Design of Individual Donor Feedback Processes in Biobank Research

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Abstract: In this paper we discuss both ethical/legal and technical/organisational aspects of *genetic feedback* processes. By this term, we denote the purposeful activity of a genetic biobank sponsor/operator to actively inform genetic sample donors on their individual genetic constitution when biostatistical findings indicate medical relevance. We demarcate active feedback from the legally guaranteed right of access to stored personal information, and analyse the obligation of the biobank sponsor/operator to design and offer such a feedback process. The paper highlights the implications of genetic feedback on electronic data custodianship by an in-depth presentation of the design of the genetic feedback process for Schering AG's GENOMatch biobank system.

1 Introduction

Biobanks represent a basic resource for modern pharmacogenomics, pharmacogenetics, and population genetics. Biobanks are defined as collections of samples of biological material like cells, tissues, blood or DNA, which are connected to medical and other information about the donor. Such collections can differ considerably with respect to scope, structure, size and objectives.

Biobank research in pharmacogenomics, pharmacogenetics, and population genetics aims to identify genes or genetic polymorphisms which are involved in disease development and reaction to treatment. Molecular analysis of DNA from Icelandic biobank samples has, e.g., identified a genetic variant which doubles the risk of myocardial infarction [HMT+04] and opened a way for the development of preventive drugs [HTH+05], and pharmacogenetic research on samples derived from clinical trials has succeeded to find several genes which are involved in drug efficiency and adverse drug reactions [KFSv04]. Though genetic factors may increase the probability of disease development or adverse drug reactions, they do not cause them in the narrow sense of the term. Since the influence of single risk factors is small, large numbers of samples and data have to be statistically

analyzed.

In this paper, we discuss ethical-legal as well as organizational and technical aspects of individual feedback processes, which allow donors to get access to information about their individual genetic constitution which has been extracted from their samples in the course of biobank research. The design of such feedback processes poses considerable challenges for the protection of data. Therefore, the concept of electronic data custodianship becomes especially important in this context.

In the following chapter we discuss the legal starting points and some ethical arguments pertinent to the question of feedback, before we present in the third chapter the technical and organisational design of the GENOMatch feedback process, which has been developed in the context of the pharmacogenetic research of Schering AG, Berlin.

2 Legal situation and ethical considerations

At least in the German context it is indisputable that everyone has the right to make inquiries about personal data which have been collected about him or her. This also applies to genetic data. Such claims can be made against any data processing body involved. This is especially applicable if data comprise not only preliminary research results but relevant medical information like validated genetic disease predispositions: "If others know about genetic predispositions, there are no economic or even legal grounds (for example patent protection, intellectual property right, personal rights of third parties) to exclude data subjects from that knowledge" [Wei02] [*translation by rk*]. Therefore, suitable mechanisms for granting access to (possible pseudonymized) personal genetic data are required [Wei02].

Clearly different from this donor-driven inquiry process is what we call an *individual feedback process*. When biobank research yields biostatistical research results, which are of direct diagnostic or therapeutic relevance, it may be up the biobank researchers to take the initiative to open an individual feedback process, i.e. a process by which donors who contributed to the research results, and who have consented in advance to such a feedback, are approached and informed about the findings in general and asked whether they would be interested to get (or not to get) individual genetic information. Since such information often is not easily comprehensible for lay persons and also could have negative social or psychological consequences, it would also be required to bring in a physician or geneticist for consultation and genetic counselling.

A prerequisite for such a feedback process is that genetic data are not anonymized, but can be linked back to a specific person. In order to protect rights and interests of donors, the feedback process itself must be designed such that in the course of the feedback process no unauthorized person may learn about the genetic constitution of a specific individual. The process design therefore must not only take into account numerous medical, ethical and legal aspects, but also organizational issues and questions of technical data protection.

Most far-reaching is the question, whether the sponsor of a study or a biobank is *obliged* to actively return personal genetic (and/or medical) data to persons concerned. Up to now,

this question has only marginally and rarely explicitly been treated in ethical and legal discussions on biobanks. One of the few exceptions is a recently published analysis of eleven related legal and ethical documents from Europe, the US, and the international context [RWS$^+$06][1]. Among these eleven documents, seven propose criteria concerning individual feedback. Four of them refer explicitly to genetic research. Other four documents, which only partially overlap with the ones just mentioned, point the right to know out to study participants. Three documents finally recommend that donors should have the right to choose whether they want to know or not. In sum, the authors conclude that "there appears no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations in the US or the EU that research results have to be, in all circumstances, returned to study participants. However some guidelines advocate a proactive return of data in certain instances." [RWS$^+$06]

According to currently available documents there does not seem to be a *legal* obligation of biobanks to offer individual feedback processes. In view of the possible importance and implications of this question for donors and researchers one has to ask, however, whether and under what circumstances an *ethical* obligation to offer such a process exists.

It might be difficult to argue that a *general obligation* exists to actively feedback research data to sample donors. Nobody expects, for instance, the active feedback of traffic control video monitorings—these data are in most cases meaningless for the individual that might appear in one of those videos. A similar argument applies in the research context, when the implications of research data are not (yet) fully understood.

