Ethical issues in genetic research: disclosure and informed consent

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As research to correlate genetic status with predisposition to disease has accelerated, so has the concern that participation in such studies creates the risk of genetic discrimination and emotional distress. There is a need to broaden disclosure during the consent process to ensure that potential subjects understand these risks and other issues and to address them in the consent form. We describe the broad approach that we have taken in regard to disclosure and consent in gene mapping studies.

As research has increased to identify genes which are responsible for monogenic disorders or which increase the risk for common, multifactorial diseases such as cancer and diabetes and traits such as obesity, concern that genetic information can be harmful has also grown. In the United States the major concern has been that genetic information might be used to limit or deny access to health insurance or cause emotional distress[1]. This concern has been raised mainly in regard to persons who undergo clinical diagnostic testing, but it is also emerging as a concern for those who agree to participate as subjects in genetic research.

Although risks associated with clinical genetic testing ultimately will affect many more individuals than those who face risks as a consequence of participating in research studies, we focus here on the research setting. We do so largely because we think researchers involved in gene mapping studies face two important ethical challenges—namely, assuring that subjects are reasonably educated about the risks and reducing the threat of those risks. Failure to meet these challenges could harm individuals and slow the course of genetic research.

Ethical issues

Most of the ethical issues that arise in genetic research concern the dissemination and use of information. For example, does the subject have a duty to share genetic information with close relatives who are also at risk? Does a physician-investigator have a right (or an obligation) to warn relatives of a patient or research subject about a possible genetic risk? Under what circumstances, if any, is it proper to enroll children in genetic research to identify predispositions for which there are no established clinical interventions? What right, if any, do insurers, employers, schools and other major social institutions have to ask about genetic information acquired during an investigation?[2]

Recently, formal recommendations have been issued by blue ribbon legislative committees, professional societies, special branches of scientific agencies, and consumer groups concerning the proper uses of genetic information. Examples include those from the 1995 Report of the Science and Technology Committee of the House of Commons[3], a 1994 report by a committee of the Institute of Medicine[2], an American Society of Human Genetics position statement[4], and opinions about the value of predictive testing issued by the National Action Plan on Breast Cancer[5]. In the commercial sector, the Biotechnology Industrial Organization (BIO) is actively addressing issues and developing position papers on genetic privacy and genetic discrimination.

Many of the organisations making these statements, which focus on clinical medicine, urge caution, warn that rapid diffusion of predictive genetic tests into medicine could cause more harm than benefit and call for more oversight of genetic testing. They are especially concerned about the use of tests that cannot provide at-risk persons with firm clinical advice. They also worry that often there will be no clearly beneficial intervention to ameliorate risk so that foreknowledge may be of little value. Another worry is that relatively few primary care providers have a sound training in how to counsel about genetic tests. Finally, these bodies are concerned that genetic information can create barriers to insurance and employment[2].

The sense that these ethical and public policy problems need resolution is growing, as is evident from a dramatic increase in legislative interest. From 1975 to 1994, only one bill intended to deal with protecting the privacy of genetic information was introduced in the U.S. Congress. In contrast, in late 1995 at least five bills were introduced in the Congress, and another, which recognizes genetic information as a protected class of medical information (for example, data that cannot be classified as a 'pre-existing condition' in order to limit coverage when an individual changes health plans) was enacted[6]. Since 1990, dozens of bills at the state level have been proposed to regulate the use of genetic information, largely in regard to health insurance. About 15 states have already enacted such laws and more will follow[7]. The most important governmental action to date is the decision in 1995 by the Equal Employment Opportunity Commission to issue an interpretative guideline that explicitly states that a person denied employment because he or she carries a disease susceptibility gene may claim the protection of the Americans with Disabilities Act[8]. That ruling has not yet been tested in court.

Ethical concern about the potential risks associated with the impact of genetic information on the subject and the potential threat associated with the loss of genetic privacy has begun to affect the conduct of genetic research. In March of 1992, the American Association for the Advancement of Science sponsored a Conference on Ethical and Legal Aspects of Pedigree Research that considered disclosure issues that had arisen in gene mapping research involving bipolar affective disorder, polycystic kidney disease, Huntington's Disease, fragile X syndrome and colon cancer. The conference report observed: "since pedigree research projects are designed to study the inheritance of a disorder or other characteristic rather than to test a treatment protocol, the risks to which subjects might be exposed are typically economic, social or psy-

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Legislation and Genetic Privacy

The United States does not provide universal access to health care, and the health care delivery system is under tremendous pressure to control costs. Bioethicists, consumer groups and others are concerned that genetic information that predicts increased risk for disease will be used improperly by insurers in underwriting decisions.

