

Chapter 2

The Need to Downregulate: A Minimal Ethical Framework for Biobank Research

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Abstract

There are currently multiple international bodies suggesting legal and ethical frameworks for regulating international biobank research. One will for obvious reasons find inconsistencies in terminology and differences in procedures suggested for biobank research among all those guidelines, emanating from many different moral and legal traditions. A central question is whether this constitutes a threat to making progress in international biobank research, as some have argued. In this book, Chapter 1 suggests that there are sufficient and well-established instruments and ethical principles available to guide research in this area. Basically I argue that there is no need for a top-down superstructure of detailed rules and guidelines to be imposed on biobank researchers. With the existing ethical review boards (ERBs) playing a central role guided by well-established ethical guidelines (e.g., the Helsinki Declaration) and solutions to specific ethical problems suggested in the literature, self-regulation by researchers providing arguments for balancing of interests in association with different research initiatives and protocols will be sufficient. Traditional information and consent procedures suffice and data protection implies a sovereign right of the individual citizen to grant the use of biobank material and personal data that is needed for biobank research. Clearly, there may still be inconsistencies in terminology when researchers of different nationalities meet in common enterprises, but both they and the ERBs are well equipped to sort out what is actually meant and propose different instruments for, for example, coding following recently established nomenclatures. The existing ERBs should play the key role, guided by the sound argumentation of the researchers in their applications to the board.

Key words: Ethics, Informed consent, Autonomy, Privacy, Public trust

1. Introduction

As has recently been described by Knoppers et al., there are currently multiple international bodies suggesting legal and ethical frameworks for regulating international biobank research (1). UNESCO issued its universal declaration on human genome and human rights in 1997. The European Council agreed on a convention on biomedicine and human rights in 1996, a document that has been

a beacon to many legislators. A follow-up came in 2006 regarding research on biological material. WHO issued in 2003 a report on genetic databases. OECD and its working party on biotechnology provided a draft of guidelines for human genetic research databases in July 2007. Don Chalmers has in his chapter in this book (Chapter 1) provided a comprehensive account with full references to these and other official documents. Different academic bodies have taken several initiatives, notably the HUGO Ethics Committee in its statement on human genomic databases from 2002. National biobank consortia provide their own guidelines (e.g., the UK Biobank) and the recent initiative called P³G has the ambition to suggest a comprehensive global framework of guidelines for genetic research using human biological material.

One will for obvious reasons find inconsistencies in terminology and differences in procedures suggested for biobank research among all those guidelines, emanating from many different moral and legal traditions. A central question is whether this constitutes a threat to making progress in international biobank research. Knoppers et al. conclude that in the absence of “common ... norms, laws and approaches within a properly harmonized international framework, international collaboration will remain an empty platitude” ((1) p. 311). I seriously doubt that this is the case. As witnessed in this book, there are already many ongoing successful international collaborations using biobank material. I will in this chapter suggest that there are sufficient and well-established instruments and ethical principles available to guide research in this area. Basically I will argue that there is no need for a top-down superstructure of detailed rules and guidelines to be imposed on biobank researchers. With the existing ethical review boards (ERBs) playing a central role guided by well-established ethical guidelines (e.g., the Helsinki declaration) self-regulation by researchers providing arguments for balancing of interests in association with different research initiatives and protocols will be sufficient. Taking into consideration the low risks for sample donors associated with biobank research, something most participants in the discussion seem to agree on (see, for example, Chapter 1), the current efforts to create long and complex lists of “principles” and “best practices” looks like trying to kill a mosquito with a baseball bat. Before suggesting the components of a more appropriate, minimal framework, I will go through some of the central questions in the current discussion.

2. The Claim That Biobank Research Implies “New” Challenges

It is often claimed that genetic research using human biological material together with personal data and different medical records gives rise to a number of “new” ethical issues to be handled by

the research community. Gibbons and Kaye state that “genetic databases raise a host of challenging issues, many of which test our traditional legal concepts, governance provisions and bioethical principles” ((2) p. 204). However, as recently argued by Ruth Chadwick and Mark Cutter:

the concept of collection of information into databases is not a new phenomenon; similarly, the collection and use of genetic information is not a new practice. The use of “family history” in determining life insurance, assurance and relative premiums is well documented, as is its use in diagnosis during genetic counseling sessions. Equally the storage of human genetic material and information in the form of medical records is not unusual or new. Arguably, since Gregor Mendel’s original experiments with the hereditary characteristics of pea plants, through to James Watson and Francis Crick’s identification of the double helix of DNA, the biological sciences have been on a trajectory that seems naturally to culminate in the creation of human genetic research databases or biobanks ((3) p. 225).

This view is shared by Thomas Murray who early on questioned the view that genetic information is something exceptional in comparison with other kinds of medical information (4). Along the trajectory of genetic research, ERBs and data protection authorities seem to have managed quite well to keep up with new research initiatives to balance the different interests at stake. Chadwick and Cutter suggest that it is the negotiation between the individual and public interests that cause population-based genetic databases to be something special. I will come back to this claim in a discussion of the concept of autonomy.

3. The Role of Patient and Public Surveys

Wendler has recently made an overview of 30 studies published in English that reported the views of individuals on consent for research with human biological samples (5). He concludes that:

Data from more than 33,000 people around the world support offering individuals a simple choice of whether or not their samples can be used for research purposes, with the stipulation that an ethics committee will decide the studies for which there samples are used. This approach offers a method that could be adopted across institutions and around the world ((5) p. 547).