But when a research process yields clear findings being of actual or potential relevance for a person—e.g. his or her present or future health status—it is well possible to find valid arguments for a *specific obligation* to feeding back research results, especially when a sample donor or patient explicitly stated his/her interest in participating in a feedback

[1]The following documents were analyzed: UNESCO. 1997. Universal Declaration on the Human Genome and Human Rights. http://www.unesco.org/shs/human_rights/hrbc.htm. UNESCO. 2003. Draft International Declaration on Human Genetic Data. http://unesdoc.unesco.org/images/0013/001312/131204e.pdf#page=27. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/e/policy/pdf/17c.pdf. CIOMS. 2002. International Ethical Guidelines for Biomedical Research Involving Human Subjects, First Revision. Articles 5 and 18. National Bioethics Advisory Commission. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. http://www.georgetown.edu/research/nrcbl/nbac/hbm_exec.pdf. United States Department of Health & Human Services. Federal Policy for the Protection of Human Subjects (The Common Rule). http://www.hhs.gov/ohrp/policy/#common & The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Available at: http://ohsr.od.nih.gov/guidelines/belmont.html. Centers for Medicare & Medicaid Services. The Health Insurance Portability and Accountability Act of 1996 (HIPAA). http://www.cms.hhs.gov/hipaa/default.asp? Council of Europe. 1997. Recommendation No. R(97)5 of the Committee of Ministers to Member States on the Protection of Medical Data. The European Parliament and the Council of the European Union. Directive on the Protection of Individuals with Regards to the Processing of Personal Data and on the Free Movement of Such Data (95/46/EC). Official J Eur Communities No. L 281: 31—50. Data Protection Working Party. 2004. Article 29 Working Document on Genetic Data. http://europa.eu.int/comm/internal_market/privacy/docs/wpdocs/2004/wp91_en.pdf. The European Parliament and the Council of the European Union. 2001. Directive of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official J Eur Communities L121: 34—44.

process in advance. The ethical principle to be applied here is the principle of avoiding harm: If a research process either intentionally or accidentally yields information that helps to avoid sickness or adverse drugs reactions, then the sample donor must be enabled to use this information.

A conservative claim would be to feedback only research results with proven *clinical* validity. This strong rule is suited to withhold from sample donors evidence that is still incomplete. But even such "weak" evidence could nevertheless be a starting point for more thorough investigations. Other authors propose to feedback research results to sample donors only if they have clinical relevance, *and* if effective therapies or strategies of prevention are available [RWS+06]. It can nevertheless be argued that the clinical information by itself is of high value for the sample donor. Beyond clinical aspects, social aspects concerning the interaction between researchers and sample donors should be considered as relevant for deciding on feedback [ZRE+05].

Evidently, the ethical discussion on what kind of information to feedback from biobank research to sample donors, and on what kind of validity criteria to apply to this information, has not yet come to a generally accepted conclusion. Nevertheless, good ethical reasons advocate or make it even imperative to feedback information to sample donors. This obviously implies that the biobank sponsor/operator must offer a well-designed feedback process that fully respects data and privacy protection principles.

In order to show in more depth the technical and organisational problems involved in genetic feedback processes we discuss in the following the design of an individual genetic feedback process that has been developed in the context of the GENOMatch biobank, which is used by Schering AG, Berlin, for its pharmacogenetic research. This solution is built on-top of a data custodian-approach for genetic material handling.

3 Case Study: Individual Feedback Process in the Context of Schering AG's GENOMatch Biobank

It is Schering AG's commitment in the context of pharmacogenetic studies to give sample donors the opportunity to receive individual genetic feedback in case of relevant findings—relevant both with respect to severity of the health problem and the significance of the study results. The feedback process that we are going to present in the following is fully integrated in the complex electronic data custodianship system that has been implemented for Schering's "GENOMatch" biobank (cf. [LRSS04], [LSRS05], [RSL+06]). (The GENOMatch biobank itself is operated by a contract research organization, namely the *Labor für Klinische Forschung*, Kiel.)

The GENOMatch data custodianship system relies on pseudonymization technologies: A blood sample when entering the GENOMatch biobank is labeled with the donor's *patient number* (PN) as assigned in the clinical trial center, and additionally by a randomly chosen barcode label BC1. Before a sample tube is finally stored in the biobank, the PN is removed and then, by a different person, the BC1 label is exchanged against an also randomly chosen barcode label BC2. (Thus, GENOMatch applies a two-staged pseudonymization pro-

cess.) The relation PN-BC1-BC2 is stored in a strictly access-controlled identifier database that is operated by the public IT provider *Dataport* in Kiel-Altenholz that acts as electronic data custodian.

