The range of possible benefits that researchers might confer on a community could include products, supplies, training, or services. Money is one kind of benefit that demands particular mention: paying a community for participating may raise special concerns about legality and coercion. Transfer of scientific technology is another kind of benefit that may be particularly useful in some contexts. The scale of the benefit is also a crucial concern: an enormous benefit may make the process of informed consent meaningless by making it effectively impossible for the community to say no. Finally, researchers are obligated to do no harm through a careless distribution of benefits within the community.

The North American Regional Committee of the Human Genome Diversity Project⁶³ has identified two issues that might be viewed as providing benefits – medical services and financial interests in the samples and their use – but that might in fact raise special problems. The provision of medical services in connection with collecting samples for the HGD project may seem an almost uniquely good benefit, welcomed by almost everyone. Nevertheless,

providing the medical services must be culturally appropriate for the population and the kind of medical service must be both useful and feasible. Researchers must be also prepared to provide services to the entire community, not just those who provide samples. To limit medical benefits to the latter contravenes that principle and risks coercing individuals to participate. It is recommended that the research group considering medical services investigate that possibility during their early contacts with the group, long before sampling begins.

Concerning the second issue – financial interests in the samples and their use – the HGD project requires that all financial benefits issued from patenting and commercial use of samples and of the information derived from them should be returned to the community. The manner in which this resolution should be implemented is that anyone seeking access to the Project's samples or data would have to agree to be bound by contract to a set of rules concerning the rights of the sampled populations.

The HUGO Ethics Committee⁶⁰ presented a statement on benefit sharing. The Committee made six recommendations: (1) all humanity share in, and have access to, the benefits of genetic research; (2) benefits should not be limited to those individuals who participate in such research; (3) there should be prior discussion with groups or communities on the issue of benefit sharing – such prior discussion should include consideration of affordability and accessibility of eventual therapy, and preventive and diagnostic products of research; (4) even in the absence of profits, immediate health benefits as determined by community needs could be provided – immediate benefits include medical care, technology transfer, or contribution to the local community infrastructure (eg, schools, libraries, sports, clean water); (5) at a minimum, all research participants should receive information about general research outcomes and an indication of appreciation; the ethical advisability of provision of information to individuals about their results should be determined separately for each specific project; and that (6) profit-making entities should dedicate a percentage (eg 1–3%) of their annual net profit to health-care infrastructure or for vaccines, tests, drugs, and treatments, or, to local, national and international humanitarian efforts.

Case-studies

The ALSPAC study

The Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) is a research initiative of the University of Bristol in the United Kingdom designed to monitor and analyze different courses of health and development in a geographical cohort of children.⁶⁴ It is part of an international research program with counterpart studies in a number of European centers. The main aim is to understand the ways in which the physical and social environment interact,

over time, with the genetic inheritance to affect the child's health, behavior and development. The study is designed to link together information from a variety of sources including hands-on examination of the children, questionnaires completed by parents, health records, assays of biological samples and specific measurements of the environment in the home, and to use these unique data to test hypotheses on the causes and prevention of childhood ailments and disorders. Prospective data from early pregnancy and from maternal as well as child DNA permit transgenerational studies. Since 1991, ALSPAC has followed 14,000 families originating in the Avon area (www.alspac.bristol.ac.uk).

The DNA resource available for elucidating genetic interactions with environmental exposures is unique. A biological sample is collected from all mothers and children for whom permission is received. DNA is obtained from the mother from maternal blood samples already collected, and from the child from the umbilical cord, from cord blood and from further blood samples or buccal samples taken later in childhood. Where maternal blood is not available, buccal samples are taken. It is also planned to ask partners for buccal samples (*ibid*).

ALSPAC has its own independent Law and Ethics Committee since 1989 and genetic studies are guided by its Genetics Advisory Committee. The ALSPAC Ethics Committee feels that, in general, collection of biological samples during pregnancy or at delivery can be carried out without maternal consent, but that analysis of the samples should only be carried out if the mother has given consent. The mothers received the study brochure in pregnancy; it included information on the research that was envisaged at that stage. ALSPAC staff discussed the issues with each mother during pregnancy and most mothers signed the consent form. Where written consent had not been obtained prior to the mother giving birth, attempts were made to contact her by letter or at the clinic visit. In cases where samples are collected but a consent form has not been filed, the samples have not been used for research purposes (*ibid*). In 1999, consent for DNA analysis had been obtained for over 10 000 children.⁶⁵

The core activity of the ALSPAC study lies in the maintenance of data collection and ensuring its availability for collaborators. The costs of maintaining existing samples and data accumulation anticipates that all the tests will be sponsored. Funding has been obtained from a variety of sources, such as government bodies, charitable research organizations, individual sponsorship, and industrial companies. ALSPAC has received some industrial funding, but has not yet secured a collaboration with a biotechnology or pharmaceutical company to exploit its collection for genetics research.²⁵ In order to address the problem of a short fall in core funding, ALSPAC has requested that all applications for collaborators include a contribution towards the core costs of the study. This includes the

funding of particular core personnel, the costs of particular items of data on a fee per item basis, or a lump sum (www.alspac.bristol.ac.uk).

deCODE genetics and the Act on a health sector database

In order to investigate if some diseases thought of as being acquired have inherited forms, researchers have started to hunt for small groups or populations. In Iceland, genealogical and medical records that exist for most of the population greatly extend the scope of this approach.

In 1998, the Icelandic parliament, Althing adopted a law called the Act on a Health Sector Database, making it legal for the Minister of Health to grant a license to a private company to construct an electronic database containing selected and coded data from the country's health records. The database aims to increase knowledge in order to improve health and health services and can, by prudent cross-referencing with other databases, contribute to the discovery of genetic and environmental risk factors in common diseases and statistical data on disease and treatment. The extent to which the new genetics will affect the delivery of health care remains unclear and Iceland provides a unique opportunity for testing this (Icelandic Ministry of Health 1998). The health economics aim is that since the data in the records have been paid for out of public funds they are not owned by individuals or institutions and should be used for the public benefit (*ibid*).

The Act on a Health Sector Database grants deCODE genetics exclusive rights for 12 years to use the data for purposes of financial profit, under strict conditions laid down in the Act, the Regulation and the License and within provisions of the Icelandic Competition Act and the provisions of the EEA Agreement. The Licensee shall in the creation and operation of the health sector database refrain from abusing his position as Licensee in his business with parties purchasing his services and special business terms shall be based on general and transparent business terms. deCODE has entered into a nonexclusive arrangement with Hoffmann–La Roche for the purpose of researching the genetic origins of 12 common diseases.⁶⁶

The proposal for the IHD has been highly controversial both in Iceland and internationally. The Icelandic Medical Association and the World Medical Association opposed the Act.⁶⁷ Similarly, the Icelandic Psychiatric Association, the Association for Ethics in Science and Medicine (Mannvernd), and the National Bioethics Committee opposed the Bill mainly because there was no provision for informed consent. The Icelandic Parliament attempted to address the criticisms of the proposal by redrafting the Health Sector Database Act, and the regulation that governs the establishment and running of the database was issued in January 2000.

Some of the most important concerns about the creation of the Icelandic database have centered on issues of privacy

and data protection. The dangers of invasion of privacy inherent in modern technology and science are judged to be considerable and this has led to attempts to ensure protection through various international policy documents and legislation.^{49,68–70} For instance, the recommendation from the European council³⁰ is explicit about the issue of informed consent for clinical trials on human subjects and on gathering and storing identified health-care information. However, the Icelandic legislation does not require explicit consent of the individuals whose information is to be submitted to the database, since this information will not be identified or identifiable with reasonable effort. Even if the data in the Icelandic health sector database are seen as anonymous, those who object can opt out of it, but it will generally be assumed that those who do not opt out can be included in the patient records database.

There are also fears that data cannot be kept confidential, even if the Icelandic Act includes measures 'to ensure protection of confidentiality in connecting information from the Health Sector Database with the databases of genealogical and genetic information' (Article 10) and even if 'employees of deCODE must sign an oath of confidentiality' (Article 11).⁷¹ Also, Article 14 states that 'providing information on individuals from the Health Sector Database is prohibited and only statistical information involving groups of individuals may be provided'. deCODE has developed a third-party encryption system supervised by the Data Protection Commission, but many people argue that in a country such as Iceland, where there are only 270 000 people, it will be possible to establish which data belong to which individuals, particularly in cases of rarer conditions. Moreover, since the database is a dynamic system, with data being added to it all the time from hospital records, newly added data may be identifiable.⁷²

Another set of concerns surrounds who has access to sample collections and databases of genetic information. The Icelandic Act has provision to regulate access and the use of the database, but deCODE's exclusive license to build the database and its exclusive rights to commercial exploitation of the database for 12 years as well as its (nonexclusive) arrangement with Hoffmann–La Roche have given rise to some of the major criticisms. Some scientists in Iceland believe that the health sector database will diminish their research opportunities.⁷³ The Icelandic Government's answers are that the database will increase the research opportunities for scientists in Iceland in relation to funding, access to patients and to patients' records.⁷⁴

Guthrie Cards

There are a variety of potential sources of samples that may be stored and used for subsequent purposes. The subsequent use of stored Guthrie cards is receiving increased attention as a source of DNA for research and testing

purposes.^{33,75} Guthrie cards are the name given to the way in which the blood taken from newborn babies for genetic screening programs has been traditionally stored. Recognition of the epidemiological utility of dried blood spots on Guthrie cards for HIV seroprevalence surveys and a growing interest for DNA analysis has intensified consideration of issues regarding retention, storage, and use of residual dried blood spot samples. These samples potentially provide a genetic material 'bank' for all newborns nationwide.⁷⁶ In 1994, an American study showed that although most state newborn-screening laboratories retain Guthrie cards, if at all, for only a short time, a growing number plan to keep them for an extended period and, in several cases, indefinitely. A large number of laboratories would also consider sharing anonymous cards for research purposes.⁷⁵

However, newborn screening programs vary widely in approaches and policies concerning residual dried blood spot samples collected for newborn screening. Most of the time, newborns' blood spots are obtained in screening programs for treatable diseases. In general, newborn screening programs do not require a specific written consent for the testing for treatable disorders, but if research is proposed, parental consent is necessary. In 1993, the Danish Council of Ethics recommended that 'stored newborn blood spots may be used subsequently for research without consent only if samples are anonymous'; even if parental authorization remains the norm for research using identifiable newborn samples, the Danish Council of Ethics recognizes that in some cases, using identifiable samples, it may be inappropriate to approach the parents. Since 1993 the Danish biobank, where Guthrie cards are stored, has been regulated by specific legislation, and thus assumes a unique position among biological specimen banks. Its purposes are: (1) diagnosis and treatment of diseases screened for, including repeat testing, quality assurance and group statistics; (2) other diagnostic uses during infancy; and (3) research projects. The stored samples have been used successfully to diagnose a range of genetic diseases using biochemical and molecular genetic assays.⁷⁷ Storage of neonatal screening samples is thus beneficial not only to the individual testees, but also to future generations of newborns.

Other bodies have proposed guidelines for the retention, storage, and use of Guthrie cards. In 1995, the WHO recommended that 'blood spots collected in screening newborns for treatable disorders could be used to provide epidemiological information about genetic predisposition to late onset disorders. Care must be taken to ensure that such testing remains anonymous and that results cannot be traced to individuals or families'. However, retention of some demographic data may be of considerable use to epidemiologists. It has been argued that in countries that have adopted positions on genetic epidemiology research, those requirements could apply to anonymized research on

newborn samples.¹⁹ In 1996, according to the American Council of Regional Networks for Genetic Services, a federally funded national consortium of representatives from 10 regional genetics networks, newborn screening programs should promulgate policies and rules for retention and use of residual newborn screening dried blood spot samples, based on scientifically valid information. Banking of newborn samples as sources of genetic material should be considered in light of potential benefit or harm to society.⁷⁶

Actually, most state newborn screening programs have few or no procedures for retaining, storing, retrieving, and using Guthrie card samples. Few scientifically sound procedural systems for use of dried blood spot samples remaining after newborn screening currently exist. In light of the growing interest in novel uses of stored Guthrie cards, it may be time to do so. The ethical concerns about issues related to privacy may ultimately dictate policies related to retaining or destroying residual dried blood spot samples (*ibid*). To date, no regulations exist that provide anonymity or guarantee privacy of newborn blood samples on Guthrie cards.