In the United States legislative interest in regulating the use of genetic information is at an all time high. This trend began in 1989 when a bill to limit use of genetic data by health insurers passed the California legislature, but was vetoed by the governor. In September 1990 (coincidental with the launch of the human genome project), Representative John Conyers (D–Mich.) introduced the 'Human Genome Privacy Act,' which did not come to a vote. Since 1990, scores of bills to limit use of genetic information by health insurers have been introduced in the state legislatures. At least 14 states have enacted such laws.

Towards the end of 1995, the U.S. Congress became interested in 'genetic discrimination.' At least six bills have been introduced and hearings have been held on several. In August, 1996 President Clinton signed 'The Health Insurance Portability and Accountability Act of 1996.' This law expressly recognizes 'genetic information' as 'protected medical information,' which means that it cannot be used by employer-based group health plans to deny coverage when a person moves from one job to another. In March of 1995, the Equal Employment Opportunity Commission (EEOC) interpreted the Americans with Disabilities Act of 1990 to apply to otherwise healthy persons who suffer discrimination in the workplace due to a genetic predisposition to disease.

Of the many bills concerning genetic information to watch in 1997, the most important will be the revised version of 'The Genetic Confidentiality and Nondiscrimination Act of 1996' (S.1898) which was introduced on June 24, 1996 by Senator Pete Domenici (R–New Mexico).

During the past year the legislative agenda has broadened. Lawmakers are now looking at genetic research. A new law in Oregon (which declares that individuals have a property interest in genetic information) and one in New York could affect the ability to conduct gene mapping studies. The bill, introduced by Senator Domenici, includes a section that could (if retained) lead institutional reviews board (IRBs) that oversee human subjects research to be much more wary of gene mapping protocols.

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

"Washington is looking to the scientific community for an answer. Gee, I've wanted to say that my whole career."

chological rather than physical. Instead of being warned about the possibility of side effects from a medication, for example, pedigree research subjects must be informed that the information gathered in the study might harm them."[9] Also in 1992, the Alliance of Genetic Support Groups developed an educational brochure for persons who are considering whether or not to participate in genetic research. This document, which places a major emphasis on the subject's right to know, has been widely disseminated among families burdened with genetic disorders.

In 1994, the NIH convened a workshop to explore ethical issues that arise in collecting tissue samples. This meeting stimulated a still active debate among scientists, bioethicists, and consumers about the proper disclosures to make to a subject who will be asked to permit his or her DNA to be stored in a repository. While there is broad consensus that disclosure of risks can provide the basis for obtaining an informed consent to store DNA for future use in research, opinion remains divided about the proper uses of archived tissue samples in situations where the original consent was based on little or no discussion of informational risks[10]. The key issues have been to decide under what circumstances a researcher must seek a new consent to use an old sample for a new purpose and whether or not a researcher ever has a duty to re-contact an individual if a clinically relevant finding is made. Truly anonymous studies circumvent the need to address these and related issues, such as fear of unauthorised release of genetic information, but anonymity may minimise the yield of some studies and largely eliminates the possibility that a participant in research might gain directly from that activity. In the summer of 1996, The National Heart, Lung, and Blood Institute (NHLBI) convened a working group to study issues involving informed consent for ongoing use of the 1.7 million samples in its repository.

Disclosure and consent

The process of obtaining informed consent serves two purposes. It is intended to provide the subject with the knowledge needed to make a rational choice in a situation that usually does not confer direct personal gain and to remind the investigator of his or her ethical duty to apprise the subject of dangers even though they be subtle or remote[11]. Investigators should be aware of the full range of risks to persons whom they recruit as subjects. This awareness will help researchers to design studies that minimize the potential for harm and maximize disclosures to allow the potential subject to weigh more carefully the decision to participate.

In the United States, the minimal requirements of the consent process are embodied in Federal regulations drafted more than 15 years ago. They were written mainly to anticipate physical risks, such as those associated with trials of new drugs[12]. Efforts to determine whether or not an allele confers an increased risk of developing a serious disease may pose more subtle risks to the subject. In addition to the important concern about the impact of genetic information on one's ability to maintain or obtain health insurance or employment, there is the risk that genetic information could cause significant anxiety and stress to family relationships[13,14].

