

Ethical Issues in Genetic Research

Outline and Bibliography

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INTRODUCTION

Research in human genetics currently involves the effort to identify the location and function of the roughly 40,000-80,000 genes that make up the human genome, with the aim of developing diagnostic and treatment techniques for a host of hereditary diseases. This research involves unusual risks for subjects due to the close link between biological heritage and individual identity, and the fact that genetic information obtained from one individual usually has implications for family members. How this information is or may be used by social institutions such as employers and insurers also poses risks for prospective subjects. However, in many cases the risks are unknown or there are no clear guidelines for how to address them. This outline provides an overview of the ethical issues germane to human subjects protection, beginning with some general concerns: informed consent, confidentiality, ownership of genetic information, and future use of genetic samples. The second part identifies some of the ethical concerns specific to four general categories of genetic research: pedigree studies (that explore patterns of inheritance); positional cloning studies (that identify the location of specific genes); DNA diagnostic studies (that determine the presence of specific mutations) and gene therapy research (that seeks to develop disease treatments). The third part outlines some additional concerns in genetic research having to do with research on children and other incompetent subjects, as well as multiplex testing and epidemiological studies.

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Special concerns with genetic research

Family/cultural issues

Genetic information is often considered "special," or different from other kinds of medical information because of its close association with individual identity, which is due in part to the common assumption that genes are determinative of human health and behavior. This assumption creates opportunities for social stigma and discrimination by employers and insurers. In addition, the fact that genetic information about an individual reveals information about relatives creates new and complex ethical issues, particularly regarding privacy and confidentiality (MacKay, 1993)

Risk interpretation

Genetic information is in most cases probabilistic, providing information about risks, not definitive diagnoses. The interpretation of genetic risks is a complex process, influenced by numerous factors. For this reason, it is generally agreed that when research involves disclosure of genetic information to subjects, such disclosure should always be accompanied by genetic counseling. (*Assessing Genetic Risks*, Ch. 4; NSGC and ASCO Position papers, Holtzman and Watson, 1997).

1. ETHICAL CONDUCT OF GENETIC RESEARCH

1.1. Informed consent

Informed consent is required in all research in which genetic data may be directly or indirectly linked to subjects. Depending on the protocol, the following topics should be considered for inclusion in the consent process and forms. (Some of these topics receive more discussion later in this outline.)

1.1.1. Content of consent process

(*IRB Guidebook*; MacKay, 1993; Reilly et al., 1997; *ASHG Report*):

- What is being studied and why
- Why the particular individual or population is being asked to participate
- Who is doing the research, including any commercial partners
- Procedures involved in participation
- Psychosocial risks: issues of identity, stigma, family stress, guilt, the burden of knowledge, the possibility of unanticipated findings (i.e. false paternity, etc.)
- Benefits of participation: may provide reassurance, create opportunities for preventive interventions or medical treatment, or help others in the future
- Interests of family members: right not to know information about oneself; (arguable) duty of physicians to warn individuals at risk; confidentiality issues
- Confidentiality: how to maintain; who has access to genetic information; limits of confidentiality
- Risks of discrimination from insurers/employers; limits of legal protection
- Circumstances for collection, storage, and future use of genetic samples
- Whether and when research results will be disclosed
- Right of subjects to withdraw themselves from study without penalty

- Costs of participation

1.1.2. Layered consent (*NBAC Report*, p. 66.)

An option for protocols that involve a variety of procedures, including requesting permission for collecting and storing genetic samples for future research and consent to additional studies. "Layered consent" refers to the option of permitting research subjects to consent to some parts of a protocol and not others.

1.1.3. Process

Impediments to informed consent process: (Geller et al., 1997)

- Imbalance of power between provider and subject
- Subject's lack of experience with genetics and probabilistic information,
- Reluctance on the part of some subjects to take an active role in decision-making due to trust in the health care professional/researcher
- Coercion by family members
- Health care professionals/researchers may also suffer from poor communication skills, an inadequate grasp of the issues involved, and a tendency to be directive

1.2. Privacy and confidentiality (Reilly et al., 1997; MacKay, 1993)

Investigators must be clear about what how genetic samples or data will be identified, and what kinds of information will be revealed to whom, at what point in the course of research.