Discussion

Setting the scene

It came out during the workshop organized by the ESHG (see Methods) that DNA banking for medical and research purposes is indispensable. It facilitates the constitution of large collections, sharing of samples, multiple testing on the same samples, and repeating testing over the years. However, banking organization is complex, requires multiple actors, and concerns are expressed in various countries. Points of discussion focussed on ethical issues *vs* law requirements as well as on primary use *vs* secondary use of DNA samples, or for clinical *vs* research uses, or for new collections *vs* existing collections, or with identifiable individuals *vs* anonymous banking. Among ethical issues, informed consent, protection of confidentiality, sharing and commercial uses, guidelines within the institutions and the professional organizations, as well as control process issues were addressed. Ethical principles concerning the protection of individuals participating in research projects state that consent must be informed and confidentiality and private life must be protected. Also, human body elements may not be commercialized and genetic testing must be limited to medical or research use with the agreement of an ethics committee. Nevertheless, consent forms often do not completely fulfill ethical requirements. It has been reported that some issues are poorly addressed, such as further use of samples, feedback of results, sharing, non profit or for profit uses, consent for using specimens of died individuals. In the same way, there is no consensus about how to manage and organize collections of human material for genetic studies. Many instances promote the

free circulation and the availability of genetic information and samples for research. But it has been noted that research is a highly competitive activity, which is predominantly due to the academic pressure to publish as productivity contributes greatly to obtaining and keeping research grants. Considering the impressive costs associated with contemporary research techniques, the latter have become the principal means of survival of any research group. In addition, financial gain and lack of understanding of the research process might impair collaboration between research institutes. Consent for genetic studies has specific features which should also be taken into account at an international level.

DNA banking practices raise economic issues, such as the funding of DNA banking for research, the role of private firms, and the use of DNA banking for health care. Although the running costs are difficult to estimate because few bank managers know which financial, material, and human resources are dedicated to the banking activities, these costs can be substantial, and financing a bank may be difficult for researchers. In order to maintain the collections, some academic laboratories collaborate with private firms; nevertheless, this collaboration raises the question of the autonomy of academic laboratories *vis-à-vis* the private sector and *in extenso* the question of the mediation by private firms. The transfer from research to routine laboratories is facilitated thanks to the mediation of the industry which transforms research results into commercial products. But this ideal scheme of transfer is not always possible for all DNA activities because of the uncertain profitability which leads to short-term investments, to the transfer of costs to public laboratories, and to funding by patient's associations. Although the recognition of DNA banking as part of medical practice appears essential, questions remain concerning the financing solutions for DNA banking. Would a national or European centralization of DNA banks be a solution in order to realize economies of scale and to cut costs?

DNA banking practices also raise legal issues, such as problems of human dignity, ownership, commodification and threat to privacy. The DNA qualification has an impact on the legal issues related to DNA: the physical aspect (biological material) raises questions about attitudes towards the human body and body parts; the informational aspect (code) is linked to prevailing attitudes towards medical information generally. The commercial interests in DNA banks have risen along with the development in molecular genetic techniques allowing replication of the DNA material. Consequently, it appears necessary (1) to control the flow of banked DNA and DNA data, (2) to develop policies to regulate DNA banking more closely, and (3) to insure that DNA banking can perform its function without impinging on the rights and interests of individuals who have their DNA sample or DNA data in a bank.

Because of the recognized value of banking genetic material, many policy statements have begun to address DNA banking in the 1990s. These policy statements define the scope of informed consent extensively to ensure that individuals who provide samples are given the opportunity to make informed choices with respect to the possible uses of their stored samples. But there is some debate as to whether the principle of consent can be met in every research situation. At the time that new collections are created it is difficult to foresee all future research applications. In the case of existing collections, it may be impractical to gain consent for new research uses from the donors of the samples. For instance, specimens taken at autopsy and stored in paraffin blocks are basically DNA banking and are occasionally valuable sources for family investigation or research. Who should give informed consent for using specimens of died individuals? In other respects, worldwide research endeavors have raised the issue of access to and sharing of banked samples. While protecting confidentiality, the free circulation and the availability of genetic information and samples for research has been promoted by many regulatory bodies. Many policy statements have also begun to identify security and regulatory mechanisms for DNA banking. However, there remains a diversity of positions on the banking and further use of DNA samples regarding coding and anonymization of samples, retrospective and secondary uses, and duration of storage.

In order to prevent the abuse of individuals' rights and to protect human integrity, return of benefits to the community were also analyzed. Principles concerning samples donated for research state that they are given for the collective good of the community without possible legal claim on the intellectual property. In compensation, a suitable social return is proposed either in the form of provision of health care or information infrastructure or the collective use of a percentage of royalties for humanitarian purposes. Such is the case, for instance, for the Icelandic pharmaceutical company, deCODE genetics, which has agreed to compensate participants by providing them with free access to any tests or pharmaceuticals developed from the studies, during the life of the patents. Independence of the decision maker and of the body to receive the royalties is crucial to avoid coercion. Potential donors must be informed of the potential financial benefits for the research team in order to be free to decide whether they are willing to participate. However, the actual or future benefits should not serve as an inducement to participation. Benefits should be provided to all members of the community regardless of their participation in the research.

The concept of benefit sharing is not limited to the possible therapeutic benefit of participating in research. In the past, many researchers sought no specific reward for biomedical research. More recently, due to increasing

private investment, researchers and institutions often demand a share of monetary benefits deriving from their research. In other respects, some people consider that since the vast majority of the advances in science represent mere theoretical insight, usually procured by analyzing large numbers of samples and unfortunately not generally linked to immediate financial gain, a certain contribution to scientific progress should be considered an acceptable and suitable social return as well.

Issues to be raised

At present, there is no official census of genetic banks; the number, the kind of biological material stored, the services available, as well as the financial supports are not known. Many biological sample collections are derived from neonatal screening, research projects, and diagnostic laboratories, but the majority is not dedicated to the acquisition, characterization, identification, preservation, and distribution of DNA samples. In Italy, genetic banks supported by the Telethon are editing guidelines for quality control, in particular for material preservation and shipping and respect of privacy.

In other respects, it is reported that pathology departments have constituted the largest human biological collections and this has great potential in terms of genome investigation. DNA obtained from archived tissues, blood films, slides may be useful to establish the molecular diagnosis of a deceased patient. This information may be of value for relatives even after 10–20 years. Consequently, regulations concerning pathologic archives should be considered. However, it has been argued that apart from the interesting genetic information a tissue biopsy provides, often with regards to peculiar pathologic conditions, it also supplies invaluable immunomorphological information. In addition, although the collected material in principle allows genetic analyses of nearly any kind, it is especially suited to gain insight in the genetic mechanisms underlying particular diseases. As such, after an accurate diagnosis has been established, the biopsy is not so much of interest to the individual or his relatives, but rather serves the investigation of disease mechanisms.

DNA banking is progressively part of medical practice. A new field, called 'Community Genetics' is emerging, where DNA banking is expected to play an important role and for which the help of clinicians is requested. Although this activity may be justified, it may be problematic because some aspects risk to be in conflict within the role of the clinician, which is to contribute both to the health of individuals or families and the people as a whole. DNA banking may be in the interest of the patient when the diagnostic measure was preliminary or unsuccessful or when the patient may wish to declare this family's interest as his own. DNA banking may be also in the interest of the patient's family when a sample of an index case needs to be stored for future diagnostic purposes. But DNA banking

may be also in conflict with the interests of the patient and of his family in case of fear of unwanted information or of breach of confidentiality or of undesired research. Conflicts between patients and families may be important when a patient may wish his sample not to be stored or his existing sample to be discarded even though his sample may be of value to his relatives. It has been argued that if storage of a patient's sample is in the vital interest of a relative, it may be ethically defensible to keep the sample. Finally, at the community level, DNA banking may be in the interest of the people for instance for monitoring susceptibility alleles contributing to complex diseases, in order to take preventive action. But DNA banking may be also in conflict with the interest of the people because of discrimination's risks. To contribute to research into the genetic diseases may be an important role of the clinician provided that the desired degree of intimacy between clinician and patient is safeguarded.

DNA banking is also expected to play an important role in pharmacogenetics. For monogenic diseases current linkage methods are now efficient in identifying mutant genes, depending mostly on the total amount of family structures and DNA samples available. For susceptibility genes, identifications of confirmed polymorphisms associated with the disease have been much more challenging. For this purpose, scientists have constructed a high-density single-nucleotide polymorphism (SNP) map for disease susceptibility gene searches through large linkage regions. The construction of a whole genome high-density SNP map focuses the next stage of susceptibility disease gene research on the availability of well-constructed, accurately phenotyped patient populations. Glaxo Wellcome is now generating patient collections from multiple diseases with large unmet medical need. Pharmacogenetics does not only refer to susceptibility gene identification, but also to 'right medicine for right patient'. Genetic profiling can be used to recognize patients who will respond positively to a particular medicine or to identify patients who will have an adverse event by taking a particular medicine. It is expected that genetic profiling will be performed at a reasonable cost by using a standardized genetic map.

Analysis of practical examples

The functioning of two large-scale DNA banks was presented and discussed, ALSPAC and deCODE genetics. The Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) aims to be a general reference population for genetic and environmental epidemiology. A general description is available on website <http://www.ich.bristol.ac.uk>. ALSPAC has his own independent Law and Ethics Committee since 1989 and genetic studies are guided by its Genetics Advisory Committee. ALSPAC enrolled 14,000 pregnancies during 1991 and 1992 representing 85% of the eligible population. Samples for DNA extraction have been taken from the child (cord and ALSPAC clinic blood at 7

years old) mother (pregnancy blood) and fathers (mouthwash samples). The ownership of samples is transferred to the University of Bristol. Consent for confidential DNA analysis has been obtained on over 10 000 children. Samples are stored in an anonymous storage facility. Any proposal to de-anonymize the samples would require the cooperation of the Director and the consent of the Ethics Committee. This latter has not so far approved any such proposal and is very unlikely to do so except in the most unusual circumstances. The identity of those who provided the sample is contained in a wholly separate storage facility. Access to both stores is very limited. Individual genetic data may only be fed back if they are of clinical relevance and if a beneficial therapeutic intervention exists. This will be considered on a case by case basis by the ALPAC Ethics Committee. In other respects, the Ethics Committee would not willingly agree to use the material for purposes which were not clearly stated in the original consent form. In practice, the study is in a great deal of contact with the vast majority of the members of the sample and it is not therefore excessively difficult to make further applications for the consent.

Some scientists in England have taken the position that in principle DNA samples should be treated as in the public domain and available to all scientists free of charge. In the case of ALSPAC, although the arguments in favor of worldwide access to knowledge free of charge are acceptable, these arguments are not applicable in the present context. Mothers who entered the study received specific assurances as to the use which will be made of information and samples that they have provided. It does not seem acceptable to disregard these assurances. It is reported that mothers would probably not have cooperated in the way they have if assurances of this kind had not been made. It is an integral part of the ALSPAC study that good relationships should be maximized with mothers and children during the whole of the very lengthy period during which the study will run.

deCODE genetics is another large scale DNA bank. A general description is available on website <http://www.decode.is>. The Act on a Health Sector Database makes legal for the Minister of Health to grant a license to deCODE genetics. The terms and conditions for this license are described in a document, which, like the regulation, is available on the Health Ministry website (<http://brunnur.stjr.is/interpro/htr/htr.nsf/pages/forsid-ensk>). It came out during the workshop that 58% of the population were in favor of the Act against 19.4% who were against it. The Health Sector Database that is built by Decode Genetics will contain medical data generated within the Icelandic health system and could be linked to genealogy, environmental, and genetic data that is obtained through individual informed consent. Even if a centralized health-care information has advantages, such a database raises issues on community consent, protection of privacy and

freedom of science. No genetic data would be added to the database without informed consent by the individual. On the contrary, the medical data would be brought in without informed consent but individuals may opt out of the database at anytime. The 'opt out' clause has been criticized because patients who halt participation are not allowed to withdraw their data after entry into the database. As justification, it has been argued that the Act results from an informed democratic decision, but according a Gallup survey, only 13% of the population considered themselves to have a good grasp of the bill. It is argued that while the decision was democratic, if defined as a majority vote in parliament, such a decision should not supersede individual consent when it comes to participation in human investigations.

Conclusion

Data storage and DNA banking is receiving increasing attention as a result of the explosion of genetic research. Like in Iceland, large population-based studies have been set up or are planned at a national level in several countries including Estonia, Singapore, Tonga and UK. Consent, confidentiality, and coding are the key principles for DNA banking found in most statements. With experience in banking, with the advent of the creation of cell lines, with the need for international collaborative research teams to share DNA, and with a heightened sensitivity to patient consent to secondary uses, consent to banking was becoming more specific and personalized. Despite a consensus on requiring consent for subsequent use of identifiable or identified samples and an emerging consensus on subsequent use without consent of anonymous samples, appropriate consent requirements when anonymizing samples for retrospective and prospective studies remain controversial. Ambiguities due to the type of banked sample also prevail with respect to controlling and authorizing access to and sharing of samples with relatives or other researchers. For identifiable or identified samples, should conditions under which samples may be shared be clarified or should individuals always retain control on their samples? The feasibility of an individual to request that samples be destroyed is questionable and it may be preferable to ensure protection of the subject through other means. International standardization of ethical requirements and policies with regard to the use of DNA samples and information has been recommended.³¹ A such standardization would facilitate a greater protection of individuals as well as future international cooperation in biomedical research.

