European Journal of Human Genetics (2007) 15, 528–532

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POLICY

A legal framework for biobanking: the German experience

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Although biobanks are vital for modern medical research, serious concerns have been raised about the legal basis and framework of such endeavours. This led the German 'Telematics Platform for Medical Research Networks' ('Telematikplattform für Medizinische Forschungsnetze', TMF) to initiate a project in 2004 that was designed to place German biobanks on a sound legal footing. This project involved the planning, writing and evaluation of an expert report that addresses in great detail the legal issues concerning property rights, medical professional regulations, general liability insurance, resource continuity and research secrecy. Here, we provide a brief summary of the major results of this project.
European Journal of Human Genetics (2007) **15,** 528–532. doi:10.1038/sj.ejhg.5201810; published online 14 March 2007

Keywords: biobank; personality rights; data privacy; property rights; research secrecy

Introduction

For several decades now, the average human life expectancy has grown continuously in most industrialized countries.[1] This development may be attributed, at least in part, to the enormous expansion of our medico-scientific knowledgebase, much of which has been fuelled by molecular biological research. This notwithstanding, human populations all over the world exhibit substantial (and hitherto mostly unexplained) biological variability that has a profound impact both upon the aetiology of disease and its therapeutic prospects.[2] It is becoming increasingly clear that the scientific questions pertaining to this variability can only be addressed by patient-based research that is necessarily reliant upon access to comprehensive collections of biomaterials and associated data.[3]

The complex interactions between human genes (or gene products), and other genetic or environmental factors can rarely if ever be adequately modelled in animal or laboratory experiments. As a consequence, both genetic and molecular epidemiology must make use of the results and methodology of large-scale international research programmes (such as the Human Genome Project) in order to assess the molecular basis of health and disease in real populations.[4] In addition, patient-based cancer research aims to identify those intra- and intercellular mechanisms that contribute to tumour growth and development in order to facilitate the development of more efficient and less invasive antitumour therapies. While working on these scientific questions, the medical research community is currently undergoing a cultural change. More and more national and international infrastructure is being created for long-term and interdisciplinary research collabora-

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Received 3 January 2007; accepted 2 February 2007; published online 14 March 2007

tions.[5–8] Increasingly, these collaborations entail the establishment of centralized collections of data and biological samples (ie 'biobanks'), which provide the essential raw material for both current and future research projects.

The German National Ethics Council ('Nationaler Ethikrat') has defined biobanks as 'collections of samples of human bodily substances (eg 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'.[9] Similar definitions can be found in other contexts including, for example, the 2006 report of the European Strategy Forum for Research Infrastructure (ESFRI), which contains a roadmap for the comprehensive networking of biobanks in the EU.[10] For a facility to qualify as a biobank, the data and sample collection should not be focused exclusively on a single scientific project but rather, this material should be intended for use in the pursuit of future, probably as yet unknown research goals.[11] In this respect, biobanks are different from individual context-related clinical resources; the latter may well be easier and cheaper to establish in the first place but their inherent limitations and multitude may render them inefficient and suboptimal in the long term. Indeed, in terms of data quality particularly, dedicated sample collections may be incapable of fulfilling the needs of sustainable research into complex disease aetiologies.

The TMF biobank project

Biobanks are an absolute requirement for modern, particularly biomolecular medical research. However, serious concerns have been raised not only in Germany, but also at a European level,[12] about the legal basis and framework of such endeavours. Indeed, many of the scientific institutions, which are currently in the process of establishing or using biobanks may be operating in a legal 'grey zone', because (i) there are currently very few specific legal regulations pertaining to such collections, (ii) where such regulations do exist, they vary greatly between different countries,[12,13] and (iii) a solid experience of legal practice is widely lacking in the field of biobanking. Furthermore, a comprehensive assessment of the legal standing of a biobank would severely strain the logistical and financial resources of most interested institutions. Although this is particularly true for international collaborations,[10,12] the practical need for legal advice to biobanks currently seems to be more pressing for regional recruitment and research activities within individual countries. Therefore, in 2004, the Biobank Working Group of the German Telematics Platform for Medical Research Networks[14] ('Telematikplattform für Medizinische Forschungsnetze', TMF) initiated a project to construct a generalized legal basis for the establishment and operation of biobanks in Germany. This project was part of a larger venture which, based upon the 2004 recommendations of the German National Ethics Council, also set out to analyse biobank-specific aspects of data protection, informed consent and quality control.[9] All four components were finalized by the end of 2006, and the TMF is currently planning to expand the legal subproject into an assessment of the implications, for German biobanks, of an active collaboration with similar EU partner institutions.

