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INTRODUCTION

Human genetic research involves the study of inherited human traits. Much of this research is aimed at identifying DNA mutations that can help cause specific health problems, developing methods of identifying those mutations in patients, and improving the interventions available to help patients address those problems. The identification of genetic mutations enables clinicians to predict the likelihood that persons will develop a given health problem in the future or pass on a health risk to their children. For many disorders, however, there will be a considerable time lag between the ability to determine the likelihood of disease and the ability to treat the disease.

The ethical issues raised by this scientific trend primarily concern the management of psychosocially potent personal genetic information. For researchers and HRACs, the major challenge in addressing these issues is the fact that genetic studies typically involve families; the research subjects involved in genetic studies are usually related to each other. As a result, research findings about individual subjects can have direct implications for other subjects, information flow between subjects is increased, and participation decisions are not made entirely independently. A second set of ethical issues emerges in cases in which the results of these studies are used to develop therapeutic interventions at the genetic level. Such concerns involve the special safety precautions and subject selection considerations required for gene therapy research.

Some of the areas described in this Section present issues for which no clear guidance can be given at this point, either because not enough is known about the risks presented by the research, or because no consensus on the appropriate resolution of the problem yet exists. Because of the uncertainties involved in genetic research, HRACs may not, for some time, be able to set clear standards for investigators. What HRACs can do, however, is ensure that investigators have thought through the factors that may affect the rights and welfare of human subjects (*e.g.*, risks to privacy, psychological risks, employment and insurance risks). HRACs should require investigators to explain their thoughts on these problems, how they plan to handle them, and how they plan to communicate them to subjects.

DEFINITIONS

Lod Score: An expression of the probability that a gene and a marker are linked.

Genotype: The genetic constitution of an individual.

Phenotype: The physical manifestation of a gene function.

Proband: The person whose case serves as the stimulus for the study of other members of the family to identify the possible genetic factors involved in a given disease, condition, or characteristic.

HRAC CONSIDERATIONS

It may be useful to think of genetic research as being carried out on a continuum comprising four stages:

1. Pedigree studies (to discover the pattern of inheritance of a disease and to catalog the range of symptoms involved);
2. Positional cloning studies (to localize and identify specific genes);
3. DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); and
4. Gene therapy research (to develop treatments for genetic disease at the DNA level.

Unlike the risks presented by many biomedical research protocols considered by HRACs, the primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful HRAC review and discussion. The fact that genetic studies are often limited to the collection of family history information and blood drawing should not, therefore, automatically classify them as "minimal risk" studies qualifying for expedited HRAC review.

Pedigree Studies. When investigators attempt to document and study the natural history of an inherited disease, condition, or characteristic, they do so by identifying individual members of families presenting the disease, condition, or characteristic and obtaining information about them and the other members of their family. The result is a pedigree analysis, which, in addition to tracing the natural history of a disease and documenting the range of symptoms involved, may also reveal information about family members that individual members may not have known about previously (*e.g.*, the existence of previously unknown relatives or the presence of stigmatizing diseases, such as mental illness). It may also reveal information about the likelihood that individual members of the family either are carriers of genetic defects or will be affected by the disease.

Subject Recruitment and Retention. The familial nature of the research cohorts involved in pedigree studies can pose challenges for ensuring that recruitment procedures are free of elements that unduly influence decisions to participate. The very nature of the research exerts pressure on family members to take part, because the more complete the pedigree, the more reliable the resulting information will be. For example, revealing who else in the family has agreed to participate may act as an undue influence on an individual's decision, as may recruiting individuals in the presence of other family members. (Both would also constitute a breach of confidentiality. The problem of confidentiality will be dealt with later in this Section.)

Recruitment plans, some of which are described here, can attempt to address these problems; each approach has its own strengths and weaknesses. One strategy is to use the proband as the point of contact for recruiting. This approach insulates families from pressure by the investigator, but presents the risk that the proband may be personally interested in the research findings and exert undue pressure on relatives to enroll in the study. Furthermore, the proband may not want to act as a recruiter for fear that other family members will then know that he or she is affected by the disease. Another approach is direct recruitment by the investigator through letters or telephone calls to individuals whose identity is supplied by the proband. Direct recruitment by the investigator may, however, be seen as an invasion of privacy by family members. A third approach is to recruit participants through support groups or lay organizations. Adopting this strategy requires investigator and HRAC confidence that these organizations will be as scrupulous in their own efforts to protect subjects as the investigator would be. A fourth possibility is to contact individuals through their personal physicians. Prospective subjects contacted by their physician may, however, feel that their health care will be compromised if they do not agree to participate. In the end, the HRAC must ensure that the recruitment plan minimizes the possibility of coercion or undue influence (38CFR16.116).