In fact, biomedical research has always transcended borders. Now the demand to transfer DNA samples and data across national borders is increasing. But such transfer will not occur fluently until a number of issues are

resolved. There is a pressing need for an organization to take an international leadership and coordinating role. Several organizations, either the OECD, or the European Commission, or the WHO, or professional and trade organizations could be involved. The mandated organization could examine transborder samples and data flows. It could be concerned with the facilitation of samples and data flows as well as with data protection, ownership and legal accountability, and access to networking. It might also encourage collaborative efforts between the public and private sectors on these issues. As it has been recommended by the National Bioethics Advisory Commission,⁵ health-care organizations and professional societies should continue and expand their efforts to train researchers about the ethical issues and regulations regarding research on human biological materials and to develop exemplary practices for resolving such issues.

Proper protection of individuals relies on good regulatory mechanisms but also on transparency. Research that will ultimately benefit human health is crucially dependent on commercial involvement. Therefore access by the commercial sector – as well as academic researchers – to DNA samples might be facilitated. However, it is essential that research participants are made aware that their sample or products derived from it may be used by the commercial sector, and that they will not be entitled to a share of any profits that might ensue.^{4,15} As to researchers, when obtaining samples of human material from abroad, they must be satisfied that samples have been ethically obtained. Researchers should obtain from the clinicians providing samples assurances that they were obtained with proper consent in accordance not only with these guidelines but also with guidelines applicable in the country of origin. Furthermore, for the Medical Research Council, it is not appropriate for any one particular company to be given exclusive rights of access to collections of samples made with the benefit of public funds.

Recognizing that DNA samples are essential for biomedical research, it is also essential to respect the interests of those who participate as research subjects in regard to deciding control over and subsequent use of sample. Where human genetic material is considered as part of the 'person', providing it for research purposes is a consequence that is naturally assumed not to be associated with any financial benefit. In contrast, consideration of human genetic material as 'property' allows an individual to negotiate eventual commercial benefits, at least in the absence of legislation.⁶² With the exception of the United States (The Genetic Privacy Act 1994),²⁶ most international, regional, and national bodies prohibit payment for the procurement of human genetic material or a possible payment or interest in eventual profits. They are contemplating instead the possibility of benefit sharing from downstream profits arising from genetic information. The acceptance of the notion of benefit sharing may certainly

be seen as a recognition of the contribution of participating communities and populations.

References

- 1 Deschênes M, Cardunal G, Knoppers BM, Glass KC: Human genetic research, DNA banking and consent: a question of "form"? *Clin Genet* 2001; **59**: 221–239.
- 2 McEwen JE, Reilly PR: Setting standards for DNA banks: toward a model code of conduct, *Microb. Comp. Genomics* 1996; **1**: 165–177.
- 3 Moutel G, de Montgolfier S, Meningaud JP, Herve C: Bio-libraries and DNA storage: assessment of patient perception of information. *Med Law* 2001; **20**: 193–204.
- 4 Medical Research Council: Human Tissue and Biological Samples for Use in Research, Operational and Ethical Guidelines, 2001.
- 5 National Bioethics Advisory Commission (NBAC): *Research involving human biological materials: ethical issues and policy guidance*. Rockville, MD; August 1999.
- 6 Clinical Genetics Society Yates JRW, Malcom S, Read AP: Guidelines for DNA Banking. *Med Genet* 1989; **26**: 245.
- 7 Danish Council of Ethics: *Ethics and mapping of the human genome*. Copenhagen: Danish Council of Ethics; 1993.
- 8 Health Council of the Netherlands: *Proper Use of Human Tissue*. The Hague: Health Council of the Netherlands; 1994.
- 9 Human Genetics Commission: Inside information: balancing interests in the use of personal genetic data, 2002.
- 10 Wertz D: Archived specimens: a platform for discussion. *Community Genet* 1999; **2**: 51–60.
- 11 American society of human genetics, statement on informed consent for genetic research: *Am J Hum Genet* 1996; **59**: 471–474.
- 12 American Society of Human Genetics: Response to the NBAC on ethical issues surrounding research using human biological samples, January 15, 1999.
- 13 Human Genome Organization (HUGO): Statement on the Principled Conduct of Genetic Research. *Genome Digest* 1996; **32**: 2.
- 14 World Health Organization (WHO): Proposed international guidelines on ethical issues in medical genetics and genetic services. Geneva: WHO; 1997.
- 15 Medical Research Council: Human Tissue and Biological Samples for Use in Research. Report of the Medical Research Council Working Group to develop Operational and Ethical Guidelines, 1999.
- 16 American Society of Human Genetics, Ad Hoc Committee on DNA Technology: DNA banking and DNA analysis: points to consider. *Am J Hum Genet* 1988; **42**: 781–783.
- 17 Danish Council of Ethics: *Health science information banks – Biobanks*. Copenhagen: Danish Council of Ethics; 1996.
- 18 American College of Medical Genetics, Laboratory practice committee quality assurance subcommittee: *Standards and guidelines: clinical genetics laboratories*. Bethesda; 1994.
- 19 Knoppers BM, Hirtle M, Lormeau S, Laberge C, Laflamme M: Control of DNA samples and information. *Genomics* 1998; **50**: 385–401.
- 20 Hirtle M: International policy positions on the banking of human genetic material. in Knoppers BM, Caulfield T, Kinsella TD (Eds): *Legal rights and human genetic material*. Toronto: Emond Montgomery Publications Limited; 1996.
- 21 France Ministry of Higher Education and Research. Report of the Study Group on the Intellectual Protection of the Results of Research on the Human Genome, Cell Collection, and DNA Sequence Data, Paris, June 10, 1994.
- 22 Eisman E: *Stored tissue samples: an inventory of sources in the United States*. Washington DC: RAND Critical Technologies Institute; 1999.
- 23 Marshall E: Clinical research Company plans to bank human DNA profiles. *Science* 2001; **26**: 575.
- 24 Service RF: Can data banks tally profits? *Science* 2001; **16**: 1203.

- 25 Martin P, Kaye J: *The use of biological sample collections and personal medical information in human genetics research*. London: The Wellcome Trust; 1999.
- 26 American College of Medical Genetics, Storage of Genetic Materials Committee: ACMG Statement, Statement on storage and use of genetics materials. *Am J Hum Genet* 1995; 1499–1500.
- 27 Medical Research Council: Human tissue and biological samples for use in research. Report of the Medical Research Council Working Group to develop operational and ethical guidelines. London: Medical Research Council; 1999.
- 28 Royal College of Physicians Committee on Ethical Issues in Medicine: Research based on archived information and samples. *J Roy College Phys London* 1999; 33: 264–266.
- 29 Reilly PR: Efforts to regulate the collection and use of genetic information. *Arch Pathol Lab Med* 1999; 123: 1066–1070.
- 30 Council of Europe. Recommendation No. R (97)5 of the Committee of Ministers to Member States on the Protection of Medical Data; 1997.
- 31 HUGO Ethics Committee. Statement on DNA sampling control and access: 1998.
- 32 The Swiss Academy of Medical Sciences: *Medical-ethical guidelines for genetic investigations in human*, Approved by the Senate of the Swiss Academy of Medical Sciences; June 1993.
- 33 Clayton EW, Steinberg KK, Khoury MJ, Thomson E, Andrews L, Kahn MJE, Kopelman ML, Weiss JO: Informed consent for genetic research on stored tissue samples. *JAMA* 1995; 274: 1786–1792.
- 34 French Ordinance: Laying down various measures of a health-related, social, and statutory nature. Ordinance No. 96-452; 28 May 1996.
- 35 Nuffield Council on Bioethics: *Human tissue: ethical and legal issues*. London: Nuffield Council on Bioethics; April 1995.
- 36 Swibel LH: Tissue banking: genetic donations and informed consent. *Princet J Bioeth* 1999; 2: 6–17.
- 37 Nelkin D, Andrews L: Do the dead have interests? policy issues for research after life. *Am J Law Med* 1998; 24: 261–291.
- 38 De Renzo EG, Biesecker LG, Meltzer N: Genetics and the dead: implications for genetics research with samples from deceased persons. *Am J Med Genet* 1997; 69: 332–334.
- 39 American Society for Investigative Pathology. Use of human tissues for molecular research: 1996.
- 40 Association of American Medical Colleges: Health data security, patient privacy, and the use of archival patient materials in research, United States, 27 February 1997.
- 41 Greely HT: Informed consent and other ethical issues in human population genetics. *Ann Rev Genet* 2001; 35: 785–800.
- 42 Tri-Council of Canada, Medical Research Council, Natural Sciences and Engineering Research Council: Social Sciences and Humanities Research Council, Code of Conduct for Research Involving Humans. Ministry of Supply and Services Canada, Ottawa; 1997.
- 43 North American Regional Committee: Human Genome Diversity Project. *Houston Law Rev* 33: 1431–1473.
- 44 Lähteenmaki R: Estonian parliament considers genome law. *Nature Biotech* 2000; 18: 1135.
- 45 McQueen MJ: Ethical and legal issues in the procurement, storage and use of DNA. *Clin Chem Lab Med* 1998; 36: 545–549.
- 46 Ashcroft R: The ethics of reusing archived tissue for research. *Neuropathol Appl Neurobiol* 2000; 26: 408–411.
- 47 National Bioethics Advisory Commission: *Research involving persons with mental disorders that may affect decisionmaking capacity*, 2 Vols. Washington DC: U.S. Government Printing Office; 1998.
- 48 Council of Europe: Recommendation No. R (89)4 of the Committee of Ministers to Member States on Collection of Epidemiological data on Primary Health Care. *Int Dig Health Leg* 1990; 41: 148.
- 49 UNESCO – International Bioethics Committee: Universal declaration on the human genome and human rights. Paris; 11 November 1997.
- 50 Knoppers BM: Ethical aspects of genome research and banking. *Biotechnology* 2001; 5b: 418–427.
- 51 Health Council of the Netherlands: Heredity: science and society – on the possibilities and limits of genetic testing and gene therapy. The Hague: Health Council of the Netherlands; 1989.
- 52 Ministry of Health and Social Affairs of Norway. Biotechnology Related to Human Beings (Report No. 25) Norway, 1992–1993.
- 53 Nuffield Trust Genetics Scenario Project: *Genetics and Health: Policy issues for genetic science and their implications for health and health services*. London: Nuffield Trust; 30 May 2000.
- 54 Annas GJ, Glantz LH, Roche PA: Drafting the Genetic Privacy Act: science, policy, and practical considerations. *Law Med Ethics* 1995; 23: 360–366.
- 55 Veatch RM: *A theory of medical ethics*. New York: Basic Books; 1981.
- 56 Skene L: Ownership of human tissue and the law. *Nat Rev Genet* 2002; 3: 145–148.
- 57 Human Genome Organization: *Position statement on cDNAs: Patients*. London, 6 January 1992.
- 58 Human Genome Organization: *Statement on patenting of DNA sequences*. *Genome Digest* 1995; 6: 2.
- 59 Greely HT: The control of genetic research: involving the “groups in between”. *Houston Law Rev* 1997; 33: 1397.
- 60 Human Genome Organization: Statement on Benefit-Sharing. Vancouver, 9 April 2000.
- 61 World Health Organization: *Control of hereditary diseases – report of a WHO scientific group*. Geneva: WHO; 1 January 1996.
- 62 Knoppers BM: Status, sale and patenting of human genetic material: an international survey. *Nature Genet* 1999; 22: 23–26.
- 63 North American Regional Committee–Human Genome Diversity Project: Model Ethical Protocol For Collecting DNA Samples. *Houston Law Review* 1997; 1431–1473.
- 64 Jones RW, Ring S, Tyfield L et al.: A new human genetic resource: a DNA bank established as part of the Avon longitudinal study of pregnancy and childhood. *ALSPAC* 2000; 8: 653–660.
- 65 Pembrey M, Golding J: *The Avon Longitudinal Study of Pregnancy and Childhood*. VIIIth CEPH Annual Conference on Human Genetics. Paris; 1999; 65.
- 66 Haraldsdottir R: Fire and fury in Iceland. Will Iceland’s privately-financed central health database compromise patient confidentiality? Science Public Affairs, British Association for the Advancement of Science. The United Kingdom, February: 2000.
- 67 Duncan N: World Medical Association opposes Icelandic gene database. *BMJ* 1999; 318: 1096.
- 68 Council of Europe. Recommendation R(81) 1 on Regulations for Automated Medical Data Banks: 1981.
- 69 Council of Europe: Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine. *Int Dig Health Leg* 1997; 48: 99.
- 70 Council of Europe, Recommendation 152. Protection of the Human Genome: 2001.
- 71 Andersen B, Arnason E: Iceland’s database is ethically questionable. *BMJ* 1999; 318: 1565.
- 72 Berger A: Private company wins rights to Icelandic gene database. *BMJ* 1999; 318: 11.
- 73 Chadwick R: The Icelandic database—do modern times need modern sagas? *BMJ* 1999; 319: 441–444.
- 74 Haraldsdottir R: A tool for the future. *BMJ* 1999; 318: 11.
- 75 McEwen JE, Reilly PR: Stored Guthrie cards as DNA banks. *Am J Hum Genet* 1994; 55: 196–200.
- 76 Therrell BL, Hannon WH, Pass KA et al.: Guidelines for the retention, storage, and use of residual dried blood spot samples after newborn screening analysis: statement of the Council of Regional Networks for Genetic Services. *Biochem Mol Med* 1996; 57: 116–124.
- 77 Norgaard-Pedersen B, Simonsen H: Biological specimen banks in neonatal screening. *Acta Paediatr Suppl* 1999; 88: 106–109.

