Genetic Research in Human Populations

1 Introduction

Genetics research raises ethical issues that differ in many ways from those that arise in other kinds of human subjects research. Some of these differences are of kind and some are of magnitude. We can locate the leading ethical issues under the following headings:

- **Privacy and confidentiality.**
- **Informed consent.**
- **Risks of harm.**

2 Privacy and confidentiality

The terms "privacy" and "confidentiality" are not synonymous. Generally, "privacy" refers to *persons* and "confidentiality" to *information*. If, for instance, one surreptitiously obtains a quantity of residual blood from hospital testing and analyzes it for cancer markers or mutations, then we should say that the blood source's privacy has been violated. If, on the other hand, one were to sneak a look at the source's medical record and learn that she has breast cancer, her confidentiality has been breached.

For a number of reasons, including increased risk of bias, discrimination and stigma, genetic privacy and confidentiality are sometimes thought to be more important than privacy and confidentiality in other kinds of research. Genetic information is for these reasons sometimes likened to information about sexually transmitted diseases or certain mental health problems.

Investigators preparing to conduct genetic analyses must tell potential subjects which entities and persons will have access to the data. This might include investigators at other institutions, corporate sponsors, a government, employers, insurance companies, etc. If information obtained during research will be placed in a patient's medical record, this too must be disclosed. Subjects must also be told of the risks of an employer or insurer having access to an individual's genetic information.

Unlike most other kinds of health data, genetic information applies to or is about more than one person. Analyze genomes and you will learn something about a person's parents, siblings, children, and perhaps others. This means that individuals can lose privacy and/or confidentiality even if they are not the source of the specimen or information being studied.

For instance, confirming a genetic diagnosis of Huntington's disease in a person also means that at least one of his or her parents carries this gene and is at risk of developing the condition. But the parent is not a subject in the research and did not consent to it.

Research that includes follow-up studies and attempts to identify clinical correlations requires that a subject's unique information be linked to the genetic information. These links, in conjunction with particular aspects of research protocols, might be used to seek out or re-contact subjects in the future. These links and their uses must be disclosed to subjects.

For this and other reasons, many investigators seek to unlink or decouple personal identifiers from genetic data or biological specimens. Successful unlinking reduces or eliminates some threats to privacy and confidentiality. However, it is increasingly possible to take even "unlinked" data or samples and use "surrogate identifier ensembles" (demographic information, birth date, postal code, diagnostic code, etc.) to pick out or identify a unique individual. Some scholars question whether genetic samples can ever be completely unlinked or "anonymized."

3 Valid Consent

Ethical research on humans generally requires that three conditions be met. Subjects must be:

- Adequately informed.
- Free from coercion or undue influence.
- Competent.

3.1 Adequate Information

Many familiar challenges in human subjects are based on questions or difficulties that arise in meeting these three conditions. In the case of genetics research, the challenges are amplified. For instance:

- It is difficult in the case of traditional medical and behavioral research to determine how much information is adequate and, moreover, what level of complexity or detail is appropriate. These problems are magnified by genetics research, which most non-scientists find difficult to understand.
- It is often unclear how to describe risks of harm to potential subjects. In genetics research, the risks are generally not physical but psychological,

social, economic, etc. These risks are sometimes more difficult to present and evaluate.

- In pedigree and other studies, information collected might affect entire families, including members who do not wish to know or participate. Special precautions are needed to protect against or manage pressure or coercion and to communicate risk. There is growing urgency to include genetic counseling in the consent process for genetics research.

3.2 Autonomous Consent

The consent process must take into account the questions whether and when investigators will re-contact subjects. If the samples will be unlinked and researchers will not inform subjects of any results, this must be disclosed. If subjects want the results they can then be urged to be tested independent of the research. If re-contact is possible but not planned, disclosure is required for the same reason. If re-contact is planned—perhaps to measure subsequent clinical correlations—disclosure is crucial for those who might not want to know their genetic status.

Generally speaking, the following are some items that should be disclosed to prospective subjects during the consent process:

- The purpose of the research, in simple language.
- How the specimens will be stored and who will have access to them or the information they contain.
- Whether sources will be re-contacted later with information about the study findings.
- Whether the samples are linked to the sources with a code or identifier. (If a sample is coded it is linked and therefore not anonymous.
- Whether the research will be used to develop proprietary products or assays and whether the subject can share any financial rewards from the project.

