Ethical Issues in Human Genome Epidemiology: A Case Study Based on The Japanese American Family Study in Seattle, Washington

Melissa A. Austin

Recent completion of the draft sequence of the human genome (1, 2) has been met with both excitement (3) and skepticism (4). Although this remarkable accomplishment has been denoted the “end of the beginning” of the genetics revolution (5), its potential for advancing public health has been tempered by ethical concerns about the protection of human subjects (6). The three principles of ethical research in which human subjects are used (respect for persons, beneficence, and justice), and their applications (informed consent, risk/benefit assessment, and selection of study populations, respectively), were established in the 1979 Belmont Report (7) (table 1) by the US congressionally appointed National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Additional guidance for genetic research can be found in the fifth revision of the Declaration of Helsinki (8) and a recent report of the National Bioethics Advisory Commission (NBAC) on human biologic materials (9), which demonstrate the growing sensitivity to issues that may arise in genetic studies. The issues are particularly relevant to human genome epidemiology, “an emerging field of inquiry that uses systematic applications of epidemiologic methods and approaches in population-based studies of the impact of human genetic variation on health and disease” (10, p. 2). Practical guidance for implementing ethical principles when conducting research in the United States is limited and may not always be applied easily to human genome epidemiology studies (11–13). Recently, however, the Centers for Disease Control and Prevention convened “a multidisciplinary group to develop an informed consent approach for integrating genetic variation into population-based research” (14, p. 2315). The language that this group suggested for consent forms and for a supplementary brochure is likely to be very valuable for investigators.

This commentary explores ethical issues arising in human genome epidemiology by using a case study approach based on the ongoing Japanese American Family Study. Following a brief description of the study itself, ethical issues encountered in designing the study, collecting the data, and reporting the study results are considered.

JAPANESE AMERICAN FAMILY STUDY

The Japanese American Family Study at the University of Washington in Seattle is an investigation of risk factors for coronary heart disease and diabetes among extended kindreds...
TABLE 1. Ethical principles of research based on the Belmont Report

<table>
<thead>
<tr>
<th>Ethical principle</th>
<th>Research application</th>
<th>Comments and implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respect for persons</td>
<td>Informed consent</td>
<td>Components include information, comprehension, voluntariness, and confidentiality</td>
</tr>
<tr>
<td>Beneficence</td>
<td>Risk/benefit assessment</td>
<td>Benefits can be direct, collateral, and/or aspirational; harms can be physiologic, psychological, and/or socioeconomic</td>
</tr>
<tr>
<td>Justice</td>
<td>Selection of populations</td>
<td>Ensure that the results benefit the community; avoid exploiting convenient populations; include affected populations</td>
</tr>
</tbody>
</table>


of second-generation (Nisei) probands. These probands participated in the Japanese American Community Diabetes Study (1994–2003) investigating whether the increased risk of diabetes among Japanese Americans is attributable to the effects of a more westernized lifestyle on underlying genetic susceptibility (15, 16). The cohort consists of Nisei and Sansei (third-generation) men and women residing in the Seattle area who have been followed prospectively to better understand risk in this community.

Building on this cohort, The Japanese American Family Study is examining the genetic epidemiology of risk factors for cardiovascular disease and diabetes in extended kindreds. Nisei probands with a spouse of Japanese descent and with children were selected for the study. Eligible relatives included the spouse and offspring of the proband, his or her brothers and sisters, their spouses, and offspring of Japanese descent residing anywhere in the United States. Members of the Nisei generation now range in age from approximately 65 to 75 years. Because most Nisei married other Japanese Americans, the Sansei generation is predominately of Japanese descent, and their ages now range from about 30 to 55 years.

Each Nisei proband is contacted by letter and phone to determine whether he or she is interested in participating in the family component of the project. If so, the proband is asked to provide a blood sample for risk factor measurements and genetic studies, to complete a medical history form, and to give permission to contact family members about participating in the study. If permission is given for family contact, the proband is asked to provide the names of and contact information for eligible relatives. Each relative is then contacted individually by letter and phone to ask to participate in the family study by providing a fasting blood sample and medical history questionnaire with written informed consent. For relatives living outside of the Seattle metropolitan area, blood samples are shipped by overnight mail to the University of Washington laboratory for analyses at no cost to the participant. All participants are provided with the results of lipid tests and with their blood pressure and glucose levels.

