Nationaler Ethikrat

German National Ethics Council

Biobanks for research

Biobanks for research

OPINION

Nationaler Ethikrat

Biobanks for research

OPINION

Published by the German National Ethics Council

Chair: Prof. Dr Drs h.c. Spiros Simitis
Jägerstraße 22/23 · D-10117 Berlin
Phone: +49/30/203 70-242 · Fax: +49/30/203 70-252
E-Mail: kontakt@ethikrat.org
www.ethikrat.org

Design and production: Bartos Kersten Printmediendesign, Hamburg
English translation by Philip Slotkin MA Cantab. MITI, London
Printed and bound by Saladruck, Berlin 2004

Contents

Summary; regulatory proposals by the National Ethics Council

For the purposes of this Opinion, biobanks are defined as collections of samples of human bodily substances (e.g. cells, tissue, blood, or DNA as the physical medium of genetic information) that are or can be associated with personal data and information on their donors. Biobanks have a twofold character, as collections of both samples and data.

This Opinion relates exclusively to biobanks used for medical research. These are deemed to include biobanks containing samples and data originally collected or recorded for medical purposes – e.g. diagnosis – but subsequently to be employed for medical research (for instance, specimens for cellular examination in pathology departments, DNA samples in human genetics departments, or blood samples collected in the course of neonatal screening).

Biobanks are an important resource for identifying the causes and mechanisms of a large number of diseases, including in particular ones that are widespread among the population. Our ever greater understanding of the human genome is increasingly making it possible to determine the role not only of external factors such as environmental agencies or lifestyle, but also of hereditary factors (genes) in the causation of or disposition to disease (genetic epidemiology). Like its conventional counterpart, genetic epidemiology studies not the individual but population groups, which may in certain circumstances be very large.

Human bodily substances of all kinds have been collected, stored and used for a variety of purposes since the beginnings of scientific medicine. As a consequence of modern methods of molecular genetic analysis and electronic data processing, the information content of biobanks and the possibilities of dissemination of the data contained in them are increasing apace.

The majority of existing biobanks are relatively small collections devoted to specific diseases, established, for example,

in university departments and comprising a few hundred to a few thousand donor samples. These biobanks will remain important in the future. In addition, large-scale population-related biobanks are being set up in some countries and will allow not only research into individual diseases but also approaches to a wide range of health-related issues.

Biobanks may be operated under the auspices of public-sector institutions, such as university departments, or of individuals or private bodies – for example, pharmaceutical companies. Irrespective of the responsible institution, they may be funded from public or private resources.

Biobanks may be established and/or used to serve a variety of interests – for instance, purely scientific interests, the interests of donors in the development of therapies for their own diseases (e.g. in the case of self-help groups) and commercial interests.

While biobanks hold out the prospect of significant breakthroughs in medical and pharmaceutical research, they also arouse anxiety and distrust. The main concern is donor protection. What is feared is the uncontrolled use of samples and data. Another source of anxiety is the possibility that potential donors might be pressurized into assuming unreasonable risks or imprudently divulging personal information. Although these problems exist irrespective of whether the samples undergo genetic or other analyses, the former are a particular object of concern because they generate information that may touch upon the personality of the donor in quite specific ways. Apart from the legal aspects of data protection, a vitally important issue is whether donors and their genetic relatives have effective protection from genetic discrimination and stigmatization. The question of protection from discrimination may arise for entire population groups if their samples are collected in biobanks and associated with personal data. These concerns and anxieties must be addressed by regulatory provisions on the establishment and use of biobanks. At the same time, the world of research requires adequate legal certainty.

The National Ethics Council considers that the following points should constitute guiding principles of the legal position in Germany. They should also apply to commercial research over and above existing provisions.

1. The central element of all regulatory proposals must be the donor's right of self-determination. This means that the collection of bodily substances from his body and the gathering of personal data, in both cases for subsequent use in biobanks for the purposes of medical research, must be subject to the donor's consent. The consent is effective if the donor has the capacity to give consent, the consent is given voluntarily and the donor has been appropriately informed of the purposes, nature, significance and implications of the collection and use.

2. The requirement of consent must also apply whenever samples and data obtained for other reasons – e.g. diagnosis or therapy – are subsequently to be used for research. This kind of multiple sample use is extremely valuable for medical research, but in the past it usually took place without explicit consent. To ensure that these samples remain available for research in the future, the process of obtaining consent must not be unnecessarily complicated. A form-based declaration that the samples may also be used for medical research subject to appropriate donor protection conditions ought to suffice.

3. If samples and data lawfully obtained for diagnostic or therapeutic reasons are subsequently used for medical research, the requirement of consent may be waived if the samples and data are completely anonymized. Since no relation to the person then exists, donor interests calling for protection are not at issue. However, if the donor has expressed a contrary wish at the time of collection of the samples, it must always be respected.

The same applies if the samples and data have been pseudonymized and the research worker has no access to the code, so that he cannot by himself relate them to the person concerned. In this case, as in that of anonymization, the researchers lack the possibility of relating samples and data to their donors. Ensuring the observance of data protection requirements is a matter for the data protection officer.

4. Under Germany's current data protection legislation, the requirement of consent may also be waived in the case of samples and data lawfully obtained for diagnostic or therapeutic purposes if, although the samples and data are to be used in personalized form, the scientific interest in the conduct of the research project substantially outweighs any interest of the donor in exclusion from use and if the purpose of the research cannot be achieved in any other way, or can be achieved only with disproportionate effort and expense. Even so, donor consent to the research should be obtained if reasonably possible.

   This exceptional situation ceases to be of practical relevance if, when bodily substances are collected for diagnostic or therapeutic purposes, precautionary consent is obtained for their use for medical research purposes too.

   "Exceptional situations" also includes cases where personalized samples and data obtained with donor consent for a specific research project, such as research on particular diseases, are to be used for research on further diseases. This exception need not be invoked where wide-ranging consent was granted at the time of collection of the samples.

   If an exceptional situation is to be invoked, an ethics committee must first be involved and have issued a favourable opinion (see Regulatory Proposal 17).

5. The scientific potential of biobank samples and data can often be fully exploited only if their use is not confined to individual research projects specifiable in advance. Donors

should be able to give generalized consent to the use of their samples and data for the purposes of medical – including genetic – research.

6. The same applies to consent relating to the duration of storage and utilization of samples and data. Donors should be able to consent to the use of their samples and data for an indefinite period. Moreover, compulsory time limits on the storage of samples and data appreciably limit the scientific value of biobanks. Epidemiological studies may extend over several decades. It must also be possible at any time to withdraw consent given to the use of samples and data for an unlimited period (see Regulatory Proposal 10 below).

7. Modern research is dependent on national and international cooperation and networks. For this reason, donors should also be able to consent to the transfer of samples and data from biobanks to third parties for the purposes of medical research. However, except in circumstances prescribed by law, the transfer must take place only in anonymized or coded form, with the recipient in the latter case having no access to the code. Should the recipients' research require an association with personalized data, this may be provided only by an officer of the biobank to which the donors originally entrusted their samples and data.

   All transfers of samples and data to third parties must be fully documented for future reference.

8. Subject to donors' consent, transfer of an entire biobank should be permissible provided that the recipient is subject to standards of donor protection and quality assurance equivalent to those applicable to the original institution in charge of the biobank. Transfer of a biobank without donor consent is acceptable only if the samples and data have first been anonymized. Transfers of existing biobanks to third parties with the inclusion of personalized donor data ought

to be possible only with the approval of an ethics committee.

9. Whether donors should be able to choose between declarations of consent providing for different levels of authorization ultimately depends on the purpose of the research. The absence of options does not constitute a violation of the right of self-determination, for it is up to the donor to decide whether or not to participate in the research under the specified conditions.

10. Donors must have the right to withdraw their consent to the use of their samples and data at any time. It should not be possible to waive this right. However, there should be provision for donors to allow samples and data to continue to be used, in the case of withdrawal, if they are anonymized – that is, if their personalization has been eliminated.

11. Consent must always be subject to the furnishing of appropriate information on all circumstances recognizably relevant to the donor's decision. These as a rule include:
    - the voluntary nature of participation
    - the purposes, nature, extent and duration of the proposed use, including the possibility of genetic analyses
    - the extent of, and conditions for, the possible transfer of samples and data
    - the possibility or otherwise of communication of research results to the donor
    - information on the possible consequences of the communication of results of genetic analyses for the donor and his relatives, including possible obligations to divulge (e.g. to insurance institutions)
    - the form of data storage and combination
    - anonymization or pseudonymization of samples and data
    - other ancillary donor protection measures

- any provision for State access to samples and data
- the right to withdraw consent
- the fate of samples and data if consent is withdrawn and if the biobank closes down
- any commercial prospects of the proposed research (including the possibility of filing patent applications on the results)
- issues of payment of expenses, remuneration or benefit sharing

It should not under any circumstances be possible to dispense with the provision of this information.

12. The information need only cover personal risks to the donor arising directly in connection with the use of samples and data in biobanks. The general risk that existing safeguards might not be observed, or the possibility that research results obtained by means of the biobank might lead to undesirable societal trends, cannot form part of the information provided by the research worker.

13. If individual communication of research results to the donor is agreed, he must also be told, as a part of the information to be given, that he must divulge these details in certain circumstances – for instance, when concluding new employment or insurance contracts in the future. In addition, where such individual communication to the donor has been agreed, the findings must be imparted by a person with the appropriate counselling skills. This applies in particular to the communication of results of genetic diagnosis.

14. To protect donor privacy, when biobank samples and data are stored and used, personal information allowing inferences as to donor identity shall as far as possible be concealed by coding. Organizational measures shall be adopted to ensure that the code and the encrypted data are stored and administered separately from each other.

15. There is no need for a general approval requirement for biobanks. The collection and use of human bodily substances and personal data are part of the normal course of medical research. They do not as a rule carry any particular risks to donors, and are covered by the established standards governing medical research. For this reason, blanket prior oversight by an authority is not necessary.

    However, it might be appropriate to require the licensing of large-scale biobanks – along the lines of the national biobank planned in the United Kingdom – that are relatively permanent organizations combining a number of different major resources under a single umbrella. In this case, a crucial regulatory consideration, in addition to donor protection, would be a guarantee of appropriate access to an infrastructure important for research.

16. Under the current data protection legislation, biobanks are in all cases subject to the supervision of a data protection officer, who must where appropriate be appointed specifically by the institution and who is responsible for ensuring compliance with the legal requirements applicable to the handling of personal data. As a rule, no other internal or external supervisory body will be necessary. Different arrangements may be indicated for large-scale biobanks with divided organizational responsibilities, which might need higher-level coordination and oversight.

17. Prior to the conduct of a research project involving the use of biobank samples and data, it should be necessary for the consent of an ethics committee to be obtained where
    - bodily substances are to be collected from a donor's body for research purposes
    - the project calls for the linking of samples to personalized data
    - bodily substances in personalized or pseudonymized form are to be transferred to external researchers

- existing biobanks are to be transferred in toto to third parties with the inclusion of personalized donor data
- exceptional situations are to be invoked (see Regulatory Proposal 4)

The involvement of an ethics committee and the need for its favourable opinion are intended to ensure that a narrowly worded consent is not exceeded, that a consent in broad terms is not inappropriately given an even wider interpretation, and that exceptional situations in which consent may be waived are not illegitimately invoked.

18. On the other hand, there should be no requirement for an ethics committee to be involved if samples and data are anonymized. In this case there is no particular need for donor protection.

19. Donors must be protected by an obligation of confidentiality on the part of all concerned with the establishment and use of biobanks. Where not provided for by law, the obligation of confidentiality must be imposed by the institution itself, for instance in its statutes or by contract.

20. Donors will often grant biobanks the right to use their samples and data for medical research with hardly any limitation of content and time. This seems reasonable only if this application (i.e. research) is strictly adhered to. For this reason, confidentiality of research must be enshrined in law, to preclude any access to samples and data other than in the context of research. This protection should also, in all cases, extend to access by the State.

21. The risk of results of genetic diagnosis being used in society to discriminate against people on the grounds of their genetic characteristics must be precluded by statutory regulation of fields in which the relevant information can be used in discriminatory ways, for instance by stipulating

restrictions on the use of genetic findings in the sphere of employment and insurance. Specific provisions for biobanks are not necessary.

22. Owing to the sometimes excessive importance hitherto assigned to the genetic element of physical and, in particular, mental characteristics in both the general and the scientific debate, the possibility cannot be ruled out that research results associating diseases with genetic endowment may be perceived as stigmatizing by those concerned and in their social environment. This perception reflects an overvaluation of genetic factors that fails to do justice to the significance of other conditions of human life (such as education, experience or environment). It must be corrected by information, not by regulation of research.

23. Genetic analyses of samples may also generate information applicable to a donor's relatives. Donors should nevertheless be able to consent to the analysis of their own samples without the need for the relatives' consent. However, information on their genetic status must not be forced on relatives.

24. Genetic analyses of donor samples may result in findings concerning the genetic particularities and risks of patients suffering from a specific disease or of ethnic groups in which such diseases are particularly prevalent. The relevance of the results to these groups cannot constitute grounds for a requirement of group consent in addition to the consent of individual donors. The particular problems presented by research on indigenous populations do not arise in Germany.

25. People incapable of giving their consent are just as entitled as those possessing that capacity to information on the use of their samples and data and the results of the relevant research. The collection and use of such subjects' samples and

data should be conditional on their having as far as possible given their consent, or at least not having shown any sign of refusal. In the case of someone who lacks the capacity to give consent, the decision must always be made, after the required information has been imparted, by the legal or duly authorized representative. Medical research involving people who lack the capacity for consent is, however, currently a matter of intense debate in a number of fields (e.g. pharmaceutical research). A detailed resolution of these issues is beyond the scope of an Opinion on biobanks. Instead, it is necessary to develop universally applicable principles combining proper protection of those incapable of giving their consent with – as far as possible – a recognition of the need for research for the benefit of others.

26. Deceased persons' samples and data can be obtained and used by biobanks on the same conditions as those applicable in the case of living individuals. If the deceased has not given the necessary consent during his lifetime, his next of kin can supply it, provided that this does not conflict with the deceased's wishes, expressed or presumed, during his lifetime.

27. For thorough utilization of the scientific potential of biobanks, access should be granted to as many research workers as possible. This requirement should be allowed for in the determination of the form of donor consent and when public funds are allocated for the establishment of biobanks. However, research workers who have contributed preliminary work of their own to the establishment of a biobank should be accorded priority of use for a certain period.

28. To a greater extent than was usually the case in the past, biobanks should be structured and maintained in accordance with uniform scientific standards. Adequate quality

assurance measures are the only way to guarantee that biobanks will remain usable for a variety of research projects for an extended period.

29. The establishment of biobanks should be subject to the principle of unpaid donation. The tendency to pay expenses at a level approaching that of actual remuneration should be counteracted. This would not only address any ethical reservations about commercialization of the human body, but also prevent any undermining of solidarity.

30. In consideration of the possibility of economic gain accruing from the subsequent exploitation of research results, forms of benefit sharing for the individual donors or donor groups concerned or for society are being debated. However, as a rule individual donors will not be able to benefit, if only because the contribution of an individual donor to the result of the research and the return on it is almost impossible to determine. Benefit sharing at a level higher than that of the individual, in the form of voluntary contributions to welfare funds, is conceivable and desirable. Compulsory funds, however, would compete with State corporate taxation and with the balancing of private gain and public benefit which it is intended to bring about. The regulatory issues of principle associated with the establishment of such funds extend far beyond the matter of biobanks.