Appendix A

International and national regulatory frameworks

Many policy statements address the storage of human genetic material when it is carried out in a clinical context principally for diagnostic purposes. Policy statements have begun to address DNA banking for research purposes more recently mainly because of the recognized value of banking human genetic material for the advancement of research. These policy statements do not specify any precise research use or any restrictions as to the types of research that can be conducted. These policy statements define the scope of informed consent extensively to ensure that individuals who provide samples are given the opportunity to make informed choices with respect to the possible uses of their stored samples. These policy statements attempt to recognize that respect for the rights of individuals and respect for human dignity constitute the ethical and legal foundations for excluding human tissues and cells as possible objects of commerce.^{20,50,62}

International Organizations

- **UNESCO, *The Universal Declaration on the Human Genome and Human Rights, November 1997.*** Two articles of the present Declaration are fundamental regarding DNA banking. Article 1 recognizes both the individuality of the human genome and its shared character: 'the human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity'. Article 4 recognizes the principle of noncommercialization: 'the human genome in its natural state shall not give rise to financial gain'. Although nonbinding to member nations, the declaration provides grounds for individuals within those nations to challenge laws that appear to run counter to the declaration.
- **UNESCO International Bioethics committee, *Report on confidentiality and genetic data, 1999.*** The report consists of five parts. The third part of the report deals more specifically with the principle of confidentiality as applied to genetic data. Although genetic data may be qualified as medical information, it should be brought under a specific framework inasmuch as it provides sensitive information not only about an individual but also about his family. This part also includes a detailed analysis of Article 7 of the Universal Declaration on the Human Genome and Human Rights according to which data must be 'associated with an identifiable person and held confidential in the conditions set by law'.
- **HUGO Ethical, Legal, and Social Issues Committee, *Statement on the Principled Conduct of Genetic Research, 1996.*** HUGO considers the human genome as part of the 'common heritage of humanity'. This principles has for consequence a 'loss of access to discoveries for research purposes, especially through patenting and commercialization'. The Organization recommends that 'undue inducement through compensation for individual participants, families, and populations should be prohibited. This prohibition, however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of health care or information infrastructures, reimbursement of costs, or the possible use of a percentage of royalties for humanitarian purposes'.
- **HUGO Ethics Committee, *Statement on DNA Sampling Control and Access, 1998.*** This statement reaffirm HUGO commitment to its position given previously in its Statement on the Principled Conduct of Genetic Research. 'It maintains that respect for free and informed consent and choice as well as for privacy and confidentiality in the collection, storage and use of human DNA are the cornerstones of ethical conduct in research. It reiterates the importance of recognizing that the pursuit of scientific knowledge is essential to human progress and to the relief of human suffering. This pursuit must adhere to international norms of human rights. In the context of research involving human beings, the acceptance and upholding of human dignity and freedom require prior ethical review. Respect for individual values, familial needs and cultural differences as well as the possibility of withdrawal of consent to participate without prejudice are ethical prerequisites'.
- **HUGO Ethics Committee, *Statement on benefit Sharing, 2000.*** The HUGO Ethics Committee recommends: (1) that all humanity share in, and have access to, the benefits of genetic research; (2) that benefits not be limited to those individuals who participated in such research; (3) that there be prior discussion with groups or communities on the issue of benefit sharing; (4) that even in the absence of profits, immediate health benefits as determined by community needs could be provided; (5) that at a minimum, all research participants should receive information about general research outcomes and an indication of appreciation; (6) that profit-making entities dedicate a percentage (eg, 1–3%) of their annual net profit to health-care infrastructure and/or to humanitarian efforts'.
- **The World Medical Association, *Declaration on the Human Genome Project (WHO), Geneva, 1992.*** The recommendations emphasize the need to state general ethical and legal guidelines to prevent discrimination and the genetic stigma of the population at risk.
- **The World Health Association, *Proposed international Guidelines on Ethical Issues in Medical Genetics and the Provision of Genetic Services, Geneva, 1997.*** While recognizing the individuality of the human genome, WHO emphasizes its familial basis: 'DNA is both unique to an individual and shared by other individuals who are biologically related. Therefore, DNA should not be

considered private property and control of DNA should be familial not individual'. (...) 'DNA should be banked as long as it could be of benefit to living or future relatives or fetuses. Banked DNA could also serve public health purposes. As for stored pathological tissue specimens, they may be useful to families in the future'. (...) Existing stored specimens or samples, such as those in university or hospital departments should not be subject to new rules for consent or recontact that may be established in the future.

European Institutions

- **Council of Europe, Recommendation R(81) 1 on Regulations for Automated Medical Data Banks, 1981.** The following principles apply to automated medical data banks set up for purposes of medical care, public health, management of medical or public health services or medical research, in which are stored medical data and, as the case may be, related social or administrative data pertaining to identified or identifiable individuals (automated medical data banks). (1) Every automated medical data bank should be subject to its own specific regulations, in conformity with the laws of the state in whose territory it is established. The regulations of medical data banks used for purposes of public health, management of medical and health services, or for the advancement of medical science should have due regard to the pre-eminence of individual rights and freedoms. (2) The regulations should be sufficiently specific to provide ready answers to those questions likely to arise in the operation of the particular medical data bank. (3) Where a medical data bank combines several sets of medical records or subsystems of medical data, each of these elements may require separate supplementary regulations relating to its special features. And (4) The requirements and obligations following from this recommendation are to be taken duly into account not only with regard to medical data banks which are operational, but also those which are in the development phase.
- **Council of Europe, Recommendation on the Collection of Epidemiological Data on Primary Health Care, 1989.** This recommendation requires an express and informed consent to data collection even for epidemiological purposes.
- **Council of Europe, Recommendation R (92) 3 on genetic testing and screening for health-care purposes, 1992.** Council of Europe proposed principles for genetic information storage: 'genetic information gathered during genetic testing and screening may be collected, processed, and stored only for the purpose of health care, diagnosis, disease prevention, and for research closely related to these matters' (Article 8). But 'samples collected for a specific medical or scientific purpose may not, without permission of the persons concerned or the persons legally entitled to give permission on their behalf, be used in ways which could be harmful to the persons concerned' (Article 13).
- **Council of Europe, Recommendation R (94) 1 on Human tissue Banks, 1994.** The Recommendation states that (1) activities related to the banking of human tissue be divided into the following separate functions: organization; processing; preservation: internal quality control; storage; distribution. (2) These functions be carried out by non-profit-making institutions which are officially licensed by national health administrations, or recognized by the competent authorities. (3) Tissue banks store the tissue safely according to scientifically recognized state-of-the-art techniques and respecting the criteria established by general medical and laboratory practice. (4) Records of all tissues retrieved and issued be kept by the tissue banking organizations in such a way that their source and their destination are clearly identifiable, providing always that access to such records will be restricted to the extent necessary to protect confidentiality of information and individual privacy. (5) Close mutual cooperation be pursued by all officially recognized exchange and tissue banking organizations and that follow-up data on donor/recipient combinations should be shared between relevant institutions within the framework of national guidelines and legislation providing always that the privacy of the person concerned is fully respected.
- **Council of Europe Parliamentary Assembly, Recommendation 1240 (94) on the Protection and Patentability of Material of Human Origin, 1995.** According to Article 1, individuals may not be alienated (extra commercium) nor be appropriated (extra patrimonium): 'Human beings are subjects not objects of law, that the human body is inviolable by virtue of its relationship to a person endowed with rights, and that limits must therefore be set to how it is used'.
- **Directive 96/9/EC of the European Parliament and of the Council of 11 March 1996 on the legal protection of databases.** This Database Directive gives database builders specific protection – database rights – recognizing the work and costs entailed in compiling, verifying and presenting data.
- **Council of Europe, Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine, Oviedo, 1997.** The Convention sets out to preserve human dignity, rights and freedoms, through a series of principles and prohibitions. Six articles of the Convention should be considered in view of DNA banking: Article 5 which states a 'voluntary and informed consent for any intervention in the health field', with 'limited exceptions for the protection of persons not able to consent to research' (article 17),

while Article 3 mentions 'the possibility of freely withdrawing consent at any time'. Article 11 covers uses of genetic information. As for the uses of samples, Article 22 provides that 'when in the course of an intervention any part of a human body is removed, it may be stored and used for a purpose other than that for which it was removed, only if it is done in conformity with appropriate information and consent procedures'. Finally, Article 21 states that 'the human body and its parts shall not, as such give rise to financial gain'. The Convention is the first internationally binding legal text designed to protect people against the misuse of biological and medical advances. This text has legal effect in the Council of Europe's member States that have ratified it. Each state then has to bring its laws into line with the Convention. Belgium, Germany, Ireland, and the United Kingdom have not (yet) signed the Convention and it is not in force until it is signed and implemented into the national law.

- *Council of Europe, Recommendation R (97) 5 on the Protection of Medical Data, 1997*. Article 6.1 stipulates that 'where the data subject is required to give his/her consent, this consent should be free, express and informed'. Article 12.1 states that 'whenever possible, medical data used for scientific research purposes should be anonymous. Professional and scientific organizations as well as public authorities should promote the development of techniques and procedures securing anonymity'. 'Subject to complementary provisions determined by domestic law, health-care professionals entitled to carry out their own medical research should be able to use the medical data which they hold as long as the data subject has been informed of this possibility and has not objected' (Article 12.3).
- *European Commission, Directive of the European Commission to the European Parliament Concerning the Legal Protection of Biotechnological Inventions, 1998*. The Directive on the Legal Protection of Biotechnological Inventions came into force on 30 July 1998. It obliges the Member States of the European Community to amend their laws into conformity with the provisions of this Directive by 30 July 2000.

The Recitals in the first part of the Directive set out the legal and historical background and may be used in interpreting the articles. Important provisions of the Articles of the Directive are summarized below:

Article 2 sets out definitions of the terms used in the Directive. Article 3(2) of the Directive explicitly allows protection for biological material isolated from its natural environment or produced by means of some technical process, even if this material was previously known in nature. Article 6(2) provides specific exclusions for inventions whose exploitation would be contrary to *ordre public* or morality. Under Article 7, the European Commission's

European Group on Ethics in Science and New Technologies will have responsibility for evaluating all ethical aspects of biotechnology. The Directive excludes patents for the human body and the 'simple discovery' of an element (for example, the full or partial sequence of a gene), but states that such an element, provided it has been isolated, may constitute a patentable invention (Article 8). The industrial application of a sequence, whether full or partial, must however be 'disclosed in the patent application'. This Article reassures that the Directive explicitly allows protection for isolated elements. Current European law provides that the disclosure in a patent application encompasses both explicit and implicit elements. The protection for a product containing or consisting of genetic information is extended by Article 9 to all material in which the product is incorporated and in which the genetic material is contained and performs its function.

- *European Group on Ethics in Science and New Technologies, Ethical Aspects of Human Tissue Banking, 1998*. Article 2.2 requires that 'information be given on the potential use of the given tissues (clinical use, production of cell lines, research) and on the potential benefits (industrial use and patents). The consent should specify the will of the donor to be informed or not of unexpected findings concerning his (her) health by analysis of the given tissue. The consent should also point out the impossibility for the donor to claim any benefit resulting from the use of his (her) tissue, even if commercial applications occur'.
- *Council of Europe, Recommendation 1512: Protection of the Human Genome, 2001*. The Council of Europe's Parliamentary Assembly notes that the human genome international research project, in view of the numerous and unimaginable consequences that it might have for medicine, conjures up scenarios for all humanity that raise numerous ethical questions, while holding out the promise of enormous improvements in the quality of life. The protection of human dignity should be the guiding principle for the handling of the Human Genome Project. (...) The Assembly is fully aware of the now well-known fact that laboratories, with their associated databanks, are already actively at work on DNA separation in certain European countries and enjoy the financial support of prominent pharmaceutical companies. The Assembly is also aware that substantial economic interests are at stake in the Human Genome Project, by virtue of the very fact that it might hold out incalculable opportunities for preventing illness and improving treatment, as it involves many public and private research centres to which considerable financial resources will be allocated.