1.2.1. Existing Legal Protection

- Certificates of confidentiality (Earley and Strong, 1995)
Certificates of confidentiality may be useful in preventing discrimination based on information gained in research. A Certificate of Confidentiality protects a researcher from being required to reveal information about research subjects in any legal proceeding.
- Genetic Privacy Legislation (White, 1999)
Although federal and state interest in genetic privacy legislation has increased in recent years, existing legislation has not been tested in the courts and is likely to provide a minimum of protection for a narrow segment of the population.

1.3. Access and ownership of genetic information (Reilly et al., 1997)

Precedent legal case, *Moore v. Regents of the University of California*, ruled that the plaintiff did not have a property interest in commercial products developed from tissue removed during a surgery. This ruling also stated that the informed consent process should include discussion of whether subjects have property rights to commercial products developed from their genetic material.

1.4. Collection, storage, and future use (*IRB Guidebook*; Clayton et al., 1995; *NBAC Report*)

Genetic samples may consist of tissue, blood, saliva, or other body fluids, which may be stored indefinitely and used for research in multiple studies. If this is anticipated, the following information should be included in the consent process and form:

- Is the sample anonymous, or will it have an identifier that could link it to the source? If anonymous, the risks to subjects are minimal and consent for the use of the samples may not be required.
- If samples are coded or identified in a way that can link them to subjects, consent is required. Consent for future use should be separate from consent for clinical procedures (may use layered consent or opting out option).
- Any limits to the types of research for which samples may be used
- Confidentiality and risks of disclosure to third parties; certificates of confidentiality
- Whether, and under what circumstances research results may be disclosed to subjects
- Subjects' right—or lack of it—to profits from commercial products derived from their genetic material
- Use of samples from subjects who have died (DeRenzo et al., 1997)
- Use of tissue samples from children
- Subjects' right to withdraw their samples from future research, and anonymizing of existing data

2. TYPES OF STUDIES:

2.1. Pedigree Studies

These studies use pedigree analysis to study the incidence and progression of a disease in families. A pedigree is a diagram of a family indicating the structure of relationships between a proband (the clinically affected or at-risk individual through whom attention is first drawn to a family pedigree) and those relatives potentially affected with the disease in question. A pedigree may reveal unexpected information about family members, for example, that some individuals may be at risk for diseases of which they had previously been unaware.

2.1.1. Recruitment of subjects (IRB Guidebook, 1993)

Because subject populations in pedigree studies are related, there is potential for individuals to feel pressured to participate from family members. Recruitment through the proband, investigators, or third parties raises issues with coercion and confidentiality.

2.1.2. Risks

- Unexpected information
- Psychological and social stress—for proband and relatives
- Possibility of error
- Survivor guilt
- Social stigmatization
- Discrimination by insurers or employers

2.1.3. Benefits

- Reassurance that individual is risk-free
- Opportunities to plan ahead, if disease risk is discovered
- Satisfaction of participating in research to help others

2.1.4. Privacy and confidentiality (Botkin et al., 1998; *IRB Guidebook*)

- Individuals may not wish to share information about themselves with other family members.
- Family members are not entitled to information about their relatives without that individual's consent.
- Individuals may choose not to receive information about themselves.
- Subjects should know what information will be revealed about themselves and others as a result of participation. This is especially important when pedigrees may be published.
- Publications should also take care when publishing pedigrees to protect the confidentiality of subjects.