A DEFINITION; PROBLEMS

1. Definition of biobanks; subject of the Opinion

For the purposes of this Opinion, biobanks are defined as collections of samples of human bodily substances that are or can be associated with personal data and information on their donors. Examples of bodily substances are cells, tissue and blood, as well as DNA as the physical medium of genetic information. Depending on the purpose of a given biobank, both genetic information on persons and health- and lifestyle-related information on these persons may be associated with the samples. It is this association that makes the sample collections important. The particularity of biobanks, which are the subject of this Opinion, lies in their twofold character, as collections of both samples and data.

A facility is not a biobank as defined above if it merely records and stores personal data derived from bodily samples – e.g. laboratory values from blood tests or the results of genetic analyses. Data collections of this kind arise whenever research is carried out on human beings; they accrue from medical diagnosis and are also established by the health insurance funds. They are purely databases, which must be assessed by the rules of data protection – where applicable subject to special requirements concerning the use of genetic data.

The following analysis deals solely with biobanks established and/or used for the purposes of medical research. They include collections of human embryonic stem cells and of samples of fetal tissue. The particularities of these collections are not discussed in this Opinion. Any specific rules governing their extraction and use are unaffected.

Some biobanks are used for diagnostic or therapeutic purposes. These are discussed here only if, in a departure from their original function, they are to be used wholly or partially for medical research. For this reason, blood banks, including

umbilical cord blood banks, and semen banks, as well as organ collections assembled solely for clinical use, are beyond the scope of this Opinion. The same applies to collections established for forensic purposes – i. e. for combating crime – or for non-medical applications of genetic diagnosis, for instance by companies providing commercial paternity testing services. A final group of exclusions concerns biobanks used solely for projects in the field of population genetics or evolutionary biology, which are directed not to medical investigations but to exploring the distribution of genetic diversity in populations and illuminating the phylogeny of the human race.

The reason for limiting the subject-matter of this Opinion is the particular constellation of individual and public interests presented by biobanks intended for medical research. There is an indisputably legitimate public interest in the establishment of biobanks and in making them available for research. However, in order for this interest to be translated into reality, sample donors must, to a greater extent than in other fields, allow access to personal data (including genetic findings) that touch upon central aspects of their private lives. The considerations necessarily entailed by this situation justify the special treatment and regulation of biobanks for medical research.

Medical research hopes for significant breakthroughs from biobanks because they can play an important part in identifying the causes of diseases not only in individual patients but also at epidemiological level, as well as in the development of diagnostic, preventive and therapeutic methods and applications. Biobanks can potentially make a valuable contribution to combating common severe illnesses, such as cardiovascular diseases (for instance hypertension or coronary heart disease), metabolic disorders and hormonal pathologies (e.g. diabetes and osteoporosis) and cancer, as well as diseases of the nervous system (such as multiple sclerosis, Parkinson's disease, muscular dystrophies and schizophrenia), infectious diseases and diseases of the immune system (for example rheumatism, neurodermatitis, tuberculosis or allergies). Insights into correlations

between genes, lifestyle, environmental factors and susceptibility to illness may be of great therapeutic and prophylactic significance. Biobanks may also constitute an important foundation for the development of drugs tailored to the particularities of individual patients or specific diseases (pharmacogenetics and pharmacogenomics).

Biobanks that contribute to medical research may differ greatly in size and structure (see Section B.1 below). Particularly valuable results are expected from biobanks of the kind currently planned in certain countries, in which samples and data from large sections of the population are to be collected and made available for use. However, some sceptics consider that the proposals hitherto advanced for research using biobanks of this type are somewhat vague and that it is risky to tie up scarce financial resources for medical research in such large-scale projects.

Biobanks for medical research serve not only the interests of science but often also the individual interests of the donors who provide the samples and data. Patients who provide clinically relevant bodily substances, such as tumour tissue, are as a rule very willing to make these substances available for research, because they hope that they themselves or other sufferers will benefit from its possible results. For similar reasons, it may be advantageous to store residual blood from neonatal screening in the interests of the babies concerned.

2. Problems, fears and the need for regulation

Human bodily substances of all kinds have been collected, stored and used for various purposes since the beginnings of scientific medicine, and a need for specific regulation in this field has never been felt. There are countless collections of different sizes, purposes and types, established in research institutions – e.g. university departments or the pharmaceutical

industry – for diagnosis, therapy, research or the clinical testing of medicines. Ever greater cooperation is also observed between academic institutions and private enterprise; these links are in the public interest and are increasingly demanded by government.

However, in consequence of modern methods of molecular genetic analysis and electronic data processing, the information content of biobanks and the possibilities of dissemination of that information are currently increasing apace. This trend casts a fresh light on the question of the need for regulation.

Whereas biobanks could lead to significant breakthroughs in medical and pharmaceutical research, they also arouse anxiety and distrust. The main concern is donor protection. What is feared is the uncontrolled use of samples and data. Another worry is that potential donors might be pressurized into assuming unreasonable risks or imprudently divulging personal information. Although these problems exist irrespective of whether genetic or other analyses are conducted on the samples, they are particularly relevant in the case of genetic analyses, because these generate sensitive information that may touch upon the personality of donors in particular ways. Apart from matters of data protection law, one of the most important issues is whether donors and their genetic relatives are effectively protected from genetic discrimination and stigmatization. The question of protection from discrimination may also arise for entire population groups, if their samples are collected and associated with personal data in biobanks.

Few specific instruments and provisions exist concerning the handling of human bodily substances and personal data. It is clear from the international debate in the last ten years that biobanks present a variety of ethical, legal and social challenges. To tackle these, there is an evident need for a framework of new and consistent rules, particularly as cooperative projects involving researchers from different countries are increasingly likely. The main reasons for this need are outlined below.

1. Many biobanks – in particular, the planned large-scale population-related projects (see Section B.2.2) – are designed in such a way, in terms of their objectives, that bodily substances and data, as well as information from and about persons, are stored for long periods of time. This raises the question of the degree of specificity required for donor consent to the handling and use of their samples, data and information prior to collection and/or recording, in order to meet the criteria of ethical and legal acceptability. This question arises in particular if the research for which the samples and data are to be used cannot be concretely identified at the time when consent is to be obtained because the details are not yet known.

2. Numerous collections of bodily substances established for the purposes of medical diagnosis or therapy in the past, often very long ago, have now assumed great value for research owing to the development of new techniques of molecular genetic analysis. In order for this value to be realized, the specified application of such collections must be changed. However, in most cases the donors will not have consented to the use of their samples for research – in particular, for specific genetic investigations. Nor, in many instances, can consent be obtained later, because, for example, the donors may have since died. This raises the question of whether the use of such biobanks for research can be justifiable.

3. For optimum use of biobanks, it may be appropriate to link data and information from a variety of sources. With modern electronic techniques and the Internet, biobank data can be exchanged and pooled across networks. This may yield information of a quantity and quality beyond those envisaged when the donors gave their consent. Consideration must be given to the rules for limiting the arbitrary transfer and linkage of samples and data collected for biobanks.

4. Genetic data not only yield information on the donors of the relevant bodily substances, but also have implications for their genetic relatives. Again, genetic analyses may generate information on groups – e.g. ethnic groups or groups of sufferers from a given disease. A significant issue is therefore what needs to be done to protect third parties whose interests may be affected by the research to be facilitated by biobanks.

5. In the case of biobanks in which, owing to the complexity of the tasks in hand, responsibility for the collection, storage, handling and use of samples and data is necessarily divided for organizational reasons, the question arises of how to provide for a consistent "chain of responsibility" to ensure observance of the rules – in particular, those of donor protection – at all levels of the organization.

6. Another point to be clarified is whether, and subject to what conditions, third parties, from the fields of both academic and industrial research, should be given access to biobanks, and under what conditions samples and data may be transferred and, where applicable, exported.

7. A final point to be determined is the procedure to be adopted if a biobank is closed down. There must be rules governing what is to be done with the stored tissue samples and data.

Biobanks may be operated by public-sector institutions or by individuals or private organizations. The latter may be either non-profit-making or commercial (foundations and business enterprises respectively). The different legal forms and objectives may call for different regulatory frameworks.

With regard to the rules governing biobanks, a balance will have to be struck between all the diverse interests involved. In the interests of research and of donors wishing to contribute to

it, the need is for a regulatory framework allowing optimum utilization of the collected samples and data in medical research. At the same time, limits must be set to protect donors and other potentially affected parties from the risks that may be associated with the establishment and spread of biobanks. The guiding ethical principles applied by the National Ethics Council in drawing up these rules are set out in Section C.1 of the Opinion. First, however, some examples of present-day biobank practice and emerging trends are outlined in the next section.

B SCIENTIFIC RELEVANCE OF BIOBANKS

1. Biobanks as an infrastructure for research

According to experience in medical epidemiology, biobanks in which human bodily substances are collected and linked to information on donors' states of health or lifestyle, as well as on their working and environmental conditions, may be expected to contribute to identifying the causes and mechanisms of diseases. By investigating the frequency and distribution of diseases among the population, epidemiologists have in many cases established correlations between environmental factors and the incidence of disease. For example, epidemiological methods have established links between a number of cancers and chemical substances to which sufferers were exposed at work (e.g. pulmonary tumours and uranium; bladder tumours and aniline dyes; or liver tumours and vinyl chloride). The high prevalence of limb malformations in newborns in the late 1950s was ultimately found to be due to the mothers' ingestion of thalidomide during pregnancy.

With today's ever greater understanding of the human genome, the methods of epidemiological research can increasingly identify not only "external" but also "internal" pathogenic factors. This applies in particular to the correlation between diseases and genetic predisposition (genetic epidemiology).

Like its classical counterpart, genetic epidemiology studies not individuals but population groups. Large series of samples from donors (several hundred to several thousand) with a given multifactorial hereditary condition – such as hypertension, asthma or epilepsy – are compared with corresponding series from healthy donors. The distributions of a large number of genetic markers (genotypes) in chromosomal regions where prior studies suggest the presence of genes relevant to the disease in question are compared in samples from patients and from healthy subjects. By means of a specifically directed but

highly complex strategy, comparison of markers permits an ever closer, step-by-step approach to a disease-relevant gene whereby it can ultimately be identified. The investigation of large groups is necessary because genetic factors involved in the causation of multifactorial diseases can only ever supply partial explanations. There is only a certain probability that genetic factors will result in a given multifactorial disease, so that statistical conclusions are all that is possible. Even so, the identification of genetic factors of this kind in pathogenesis may eventually prove significant not only for prevention but also for therapy of a disease. This information may also provide a basis for the identification of molecular drug targets.

In many studies directed towards the identification of genetic factors in the genesis and course of diseases, it is necessary, or at least desirable, for the persons who have provided samples and data to remain identifiable. It must be possible to approach them again to obtain further information on diseases that develop only during the course of life (cohort studies). Names may be coded (pseudonymized) to protect confidentiality, but donors must be re-identifiable for the purposes of follow-up studies. In the case of cross-sectional studies conducted in the form of a single interview and/or survey of subjects, personalization could in principle be wholly dispensed with by anonymization of samples and data. Even then, however, it may be desirable for donors to be identifiable, for instance to re-evaluate the study results in the light of new discoveries.

Biobanks established for research may differ greatly in structure and scale. A number of projects are directed towards the collection of bodily substances and data from large random samples of the general population (up to a few hundred thousand). Public attention, as well as criticism, has been levelled at some countries' plans to establish national biobanks for "stocking" samples and data from a substantial proportion of the population, with a view to optimizing exploitation of the scientific potential of genetic epidemiology. These projects are a paradigmatic expression of the fact that biobanks constitute an

important infrastructure for research. Either DNA or cell cultures from the donor samples are kept in these biobanks. Donor data may be stored in either coded (pseudonymized) or anonymized form.

However, large, population-wide collections of samples and data are by no means the norm for biobanks. The establishment and maintenance of such collections are extremely labour-intensive and expensive. For this reason, they can only ever exist in small numbers. The majority of biobanks established for medical research constitute fairly small collections of a few hundred to a few thousand samples from, for example, donors suffering from a specific disease. These facilities are established for projects at research institutions (such as universities), quite often in the context of a doctoral thesis or a dissertation submitted for qualification as a full professor, involving individual researchers or small working groups. In most cases, DNA is taken from the donor samples and stored in the form of a chemical substance or cell culture. Depending on the study design, the samples and donor-pathology information may be personalized, coded (pseudonymized) or anonymized for storage purposes. Small-scale biobanks are established mainly for case control studies, in which patients suffering from a given disease are compared with healthy controls in regard to certain risk factors, such as a specific genotype. These studies represent an indispensable scientific prerequisite for, or supplement to, the epidemiological studies permitted by large-scale biobanks. Biobanks of this kind exist both in Germany and throughout the world in such large numbers that it is impossible to give precise information on their nature, scale and geographical distribution.

In the pharmaceutical industry, biobanks are established for research purposes mostly in connection with clinical drug trials. The aim may be, for example, to identify molecular drug targets in cells, or to discover genetic factors responsible for the various effects and side-effects of drugs observed in patients (pharmacogenetics). These facilities store DNA or cell cultures

from a few tens of donors to a few hundred. As a rule, the data are coded and not anonymized.

Biobanks used in research need not originally have been established for that purpose. Systematic collections of human bodily materials have existed since the beginnings of scientific medicine. Many come into being in the course of medical diagnosis. One of the largest such collections is surely that of the blood samples taken from all neonates in the course of screening for treatable congenital metabolic disorders.

However, the value of that collection as a potential biobank for medical research is limited by the quality and quantity of the individual samples (dried blood spots). More important collections are those established at university pathology departments, comprising tissue samples collected in post-mortem examinations or submitted for cellular diagnostic examination. The samples are usually fixed in paraffin blocks and stored as dead material for future scientific purposes. In laboratory diagnosis too, unused blood samples are occasionally retained (frozen) for scientific purposes. University departments of human genetics or similar institutions to which blood samples are sent for genetic diagnosis store the residual DNA samples either for subsequent diagnosis in other family members or for scientific purposes. In this way, very large biobanks usable for research may be amassed at research institutions over the course of several decades. The quality of the relevant donor health status information varies. Since the samples are submitted primarily for diagnostic purposes, the stored materials are as a rule not anonymized.

While these collections are not a focus of public attention, they are very important for medical research. Much of our present-day medical knowledge was acquired with the aid of such collections.

Although not all biobanks were originally established for genetic analyses, they can as a rule nevertheless be used for this purpose. The specific analytical possibilities depend on the nature of the stored material, as well as on other factors.

1.1. Biobanks containing fixed tissue samples

Some biobanks store dead matter from which genetic material can be isolated for use in genetic analyses. However, the analytical possibilities are often limited, because the samples are usually derived from pathologically altered tissue and include normal tissue only at the margins. Depending on the fixing process, the potential for isolating genetic material may also be restricted.

1.2. DNA banks

Other biobanks contain genetic material (DNA), usually isolated from white blood corpuscles, or, more rarely, from other donor tissue. DNA samples can be stored as chemical substance in deep-frozen form, and are then available for a large number of analyses (although the number is limited by consumption of the material) whereby genetic variants (mutations) can be sought. However, these samples remain usable for no more than a few decades.