The Assembly calls, *inter alia*, through the establishment of a Euroforum on Human Genetics, for the widest possible

participation by citizens in the discussion on the human genome through the involvement of the European media and suitable and accurate information by the Council of Europe.

European countries

Austria

- *The Gene Technology Act, 1994*. This Act regulates work with genetically modified organisms, the release and marketing of genetically modified organisms, and the use of genetic testing and gene therapy in humans. Gene analysis, as it is defined in this Act, comprises molecular biological investigations of human chromosomes, genes or DNA segments for the identification of disease-causing mutations. Such examinations are allowed only for research or medical purposes. According to this act, laboratories where genetic tests for the diagnosis of a predisposition or for the identification of a carrier status of inherited diseases are performed, have to be accredited by the competent authority.

Belgium

- *Law of 8 December 1992 safeguarding privacy compared to the processing of personal data*. This law has been changed by a law of 11 December 1998, but this latter has not yet entered into force. This law stipulates that it is sometimes allowed to process data concerning a certain disorder of the person concerned in order to treat the relative of this person.

Denmark

- Filing of patient data is regulated by law. Patients must give informed consent for anybody to take part of the information.
- *Danish Council of Ethics, Protection of Sensitive Personal Information – A Report, Copenhagen, 1992*.
- *Danish Council of Ethics, Ethics and Mapping of the Human Genome, Copenhagen, 1993*. The publication contains three separate reports: protection of sensitive personal information; genetic screening and its ethical aspects; and finally, a section on genetic testing, which includes a copy of a bill that would forbid genetic testing in the workplace and in insurance underwriting. The Council views genetic information as different from other private information since it reveals knowledge not only about an individual, but also the individual's relatives, and because analyses will provide comprehensive information about both individuals and population groups.
- *Law No. 286 of 24 April 1996 on the use of health information*.
- *Danish Council of Ethics, Health Science Information Banks – Biobanks, Copenhagen, 1996*. The Danish Data

Surveillance Authority has jurisdiction over biobanks, which must be registered.

Estonia

- *Estonian Genome Foundation, Human Genes Research Act, 2000*. The objectives of this Act are to regulate the establishment and maintenance of the Gene Bank, to organize the genetic research necessary therefor, to ensure the voluntary nature of gene donation and the confidentiality of the identity of gene donors and to protect persons from misuse of genetic data and discrimination based on an interpretation of the structure of their DNA and the genetic risks arising therefrom.

Finland

- *Acts and Decrees Concerning Protection of Personal Data and Confidentiality of Medical Data, 1987*. The Personal Data Files Act contains the right to know whether a file includes data about him/herself, the right to demand and in most cases get such information from a file keeper, the right to require the correction of incorrect information on a file concerning him/herself, the right to be informed of the source of information regarding him/herself, how that information is used and to whom that information is given.
- *Medical Research Act, 488/1999*. The act regulates medical research carried out on persons, human embryos and human foetuses. Medical research on persons may not be conducted without the research subject's informed consent in writing. Exceptions to this may be made where consent cannot be obtained owing to the urgency of the matter and the patient's state of health and the measure is expected to be of immediate benefit to the patient's health. Research subjects shall have their rights, the purpose and nature of the research and the procedures it involves as well as the potential risks properly explained to them.
- *Personal Data Act, 523/1999*. The Personal Data Act regulates that personal data may be processed for purposes of scientific research (1) if the research cannot be carried out without data identifying the person and the consent of the data subjects cannot be obtained owing to the quantity of the data, their age or another comparable reason; (2) the use of the personal data file is based on an appropriate research plan and a person or a group of persons responsible for the research have been designated; (3) the personal data file is used and data are disclosed therefrom only for purposes of scientific research and the procedure followed is also otherwise such that the data pertaining to a given individual are not disclosed to outsiders; and (4) after the personal data are no longer required for the research or for the verification of the results achieved, the personal data

file is destroyed or transferred into an archive, or the data in it are altered so that the data subjects can no longer be identified.

Regardless of secrecy provisions, everyone shall have the right of access, after having supplied sufficient search criteria, to the data on him/her in a personal data file, or to a notice that the file contains no such data. There is no right of access if providing access to the data would cause serious danger to the health or treatment of the data subject or to the rights of someone else or if the data in the file are used solely for scientific research or statistical purposes. If only part of the data on a data subject is such that it falls within the restriction on the right of access, the data subject shall have the right of access to the remainder of the data.

The Personal Data Act contains also provisions on data security and storage of personal data.

- *The draft bill on medical use of human organs and tissues, 2000.* The draft includes provisions on informed consent of the donor of organ or tissue for transplantation or other medical purposes. It will regulate the medical use of organs and tissue removed for diagnosis or treatment of the patient. Collection and storage would require written and informed consent which can be withdrawn at any time before the tissue is used. The units which remove, use or storage organs or tissues must have a register for the safety and traceability of organs and tissues and for the purposes of legal surveillance of their actions if the organs are used for transplantation. The registers would include identifying information of the donor and the patient.

If an organ or tissue cannot be used for the purpose it was removed, collected or stored for, it may be used for another justified medical purpose with the consent of the donor.

Tissue samples taken in connection of care or diagnosis may be used for medical research with the consent of the patient. The National Authority for Medico-legal Affairs would be able to grant a license for research use if the consent could not be obtained owing to the quantity of the samples, their age or another comparable reason. A license could also be granted for a new research of samples that have been collected for research if the donor has died. Samples that do not contain identifying information could be used for medical research with the authorisation of the health-care unit for which the samples were taken. The samples could be used for the purpose of detecting hereditary disease of a relative only with the consent of the donor. The samples could be used for detection of paternity if asked by a court or a competent authority.

The act would prohibit financial gain. No fees could be paid to the donors. The health-care units involved may not seek for financial gain but would be able to get their costs paid by another health-care unit.

France

- *National Consultative Ethics Committee for Health and Life Sciences, Opinion on medical registries for epidemiological and preventive studies, Paris, 1985.* The Committee recommended that (1) collecting and processing of nominative information with the object of epidemiological research, and the expectation of better individual and collective medical prevention must be subordinated to specific conditions, (2) collecting and processing nominative medical information must be carried out in compliance with all articles of law no. 78-17 of 6 January 1978 on computerized information, records, and liberties, (3) legislation must be passed, (4) once attending physicians have given due warning of risks incurred and means of averting them, those concerned must remain entirely free to draw their own conclusions, and (5) so as to be confident that collecting and processing of nominative information by accredited organizations takes place in irreproachable moral and technical conditions which are worthy of the trust of those concerned, it is necessary and urgent to educate and train physicians.
- *National Consultative Ethics Committee for Health and Life Sciences, Opinion on problems arising because of the development of methods using human cells and their derivatives, Paris, 1987.* The Committee reiterates the principle that products of human origin are without price and therefore can neither be bought nor sold.
- *Law No. 88-1138 of December 20th on the protection of persons accepting biomedical research, 1988 (Huriet-Sérusclat Law)* (revised 25 July 1994). For research, the law gives a detailed description of information provided so that a person's consent can be considered to be truly informed.
- *National Consultative Ethics Committee for Health and Life Sciences, Opinion regarding the application of genetic testing to individual studies, family studies and population studies (problems related to DNA 'banks', cell 'banks' and computerisation), Paris, 1991.* DNA banks necessarily require computerized recording of personal data concerning donors of cells stored in the bank. Consequently, all the rules which apply to keeping and using medical registers also apply jointly to the DNA banks themselves and to the recording of data which unavoidably follows. These rules were defined in the Opinion published by the Committee on May 6th 1985, and in various other Opinions which clarified and complemented it. They are as follows: (1) Registers are to be kept only by a small number of centers approved by a public authority and in accordance with all the necessary scientific and ethical safeguards. The same principle should apply to DNA banks. (2) To meet the need for medical confidentiality centers keeping registers are to be placed under the responsibility of a physician who agrees to consider himself a consultant in his

dealings with other practitioners who supply the information which is recorded. He is of course bound by the rules of medical confidentiality and should give these practitioners his views regarding the diagnosis and the therapy to be applied to the case for which information is provided. (3) The law dated January 6th 1978 on Computerization, Records and Liberties stipulates that any interested party: (a) will be duly informed of his right to oppose the dissemination of information (and consequently also the DNA sampled) about himself, will not have stated his opposition and, in practice, will have given written consent to such dissemination; (b) will have access at any time to the recorded information, through a physician of his choice; (c) will have been advised of his right to ask that the information concerning himself be deleted from the records, if he has a serious reason to do so, and therefore that his DNA be removed from the bank. (4) The Committee feels it is not qualified to pronounce an opinion on whether sampling and transmission of human cells to a DNA bank, and the resultant recording of personal data in a register, is covered by the law dated 20 December 1988, modified on 20 January 1990, which stipulates that an investigator, before undertaking research on human beings, should submit the project to a Consultative Committee for the protection of subjects in biomedical research, located in the region of the investigator's activity. (5) It should be prohibited for any third party, particularly employers or insurance companies, not only to have access to the information contained in a register, therefore in a DNA bank, which is already implied by the above rules, but also to ask the subject to supply information about himself, contained in the DNA bank.

- *Law No. 94-548 on the processing of nominative data with the objective of research in the health field, and amending Law No. 78-17 of 6 January 1978 on informatics, personal card-indexes, and freedom, 1994.* The aims of this law is to give a legal basis to the development of epidemiological studies.
- *Law No. 94-653 of 29 July 1994 on respect for the human body (Law of Bioethics).* This law modifies the Civil Code by introducing notably the notions of the fundamental right to respect for one's body, therapeutic necessity as the only acceptable reason for violating bodily integrity and this only if the individual has consented (in particular articles 16-10 and 16-11).
- *Law No. 94-654 on the donation and use of elements and products of the human body, medically assisted procreation, and prenatal diagnosis, 1994 (Law of Bioethics).* This law includes principles applicable to the donation and use of elements and products of the human body. Article L. 145-15 states that the examination of the genetic characteristics of a person or his identification by genetic fingerprinting, when such identification is not carried out as part of a legal procedure, may only be undertaken for medical purposes or for scientific research and after

having obtained the consent of the person concerned. The cytogenetic and biological analyses must be carried out in authorized establishments.

- *Ministry of Higher Education and Research, Report of the Study Group on the Intellectual Protection of the Results of Research on the Human Genome, Cell Collection, and DNA Sequence Data, Paris, June 10, 1994.* This report based its recommendations on the principle of 'nonproprietaryship of the elements and products of the human body'. Hence, not having any property rights in body parts, individuals should 'donate' such substances and would be protected through consent procedures. In addition, this report clearly denied to every person involved in the collection of samples (donor, investigators or promoters), any proprietary rights in the material although the promoter (granting agency) would have other rights with respect to the collection.
- *National Ethical Consultative Committee for Health and Life Sciences in France, Genetics and Medicine: From Prediction to Prevention, Paris, 1995.* The recommendations cover the following topics and ethical principles: respect of the autonomy of the subject, respect of medical confidentiality; respect of privacy in computerizing personal data; the use of biological samples; the prohibition of using results of genetic tests for purposes other than medical or scientific; procedures of accreditation of the materials involved in genetic testing; prior evaluation of the impact of the tests; information and formation of all medical personnel in genetics; the need to guarantee correct public information; prohibition of all uses that would contribute to stigmatisation or unfair discrimination in the social and economic spheres.
- *Ordinance N. 96-452 of 28 May 1996 laying down various measures of a health-related, social, and statutory nature, 1996.* This ordinance mandates that 'no person may take samples with a view to constituting a collection of human biological specimens, or use, to this same end, samples already taken or derivatives thereof if he has not notified the competent administrative authority of the proposed collection'.
- *National Ethical Consultative Committee for Health and Life Sciences, Re-examination of the law on bioethics, Paris, 1998.* Article 21 of law no. 94-654, dated 29 July 1994, provides for re-examination by Parliament no later than 5 years after the law's entry into force. This clause is inspired by the fact that the law's scientific foundation is in a permanent state of evolution so that it is advisable to consider possible consequences of this fluctuation on the state of law.