In contrast to inappropriate pressure placed on prospective participants to join the study is the possibility that a subject may agree to participate out of a misguided effort to obtain therapy. The purposes of the research and how subjects will or will not benefit by participation must be clearly explained. (*See* discussion below on informed consent).

Investigators and HRACs need to consider each of these concerns in arriving at a recruitment strategy that protects these various interests.

Defining Risks and Benefits. Potential risks and benefits should be discussed thoroughly with prospective subjects. In genetic research, the primary risks, outside of gene therapy, are psychological and social (referred to generally as "psychosocial") rather than physical. HRACs should review genetic research with such risks in mind.

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. For example, researchers involved in developing presymptomatic tests for Huntington Disease (HD) have been concerned that the emotional impact of learning the results may lead some subjects to attempt suicide. They have therefore asked whether prospective participants should be screened for emotional stability prior to acceptance into a research protocol.

Note that these same disclosures of information can also be beneficial. One of the primary benefits of participation in genetic research is that the receipt of genetic information, however imperfect, can reduce uncertainty about whether participants will likely develop a disease that runs in their family (and possibly whether they have passed the gene along to their children). Where subjects learn that they will likely develop or pass along the disease, they might better plan for the future.

To minimize the psychological harms presented by pedigree research, HRACs should make sure that investigators will provide for adequate counseling to subjects on the meaning of the genetic information they receive. Genetic counseling is not a simple matter and must be done by persons qualified and experienced in communicating the meaning of genetic information to persons participating in genetic research or persons who seek genetic testing.

Social risks include stigmatization, discrimination, labelling, and potential loss of or difficulty in obtaining employment or insurance. Changes in familial relationships are also social ramifications of genetic research. For example, an employer who knew that an employee had an 80 percent chance of developing HD in her 40s might deny her promotion opportunities on the calculation that their investment in training would be better spent on someone without this known likelihood. Of course, the company may be acting irrationally (the other candidate might be hit by a car the next day, or have some totally unknown predisposition to debilitating disease), but the risk for our subject of developing HD is real, nonetheless. One problem with allowing third-parties access to genetic information is the likelihood that information, poorly understood, will be misused. Likewise, an insurer with access to genetic information may be likely to deny coverage to applicants when risk of disease is in an unfavorable balance. Insuring against uncertain risks is what insurance companies do; when the likelihood of disease becomes more certain, they may refuse to accept the applicant's "bet."

Privacy and Confidentiality Protections. Special privacy and confidentiality concerns arise in genetic family studies because of the special relationship between the participants. HRACs should keep in mind that within families, each person is an individual who deserves to have information about him- or herself kept confidential. Family members are not entitled to each other's diagnoses. Before revealing medical or personal information about individuals to other family members, investigators must obtain the consent of the individual.

Another problem that arises in genetic family studies that is also common in other areas of research involving interviews with subjects is the provision by a subject of information about another person. In pedigree studies, for example, the proband or other family member is usually asked to provide information about other members of the family. The ethical question presented by this practice is whether that information can become part of the study without the consent of the person about whom the data pertains. While no consensus on this issue has yet been reached, HRACs may consider collection of data in this manner acceptable, depending on the nature of the risks and sensitivities involved. It may be helpful, for example, to draw a distinction between information about others provided by a subject that is also available to the investigator through public sources (*e.g.*, family names and addresses) and other personal information that is not available through public sources (*e.g.*, information about medical conditions or adoptions).

HRACs should require investigators to establish ahead of time what information will be revealed to whom and under what circumstances, and to communicate these conditions to subjects in clear language. For example, if the pedigree is revealed to the study participants, family members will learn not only about themselves but about each other. The possibility that family members who did not participate might also learn of the pedigree data should not be overlooked. Subjects should know and agree ahead of time to what they might learn (and what they will not learn), both about themselves and others, and what others might learn about them. One approach would be never to reveal the pedigree to participating subjects. Many investigators record their pedigrees using code numbers rather than names. HRACs should note, however, that when a study involves a rare disease or a "known" family, the substitution of numbers for names does not eliminate the problem.