The prospects for success and the general competitiveness of medical research are becoming more and more dependent upon whether the planned research is to be carried out on an interdisciplinary and collaborative basis. Under the umbrella of the TMF, a number of institutions work together on the identification and solution of frequently encountered technical, legal and organizational problems that arise during collaborative medical research, and which are often unconnected to the specific clinical or scientific context. As a meta-organization, the TMF seeks to improve the organizational and infrastructural conditions for medical research in Germany. TMF members include all of the German Competence Networks in Medicine ('Kompetenznetze in der Medizin'), most Coordinating Centres for Clinical Trials ('Koordinierungszentren für Klinische Studien'), a number of research networks for rare diseases, epidemiological networks, the National Genome Research Network ('Nationales Genomforschungsnetz', NGFN) and various other networked medical research organizations. A large proportion of TMF work is performed by working groups and forums, which deal with specific projects that constitute the core of all TMF activities. In this way, the TMF can draw upon the diverse expertise of its member institutions, particularly in the fields of medical informatics and biometrics.

In what follows, a 'donor' to a biobank will be regarded as any individual from whom a body substance has been taken, including patients whose material has been obtained during a therapeutic or diagnostic intervention as well as volunteers from outwith a treatment context. One of the key concerns in the development and operation of biobanks is to secure the privacy and property rights of the individual donors, particularly when set against the presumed background of the inherent impossibility of completely anonymizing human biomaterials. In addition, the TMF project considered the basic requirements for the legally sound handling of biomaterials, particularly with regard to the scientific and possibly commercial use of such materials, and sharing them with third parties. It was anticipated that addressing these issues would help to improve public confidence in medical research that employs human biomaterials. Another topic addressed by the TMF project was the most appropriate choice of company status for biobanks, a decision that is critically dependent upon the way(s) in which the biomaterial is to be exploited. Here, the focus of the project was on minimizing the liability risks of the scientists involved,

on safeguarding the reputation of the biobank in the eyes of the general public, and on ensuring its continuity.

Work on the TMF project mainly comprised the planning and evaluation of an expert report[15] that addressed the following legal issues in some detail:

1. Company status
2. Property rights
3. Relevance of medico-legal and professional regulations
4. Responsibilities, liability and insurance
5. Continuity
6. Sample storage and use
7. Material transfer
8. Requirements for incapacitated donors
9. Confiscation protection and research secrecy

A brief summary will be given of the major results of the report.

Company status

Most biobanks in Germany are currently operated by public institutions such as university clinics, institutes or departments. However, a recent survey by the TMF has revealed that a substantial proportion of these biobanks have seriously considered 'going private'. In principle, a biobank run as a private company can assume any legal status as long as this status does not require the biobank to be a trading entity. None of the different possible forms of a company was found by the TMF report to confer any particular advantages or disadvantages in the specific context of biobanks. The report concludes, however, that among the most suitable organizational forms for a private biobank are the registered society ('eingetragener Verein'), the limited company and the chartered foundation. Registered societies are generally recognized by the public as being trustworthy because most such institutions are tasked with jointly pursuing a non-material goal. Several research collaborations in Germany currently operate as registered societies, including the TMF itself. The most prominent disadvantages of registered societies, however, are frequent inefficiencies in internal organization and the significant legal liabilities imposed upon their boards of directors. Limited companies, by contrast, provide their members with considerable protection against financial ruin because the liability of the company is limited to its common stock. On the other hand, this limitation can render the acquisition of investments on the financial markets both difficult and cumbersome. Many investors have therefore started to request extra guarantees from limited company members, a request which somewhat undermines the basic idea underlying this form of legal status. Chartered foundations usually guarantee their stakeholders' total financial independence and low liability risks, but substantial up-front donations are generally required in order to establish a foundation. Whether the simple basic financial support of a biobank would represent a sufficient incentive for potential donors to invest their money into such a foundation is, at present, unclear.