2.2. Gene localization and identification studies (Glass et al., 1996; *IRB Guidebook*)

These studies involve identifying the location and function of disease bearing genes. They may involve pedigree studies or studies of specific at-risk populations. Issues of confidentiality are critical, as are concern for psychosocial burdens. Additional issues may include:

2.2.1. Access to data (*MacKay, 1993*)

- Subject's right "not to know"
- Investigators' duty to warn subjects of genetic risks
- Whether family members have a right to genetic data
- How to handle incidental findings—such as false paternity
- Secondary use of research data

2.2.2. Interim findings (*IRB Guidebook; NBAC Report*)

- When does data constitute "information" that should be revealed to subjects?
- Do subjects have a right to research results? If so, when?
- What benefits and harms may arise from disclosure?
- Are there liability issues for investigators involving failure to disclose research results?

2.3. Diagnostic and screening studies (Glass et al., 1997; *IRB Guidebook*)

2.3.1. Types of genetic screening or testing

- Newborn screening
- Carrier screening
- Prenatal testing
- Disease susceptibility testing

2.3.2. Need for risk analysis and genetic counseling prior to consent and when results are communicated to subjects (*NSGC Report, 1997; ASCO Statement, 1996; Geller et al., 1997*)

- Informed consent
- Risk of misunderstanding risks

- Risk of misunderstanding test results
- Genetic counseling

2.3.4. *Significance of test results* (Holtzman and Watson, 1997; *Genethics*, 1995)

- Clinical validity and utility
- Difficulty of assessing predictive power of tests
- Laboratory quality issues
- Proficiency testing issues
- Provision for genetic counseling

2.3.5. *Areas needing further research* (Wilfond et al., 1997)

- Informed consent—effectiveness of counseling
- Privacy and confidentiality
- Familial issues—importance of confidentiality vs. access to information
- Psychosocial and medical consequences of testing
- Issues in testing children
- Issues in reproduction
- Health policy

2.4. Gene Therapy (*IRB Guidebook*)

The following concerns in evaluating research have been identified by the Recombinant DNA Advisory Committee (RAC) at NIH.

2.4.1. *Description of study*

- How a disease is selected for study
- Therapeutic goal of study
- Available alternative therapies
- How DNA will be transferred, and where

2.4.2. *Research design, risks, and benefits*

- Description of methods and materials
- Pre-clinical studies, including evidence of safety and effectiveness
- Treatment method and means of monitoring effects
- Medical risks to subject
- Qualifications of investigator and clinical facilities

2.4.3. *Means of subject selection*

- Eligibility criteria
- Numbers of subjects
- Recruitment procedures

2.4.4. *Informed consent—additional issues*

- Potential adverse medical effects
- Cost issues

- Possible media attention
- Irreversibility of treatment

3. ADDITIONAL ISSUES IN GENETIC RESEARCH

3.1. Testing of Children (ASHG/ACMG Report on Genetic Testing in Children, 1995; *IRB Guidebook*)

Family members may wish their children to participate in research, which could have both medical and psychological benefits as well as result in life-long consequences for the child in terms of social stigma or institutional discrimination. Although arguments may be made for and against genetic testing of children, there is a general consensus among professional geneticists that unless there is direct medical or psychological benefit to be derived from participation, children should not be enrolled in genetic studies that could reveal information about their genetic risks. Testing should be deferred until the child is of legal age to decide independently whether or not to be tested.

3.1.1. Risks and benefits of genetic testing

- Burden of knowledge
- Social stigma
- Discrimination
- Diminished parental expectations
- Medical benefit, when possible
- Relief from anxiety

3.1.2. Family involvement in decision-making

- Consent vs. assent
- Mature minors
- Provider as child advocate

3.2. Behavioral Studies (*IRB Guidebook*, 1993)

Subjects of behavioral studies may suffer from dementia or other forms of mental illness which creates difficulties in obtaining consent to participate. For these subjects, federal regulations provide for a "legally authorized representative" to consent to participation. Consent should be based in part on whether participation would offer any medical benefit to subjects. When possible, subjects' assent should be sought, and dissent honored.