Even where the protocol calls for providing certain information to subjects, participants in genetic studies should be given the option of not receiving genetic information about themselves or others that they do not wish to receive. In genetic research, the potential for psychosocial harm accruing to persons who express a desire not to receive information gained through the study and the uncertainties surrounding the disease-predictive value of the early phases of contemporary genetic research is felt to outweigh benefits of required disclosure. (A possible exception involving circumstances where early treatment of genetically-linked disease improves prognoses is discussed in the section on identifying and deciphering genes, below.)

Data must be stored in such a manner that does not directly identify individuals. In general, except where directly authorized by individual subjects, data may not be released to anyone other than the subject. An exception to requiring explicit authorization for the release of data may be secondary research use of the data, where the data are not especially sensitive and where confidentiality can be assured. HRACs should exercise their discretion in reviewing protocols that call for the secondary use of genetic data. Furthermore, when reviewing a consent documents, HRACs should note agreements made by investigators not to release information without the express consent of subjects. Subsequent requests for access to the data are subject to agreements made in the consent process. For studies involving socially sensitive traits or conditions, investigators might also consider requesting a certificate of confidentiality (see HRAC policy 13.1).

Informed Consent. The information presented to subjects in the informed consent process should be as specific as possible. Subjects should be told both the known risks, as well as the uncertainty surrounding the risks of participation. Among the uncertainties is the likelihood that useful information will result from the study (it may not). Prospective participants often come into genetic studies with unrealistic expectations of how they will benefit from the study, and without an appreciation of low-probability risks that are not well-understood by anyone. To the extent possible, unrealistic expectations should be dispelled in the informed consent process.

The provision of relevant information should take place as a thoughtful discussion with prospective subjects. Through this process, subjects should be informed:

1. About the kind of information they will be provided (*e.g.*, that they will receive only information the investigator feels is significant and reliable, or that no genetic information will be provided) and at what point in the study they will receive that information;

2. That they may find out things about themselves or their family that they did not really want to know, or that they may be uncomfortable knowing;

3. That information about themselves may be learned by others in their family

4. Whether information they learn or information generated about them during the study may compromise their insurability;

5. That actions they may take as a result of their participation may expose them to risks (*e.g.*, submitting insurance claim forms for reimbursement for costs of genetic counseling or procedures whose costs are not covered by the protocol);

6. About what assurances can be given to protect confidentiality and what lack of assurance can be given;

7. About the rights they retain and the rights they must give up regarding control over what can be done with tissue they donate (*e.g.*, blood samples);

8. What the consequences of withdrawal from the study will be; and

9. Of any costs associated with participation (including, for example, the cost of genetic and/or psychological counseling, if those costs will not be covered by the investigator or the institution).

Information should be given to subjects in clear language, suitable to their age, cultural background, and physical and mental capabilities. Accommodations should be made for persons with learning disabilities (as distinguished from persons who suffer diminished mental capacity). The consent process should take place in the subject's native language, through an interpreter, if necessary; consent documents should be translated into the subject's native language. The HRAC should satisfy itself that great care will be taken by the investigator to ensure that prospective subjects fully understand the risks and benefits involved in participation.

Disposition of DNA Samples. When tissue samples are to be collected for later DNA analysis, numerous issues must be addressed by investigators and HRACs. Primary among them are through what mechanism samples should be collected, who can have access to the samples and for what purposes, who owns the DNA, and how incorrect genetic information (due, for example, to faulty laboratory analysis) can be corrected. The American Society of Human Genetics' Ad Hoc Committee on DNA Technology has published a set of Points to Consider on DNA banking and DNA analysis (1987), with which HRACs may wish to acquaint themselves. While not all of the Society's recommendations may be directly applicable to the HRAC's concerns, it is worth noting the importance the Society places on appropriate counseling and limited access to familial genotypes.

The genetic information (and tissue samples, where applicable) collected under a research protocol are of continuing importance to the families involved in the research. An important question for HRACs to consider is what will happen to the data (and samples) when funding for the research ends. Particular attention should be paid to protecting the confidentiality of the data and obtaining consent from the participants for any use of the data (and samples) that is not strictly within the original uses to which the participants agreed.