Federal regulations do not provide explicit guidance on whether investigators must disclose such risks to potential subjects, but there is a growing trend among those concerned with protecting human subjects, such as the Office of Protection from Research

Risks (OPRR) at NIH[15], bioethicists who study the research enterprise[16], consumer groups[17], and scientists[9], that research intended to discover genetic information about disease status or risk and that carries the possibility of discovering sensitive biological facts about families must be conducted only with subjects who are aware of these risks and who have decided to assume them. This trend is consistent with the Federal rule that risks that are more than 'minimal,' that is, greater than the risks of everyday life, demand warning about the potential for harm[18]. As awareness of new risks arises, disclosure practices must be amended accordingly.

The most significant development signalling a new standard for disclosure in genetic research was the OPRR publication in 1993 of *Protecting Human Research Subjects: Institutional Review Board Guidebook*[15]. Although its proposals do not have regulatory force, the document has been distributed to institutional review boards (IRBs) throughout the nation and has raised awareness about genetic discrimination. Another important document, *The Genetic Privacy Act*[19], a proposal for model legislation that addresses disclosures in research, has influenced a number of state legislatures.

Key dimensions for disclosure and consent

In response to these developments we have considered the dimensions of disclosure in genetic research. Over the last two years we have expanded the scope of disclosure that we provide during the consent process in human gene mapping studies with which we are involved. We think that the following specific topics should be discussed with persons considering participation in such studies and should be addressed in the consent form. To the extent that this list goes beyond those disclosures that IRBs currently require, we believe that the scope of disclosure should be enlarged.

1. A general description of the nature of the study. The investigator must describe in terms understandable to the subject the overall project and the subject's role in it. In the case of genetic research this usually involves reviewing the subject's medical history, performing a clinical examination, and taking a small sample of blood for DNA analysis in an effort to identify an allele that predisposes to an illness that is prevalent in the subject's family.

2. The identification and description of the research teams. The investigator should identify the research team, including the participants who are commercial partners and identify them as such. Genetic research often involves companies that sponsor the research, study the DNA, and store DNA and genetic and clinical information for future use. There may be individuals who will object to participating in a research activity involving a commercial entity. Respect for persons requires that the subject be given an opportunity to weigh this fact in his or her decision on whether or not to participate.

3. The privacy guidelines for the study. Disclosures about the plans of academic investigators to protect the confidentiality of data are standard. But, unless a similar disclosure is made about the commercial partner, a subject may conclude erroneously that the commercial entity at which his or her sample has been analysed and/or stored will have direct or indirect access to data and could act as an information source concerning discoveries made about him or her. Some genetic studies are designed with the intent to disclose no information of potential clinical relevance to the subject. Some subjects may develop an interest in the research and their genetic status subsequent to their participation in the study and request data from the clinical investigator. A simple statement that a commercial partner will not know the identity of the individuals from whom samples are derived will forestall inquires that may arise if a subject later regrets his or her decision to participate in a study that will not report findings. Such a statement will also reassure those who fear that a company could be the source of a 'leak' of personal information to third parties such as insurers.

4. Archiving. The plans should be revealed for archiving the subject's DNA and/or cell lines derived from the subject's DNA.

5. Distribution and other uses of the subject's DNA. Divulgence of the plans of the academic or commercial partner, if any, to analyze the subject's DNA as part of other research activities and/or to share non-anonymous or anonymous aliquots of the DNA sample with other researchers.

The 1993 OPRR IRB guidelines argue that investigators must prospectively disclose plans for secondary use of samples or data derived therefrom. The guidelines state: "Where secondary uses can be foreseen, consent to the use should be sought."[15] One result of the aforementioned 1994 NIH workshop held to discuss permissible uses of archived samples in situations where the original consent process had not addressed secondary use, was a position paper asserting that in most cases the individual has a right to decide prospectively the future uses of his or her sample. This position was adopted with full recognition that it could necessitate a substantial effort to re-contact and 're-consent' each individual[20]. More recently, the American Society of Human Genetics has taken a position that would give an investigator somewhat greater flexibility in using archived samples[21].