Property rights

One of the central findings of the report was that biomaterials, once extracted from the body of the donor, constitute inanimate matter that is covered by the legal regulations laid down in §§ 854–1296 of the German Civil Code ('Bürgerliches Gesetzbuch', BGB). In particular, as § 953 BGB implies that any part of a subject is owned by the owner of the whole subject, body materials belong primarily to their original donor. As a consequence, a donor would have to explicitly transfer their property rights, that is by way of a written contract, for a biobank to become the legal owner of the sample. If such an agreement were made and properly executed, the biobank could then handle the biomaterial at its own discretion as long as this did not violate any other legal regulations or third party rights. The report explicitly excluded the possibility of property rights being transferred to the biobank through 'implied consent'. That is, the biobank would not be entitled to assume that, by originally consenting to the donation, the donor had automatically given their consent for their biomaterial to become biobank property. Although these constraints can easily be accommodated prospectively, they would create serious problems for existing sample collections where the retrospective request for a comprehensive property transfer agreement would be logistically prohibitive. Nevertheless, the TMF report concluded that existing collections could still be used for scientific purposes as long as such use was covered by the donor's original informed consent. In this case, the biobank would be entitled to claim the *usufruct* of the samples according to §§ 1030 ff BGB, which would allow them to carry out research but not to commercially exploit (ie sell) their samples.

As long as a given sample of a body substance has been anonymized (ensuring that the relationship between the biomaterial and its original donor cannot subsequently be reconstructed), no aspect of the donor's right of informational self-determination can be infringed by handling their sample. This means that the transfer of anonymized samples to third parties would be legally admissible and that the donors' consent would be required only if this was agreed upon in advance. However, even the use of anonymized biomaterial can still violate other, common personal rights of a donor if, for example, the original consent to their material being used had been confined to certain purposes, and if this restriction were to be ignored.

In a situation where the biobank was the legal owner of a particular sample, the donor would not normally have the right to request the return of their sample, or to request for it to be destroyed. This would only be the case if, and only if, the biomaterial still belonged to the donor, or if the biobank's use of the material were to have violated an agreement made in connection with the property transfer. In cases where the donor was still the owner of the material, the duty to respect the donor's property and personal rights would automatically transfer to any third party receiving the material. If the sample had been illegitimately destroyed, or if it had been secondarily processed or mixed with other samples without permission, then the donor might even be legally entitled to financial compensation. However, property rights relating to samples do not normally imply intellectual property rights, for example, over research results obtained using the samples.

Relevance of medico-legal and professional regulations

The TMF report emphasized the point that, according to German law, a patient–doctor relationship only exists between a biobank and a sample donor if the sample was taken in order to treat or diagnose a disease. Outside of a therapeutic or diagnostic context, that is, if the sample was taken purely and simply for research purposes, only the process of physical extraction of the sample itself represents an intervention that falls under medical professional regulations. The subsequent processing and analysis of the sample would not be subject to these regulations. In Germany, the authorization to extract body fluids, tissues or organs, even with the donor's consent, is legally confined to medical doctors. Only in a few exceptional instances can a doctor delegate the extraction to other, sufficiently qualified staff, such as nurses. In any case, the physical intervention itself requires the informed consent of the donor. Otherwise, extraction would constitute an act of bodily injury according to § 223 f of the German Criminal Code ('Strafgesetzbuch', StGB). Interestingly, this would also be the case if the donor had been demonstrably misled when giving their consent.

In § 15, the professional rules for German medical doctors ('Medizinische Berufsordnung für Ärzte', MBO-Ä) require any medical institution that is planning to carry out invasive research on humans to consult, and seek permission from an ethics committee before commencement of the experiment. Although this regulation was primarily intended to apply to clinical trials, it also covers the extraction of biomaterials for simple laboratory-based research. This is because the act of extraction represents an invasive intervention according to § 15 MBO-Ä. The TMF report concluded, however, that the requirement to involve an ethics committee should be confined to instances where the biomaterial is to be obtained exclusively for research purposes. In other words, *post hoc* research on samples that have been extracted in a diagnostic or therapeutic context would be exempt from this requirement.