Withdrawal from Participation. Attention should be paid to subjects' rights when they decide to withdraw from participation in the study. The federal regulations clearly require that subjects be free to withdraw from participation without penalty or loss of benefits to which they are otherwise entitled [38 cfr 16.116(a)(8)]. What the regulations do not address, however, is how to treat data or tissue samples obtained from subjects who subsequently withdraw from the study. A similar question was addressed by the California Supreme Court in the Moore case [*John Moore v. The Regents of the University of California* (1990)]. While *Moore* constitutes binding legal authority only in California and has not, as of this writing, been adopted in other jurisdictions, the court's findings may be helpful for exploring possible approaches to handling the treatment of data and tissue samples when a subject withdraws from a genetic study.

In *Moore*, the California Supreme Court held that cell lines established from a donated sample are not the property of the person who donated the sample. Extrapolating to the broader context of genetic research generally, the underlying principle would be that withdrawal releases the subject from providing further information or tissue samples, and perhaps requires the removal of the subject's identity from all research records, but does not require the investigator to eliminate the resulting data from the study or to destroy the cell line.

In pedigree studies, for example, investigators may respond to a request to withdraw by removing all information about that person and his or her spouse and children from the pedigree, but it is not clear that removal of the information is required by the human subjects regulations or any other legal principle.

Secondary Use of Tissue Samples. Where a new study proposes to use samples collected for a previously conducted study, HRACs should consider whether the consent given for the earlier study also applies to the new study. Where the purposes of the new study diverge significantly from the purposes of the original protocol, and where the new study depends on the familial identifiability of the samples, new consent should be obtained.

Vulnerable Populations. HRACs should ensure that the investigator conduct the research with sensitivity to the specific mental and physical manifestations of the particular disorders being investigated. Depending on the disease, and, therefore, the likely presenting population, investigators should be prepared to communicate effectively and with sensitivity with persons who have physical limitations (*e.g.*, deafness or blindness), learning disabilities, cognitive impairments, or any other life circumstance that may affect their participation (*e.g.*, severe pain).

The nature of genetic research raises some special concerns when the research will involve children, physically or cognitively impaired persons, older persons, or any subject population likely to have special needs. Not only must the HRAC ensure that their participation is fully voluntary and informed, HRACs must also be sure to evaluate the risks and benefits of the research as they apply to these special populations. The risk of participation for an adult differs from that of children; persons who suffer from diminished mental capacities may be subject to different risks than persons who do not. If children will be involved in the research, HRACs should seriously consider consulting with experts in child development and others knowledgeable about risks to children and families. Similarly, if physically or cognitively impaired persons will be involved in the research, HRACs should consider consulting with experts who can advise them on the special concerns their participation raises. Where applicable, 45 CFR 46 Subparts B, C, and D (pertaining to women, fetuses, prisoners, and children) must be followed. The involvement of children in genetic research raises many concerns, including pressure brought by family members on the child to participate and the potential for harm that may result from disclosure of genetic or incidental information. Even seemingly harmless research may actually present serious risks of harm to children. For example, interviewing children for genetic research on psychological disorders, such as schizophrenia or depression, or on alcoholism may inadvertently convey information about family members (the child may well wonder why he or she is being asked about alcoholism in the family) or cause self-doubt or stigmatization on the part of the child. Furthermore, disclosures of data to third-parties may result in children being labelled or stigmatized as, for example, potential alcohol abusers. HRACs must look carefully at both the questions that will be asked of children and the information that will be directly conveyed to them to determine whether the research involves more than minimal risk. The advisability of including children in studies of untreatable, fatal disorders such as HD has been strongly questioned [MacKay (1984), p. 3].

HRACs should also consider the mental capacities of participants in genetic research. In some diseases, such as Alzheimer Disease, patients will suffer loss of mental capacity over a period of time. In addition, it is possible that a family member might be comatose or legally incompetent for reasons unrelated to the disease under study. Special attention should be paid to methods of ensuring voluntary consent by the subject or the subject's legally authorized representative [38 cfr 16.102(c), 38 cfr 16.116]. Under the regulations, a "legally authorized representative" is defined as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research" [38CFR16.102(c)]. HRACs should pay particular attention to state and local laws relating to persons authorized to give permission for participation in research on behalf of prospective subjects, noting that such "proxy" consent to participation in research that does not involve a direct medical benefit may differ from consent to receive medical treatment. Where possible, the subject's assent should be sought; his or her dissent should be honored.