1.3. Cell culture banks

Biobanks for which donor samples (usually blood cells) are transformed into permanent cell cultures theoretically constitute an inexhaustible source of DNA of almost unlimited durability for the determination of genetic variants. They can also be used for studies of gene function, gene expression and cell function. The production of cell cultures of this kind is a highly complex and expensive process.

1.4. Biobanks containing pathologically altered vital tissue

Biobanks also store frozen tissue or cell cultures from donor samples specific to certain pathological conditions – e.g. blood vessels in cardiovascular diseases, brain tissue in nervous diseases, or tumour tissue in cancers. These samples can be used for genetic analyses to identify hereditary factors associated with the disease, at the level either of DNA (somatic mutations) or of gene expression.

2. Examples of biobanks

This section begins by presenting some examples of classical epidemiological studies for which samples and data from a large number of donors were collected. As a rule, the collections were established for concrete research projects on specifically defined diseases. They were not originally intended for genetic analyses, but can in principle be used for them. An outline is then given of some more recent projects that have been the subject of public debate, for biobanks established with a view to exhaustive exploitation of the scientific potential of genetic analysis by the use of samples and data from large populations.

2.1. Biobanks in past and present epidemiological research

2.1.1. Framingham Heart Study

One of the first and most important studies in the field of medical epidemiology was the long-term investigation of the factors contributing to cardiovascular diseases in almost the entire population of the small town of Framingham, Massachusetts, USA. Starting in the late 1940s, subjects were examined continuously for a period of some 40 years. The parameters monitored

included, for example, the changing lifestyles of men and women who were healthy at the beginning of the study, which were correlated with stature and weight and the occurrence of diseases. This study yielded the "Body Mass Index" (BMI), a coefficient that has since been universally adopted in the fields of health research and clinical practice. The study also included the measurement of blood sugar levels, hypertension and cholesterol values, to test for correlations with the incidence of strokes, angina pectoris, heart attacks and cardiac infarctions. At a later stage, DNA analyses were added to the study protocols.

2.1.2. MONICA ("Monitoring of Cardiovascular Diseases") and KORA ("Cooperative Health Research in the Augsburg Region")

The MONICA project comprised three consecutive representative cross-sectional studies initiated by the WHO and conducted since 1984 in 25 countries in Europe, Australia and North America with standardized protocols. The institution responsible for the German part of this international project was the GSF Research Centre for Environment and Health. The project was directed mainly towards identifying trends in and determinants of cardiovascular disease morbidity and mortality. This was the first multinational-scale attempt to correlate the incidence of these diseases with known risk factors (personal lifestyle, quality of the healthcare system and economic conditions). The number of samples included in the project was 20000.

A MONICA follow-up project is the KORA study, also conducted under the auspices of the GSF Research Centre for Environment and Health, which began in Augsburg and the surrounding region in 1985. It investigates risk factors for cardiovascular diseases, diabetes mellitus and allergies. Medical information on the subjects is recorded, and blood samples and in some cases tissue samples and cells are stored.

2.1.3. PROCAM ("Prospective Cardiovascular Münster")

PROCAM is thought to be the largest recent population-based national cohort study of the causes of cardiac infarction in Europe. The responsible institution is the Arteriosclerosis Research Department of the University of Münster. More than 30000 employees of major industrial and commercial enterprises and public authorities in Westphalia and the northern Ruhr area were examined between 1978 and 1985. These subjects have undergone regular follow-up monitoring ever since. The study has yielded many new discoveries concerning the genesis of cardiac infarction and its prevention. Particular attention was attracted by the findings on the role of cardioprotective HDL cholesterol and of triglycerides in the development of cardiac infarction. The results of this study have led to the establishment of computer-based personal risk profiles whereby doctors can calculate the risk of infarction in their patients on the basis of blood cholesterol values, blood pressure, smoking habits and other risk factors.

2.2. New projects for population-related biobanks

Recent projects for biobanks intended to cover large sections of the population are all directed towards creating an optimum infrastructure for an indefinite number of future research projects to identify correlations between genetic characteristics and diseases. As a rule, the focus here is not on the rare monogenic hereditary conditions but on the common severe diseases, in which the influence of genetic factors is confined to probabilities.

2.2.1. Iceland: Health Sector Database

Of all the biobanks projects featuring in the current debate, the one that has attracted most public attention is the Icelandic Health Sector Database (IHSD). Health data for the entire pop-

ulation of Iceland are to be assembled in a database and made available to research workers for linkage with genetic and genealogical data. The database is to include information from all medical records kept at the country's medical practices and hospitals. Such medical records have been kept in Iceland since 1915. They contain the individual medical histories of all patients treated. Another reason why the IHSD is considered to be particularly valuable for scientific purposes – in particular, investigating possible correlations between common diseases and genetically based dispositions – is that the relationships and lines of descent of all Icelanders (in a population numbering some 270 000) are well documented in publicly accessible genealogies.

The initiative for the project came from the biotech company deCode Genetics (CEO: Kari Steffanson), which offered private funding for the establishment of the database, whose cost (estimated at between 100 and 200 million US dollars) far exceeded the capacity of the Icelandic State budget. In return, deCode was to be granted exclusive rights of use for a specified period. The Icelandic Parliament laid the legal foundations of the project by the 1998 Act on a Health Sector Database. The Act provides that all medical records shall be entered into the database – unless patients object – and that an exclusive licence for commercial utilization of the database may be granted for a 12-year period. The licence agreement concluded in 2000 with (a subsidiary of) deCode provides for payment to the Icelandic State of up to $1.9 million in licence fees and benefit sharing.

The Icelandic project is currently at a standstill. Criticisms concerning issues that must be addressed in all biobank projects have been voiced in the relevant debate:

(1) Systematic limits of data protection. In the proposed project, patient data are to be entered in the database in encrypted form (using code numbers), and an independent State data protection commission is to supervise the observance of confidentiality. Objectors nevertheless consider

there to be a risk that the linkage of a number of different (coded) donor data items might result in donors becoming identifiable. The question is therefore whether technical data protection measures can control the risk to donors.

(2) Departures from the requirement of informed consent. Under the Icelandic Act, data will be entered in the database unless the patients concerned object. This approach has been criticized as a violation of autonomy. Involving as it does a presumption of consent, it represents a departure from the strict requirement of explicit informed consent. At issue is whether and, if so, subject to what conditions such departures may be acceptable.

(3) Access to biobanks. The granting of an exclusive licence for the use of the IHSD to a private commercial undertaking has been criticized as a sell-out of public resources and the establishment of a monopoly. The question here is whether biobank projects ought to be funded by private enterprise and how access to them should be managed equitably.

2.2.2. Estonia: Estonian Genome Project

Estonia is planning to establish a database that will bring together phenotype and genotype data from a high proportion of the Estonian population. Samples and data from up to 1 million people (out of Estonia's total population of 1.4 million) are to be obtained over a five-year period. The database is to be used in research to identify correlations between genetic factors and common diseases.

For the phenotype aspect of the project, data on the subjects' health status, tolerance of medicinal drugs, lifestyle, relevant environmental conditions and genealogy are to be recorded. The genotype element involves taking a blood sample, from which DNA (1–2 mg per individual) and plasma will be isolated and stored separately. Between 60 000 and 100 000 SNPs

(single nucleotide polymorphisms – i.e. variants of the DNA sequence) per person are to be analysed. Unused DNA will be kept for further analyses.

Data recording and storage will be subject to the donors' explicit consent. For entry in the database at the responsible institution (the Estonian Genome Project Foundation), the personal element of the data will be encoded; a second encoding level will then be applied before third parties (researchers, commercial undertakings, etc.) are granted access to the data. Donor re-identification by the database owner will be permissible in certain cases – for instance, on request by donors themselves or where further samples or data from a donor are desired.

The project was enshrined in law in December 2000 by the Human Genes Research Act. The Act includes ancillary prohibitions affording protection from genetic discrimination in insurance and employment contracts. All samples and data are the property of the Estonian State and may not be alienated by it; however, donors have the right to demand their destruction. The private company EGeen (whose head office is in California, USA), which was formed specifically for the purpose, is to be given a 25-year exclusive licence for commercial utilization of the database. The model, however, differs from that of the Icelandic project because Estonia at present holds 100% of the shares in EGeen (through the Foundation) – although private co-investors are now being sought.

The project has not given rise to any appreciable public debate. It remains to be seen whether the Government's plan to have the major part of the cost of the database (some $100–150 million) met by private investors will be translated into reality. The project has so far not proceeded beyond the pilot phase, in which 10000 donors are to be recruited.

2.2.3. BioBank UK

In the BioBank UK Project, a comprehensive study of the health effects of environmental factors, lifestyle and heredity is

to be conducted. Besides the identification of risk factors for specific disorders, the scientists hope to obtain a better understanding of the heterogeneity observed within individual groups of diseases and to identify biomarkers in human blood.

The plan is to record data from a total of 500 000 randomly chosen subjects in the 45-69 age group, who are to be followed up over an extended period. To ensure that the results are as meaningful as possible, the subjects will undergo regular examinations at intervals of not more than ten years. In addition to genetic and biochemical data obtained from the blood samples, information is to be gathered on the course of individual lives. Anamnestic data will be evaluated from National Health Service medical records.

The plans for the BioBank UK project date back to June 1999. Funding for the first seven years of the project amounting to £61 million has now been approved by the Wellcome Trust, the UK Medical Research Council (MRC) and the Department of Health. The exact experimental protocols have not yet been finalized. The first blood samples are to be taken in pilot projects during 2004. If the pilot projects are successful, the setting up of the full-scale biobank will commence in 2005.

The Management of BioBank UK, which is hosted by the University of Manchester, is advised by a Science Committee, whose members also include scientists from the six centres with which BioBank UK will cooperate at regional level. There is to be an independent Ethics and Governance Council, which will receive regular information from Management and in turn issue recommendations to Management. A draft regulatory framework for BioBank UK has been prepared by an Interim Advisory Group and opened to public discussion. Among other provisions of the draft, subjects will be able to withdraw from the project at any time, and the transfer of samples to third parties will not be allowed. Conversely, stored information will be made accessible for such purposes as the development of new diagnostic tools. However, there will be no access to information on individual subjects.

One of the findings of a large-scale public consultation carried out in 2002 on the collection and storage of human tissue for research purposes was that acceptance of BioBank UK among the British population substantially depends on the consent of the subjects and on public-sector operation of the facility.

2.2.4. POPGEN – Schleswig-Holstein

The institution in charge of POPGEN is Kiel University Hospital. The study, which began in 2002, is being funded by the Federal Ministry of Education and Research for an initial three-year period in the context of the National Genome Research Network. Schleswig-Holstein was chosen as the sample and data collection region owing to its relatively stable population and clear-cut geographical boundaries. Specialist medical practices are approached to maximize the coverage of patients suffering from specific disorders of relatively high prevalence among the population – e.g. coronary heart disease, chronic inflammatory intestinal disorders, asthma and periodontitis. The project is to be extended to further diseases in a subsequent phase.

POPGEN is concerned with conditions for which initial disease genes have either already been or are expected to be discovered in the near future. The aim of the project is to link disease-relevant genotypes to patients held to be fairly representative of the population. A total of some 50000 subjects are to be included. The form of data recording allows not only typical but also atypical or unusual pathological processes to be taken into account. The project substantially takes the form of a prevalence-based random-sample study (prevalence in epidemiology is defined as the total number of individuals exhibiting the relevant characteristic in a population). Subgroups of subjects are interviewed at six-month intervals on the course of their disease.

A 30 ml blood sample is taken from each subject and DNA is isolated from it. The resulting genotype information is linked to information on the clinical picture, account being taken of living conditions. The informed consent obtained from subjects relates only to the research topics covered by the project. If the purpose of the research project were to change, the subjects would have to be contacted again for further consent. The data collected are pseudonymized. Observance of security requirements is monitored both by the Ethics Committee of Kiel University Hospital and by the data protection officer for the Land of Schleswig-Holstein.

External scientists may be granted access to the collected samples and data if the Ethics Committee agrees. Cooperative projects are also possible subject to this condition. The first research results are expected in 2004/2005.

A glance at the practice of medical research with biobanks shows that the smaller sample and data collections and those tailored to specific research topics are currently of very great scientific value. Another important aspect is the secondary use for research purposes of patient samples collected in clinical therapy and diagnosis. The large-scale national biobank projects, on the other hand, are still at the planning stage, and it is not yet known whether they will be implemented and yield the hoped-for results. For that reason alone, it would be inappropriate to base the setting of rules for biobanks on these large-scale projects. Instead, these rules must provide a practicable and at the same time legitimate framework for the normal situation as represented by the biobanks already in existence today. Such a framework must be based on the recognized principles of medical and general ethics.

C PRINCIPLES AND FOUNDATIONS OF ETHICAL AND LEGAL APPRAISAL

1. Ethical principles and foundations of appraisal

The ethical appraisal of biobanks is based on the moral values and principles upheld by our culture. It is underlain by the premises enshrined in man's moral consciousness, as well as by the basic values of the German Constitution. Their starting point is respect for the dignity of man.

Respect for the dignity of man constitutes the core of our ethical and legal obligations. It is based on the inalienable intrinsic value of man, presupposes his freedom and includes the equality of all human beings as a matter of principle. The obligation to treat man as an "end in himself" (Immanuel Kant) necessarily follows. This means that man must never constitute a mere means to an end. Human beings must be respected in their uniqueness. Their physical and psychological integrity must be protected. Individuals must never be reduced to their genetic characteristics, and they must not be discriminated against on the grounds of their genetic endowment.

Hence a central component of human dignity is self-determination of the individual. This must also be the focus of attention in the consideration of biobanks. Self-determination implies that an individual can decide for himself whether or not to agree to actions affecting his body or to measures concerning his own personal sphere. The personal sphere is also involved in the handling of bodily substances intended for biobanks. Self-determination includes the right to decide on the use to which one's own personal data are put ("informational self-determination"). Any restriction of the right of self-determination calls for special justification.

As to consent to medical research on human beings, medical ethics has formulated a series of conditions intended to protect the right of self-determination. These provide that consent

must always be not only voluntary, but also given explicitly and on the basis of full information. The consenting person must first have been fully informed of the nature and possible risks of the action on his body and of the content and objectives of the research (see Section D.3). However, whereas these principles are applicable to the generality of research on human beings, it is necessary to determine how far they are appropriate and necessary in the specific case of biobanks.

Again, while donor self-determination is a necessary condition of the legitimacy of the establishment and use of biobanks, it is not a sufficient condition. No one can invoke his autonomy to justify actions whereby the rights of others or public objects of legal protection are infringed. For this reason, irrespective of donor consent, the question arises whether biobanks present unacceptable risks to third parties and to society in general, for instance in terms of stigmatization or discrimination (see Section D.7).

Doctors are bound by professional ethics to promote the welfare of their patients. If this requirement is not confined to the specific doctor-patient relationship, but extended to potential patients, it implies that the promotion of medical research intended to help future patients is, if not a professional obligation, something that can be legitimately expected of the medical profession. A doctor who asks donors to provide samples and data for biobanks serving the purposes of medical research is not merely pursuing his professional interests; he also wishes to make a positive moral contribution. This is another aspect of appraisal of the legitimacy of such donations.

Biobanks in general must be considered not only from the point of view of avoiding possible dangers and risks, but also in terms of their individual and social utility. The realization of this utility may also be demanded by considerations of solidarity. Many donors regard their willingness to supply samples and data as an expression of their moral duty to help others. The positive moral obligation to help others in need complements the negative moral obligation not to harm others.