Wendler admits that framing effects can affect survey results and that some questions may not have been fully understood by the respondents. However, the data seem to be consistent across many different studies using different questions and different methodologies in different cultures. We have in similar studies acquired the same results (6). Caulfield is skeptical to this use of surveys (7). He claims, rightfully so, that at best they represent the majority view and there are examples of individuals wanting

other information and consent procedures. However, in the majority–minority negotiation, it should be observed that whether there is an instrument available to protect the minority view (e.g., those individuals wanting specific information and consent for each new research project) one may feel more comfortable in acting on behalf of the majority view (e.g., broad consent with surrogate decision by an ERB). As a matter of fact, there is such an instrument available that can serve this purpose and that is the right of an individual to withdraw his or her consent. This is part of the information and consent procedure to be decided by the ERB. As Caulfield argues, majorities may change so there is a continuous demand on all involved parties to secure public understanding and public trust.

4. The Role of Commercial Interests

Caulfield argues, furthermore, “there is evidence that some members of the public are uneasy about the involvement of private interests” (op. cit. p. 220). There seems to be support for such a conclusion from several studies. However, the picture is complex and one question here concerns what conclusions that may be drawn from public surveys. A question that was discussed above in connection to the selection of appropriate information and consent procedures. Caulfield mentions an Australian study as a source of evidence: “Thus, an Australian study exploring public attitudes to biobanking found that ‘75% indicated concerns over commercialization’ of the research process and access to information by health insurance companies” (Ibid. 221). Williams performed the study with 358 patients attending a cardiology department who were given a questionnaire while registering for a gene bank, thus a highly select group and not representative of the general public (8). Williams concludes that “75% indicated concerns over commercialization and access to information by health insurance companies” (p. 1774), so Caulfield’s quote is partly right even if it was not the public view as he claimed. However, a closer look at the questionnaire that is presented in the article shows that Williams’ conclusion does not follow from her data. Question 10 was phrased: “Do you think insurance companies should be allowed access to your genetic information?” 7% answered *yes*, 74% answered *no*, and 9% were unsure. There is no question regarding commercial interests involved in the research process presented in the questionnaire.

It is well known that people are concerned about insurance companies getting access to genetic information through medical databases. Whether and under what conditions they should have access is a complex question that I will not go into

here. As indicated by Chadwick and Cutter earlier, the question is not new since insurance companies have access to other kinds of medical data. However, I think one should distinguish between access to information by private insurance companies and by pharmaceutical companies. If properly informed I believe that most people will understand the need of partnership between academic and commercial interests. Scientists at the universities have simply no possibility to assume responsibility for the whole chain of research and development from a basic scientific finding to a new medical product. In practice, however, the question about the access of pharmaceutical companies to biobanks may not be so difficult to resolve since they often have their own biobanks, collected under very strict conditions.

5. The Importance of Public Trust

To realize the potential of biobanks, efficient collaboration between many actors is essential and the practice as a whole rests upon the confidence of patients and healthy persons donating blood and tissue samples. Trust must be established both within the medical and the research community and with the general public. Decreased patient confidence in biobanking practice may have damaging consequences. If individuals start revoking their consents the banks will not be complete, the possibility to draw scientifically valid conclusions will decrease and the potential for follow-up examinations and medical treatment will not be fulfilled. In Sweden, there is an efficient legal instrument available for those individuals losing confidence in the system through the Biobank Act which gives each sample donor or sample source such a right to withdraw their consent and have the sample destroyed or stripped of identification possibilities, strongly decreasing the potential by precluding the important possibility to match the information of the sample with information in different medical and personal registries ((9), 3 kap, [Subheading 6](#)).

Conflicts between the researchers and between the universities and hospitals are not instrumental for increasing the trust essential for the success of biobank research (10). The main victims of the distrust are the actual and future patients waiting for improved methods in diagnosis and treatment. The success of core facilities for biobank research and collaborative projects depend on appropriate acknowledgment of the different contributions to these facilities and research results. Collaboration should be based on a transparent organization of the research and on legally binding agreements. Such agreements should also include policies and rules regarding the sharing of samples, data, and research results.

Patient confidence in biobank research is maintained by keeping strict rules for privacy protection and respecting patient–physician relationship. However, it should be observed that ERBs and regulatory bodies setting up rules for biobank research are themselves subjects to public trust. Patients and healthy donors have interests at the beginning of the research line, for example, being assured about the protection of their integrity and providing tissue material and access to personal data for good scientific reasons, but they have also general research interests connected to the potential of providing new treatment and new medical products (11, 12). A too strict interpretation of the legal principles governing this kind of research, for example, regarding the possibility to use previously collected samples without a renewed consent, may be detrimental to their research interests. They may have good reasons for wanting to waive the right to be informed. As shown by Wendler and others, it has in fact been shown in public surveys that a majority want broad information and consent procedures and want to waive their right to provide an explicit and specific informed consent for each research project, handing over the decision to an ERB (5, 6, 13).

6. The Concept of Autonomy

In our research team, we have often argued for different practical solutions regarding biobank research on the basis of a respect for autonomy. McQuillan et al. have suggested that “specific consent must be obtained if an individual’s autonomy is to be respected in all aspects of the research, both current and future” ((14) p. 40). This represents indeed a very limited view of autonomy and, as O’Neill has pointed out “there are many distinct conceptions of individual autonomy, and their ethical importance varies” ((15) p. 4). However, I do not entirely agree with Knoppers and Chadwick that we need to “move away from autonomy as the ultimate arbiter,” even if we should pay attention to other fundamental notions related to biobank research, such as solidarity, reciprocity and citizenry ((16) p. 75).