In appropriate circumstances the HRAC might consider granting waivers of consent or alteration of the consent process. [*See* MacKay (1984), pp. 3-4, and Levine (1986).] The federal regulations allow for waivers or alterations in the consent process where the HRAC finds that: (1) the research involves no more than minimal risk; (2) the waiver or alteration will not adversely affect the rights and welfare of the subject; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation [38CFR16.116(d)]. Again, HRACs should carefully consider whether the research qualifies as "minimal risk."

Publication Practices. One final issue involving consent is the publication of research data. The publication of pedigrees can easily result in the identification of study participants. Where a risk of identification exists, participants must consent, in writing, to the release of personal information. Various authors have noted the problem of obtaining consent for the publication of identifying data, and have recommended that consent to the publication be obtained immediately prior to the publication, rather than as part of the consent to treatment or participation in research. [*See, e.g.*, Rost and Cohen (1976) and Murray and Pagon (1984).] It is worth noting, however, that to address this concern, HRACs must also resolve the following questions: Who determines the risk of identification, and on what grounds? Who are defined as participants (is it everyone listed in the pedigree, some of whom have been contacted by investigators, some of whom have had information about them provided by a family member)?

While HRACs must be careful to avoid inappropriate restrictions on investigators' research publications, some evaluation of publication plans is important as part of the HRAC's overall interest in preserving the confidentiality of research subjects. One approach for investigators to use in evaluating their publication plans might be to work in a step-wise fashion: First, is publication of the pedigree essential? If publication of the pedigree or other identifying data (*e.g.*, case histories, photographs, or radiographs) is essential, can some identifying data be omitted without changing the scientific message? (The practice of altering data — such as changing the birth order and gender — is controversial, and no clear professional consensus yet exists as to whether this is an appropriate practice.) Finally, if the pedigree must be published, and if identifying data cannot be omitted in an appropriate manner without changing the scientific message, subjects must give their permission for publication of data that may reveal their identity.
Another concern about publication is the potential for publicity of the research results, and the exposure of participants to such publicity. Consent by individuals to such publicity does not resolve the question. Because genetic research involves families, the agreement of one subject to participate in releases of information to the media (including interviews and the like) has significant implications for other members of the family, particularly where the research is of a sensitive nature. HRACs should ensure that the investigator has addressed this possibility.

Expedited Review and Exemption from Review. The expedited review process is available for minimal risk research where the research activity is limited to one of a specified category (as published in the *Federal Register*), including the provision of blood samples [38CFR16.110; *Federal Register* 46 (January 26, 1981): 8392]. In genetic studies that involve a blood draw, the additional psychosocial risks are likely to raise the risk beyond the "minimal risk" level allowable for expedited review. When an expedited review is requested, HRACs should review the question of minimal risk carefully.

With respect to exemption from review, the development of a pedigree through interviews with family members is likely to create identifying information, even where individuals will not be identified. Such research would not, therefore, qualify for exemption from review under the federal regulations [38 cfr 16.101(b)(2)].

Identifying and Deciphering Genes. Research focusing on identifying the specific genetic component of a particular disease, condition, or characteristic relies upon DNA analysis of tissue samples taken from the members of families in which the condition appears. Many issues raised by pedigree analysis are relevant to this stage of research as well: pressure or coercion in recruiting subjects; informing prospective subjects of the possible harms; minimizing psychological harm through counseling and education; protection of confidentiality (which is particularly problematic when family members constitute the subject population); control over the use of DNA tissue samples; and protecting particularly vulnerable persons, all of which were discussed in the previous section. Additional issues include: determining when the data constitute "information;" additional risks presented by this stage of research (*e.g.*, the possibility of incidental findings); and possible conflicts between subjects' rights and investigators' duties with respect to revealing the results of the study to subjects [*i.e.*, telling subjects whether they (or their relatives) carry the defect, and the meaning of their status with respect to the likelihood of suffering from the disease or passing it along to their children].