Biobanks must also be considered from the point of view of justice. The main relevant aspects are those of distributive justice and compensatory justice. For instance, can it be acceptable for the possible risks to be borne solely, or particularly, by specific groups (e.g. age, population or patient groups) who are unlikely to be able to share in the possible benefits in the foreseeable future? Issues of justice also arise in connection with the decision as to which individuals and institutions may use biobanks – that is, are granted access to the bodily substances and data stored in them. A final question in this context is whether the persons or groups who contribute to a biobank with their donations should share in the benefits accruing from research using biobanks ("benefit sharing" – see Section D.12).

2. Legal framework

The principles set forth above are reflected in our legal order. At constitutional level, the protection of human dignity is enshrined in Article 1(1) of the German Constitution (the Basic Law). Donors' rights of self-determination with regard to their bodies, their bodily substances (even when separated from their bodies) and their personal data are protected in the form of the right to life and physical inviolability (sentence 1 of Article 2(2) of the Basic Law) and of general rights of personality (Article 2(1) in conjunction with Article 1(1) of the Basic Law). However, countervailing principles are those of the freedom of science, research and teaching (sentence 1 of Article 5(3) of the Basic Law) and free choice of profession for research workers (sentence 1 of Article 12(1) of the Basic Law). Again, the basic rights of donors should not be seen merely as countervailing rights against research, for they also include a donor's right to participate in research of his own free will.

A donor's right of self-determination in respect of his body is protected, on the level of common legislation (i.e. the level below that of the Constitution), by way of the general provi-

sions on the infliction of bodily injury contained in the criminal and civil law (Sections 223ff. of the Penal Code and Section 823(1) of the Civil Code). These provide that any action affecting the integrity of an individual's body requires that individual's consent. This requirement is not qualified by the freedom of research and by researchers' free choice of profession. The consent is effective only if the person concerned has been appropriately informed of the purposes, nature, significance and implications of collection (i.e. there must be informed consent). Any deception as to the purpose of collection may result in the consent being ineffective.

With regard to the use of bodily substances already separated from the body, as well as to the use of data and information, however, current German law is not based in the same way on the primacy of self-determination. Whereas use of an individual's bodily substances and/or personal data notwithstanding his express wish to the contrary may be regarded as unlawful, it is not the case that any use of bodily substances or personal data is subject to the legitimizing consent of the individual concerned, as the following considerations show.

On the use of bodily substances already separated from the body, the prevailing view is that it is mainly the general right of personality that constitutes the foundation of donor protection; this is so even if property rights are presumed to exist in human bodily substances (separated from the living body) and if the bodily substance concerned has become the property of the researcher through assignment or processing. After all, despite the researcher's acquisition of ownership, relations in the nature of rights of personality persist between the bodily substance and its former carrier, and these relations can be apprehended by way of the general right of personality. The general right of personality is protected by the law of tort in the form of the "other right" provided for in Section 823(1) of the Civil Code (but not by the criminal law). However, most legal authorities consider that a comprehensive appraisal of the competing goods and interests must be conducted in order to

determine whether a specific measure actually violates the general right of personality in a manner contrary to law.

Whether or not a given use of bodily substances results in an unlawful violation of personality rights presumably depends, first, on the significance and implications of the measure for the person concerned and, second, on, for instance, the nature, scale and objectives of that use. An important consideration in this determination is the freedom of research, which enjoys particular protection under the German Constitution. For the purposes of the appraisal of goods and interests, another essential aspect is anonymization of the bodily material – because as a rule the personality rights of the former carrier of the bodily substance are unaffected if the substance is used without any individualizing linkage to his person.

The data protection legislation allows a comparable situation-specific consideration of whether the use of personal data is permissible even without the specific consent of those concerned. On the one hand, the data protection legislation is not applicable to anonymized data. On the other, its requirements are relaxed in favour of research in a number of respects. For instance, both public and non-public bodies (Section 13(2) No. 8 and Section 28(6) No. 4 respectively of the Federal Data Protection Law) may record data subject to particular protection, such as information on health, sexual life or ethnic origin, even without the relevant parties' consent if the scientific interest in the conduct of a specific research project substantially outweighs the interest of those parties in the non-recording of the data and if the purpose of the research can either not be achieved in any other way, or otherwise be achieved only at disproportionate expense. In addition, public bodies are entitled (Section 14(2) No. 9 of the Federal Data Protection Law) to use data for a purpose other than that originally specified if the data are to be used for a research project of the bodies' own or if they are to be transferred to non-public bodies and the interest in the project substantially outweighs the interest of the parties concerned in there not being a change of purpose and the pur-

pose of the research can either not be accomplished in any other way or otherwise be accomplished only at disproportionate expense. Finally, subject to exactly the same conditions, non-public bodies are allowed (Section 28(3) No. 4 of the Federal Data Protection Law) to use the personal data processed by them for a purpose different from the original one or to transfer them to third parties.

In addition to the Federal Data Protection Law, the individual Federal Länder have general data protection laws applicable in their own territory, as well as specific data protection laws and orders applicable to hospitals and the health sector, which also privilege research to a greater or lesser extent. They vary substantially in their requirements. A distinction between in-house research and research outside the relevant medical institution is often made. Many of these instruments provide that the permissibility of the use of personal data shall depend on an appraisal of competing goods and interests (the public interest in the conduct of the research project must outweigh, or substantially outweigh, the subject's protection-related interests); in some cases a provision is included to the effect that there must be no countervailing protection-related interests on the part of the subject or that such interests must not be infringed. The (or a) decisive criterion is often that there shall be no alternative to the use of personalized data. Occasionally the furnishing of information to the subject and the absence of opposition following the imparting of the information are deemed sufficient. Finally, some of these instruments require approval of the use of the data by a specified authority. The overall conclusion must be that, while the relevant data protection legislation presents an extremely complex and diverse picture, it cannot be asserted that, under the relevant provisions, personal data (including health-related data) may be used for scientific purposes only with the (written) consent of the subjects concerned.

D IMPLICATIONS FOR THE REGULATION OF BIOBANKS

1. Donor consent as the foundation of biobanks

Where bodily substances are to be collected from the body of a living human being for use as samples in biobanks for research, there can be no question of limitations on the requirement of consent to their collection. From the legal point of view, encroachments on the fundamental right to physical inviolability may admittedly be conceivable even without consent if these are in the public interest and permitted by a specific law. However, such a solution should not be contemplated in the case of acts in favour of research. Instead, to reinforce the legitimacy of research and public confidence in it, the principle should be that donation is voluntary. This does not preclude the idea of a moral obligation to contribute to medical research by the donation of samples and thereby to help relieve the suffering of others. This view can be justified on the grounds of solidarity – in particular, where an individual wishes to take advantage of the results of medical research to which others have contributed. There is no need to go into this issue in more detail here. A high degree of willingness to donate to biobanks is observed both in the population at large and among the patient groups particularly relevant to research. There is therefore no reason to put anyone under moral pressure in the name of solidarity.

Where bodily substances and data accruing in the ordinary course of therapy or diagnosis are to be collected and/or stored in biobanks and used for research, current law provides, as stated above, that explicit donor consent can be dispensed with subject to certain conditions. This flexibility has been very important to medical research in the past. Nor can its legitimacy be denied on ethical grounds. In the appraisal, it accords precedence to the public interest in research over donors' interest in having the sole right of decision on the fate of their bodily sub-

stances and data. After all, these substances have already been separated from the body and their "donors" do not have any manifest interest in reusing them themselves; furthermore, they would otherwise simply be destroyed, as in the case of tissue removed in surgery or of residual material from diagnostic samples. Moreover, the confidentiality of patient data used in research can be protected by suitable guarantees. However, this consideration would justify only sample and data use notwithstanding the absence of consent, but not use contrary to the donor's declared wishes.

Even if the flexibility allowed by the relevant laws and regulations is acknowledged to be legitimate, it may nevertheless be preferable to require subjects' explicit consent for the large-scale use of samples and personal data for research purposes. A number of different situations must be distinguished.

Use of anonymized samples and data

Use without consent raises the least concern where legitimately obtained samples and data have been completely anonymized – that is, where any personal reference allowing donor identification (name, address and date of birth) has been eliminated. Whereas, in this case too, there must be no use against the declared wishes of the subject, ethically unobjectionable research on anonymized material ought to be possible even without the subject's consent. In such cases, there are no evident appreciable personal interests that take priority over the public interest in research. This is true to an even greater extent of material that never has been personalized. However, if there is already considered to be any likelihood of the future use of bodily materials for research purposes, the subjects concerned should be informed of the possibility of such use (where appropriate, by means of a form), so that they can exercise their right of self-determination by refusing to allow it.

External use of personalized samples and data

The other end of the spectrum comprises cases where bodily

substances are to be transferred to an external institution in combination with personalized patient or subject data. In this situation, the samples and data move outside the area of confidentiality and control in which they were supplied. An example might be the establishment of a tumour bank, for which both tissue samples and the associated patient data from a large number of hospitals and medical practices are to be assembled. In such a case, donor consent and the approval of an ethics committee (see Section D.6.3.3) are essential.

Internal use of personalized samples and data

A midway position is occupied by cases where research is to be undertaken using personalized or pseudonymized samples and data at the institution in which the samples and data were originally obtained. The question whether the subject or patient must consent not only to the collection of the sample from the body but also to the research concerned arises in two cases of a change of purpose: first, where samples and data obtained for the purposes of diagnosis or therapy are to be used for research; and, second, where consent to a specific research project has already been obtained but further research is to be conducted. In these cases consent should always be obtained, perhaps by a formalized procedure. In accordance with the data protection legislation, however, use without consent should be possible in exceptional circumstances – with the approval of the ethics committee (see Section D.6.3.3 below) – if the scientific interest in the conduct of the research project substantially outweighs the subject's interest in non-use and the purpose of the research can either not be accomplished in any other way, or otherwise be accomplished only at disproportionate expense. The narrow formulation of this exception appreciably widens the scope of the consent requirement compared with the previous situation.

A situation that may be equated with internal use exists where samples and data are transferred to external bodies in pseudonymized form, but donor identification is possible only

at the institution where the samples and data were obtained or collected. In these cases the institution to which the data were entrusted remains exclusively responsible for them, and the external researcher has no access to the code.

2. Scope of the consent to use

2.1. Restriction to a specific purpose

Where, in accordance with the above considerations, consent to the use of samples and data in biobanks is required, it is legally effective only if it is given voluntarily and the subject has been appropriately informed of the purposes, nature, significance and implications of that use. The subject must know what he is agreeing to. To this end, in the case of research on human beings, information on the specific research project is as a rule necessary. Hence other research projects are not covered by the consent (this is the principle of restriction to a specific purpose).

However, restriction to a specific purpose, in the form of a concrete research project, may give rise to problems in the case of biobanks. These emerge particularly clearly with the national biobanks planned in a number of countries, in which samples and data from several hundred thousand donors are to be kept for medical research. As infrastructure facilities for an indefinite number of future research projects, they are unsuitable for their purpose if consent is narrowly restricted to use for specified concrete projects. Changes of purpose may arise with other biobanks too. After all, the research conducted, or research in another field, often raises connected questions that could not previously have been foreseen, but can be answered by means of the samples and data in the biobank. Attempts could admittedly be made in such cases to obtain fresh consent from donors in each case, but this will often be possible only at disproportionate expense, or not at all, for example because the donors have since died.

To ensure that biobanks, once established, do not quickly lose their value, it must be made possible for donors to consent to the use of their samples and data for undefined research projects to be specified only at some future date.

It is occasionally objected that such a broad consent to use does not constitute informed consent because the donors do not know the exact purpose for which their samples and data will ultimately be used. However, if donors have been informed of the indefinite nature of the actual future applications, they will be aware that they are agreeing to an uncertainty. But this uncertainty is one that also affects the researchers, and does not relate to the forgoing of available information.

Research must not accept everything that subjects are prepared to give of their own accord. For this reason, research on human beings for the benefit of others is not acceptable, even with consent, if it entails appreciable health risks for the subject. However, such risks are unlikely to arise in the case of biobanks. Bodily risks are precluded from the outset because the samples used for research are already separated from the body. Risks arising out of the research results and their transfer to others must be controlled by appropriate donor protection measures (see Section D.6 below). Provided that these conditions are satisfied, there is no reason not to accept broadly worded consent to use by donors if they have been adequately informed of the uncertainty to which they are agreeing.

Yet even consent of this kind is not totally limitless, because, firstly, the research must of course satisfy the applicable legal and ethical conditions and, secondly, it remains confined to medically relevant research, in accordance with the terms of the donors' consent. Now the definition of what constitutes the subject-matter of medicine is not totally clear. For instance, problems not traditionally assigned to the field of competence of medicine (such as certain forms of idiosyncratic behaviour) are occasionally redefined as medical problems. This situation is not necessarily negative, because it may be appropriate, and afford relief to those concerned, to extend medical concepts of

explanation and treatment to conditions and states not previously recognized as pathological. On the other hand, however, this trend is also seen as problematical because it increasingly involves the pathologization of variations in the spectrum of the normal and their reduction to a scientific cause-and-effect model, while psychosocial factors are relegated to the background. With regard to biobanks, the vagueness of the definition of "medical purposes" must be borne in mind. Whether this vagueness does or not does not call into question the utility of the term "medical" to distinguish the relevant purposes from others is admittedly disputed. Again, the ill-defined nature of the term is not specific to biobanks. Even so, on the margins of the field of action that can thereby be legitimized, situations could arise in which research generally perceived not to be serving the purposes of medicine is carried out.

2.2. Period of validity of consent

Demands are occasionally voiced for samples of human bodily substances and personal data collected for research purposes to be subject to compulsory destruction after a given period (10 or 20 years). The underlying idea is that subjects should not commit themselves for indefinite periods extending into an unpredictable future. It is indeed a principle of data protection law that personal data may be stored for only as long as really required. However, there are good reasons for the absence of compulsory deadlines for data deletion in the data protection legislation. In the case of biobanks too, the demand for rigid time limits on storage and use is counterproductive, as many important studies depend on the long-term availability of samples and data. For example, past pioneering epidemiological cohort studies that analysed health trends in large populations over several decades would thereby be precluded.

Nor is there any obvious ethical reason why subjects should be prevented from consenting to the long-term use of their

samples and data of their own free will and in full knowledge of the situation. They are not then irrevocably placing their own freedom of decision at the disposal of others – something that could at most justify a curtailment of their autonomy "to protect them from themselves". After all, in spite of their consent, they have the right to withdraw their personal samples and data from the biobank at any time (see Section D.6.1 below).

2.3. Transfer of samples and data to third parties

Samples and data from biobanks must not be transferred and used for purposes other than those of research. Within the field of research, however, it should as a rule be possible for them to be transferred, because modern research mostly calls for cooperation with other workers and because the efficient use of a facility such as a biobank depends – as stated above – on the possibility of using its samples and data for a large number of research projects. These particularities must be allowed for in the requirements governing subjects' consent. Where the identity of certain cooperating partners is already known at the time of establishment of a biobank, subjects should be informed of this. However, it should also be possible for consent to be given to the transfer of samples and data to as yet unknown researchers. The same applies to transfers to the privately funded research sector.

Such a broadly framed consent must, however, be offset by a requirement that the samples and data, if they cannot be anonymized, may leave the area of control of the biobank only in coded form, except in circumstances provided for by law. Personal data such as names, birth dates and addresses must not be passed on to third parties. In cases where external researchers require additional relevant data on subjects for their research, the data may be supplied only by an officer of the biobank to which the donors originally entrusted their samples

and data, so that the external workers cannot identify individuals.