Where new information has been obtained during the research process that could be of critical importance to the donor (ie information that might indicate the presence of, or predisposition to, a serious medical condition), § 323c StGB ('neglect of duty to provide assistance') may in principle oblige both medical and non-medical researchers to relay this information to the donor, if that is possible. The TMF report concluded, however, that a legal conflict arises if, and only if, biomaterial had been anonymized that was originally obtained for diagnostic or therapeutic purposes. This is because the contractual relationship between patient and doctor generally obliges the latter to ensure the avoidance of any harm to the patient, even after the actual diagnosis or therapy is complete. If a doctor intends to anonymize a sample for research purposes, the report therefore recommends explicit inclusion of the *modus operandi* on the patient's consent form. By contrast, if the biomaterial was originally obtained for research purposes only, then the responsibilities of the doctor are usually confined to the act of material extraction and do not include the subsequent analysis of the sample. Whether the obligations of § 323c StGB also cover health information generated in a non-therapeutic context is somewhat unclear. This notwithstanding, most published comments on the practical implications of § 323c StGB are united in expressing the view that this is probably not the case because the prerequisites for its applicability do not seem to include covert disease states.

Continuity

In the eventuality of the insolvency of a biobank, all samples would remain the property of the operator of the biobank given that the operator was indeed the legal owner of the samples. Under certain conditions, however, creditors of the biobank could request that the right to use the biomaterials should be transferred to them. The same would apply in cases where the biobank has been placed under the financial direction of an insolvency administrator who could then request the samples to be disposed of (eg sold) in anonymized form. Should the samples still belong to the donors, however, then they could request the samples to be returned to them, or destroyed.

According to § 14 of the German federal data protection law ('Bundesdatenschutzgesetz', BDSG), it is neither permissible nor possible for an individual or institution to assume property rights over data. Moreover, data can only be retained for the minimum period of time necessary to serve the purpose for which they were initially obtained, and should be destroyed immediately afterwards. This stipulation also refers to all medical and personal data associated with the biomaterials so that, once a biobank

has ceased to exist, there would be no legal basis for further use of its database. An exemption to this rule may however be possible under § 40 BDSG, which permits transfer of the data in anonymized form to another research institution if that institution undertakes to use the data solely for the same purpose as was originally consented by the donor(s) (ie that institution will pursue the same research under comparable conditions).

In this context, the TMF report suggests that, in view of the legal constraints described above, it may be advisable for interested parties to run a biobank as two independent subsidiaries, one holding the property rights over the biomaterials, a second being responsible for the operation of the biobank itself, that is, managing the processes of sample acquisition, storage and transfer, and owning the technical equipment and other accessories necessary for these activities. In this way, the biobank would be fully functional in terms of its operation but would not run the risk of losing its rights over its samples in the case of insolvency.

Confiscation protection and research secrecy

Regarding the endowment of biobanks with guaranteed research secrecy, the TMF report concluded that such a right would currently only apply to the doctor–patient relationships involved. For it to extend to entire biobanks, the corresponding legal regulations would have to be rephrased so as to include other medical and non-medical research personnel. This would imply that a biobank would have legal protection against any interference or invasion by the police or judiciary. Samples, data and data media would in this case be immune from confiscation, that is, they could not be removed from the biobank without the consent of the biobank owner or operator and of all scientists involved. However, the report emphasizes that this kind of regulation could create a legal 'grey zone' in which the police would no longer be able to investigate whether the samples and data of a biobank had been obtained and handled according to the legal regulations. As this would entail the potential for important evidence to be inaccessible to the police, the question of whether or not guaranteed research secrecy for biobanks is desirable is clearly a political one.

Conclusions

With its report on the legal framework of biobanking in Germany,[15] the TMF has provided a guide to establishing and operating national biobanks in a legally sound way. The report therefore seeks to improve the quality of collaborative medical research within the country. The report has nevertheless left some legal questions open and these will only be answered and clarified once new legal regulations in the context of patient-based biomedical research have been implemented. With an increasing proportion of patient-based research being performed through international collaborations, it will be important to compare and contrast the legal situation of German biobanks with those in other countries.[13] Over and above a mere academic interest in this topic, the results of such a comparative analysis promise to be vital for the appropriate planning and execution of future large-scale medical research projects, including those envisaged under the forthcoming seventh EU Framework Programme for Research and Technological Development.[10,16] A TMF project to assess the implications, for German biobanks, of collaborations with similar EU partner institutions is currently in its planning phase.

Acknowledgements

We thank Regina Becker (Brussels), Michael Hummel (Berlin), Peter Ihle (Köln), Michael Kiehntopf (Jena) and Klaus Pommerening (Mainz) for helpful discussion and continuous input into the project. The support and encouragement by Eva Sellge, Sebastian Semler and all staff at TMF are gratefully acknowledged. This study was partly supported by the German Ministry of Science and Education ('BMBF') through an NGFN SMP-GEM grant to MK (01GS0426).

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