3.3. Multiplex testing (*AMA Council on Ethical and Judicial Affairs*, 1998)

Multiplex testing involves testing for multiple conditions simultaneously. It is not yet widely available. Practical and ethical issues of concern include the following:

- Sensitivity, specificity, and predictive value of each test will vary
- Need for genetic counseling for each test included
- Risk of misunderstanding significance of test results
- Shortage of qualified genetics professionals for counseling

- Population targeting and discrimination potential

3.4. Epidemiology (Holtzman and Andrews, 1997; Foster et al., 1998, Weiss et al., 1997) Genetic epidemiology embraces the concerns discussed above with respect to recruitment, disclosure of results, confidentiality, etc. but the focus is not on individuals, but groups. Often this work involves collective risks for the members of the group, primarily of social stigma or discrimination, in which case some form of community consent may be necessary.

Whether such an approach is effective in protecting subjects is debatable. Arguably, no subgroup can represent the interests of the group as a whole, and research of this sort suggests there is a biological basis for the differences between social groups, which may lead to discrimination. (Jeungst, 1998)

3.4.1. Process of group consent

- Formation of a community review board with legitimate representatives
- Dialogue between researchers and community
- Negotiation and consensus
- Recruitment of subjects
- Standard informed consent

3.4.2. Concerns to be addressed in community dialogue

- Cultural concerns
- Property rights
- Banking of genetic samples and future use
- Publication reviewing
- Option of population remaining anonymous

BIBLIOGRAPHY

American Society of Clinical Oncology (1996) Statement on genetic testing for cancer susceptibility. *Journal of Clinical Oncology* 14(5):1730-36. (ASCO Statement)
Summarizes the clinical and ethical issues for health professionals preparing to offer genetic testing for cancer susceptibility.

AMA Council on Ethical and Judicial Affairs (1998) Multiplex genetic testing. *Hastings Center Report* July-August: 15-21.
This is the only paper of which I am aware that outlines the ethical issues and practical problems in multiplex testing.

ASHG Report (1996) Statement on informed consent for genetic research. *Am J. Hum. Gen.* 59:471-474. (ASHG Report)
A short and very general account of the ethical issues in genetic research.

ASHG/ACMG Report (1995) Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *Am J. Hum. Gen.* 57:1233-1241. (ASHG/ACMG Report)
An excellent job of outlining the ethical issues involving children in genetic research.

Botkin, JR, McMahon WM, Smith KR, Nash JE (1998) Privacy and confidentiality in the publication of pedigrees. *JAMA* 279(22):1808-1812.

A summary of a study of how journals handle publication of genetic pedigrees, concluding with some recommendations.

Biesecker LG, DeRenzo EG, Grady C, MacKay CR (1995) Genethics: Commentaries *Cambridge Quarterly of Healthcare Ethics* 4:387-400. (*Genethics*)

These commentaries offer some of the best descriptions I have seen of the difficulties of translating genetic research into clinical practice.

Clayton EW, Steinberg KK, Khoury MJ et al. (1995) Informed consent for genetic research on stored tissue samples. *JAMA* 274(22):1786-1792.

An excellent analysis of the issues, preferable to the *NBAC Report* in some ways, shorter too.

DeRenzo EG, Biesecker LG, Meltzer N (1997) Genetics and the dead: Implications for genetics research with samples from deceased persons. *Am. J. Med. Gen.* 69:332-334.

This is the only article I have seen on this subject—it takes a case-based approach.

Earley CL, Strong LC (1995) Certificates of confidentiality: A valuable tool for protecting genetic data. *Am J. Hum. Gen.* 57:727-731.

This is the only article I know of on this subject—which deserves a lot more attention than it has received to date.

Foster MW, Bernsten D, Carter TH (1998) A model agreement for genetic research in socially identifiable populations. *Am J. Hum. Gen.* 63:696-702.

A proposal for a process and recommended content for group consent.

Geller G, Botkin JR, Green MJ, et al. (1997) Genetic testing for susceptibility to adult-onset cancer: the process and content of informed consent. *JAMA* 277(18):1467-1474.

A summary of the purpose, content, and pitfalls of obtaining informed consent in genetic research on late-onset disorders..