I have at length recently discussed the notions of autonomy and privacy elsewhere and shall just briefly mention some important points here (17). It seems that the view taken by McQuillan et al. about the research subject’s autonomy is shaped by a political concept that basically derives from the ancient world. In ancient Greece, autonomy was a political concept that emphasized independence. An individual is autonomous when he takes charge of his own affairs and is protected from external interference, even if its price is isolation from other people and from the world around. It was first with Kant that autonomy was

defined as a moral concept (18). Respect for people's autonomy entails, according to Kant, a respect for their capacity to participate in the formulation of the moral principles that every human being would wish to endorse. In this sense, human beings are self-legislators, but it is a question of laws and rules with, in principle, a universal sphere of application.

Making autonomous decisions in accordance with the Kantian tradition thus involves taking account of the well-being of others through a judgment of how one's own decisions affect other people's ability to act in a morally responsible way and to attain their own goals. Kant has, in his concept of autonomy, incorporated an element of intersubjectivity. The individual is a member of a moral community of beings and is expected to take into account how one's own interests may affect other individuals. Autonomy is inherently social, with the implication that the working out of legal protection for self-determination and integrity in association with biobank research must simultaneously do justice to both the research subject's independence and this individuals' dependence on others for fulfilling mutual interests. Furthermore privacy interests should not, as it is commonly understood be set in direct opposition to public interests (for one example of this confusion see (3) pp. 225f). The individual wishes simultaneously to enjoy a private sphere protected from insight but also to participate and to be a member of society. This view implies the importance of protecting private information, for example, through different coding measures in association with biobank research while at the same time ensures that the individual can take part in a common enterprise such as the production of medical knowledge and treatment opportunities that is provided through large population-based biobank research platforms (12).

O'Neill has suggested that respect for autonomy implies control over how one's samples are used (15). As she acknowledges, this includes a possibility to affirm requests for broad and future consents without the opportunity to be approached in the future. However, in my view it does not necessarily imply that there in addition must be an opportunity for individual control after the initial sampling has taken place so that those who wish should have a possibility of being recontacted for new research projects, something O'Neill suggests. Taking the Kantian view on moral autonomy in consideration where the individual is called upon to take also other individual's interests into consideration (e.g., future members of society), it may be sufficient if there is a democratic instrument available that ensures the individual citizen insight into how the biobank is organized and that principles for balancing of interests at the ERBs take all relevant interests into account. It may for instance be openly declared that in some cases public health interests have been judged to be of overriding importance compared with individual interests.

An example of when this level of democratic control is applied is medical registries, for example, cancer registries, which are instituted by the parliament and under the care and supervision of public authorities and do not allow any possibility for individuals to withdraw their data.

7. The Selection of Appropriate Information and Consent Procedures

Timothy Caulfield argues that “biobanks have created some of the most difficult legal and ethical dilemmas within modern biomedicine” and that “maintaining traditional consent norms may harm the social utility and scientific value of large-scale biobanking initiatives” ((7) p. 210). However, as I argued already in 1998, ERBs have in their tool box several information and consent procedures that are all legitimate and that are appropriate for different purposes (19). The key task for the ERB is to select an appropriate procedure that represents a reasonable balancing of the risks and benefits associated with a specific research protocol.

For competent adults the rules of informed consent are rather straightforward. Incompetent research subjects constitute a greater problem. Informed consent cannot be a general solution. I have recently argued that one should also apply a “safety principle,” which take into consideration patient safety with regard to diagnosis, treatment, care, and prevention, implying that research may be conducted on these individuals even if no consent is available (and cannot be) (20).

Rules of informed consent are based on a respect for the moral authority and autonomy of individual research subjects. In the practice of medical research, this implies that research subjects should never be exposed to a risk in association with a research project without their consent. It does not follow that research subjects should never be exposed to any risks. There are few, if any, research protocols that do not carry a potential risk to the research subject. The researcher has to control as far as possible for short- and long-term risks. After informing the research subject about the purpose of the research, its expected benefits, the risks associated with it, and how these risks will be managed, informed consent is obtained from the subject – a way of handing over the decision to the research subject – Are you willing to assume the remaining risk (indeed in Phase 1 and 2 clinical trials the unknown risk)? Information is also given about stopping rules and procedures for control of the risk and about the opportunity to withdraw from the study without this having any effect on evidence-based treatment provided, and care is taken to make sure that the research subjects are not object for exploitative incentives of any sort.

In practice, there are many pieces of legitimate information and consent procedures available (19). The appropriate procedure is selected on the basis of balancing the scientific value against the risk entailed by the project. It is not reasonable that the rule of obtaining an informed consent shall be the same in situations of ordinary treatment, in clinical trials and in protocols of epidemiological biobank research where no personal identification is possible or both the biological material and the personal data are coded and strictly protected. I have earlier argued that: “The quality of consent needs to be balanced against the different values that are at stake in different contexts. The kind of information, the way it is given, the degree of voluntariness and the format of authorization must be adjusted accordingly” (Ibid. p. 182). According to the model I have suggested, “appropriate information and consent procedures vary depending on context between extensively informed consent with written and oral information to informed refusal with only a limited amount of information given. At the other end it should just be a matter of making relevant information available” (Ibid). In biobank research, one has to distinguish between two fundamentally different kinds of research protocols, those using only previously collected samples and those associated with the collection of new samples for future research.