ETHICAL ISSUES IN DESIGNING THE STUDY

Restriction to specific racial or ethnic groups

A growing literature is debating the value of using genetically homogeneous populations for genetic studies of complex disease susceptibility to reduce locus and allelic heterogeneity (17). Some authors advocate the use of such populations (18, 19), and others claim that the advantages are overstated (20, 21). In gene mapping studies, using genetically homogeneous samples is intended to increase statistical power for gene discovery. In molecular epidemiology studies, such samples should decrease the possibility of false-positive associations between polymorphisms and disease due to population stratification (22). In The Japanese American Family Study, a series of candidate genes potentially influencing the risk factors of interest is being studied. When these data are complete, it will be possible to rigorously evaluate the genetic homogeneity of this sample of families in comparison with other populations.

Deciding whether to restrict a study to a specific racial/ethnic group implicates the ethical principle of justice. As described in the Belmont Report, “injustice arises from social, racial, sexual and cultural biases institutionalized in society” (7, p. 8). In human genome epidemiology research, the notion of distributive justice, or how society’s benefits and burdens are allocated fairly, is the most relevant (23). When the Belmont Report was written, justice was focused primarily on issues of exploitation. However, it also underlies passage of the National Institutes of Health (NIH) Health Revitalization Act of 1993 (24). This US federal law requires that women and minorities be included as subjects in clinical research funded by the NIH to provide assurance that the benefits of federally funded research are distributed fairly to all. The law further requires that results of clinical trials be valid for evaluating whether women or racial and ethnic groups respond differently than other subjects (25). By implication, findings from observational human genome epidemiology studies need to be based on sufficient sample sizes to provide statistical power for comparisons between gender and racial groups. Thus, including racial and ethnic groups in population-based studies is virtually required to obtain NIH funding and is nearly always considered in designing human genome epidemiology studies in the United States.

The widely accepted concept that race is a social and cultural construct with no scientific justification in human biology (26, 27) is essential to study design considerations. Much has been written to document that genetic differences within racial groups are greater than differences between such groups (28), although even small genetic differences
between persons may have important roles in disease susceptibility (29). If differences in associations between genetic polymorphisms and disease are found to differ by racial groups, investigators are often compelled to explain these differences when reporting study results. Although genetically influenced biologic differences between races, and varying effects of gene-environment interactions, might contribute to such differences, authors often spuriously conclude that a single genetic difference between races detected in a particular study must explain their findings (30). Such statements implying genetic determinism are common in the growing molecular epidemiology literature, and they demonstrate the urgent need for increased awareness and education about human genetics among epidemiologists (26). The use of racial/ethnic classifications in epidemiologic research has recently been debated in an informative series of commentaries, including the potential for racism (31–33).

Population-based studies limited to a single racial or ethnic group cannot generalize the findings to other groups without using other confirmatory studies, especially those for genetic association that may detect linkage disequilibrium. Furthermore, the possibility that a “bad gene” may be discovered based on studies in a specific racial group can stigmatize this group in ways never intended by the investigators. For example, if an apparently unique susceptibility allele for diabetes were to be discovered in The Japanese American Family Study, the findings would need to be replicated in studies among other ethnic groups before the clinical significance could be evaluated fully. Until then, this bad gene could be associated only with Japanese American ancestry, raising the possibility of discrimination against this ethnic group.

Finally, family recruitment difficulties can be encountered when spouses of different ethnic groups “marry in” to the kindred. In The Japanese American Family Study, there has been little such outmarriage in the proband Nisei generation. However, when it does occur, the spouses technically are not eligible for the study, nor are their offspring who are not of full Japanese descent. Because these families often consider themselves an integral part of the Japanese American community, not allowing these family members to participate in the study could seriously jeopardize community relations and the success of the study as well as violate the ethical principle of justice. Thus, despite lack of funding for such recruitment, these family members are considered full participants in the study, even if their data are not included in the statistical genetic analyses.