Concerning DNA collections, they should be:

- Free, express, and informed consent given by persons from whom biological samples are taken for the purpose of genetic study;

- Instigators of a research procedure using biological samples must inform the persons concerned of what happens to those samples once research has ceased;
- If a different scientific purpose from the one for which consent was given using samples taken and associated identifying and nominal data, renewed consent must be secured;
- In cases where instigators of research abandon the project as far as they themselves are concerned, they must inform the persons concerned of any modifications in the conduct of research procedures as a consequence of their decision to abandon;
- Researchers working on samples from collections must make sure that the best interests of persons contributing samples are protected, in particular as regards preserving samples which could become necessary at a later date for diagnostic testing on themselves or their families;
- Individual samples and collections of samples may not be bought, sold, or patented;
- Collections could be managed by national or international organizations according to the principle of authorised collections on the basis of rigorous respect of ethical principles;
- In any event, instigators of such collections must receive approval from appropriate authorities;
- *Parliamentary Office for Evaluating Scientific and Technological Choices, Report on the application of the law of 29 July 1994 concerning the donation and use of elements of the human body, medically assisted procreation and prenatal diagnosis, 1999.* This report will serve as the basis for the parliamentary discussion scheduled for the second semester of 2000.
- *Decree no. 2000-570 dated 23 June 2000 fixing the conditions of prescription and implementation of genetic characteristics and genetic identification investigations of a person for medical reasons and modifying the Public Health Code.* This decree fixes five conditions for prescribing and implementing genetic testing for medical purposes: (1) condition of prescription; (2) condition of approval from appropriate authorities both for clinicians and laboratories; (3) conditions of reporting results; (4) conditions of medical record protection; and (5) approval from the National Consultative Commission created for this purpose.

Germany

- If the banking of human genetic material includes the collection and storage of personal data associated with an identifiable person, the Data Protection Law has to be taken into account. The German Data Protection Law is very complex, since the applicable law depends on the status of the data collecting and storing institution (public, private, federal, state), it contains different permissions for collecting, storing, using, transferring

for own or for other purposes and there are numerous exceptions in other laws. The Data Protection Laws are subsidiary towards these special provision in certain areas (Simon, personal communication).

- *Federal Data Protection Law (BDSG) 1990.* Non public DNA banks, which process personal data have to take into account the Federal Data Protection Law if data are processed into or out of file commercially or for professional or commercial purposes (Section 1 II No. 3, BDSG). The processing of personal data and their use is only allowed if there is a legal permission or a consent of the affected person (Section 4 BDSG). In accordance with the Section 28 I, No 4, the transmission of personal data is permitted if it is necessary for scientific research. This permission does not apply for medical data in accordance with Section 39 of the Federal Data Protection Law.
- *Data Protection Law of the states.* The application field of the data protection laws of the states include all public authorities of the respective states. They have to be applied in public hospitals or the state or the municipalities. The University hospitals are either non-self-maintained public state institution or state companies with restricted independence. If these institutions bank identified or identifiable human genetic material, they have to take the state data protection acts into account. These laws are subsidiary towards special data regulation in law, specific for certain areas, for example the hospital laws.
- *Law of 20 June 1990 to regulate matters relating to gene technology.* The aims of this law are: (1) to protect life and health of human beings, animals and plants against possible threats of gene technology, and (2) to give a legal framework for research, development and support of scientific, technical and economic possibilities of gene technology.
- *The German Bundestag, Chancen und Risiken der Gentechnologie Enquete-Commission, 1987.*
- *Resolution of the Conference on the Privacy of Information of Rheinland-Pfalz on the Subject of Gene Analysis and Informational Self-Determination (26–27 October 1989).*
- *The Federal and State Governments, Final Report of the Bund-Länder-Arbeitsgruppe Genomanalyse, 1990.*
- *Minister of Research and Technology, Arbeitskreis Genforschung Report, Frankfurt, 1991.*
- *German Parliament, Periodic Report of the Büro für Technikfolgen, 1992, 2000.*

Greece

There are no specific regulations in place regarding DNA banking.

Hungary

There are no specific regulations in place regarding DNA banking.

Iceland

- *Act no. 121/1989 on Personal Privacy and Data Protection, Ministry of Health, 1989.* The implementation of the Data Protection Act is monitored by the Data Protection commission, a special independent official agency, appointed by the Minister of Justice for a period of Four years. The commission has an important role both as a standard setting and a monitoring body.
- *Act no. 74/1997 on the Rights of Patients, Ministry of Health, 1997.* This Act includes fundamental rights of patients including rules on consent, confidentiality and handling of information in clinical records. This Act stipulates that in order to use material or information from patients for research, they must have given an *a priori* written informed consent.
- *Act no. 139/1998 on a Health Sector Database, 1998.* See Section IV, 4.2.
- *Act on Protection and Handling of Personal Information, Ministry of Health, 2000.* This Act supercedes the Personal Privacy and Data Protection Act (121/1989).
- *Act on Biobanks no. 110/2000.* 'The objective of the Act is to authorize the collection, keeping, handling and utilization of biological samples from human beings, in such a way that confidentiality is ensured, the interests of donors of biological samples is safeguarded and that the utilization of the biological samples serves the purposes of science and medicine, and is conducive to the public good. The interests of science and of the community shall never be given priority over the interests of the donor of a biological sample. It is prohibited to discriminate against a donor of a biological sample on the grounds of data derived from a biological sample' (Article 1).

Ireland

There are no specific regulations in place regarding DNA banking.

Italy

- *Law no. 675, 31 December 1996, D.P.R. n. 318, 28 July 1999, on Medical Information Privacy.*
- *The Italian Committee on Bioethics, Orientamenti bioetici per i test genetici, 19 November 1999.* Genetic information must be treated as the general medical information and therefore it is forbidden to give this information to third parties without consent.

Norway

There are no specific regulations in place regarding DNA banking.

Portugal

The Ratification of the 'Convention for the Protection of Human Rights and Dignity of the Human Being and the

additional protocol on the prohibition of cloning human beings' was published in January 2001. Some guidelines prepared by a task force were also published by the Ministry of Health. These guidelines are concerned with the ethical and professional rules on genetic testing and prenatal diagnosis namely confidentiality, genetic counseling and genetic testing of children.

- *Act No 10/1995 related to the Protection of Personal Information.*
- *The National Ethics Committee, Report on the draft bill regulating the therapeutic use of human-origin biological products and of biotechnology, 1998.*
- *Convention for the Protection of Human Rights and Dignity of the Human Being and the additional protocol on the prohibition of cloning human beings, 2001.*

Spain

There is no specific legislation to ensure the appropriateness of genetic procedures and the confidentiality of personal data. Consent to undergo to any medical tests is granted through General Health Law of 25 April 1986. Protection of data related to health may be reached through general rules concerning personal data protection, as well as through provisions which recognise the duty of confidentiality in the health field.

- *The Organic Law regulating the automated processing of personal data of 29 October 1992.* The Organic Law regulating the automated processing of personal data of 29 October 1992 provides special measures of protection for personal health data (Articles 7.3 and 8).
- *The Organic Law regulating the automated processing and protection of personal data of 13 December 1999.* This law includes automated data and any type of personal data.

Sweden

- *Data Storage in Health Care Act (1985:562).* This act addressed patients personal files. Files are confidential and patients must give informed consent to anybody who wants to consult this information.
- *Law no. 114 of March 1991, on the Use of Certain Gene Technologies within the Context of General Medical Examinations (1993).* The study of human genetic codes by analyzing genetic DNA requires special permission if it constitutes or forms part of a screening program. Questions relating to permits are decided by the National Board of Health and Welfare. The requirement of permits is defined by statute.
- *The Personal Data Act (1998:204).* The purpose of this Act is to protect people against infringement of their privacy through the processing of personal data. The Act supersedes the 1973 Data Act. Both Acts will apply for a

transitional period until 1st October 2001. The Personal Data Act (PDA) is based on common rules adopted within the European Union, in the form of the directive on Data Protection. The Act applies to processing of personal data as is wholly or partly automated and also to manually compiled personal files. Purely private processing of personal data is excluded. Exemptions are also made in deference to the principle of public access to official documents and to the freedom of the press and freedom of expression. In addition, the Medical Registers Act (1998:544) and special provisions of other enactment take precedence over the provisions of PDA.

PDA defines basic stipulations concerning the processing of personal data and indicates when processing is permitted. Specially restrictive provisions apply concerning the processing of sensitive data. The Act is to a great extent based on the consent of the registered person. It also contains provisions on information to the persons registered, on the rectification of personal data and on security in processing.

- *National Board of Health and Social Welfare, Genetics and Genetechnology in Health Care. State-of-the-Art and Guidelines for Ethical Considerations, 1999.*
- Medical Research Council, Research ethics guidelines for using biobanks, especially projects involving genome research, Dnr 1999-570. The Swedish Medical Research Council has adopted research ethics guidelines for using biobanks, regardless of whether the samples are collected as a component of routine medical care or for previous or current research purposes.
- *Proposed Act concerning Biobanks in Medical Care etc., 2000.* The Medical Research Council has requested that the Ministry of Education and the Ministry of Health and Social Affairs appoint a commission to review existing legislation and its application in these special issues. The handling of human material in activities closely associated with health and medical care such as evaluation and quality assurance are important to consider and should be dealt with the National Board of Health and Welfare. In May 2000, a review has been presented. The main purpose is to make important knowledge obtainable from biobanks in medical care available for research, care and treatment, whereas its use must not imply harm to the individual person, genetic relatives or their personal integrity.

Switzerland

- The Swiss Federal Constitution, 1992. Article 119 (introduced in 1992 as article 24novies, old numbering) paragraph 2 states that the genetic heritage of an individual may be analyzed, registered or divulged only with his consent or on the basis of a legal prescription.

- *The Swiss Academy of Medical Sciences, Medical-ethical Guidelines for Genetic Investigations in Humans, Approved by the Senate of the Swiss Academy of Medical Sciences on 3 June 1993.* The medical-ethical guidelines define the spectrum of activities belonging to genetic services in general. Quality control standards exist for laboratory investigations. The Swiss academy of Medical Sciences guidelines are not legally binding, unless cantonal legislation gives them binding force.
- *Bill regarding Genetic Investigations in Humans, September 1998.* This bill has not yet been debated in Parliament.

The Netherlands

Patients data protection is regulated by law and quality control has been implemented.

- *The Data Protection Act, 1984.* This act provides for the registration and supervision of data users. The Data Protection Act 1998 will come into force shortly and supersedes the 1984 Act. The new Act includes personal information held in paper filing systems as well as computers.

Personal data used for research purposes is exempted from the Act if the purpose of the research is not measures or decisions targeted at particular individuals and it does not cause substantial distress or damage to a data subject. This means that under the Act personal data used in this kind of research can be processed for purposes other than that for which it was originally obtained and be held indefinitely. Individuals do not have a right to be told how information is being processed if that data is anonymous.²⁵

- *The Health Council of the Netherlands, Heredity: Science and Society, The Hague: Health Council of the Netherlands, 1989.* The Council recommended that written agreements should be made at the time of collection of samples setting out the specific rights of the donor, including, time of storage, use of material, confidentiality, withdrawal of consent, etc.
- *The Health Council of the Netherlands: Committee on Human Tissue for Special Purposes, Proper Use of Human Tissue, The Hague: Health Council of the Netherlands, 1994.* The Council introduced ethical principles for the prospective use of removed tissue: human material cannot be stored 'without a good reason'. Although the Health Council did not take an explicit position on the legal status of human tissue, it did state that individuals have the right to determine what happens to identifiable material as a 'personal right'. Moreover, in commenting on its earlier 1989 report, it reiterated that 'should exceptional cases arise in which cell material is identifiable, then the principle of non commercialism means that the 'donor' has no claims to any revenue that may be earned'.

