RESEARCH ETHICS

Building on relationships of trust in biobank research

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Trust among current and future patients is essential for the success of biobank research. The submission of an informed consent is an act of trust by a patient or a research subject, but a strict application of the rule of informed consent may not be sensitive to the multiplicity of patient interests at stake, and could thus be detrimental to trust. According to a recently proposed law on “genetic integrity” in Sweden, third parties will be prohibited from requesting or seeking genetic information about an individual. Cumbersome restrictions on research may be lifted, thus creating a more favourable climate for medical research.

federal legislation.⁴ The Genetic Privacy Act states that:

...to effectively protect genetic privacy unauthorized collection and analysis of individually identifiable DNA must be prohibited. As a result, the overarching premise of the Act is that no stranger should have or control identifiable DNA samples or genetic information about an individual unless that individual specifically authorizes the collection of DNA samples for the purpose of genetic analysis, authorizes the creation of that private information, and has access to and control over the dissemination of that information” (Annas, *et al*,⁴ p vi).

It is widely agreed that the use of human biobanks has great potential for biomedical research.¹ DeCode Genetics in Iceland, the UK Biobank, the national biobank in Estonia, National Children’s Study in the USA, and the blood biobank established in Umeå, Sweden, are examples of large national and regional efforts. The practice as a whole rests upon the trust of patients and healthy persons donating blood and tissue samples. This trust is essential for the success of biobank research. It is, as I will argue, within reach if well established legal and ethical frameworks are kept in mind.

INFORMED CONSENT—ITS VALUE AND LIMITATIONS FOR SECURING TRUST

The requirement to obtain informed consent is the key principle of medical ethics and medical law. It represents respect for the moral authority of patients and research subjects.² Informed consent is an expression of trust through which patients and research subjects declare their confidence in risks associated with a research protocol being properly managed. Based on given information they also trust that their participation is for good reasons, with a reasonable potential for gaining new knowledge, and that the research will be carried out in accordance with legal and ethical rules. The requirement of obtaining informed consent is reflected in all the major ethical declarations—for example, the Convention on Human Rights and Biomedicine of the European Council from 1996,³ and it is restated in several national legal documents—for example, The Swedish Biobanks Act 2002 and the Swedish Ethical Review Act 2003. The priority of informed consent is argued by leading ethicists and lawyers.^{4–5} The same concern is also reflected in the Genetic Privacy Act in the United States, drafted as a proposal for

The rule of informed consent is rightly conceived as the key rule. It has its limitations, however, in particular within the context of biobank and genomic research.

i) Its core element is that an individual patient will, based on information about short and long term benefits and risks, authorise a medical intervention.⁶ In order for that requirement to be meaningful the patient must be able to understand the information, but this is not possible regarding some biobank research where samples are stored for long periods and not even the scientists can accurately predict what use will be made of them. The legitimacy of the informed consent depreciates as time proceeds and science makes progress.

ii) For natural reasons, it is hard for the rule to fully accommodate the need for protection of patients who are minors or for other reasons incapable of understanding the relevant information, a difficulty that is only partly solved by rules of proxy consent.

iii) The rule of informed consent in its classical individualistic form is unable to take into account the interests of families and genetic relatives of the patients, individuals who are directly concerned by genetic information. Professional secrecy will prevent a doctor from communicating genetic information to genetic relatives if this is not authorised by the proband. However, because the interests of directly concerned genetic relatives must be considered, a too strict adherence to the rule of professional secrecy may be ethically questionable. Normally, a proband who undergoes genetic testing will inform his or her relatives. In some cases, however, the proband may declare that he or she will not do that, perhaps because of conflicts within the family or to social distance between family members. There is reason to believe that such situations will become more frequent as

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normal social and moral bonds between family members become less tight because of disintegration of families—for example, through divorce, new marriages, and family members living at great geographical distances from each other. In such a case, when the genetic information is reliable, the risk for a serious disease is high, and there is effective treatment or prevention available, upholding the rule of professional secrecy may have too high a price.

iv) As argued by Graeme Laurie, the rule of informed consent is impossible to harmonise with an individual's interest in not knowing about his or her genetic disposition or risk.⁷ The patient has an interest in being informed, but sometimes also an interest in being let alone and not receiving any information about a genetic risk.

v) With regard to the obtaining of renewed consent to research for a new purpose on previously collected biobank samples, a strict application of the rule of informed consent, as suggested in The Genetic Privacy Act, is not sensitive to the multiplicity of patient interests at stake. The difficulty may be illustrated with reference to the Convention on Human Rights and Biomedicine, article 22 of which lays down that:

When in the course of an intervention any part of a human body is removed, it may be stored and used for a purpose other than that for which it was removed, only if this is done in conformity with appropriate information and consent procedures (Council of Europe,³ article 22).