Community involvement

It was recently noted that there is a “growing public concern that added protections for communities in biomedical research are needed” (34, p. 1142) because specific communities “may become the target of discrimination” (34, p. 1142), especially in relation to genetic research. Taking into account the wide variety of human relationships described by the term “community,” ranging from “tribes to municipalities to religious adherents” (34, p. 1142), Weijer and Emanuel have proposed five potential protections at the community level:

1. Consultation in protocol development
2. Information disclosure and informed consent
3. Involvement in research conduct
4. Access to data and samples
5. Dissemination and publication of results

On the basis of examples from two Native American communities, Foster et al. also concluded that community review can minimize research risks from genetic studies as well as facilitate study participation by community members (35).

From a group perspective, these concerns and recommendations reflect all of the ethical principles outlined in the Belmont Report (table 1, (7)). There may be ethical grounds for requiring community consent in some human genome epidemiology studies. However, it has also been stated that specifically requiring community consent is “conceptually confusing, morally hazardous and practically useless” (36, p. 183). Such authors argue that human groups are largely unidentifiable and that community protections can compromise the interests of individual research participants. Furthermore, it is often difficult to determine who the community leader is and thus who can make decisions on the behalf of individual community members. Ethical principles also support taking into account possible group harm. This concern is reflected in the NBAC report on human biologic materials regarding potential group harms and recommends that “investigators should to the extent possible plan their research so as to minimize such [group] harms and should consult, when appropriate, representatives of the relevant groups regarding study design” (9, p. vii). Potential research benefits also need to be considered from a group perspective. The most recent Declaration of Helsinki explicitly states that “medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research” (37; 8, p. 3044). Overall, these considerations emphasize that the principles of ethical research apply to communities as well as individual study participants.

For the Japanese American Community Diabetes Study and The Japanese American Family Study, community involvement has been an active component of this research, including two ongoing community advisory boards. The first, consisting of Nisei community leaders, was formed in 1983 and has been active ever since (38). Its goals are to foster mutual cooperation and understanding between University of Washington research projects and the Nikkei (Japanese American) community. The Sansei board was formed in 1998 to represent this generation of the community, and it is particularly interested in increasing awareness of diabetes risk in the Nikkei community. Because of the history of the Japanese American community, including the legacy of the internment camps during World War II, these boards are especially concerned that research conducted in their community has the potential to improve the health of Japanese Americans. In relation to the five proposed protections listed above, investigators consult the community
advisory boards when new studies are being planned and study protocols are being developed. The boards also assist in study recruitment (39) and public relations, and they work with researchers to plan the biannual health fair as a means of disclosing information to the community about ongoing studies and about the research findings.

ETHICAL ISSUES IN COLLECTING DATA

Informed consent for DNA banking

Perhaps one of the most controversial issues in human genome epidemiology is obtaining informed consent for banking of DNA specimens to ensure that the ethical principle of “respect for persons” is applied appropriately in genetic studies. The use of such DNA samples in research, including those from large, population-based studies, has tremendous potential for understanding genetic influences on disease susceptibility. For investigators, these resources can facilitate genetic research and encourage innovative and productive collaborations. However, these benefits to public health must be balanced against risk to persons, including the potential for discrimination and invasion of privacy, an application of the ethical principle of beneficence.

On the basis of a workshop and consensus process among scientists, ethicists, lawyers, and consumers sponsored by the then National Center for Human Genome Research and the Centers for Disease Control and Prevention, the participants concluded the following:

1) Informed consent is required for all genetic research using linkable samples unless conditions for waiver are met; 2) informed consent is not required for genetic research using anonymous samples but may be considered if identifiers are to be removed from currently linkable samples; 3) institutional review boards could usefully review all protocols that propose to use samples for genetic research (40, p. 1786).

Although some researchers (41) view these guidelines as overly restrictive, correct interpretation requires clear definitions of the terms used for research samples (9, p. i):

- Unidentified or anonymous: samples supplied by repositories to investigators from a collection of unidentified human biological specimens;
- Unlinked or anonymized: samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being;
- Coded, linked, or identifiable: samples supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information;
- Identified: samples supplied by repositories from identified specimens with a personal identifier (such as a name or patient number) that would allow the researcher to link the biological information derived from the research directly from whom the material was obtained.