Furthermore, full records should be kept of any transfer to third parties, to maximize transparency and to ensure that donors can withdraw their samples and data at any time. Donors' rights of withdrawal must be guaranteed whenever samples and data are transferred.

The protective mechanisms described above are all the more important in the light of modern communications technologies, which allow the networking of a number of different biobanks. Whereas this networking can appreciably increase the value of biobanks for research, the accumulation of huge volumes of data may also increase the potential for abuse. However, if only coded samples and data are linked by networking, there are no fundamental objections from the point of view of donor protection. After all, a network too must not allow potential re-identification or create a new pool of personal samples and data. In cases where sample and data re-identification is necessary for research, a fresh approach must be made to the officers of the individual biobanks concerned.

2.4. Provisions governing succession for biobanks

A donor's consent should also extend to the procedure to be adopted if the operators of a biobank to which samples and data are supplied are no longer present – because the responsible scientists are no longer working, or because a research institution is closed down or no longer wishes to continue with the biobank. If the destruction of all samples and the deletion of all data are not to be made compulsory in such cases, with the consequent loss of valuable potential research material, it will be necessary to provide for the possibility – subject to donor consent – of transfer of a biobank as a whole, including all rights and obligations, to a third party as the new operating institution. In this case, it must also be permissible to transfer

the codes for donor re-identification. In the absence of donor consent, the transfer of a biobank to third parties is acceptable only if the samples and data have first been anonymized.

A non-specific consent by a donor to transfer should as a rule be interpreted as meaning that samples and data may be transferred only to an equivalent institution. This would mean that in cases of doubt, for example, a biobank could not be transferred from a university to the commercial sector.

The problem of succession is reduced if the operators of biobanks are from the outset not individuals but institutions (e.g. universities). The legitimate interests of the research workers, in particular in a time-limited exclusive right of use, should be protected by appropriate rules governing their internal relationship with the body in charge of the biobank. This construction corresponds to the practice in many research institutions and in many cases also to the conditions laid down by public research-funding institutions. At the same time, it shifts the responsibility for a biobank – and for observance of the donor protection rules – away from the immediate users and on to the institution.

3. Obligation of informed consent

Before giving their consent, donors must be informed of all circumstances likely to be relevant to their decision to grant or refuse it. It must not be possible to dispense with the imparting of this information. Relevant circumstances include in particular the following: the voluntary nature of participation; the purposes, nature, scope and duration of the proposed use, including proposed genetic analyses; the extent and conditions of a possible transfer of samples and data, in particular if exported; the possibility or otherwise of the communication of research results to the donor; advice on the possible consequences of the communication of the results of genetic analyses for the donor and his relatives, including any possible duty to divulge (e.g. to

insurance companies); the form of data storage and linkage; anonymization or pseudonymization of samples and data; other ancillary donor protection measures; any State right of access to samples and data; the donor's right to withdraw his consent at any time without sanctions; the fate of samples and data in the case of withdrawal or if the biobank is closed down; any commercial prospects of the proposed research (including the possibility of filing patent applications for the results); and issues of the payment of donor expenses, remuneration or benefit sharing.

In view of the complexity and implications of the decision to donate samples and data, all aspects of the information given must be comprehensible and the position must be presented a form consistent with the patients' or subjects' need for information. As in other fields of medical activity, it would be appropriate for biobanks to develop and validate suitable methods of guaranteeing information quality.

As to the extent of the information, however, it must be borne in mind that too much information may hamper understanding and therefore be counterproductive. The object of the information is to ensure that donors do not grant consent in ignorance of its significance and implications. However, this is precisely what is likely to happen if the information is too complex to be grasped by the donor. In this case, the plethora of information is more likely to serve as a safeguard for the researcher than to facilitate donor understanding. The situation is analogous to the provision of information on the side-effects of medicines. For this reason, the information requirement must be tailored to the individual case.

In particular, there is no need to provide information about circumstances that are generally known – for instance, the risk, which can never be entirely precluded, that regulations and safeguards might be violated with criminal intent, through, for example, hacking into protected databases. Another unconvincing demand that is sometimes voiced is that, before obtaining a donor's consent, the researcher should inform him

of the possible risk of undesirable social developments. As a rule, such risks are the subject of a wide range of conflicting opinions and hypotheses. Individual researchers cannot be expected to reflect all these different opinions in the context of an individual information interview. Instead, such risks should be tackled by thorough debate at all levels of society and, where appropriate, regulation. Donors wishing to make their consent conditional upon an appraisal of the risks to society will have to obtain full information on the state of the public discourse in their own way.

4. Options for the declaration of consent

The demand is occasionally voiced that, when giving consent, donors should be given a choice between consent declarations of differing scope. While such options may help to demonstrate the full implications of their decision to subjects, they may make the consent unclear and thereby fail in their aim. Moreover, they cannot always be harmonized with the functions of a biobank. In the case of a cohort study, for example, it is impossible to give donors the choice of making their samples available for only five instead of ten years or of insisting on data anonymization. The possible options must depend on the purpose of the research. The consent relates to the conditions governing the furnishing by donors of their samples and data. The design or content of research cannot be made dependent on donors' individual wishes.

If it is accepted that biobanks are a legitimate resource for medical research and that donors are protected by a number of objective measures and guarantees, there would appear to be no objection to expecting donors, when giving their consent, to make a yes-or-no decision that does not allow of any other alternative. Although it is essential to ensure that donors are aware of the implications of their decision, different options for each individual aspect of the decision need not be provid-

ed for. All that is necessary is for attention to be expressly drawn to the relevant points and for the required information on them to be provided. The researchers should formulate as clearly as possible what they consider to be the necessary conditions for the use of the samples and data. It is then up to donors to decide whether or not to participate on the basis of these conditions. This does not affect the right of donors to withdraw their consent at a later date should they subsequently have misgivings.

5. Communication of research results to donors

In many situations, the entitlement to find out what others know about one is a function of the right to informational self-determination, especially where one's own person is particularly affected. However, if this were interpreted as meaning, in the case of research with human bodily substances, that each donor – perhaps even without having requested it – must be informed of all results of the research, this would often involve unacceptable effort and expense. On the one hand, recontacting donors may present appreciable problems, and, on the other, donors would have to be given a detailed explanation of their personal results in the form of medical counselling, and would then have to be counselled on the possible consequences. Finally, as a precaution, donors would have to be informed in advance of the possible results, so that they could exercise their right not to know. All this would extend beyond the boundaries of research.

An appropriate solution must be based on the principle that donors, in the exercise of their right of self-determination, can agree to forgo individual communication and that the researchers may stipulate the forgoing of this communication as a condition for participation in the research. However, in the case of information vital to the subject's life there is as a rule

an obligation, over and above normal communication with specialists in the researchers' own discipline, to seek personal contact with donors.

Where information is to be communicated to donors, they must receive special protection. Information on donors' genetic characteristics, in particular, may have appreciable effects on both their subjective state and their objective life situation, if the findings imply a possible prognosis of future disease. For this reason, information on donors' individual genetic and health status should always be imparted by a person with specific counselling skills.

Where the individual communication of research results to a donor is agreed, he must be told, when the consent-related information is imparted, that he may be required to divulge the findings in certain circumstances – for example, when concluding new contracts of employment or insurance in the future.

6. Donor protection: ancillary measures and mandatory rules

Donor self-determination, while the most important element, is not the only factor in appraisal of the legitimacy of biobanks. Objective, legal barriers to research are unaffected: what is prohibited by law does not become permissible by virtue of a donor's consent. With regard to the form to be assumed by the specific regulatory framework for biobanks, the following aspects are important over and above the general limits of research.

6.1. Right to withdraw consent to the use of samples and data

Donors should be able to allow for the interests of research by giving a blanket consent to use, but should not be permitted to hand over control of their samples and data to someone else

completely and definitively. This should be ensured by making it impossible to relinquish the right to withdraw consent to the use of samples and data at any time. However, withdrawal can of course relate only to identifiable, not yet anonymized samples and data. Even for identifiable samples and data, though, there should be no obligation on researchers to set aside results that have already been evaluated provided that the relevant data exist only in aggregated, unpersonalized form. Research already conducted would otherwise be rendered valueless even though no donor interests calling for protection were at stake. In this case, the interests of the researchers should take precedence over a donor's subsequent change of mind. In addition, it ought to be possible to agree with donors that, in the event of a withdrawal of consent, samples and data need only be anonymized and not destroyed.

6.2. Coding of personal data

It is an elementary professional principle that, where personal data are used in research, donor privacy should be protected by as far as possible encoding anything whereby identities could be inferred. It is essential for the relevant codes to satisfy certain quality criteria and for them not to be easily breakable; a code number made up of a subject's initials and date of birth, for instance, does not satisfy this requirement. The organizational system used must provide for separate storage and administration of the code and of the encrypted data.

The risk of donor identification without recourse to the code – i. e. indirectly through linkage of general parameters (age, sex, occupation, disease, etc.) – is no greater with coded than with anonymized information. The same applies to genetic data; for these to be linked to a specific individual, a personalized reference sample would have to exist. If anonymization is considered to be sufficient for data protection (as it is in the data protection laws), the abstract possibility of identification

through the linkage of non-personal data does not give rise to any particular objection to the legitimacy of biobanks. However, where samples and data from biobanks are transferred, the researcher who receives them should, provided that the research design so permits, be given access not to encrypted data on individual donors, but only to combined data on groups of donors.

6.3. Donor protection through organization and procedures

Comprehensive donor consent gives research great flexibility in the use of samples and data for projects not defined, or definable, in advance. The question therefore arises whether the establishment and/or use of biobanks should for this reason be subject to particular controls. These might include licensing procedures prior to the establishment of biobanks, special supervisory bodies to monitor their ongoing operation, and the involvement of ethics committees to evaluate concrete research projects.

6.3.1. Should biobanks be licensed?

Collections of human bodily substances that are or can be associated with personal data are part of the routine of diagnostic medicine. Very often, they are formed with no intention of subsequent use as biobanks for research: a potential biobank exists whenever samples taken for diagnostic purposes are stored. To impose a licensing requirement for the establishment of such collections would subject important areas of medical activity to individual-case control over and above the generally applicable requirements of registration and approval. Such a demand has rightly never yet been expressed.

The question arising is at most whether a licensing requirement should be imposed if these collections are to be used for

research. This situation should be treated in the same way as that of biobanks to be established with the explicit intention of medical research. After all, the collection and use of human bodily substances is part and parcel of normal medical research. As a rule, it does not present any particular risks to donors and is covered by the established standards of medical research. There is therefore no reason to subject precisely those forms of medical research that depend on the collection and use of human bodily substances to what would in practice amount to blanket prior control. Again, any such reservations as to approval would scarcely be consistent with the freedom of research guaranteed by the Constitution.

However, many regard genetic research as calling for particular regulation, because the danger of abuse in this case is felt to be especially great. For instance, secret paternity tests are a hotly debated issue at present. Here there is indeed a need for regulation. But these risks apply to genetic analyses in general and not specifically to the establishment and use of biobanks. After all, individual samples are just as liable to be misused as collections comprising a large number of samples. This matter should therefore be addressed by a law that comprehensively regulates all aspects of genetic investigations.

It might be appropriate to contemplate the compulsory licensing of large-scale biobanks, like, for example, BioBank UK, which are established as relatively permanent facilities combining major resources from different institutions. In this case, however, a crucial regulatory consideration, besides donor protection, would be the safeguarding of appropriate access to an important research infrastructure. There are as yet no plans for such a biobank in Germany.

6.3.2. Supervision of biobank operation

In view of the complex organizational structure of some biobanks, it seems appropriate for an independent internal or external body to monitor observance of the ethical standards

and legal requirements applicable to the handling of samples and data – for instance, the collection and subsequent use of bodily substances, or the processing of the personal data used in each case. This body should therefore be responsible for ensuring, for example, that donors' expectations, as recorded in their declarations of consent, are complied with; that the relevant conditions of access to the biobank are observed; that the limitations on the transfer of materials or data set by the research vocation of the biobank and by the declarations of consent are not exceeded; and, finally, that if the biobank is closed down, its stored bodily substances and information are not misused.

Accordingly, the joint paper by the French and German National Ethics Councils refers to a "trustee". It should, however, be borne in mind that the data protection laws applicable to entities such as biobanks that record, process or use personal data already explicitly provide that a data protection officer must be appointed (e.g. Sections 4f and 4g of the Federal Data Protection Law) and that most of the functions mentioned above must be entrusted to him. The internal control required by law is supplemented by external supervision, to be exercised in the public sector by data protection officers (e.g. Section 24 of the Federal Data Protection Law) and in the private sector by special supervisory authorities (Section 38 of the Federal Data Protection Law). Experience so far indicates that the establishment of a supervisory body with more extensive functions is unnecessary.

Again, any organizational provisions would have to take account of the differing scales and structures of biobanks and the associated widely differing risks. In particular, complex and expensive organizational requirements that might be appropriate, say, for national-scale biobanks must not be automatically applied to all biobanks. Nor is there any need for all-embracing controls on the generality of biobanks to prevent misuse, over and above the requirements of general legislation.

6.3.3. Involvement of ethics committees

A common demand is that the opinion of an ethics committee should be obtained before the implementation of any research project using biobank samples and data. This would entail more stringent rules than those hitherto applicable to the involvement of ethics committees. Up to now, the involvement of ethics committees has been stipulated for certain hazardous situations – by law (research on pharmaceuticals and medical products, or research with radioactive substances or ionizing radiation), by professional codes for certain professions (medical practitioners), by the statutes and organizational codes of certain bodies (e.g. university staff) or by the requirements of research-funding institutions – where research on live human beings is concerned. The aim is to avoid physical and psychological risks to the patients and subjects recruited for such research. However, the use of samples from biobanks – i.e. bodily substances already separated from the donor's body – for research purposes does not, as such, involve any physical or psychological risk to the donor. Any risks to the individual would concern the violation of confidentiality and rights of personality, and would arise at most in the event of a possible linkage of samples with personal data. For this reason, research projects in which such a linkage is proposed should be subject to compulsory prior approval by an ethics committee. This requirement should apply, over and above current legal provisions, to all research workers wishing to use bodily material from biobanks. The ethics committee's consent is accordingly also necessary where an existing biobank is to be transferred to third parties with the inclusion of personalized donor data.

The involvement of an ethics committee and the requirement of its approval are intended to ensure that a narrowly worded consent is not exceeded, that a consent in broad terms is not inappropriately given an even wider interpretation, and that exceptional circumstances in which consent may be waived are not illegitimately invoked (see Section D.1 above).

The approval of an ethics committee is also required where bodily materials are to be transferred to external institutions in pseudonymized form. Although in this case the researchers have no access to personalized data, so that the situation for them is the same as with anonymized samples and data, re-identification by the responsible officers of the biobank is possible.

Conversely, a requirement to involve ethics committees should not be extended to cases where only anonymous or anonymized material is to be used in the research. In these instances there is no particular need for donor protection. Nor are ethics committees responsible for general monitoring of the legality of research and for overall prevention of abuse. The National Ethics Council sees no reason for such an extension of the competence of ethics committees or for a requirement to involve them prior to any use of a biobank.