The Genetic Privacy Act[19] would require that subjects be given the opportunity to decide whether their tissue may be used anonymously in other studies. A new Oregon law requires, except where the subject has provided written informed consent, "that a DNA sample from an individual that is the subject of a research project shall be destroyed promptly upon completion of the project,"[22] a policy that will force investigators in that state to decide the scope of future use in advance. A recently enacted New York statute pertaining to testing for genetic predisposition to disease requires the destruction of all clinical samples within 60 days of testing, the exception being if they are to be retained pursuant to an IRB-approved study that is to be conducted anonymously[23].

Subjects have a right to know that the academic investigator or the commercial partner wants to retain DNA samples for use beyond the scope of the particular study in which they may participate and whether or not future studies involving their sample will be done anonymously. Respect for persons requires this disclosure. There may be subjects who want to limit the use of their DNA to a single study or to a particular class of studies (for example, to research on a disorder that burdens their families). A subject's decision not to consent to use of a sample or related clinical data beyond the time needed to conclude the primary study, or not to consent to the secondary use of samples, or to do so only under strict provisions of anonymity does not threaten the primary research project.

6. Development of products for commercial gain. The disclosure that the analysis of each DNA sample may contribute to the success of a patent application and /or to the development of diagnostic tests, medicines or other products from which the academic investigator and/or the commercial partner could derive economic benefit, but in which the subject will not share.

A decision by the California Supreme Court, *Moore* v. *Regents of the University of California*[24], is relevant. In this case, the court ruled that the individual concerned did not retain a property interest in tissue removed during surgery that his physician then used to develop a commercially valuable product. But it also held that the principle

of informed consent requires that the patient should be told of the possibility of such an event occurring and should be given the opportunity to decide whether or not to permit such use of the sample.

Because a commercial partner hopes eventually to gain financially from genetic studies and because a potential subject may object to indirectly supporting that gain, respect for the subject's autonomy and the principles underlying the consent process argue for a disclosure on this point. As commercial gain, if it flows at all, will likely originate only from the analysis of many samples, it is unlikely that this disclosure will chill participation by a subject or family in the research. It is possible, however, that some potential subjects will be opposed in principle to the use of patents to secure intellectual property rights related to the human genome and will refuse to participate in a study which could be used to support a patent application. This is their right, and they should be given the opportunity to exercise it.

7. Other sensitive biological information. The disclosure that the research could discover sensitive biological information (such as non-paternity) about individuals and families that could, if disseminated, have harmful effects.

The inadvertent discovery of nonpaternity or unrevealed adoption is an infrequent, but not rare, event in the conduct of genetic research. The 1993 OPRR IRB guidebook acknowledges that "in intergenerational pedigree analysis, 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."[15] The 1993 OPRR IRB guidebook asserts that "subjects should be informed: about the kind of information they will be provided ... and at what point in the study they will receive that information; 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; that information about themselves may be learned by others in their family ..."[15]. We agree that investigators should routinely raise these issues in the consent process for participation in any study in which such discoveries could occur and could be communicated.

Some clinical investigators have argued that this disclosure may dissuade potential subjects from participating in genetic research. We believe, however, that disclosure on this point is the ethically proper course to follow, particularly in view of the fact that scientists in the laboratory may need to disclose such findings to their clinical collaborators in order to avoid confounding the analysis of the research data. This disclosure has been incorporated in consent forms we use in our family-based, genetic studies, and it has not deterred individuals from enrolling in those studies.

One of us has been consulted about a gene-mapping study in which a case of nonpaternity was discovered. After much discussion and consultation, the researchers decided that it was in the best interest of the family not to disclose the finding. The work has been submitted for publication in a manner that does not reveal the nonpaternity, but which preserves scientific accuracy. The journal editor was informed and, after receiving assurances from independent consultants, agreed that it was an ethically acceptable course of action.

8. Consequences of the findings of the study. The disclosure that should the subject learn that he or she has a genetically increased risk for a serious illness that such knowledge could harm his or her ability to maintain current healthcare coverage or to obtain health, life, disability or other insurance coverage.

Although there have been few studies to quantify the reality of this risk, a growing number of state laws attempt to deal with some aspects of it[7]. The 1993 OPRR IRB guidebook emphasizes the need to make this disclosure to potential subjects. It states that the consent form should indicate to potential subjects "whether information they learn or information generated about them during the study may compromise their insurability."[15] Elsewhere, the guidelines warn that actions that subjects may take as a result of their participation may also expose them "to risks of loss of confidentiality (for example, submitting insurance claim forms for reimbursement for costs of genetic counseling or procedures whose costs are not covered by the protocol)"[15]. They note that even though most researchers try to protect the privacy of research data, that "the practical limits of the confidentiality and the potential consequences of the unintended release of information need to be explained to subjects." Although the option that Federally funded investigators have of obtaining a Certificate of Confidentiality from the Assistant Secretary for Health and Human Services[25] to restrict access to research data should be seriously considered, it does not eliminate the risk. Once information is known to an individual, he or she may have an obligation to disclose it if asked to answer a question during the insurance underwriting process.