Against this view Caulfield argues that “most large-scale biobanks should be thought of not as discrete research projects, but as ‘research platforms’ that will be used by a number of researchers, for various research initiatives, over many decades, which are not fully known when the genetic information is obtained from participants. As a result, it is impossible to obtain truly informed consent from biobank participants” (Op. cit. p. 213). Biobank research implies broad consent to future research and this cannot be a “truly” informed consent. Caulfield’s view is shared by Vilhjálmur Arnason who argues against the use of broad or generally formulated consent forms. Arnason argues that:

If we are to preserve a meaningful notion of informed consent for participation in research, it should only be used about specified research where the participants are informed about the aims and methods of a particular research proposal. ... There is no such thing as “general informed consent.” The more general the consent is, the less informed it becomes. It is misleading to use the notion of informed consent for participation in research that is unforeseen and has not been specified in a research protocol ((21) p. 41).

The success of biobank research implies that large repositories of human tissue material are collected together with well-described and managed clinical and personal data. As described in the previous chapter, there are now several large national biobanks working in this way. The specific nature of the research is unknown and only general descriptions about the goals of these biobanks are possible, for example, for biomedical research or research on

large groups of common diseases. A specific consent to a narrowly described research protocol is not possible and there is a need to ask for a broad consent covering future research. Caulfield and Arnason argue that the traditional meaning of informed consent cannot accommodate these broad and future consents. Consent should be based on specific information otherwise it is not a valid consent. However, as we have pointed out earlier this only raises the question: “What is appropriate information? If the information covers all aspects relevant for a person’s choice, then that person’s consent is appropriately informed. If the essential risk and benefit levels are general to a number of studies, then general information on these studies may be sufficient for the donor of the sample to make an informed decision” (22). As has been described there are many pieces of legitimate information and consent procedures that balance the scientific value of the biobank, the nature of research and the risks that are believed to be at stake.

We have recently argued that “accepting broad and future consent implies a greater concern for autonomy than if such consents are prohibited. Respect for autonomy does not imply total self-governance when a decision also affects others such as family members. However, infringement on autonomy should only be done with good cause. Under the condition that information is coded and safely handled and that secrecy is maintained, both donors and families are protected from harm, no limitation of autonomy is necessary” ((22) p. 267). Asking for a broad consent to future research, for example, biomedical research, implies a respect for each individual to decide for him- or herself if the general information is sufficient. A mechanism that allows individuals to change their minds and withdraw their consent will provide an extra protection. There are different mechanisms for this, for example, withdrawal allowing further use (with or without de-identification) and withdrawal prohibiting further use. Accepting broad and future consent is consistent with a policy where the ERBs will examine and give permission to each new research project using these large biobanks. “In order for an ERB to evaluate the risk/benefit relationship for a donor, it must review the coding measures, information security and other potential risks for the donor that may arise from, for example, changes in legal status, principal investigators or organization of the original biobank” (Ibid. p. 269). Broad consent, not broad permissions, is the favorable policy. This policy of broad consent seems now to emerge internationally as the generally preferred solution according to a recent review of the literature (23).

It is not at all implausible that donors to biobanks may understand the medical importance of creating such research platforms, including the cost of returning for renewed consent. Biobank research has been going on for some time and many patients and research subjects seem to be willing to take part also for broadly

described purposes. Furthermore, as argued by Campbell, to safeguard altruism and trust in biobank research one should refrain from “suggesting that individual donors have ongoing rights to exercise control over uses of their donated materials and the resource itself ” ((24) p. 242). Campbell emphasizes that maintaining trust is essential and this includes also a requirement on those issuing rules and guidelines not to impose too many restrictions that will constitute a hindrance in fulfilling important donor interests related to the production of new medical knowledge and treatment opportunities (11). For some examples of how biobanks in association with good clinical data are vital assets for understanding the underlying mechanisms of human diseases and for providing medical care and for treatment of current and future patients see Sigstad et al. (25) Kaijser (26), Lindberg (27), and Sundstrom et al. (28).

The use of previously collected samples seems to constitute a special problem in international collaboration. Recontacting donors who earlier have contributed to pathology biobanks or to a research biobank to obtain a renewed informed consent for a new research project may not be practically feasible. However, the major ethical reason for abstaining from asking again is the cost in scientific value it implies, and consequently decreased potential for providing new biomedical knowledge and medical treatment. Asking again may be seen as an act of respect for autonomy but if the donor learns to know that this is detrimental to his/her general research interests they may very well instead feel a disrespect. The European Council has acknowledged the need of balancing in a commentary to article 22 in the European Convention on Biomedicine and Human Rights (29) where they state that: “information and consent arrangements may vary according to the circumstances, thus allowing for flexibility since the express consent of an individual to the use of parts of his body is not systematically needed” ((29), Commentary 137 to Article 22).