4 Risks of Harm

One of the most difficult components of the consent process in genetic research is how to identify and communicate risks of harm. The harms that might result range from minor to major, and from physiological to psychosocial and even economic.

- Blood draws carry a risk of bruising.

- The idea of testing can cause pre- and post-test anxiety, which can vary with existence/availability of treatment.

- Disclosure of results may result in employment and social bias, discrimination and stigmatization.

- Disclosure of results may cause loss or increased cost of health and/or life insurance.

- Family members of the index subject may face similar risks of harm.

It can be very difficult to assess these risks. "Anxiety" will vary by individual and malady, and the most frequently cited risks of genetic research (loss of insurance or health benefits and employment discrimination) are dependent on the existence of legislation to prevent such discrimination. This varies by jurisdiction.

Further, "stigmatization" can be quite vague, perhaps even subjective. Yet there is growing evidence of some ethnic groups and subgroups becoming associated with genetic disorders. This possibility should be disclosed to potential subjects.

Note that the concept of "risk" includes the notion of probability or likelihood. In other words, risks are inherently probabilistic. For this reason, the phrase "potential risk" is redundant. The risks are quite real—they just might not be realized. Some think the phrase "potential risk" therefore misleadingly downplays the chances that a subject will come to grief.

5 Stored Biological Samples

Research on stored biological samples allows investigators to conduct studies long after the subject has moved on. It is helpful to think of research on stored samples as two kinds:

- Retrospective, in which investigators use blood, tissue, etc. from pre-existing collections.

- Prospective, in which investigators collect samples to create new banks.

5.1 Retrospective Research

If the research is retrospective and if adequate steps are taken to prevent identification of the samples' sources, then genetic research can often proceed without an IRB requiring that individual subjects provide valid consent. The benefits of such research can be quite valuable and may outweigh the violation of the principle of obtaining informed consent from all the sources of stored

biological samples. However, an IRB must scrutinize such waivers of consent carefully.

Even if federal regulations may permit research on existing samples without consent, an IRB may determine that consent is necessary if the cohort is small, the disorder or trait is stigmatizing, and there are concerns about maintaining confidentiality. Note that if it is possible to re-contact sources, the following problem needs to be addressed.

Suppose you have received IRB approval to study banked tissue without obtaining the consent of the tissue sources. Your protocol meets the federal criteria for waiver of consent. Now imagine that you discover a medically important mutation in the tissue sample belonging to patient XYZ. You do not know who XYZ is, or even if s/he is alive. But you can find out XYZ's identity because the sample is linked to patient records with a code number. *Should you use the link to find and warn XYZ? What if XYZ does not want to know of this malady, and you tell her anyway? What if she would want to know, and you don't tell her? What about XYZ's children? Is there a duty to warn or inform them?* Laws and regulations do not usually address these difficult ethical issues. On the other hand, consent is required to take blood or tissue for prospective genetic studies.

5.2 Prospective Research

IRBs face difficult challenges when investigators seek permission to bank or archive biological specimens for future, unspecified, research. If investigators want to bank tissue but are unable to say what it will be used for, then it is difficult to obtain valid consent at the time of recruitment, at least if one assumes that subjects must know the purpose of the research to consent to it.

It is possible to inform prospective sources/subjects that their tissue will be banked for future, unspecified research, but this is increasingly difficult. *Will the samples be used for research in cancer genetics or behavioral genetics? Will results be correlated by race or ethnicity? Will the results be used to develop proprietary products?* These are all questions that subjects increasingly want answered before they consent to participate in research.

Indeed, the secondary use of tissues or the information they contain is emerging as one of the greatest challenges of genetic research. Researchers need to consider how much information is adequate at the outset to permit subsequent analysis to be conducted without additional consent.

The growth of bioinformatics, or computational genomics, makes it clear that in the near future the concern will not be so much with stored biological samples but with digitized samples—electronic data that can be stored, transmitted, and analyzed with new ease and power.