Access to Data: Interim Findings. An issue that must be resolved prior to beginning any genetic study is who will have access to the data and the stage in the research at which they will have access. The issue of information transfer is vitally important in all genetic research, but particularly in the first three stages of investigation. A crucial question investigators and HRACs must address is whether (and which) interim findings will be communicated to subjects.

Experts disagree about whether interim or inconclusive findings should be communicated to subjects, although most agree that they should not (that only confirmed, reliable findings constitute "information"). Persons who oppose revealing interim findings argue that the harms that could result from revealing preliminary data whose interpretation changes when more precise or reliable data become available are serious, including anxiety or irrational — and possibly harmful — medical interventions. They argue that such harms are avoidable by controlling the flow of information to subjects and limiting communications to those that constitute reliable information. MacKay (1984), writing about the development of genetic tests, argues against revealing interim findings, contending that preliminary results do not yet constitute "information" since "until an initial finding is confirmed, there is no reliable information" to communicate to subjects, and that "even...confirmed findings may have some unforseen limitations" [p. 3]. He argues that subjects should not be given information about their individual test results until the findings have been confirmed through the "development of a reliable, accurate, safe and valid presymptomatic test" [pp. 2-3; *see also* Fost and Farrell (1990)]. Others have argued that all interim results should be shared with subjects, based on the principle of autonomy — that subjects have a right to know what has been learned about them.

These arguments are equally relevant at any of the first three stages of genetic research. HRACs should consider these arguments, weighing the possible harms and benefits. Investigators should determine, prior to initiation of the study, the point at which the data will be considered solid enough to be constitute information that should be provided to subjects. Investigators should further consider coding the data and separating the research records from individuals' medical records, so that neither the investigators nor the subjects may gain access to them [MacKay (1984), p. 3].

Reilly (1980) suggests that HRACs develop general policies governing the disclosure of information to subjects, to help make these determinations. He suggests that at least the following three factors be considered: "(1) the magnitude of the threat posed to the subject, (2) the accuracy with which the data predict that the threat will be realized, and (3) the possibility that action can be taken to avoid or ameliorate the potential injury" [p. 5]. HRACs should ask investigators to define three categories of disclosure: (1) "findings that are of such potential importance to the subject that they *must* be disclosed immediately;" (2) "data that are of importance to subjects..., but about which [the investigator] should exercise judgment about the decision to disclose.... [i]n effect, these are data that trigger a duty to consider the question of disclosure;" and (3) "data that do *not* require special disclosure" [pp. 5, 12].

HRACs should consider whether the investigator's approach appropriately balances the risks and benefits involved in providing access to the data. Subjects should be told, as part of the consent process, whether, when, and what information they will receive. Any disclosures of genetic information should be accompanied by appropriate counseling by trained genetic counselors. However the HRAC resolves this question, investigators should explain to prospective subjects the basis according to which they will decide which data will be disclosed to whom, and when those disclosures will be made.

Access to Data: The Subjects' "Right Not to Know." Subjects generally retain the right not to receive information about the results of a study that reveals their genetic status. A possible exception involves circumstances where early treatment of genetically-linked disease could improve the subject's prognosis. In such circumstances, investigators may have a duty to inform the subject about the existence of the genetic defect and to advise him or her to seek medical advice. [*See, e.g.*, Andrews (1991).] (As of this writing, a legal duty of investigators to inform subjects about the existence of genetic defects has not been firmly established.)

Furthermore, the existence of a genetic defect that is linked to disease may have important implications for family members; can or should the confidentiality of subjects' data be compromised to allow other family members to be warned? The President's Commission (1983), addressed this question with respect to information generated from genetic screening. The Commission's discussion may also be relevant to information obtained as the result of genetic research, at stages that precede genetic screening. The Commission concluded that:

> [the] ethical duty of [providing confidentiality] can be overridden only if several conditions are satisfied: (1) reasonable efforts to elicit voluntary consent to disclosure have failed; (2) there is a high probability both that harm will occur if the information is withheld and that the disclosed information will actually be used to avert harm; (3) the harm that identifiable individuals would suffer would be serious; and (4)

appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed [p. 44].

The Commission further advised that, to the extent possible, persons undergoing genetic screening should be asked to consent in advance to the disclosure of genetic information to relatives in the event that such useful information is discovered [pp. 43-44]. Whether a legal duty exists to warn relatives of possible genetic defects has not yet been established. [*See* Robertson (1992), pp. 92-94.]