Some of our clinical collaborators have argued that this disclosure will dissuade potential subjects from participating in gene-mapping research studies. The incontrovertible fact is that the concern about loss of insurability is now so widespread in the United States that failure to warn may create a liability risk for the investigators. We, however, would prefer not to ground our argument solely on fear of litigation. We think that respect for persons requires a warning that genetic information could be used to limit access to insurance or increase the cost of obtaining it. We have required our clinical collaborators in the United States to include this disclosure in consent forms used in studies intended to map genes that predispose to serious illness. We are not aware of any instances in which a potential subject declined to participate in view of this insurability disclosure. Moreover, even if it did deter participation, this would present an even stronger argument for the necessity of its disclosure in a document that is intended to elicit a truly informed consent. We believe that IRBs will soon routinely require this disclosure in such studies.

Other emerging issues

DNA-based testing that can disclose future risk of disease has generated questions about the testing of children. In general, unless testing will confer a direct clinical benefit, investigators should avoid enrolling children in studies that could yield risk information. Testing should be deferred until the child has reached legal age and is able to decide if he or she wants to acquire such knowledge [26]. Clinical investigators and their sponsors should also be aware that Federal research guidelines require that proxy consent be exercised on behalf of the child and that when the child is capable of assenting (for example, indicating an awareness that he or she understands the nature of the study and is not opposed to being a subject) in writing to participate in research studies, that his or her assent should be sought[27].

Under current Federal regulations, investigators may obtain a waiver of the duty to seek informed consent if the proposed study constitutes 'minimal risk' to the subjects, the research does not adversely affect their rights or welfare, the research could not practicably be carried without the waiver, and, whenever appropriate, subjects provided with additional pertinent information[28]. In the past, studies involving phlebotomy and DNA analysis have been characterized as having minimal physical risk. Increasingly, the possibility that a subject may discover that he or she is at risk for a disease or may learn an unexpected biological fact within a family is seen as constituting more than minimal risk. IRBs probably vary widely in their perception of the risks to a subject that arise from participation in a study that could yield genetic information about

oneself. In using a consent process that broadly addresses potential informational risks, investigators might well be providing warnings that would not rountinely be required by IRBs, and, thus, elevating the standard of protection afforded to potential subjects. Investigators should always remember that it is exceedingly important to use clear language both in communicating orally and in the drafting of the consent document. This is necessary to ensure that disclosures have been understood and that the consent really is informed.

Federal guidelines direct that, regardless of the nation in which research involving human subjects takes place, investigators working within Federally funded grants should abide by U.S. rules. We believe that whether or not they are working pursuant to such grants and regardless of the site in which the studies are to be performed, U.S.-based academic investigators and their commercial partners should strive to conduct their research according to the guidelines we suggest in this paper. On occasion this may create problems, such as when compliance with NIH rules conflicts with normative practices in a different culture. Such problems can be resolved on a case-by-case basis involving, whenever possible, the appropriate officials in the nation in which the research is being conducted.

Conclusion

The foregoing is not an exhaustive list of disclosures and issues; it is intended to stimulate discussion within the research community about whether the current scope of disclosure practices is fair to the recruited subjects. We think (with some exceptions) that the ethically proper course for investigators in genetic research is to follow the guidelines embodied in the 1993 OPRR IRB guidebook. In the last two years we have used consent forms that address each of the points discussed above. They have been approved by the IRBs overseeing the research and they are being used to enroll subjects in studies to identify genes involved in major diseases, such as obesity, diabetes, heart disease, asthma, affective disorders and osteoporosis. We know of no data that suggest that the approach to disclosure that we advocate will dissuade subjects from agreeing to participate. Even if that were the case, it must be remembered that informed consent to research is premised on the disclosure of risks. As new risks evolve, often as a consequence of new scientific tools that provide new levels and types of knowledge, it is the obligation of the academic and commercial research communities to alter their disclosure practices.

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