Strict application of this principle may not be in the best interests of the patient or the donor of a sample. It is well known that the response rate in association with collection of data from any larger population is 70–80% at best. Irrespective of how skilled the researcher is in formulating questions and regardless of how many reminders are sent out, the response rate will rarely exceed these figures. If explicit and specific informed consent has to be obtained for each new use of material already collected, the scientific value of the study will decrease because not all will respond. The researcher will, furthermore, not know if those not responding might have been of particular interest in the study. If the research subjects come to realise that, in order to protect their privacy, a legislator or an ethical review board demands such a rigid interpretation of the duty to inform and obtain consent that the scientific value of the study decreases and, accordingly, the potential for providing new treatment and new medical products is endangered, they may feel that other vital interests are being frustrated. They will have less reason to trust the ethical review system and its ability to establish procedures for harmonising their double interests in being both sample donors and end users of medical research.

Article 22 has been a beacon to legislators both in Sweden and other member states of the Council of Europe. Unfortunately, however, it is seldom recognised that the explanatory report to the convention provides valuable guidelines regarding the transposition of this article into national legal and ethical frameworks. In comment 137 to the convention it is stated that:

The 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. Thus, sometimes, it will not be possible, or very difficult, to find the persons concerned again in order to ask for their consent. In some cases, it will be sufficient for a patient or his or her representative, who have been duly informed (for instance, by means of leaflets handed to the persons

concerned at the hospital), not to express their opposition. In other cases, depending on the nature of the use to which the removed parts are to be put, express and specific consent will be necessary, in particular where sensitive information is collected about identifiable individuals" (Council of Europe,³ comment 137).

The explanatory comment opens the way for a more flexible use of the rule of informed consent in order to protect vital values at stake for current and future patients. Patients may find it too costly to exercise a right of self determination in each particular case and may instead want to waive their right to informed consent and leave the decision to the members of the review board, especially in cases where the risks are of a minor nature. This interest is recognised in the explanatory comment above. It is also recognised in national legal documents—for example, the Swedish Ethical Review Act 2003, effective from January 1 2004. In a recent survey among individuals who had donated blood to a large biobank in northern Sweden it was found that a majority of the respondents were willing to waive their right to informed consent and leave the decision about what kind of research should be carried out on the stored samples to the ethical review board.⁸ The respondents were more concerned with the security of the procedures and that secrecy was maintained than in the kind of research for which their samples were used. It may be observed that the explanatory comment is still inclined to uphold the value of informed consent as the appropriate instrument for ethical balancing. It fails to appreciate the possibility of securing current and future patients' interests through protection of privacy and personal integrity.

A BALANCE IN THE BEST INTERESTS OF THE PATIENT

The Swedish Ethical Review Act will, together with the Official Secrecy Act, make the legislation on biobank research much more sensitive to patient interests. The focus of the explanatory report to article 22 is on risks of damage and the handling of sensitive information. Ulrik von Essen has described the premises on which the ethical review will be based, and the focus is similar to the explanatory report of the convention with, however, a stronger emphasis on protection of privacy.⁹ The central provision of the Ethical Review Act is that a research project may be approved only if the risks it entails to the research subject's health, security, and personal integrity are counterbalanced by its scientific value. The Board for Research Ethics will first consider the research on the biological material and then, separately, examine damage risks related to the handling of personal data. Regarding research on the biological material, a risk of harm will only arise in exceptional cases. The major possible kind of harm is violation of personal integrity, and because the samples will as a rule be coded, that risk is minimal. As von Essen observes, however, if the samples are not coded or if the code may be broken later on, the board for research ethics will also carry out an ethical review of the project, which will include any processing of sensitive personal data. When determining the risk, the board will assess the security in the processing of data and then acknowledge that if the principal investigator is a public representative—for example, a university scientist, secrecy will apply to personal information about individuals. The degree of the risk of violation of personal integrity may then be considered low and the counterbalancing of risk of integrity violation and scientific value will normally lead to approval of the research project.

Potential risks of damage to individual integrity may thus be controlled by maintaining strict coding and secrecy procedures, in accordance with the legal rulings in effect. There may, however, still be a risk of harm to a group of

individuals associated with a specific research protocol. An example of such a case might be a study in which 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. Such information may be judged to be sensitive and the group in question may experience a harm done to them simply by it being revealed that they are members of this group. They may, as an effect of the dissemination of this information, be stigmatised and suffer different kinds of discrimination in public, or at the hands of public and private authorities. The problem of handling potential harm done to groups of individuals is, however, complex. At least three different cases should be clearly distinguished in any and all discussions.

First, biobank research may identify new genetic factors behind conditions that have so far been explained exclusively with reference to environmental conditions or chance. Genetic factors have been identified or suggested for several multifactorial conditions, such as alcoholism, sexual identity, and cognitive capacity. Developments in genetic research indicate that genetic components are involved in a number of psychiatric disorders as well as in complex human behaviour—for example, schizophrenia, dyslexia, attention deficit/hyperactivity disorder, and autism. It is possible, and perhaps even likely, that research of this kind will inflict harm upon groups of individuals identified in this way. Consequences of this kind are, however, something that must be dealt with on a societal level and political decisions have to be made in order to protect exposed groups—for example, in order to provide equal opportunities for a good life despite different initial values. Scientists have the responsibility to provide reliable information and informed consent is not an appropriate measure for preventing harm from being done. Secrecy is, however, still relevant in order to protect personal integrity.