Access to Data: Incidental Findings. HRACs should also ensure that investigators adequately deal with how they will handle incidental findings; that is, what will be done with genetic information that is learned during the course of the study that does not directly relate to the research. For example, in intergenerational pedigree analyses, questions of paternity or parentage can come up. DNA analysis will reveal information indicating that an individual's biological parents are not who he or she thought they were; blood typing may reveal similar information. DNA analysis may also reveal information about diseases or conditions other than the disease or condition under study. Prospective subjects should be informed during the consent process that the discovery of such information is possible. Appropriate counseling should be provided to educate subjects about the meaning of the genetic information they have received, and to assist them in coping with any psychosocial effects of participation.

Access to Data: Secondary Use. Investigators should also address secondary use of research data (*e.g.*, by other investigators, or by themselves for different research purposes). Where secondary uses can be foreseen, consent to the use should be sought. Express consent to access to data for secondary uses should be obtained for sensitive data and for circumstances under which confidentiality cannot be assured.

Research on Genetic Testing

Testing individuals to determine the presence of genetic defects falls into four basic categories:

1. Testing newborns to detect serious genetic diseases. The screening of newborns is considered to be of value to the extent that infants can benefit from early intervention. In the case of phenylketonuria (PKU), for example, a genetic disease for which a test is available, a special diet can prevent most of the serious effects of the disease (which include brain damage).
2. Testing for carrier status to identify individuals whose genetic makeup includes a gene or a chromosome abnormality that might have serious health implications for their children. Carrier testing is usually requested by adults who have some indication that they may be carriers of a genetically-linked disorder (e.g., because they are members of an ethnic group known to have a high incidence of the disorder, because a relative has a genetic disease, or because a spouse knows that he or she is a carrier). Testing will provide such persons information about the risks of being a carrier and of passing on either the disease or abnormal genes to their children. For recessive diseases, for example, a carrier will pass on the disease to their children only if the other biological parent is also a carrier of the same defective gene.
3. Prenatal testing is aimed at detecting the presence of genetic or chromosomal abnormalities in fetuses. Examination of the genetic makeup of the fetus is done through amniocentesis, chorionic villi sampling, blood sampling from the umbilical cord and blood samples from the mother.
4. Risk assessment testing (sometimes referred to as "presymptomatic testing") determines the probability that a person will develop a genetically-linked disease at some point in the future. The degree of certainty with which risk assessment tests can predict the likelihood of disease differs depending on the disease. For some diseases the actual gene has been located, making tests more accurate than for diseases for which only a marker has been found. Further, some markers are more closely linked to the gene than are others, thereby having a more predictive quality than others.

Protocols involving genetic testing raise somewhat different issues, depending on whether the tests are under development or are already established as reliable. HRACs are concerned with research aimed at developing genetic tests.

The ethical issues raised by the various kinds of genetic testing largely concern the concept of autonomy or self-determination. Before consenting to undergo genetic tests, whether new tests that are being developed, or already-established genetic tests, subjects should fully understand what it is they are going to learn about themselves, what they are *not* going to learn about themselves, and how reliable the information will be. Subjects must have information on which to base their decisions whether or not to go ahead with the testing. When the research involves the development of a genetic test, however, the uncertainties involved make the consent process problematic: How does one adequately alert subjects to the psychosocial risks of testing when the point of the study is to try to help define those risks? Research on pre-test education in effect experiments with the informed consent process. Can subjects consent to research knowing that one of the risks is that they may not be adequately informed about what they are agreeing to? The federal regulations allow HRACs to approve consent procedures that do not include or that alter some or all of the elements of informed consent; one of the requirements is that the research must involve no more than minimal risk [38 cfr 16.116(d)]. Research that involves deliberate withholding of information or deception is reviewed pursuant to those provisions. Even where it is permitted, purposeful nondisclosure of pertinent information is allowed only to the extent necessary to conduct the study (*e.g.*, when disclosure of the information would affect the outcome of the study). Furthermore, subjects must consent to the nondisclosure; that is, they must be told that there is some relevant information about the study that they will not be told prior to consenting to participate (Levine 1986, p. 117).