Most of the controversy surrounds blood samples and DNA collected retrospectively in ongoing or completed studies, before such guidelines were developed. For new or prospective studies, a Special Emphasis Panel of the National Heart, Lung, and Blood Institute (42) recommended using a “layered” approach for informed consent to facilitate the use of DNA specimens for future genetic research. Specifically, the panel recommended that study participants be given the opportunity to consent separately to

- participate in the genetic research on broadly defined disease area(s)
- be recontacted by the investigators
- store, transfer, and use the participant’s specimen in future studies broadly related to the main study
- anonymize the specimen for use in future studies broadly related to the main study

In The Japanese American Family Study, one of the primary goals is to create a repository of DNA samples to be used to identify disease susceptibility genes in this population. When the genetic analyses are complete, it is possible that information about biologic relationships may not be completely consistent with the reported family tree data. Thus, genotype data files based on DNA results are kept secure and completely separate from family recruitment information and are not accessible to family interviewers or phlebotomists.

Protecting privacy and confidentiality of family members

Human genome epidemiology is distinct from most other types of epidemiologic research in that genetic information obtained about a specific study participant also provides information about his or her relatives. Thus, protecting the privacy and confidentially of participants and their family members is a critical component of any such study to ensure that the ethical principle of beneficence is fulfilled. First, it is important to distinguish between these two closely related concepts (43).

1. Privacy refers to freedom of the person to choose for himself or herself the time and circumstances under which and, most importantly, the extent to which, his or her attitudes, beliefs, behavior, and opinions are to be shared with or withheld from others.
2. Confidentiality refers to managing private information; when a subject shares private information with (confides in) an investigator, the investigator is expected to refrain from sharing this information with others without the subject’s authorization or some other justification.

In examining issues of privacy and confidentiality in relation to health, eight “fair information practices” are often invoked (44, p. 6):

1. Being open about the existence and purposes of data collection;
2. Allowing individuals to inspect data about themselves and request corrections or amendments;
3. Following lawful and proper procedures when collecting data;

4. Only collecting or keeping data that are relevant, correct, and timely; 
5. Limiting uses of data; 
6. Limiting disclosures of data; 
7. Protecting data against unauthorized access, use, alteration, and destruction; 
8. Maintaining accountability of the data holders. 

Similar to the recently issued US regulation, “Standards for Privacy of Individually Identifiable Health Information” (45), these practices are intended to be applied broadly and can provide general guidance for human genome epidemiology researchers when examining privacy issues in their studies. 

The potential impact of this issue was dramatically illustrated in 2000 when all projects involving human subjects were suspended at Virginia Commonwealth University because the father of a woman being recruited for a twin study complained about privacy issues. 

Her father read a mailed survey instrument that included questions about the health of her parents and other family members. … [He] was concerned that providing this information constituted a threat to personal and family privacy and that informed consent should have been sought from family members (46, p. 207).

The federal Office for Protection from Research Risks (now the Office for Human Research Protections) agreed and ruled that the local institutional review board should have considered this potential risk to family members. Concern over the impact of this ruling on genetic research prompted a March 28, 2000, electronic mail “membership alert” from the American Society of Human Genetics informing members of the following:

At this time, there is no overarching rule stating that informed consent must be obtained from family members on whom medical history information is collected through someone else in their family who is a full participant in a research study. . . . The determination about whether collecting this information represents more than minimal risk and affects the subjects’ rights and welfare will have to be made in each case, as protocols are reviewed at the local level. 

The alert also cited a 1998 paper, entitled “Professional Disclosure of Familial Genetic Information,” concluding that genetic information should be considered medical information because it is both individual and familial (47).

In an analysis of the ethical issues involved in this case and the current relevant regulatory standards, Botkin recently concluded that “strong protections for the rights and welfare of subjects and their family members can be incorporated into survey and pedigree research protocols without hindering projects with extensive consent requirements” (46, p. 207), much to the relief of many genetic epidemiologists. His analysis is summarized in Table 2 and is based on a consideration of whether family members are human subjects and, if so, whether informed consent can be waived. 

In The Japanese American Family Study, each eligible family member is contacted about participating in the study only after permission for that contact has been obtained from the proband in that family. As described above, to ensure that the ethical principle of “respect for persons” is implemented appropriately, each family member is contacted individually by letter and by phone and asked whether he or she is interested in participating in the study.