Second, although information revealed through biobank research may be relevant and stigmatising to a group of individuals, the assessment of the interests at stake must also take into account other parties concerned. A carrier of a sexually transmitted disease or some other infectious disease cannot have an exclusive right to this information since the health and safety of other individuals are concerned. For this reason there are laws giving public authorities a right to control transmission of infection. Official secrecy acts will protect the personal integrity of the disease carrying individual but a balance has to be struck that takes into account the interests of other individuals.

Third, there may be cases where it is only an exposed group that is directly concerned and there is a potential harm associated with a study protocol. Through biobank research a linkage may 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. This is not, however, an entirely new phenomenon. In order to minimise 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. In their balancing they need also to assess the positive effects of openly publishing the information and thus providing information that members of a group may want to act on—for example, by adjusting a health adverse behaviour or approaching a hospital for control and treatment.

Patients provide valuable material for research but they also have interests at the other end of the research line, as beneficiaries of the research results. A too strict interpretation regarding new purposes may thus be detrimental to their interests. They may have good reasons for wanting to waive

the right to be informed. The Board for Research Ethics has been given the exclusive right to decide which information and consent procedures are appropriate regarding a specific research protocol. An explicit wish on the part of the patient for a sample not to be used for research should always be respected. Detailed information is relevant for specific research projects. Too many details about the nature of this research are not, however, meaningful to the patient or the sample donor. With safe and effective coding procedures in place and secrecy laws available, donors of biological samples should be granted the possibility of accepting broad consent forms.

REGULATING THE USE BY THIRD PARTIES IN ORDER TO INCREASE TRUST IN BIOBANK RESEARCH

Much of the public debate on biobanking has been caused by excluding the patients from information about the purpose of human tissue sampling and what is happening with the samples. It may be that public trust can only be restored through a policy of transparency as to how the multiple interests of current and future patients are recognised and handled. The ethical review board will play a key role in maintaining public trust. Much of the concern around biobank research is, however, likely to be centred on questions of trust about what might happen when third parties acquire information derived from research data, either legitimately or illegitimately. The ethical review board bears the primary responsibility for setting up requirements for the coding and secure handling of information. As described above, the legal instruments necessary for this are available in Sweden through the Official Secrecy Act and the Ethical Review Act. There is still, however, reason for concern since insurance companies, employers, and other third parties may have a great interest in information acquired through human tissue sampling. A Swedish parliamentary commission has recently tackled this problem.¹⁰ It reasons that an essential part of the public trust in medical research using genetic and other kinds of sensitive medical information, depends on patients and research subjects knowing that third parties are prohibited by law from requesting, or inquiring about, genetic or medical information from an individual, with the exception of specified medical situations.

The parliamentary commission proposes a new Swedish law on genetic integrity with this content. In the proposed law it is 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. It is proposed that in the same legislation 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” (Swedish Government,¹⁰ p 38). According to the parliamentary commission there should not be any legitimate area of application in the general field for genetic information, apart from the medical field, the judiciary and other areas that are subject to special regulation. The proposed prohibition is not to be applicable to genetic information that is sought for medical purposes, for scientific or genealogical research, or in order to obtain evidence in legal proceedings. For criminal investigations and for insurance purposes there is regulation in place or suggested. Illegitimate requests for, or uses of, information may still be a problem, but this risk is minimised since such actions will, according to the new law, constitute criminal offences. The proposed prohibitions will be enforced by a scale of penalties that includes fines or a term of imprisonment not exceeding

six months. From a patient perspective the proposed law is of great significance. Cumbersome restrictions on research—for example, in the form of strict requirements to obtain renewed consent for research on previously collected samples, may now be lifted and replaced by strict requirements regulating the potential misuse by third parties. Thus, together with protections of integrity already in place, a more favourable climate for medical research will be created that may benefit current and future patients. The proposed law represents a significant and timely step towards restoring public trust in biobank research. When the proposed law comes into effect it is possible that we will see a development whereby ethical approval of biobank research is brought more into line with epidemiological research, which uses different kinds of medical registries.

CONCLUSION

The potential of biobanks may be realised and the trust necessary for the benefit of current and future patients maintained, if the following directions based on law and suggested ethical guidelines are implemented.

1. Samples must be collected and stored with the consent of patients and research subjects based on general information available to patients and in accordance with appropriate information and consent procedures as determined by an ethical review board.

2. Samples and information (medical and personal) must be safeguarded in accordance with official secrecy regulations and coded in such a way that unauthorised access is impossible while at the same time enabling an efficient matching of genetic, medical, and personal information.

3. Provisions must be made that preclude third parties from requesting or using genetic information

4. Research must be carried out only after approval by an ethical review board, in accordance with their selection of information and consent procedure and in collaboration with doctors and hospitals providing clinical data; sample donors' right to give a broad consent and to waive their right to a renewed informed consent must be secured.

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