Glass KC, Weijer C, Lemmons T, Palmour RM, and Shapiro, SH (1996) Structuring the review of human genetics protocols: Gene localization and identification studies. *IRB* 18(4):1-9.

Summarizes concerns for IRBs reviewing this type of genetic protocol.

Glass KC, Weijer C, Lemmons T, Palmour RM, and Shapiro, SH (1997) Structuring the review of human genetics protocols: Diagnostic and screening studies. *IRB* 19(4):1-13.

Summarizes concerns for IRBs reviewing this type of genetic protocol.

Holtzman NA and Andrews LB (1997) Ethical and legal issues in genetic epidemiology. *Epidemiologic Reviews* 19(1):163-174.

One of relatively few review articles that summarizes the ethics of genetic research from an epidemiological perspective.

Holtzman, NA and Watson MS (1997) *Promoting safe and effective genetic testing in the United States: Principles and Recommendations*. Bethesda, MD. National Institutes of Health.

A description of the current regulations that govern the transition from research to clinical use, detailing the areas in which regulation is currently ambiguous or absent and the risks those lapses pose to public safety. Excellent but long.

Institute of Medicine (1994) *Assessing genetic Risks: Implications for Health and Social Policy*. Washington D.C.: National Academy Press. Chapter 4, Genetic Counseling.

This excellent, though slightly old book covers the spectrum of issues in genetic research and clinical practice. The chapter on genetic counseling includes a good summary of the difficulties of communicating and interpreting risks.

Jeungst ET (1998) Group identity and human diversity: Keeping biology straight from culture. *Am. J. Hum. Gen.* 63:673-677.

Jeungst argues that group consent is morally problematic, both because no sub-group can possibly represent the concerns of an entire population, and efforts to study genetics based on the social and political identity of a particular group may reinforce biologically sanctioned discrimination.

MacKay CM (1993) Discussion points to consider in research related to the human genome. *Human Gene Therapy* 4: 477-495.

Taking the perspective of IRB reviewers, in question and response form, this lengthy and detailed article examines the range of psychosocial, logistical, familial, and ethical concerns surrounding participation in genetic research.

National Bioethics Advisory Commission (1999) Research involving human biological materials: Ethical issues and policy guidance. Vol. 1. (*NABC Report*)

An examination of the ethical issues in collection, storage, and future use of biological samples. The issues are summarized pp. i-viii.

NIH Office of Protection from Research Risks (1993) *Protecting Human Research Subjects: Institutional review Board Guidebook*, Chapter 5H. "Human Genetic Research." U.S. Government Printing Office, Washington, D.C. (*IRB Guidebook*)

An excellent chapter containing information on different types of genetic testing, the regulations governing research and development of genetic tests, current safety and quality control mechanisms for new tests, the role of providers in ensuring that tests are used appropriately, and genetic testing for rare diseases.

National Society of Genetic Counselors (1997) Predisposition genetic testing for late-onset disorders in adults. *JAMA* 278(15):1217-1220. (*NSGC Report*)

Summarizes the issues genetic counselors should cover in pre-and post-test counseling in view of cancer testing.

Reilly PR, Boshar MF, Holtzman SH (1997) Ethical issues in genetic research: Disclosure and informed consent. *Nature genetics* 15 (January):16-20.

A short and very good article on these issues, if not as complete as some.

Weiss KM et al. (1997) Proposed model ethical protocol for collecting DNA samples. *Houston Law Review* 33(5):1431-1473.

A lengthy article proposing ethical guidelines for obtaining group consent.

White MT (1999) Underlying ambiguities in genetic privacy legislation. *Genetic testing* 3(4):341-345.

For those concerned about the risks of genetic discrimination and the protections provided by existing legislation, this article explains the limitations of those protections.

Wilfond BS, Rotherberg KH, Thomson EJ, Lerman C (1997) Cancer genetic susceptibility testing: Ethical and policy implications for future research and clinical practice. *Journal of Law, Medicine, and Ethics* 25:243-251.

Identifies many questions calling for further research in the clinical use of genetic testing.