All family information, including whether each family member chooses to participate, is kept confidential. Of particular importance in this study is maintaining the security of pedigree information, since the families are often large and thus easily identifiable.

A valuable resource for researchers conducting family studies is the availability of NIH Certificates of Confidentiality (48, 49). The purpose of these certificates is to protect investigators from being compelled to disclose identifying information on study participants in any civil, criminal, administrative, legislative, or other proceedings, whether federal, state, or local. The certificates are issued to only those projects that involve collection of sensitive infor-

<table>
<thead>
<tr>
<th>TABLE 2. Recommendations for investigators and institutional review boards regarding privacy of family members in research*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Are family members human subjects?</td>
</tr>
<tr>
<td>A. Are family members readily identifiable by investigators?</td>
</tr>
<tr>
<td>B. Does the information obtained from the primary subjects about family members constitute private information?</td>
</tr>
<tr>
<td>Responding no to either item IA or IB means that the person is not a human subject.</td>
</tr>
<tr>
<td>II. If family members are human subjects, can informed consent be waived?</td>
</tr>
<tr>
<td>A. Does research involve more than minimal risk?</td>
</tr>
<tr>
<td>B. Does the waiver adversely affect the rights and welfare of the subjects?</td>
</tr>
<tr>
<td>C. Can the research be practically carried out without the waiver?</td>
</tr>
<tr>
<td>D. When appropriate, can the secondary subjects be provided pertinent information after the research has been completed?</td>
</tr>
<tr>
<td>Responding no to items IIA, IIB, and IIC and yes to item IID mean that informed consent can be waived for secondary subjects.</td>
</tr>
</tbody>
</table>

* Adapted from Botkin JR. Protecting the privacy and confidentiality of family members in survey and pedigree research. JAMA 2001;285:207–11.
nlation (including genetic testing, mental illness, sexual practices, substance abuse, etc.) that, if disclosed, could be damaging to financial standing, reputation, insurability, or employability. Although the protections of the Certificates of Confidentiality have not been tested in court, they may promote participation by assuring confidentiality to study subjects. Furthermore, study subjects themselves can authorize disclosure of study data (48).

ETHICAL ISSUES IN REPORTING STUDY RESULTS

Reporting genotypes to study participants

Most human genome epidemiology studies include genotyping of study participants for polymorphisms that may be linked or associated with disease susceptibility. Investigators must then decide whether to report these genetic results to the participants, often creating a difficult dilemma relating to the ethical principle of beneficence. That is, the researcher must weigh the potential benefits and harms of reporting genotypes to study participants. Fortunately, the NBAC report has provided specific guidelines for making these decisions (9). The guidelines recommend that genetic results be disclosed to study participants only when

1. findings are scientifically valid and confirmed, and
2. findings have significant implications for the subject’s health, and
3. a course of action or treatment is available, and
4. appropriate medical advice or referral is provided.

Criterion 4 concurs with American Society of Human Genetics recommendations that “research results [should] only be transmitted to subjects by persons able to provide genetic counseling” (11, p. 471). Although these criteria still require considerable judgment on the part of investigators, they do provide a valuable framework for making decisions.

In The Japanese American Family Study, this issue arose regarding the possibility of reporting apolipoprotein E genotypes to study participants. This polymorphism with three alleles (*ε2, *ε3, and *ε4) was determined from the onset of the study because of its known association with increased cholesterol levels and risk of coronary heart disease (50–52). Although these relations have been confirmed in numerous studies, they are not of sufficient magnitude to predict coronary heart disease in a clinically useful way and thus were not initially reported to study subjects. However, during the course of the study, the apolipoprotein *ε4 allele was associated with risk of Alzheimer’s disease (53). When this relation was revealed, the investigators reevaluated whether to report apolipoprotein E genotypes to participants. In general, the first criterion of the NBAC guidelines has been met, although the association between apolipoprotein *ε4 and Alzheimer’s disease varies considerably for early- versus late-onset disease and for familial versus nonfamilial disease (54, 55). A recent analysis of the utility of genetic testing concluded that using apolipoprotein E genetic testing for Alzheimer’s disease may in fact be harmful in terms of possibly creating anxiety, stigmatization, or discrimination (56), outweighing possible health benefits and indicating that NBAC criterion 2 has not been met. Most importantly, because in general no course of effective treatment is currently available, NBAC criterion 3 has not been met. Furthermore, since family members live all over the United States, providing appropriate genetic counseling was not feasible, especially for relatives who had participated in the study several years before. Thus, criterion 4 was not met, which will always be difficult in studies in which participants are in disperse locations. Taken together, the NBAC criteria were not fulfilled, and the investigators determined that it was not appropriate to provide apolipoprotein E genotypes to study participants.