In genetic testing research, however, the nondisclosure is not purposeful; rather, the nature and extent of the psychosocial risks involved is simply unknown. HRACs must look carefully at such studies to ensure that subjects are adequately protected. Investigators should provide the HRAC their assessment of unknown risks. Subjects should be informed, in clear, understandable language, of the possibility of undisclosed risks, including any information the investigator has about their possible nature and extent.

Someone who possesses the appropriate medical and counseling expertise with which to explain the meaning of the test results should communicate research results to the subject. That person should ensure that the subject comprehends the information that has been provided to him or her, regardless of the time that may be involved. Furthermore, it may be appropriate to provide counseling not just for the subjects themselves, but also for their families. Consent to involve family members, should the need arise, should be sought as part of the consent to be tested.

Smurl and Weaver (1987) have developed a set of proposed ethical guidelines for the clinical testing of risk assessment tests for HD. HRACs reviewing investigations of risk assessment genetic tests should find their recommendations helpful. Many of their recommendations follow the arguments set forth in the discussions in the Guidebook on pedigree analysis and identifying and deciphering genes.

The misuse of genetic information due to misunderstanding its meaning is a risk faced by all participants in genetic research. Investigators can minimize this risk by working to educate not only subjects, but also the medical profession and the public about genetic testing. The term "diagnostic" is often used, but the term does not really apply. Genetic tests identify risks rather than "diagnose" the presence of disease. Discrimination in employment or in obtaining insurance are two areas that are of major concern, particularly where the genetic trait is one that is thought to indicate a predisposition to diseases or conditions caused by exposure to environmental agents. Significant damage has been done by, for example, misperceptions about what it means to be a carrier of sickle cell trait. Persons who carry the sickle cell trait have been denied jobs or have been otherwise discriminated against. Education, together with protecting subjects against disclosure of genetic information, can help minimize the risk of discrimination.

Gene Therapy Research

Gene therapy attempts to treat genetic disease by altering an individual's cells. Gene therapy can involve treatment of either somatic (nonreproductive) cells or germline (reproductive) cells. Genetic changes made to somatic cells affect only the individual who has received treatment; genetic changes made

to germline cells may be passed on to the patient's descendants. A distinction must be made between gene therapy designed to treat or eliminate disease or serious medical, psychological, or behavioral conditions (*e.g.*, cystic fibrosis), and the "improvement" of human characteristics (*e.g.*, height).

Gene therapy techniques involving somatic cells are aimed at curing genetic disease in individuals by inserting properly functioning genes into the individual's somatic cells [Walters (1989), pp. 220-221]. The approach for making genetic changes to germ line cells is to add new DNA to early embryos in an attempt to change the genes not only in the individual, but also the genes passed on to his or her progeny. Walters (1989) has described the process as follows:

> In studies involving mice, for example, genes have been added to one-cell mouse embryos after the sperm had penetrated the egg but before the genetic material from the sperm and egg are joined within the same nucleus. If the experiment is successful, these added genes are then adopted by the embryo. As the embryo grows and the number of embryonic cells increases, the added genes become part of every new embryonic cell. Later, when the sperm or egg cells of the mouse develop, the added genes are included in approximately half of these reproductive cells. Thus, when the mouse reproduces, some of its progeny receive the added genes, and so on through the generations [p. 221].

After being reviewed and approved by the HRAC and the local institutional biosafety committee, gene therapy protocols for research conducted at or sponsored by an institution that receives any support for recombinant DNA research from NIH must be reviewed by the Recombinant DNA Advisory Committee (RAC) at NIH. At present, the RAC will consider human somatic cell gene therapy protocols, but not germline cell gene therapy protocols. The process of review is as follows: The Human Gene Therapy Subcommittee conducts a public review of the protocol, then submits its recommendation to the RAC; if the RAC approves the protocol, it is forwarded to the director of NIH for final approval.

The RAC, through a Points to Consider Subcommittee, has established "Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into Human Subjects." Among the ethical concerns that investigators must address are subject selection, informed consent, and privacy and confidentiality. Investigators must also justify the use of recombinant DNA techniques against alternative methodologies and delineate the risks and benefits of the research. A summary of the Points to Consider follows; HRACs would be well-served to follow a similar line of inquiry when reviewing protocols that involve the transfer of recombinant DNA into human subjects.