When potential risks of a breach of privacy and unauthorized use of samples and personal data is kept low by applying strict coding procedures, the use of previously collected samples should be permitted without the need for a renewed consent. An opt-out scheme with information in national media or advertising in local newspapers with an associated right to withdraw from the study may be used when feasible. We have recently provided a template for handling consent issues related to the use of different sample collections where the original information and consent arrangements vary (30). An expressed *no* to any future research in the original consent form should always be respected as a respect for autonomy and in line with the importance of preserving trust in biomedical research. “Specific considerations apply to the case of a donor who once agreed to participate in a research study, when the donor is no longer alive and therefore no longer available for

either informed consent, opt out, dissent, or reports of results. This may frequently be the case, for example, in cancer research. Systematic exclusion of deceased participants would introduce a significant selection bias abolishing the chances for objective scientific studies. Inclusion of the donor's sample cannot impose harm on the donor, and therefore the sample may be included, with the single exception that the donor's survivors have specifically requested that the donor's samples not be used for research – in which case the sample should be excluded, while maintaining a record for future statistics that this has occurred” (30). To let relatives have a veto when the deceased earlier has affirmed his or her willingness to donate tissue for research would constitute a breach of respect for autonomy. However, when the attitude of the deceased is not known, using the tissue against the expressed wish of the relatives would jeopardize the trust in research.

8. Benefits and Harms

Due to long lead times in biomedical research aiming at providing better treatment and new medical products there are seldom, if at all, any direct benefits for the actual donors in biobank research. However, all patients depend for their medical treatment on previous research results and, accordingly, on the fact that earlier generations of patients and healthy volunteers have participated as research subjects and donated tissue samples both to the pathology biobanks and to the biomedical research projects (20).

8.1. Breach of Privacy

The major risk of harm in biobank research is associated with the processing of sensitive personal data. Such processing may be seen as a breach of privacy and if unauthorized parties access information this may put the donor at risk. Insurance companies, employers, and other third parties may have a great interest in information acquired through human tissue sampling. Maintaining strict coding and secrecy procedures controls potential risks of damage of this kind. These coding procedures must, as was the case regarding information and consent procedures, be sensitive to the interests and risks that are at stake. In its latest Report on *Personal Information in Biomedical Research* (2007) (<http://www.bioethics-singapore.org/resources/reports.html> – in Subheading 4), the Singapore Bioethics Advisory Committee argued that protection measures should be proportional to the sensitivity of the information, so that not every kind of information need be protected with the same vigor, for example, a database of children with myopia (very common among children in Singapore) would obviously need much less protection than a database on HIV/AIDS patients. As argued by Terry Kaan Sheung-Hung in his comments

to my first draft of this chapter, this avoidance of a mechanical broad-brush approach requires data custodians to apply more intelligent rules and measure for the protection of information.

8.2. Misuse by Third Parties

According to Swedish legislation, there has in addition been a shift of attention from putting cumbersome restrictions on research to prevent unauthorized use to making such use in itself unlawful. The new law on genetic integrity (31) which came into effect 1 July 2006 laid down that nobody may stipulate as a condition for entering into an agreement, that another party should undergo a genetic examination or submit genetic information about themselves. There should also be a general prohibition to the effect that without support in law, genetic information may not be sought after or used by anyone other than the person that the information is about. This applies even if the person concerned has given his or her consent to such an investigation or use, but not if they themselves have requested it. The proposed prohibition is not to be applicable to genetic information that is sought for medical purposes, for scientific or genealogical research or to obtain evidence in legal proceedings. For criminal investigations and for insurance purposes, there is regulation in place or suggested. Illegitimate requests of or uses of information may still be a problem, but this risk is minimized since such actions will according to the new law constitute criminal offences. A scale of penalties that includes fines or a term of imprisonment not exceeding 6 months will enforce the proposed prohibitions (Law 2006:351).

8.3. Harm to Groups

There may also be a risk of harm to a group of individuals associated with a specific biobank-related research protocol, for example, when a linkage is suggested between an ethnic group and the prevalence of a specific disease, for example, a sexually transmitted disease or a psychiatric condition. The individuals pointed out may experience a harm done to them just by the information being revealed of them as members of this group. This problem is, however, complex (see (10) for discussion). When genetic factors are revealed for multifactorial conditions such as alcoholism, sexual identity, and cognitive capacity and psychiatric disorders such as schizophrenia, dyslexia, ADHD, and autism, individuals belonging to these groups may feel stigmatized. However, such consequences of increased knowledge must be dealt with on a societal level and political decisions have to be made to protect exposed groups, for example, to provide equal opportunities for a good life, not by limiting the search for knowledge. “Through biobank research a linkage may (also) be established between sensitive medical information and groups of individuals that without much difficulty can be identified after the results of the research have been published, for example, a geographically distinct group of individuals, persons with a certain job position,

education, income, etc. However, this is not an entirely new phenomenon. In order to minimize the risk of damage done, the researcher and the research ethics committee may decide that the information should be disguised or coded in a way that makes it impossible or very difficult to identify the group being studied” (Ibid. p. 417).

8.4. Dignitary Harms

Regarding research that uses previously collected human tissue samples an ERB has to select an appropriate information and consent procedure. Under certain conditions, for example, strict coding measures are applied and it may not be practically feasible to ask for a renewed consent, the board may decide that the research may be carried out without an informed consent or decide that an opt-out scheme shall be used. If individuals who should not want research to be carried out on their samples, or are negative to a specific kind of research, learn to know that research is carried out without their consent they may feel disrespect. I call this kind of harm “dignitary” harm. They may feel that their dignity as political citizens with moral authority has been violated. However, this kind of harm would arise in many other situations as well when a decision is taken on behalf of a public interest but at the price of not honoring the interests of each individual. An analogous example to biobank research is the establishment of national medical registries, such as a cancer registry or a death cause registry. These decisions are taken by the parliament or by a public authority to protect vital public health interests. Because of their public interest importance they do not need an approval by each individual and they do not admit any right on the part of individuals to have their information removed.