The United Kingdom

- **Clinical Genetics Society, Guidelines for DNA banking, 1989.** The main indications for banking are for clinical diagnosis. Banks also constitute a resource for genetics research; banking should then be available for 'any single gene disorder for which there is a consensus among professionals providing banking services that DNA banking should be provided'.
- **House of Commons Select Committee on Science and Technology, Human Genetics: the Science and Its Consequences, Third Report, HMSO, 1995.** This report examines the ethical issues arising from genetic technology and recommends the setting up of a Human Genetics Commission to regulate the advance of genetic technology.
- **Nuffield Council on Bioethics, Human Tissue: Ethical and Legal Issues, London: Nuffield Council on Bioethics, 1995.** The report states that there is an important and urgent need to consider, clarify and, where necessary, strengthen the ethical and legal framework within which the clinical and research uses of human tissue take place. The ethical issues relate directly to the core of respect for human beings, namely that they and their bodies should not be injured and that nothing should be done to them and their bodies without their consent. The legal status of human tissue is unclear. The limitations of the existing framework of legal and professional regulation point to the conclusion that a coherent approach is needed to any further regulation. That approach will not necessarily require legislation; given the pace of change in biomedical research, a more rapid and flexible approach to regulation may be preferable. But the need to clarify the law is important insofar as its uncertainty may impede legitimate treatment, teaching, study or research or even, at worst, may encourage illegitimate uses of human tissue.
- **The Advisory Committee on Genetic Testing, Advice to Research Ethics Committees, 1998.** The ACGT provides Research Ethics Committees with guidance in the form of a 'Points to Consider' document intended to help committees identify the questions that they might raise with researchers. Issues that Research Ethics Committees may wish to consider before giving ethical approval to research that includes genetic testing are: (1) research and service interface; (2) disclosure of research findings; (3) use of stored specimens for further research; (4) multiple genetic testing; and (5) research involving 'at risk' individuals and their families.
- **Genetic Interest Group, Confidentiality Guidelines, London, G.I.G., 1998.** These guidelines deal with individual confidentiality in medical genetics: the sharing of genetic information within families and between professional clinical geneticists.
- **The Data Protection Act, 1998.** This act aims to protect the personal information contained in medical records.
- **Royal College of Physicians Committee on Ethical Issues in Medicine, Research based on archived information and samples, 1999.** In 1996, the College published Guidelines on the Practice of Ethics committees in Medical Research involving Human Subjects (3rd edition) which includes a section on non intrusive research. The recommendations published in 1999 are intended to clarify the issues surrounding this category of research as they relate to consent to the use of archived information and samples.
- **Medical Research Council, Human Tissue and Biological Samples for Use in Research, Report of the Medical Research Council Working Group to Develop Operational and Ethical Guidelines, 1999.** This report draws attention to the ethical, legal and practical issues that should be considered when making and using collections of human biological material for research, and recommends best practice to ensure that such collections can be used optimally to increase scientific understanding for the benefit of human health. Guidelines developed into this report should be followed by (1) those preparing research proposals for support by the MRC that include the collection of samples of human biological material, (2) Those planning, undertaking or collaborating in research funded by the MRC using existing collections, whether the collections were made by themselves or by others, and (3) Those managing collections of human materials made with MRC funding, or research using such collections.
- **Medical Research Council, Human Tissue and Biological Samples for Use in Research, Operational and Ethical Guidelines, 2001.** It is stipulated that the following principles should guide all MRC funded research using samples of human biological material: 'samples of human biological material obtained for use in research should be treated as gifts; the human body and its parts shall not, as such, give rise to financial gain; informed consent is required from the donor whenever a new sample is taken wholly or partly for use in research; patients should always be informed when material left over following diagnosis or treatment might be used for research; all research using samples of human biological material must be approved by an appropriately constituted research ethics committee; researchers should treat all personal and medical information relating to research participants as confidential; research participants have a right to know individual research results that affect their interests, but should be able to choose whether to exercise that right'.
- **House of Lords' Select Committee on Science and Technology, Human Genetic Databases: Challenges and Opportunities, 2001.** This report is about the opportunities and challenges arising from the use of human genetic databases. These are set to become valuable tools in developing a full understanding of the

effects of genes and their variations. Regarding databases, it is recommended that ‘the HGC and Government should conclude that the primary means of regulating human genetic databases should continue to be the *Data Protection Act 1998* and that, except as recommended in paragraph 7.58, no additional protection is required for personal genetic data. (*Paragraph 3.17*)’.

Regarding consent, it is recommended that ‘the HGC and the Government should promulgate guidance for all those who collect or hold genetic data about identifiable individuals, reminding them of their obligations under the *Data Protection Act 1998* and stressing the need to record, alongside the data or in an appropriately accessible form, whether or not the individuals concerned had been informed of the use to which their data might be put and whether they had expressed any reservations (*Paragraph 7.56*). (...) The procedure to be followed by all those involved in seeking consent for participation in research involving the collection and retention of biological samples that could be used for genetic analysis should include the following elements: (a) pointing out that (i) the medical treatment that all receive is based on studies carried out on very many earlier patients and that the request is for them to provide similar help for future generations, (ii) because medical science is changing very rapidly, some of the valuable uses to which the data could sooner or later be put are not foreseeable; (b) seeking the individuals’ agreement (i) to participate in the study, (ii) to entrust oversight of secondary use of their data to the arrangements in place under the proposed medical data panel; (c) asking whether participants would wish to be informed of any element in their genetic make-up that might be a cause for concern based on current knowledge – or to be alerted in the future in the light of new discoveries; (d) explaining the arrangements for withdrawing the consent; and (e) thanking participants for their help (*Paragraph 7.65*)’.

- *The Human Genetics Commission, Inside information: balancing interests in the use of personal genetic data, 2002*. The report is based on two overarching principles: the principles of genetic solidarity and altruism, and respect for persons. The report makes recommendations on the use of genetic information in clinical practice and medical research, and for nonclinical purposes such as insurance, employment, forensic databases and family relationship testing. In the area of genetic research and large genetic databases, the Commission suggests the establishment of independent oversight bodies for all such databases and recommends that databases established for medical research should not be accessible for other purposes such as forensic uses. The report stresses the importance of the informed consent of volunteers participating in this type of genetic research. It considers

that one-off consent should be sufficient if identifiers are encrypted.

The United States of America

- *American Society of Human Genetics, Ad Hoc Committee on DNA Technology, DNA Banking and DNA Analysis: Points to Consider, 1988*. These ‘Points to Consider’ are designed to provide accurate and authoritative information in regard to DNA banking and DNA analysis. These ‘Points to Consider’ are offered primarily to help ensure that patients and families affected by genetic disease obtain and understand the information they need and desire. For this to occur, health-care professionals involved in counseling, banking, or analysis must recognize their individual responsibilities.

There are 11 points to consider: (1) Should a DNA diagnostic laboratory or DNA bank accept samples directly from patients or only from health-care professionals? (2) Who owns the DNA in a bank? (3) How can the risk of misunderstandings between the depositor and the DNA bank be minimized? (4) Under what circumstances, if any, should the DNA diagnostic laboratory release results to anyone other than the patient? (5) Under what circumstances, if any, should the DNA bank or laboratory transfer deposited DNA to a party other than the patient? (6) What is the responsibility of the DNA diagnostic laboratory for the accuracy of the reported result? (7) Under what circumstances is it permissible to use deposited DNA for purposes unrelated to the original request of the depositor? (8) Under what circumstances is it permissible to use deposited DNA for purposes unrelated to the original request of the depositor? (9) How should the competence of the director of a DNA laboratory be demonstrated? (10) Should DNA banks and/or DNA diagnostic laboratories be certified? And (11) What role should the American society of human genetics take to ensure that DNA banks and laboratories meet patient needs?

- *The Genetic Privacy Act and Commentary, 1995*. The premise of the Act is that no stranger should have or control identifiable DNA samples or genetic information about an individual unless that individual specifically authorizes the collection of DNA samples for the purpose of genetic analysis, authorizes the creation of that private information, and has access to and control over the dissemination of that information.

The rules protecting genetic privacy must be clear and known to the medical, scientific, business and law enforcement communities and the public. The purpose of the Genetic Privacy Act is to codify these rules. It has been drafted as a federal statute to provide uniformity across state lines. Under the Act, each person who collects a DNA sample (eg, blood, saliva, hair or other tissue) for the

purpose of performing genetic analysis is required to: provide specific information verbally prior to collection of the DNA sample; provide a notice of rights and assurances prior to the collection of the DNA sample; obtain written authorization which contains required information; restrict access to DNA samples to persons authorized by the sample source; abide by a sample source's instructions regarding the maintenance and destruction of DNA samples. Special rules regarding the collection of DNA samples for genetic analysis are set forth for minors, incompetent persons, pregnant women, and embryos. Research on individually identifiable DNA samples is prohibited unless the sample source has authorized such research use, and research on nonidentifiable samples is permitted if this has not been prohibited by the sample source. The sample source has the right to: determine who may collect and analyze DNA; determine the purposes for which a DNA sample can be analyzed; know what information can reasonably be expected to be derived from the genetic analysis; order the destruction of DNA samples; delegate authority to another individual to order the destruction of the DNA sample after death; refuse to permit the use of the DNA sample for research or commercial activities; and inspect and obtain copies of records containing information derived from genetic analysis of the DNA sample.

- *American College of Medical Genetics, Statement on Storage and Use of Genetics Materials, 1995.* For the collection and storage of samples that may be used for genetic analysis in the future, the ACMG recommends that when obtaining samples for clinical tests, one must clarify the following: (1) description of current test including its purpose, limitations, and possible outcomes, as well as methods for communicating and maintaining confidentiality of results; (2) anticipated use of samples, including whether samples will be used only for the purpose for which they were collected and then be destroyed; (3) if samples will be retained after initial use, the following issues should be clarified as well: (a) the scope of permission to use samples or results in counseling and testing relatives and if so, which relatives; (b) the possibility of future test refinements and subjects' expectations that their samples will be analyzed using these new tests and that the results will be communicated to them; (c) permission to use samples from which identifiers have been removed in research, including what type of research; (d) duration of storage of genetic materials, including provision for future access by patients or their designee; the option to have their samples withdrawn or destroyed at any time; and the possibility of inadvertent sample loss.

When obtaining samples for research, one must clarify the following: (1) Description of current research: purpose,

limitations as above, possible outcomes, and methods for communicating and maintaining confidentiality of results: (2) Possibility that research will lead to the development of diagnostic tests. If so, the possibility their samples will be tested or made available for testing and the results communicated to them must be disclosed, as well as the extent to which subjects can expect to receive any profits from test sales: (3) Permission to use their samples without identifiers for other types of research: (4) Policy for future recontact if permission for future research is not obtained with the sample: (5) Duration of storage of genetic materials and plans for discarding: (6) Note that the regulations on protection of human subjects applicable to institutions receiving federal funds require that the purpose, duration, procedures and alternative procedures, risks and benefits, compensation, voluntary participation and withdrawal, associated additional costs, and communication of results all be described.

For the use of stored DNA or genetic materials previously collected for clinical tests or research, the following factors should be considered in deciding whether it is appropriate to use previously collected samples without contacting the individual: are or will the samples be made anonymous? the degree to which the burden of contacting individuals may make it impracticable to conduct research; existence and content of prior consent; and risks and benefits. Contacts regarding new diagnostic tests should address permission to use stored samples; purpose, limitations, and possible outcomes of new tests; methods for communicating and maintaining confidentiality of results; permission to use samples or results in testing relatives; and duration of storage. Contacts regarding new research should address its purpose, limitations and possible outcomes, methods for communicating and maintaining confidentiality of results, duration of storage, uses of samples or results in studying others (anonymously), and sharing samples with other researchers for other types of research. Finally, in all research, the regulations related to protection of human subjects must be addressed.

- *American Society of Human Genetics, Statement on Informed Consent for Genetic Research, 1996.* Because of a variety of important and complex issues surrounding the use of previously collected biological samples, investigators are encouraged to develop procedures for obtaining informed consent when prospectively collecting specimens for genetic research purposes. It is strongly recommended that research results only be transmitted to subjects by persons able to provide genetic counseling. Because of the sensitive nature of genetic information, even those institutions not covered by federal regulations should develop a process for human subjects review. The recommendations apply to any specimen or sample that is used in genetic research.

The recommendations concern (1) research using prospectively collected samples, (2) consent disclosures, (3) disposition of samples and results, and (4) retrospective studies of existing samples.

- *American Society for Investigative Pathology, Use of Human Tissues for Molecular Research, 1996.* Pathology departments must have a written policy about confidentiality and privacy rights. The policy must include specific procedures for access to the medical record, confirmation of IRB approval of research involving tissues when appropriate, a description of safeguards to prevent unauthorized access, procedures for the release of information, methods of assuring that everyone with access or who may gain legitimate access embraces the need for privacy, confidentiality, and security of patient information, procedures specific for records kept in electronic form, and procedures that specifically apply to the release of information for research.

Anonymized existing or prospective specimens should be, for research purposes, treated as specimens that were never linked to a source. Where specimens or data are identifiable or linked, researchers must agree to prohibitions restricting them from contacting patients who are the sources of specimens used in research or their families. The prohibition of patient contact does not preclude obtaining information from tumor registries. Stewards of specimens should ensure that researchers have IRB-approved research proposals and have signed nondisclosure statements before releasing specimens to researchers.

For tissue research, general consent for research should be sufficient. General consent forms should be worded broadly and include statements that tissues may be used in research approved by Institutional Review Boards and for educational purposes.