The feedback process was designed according to the following principles:

1. No persons other than the sample donor requesting genetic feedback and his/her physician of choice get access to the donor's genetic data in conjunction with data identifying the donor.
2. The sample donor and his/her physician get access to individual genetic data only together; neither party alone can see these data.
3. The donor's physician of choice must prove to be entitled to trigger an individual genetic feedback process.
4. Before individual data are forwarded to the physician of choice of the requesting donor, the GENOMatch biobank and the GENOMatch *Pharmacogenetic Biostatistical Expert* (PBE) take care for genetic data validation without learning any personal data of the donor.

The GENOMatch process for providing individual genetic feedback comprises six steps (see also [ULD06]):

Step 1—Setup: A so-called *Feedback Handler* (FH) is installed. The FH may be a subfunction of the electronic data custodian or it may be independent. The FH orders from the data custodian a list of the PNs of all those study participants whose samples contributed to the biostatistical study result, and who showed a preliminary interest to participate in an individual genetic feedback process. This interest is expressed by a sample donor by purposefully signing a dedicated feedback-related clause in the Informed Consent form that constitutes a donor's participation in a pharmacogenetic study. The electronic data custodian returns the list of PNs to the FH with an assigned *Feedback Number* (FN) per donor. The FH then registers a cryptographic key K1 per PN and forwards to the study investigator a sealed paper envelope per donor each containing a key K1. Key K1 is a symmetric split-key; it is used in step 6 for decryption of individual genetic data in conjunction with key K2 (see below).Key K1 is used by the physician of choice, key K2 by the donor.

Step 2—Contact donors: The study investigator contacts all eligible donors to find out which donors are finally willing to enter an individual feedback process. Such a donor may decide to chose a physician other than the study investigator for counselling. (We name the physician chosen by the sample donor simply the "physician of choice".) Thus, the study investigator possibly has to pass the sealed K1 to the donor to let the donor forward that letter to his/her physician of choice. The donor fills out and signs a 2nd *Informed Consent* (IC) stating his/her willingness to participate in an individual feedback process. The physician of choice proves to the FH to be authorized by the donor by submitting the signed 2nd IC. The physician of choice keeps the sealed K1. If the physician of choice finds the seal protecting the K1 key broken, he/she is to stop the individual feedback process.

Step 3—Open an individual genetic feedback process: The FH opens an individual genetic feedback process by sending the PN of the involved donor to the electronic data custodian. The electronic data custodian informs the respective parties to initiate the following steps:

- drawing of a validation blood/tissue sample from the donor (step 4)
- validation of the donor's genetic data (step 5), and
- generating and sending an encrypted genetic data report (step 6).

Step 4—Sample for genetic data validation: The electronic data custodian sends to the GENOMatch biobank a "validation sample order". This order comprises the donor's (PN, FN) tupel together with other required information like e.g. the address of the physician of choice. In following this order, the biobank *Sample Registrar* (SR) registers with the electronic data custodian the above mentioned key K2 and a sample tube identifier—called BC3—to the donor PN. The SR then forwards a both PN- and BC3-labeled sample tube and a sealed paper envelope containing the key K2 to the physician of choice.

The physician of choice hands over to the donor the sealed K2. If the donor finds the seal unbroken, the physician of choice is allowed to draw a validation blood/tissue sample and to return the sample to the GENOMatch biobank. The sample now enters the above explained two-staged pseudonymization process (with BC3 playing the role of the above mentioned BC1). After that, the validation blood/tissue sample can no longer be distinguished from a "normal" BC2-labeled sample, i.e. it cannot be identified as a validation sample. (For simplicity, we nevertheless call it BC2' in the course of this text.)

Step 5—Genetic data validation: The electronic data custodian sends a "validation order" for the BC2'-labeled sample to the PBE. This order comprises the above mentioned FN. The PBE instructs the GENOMatch biobank *Sample Manager* (SM) to extract genetic data from the BC2'-labeled sample. This sub-process is fully identical to the "normal" sub-process for genetic data extraction. When a BC2'-labeled genetic data record arrives at the PBE, the PBE compares the contents of this record with the contents of other BC2-labeled records from the same donor.

Step 6—Generating and sending an encrypted individual genetic data record: In case of a positive validation result, the PBE encrypts the final report, containing the individual genetic data of the donor, with both the K1 and the K2. The PBE gets access to these tokens by the electronic data custodian by presenting the FN. The PBE burns the encrypted report to a Compact Disc, labels the CD with the FN, and sends this report to the FH which then forwards it to the donor's physician of choice. It is now up to the physician to open the report together with with donor. During this process, the PBE never gets in contact with donor personal data, not even his/her PN.

4 Summary

The discussion on the potential obligation of a biobank sponsor/operator for providing individual genetic feedback to sample donors in case of relevant findings led us to a case

study where such a feedback process has been implemented. The GENOMatch process has been designed such that neither the biobank sponsor nor its operator ever learns which donors request individual genetic feedback. It also guarantees that genetic advice is given to sample donors when learning about their individual genetic predispositions. This kind of process design was enabled by the design of underlying biobank processes for sample handling that make use of pseudonymization technology. It is now up to future practical experience to evaluate the quality of this feedback process design.

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