6.4. Confidentiality obligations

Where the research workers engaged on a project know or can discover donors' identities, donors must be protected by an obligation to observe confidentiality incumbent on everyone participating in the project.

Both the criminal law and professional codes impose such a duty of confidentiality on medical practitioners. They must not divulge what has been entrusted to them in their capacity as doctors to third parties without the patient's consent (or without a reason provided for in law). Medical confidentiality also extends to a doctor's ancillary staff. Any obligation of confidentiality applicable to other professional groups, as well as to doctors who have received samples and data independently of their medical functions, would at most be that ensuing from the general data protection legislation. The duty of confidentiality, where not prescribed by law, must be specifically imposed and enforced by sanctions, for example by statutes or contract.

6.5. Prevention of access to biobanks for non-research purposes

Biobanks are subject to the same requirements as any other institution that uses personal data: the data may be processed only for the purpose for which they were recorded and stored – at least, in the absence of any statutory provision to the contrary or of the subject's consent. For this reason, biobanks that use data for research purposes are required from the outset to confine the processing of such data to research purposes. This means, for example, that data must not be passed on to employers or insurers.

The first of the exceptions provided for by law is the requirement that data from clinical drug trials be made available to the State licensing authorities so that they can where necessary check the results of these trials against the original data. Unlike the situation in these cases, however, research ceases to be the purpose when public bodies desire access to information, for example in application of relevant provisions of the data protection laws. This may be, say, to safeguard important public interests, or to avoid dangers to public security or threats to the welfare of the community. The implications of such access are particularly evident in the case of biobanks that record and process a large volume of detailed personalized data on broad sections of the population over an extended period. It is essential for this situation to be addressed by a statutory requirement of confidentiality of research, prohibiting any use whatsoever for non-research purposes – particularly as donors' trust and willingness to supply bodily substances and information, and hence ultimately the acceptance of biobanks, depend crucially on the certainty that both bodily substances and information will not be used for any purpose other than scientific research.

Another argument in favour of a requirement of confidentiality of research is that research using biobanks is not subject to the narrow restriction of purpose otherwise commonly pro-

vided for in the data protection legislation. The access to large volumes of data thereby permitted gives rise to particular risks of linkage, which can only be justified if they are mitigated by compulsory confidentiality of research.

Impossible as it surely is to overlook the importance and urgency of a requirement of confidentiality of research precisely for biobanks, it is equally clear that the demand for this confidentiality to be enshrined in law inevitably gives rise to a number of difficult considerations that call for the striking of an appropriate balance, especially as regards the possibility of access to data for the investigation of serious criminal acts.

7. An essential condition for biobanks: protection from genetic discrimination and stigmatization

7.1. Genetic discrimination

Knowledge of a person's genetic characters can be used to justify unequal treatment. If there is no objective reason for the inequality of treatment, discrimination is then being practised. Such a risk is considered to apply in particular to employment and insurance contracts – for instance, if a candidate for a post is turned down on the grounds of genetic disposition to a future disease or if someone wishing to take out insurance is refused cover. This risk is increased as more and more knowledge is amassed about genetic dispositions – especially where large volumes of data are assembled, as in biobanks, and must be addressed by adequate protective mechanisms. In the case of biobanks, these include the coding of personalized data; restriction of the purpose for which the data may be used, coupled with a ban on access for non-research purposes; and confidentiality requirements (see Sections D.6.2ff. above). Provided that these conditions are satisfied, there are no fundamental discrimination-related objections to biobanks. Indeed, the

risk of unauthorized persons gaining access to confidential data is lower in the case of biobanks, owing to coding, than in routine clinical practice, where a plethora of health-related information is often kept in unencrypted form together with the names of the persons to whom it applies – and no one would conclude that this practice is illegitimate because of the danger of discrimination. The risk of discrimination on the grounds of results of genetic diagnosis must be avoided by statutory regulation of the sectors in which information can be used in discriminatory ways – for instance, by restricting the use of genetic diagnoses in the fields of employment and insurance.

7.2. Genetic stigmatization

The risk of genetic discrimination due to genetic research can be controlled by regulation. It is more difficult to respond to the risk that people might be stigmatized by the results of genetic research. Stigmatization is a problem of perception – both perception by others and self-perception.

If the genetic causes of diseases are identified, it may be possible to determine that sufferers are carriers of the relevant genes. It may also become generally known that members of certain ethnic groups have a higher probability of developing certain diseases for genetic reasons (e.g. Tay-Sachs disease in Ashkenazi Jews or sickle cell anaemia in Africans). The fear is that this knowledge might be applied to those concerned like a blemish, so that, in the eyes of those around them, they are "classified" or "marked". Conversely, the perception that a characteristic has genetic causes may free those concerned from stigma because that characteristic – e.g. congenital obesity – is no longer perceived as their personal "fault". Again, social classification or labelling can ensue from any form of medical knowledge; it is not a specific consequence of a genetic finding. An example is the diagnosis of a sexually transmitted disease, such as AIDS. Admittedly, genetic findings are regarded in

the public mind as particularly significant and serious. Past pronouncements by scientists may have contributed to this perception. Yet it reflects a one-sided singling out of genetic factors that minimizes the importance of other conditions of human life (such as education, experience or environment).

8. Impact of genetic analyses on third parties

The requirement of informed consent protects donors of samples and data. However, the medical research facilitated by a biobank may have effects that extend beyond donors. Genetic analyses may permit inferences about members of a donor's family or lead to general findings concerning entire groups of people. The question is whether third parties who might possibly be affected ought to be consulted when consent is given for donation to a biobank.

8.1. Donors' relatives

Genetic analyses of donor samples may generate information about relatives who do not possess this information, may not wish to possess it and might not divulge it of their own accord. Even so, it should be up to every individual family member to decide whether or not to have his own genes examined. This is because the right of those directly affected to self-determination in relation to their own bodies and personalities takes precedence over the self-determination of others who are only indirectly affected. This is generally accepted in the case of medical diagnostic examinations or of family planning for identification of an increased risk of illness in potential children. The same must also apply to consent to the conduct of such analyses for research purposes on bodily substances supplied to a biobank. Where biobank sample donors are

informed of research results that affect them, it may be hoped that they will exhibit restraint, tact and empathy in regard to the interests of relatives who may be affected in the same way as themselves.

8.2. Impact on groups – community consent?

Genetic analyses of donor samples may yield results relevant to the genetic particularities and risks of patients suffering from a given disease or of ethnic groups in whom such diseases are especially prevalent. Depending on the nature of the data recorded, they may also provide information on people in certain occupations or age groups. The issue here is whether these groups, because they may be "affected" by the research, must also give their consent as groups before individual group members are allowed to offer their bodily substances to a biobank ("community consent").

The demand for community consent has been voiced mainly in connection with projects involving the collection of samples and data from members of traditional communities (such as indigenous peoples) incorporated or formerly incorporated in nation states as minorities. The custom of such communities may dictate that no one may decide even on matters concerning the personal sphere without the consent of the group and that an individual's bodily substances, data and genes "belong" not to that individual but to the community. Such issues do not arise in Germany.

The demand for community consent in relation to other groups (e.g. age or patient groups) cannot be seriously entertained. If such groups are particularly affected by research using biobanks and are therefore in need of special protection, it is the responsibility of the legislature to initiate the necessary measures. Collective rights of veto that take precedence over the autonomy of an individual donor and restrict the freedom of research are foreign to our Constitution.

On the other hand, "affected" groups could perhaps be involved in the establishment and, where appropriate, monitoring of biobanks at a level below that of a right of veto. However, such involvement would be feasible at most for large-scale projects concerning relatively permanent infrastructures usable for a wide variety of research projects. Its aim would be to increase the transparency and openness of science to society.

9. Samples and data of those incapable of giving their consent and of deceased individuals

9.1. Incapacity for consent

Effective consent presupposes the relevant capacity. The capacity to give consent is defined as the ability to understand the purposes, nature, significance and implications of the measure calling for consent, to weigh the pros and cons and to exercise the right of self-determination in the light of the understanding arrived at. The capacity to give consent may be lacking owing to age (in the case of children and adolescents), disability or disease (e.g. dementia), or accident.

Decisions on behalf of someone incapable of giving consent – as in other instances, after the necessary information has been imparted – must always be made by the legal representative: the parents in the case of minors or a carer for an adult. An adult could be represented by a legally authorized representative. The representative's powers come to an end, for a child or an adolescent, when the individual becomes capable of giving his consent.

Those who lack the capacity to give consent have the same right to information, including information on the use of their samples and data and on the findings accruing from the research conducted on them, as people who have this capacity. Their natural wishes must be taken into account in every case,

provided that they are capable of understanding. Hence samples and data may be collected from them and used only if they have as far as possible given their consent, or at least do not show any signs of refusal. Appropriate means of communication must be used or, as the case may be, developed.

In addition, it is essential to ensure that anyone lacking the capacity to give consent is not confronted with genetic findings from research on his samples and data that have no direct therapeutic and diagnostic relevance to him.

Medical research on subjects lacking the capacity to consent is at present a hotly debated issue. No one disputes that those incapable of giving consent may be involved in research from which they themselves are likely to benefit therapeutically. Disagreement centres on whether, and subject to what conditions, research for the benefit of others is legitimate.

On the one hand, it is argued that, given a low level of risk, the involvement of subjects lacking the capacity to give consent may be contemplated if the research concerned is intended to benefit others affected by the same disease or (in the case of children) persons in the same age group. At any rate, those incapable of giving their consent ought not to be exposed to any non-minimal risks (whether physical or psychological) or stresses for the purposes of research carried out for the benefit of others. Limits are thus set to the taking of samples from the bodies of those lacking the capacity to give consent. However, in the case of residual material from therapy or diagnosis, use for research purposes does not call for action on the body. Provided that the protective mechanisms described above (Section D.6) are observed, the risks of violation of confidentiality and rights of personality associated with the storage and use of personalized samples and data may be regarded as minimal. Where the involvement of subjects incapable of giving consent is the only possible way of conducting research for the benefit of fellow-sufferers, the representative should therefore be permitted to consent to the use of samples and data following the imparting of appropriate information (Section D.3). Subject to

the requirement of group benefit, it should also be possible for this consent to cover more than one research project.

On the other hand, some hold that consent to research is a strictly personal matter and as such must be left to those concerned. Moreover, according to this view, it is not readily, if at all, possible to determine whether risks and stresses are in fact minimal. Finally, the welfare of the individual might be endangered by a consideration based on the notion of benefit to the group. In view of the particular protection needs of those incapable of giving their consent, verifiable criteria and methods for the definition of minimal risks should be developed.

The precise conclusions to be drawn from these arguments cannot be definitively established in the context of an Opinion on biobanks. The same problems arise in a number of other situations – for instance, in pharmaceutical research. This makes it all the more important to develop generally applicable principles both to guarantee the protection of subjects incapable of giving their consent and, so far as is feasible, to take account of the importance of research for the benefit of others.

9.2. Deceased persons

Bodily substances from deceased persons may also be extremely valuable to medical research. Samples and data from deceased individuals can be collected and recorded for biobanks and subsequent use in research on the same conditions as for living donors. If the deceased has not given his consent during his lifetime, the next of kin can furnish it, provided that this is not inconsistent with the deceased's wishes as expressed during his lifetime or with his presumed wishes.

10. Transitional solutions for "old" collections

Old collections of samples taken in the interests of patients for diagnostic or therapeutic reasons and stored for scientific purposes cannot be judged by present-day criteria, which are the fruit of increasing awareness of the importance of personality rights. As a rule, it is no longer possible to obtain the subject's consent. However, the longer ago the samples were taken, the less the subjects are personally affected by the research. These collections would be lost to research if they were to be judged retrospectively by present-day criteria and if effective informed consent were demanded for their use. As explained above, current law is perfectly consistent with their scientific use provided that no interests affecting the personality rights of the donors, or no such interests that take precedence over science, are affected. Additional donor protection is afforded by the requirement (see Section D.6.3.3 above) that an ethics committee must approve the conduct of research projects for which personal samples and data are to be used.

11. Access to biobanks

It is in the public interest for biobanks to be available for medical research. They should therefore be at the disposal of as large a group of interested researchers as possible. The conditions – in particular, as to consent – on which biobank owners may make the samples and data they have received available to third parties are set out in Section D.2.3 above. Another issue is whether they must make them available to other researchers.

To ensure optimum utilization of the potential of biobanks, it is desirable for access to be granted to as many research workers as possible, especially where biobanks are publicly funded. To a greater extent than was usually the case in the past, biobanks should be established and maintained in ac-

cordance with uniform scientific standards. Adequate quality assurance measures are the only way to ensure that biobanks remain usable for a variety of research projects over very long periods of time.

However, research workers who have contributed preliminary work of their own to the setting up of biobanks may legitimately expect, in the initial period, to reap the fruit of their investment in time and labour and to enjoy priority of use for their own research. These interests can be taken into account by providing that the funding institutions set a period during which the researchers who establish a biobank have exclusive use of it. The funding conditions should specify the rights and obligations applicable to third-party access once this period has elapsed.

The owners of privately funded biobanks must enjoy sole rights to their use within the limits of the donors' consent. Compulsory opening up of a private biobank to other researchers – or commercial competitors! – would be equivalent to expropriation and hence impermissible without compensation.

12. Payment for biobank samples; benefit sharing

12.1. Payment for biobank samples

There are many arguments in favour of establishing biobanks on the basis of unpaid donations of material and data. It is held that patients and other subjects are perfectly prepared to participate without a financial consideration. They take the view that their contribution is promoting a public good – namely, medical progress – and do not as a rule aim to benefit financially from it. The willingness to donate deserves recognition and support. This does not preclude the payment of expenses, as allowed, for example, by the German Transfusion Law

for blood donations. There is admittedly a tendency to offer expenses at a level tantamount to actual remuneration. Apart from the ethical reservation that such remuneration might constitute a crossing of the boundary of impermissible commercialization of the human body and its parts, this tendency should be opposed also because of its potential undermining of solidarity. The National Ethics Councils of France and Germany have already drawn attention to this possibility in their joint declaration of 2 October 2003. At any rate, public and private funding institutions should not provide resources for the payment of excessive expenses.

12.2. Benefit sharing

It is often asserted that donors who have made their samples and data available to biobanks ought somehow to benefit from the profit accruing from research based on the use of biobank material. This demand is directed primarily at the pharmaceutical industry. However, most biobanks are initially used only for fundamental research, which, as such, does not as a rule generate a financial return. It is only when research results are subsequently applied and economic gain accrues that the question arises whether individual donors, groups of donors or society should share in the benefit.

An obstacle to benefit sharing for individual donors is that an individual's contribution to the result of the research and to the benefit accruing from it cannot as a rule be ascertained.

This does not preclude the possibility that the users who gain financially from research with biobanks could make voluntary contributions to funds devoted to public welfare – especially if the notion of an obligation to uphold solidarity (see Section C.1) is accepted. In the case of profit-oriented biobank users, this could entail the making of voluntary contributions to public-welfare funds, which could be located and organized at different levels:

- Project-related funds: In this case the revenue accruing directly or indirectly from the research projects (e.g. from patents, licences or the granting of user rights to third parties) would flow back into the research project or the relevant institutions.
- Disease-related funds: In this case the resources would benefit groups of patients suffering from a given disease.
- Group-related funds: These would be established to support, for example, indigenous peoples or groups with certain genetic, health-related or social characteristics.
- National funds: These would be established, for example, for the purposes of specifically directed disease prevention.
- International funds: These would contribute to improving the provision of effective medicines to patients in poor countries.

