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Subject: Reviews Requiring Special Consideration
Division: IRB
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IRB Policy 110.6: GENETIC RESEARCH

Policy

Human genetic research involves the study of inherited human traits through genetic testing and/or the collection of genetic information. The FRI IRB requires that special consideration be given during the review of genetic research. Genetic research may create a vulnerable population in that subjects' autonomy may be compromised. The FRI IRB will focus on issues surrounding selection of participants, confidentiality, disclosure of information, storage of data and samples, and participant withdrawal.

Privacy and Confidentiality Issues

Privacy and confidentiality issues are one of the most challenging regulatory aspects of genetic research. Because of the sensitive nature of the information that may be generated from genetic research studies, it is critical that investigators establish a method to secure information in a highly confidential manner. Studies that have the potential to ultimately predict the likelihood of subsequent serious illness could place participants at high risk for psychological and social harm. This type of sensitive information could adversely affect an individual's future insurability and employability as well as have significant impact on his or her psychological well being. Thus, IRB review must be scrupulous in assuring that privacy and confidentiality are always maintained.

As genetic research may yield information of the most private nature, the IRB and potential research subject must understand exactly who will have access to study information and under what circumstances. This issue of disclosing research results to the subject should be explicitly addressed in the protocol and consent. Investigators and IRBs have to weigh the risks and benefits of giving a subject access to research results. Something that may be overlooked is the possibility that the disclosure of unanticipated or incidental information may harm the subject. An additional important consideration is the potential need for genetic counseling. It is impossible to clearly define the situations for which counseling is indicated, but IRBs should consider the potential benefits of genetic counseling to participants in these studies.

Psychological and Social Risks

Genetic research typically presents risks of social and psychological harm to participants. Psychological risk includes the risk of harm from learning genetic information about oneself (*e.g.*, that one is affected by a genetic disorder that has not yet manifested itself). Complicating the communication of genetic information is that often the information is limited to probabilities. Furthermore, the development of genetic data carries with it a margin of error; some information communicated to subjects will, in the end, prove to be wrong. In either event, participants are subjected to the stress of receiving such information.

Social risks include stigmatization, discrimination, labeling, and potential loss of or difficulty in obtaining employment or insurance. Changes in familial relationships are also social ramifications of genetic research.

The IRB's concern is, first, to ensure that these risks will be disclosed to subjects, and, second, to protect subjects against unwarranted disclosures of information.

Use of Tissue or Cell Banks

Genetic studies often involve the use of tissue or cell banks that may involve the long-term storage of biological materials. Because the results of future studies may pose harm to individuals, it is crucial that participants be fully informed about their subsequent knowledge or research results. Whenever possible, genetic test results should be stored in a secure manner. During the informed consent process, it is critical that participants understand both the inherent risk of this type of research and, if it is the case, that they will not be informed of the results of subsequent studies performed on their tissue.

Subjects' Rights to Withdrawal

Ethical research requires that subjects have the right to withdraw from research participation at any point in the study. In genetic research, there is the potential for continuation of individual risk after withdrawal from the study when there is long-term storage of tissue. For this reason, it is important to determine if the research plan provides for the destruction of all stored data and tissue if the subject wants this to be done. If the research plan does not provide for tissue or data destruction, the study may still be ethical as long as participants understand this limitation.

IRB Review

A critical first step in the IRB review process of genetic studies is the determination of the predictive value of the study results. If there is no clear evidence that a particular marker has predictive value, then there is virtually no risk to participants. If there is reasonable scientific evidence that the expression of certain genetic markers within a study accurately predicts for a particular disease or condition, then participants are at risk, and the IRB must know the answers to a detailed list of questions before a determination can be made:

1. Are clear guidelines established for disclosure to participants of interim or inconclusive research results?

2. Will participants be informed of research results at each point in the research?

3. If information is discovered about the participant that may have implications for biologic family members, what are the plans to protect confidentiality?

4. Will limits on such protections be clearly communicated to participants, including obtaining advance consent to such disclosures (e.g., when family members will be warned about health risks)?

5. Will the possible psychological and social risks of genetic research be adequately considered in the consent process?

6. Will appropriate counseling be provided, both as part of the consent process and when communicating test or other research results to participants?

7. Will participants be informed about the possibility of important incidental findings such as paternity, disease, or conditions other than the one(s) that is/are the focus of the study?

8. Will the data be protected from disclosure to third parties, such as employers and insurance companies?

9. Will the participant be told about the potential consequences if a third party becomes aware of the study findings?

10. Will the data be stored in a secure manner?

11. Will the data be coded so as to protect the identity of the subjects?

12. Is a request for a certificate of confidentiality appropriate?

13. Does the PI plan to disclose research findings to subjects' physicians for clinical use? Are such plans appropriate?

14. Will the possibility of such disclosures be discussed in the consent process?

15. Will vulnerable populations be adequately protected?

16. Under what circumstances can a research participant give permission to involve a minor or an adult who lacks decision-making capacity in an aspect of this study?