- *NCHGR, NCHGR-DOE Guidance on Human Subjects Issues in Large-Scale DNA Sequencing, 1996.* Those engaged in large-scale sequencing must ensure that both the protections normally afforded research subjects and the special issues associated with human genomic DNA sequencing are thoroughly addressed. For the foreseeable future, establishing effective confidentiality, rather than relying on anonymity, will be a very useful approach to protecting donors. Investigators should introduce as many disconnects between the identity of donors and the publicly available information and materials as possible. No phenotypic or demographic information about donors should be linked to the DNA to be sequenced. The disclosure process to potential donors must clearly specify what the process of DNA donation involves, what may make it different from other types of research, and what the implications are of one's DNA sequence information being a public scientific resource. Library makers are encouraged to establish

a collaboration with one or more human genetics units [or tissue banks]. The library maker should have no contact with the donor and no opportunity to obtain any information about the donor's identity. Effective immediately, projects to construct libraries for large-scale DNA sequencing must obtain IRB approval before work is initiated. Existing libraries can continue to be used for large-scale sequencing, only if IRB approval and consent for continued use are obtained and approval by the funding agency is granted.

- *The College of American Pathologists, Recommended Policies for uses of Human Tissue in Research, Education and Quality Control, 1997.* As recipients of tissue and medical specimens, pathologists and other medical specialists consider it their duty to protect the best interests of both the individual patient and the public. The decision to provide human tissue for research, education, and quality control purposes should be based on the specific (ie, direct patient care) and general (ie, furthering medical knowledge) interests of the patient and of society. The same standards of responsibility should apply to all medical professionals who receive and use specimens.
- *Association of American Medical Colleges, Health Data Security, Patient Privacy, and the Use of Archival Patient Materials in Research, 1997.* The AAMC endorses principles and practices for responsible research conduct to protect individuals from the unauthorized release of their identified health and medical information. As a rule, molecular, clinical, epidemiological and health services research on archival patient materials does not require that patient identities be known. However, archival research materials, although coded and not identified, must remain linkable to individuals. Research on archival patient materials, whether linkable or not, should be permitted under a general informed consent mechanism. Organizations that deliver medical care, or conduct biomedical, epidemiological or health services research, must be responsible and accountable for the development and implementation of appropriate policies to ensure protection of confidentiality of medical information through such mechanisms as informed consent, IRB review and approval, and adherence to accreditation standards and state laws and regulations.
- *North American Regional Committee - Human Genome Diversity Project, Model Ethical Protocol for Collecting Samples, 1997.* See Section 3.4.
- *National Bioethics Advisory Commission, Research Involving Human Biological Materials: Ethical Issues and Policy Guidance, Rockville, Maryland, 1999.* In this report, NBAC offers a series of recommendations that have been developed to address perceived difficulties in the interpretation of federal regulations and in the language of position statements of some professional organizations; ensure that research involving human biological

materials will continue to benefit from appropriate oversight and IRB review, the additional burdens of which are kept to a minimum; provide investigators and IRBs with clear guidance regarding the use of human biological materials in research, particularly with regard to informed consent; provide a coherent public policy for research in this area that will endure for many years and be responsive to new developments in science; and provide the public with increased confidence in research that makes use of human biological materials.

- *National Bioethics Advisory Commission, Ethical and Policy Issues in Research Involving Human Participants, Rockville, Maryland, 2001.* Since 1995, NBAC focused on several issues concerning research involving human participants, issuing five reports and numerous recommendations that reflect its evolving appreciation of the numerous and complex challenges facing the implementation and oversight of any system of protections. The concerns and recommendations addressed in these reports reflect NBAC dual commitment to ensuring the protection of those who volunteer for research while supporting the continued advance of science and understanding of the human condition. This report views the oversight system as a whole, provides a rationale for change, and offers an interrelated set of recommendations to improve the protection of human participants and enable the oversight system to operate more efficiently.
- *American Medical Association, Report of the Council on Ethical and Judicial Affairs: The Use of DNA Databanks in Genomic Research: The Imperative of Informed consent, Chicago, 2001.* The Council recommends that 'The following safeguards should be applied to the use of databases for the purpose of population-based genomic research: (1) Physicians who participate as investigators in genomic research should have adequate training in genomic research and related ethical issues so as to be able to discuss these issues with patients and/or potential research subjects. (2) If research is to be conducted within a defined subset of the general population, that is, an identifiable community, then investigators should consult with the community to design a study that will minimize harm not only for individual subjects, but also for the community. When substantial opposition to the research is expressed within the community, investigators should not conduct the study. When the community supports a proposal, investigators nevertheless should obtain individual consent in the usual manner. The same procedure should be followed whether the investigators intend to collect new samples and data or whether they wish to use previously archived data sets. (3) When obtaining the informed consent of individuals to participate in genomic research, standard informed consent requirements apply (see Opinion 2.07). In addition: (a) special emphasis should be placed on

disclosing the specific standards of privacy contained in the study: whether the material will be coded (ie, encrypted so that only the investigator can trace materials back to specific individuals) or be completely de-identified (ie, stripped of identifiers); (b) if data are to be coded, subjects should be told whether they can expect to be contacted in the future to share in findings or to consider participating in additional research, which may relate to the current protocol or extend to other research purposes; (c) individuals should always be free to refuse the use of their biological materials in research, without penalty; (d) disclosure should include information about whether investigators or subjects stand to gain financially from research findings (see Opinion 2.08). Such disclosure should refer to the possible conflicts of interest of the investigators (see Opinion 8.0315); (e) subjects should be informed of when, if ever, and how archived information and samples will be discarded. (4) To strengthen the protection of confidentiality, genomic research should not be conducted using information and samples that identify the individuals from whom they were obtained (ie, by name or social security number). Furthermore, to protect subsets of the population from such harms as stigmatization and discrimination, demographic information not required for the study's purposes should be coded'.

Appendix B Contributions

This document was reviewed by the ESHG Public and Professional Policy Committee (PPPC). Members of the PPPC are:

Ségolène Aymé (Paris, France) Chair
 Martin Bobrow (Cambridge, UK)
 Jean-Jacques Cassiman (Leuven, Belgium)
 Domenico Coviello (Modena, Italy)
 Gerry Evers-Kiebooms (Leuven, Belgium)
 Peter Farndon (Birmingham, UK)
 Helena Kääriäinen (Helsinki, Finland)
 Ulf Kristoffersson (Lund, Sweden)
 Marcus Pembrey (London, UK)
 Sandy Raeburn (Nottingham, UK)
 Joerg Schmidtke (Hannover, Germany)
 Leo ten Kate (Amsterdam, The Netherlands)
 Lisbeth Tranebjaerg (Tromsø, Norway) Secretary

The first draft of this document was sent out to a wide range of people and organizations for consultation. It was reviewed critically by the following consultants:

Australia

- Agnes Bankier, Institute Royal Children's Hospital, Parkville

Belgium

- Laurence Cordier, European Commission - DGXII - ELSA Unit, Brussels
- Christiane De Wolf-Peeters, University Hospitals KU Leuven, Laboratory for Histochemistry and Cytochemistry, Leuven
- Sonia Le Bris, Deloitte & Touche, Biotechnology Group, Diegem
- Gert Matthijs, University of Leuven, Center for Human Genetics, Leuven
- Alain Miller, Computer Cell Culture Center, Senefte
- Herman Nys, Center for Bio-medical Ethics and Law, Catholic University Leuven, Leuven

Eastern Countries

- Georges Kosztolanyi, National Institute of Hygiene, Department of Human Genetics and Teratology, Budapest
- Vaidutis Kucinkas, Vilnius University, Human Genetics Center, Vilnius
- Jiri Santavy, University Hospital, Department of Fetal Medicine, Olomouc

Finland

- Sinikka Lindh, Helsinki University, Department of Medical Genetics, Helsinki
- Minna Poyhonen, The Family Federation of Finland, Department of Medical Genetics, Helsinki
- Harri Sintonen, Ministry of Social Affairs and Health, Helsinki

France

- Jacques Beckmann, Genethon, Centre de recherche sur le génome humain, Evry
- Florence Bellivier, Université de Paris I, Département Sciences et Droit, Paris
- Alexis Brice, Hôpital de la Salpêtrière, U 289, Mécanismes et conséquences de la mort neuronale, Paris
- François Cambien, Institut National de la Santé Et de la Recherche Médicale, SC 7, Banque d'ADN pour la recherche épidémiologique et clinique dans le domaine cardiovasculaire, Paris
- Anne Cambon-Thomsen, Institut National de la Santé Et de la Recherche Médicale, U 518, Epidémiologie et analyses en santé publique, Toulouse
- Isabelle Hirtzlin, Institut National de la Santé Et de la Recherche Médicale, U 357, Recherches en économie de la santé, Le Kremlin-Bicêtre
- Anne Janin, Department of Pathology, St-Louis Hospital, Paris

- Christine Juloux, Aventis Pharma, Research & Development Worldwide Regulatory Affairs, Anthony
- Christine Noiville, Université de Paris I, Département Sciences et Droit, Paris
- Laurent Parmentier, Glaxo Wellcome, Unité Nouveaux domaines thérapeutiques et pharmacologie clinique, Marly Le Roi
- Carolyn Roistch, Transgene S.A., Strasbourg
- Sandrine Sabatier, Council of Europe, Bioethics Division, Strasbourg
- Safa Saker, Genethon, Centre de recherche sur le génome humain, Evry
- Peteris Zilgalvis, Council of Europe, Bioethics Division, Strasbourg

Germany

- Erik Harms, Department of Pediatrics, University of Münster
- Rupert Sandbrink, Schering AG, Clinical Development Cns, Berlin
- Jürgen Simon, Institut für Rechtswissenschaften, University of Lüneburg

Iceland

- Einar Arnason, University of Iceland, Institute of Biology, Population Genetics Laboratory, Reykjavik
- Ragnhildur Arnljotsdottir, Ministry of Health and Social Security, Reykjavik
- David Gunnarsson, Ministry of Health and Social Security, Reykjavik
- Arni Sigurjonsson, deCODE Genetics Inc., Reykjavik
- Kari Stefansson, deCODE Genetics Inc., Reykjavik
- Tomas Zoëga, Icelandic Medical Association, Reykjavik

Italy

- Corrado Angelini, University of Padova, Department of Neurological and Psychiatric Science, Padova
- Antonio Cao, Istituto di Clinica e Biologia dell'Eta Evolutiva – Università degli Studi di Cagliari
- Franca Dagna Bricarelli, Galliera Hospital, Laboratory of Human Genetics, Genova
- Benedetta Nacmias, University of Florence, Neurological and Psychiatric Science Department, Florence
- Giuseppe Novelli, Università Tor Vergata, Facoltà Medicina Chirurgia-Genetica, Roma
- Gaetano Thiene, University of Padua Medical School, Pathology Department, Padova

Norway

- Anne Husebekk, University Hospital of Tromso, Immunology and Transfusion Medicine, Tromso

- Camilla Stoltenberg, The National Institute of Public Health, Section of Epidemiology, Oslo

Spain

- Angel Carracedo, Instituto de Medicina Legal, Facultad de Medicina, Santiago de Compostela
- Conxi Lazaro, Institut of Oncological Research, Medical and Molecular Center, Barcelona

Sweden

- Gaby Borglund, Data Inspection Board, Stockholm

Switzerland

- Stylianos Antonarakis, University of Geneva, Faculty of Medicine, Geneva
- Christina Dahlstroem, Roche Genetics, F Hoffmann – La Roche, Basel
- Lara Hashimoto, Roche Genetics, F Hoffmann – La Roche, Basel
- Alex Mauron, University of Geneva, Faculty of Medicine, Geneva

The United Kingdom

- Kevin Cheeseman, Astra Zeneca, Department of Experimental Medicine, Loughborough
- Nick Davies, Astra Zeneca, Research, Development Genetics, Cheshire
- Michael Furnston, Institute of Child Health; Bristol University, Bristol
- John Henderson, Institute of Child Health; Bristol University, Bristol
- Liz Jazwinska, SmithKline Beecham, Department of Human Genetics, Harlow Essex

- Alastair Kent, Genetic Interest Group, London
- David Lewis, The European Collection of Cell Cultures, Center for Applied Microbiology & Research, Salisbury
- Ruth March, Astra Zeneca, Research, Development Genetics, Macclesfield
- Lefkos Middleton, Glaxo Wellcome, Clinical Genetics, Greenford Middlesex
- Joy Osborn, Roche Products Ltd, Clinical Pharmacology Operations, Welwyn Garden City
- Nicholas Wald, Department of Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, London

Turkey

- Meral Ozguc, Hacettepe University, Faculty of Medicine, Ankara

United States of America

- Tom Murray, Center for Biomedical Ethics, Case Western Reserve School Medicine, Cleveland
- Dorothy Wertz, The Eunice Kennedy Shiver Center for Mental Retardation, Waltham, Massachusetts

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