Another possibility would be funds dedicated to the protection of patients' and subjects' rights, which would advise and represent the interests of those wishing to contribute to the progress of biomedical research in the certainty that their rights and interests are protected and appropriately represented.

However, for a variety of reasons it would be difficult to gain acceptance for compulsory contributions to such funds, since this balancing of private gain with public benefit would compete with the taxation system. Whether that would be appropriate is a regulatory issue of principle that extends far beyond the question of biobanks.

Biobanks for research

APPENDIX

Selected projects of international

Country	Genebank description
Iceland	Three linkable collections: the Iceland Health Sector Database (IHSD); genealogical records, and the biobank, containing genetic samples from volunteers
United Kingdom	DNA, medical records and lifestyle questionnaires acquired from 500 000 volunteers aged 45–69
Estonia	Genotype, medical records and genealogical data on approximately one million participants
Latvia	A combination of medical, genetic and genealogical information
Sweden (Västerbotten)	Utilizes genetic and medical information from 70 000 40- to 60-year-olds of the county of Västerbotten; samples are from a previously existing 15-year-old Medical Biobank, preserved from a previous study on heart disease
Singapore	Plans include only genomic information from Asian population groups

significance

	National government role	Commercial aspects
	The Icelandic Parliament passed several pieces of legislation allowing construction of the IHSD and a biobank	deCode Genetics has a 12-year contract for exclusive commercial rights to the information in the IHSD and authorization to construct a biobank
	The Medical Research Council, the Wellcome Trust and the Department of Health are collectively providing an initial £45 million to fund the project	None at this time; commercial access remains to be determined
	The Estonian Genome Project Foundation is responsible for the project; Parliament passed a Human Genes Research Act in 2000	EGeen Inc., the Estonian Genome Foundation's commercial arm, plans to market products to the global pharmaceutical industry
	The project is being conducted by the Latvian Genome Foundation; a law allowing the database is under review	The Latvian Genome Foundation plans to market access to the database to the global pharmaceutical industry
s	The Swedish Medical Research Council (MRC) granted commercial rights to the database and passed research guidelines; information is collected within the National Health Care System; all health care centres in the region are involved	UmanGenomics has exclusive rights to genetic samples from the existing Medical Biobank and has the exclusive right to commercialize information derived from the Biobank
	The Genome Institute of Singapore is nationally funded and affiliated with the National University of Singapore	The Genome Institute of Singapore will avoid any commercialization of the project

Informed consent and confidentiality	Opposition
Data are protected by third-party encryption; presumed consent is applied with a restricted opt-out option to the IHSD; informed consent is used in collection of genetic samples	Mannverd was created specifically in opposition to the genebank; the Icelandic Medical Association also voiced concerns but has since been reconciled with deCode
Information will be stored anonymously; no genotype results will be provided to volunteers	Liberty expressed concerns about lack of detail in plans for the biobank; Genewatch UK has issued information and warnings about possible ethical, legal and social issues
Participation requires informed consent; personalized genotype information will be provided to the donor and his/her doctor; data are protected by coding and encryption	Critics suggest that an already underfunded health system should take priority; there is no organized dissent
A centre at the University of Latvia will store and process the information	None identified
Informed consent will be acquired from previous donors for each new project; UmanGenomics has access only to coded samples; the Biobank is also available for academic research; UmanGenomics complies with the MRC's research guidelines	There has been no decrease in participation in the region's health check-up programme, even though the project has been well publicized
Not specified	None identified

Current progress
A licence was granted to deCode for access to the IHSD in 1998; the Act on Biobanks was passed in 2000; deCode has collected 70 000 genetic samples
The project is planned to begin in 2003 and expected to be completed in 2013
A pilot project involving 10 000 Estonians will be carried out in 2002, depending on funding; once the pilot project is initiated, the entire project is expected to take 10 years
Current legislation is expected to pass; a pilot project of 40 000 was to begin in early 2002; entire project is expected to take 10 years
A law concerning the use of biobanks was recently passed in Västerbotten
The Genome Institute of Singapore has recently been created; future plans involve a genetic database, but no work is yet in progress

Source: Community Genetics, 2003 (6), 37 – 45

References

Opinions and directives

Arbeitskreis Medizinischer Ethikkommissionen in der Bundesrepublik Deutschland (2001). Empfehlungen für die öffentlich-rechtlichen Ethik-Kommissionen hinsichtlich der Beurteilung epidemiologischer Studien unter Einbeziehung genetischer Daten, verabschiedet auf der 19. Jahresversammlung in Köln am 24.11.2001.

Australia Law Reform Commission (2002). Discussion paper 66. Protection of human genetic information. Sydney.
http://www.austlii.edu.au/au/other/alrc/publications/dp/66

Bundesärztekammer (1999). Richtlinien zur Transplantation von Stammzellen aus Nabelschnurblut (CB=Cordblood). Deutsches Ärzteblatt 96: A-1297-1304.
http://www.bundesaerztekammer.de/30/Richtlinien/Richtidx/Transnabel_pdf.pdf

Bundesärztekammer (1991). Richtlinien zur Verwendung fetaler Zellen und fetaler Gewebe.
http://www.bundesaerztekammer.de/30/Richtlinien/Richtidx/Fetalzellpdf.pdf

Bundesärztekammer (2000). Richtlinien zur Verwendung von Blut und Blutbestandteilen und zur Anwendung von Blutprodukten (Hämotherapie). Bundesgesundheitsblatt 43, 7: 555-589. Neuformulierungen und Kommentare (2001). Bundesgesundheitsblatt 44, 12: 1240-1242. http://www.bundesaerztekammer.de/30/Richtlinien/Richtidx/Blutprodukte/

Bundesbeauftragter für den Datenschutz (2001). Bericht der 62. Konferenz der Datenschutzbeauftragten des Bundes und der Länder. Entschließung. Gesetzliche Regelung von genetischen Untersuchungen. http://www.bfd.bund.de/information/DS-Konferenzen/62dsk_ent7.html

Comité consultatif national d'éthique (2003). Problèmes éthiques posés par les collections de matériel biologique et les données d'information associées : «biobanques», «biothèques». Avis N° 77. Paris.

Commission de l'éthique de la science et de la technologie (2003). Les enjeux éthiques des banques d'information génétique : pour un encadrement démocratique et responsable. Avis. Québec.
http://www.ethique.gouv.qc.ca/fr/ftp/AvisBanquesGen.pdf

Commission of the European Communities (2001). Quality of Life and Management of Living Resources. Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human biobanks. Brussels.

Commission of the European Communities (2003). Amended proposal for a directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells. COM(2003) 0340 final.
http://europa.eu.int/eur-lex/en/com/pdf/2003/com2003_0340en01.pdf

Department of Health (2001). A code of practice for tissue banks providing tissues of human origin for therapeutic purposes. London.

Department of Health, Advice from the Chief Medical Officer (2001). The removal, retention and use of human organs and tissue from post-mortem examination. Published with the permission of the Department of Health on behalf of the Controller of Her Majesty's Stationery Office. London. http://www.dh.gov.uk/assetRoot/04/06/50/47/04065047.pdf

Deutsche Forschungsgemeinschaft (2003). Prädiktive genetische Diagnostik. Wissenschaftliche Grundlagen, praktische Umsetzung. Stellungnahme der Senatskommission für Grundsatzfragen der Genforschung.

Directive 95/46 EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Official Journal of the European Communities, 23 November 1995, 31-50.

European Group on Ethics in Science and New Technologies to the European Commission (1998). Ethical aspects on human tissue banking. http://europa.eu.int/comm/european_group_ethics/docs/avis11_en.pdf

European Society of Human Genetics (2000). Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective. Birmingham. http://www.eshg.org/ESHGDNAbankingbckgrnd.pdf

European Society of Human Genetics (2001). Data storage and DNA banking for biomedical research: technical, social and ethical issues. Recommendations of the European Society of Human Genetics. http://www.eshg.org/ESHGDNAbankingrec.pdf

Gezondheidsraad (Health Council of the Netherlands) (1994). Proper Use of Human Tissue. The Hague.

House of Lords, Select Committee on Science and Technology (2001). Fourth Report. Human Genetic Databases: Challenges and Opportunities. London. http://www.parliament.the-stationery-office.co.uk/pa/ld200001/ldselect/ldsctech/57/5701.htm

House of Lords, Select Committee on Stem Cell Research (2002). Stem Cell Research. London. http://www.publications.parliament.uk/pa/ld200102/ldselect/ldstem/83/8302.htm

Human Genetics Commission (2000). Whose hands on your genes? London. http://www.hgc.gov.uk/business_consultations2maintext.pdf

Human Genetics Commission (2000). Inside information – balancing interests in the use of personal genetic data. London. http://www.hgc.gov.uk/insideinformation/index.htm

Human Genome Organisation Ethics Committee (1998). Statement on DNA sampling: control and access. London. http://www.gene.ucl.ac.uk/hugo/sampling.html

Medical Research Council Ethics Series (2001). Human tissue and biological samples for use in research. Operational and Ethical Guidelines. London. http://www.mrc.ac.uk/b2/pdf-tissue_guide_fin.pdf

Medicinsk Fårsknings Rådet (Swedish Medical Research Council) (1999). Research Ethics Guidelines for using Biobanks, especially Projects Involving Genome Research. Lund.

National Bioethics Advisory Commission (2000). Research involving human biological materials: Ethical issues and policy guidance. Executive summary. Springfield, Virginia. http://bioethics.georgetown.edu/nbac/pubs.html

National Health and Medical Research Council (1999). Guidelines for Genetic Registers and Associated Genetic Material. Commonwealth of Australia. Canberra. http://www.health.gov.au/nhmrc/publications/pdf/e14.pdf

Nuffield Council on Bioethics (1995). Human Tissue. Ethical and Legal Issues. London. http://www.nuffieldbioethics.org/filelibrary/pdf/human_tissue.pdf

Statens Sundhedsvidenskabelige Forskningsråd (Danish Medical Research Council) (1996). Health Science Information Banks – Biobanks. http://www.forsk.dk/eng/ssvf/publ/biobanker-uk/index.html

UK Biobank (2003). Ethics and Government Framework Version 1.0. For comment. http://www.ukbiobank.ac.uk/documents/egf-comment-version.doc

UNESCO/ International Bioethics Committee (2002). Human genetic data: Preliminary study by the IBC on its collection, processing, storage and use. Paris. http://portal.unesco.org/shs/en/file_download.php/82e7c58d69d425a6fd9f100171e3c072Rapfinal_gendata_en.pdf

World Health Organization (2003). Genetic databases. Assessing the benefits and the impact on human patient rights. European partnership on patients' rights and citizens' empowerment.
A network of the World Health Organization Regional Office for Europe. Final report. http://www.law.ed.ac.uk/ahrb/publications/online/whofinalreport.rtf

World Health Organization (2002). Genomics and world health. Report on the advisory committee on health research. Geneva.
http://www3.who.int/whosis/genomics/pdf/genomics_report.pdf

World Medical Association (2000). Declaration of Helsinki. Ethical principles for medical research involving human subjects. Edinburgh.
http://www.wma.net/e/policy/pdf/17c.pdf

World Medical Association (2002). Ethical considerations regarding health databases. Washington. http://www.wma.net/e/policy/d1.htm

Zentrale Ethikkommission bei der Bundesärztekammer (1999).
Zur Verwendung von patientenbezogenen Informationen für die Forschung in der Medizin und im Gesundheitswesen. Deutsches Ärzteblatt 96: A-3201-3204.
http://www.zentrale-ethikkommission.de/10/PDF/Patientenbezogen1.pdf

Zentrale Ethikkommission bei der Bundesärztekammer (2003).
Die (Weiter-) Verwendung von menschlichen Körpermaterialien für Zwecke der medizinischen Forschung.
http://www.zentrale-ethikkommission.de/10/30Koerpermat.html

Laws

Act on Biobanks (2002). Sweden.
http://www.codex.uu.se/texts/Swedish%20Act%20on%20Biobanks%20in%20Health%20Care.doc

Charter of Fundamental Rights of the European Union (2000). Nice.
http://www.europarl.eu.int/charter/default_en.htm

Human Genes Research Act (2000). In: State Gazette (RT1 I 2000, 104, 685). Tartu.
http://www.genomics.ee/index.php?lang=eng&show=20&sub=57

Ministry of Health and Social Security (1998): Act on a Health Sector Database No. 139/1998. Reykjavik.
http://brunnur.stjr.is/interpro/htr/htr.nsf/pages/gagngr-log-ensk#allt

Ministry of Health and Social Security (2000): Act on Biobanks No. 110/2000. Reykjavik.
http://www.mannvernd.is/english/laws/Act.Biobanks.html

Ministry of Health and Social Security (1997). Act on the Rights of Patients No. 74/1997. Reykjavik.
http://brunnur.stjr.is/interpro/htr/htr.nsf/pages/act-rightspatients#allt

References (selected)

Anderlik, M. R. (2003). Commercial Biobanks and Genetic Research: Ethical and Legal Issues. American Journal for Pharmacogenomics 3: 203-215.

Anderlik, M. R.; Rothstein, M. A. (2001). Privacy and Confidentiality of Genetic Information: What Rules for the New Science? Annual Review of Genomics and Human Genetics 2: 401-433.

Austin, M. A.; Harding, S.; Mc Elroy, C. (2003). Genebanks: a Comparison of Eight Proposed International Genetic Databases. Community Genetics 6: 37-45.

Cambon-Thomsen, A.; Rial-Sebbag, E.; Duchier, J. (2003). Ethical and Legal Aspects of Biological Sample Banks: Synthesis, Practical Questions and Proposals. Revue d'Epidemiologie et de Santé Publique 51: 121-126.

Daele van den, W.; Döbert, R.; Seiler, A. (2003). Access to Human Genetic Resources – Materials from a Transnational Stakeholder Dialogue. WZB Discussion Paper SP IV 2003-107. Berlin.

Estonian Genome Project, Estonian Genome Foundation http://genomics.ee

Gray, N.; Womack, C.; Jack, S. J. (1999). Supplying Commercial Biomedical Companies from a Human Tissue Bank in a NHS Hospital – a View from Personal Experience. Journal of Clinical Pathology 52: 254-256.

Hansson, M. G.; Levin, M. (2003). Biobanks as resources for health. Uppsala.

Harris, J. R.; Willemsen, G.; Aitlahti, T.; Petrini, C.; Evans, A.; Silander, K.; Cirrincione, L.; Kyvik, K. O. (2003). Ethical Issues and Genom EU twin. Twin Research 6: 455-463.

Hirtzlin, I. et al. (2003). An empirical survey on biobanking of human genetic material and data in six EU countries. European Journal of Human Genetics 11: 475-488.

Ihle, P.; Krappweis, J.; Schubert, I. (2001). Confidentiality within the Scope of Secondary Data Research – Approaches to a Solution of the Problem of Data Concentration. Das Gesundheitswesen 63 (Suppl 1): 6-12.

Jack, A. L.; Womack, C. (2003). Why surgical patients do not donate tissue for commercial research: review of records. British Medical Journal 327: 262.

Jónatansson, H. (2000). Iceland's Health Sector Database: A Significant Head Start in the Search for the Biological Grail or an Irreversible Error? American Journal of Law & Medicine, 26: 31-68.

Kaiser, J. (2002). Population Databases Boom. From Iceland to the U. S. – Private Biobanks Spark Ethical Concerns. Science 298: 1158-1161.