At the end, dignitary harms, as well as other kinds of harm, must be balanced against the scientific value of each research project and the potential benefits of doing research. It is quite conceivable that some individuals have strong personal reasons for not wishing to participate in a certain type of medical research. “These interests should be respected as far as possible, but legislators and the authorities concerned must also apply a balancing principle which weighs one interest against others and where ultimately it is those that are worst off in society who should be favored in the outcome. In this case, the interests current and future patients have in access to new medical treatment must also be taken into account. This interest can be one of which a person who is ill or someone with a relative, who died from cancer, can be acutely aware” (20). If, therefore, it is the case that allowing people to exercise their right to consent when only dignitary harms are at stake, or to withdraw their consent, has particularly negative effect on those who are already worst off in society, there is reason to abstain from this possibility. “The interest of the sick in being cured should be given higher priority than a healthy

donor's opportunity to have his attitude to a certain type of medical research respected. Protection of the sample donor's privacy is still respected in the sense that the information is, and remains, strictly confidential" (Ibid.).

9. Using Personal Data

In data protection legislations and in regulations of biobank research, the patient/donor has the sovereign right to decide whether and how personal data and tissue material may be used, for example, a yes to use of personal data must be respected by an ERB and by the data protection authorities. These authorities may in some instances grant permission to do research using sensitive data without consent from the donor. However, the individual has normally a right to grant such use. This implies that it is essential that the information to patients and research subjects include all possible uses of personal data associated with a research project or the collection of human tissue samples, as well as the measures taken to protect the privacy of the individual donors. It should for example include information about genetic analyses and international collaboration that implies the transfer of biological material and data across borders. If the research may involve commercial partners and interests, for example, future patenting, this should also be included in the information.

Since it is the combination of human tissue material and clinical and personal data that carries the promise of providing understanding of underlying mechanisms of diseases and their treatment, data should as a general rule not be anonymized. Anonymization "precludes accumulative assessments for which multiple inclusions of the same participant must be avoided, and prevents retroactive validation and demonstration of reproducibility. That would preclude the possibility to make important links in the future. As a general strategy, anonymization can therefore not be recommended," coding is preferred (32). To evade confusion about the different coding alternatives and what "anonymization" means I suggest that the recommendations by EMEA are used (33). They recommend that regarding *anonymous* samples there are no links to the individual donor (although there may be general descriptions like "man, age 50–55, Cholesterol level >240 mg/dl"). *Identified* samples are linked to the individual in a way that makes them immediately identifiable. A *simple code* is a direct link to the individual, usually through a random set of numbers or letters, or a bar code. A *double code* implies that to link the sample and the data to the individual a second code is needed. *Anonymized* are samples that earlier have been identified or coded but the identification, or the code and the code key have been destroyed so

there is no longer any link to the individual. The International Conference on Harmonization of Technical Requirements (ICH) has in November 2007 adopted this nomenclature for the Registration of Pharmaceuticals for Human Use. In the European Union, the Committee for Human Medical Products has endorsed the guidelines, which came into operation in May 2008. This nomenclature is then an important part of an already existing international Charter regarding coding in biobank research.

10. Feedback Concerning Results of Research Studies

As a general rule, information about the progress of research from a biobank is made available through publication in scientific publications. General information may also be made through national media. Specific information to individual donors is generally not advisable since it implies assuming a responsibility for the clinical significance for an individual based on information about the odds ratio expressing risk only for a study population. Research groups may not be equipped for assuming such a responsibility. Communicating genetic information implies skills in genetic counseling and the information may be of direct concern to genetic relatives who also must be informed. “Misinterpretation can cause potential psychological, social, and economic harm – especially before validation of the clinical significance of the findings. This is particularly true if no relevant treatment or prevention modality to combat the investigated risk is yet available” (30). If clinically significant findings are expected to emanate from the research this implies that a close collaboration has to be set up from the start together with clinical departments and wards that can provide counseling and advice about treatment. As pointed out to me by Campbell in his comments to my first draft of this chapter, there was a debate in the UK biobank about avoiding the idea that participation would render a “health check,” as this would be a false promise. It should be clearly understood and stated that the only benefit for large population-based biobanks is the health of future generations, including information about the long lead times before scientifically significant results become clinically significant.

There may also be incidental findings associated with a biobank project or a research protocol, for example, a mutation in a breast cancer gene where treatment is available. These incidental findings should be handled in a manner that also implies collaboration with clinical departments that can give information and provide treatment to affected individuals. A detailed guide for researchers has recently been provided (34). A model has also been suggested for the communication of genetic information that has not been asked for by the individual (17). It takes account

of the character of the information and the possibility to provide treatment and could be used when organizing the feedback of incidental findings in association with biobank research and entails that an individual is informed first when certain conditions are satisfied. Such conditions might include one or more of the following: (1) that the information is reliable according to medical science or tested experience (2) that the information is linked to a reasonably certain risk of illness, (3) that the illness is of a reasonably serious kind or is at least nontrivial (4) that the genetic component has high penetrance, (5) that there is an effective prevention or treatment, (6) that personal support and regular checkups are offered.