Publication of pedigrees

In addition to deciding what results to provide to study participants, human genome epidemiology researchers must also decide how to report their findings in scientific publications. For family studies in particular, care must be taken to protect the confidentiality of information in such publications and thus ensure that the ethical principle of beneficence is fulfilled. Many studies choose to publish pedigrees, since these diagrams often best represent the results of the study. To protect confidentiality of data, investigators at times consider altering the pedigree structure slightly to avoid identifying individual family members.

Many investigators are not aware that, for several years, two sets of guidelines have been in place regarding publication of pedigrees from genetic studies. Specifically, the International Committee of Medical Journal Editors published the following statement in 1995: “Identifying information should not be published in . . . pedigrees unless information is essential for scientific purposes and the patient has given written informed consent. . . . Patient data should never be altered in an attempt to attain anonymity” (57, p. 1272). The Office for Human Research Protections published an updated guidebook on the publication of pedigrees in 2000 stating, “where a risk of identification exists, participants must consent, in writing, to release of personal information” (58, p. 5). Such consent has not been obtained in The Japanese American Family Study. Given the large size of many kindreds participating in the study (average of 10 family members) and therefore their identifiability, it will be unlikely that pedigrees can be published. This is unfortunate, because the risk factor information among kindreds would best illustrate the primary study results.

In a survey of investigators and editors of 26 journals, Botkin et al. examined attitudes, practices, and experiences regarding publication of pedigrees with respect to privacy and confidentiality concerns (59). They concluded that current practices in the publication of pedigrees do not conform with established recommendations and risk the privacy and confidentiality of subjects, often without informed consent. Attempts to address this problem through the alteration of data are being used, although this practice impairs the integrity of scientific communication (59, p. 1808).

Given the careful scrutiny of genetic studies, human genome epidemiology investigators need to be aware of the available guidelines and adhere to them.
SUMMARY AND CONCLUSIONS

Many ethical issues face human genome epidemiology researchers in the course of their investigations. The Japanese American Family Study, an ongoing community-based study of extended kindreds, has been used to illustrate relevant issues. In developing study designs, investigators must consider whether to restrict the study to specific racial or ethnic groups as well as whether community involvement is appropriate. Once the study design is in place, further ethical issues emerge, including obtaining informed consent for DNA banking and protecting the privacy and confidentiality of family members. Finally, investigators must carefully consider whether to report genotype results to study participants and whether pedigrees illustrating the results of the study will be published. Although these issues can be difficult for researchers, it has been suggested that treating participants as limited partners in genetic research can provide a framework for addressing many of these concerns (60). The “JAMA Patient Page” (61) recently listed “things to consider about participating in research,” perhaps an initial step toward such a partnership. Clearly, the promise of genomics for improving public health (62) must be pursued based on the fundamental ethical principles of respect for persons, beneficence, and justice. However, as with the sequencing of the human genome itself, we are at the “end of the beginning” of addressing ethical issues in human genome epidemiology research.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grants R01 HL50286 from the National Heart, Lung, and Blood Institute and P30 ES0733 from the National Institute of Environmental Health Sciences and by the University Initiatives Fund of the University of Washington.

The author thanks Dr. Wilfred Y. Fujimoto, Dr. Steve E. Humphries, Dr. Donna L. Leonetti, Dr. Barbara Burns McGrath, Dr. Ron L. Zimmerman, and Anna Mastroianni for their helpful comments on the manuscript.

REFERENCES

32. Kaufman JS, Cooper RS. Commentary: considerations for the


40. Reilly PR, Page DC. We’re off to see the genome. Nat Genet 1998;20:15–17.