Kaiser, J. (2003). African-American population Biobank proposed. Science 300: 1485.

Kaulen, H. (2003). Für eine bessere Gesundheitsforschung: Biobanken. Deutsche Medizinische Wochenschrift 128: 2629-2630.

Kort, E. J.; Campbell, B.; Resau, J. H. (2003). A Human Tissue and Data Resource: an Overview of Opportunities, Challenges and Development of a Provider/Researcher Partnership Model. Computer Methods and Programs in Biomedicine 70: 137-150.

McCaffrey, P. (2003). Iceland's Database Tussle, in: CIO Magazine/Trendlines Apr 1, 2003. http://www.cio.com/archive/040103/tl_bio.html

Moutel, G.; de Montgolfier, S.; Corviole, K.; Gaillard, M.; Durlach, V.; Leuttenegger, M.; Adnet, J. J.; Herve, C. (1999). Management of DNA Banks: Ethical Concerns. Presse Médicale 28: 135-139.

Nationaler Ethikrat (2003). Biobanken. Chance für den wissenschaftlichen Fortschritt oder Ausverkauf der „Ressource" Mensch? Tagungsdokumentation.

Noord van, P. A. (2003). Banking of Urine Sediments as DNA Resource in Epidemiologic Studies. Epidemiology: 254-255.

Nordisk kommité för bioetik (Nordic Committee on Bioethics) (1997). Human Biobanks. Helsinki.
http://www.ncbio.org/eng_udgivelser.htm

Puri, A. (2001). An International DNA Database: Balancing Hope, Privacy, and Scientific Error. Boston College for International Competition Law Review, 24: 341-380.

Redaktion Gesundheit und Gesellschaft (2002). Rundruf Biobanken: Nur ein Segen? Gesundheit und Gesellschaft, 12: 9.

Reymond, M. A.; Steinert, R. ; Escourrou, J. ; Fourtanier, G. (2002). Ethical, Legal and Economic Issues Raised by the Use of Human Tissue in Postgenomic Research. Digestive Diseases 20 (3-4): 257-265.

Rothstein, M. A. (2002). The Role of IRBs in Research Involving Commercial Biobanks. Journal of Law, Medicine and Ethics 30: 105-108.

Schröder, M.; Taupitz, J. (1991). Menschliches Blut: Verwendbar nach Belieben des Arztes? – Zu den Formen erlaubter Nutzung menschlicher Körpersubstanzen ohne Kenntnis des Betroffenen. Stuttgart.

Sorsa, M. (1998). Human Biobanks: Ethical and Social Issues. In: Sorsa, M., Eyfjörd, J., Nordic Council of Ministers. Copenhagen.

Spinney, L. (2003). UK launches tumor bank to match maligned Biobank. Nature Medicine 9: 491.

Stegmayr, B.; Asplund, K. (2003). Genetic Research on Blood Samples Stored for Years in Biobanks. Most People are Willing to Provide Informed Consent. Läkartidningen 100: 618-620.

Steinberg, K.; Beck, J.; Nickerson, D.; Garcia-Closas, M.; Gallagher, M.; Caggana, M.; Reid, Y.; Cosentino, M.; Ji, J.; Johnson, D.; Hayes, R.(??): DNA Banking for Epidemiologic Studies: a Review of Current Practices. Epidemiology 13: 246-254.

Stolt, U. G.; Liss, P. E.; Svensson, T.; Ludvigsson, J. (2002): Attitudes to Bioethical Issues: a Case Study of a Screening Project. Social Science and Medicine 54: 1333-1344.

Sulston, J. (2003). Beyond Release: the Equitable Use of Genomic Information. Lancet 362: 400-402.

Taupitz, J. (1991). Wem gebührt der Schatz im menschlichen Körper? Zur Beteiligung des Patienten an der kommerziellen Nutzung seiner Körpersubstanzen. Archiv für die civilistische Praxis, Bd. 191, 201-246.

Taupitz, J. (2003). Wem gehört das menschliche Genom? Zeitschrift für Biopolitik 3: 131-137.

Triendl, R. (2003). Japan launches controversial Biobank project. Nature Medicine 9: 982.

Wallace, H.; Terry, R. (2003). UK Biobank : in the Public Interest? Science Public Affairs 1 : 4-5.

Wellbrock, R. (2003). Datenschutzrechtliche Aspekte des Aufbaus von Biobanken für Forschungszwecke. Medizinrecht 21: 77-81.

Winickoff, D. E.; Winickoff, R. N. (2003). The Charitable Trust as a Model for Genomic Biobanks. The New England Journal of Medicine 349: 1180-1184.

Joint declaration by the NER and the CCNE supplementing their Opinions on biobanks

I. Introduction

This document sets out the results of a series of joint discussions on biobanks held between the National Ethics Council of the Federal Republic of Germany (NER) and the French Comité consultatif national d'éthique (CCNE) in 2002 and 2003. The joint debates and deliberations on this subject have made it clear that, with regard to the extraction, storage, handling and use of bodily substances and associated personal data, the two ethics councils are concerned with similar issues and that they each consider that the regulatory position needs to be clarified by legislation. Notwithstanding certain differences between the legal contexts in the two countries, the search for satisfactory answers and political solutions is governed by values and principles recognized by both countries to be of fundamental importance.

That is why it was felt appropriate for the Opinions drawn up by the two ethics councils to be supplemented by a joint declaration.

The subject of each of our Opinions is biobanks established or used for biomedical research. Biobanks, in this sense, are privately or publicly maintained institutions for the long-term storage of human bodily substances and for the storage of personal data and information on the donors of these substances. Bodily substances include cells, tissue and blood, as well as DNA, the physical medium of genetic information. Data and information are here deemed to comprise both genetic information from individuals and health- and lifestyle-related information on those individuals. The particularity of the biobanks to which these Opinions are devoted lies in this twofold character: the specific importance of the collections of samples stems from the combination of samples with such

data and information. Since any collection may become the subject of genetic research at some point, attention must also be given to the regulation of genetic research in the context of biobanks. Another important aspect is electronic processing of the data and information. This form of processing and transmission permits much faster and more effective data linking and transfer than were previously possible.

The aim of this declaration is to outline the problems and issues raised by biobanks. The slight differences between the legislative recommendations contained in the two Opinions, as well as any divergences in the significance assigned to individual aspects of the issues dealt with, are due to the respective national particularities.

II. The need for an Opinion

The extraction, storage, handling and use of bodily substances and of the personal data recorded in association with these substances are a long-established practice, which, however, is currently in the throes of significant technical development. By means of the large-scale collection and comparison of bodily substances and the data obtained from them, it is possible to identify correlations that may in the long term lead to valuable diagnostic and therapeutic discoveries. Bodily substances and the associated information may therefore possess enormous value. The establishment of large biobanks may thus decisively boost the development of the life sciences, medicine, medical research and healthcare, while at the same time furthering our knowledge of demographic and other population-related parameters.

However, biobanks not only promise benefits, but also arouse anxiety and distrust within the community. These reactions are due to concern that the data and bodily substances might be used for purposes other than those to which donors have consented. For this reason, the samples and information

accruing from a medical research project should not be made available to the police, the judicial authorities, employers or insurance companies. And even in the case of a research project, some would object to the use of their samples and data for scientific purposes not foreseeable at the time when consent was given.

The establishment of biobanks may entail the transfer of samples or information to third parties. Furthermore, personal information may be relevant not only to the individual from whom the samples were taken, but also to his or her genetic relatives, to large communities or perhaps even to a country's entire population.

The ethics councils of France and Germany agree that the ethical and legal challenges posed by biobanks are of many different kinds and that they call for a framework of new and consistent regulations applicable at both national and international level. Those who contribute to these advances by the donation of bodily substances must be protected by clear regulations from any misuse of their personal data. At the same time, it is essential to avoid the obstruction of technical progress by excessive regulation. The framework to be established must satisfy both of these aspirations.

III. Providing for a "chain of responsibility"

The regulation of biobanks must take account of the four areas mentioned above – namely, the extraction, storage, handling and use of bodily substances and data. Each of these areas raises specific issues and calls for an appropriate solution. Each area may concern different players from those involved in the others. For instance, those who collect the samples or the data and information need not be the same individuals as those who handle the collected samples – that is, who label, encode, anonymize, re-identify or conduct research on them. Yet all these areas should be regulated as a whole, consistently and

with due regard to technical progress. Hence the importance of specifying an unbroken chain of responsibility and of laying down the responsibilities to be assigned to each area. In addition, a body should be established to perform the task of monitoring compliance with the regulations applicable in each case. A suitable model is that of a specially appointed coordinating officer or trustee, whose functions and duties must be defined in detail.

Responsibility applies not only to the implementation of controls and compliance with regulations, but also to the conduct of research. The patients who furnish their samples and data generally do so in the expectation of facilitating research that will benefit the affected group.

IV. Free and informed consent

The question of consent lies at the heart of the debate on the ethical and legal regulation of biobanks. This notion is so fundamental that all activities carried on in each of the areas defined above must be structured in terms of it. In the course of their joint discussions, the two ethics councils found that specification of the scope of free and informed consent raised a number of questions.

The first of these concerns the specific research objectives to which donors' free and informed consent applies. Must the purposes for which bodily substances are collected be specified in advance, or can the samples also be used for other scientific projects that could not previously be foreseen because they were beyond the scope of the cognitive dynamics of the research process? Can donors trust in the integrity of research and grant consent from the outset to the use of their bodily substances and the information they yield for all initially unforeseen research objectives arising out of a given scientific problem complex – i.e. can they in effect give consent in the form of a blank cheque? And to what degree of data

anonymization should the consent apply? Should donors be able to choose between consent declarations providing for different levels of authorization?

The two ethics councils are aware of the difficulty that the question of free and informed consent involves two necessarily contradictory aspirations. On one side is the interest of donors in protecting their personal data, as a result of which it might be appropriate to sever the links between the samples and data and their donors as quickly as possible; while on the other is the scientific interest in the possibility of linking data back to donors and of re-accessing data and samples with a view to relating new results to actual cases. Another argument against blanket anonymization is that it may be in donors' interests for them to be informed of research results.

There is no doubt that the information to be furnished at the time of entry into the bank and before samples or data are used for any research project must be particularly precise and must take account of a wide range of possible subsequent activities. For this reason there can be no single binding model for consent. Instead, the regulations to be drawn up must be flexible enough to suit the needs of the entire spectrum of possible research projects.

In view of the complexity of these issues, the CCNE and the NER consider it necessary for the conditions of free and informed consent for biobanks to be defined in more detail. They stress the need to stimulate public debate on this question in their respective countries. In this connection, particular attention must be paid to protection of those incapable of giving their consent.

V. Functions of the coordinating officer

In view of the complex organizational structure of a biobank, it seems appropriate to contemplate the appointment of an officer or trustee with responsibility for coordinating its various

activities and for monitoring compliance with certain standards, as well as to define his or her duties.

The CCNE and the NER are agreed that the officer could perform a central, linking function within the system. The officer's role could be to ensure that the ethical principles and legal requirements relevant to each of the four areas (extraction, storage, handling and use) are observed. He or she could verify that the extraction and subsequent use of bodily substances and the recording and use of personal data have been or are being carried out in accordance with the donor's chosen form of consent. The officer's competence could also extend to monitoring access to biobanks and ensuring that bodily substances and information are issued solely for the purposes of scientific research, and then only in a manner corresponding to the donor's consent. Finally, the functions of such an officer could include preventing misuse of the stored bodily substances and information in the event of a biobank's closure. The officer could advantageously seek the advice of an ethics committee on specific aspects of his or her work.

All regulations should take account of the fact that individual biobanks differ in size and structure. The same applies to the appointment and functions of the coordinating officer.

VI. New issues of solidarity

Bodily substances and the associated information can be especially valuable for biomedical research if collected and stored in large quantities. Today's high-volume data-processing possibilities have opened up new vistas. Although neither Germany nor France has so far planned the establishment of biobanks on a quasi-national scale like those projected or in the course of implementation in Iceland, Estonia and the United Kingdom, the two countries do possess large collections of samples and data for biomedical research that raise questions of solidarity, altruism and justice.

For example, what limits are set to payment for the extraction of bodily substances by the ethical principle, which in France is moreover enshrined in law, of the non-commercialization of the living body? The two ethics councils wish to draw attention to the current international debate on the regulation of remuneration for the benefits accruing from the collection and storage of donor samples and information. Both councils are also aware of the associated risks: the notion that the bodily substances and data supplied to a biobank have the character of a donation for research could be weakened if donors had individual claims to the products of the research or received a financial consideration. One possibility that might be contemplated is that in return for intensive collaboration donors could be granted preferential access to therapies developed by virtue of their contributions to biobanks. Thorough discussion of these matters is essential. Large collections of human bodily substances can result in the joint utilization of research results, the consequent advances accruing to the benefit of all.

VII. Conclusions

In conclusion, a new regulatory framework must be established in both countries to reconcile the development and utilization of research involving the extraction, storage, handling and use of bodily substances and data in biobanks with protection of the individual. This is a task that not only confronts Germany and France but must also be tackled at international level.

Berlin and Paris, 2 October 2003

Meetings and other events organized by the German National Ethics Council on the subject of biobanks

28 June 2002	Public panel discussion with members of the National Ethics Council and of the French National Consultative Committee on Ethical Issues (Comité consultatif national d'éthique pour les sciences de la vie et de la santé – CCNE): "Biobanks – biomedical, ethical and legal aspects of the storage and use of bodily substances and genetic data"
24 October 2002	Public annual meeting of the National Ethics Council: "Biobanks – a promise of scientific progress or a sell-out of man as a 'resource'?"
24 February 2003	Joint deliberations of the National Ethics Council and the French National Consultative Committee on Ethical Issues (Comité consultatif national d'éthique pour les sciences de la vie et de la santé – CCNE)
10 September 2003	Public joint meeting of the National Ethics Council and the Human Genetics Commission: "The establishment of biobanks for medical research: ethical, legal and social aspects"

The members of the German National Ethics Council

Prof. Dr Drs h. c. Spiros Simitis (Chair)
Prof. Dr Regine Kollek (Deputy Chair)
Prof. Dr Dr Eckhard Nagel (Deputy Chair)
Dr Hermann Barth
Prof. Dr Wolfgang van den Daele
Prof. Dr Horst Dreier
Prof. Dr Eve-Marie Engels
Rt Rev. Dr Gebhard Fürst, Bishop of Rottenburg-Stuttgart
Prof. Dr Detlev Ganten
Prof. Dr Volker Gerhardt
Christiane Lohkamp
Prof. Dr Martin J. Lohse
Prof. Dr Therese Neuer-Miebach
Prof. Dr Christiane Nüsslein-Volhard
Prof. Dr Peter Propping
Heinz Putzhammer
Dr Peter Radtke
Prof. Dr Jens Reich
Prof. Dr Eberhard Schockenhoff
Prof. Dr Bettina Schöne-Seifert
Prof. Dr Dr h. c. Richard Schröder
Prof. Dr Jochen Taupitz
Dr Hans-Jochen Vogel, Former Federal Minister of Justice
Kristiane Weber-Hassemer, Former Permanent Secretary of Justice in the State of Hesse
Dr Christiane Woopen

Staff of the secretariat

Carola Böhm
Dr Katja Crone
Ulrike Florian
Dr Rudolf Teuwsen
Andrea Weichert
Bettina Weiss
Dr Christina de Wit