11. Is There a Need of Separate Ethics Boards?

As described by Don Chalmers in his chapter of this book (Chapter 1), several of the large biobank initiatives have separate ethics review boards as part of their governance structure. This organization is believed to promote public trust and also be necessary for controlling that data are securely handled. I tend to disagree with this development. Since the first Helsinki Declaration, which among other things requested that an independent body of scientists and laypeople should review all human subjects research, a strong tradition has been established with groups of scientists and lay people well experienced in handling different kinds of research protocols and making the ethical balancing. The procedures for electing them and securing relevant scientific expertise are well established and the boards have a clear mandate. In Sweden law regulates them and the government elects the members. There is also an “ethics board of appeal” which can discuss and suggest how new issues should be handled. Under the condition that both the initiation of a new biobank and each new research project emanating from this biobank are examined by the ordinary ethics review boards there is no need of extra independent bodies. Their mandate is unclear with members often elected by parties directly involved in the biobank effort. For the scientists they create a new bureaucratic level and they cost money that could be used for research. In our research group, we argued recently for broad consent (not “blanket” as Caulfield asserts (7)) but emphasized that this did not imply broad approvals to many research projects (22). There is a need for the ethics review board to check the nature of the new research project, that the legal status of the biobank is the same and that the data protection measures initially agreed upon are still applicable.

As pointed out to me by Terry Kaan Sheung-Hung in his comments to my first draft of this chapter it is essential that the

review boards guard themselves from the instinctive response to apply ethical principles evolved from the setting of therapeutic care in the relationship of doctor–patient to the quite different relationship between researcher and research subject. Also doctors participating as researchers in randomized clinical trials sometimes have problems to uphold the distinction between therapeutic ethics and research ethics. As Peter Armitage has pointed out, investigators in the same trial may sometimes move away from the region of uncertainty implied in a randomized design at different rates depending on their prior judgements, the weights attached to different criteria and psychological characteristics (35). The tensions between the two relationships are obvious in the Helsinki Declaration but they cannot be solved by simply putting the doctor–patient relationship absolutely above that of the researcher–subject relationship.

12. Conclusion – A Minimal Ethical Framework

When taking into consideration the actual interests at stake and the possibility of balancing these interests in an ethically appropriate way it seems clear that the attempt by different international bodies to create global frameworks with long lists of principles and best practices for biobank research represent an overkill of some magnitude. Traditional information and consent procedures suffice and data protection implies a sovereign right of the individual citizen to grant the use of biobank material and personal data that is needed for biobank research. Clearly, there may still be inconsistencies in terminology when researchers of different nationalities meet in common enterprises, but both they and the ERBs are well equipped to sort out what is actually meant and propose different instruments for, for example, coding. The existing ERBs should play the key role, guided by the sound argumentation by the researchers in their application to the board.

There are of course important and difficult questions remaining to be solved, for example, on sharing of results and how to design intellectual property rights, how to handle data protection in a way that acknowledges the sensitivity of the information acquired (not giving in to the legal definition that all health information is sensitive in the same sense), the way research on minors and incompetent persons may be conducted, and how to handle informed consent in longitudinal studies including minors (9, 36). However, these matters are complex and need to be the focus of sound research, not be a matter for considered opinions by different groups. In conclusion, I suggest that researchers and ERBs should have the following points to consider in mind when designing a project, informing the sample donors, applying for

approval by an ERB, conducting the research, and reporting research results. As indicated with several references in the text, the framework is based on previous research published in international peer-reviewed scientific journals.

13. Points to Consider

1. The initial collection of human tissue samples and personal data should be based on an informed consent by the sample donor.
2. The ERB has to balance the interests at stake and select an appropriate information and consent procedure for each research project that is using a biobank.
3. ERBs may under certain conditions grant research without consent on previously collected samples and may permit researchers to ask for broad consent to future research.
4. Personal data and genetic information should be protected by coding and accessible only by authorized persons.
5. An individual donor may grant permission to the researchers to handle personal information, for example, to perform genetic analyses, engage in an international collaboration that implies the transfer of biological material and data across borders and collaborate with commercial partners. This kind of information should therefore be included in the information to the sample donor.

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References

1. Knoppers, B.M., Abdul-Rahman, M.H., Bédard, K. (2007) Genomic databases and international collaboration. *Kings Law Journal*. **18**, 291–311.
2. Gibbons, S.M.C., Kaye, J. (2007) Governing genetic databases: collection, storage and use. *Kings Law Journal*. **18**, 201–208.
3. Chadwick, R., Cutter, M. (2007) The impact of biobanks on ethical frameworks. In *The ethics and governance of human genetic databases* (Häyry, M., Chadwick, R., Árnason, V., Árnason, G., eds.), Cambridge University Press, New York, pp. 219–226.
4. Murray, T.H. (1997) Genetic exceptionalism and “Future Diaries”: is genetic information different from other medical information? In *Genetic secrets: protecting privacy and confidentiality in the genetic era* (Rothstein, M.A., ed.), Yale University Press, New Haven, pp. 60–73.