17. What are the provisions for protecting the confidentiality of tissue samples?

18. What procedures will be used to get the subject's permission to store tissue or data for additional research in the future or for non-research medical practice?

19. What will happen to research data and tissue if a subject elects to withdraw from the study?

20. Are the implications of study withdrawal in terms of destruction or use of established data or tissue clearly explained in the consent document?

21. Do the plans to publish or present data from this study threaten the privacy or confidentiality of participants?

22. If the research may involve family members:

    a) Is the strategy for recruiting family members sensitive to privacy and confidentiality issues?
    b) Will information be obtained from the medical records of family members?
    c) If so, should consent be obtained from the family members to access this information?

Informed Consent

The following information should be included in the consent document:

1. Clearly explain whether the subjects will have access to information obtained as part of this study. Explain what information they will be given whether they ask for it or not.

2. Explain if subjects may learn things about themselves or their family that they do not want to know, or that they may be uncomfortable knowing.

3. Explain if family members may learn about information generated in this study and the potential implications of this knowledge.

4. Explain if participation in this study may compromise the subjects' insurability.

5. Explain if participation in the study may prompt the subject to take actions that may incur unanticipated costs or expose the subject to additional risks. (i.e. genetic counseling may be expensive)

6. Accurately describe the limitations of protection of privacy and confidentiality.

7. Explain what it means to withdraw from this study in terms of the destruction or use of data or tissue related to the study.

8. Include an appropriately detailed explanation of all costs that are likely to be incurred by the subject or family members as a result of participation in the study. Address both the costs of procedures required by the study and costs, like genetic counseling, additional genetic testing, or psychological counseling, that the subject or family may be advised to pay based on study results.

Gene Therapy Research

Gene therapy research (administration of recombinant vectors), which is carried out to develop treatments for genetic diseases at the DNA level, presents obvious and not so obvious questions, including – considerations of delivery methods, target population, and required follow-up. Such protocols will likely require use of external consultants to provide independent guidance to the IRB. If the project involves gene therapy to human subjects for other than clinical purposes, the study must be reviewed and approved by the National Institutes of Health Recombinant DNA Advisory Committee prior to IRB approval. Monitoring must be adequate, and a DSMB will be required. Because there is still little regulatory guidance and relatively few ethical precedents, genetic research will require close scrutiny, and the input of experts in this area.

Genetic Information Nondiscrimination Act (GINA)

GINA is a Federal law that prohibits discrimination in health coverage and employment based on genetic information. GINA defines *genetic information* as information about:

- An individual's genetic tests (including genetic tests done as part of a research study);
- Genetic tests of an individual's family members (defined as dependents and up to and including 4th degree relatives);
- Genetic tests of any fetus of an individual or family member who is a pregnant woman, and genetic tests of any embryo legally held by an individual or family member utilizing assisted reproductive technology;
- The manifestation of a disease or disorder in an individual's family members (family history); or
- Any request for, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education) by an individual or an individual's family members.

Genetic information does not include information about the sex or age of any individual.

Among the risks typically associated with genetic research, investigators, IRBs, and research subject advocates, among others, have identified the potential adverse impact on insurability or employability if genetic information about the subject obtained as part of the research was disclosed to, or sought by, insurers or employers.

Given that GINA has implications regarding the actual or perceived risks of genetic research and an individual's willingness to participate in such research, investigators and IRBs should be aware of the protections provided by GINA as well as the limitations in the law's scope and effect. IRBs should consider the provisions of GINA when assessing whether genetic research satisfies the criteria required for IRB approval of research, particularly whether the risks are minimized and reasonable in relation to anticipated benefits and whether there are adequate provisions in place to protect the privacy of subjects and maintain the confidentiality of their data. GINA is also relevant to informed consent. When investigators develop, and IRBs review, consent processes and documents for genetic research, they should consider whether and how the protections provided by GINA should be reflected in the consent document's description of risks and provisions for assuring the confidentiality of the data.

When making the determinations required under 45 CFR 46.111(a), IRBs need to be cognizant that (1) GINA's provisions prohibiting discrimination in health coverage based on genetic information do not extend to life insurance, disability insurance, or long-term care insurance; and (2) GINA's provisions prohibiting discrimination by employers based on genetic information generally do not apply to employers with fewer than 15 employees.

OHRP recommends that for genetic research undergoing initial or continuing review investigators and IRBs consider whether consent processes and documents should include language regarding the protections provided by GINA, and if so, ensure that such language accurately describes the impact of GINA on the risks and confidentiality protections for such research.

Applicable Regulations and Guidelines

The Belmont Report
45 CFR 46.111
21 CFR 56.111
OHRP IRB Guidebook
OHRP Guidance on the Genetic Information Nondiscrimination Act: Implications for Investigators and Institutional Review Boards (March 24, 2009)