5. Wendler, D. (2006) One-time general consent for research on biological samples. *BMJ*. **332**, 544–547.
6. Kettis-Lindblad, Å., Ring, L., Viberth, E., Hansson, M.G. (2007) Perceptions of potential donors in the Swedish public towards information and consent procedures in relation to use of human tissue samples in biobanks: population based study. *Scandinavian Journal of Public Health*. **35**(2), 148–156.
7. Caulfield, T. (2007) Biobanks and blanket consent: the proper place of the public good and public perception rationales. *Kings Law Journal*. **18**, 209–226.
8. Williams, C. (2005) Australian attitudes to DNA sample banks and genetic screening. *Current Medical Research and Opinions*. **21**, 1773–1775.
9. Helgesson, G., Ludvigsson, J., Gustafsson Stolt, U. (2005) How to handle informed consent in longitudinal studies when participants have a limited understanding of the study. *Journal of Medical Ethics*. **31**, 670–673.
10. Rose, H. (2003) An ethical dilemma. The rise and fall of human genomics – the model biotech company? *Nature*. **425**, 123–124.
11. Hansson, M.G. (2005) Building on relationships of trust in biobank research. *Journal of Medical Ethics*. **31**, 415–418.
12. Hansson, M.G. (2006) Combining efficiency and concerns about integrity when using human biobanks. *Studies in History and Philosophy of the Biological and Biomedical Sciences*. **37**, 520–532.
13. Hoeyer, K., Olofsson, B.-O., Mjörndal, T., Lynöe, N. (2004) Informed consent and biobanks: a population-based study of attitudes towards tissue donation for genetic research. *Scandinavian Journal of Public Health*. **32**, 224–229.
14. McQuillan, G., Porter, K.S., Agelli, M., Kington, R. (2003) Consent for genetic research in a general population: the NHANES experience. *Genetics in Medicine*. **5**, 35–42.
15. O'Neill, O. (2003) Some limits of informed consent. *Journal of Medical Ethics*. **29**, 4–7.
16. Knoppers, B.M., Chadwick, R. (2005) Human genetic research: emerging trends in ethics. *Nature Reviews Genetics*. **6**, 75–79.
17. Hansson, M.G. (2008) *The private sphere. An emotional territory and its agent*. In *Philosophical Studies in Contemporary Culture*, Monograph, Springer, p. 182.
18. Hansson, M.G. (1991) *Human dignity and animal well-being. A Kantian contribution to biomedical ethics*. Acta Universitatis Upsaliensis. Uppsala Studies in Social Ethics 12, Uppsala.
19. Hansson, M.G. (1998) Balancing the quality of consent. *Journal of Medical Ethics*. **24**(3), 182–187.
20. Hansson, M.G. (2007) For the safety and benefit of current and future patients. *Pathobiology*. **74**, 198–205.
21. Árnason, V. (2004) Coding and consent: moral challenges of the database project in Iceland. *Bioethics*. **18**, 27–49.
22. Hansson, M.G., Dillner, J., Bartram, C.R., Carlsson, J., Helgesson, G. (2006) Should donors be allowed to give broad consent to future biobank research? *The Lancet Oncology*. **7**, 266–269.
23. Hansson, M.G. (2009) Ethics and biobanks. *British Journal of Cancer*. **100**, 8–12.
24. Campbell, A.V. (2007) The ethical challenges of genetic databases: safeguarding altruism and trust. *Kings Law Journal*. **18**, 227–246.
25. Sigstad, E., Lie, A.K., Luostarinen, T., Dillner, J., Jellum, E., Lehtinen, M., Thoresen, S., Abeler, V. (2002) A prospective study of the relationship between prediagnostic human papillomavirus seropositivity and HPV DANN in subsequent cervical carcinomas. *British Journal of Cancer*. **87**(2), 175–180.
26. Kaijser, M. (2003) Examples from Swedish biobank research. In: *Biobanks as resources of health* (Hansson, M.G., Levin, M., eds.), Uppsala University, Uppsala, pp. 33–50.
27. Lindberg, B.S. (2003) Clinical data – a necessary requirement for realizing the potential of biobanks. In: *Biobanks as resources of health* (Hansson, M.G., Levin, M., eds.), Uppsala University, Uppsala, pp. 21–32.
28. Sundstrom, P., Juto, P., Wadell, G., Hallmans, G., Svenningsson, A., Nystrom, L., Dillner, J., Forsgren, L. (2004) An altered immune response to Epstein-Barr virus in multiple sclerosis: a prospective study. *Neurology*. **62**(12), 2277–2282.
29. Council of Europe (1997) Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine. Oviedo, ETS No. 164.
30. Helgesson, G., Dillner, J., Carlson, J., Bartram, C.R., Hansson, M.G. (2007) Ethical framework for previously collected biobank samples. *Nature Biotechnology*. **25**, 973–976.
31. Lag om genetisk integritet m.m. (Act on Genetic Integrity), 2006, p. 351.
32. Eriksson, S., Helgesson, G. (2005) Potential harms, anonymization, and the right to withdraw consent to biobank research. *European Journal of Human Genetics*. **13**, 1071–1076.

33. EMEA (2002) Position paper on terminology in pharmacogenetics. Committee for Proprietary Medicinal Products (CPMP), EMEA/CPMP/3070/01.
34. Wolf, S.M., Lawrenz, F.P., Nelson, C.A., Kahn, J.P., Cho, M.K., Clayton, E.W., Fletcher, J.G., Georgieff, M.K., Hammerschmidt, D., Hudson, K., Illes, J., Kapur, V., Keane, M.A., Koenig, B.A., Leroy, B.S., McFarland, E.G., Paradise, J., Parker, L.S., Terry, S.F., Van Ness, B., Wilfond, B.S. (2008) Managing incidental findings in human subjects research: analysis and recommendations. *The Journal of Law Medicine & Ethics* **36**(2), 219–248.
35. Armitage, P. (1998) Attitudes in clinical trials. *Statistics in Medicine*. **17**, 2675–2683.
36. Helgesson, G. (2005) Children, longitudinal studies, and informed consent. *Medicine, Health Care and Philosophy*. **8**, 307–313.



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