Materials for Panel 3:
Requirements for informed consent and institutional approvals

Multi-IC Symposium on Application of Genomic Technologies to Population-Based Studies
June 5-6, 2006

Informed Consent for Population-Based Research Involving Genetics

Laura M. Beskow, MPH
Wylie Burke, MD, PhD
Jon F. Merz, MBA, JD, PhD
Patricia A. Barr
Sharon Terry, MA
Victor B. Penchaszadeh, MD, MSPH
Lawrence O. Gostin, JD
Marta Gwinn, MD, MPH
Muin J. Khoury, MD, PhD

Bridging the gap between gene discovery and our ability to use genetic information to benefit health requires population-based knowledge about the contribution of common gene variants and gene-environment interactions to the risk of disease. The risks and benefits associated with population-based research involving genetics, especially lower-penetrance gene variants, can differ in nature from those associated with family-based research. In response to the urgent need for appropriate guidelines, the Centers for Disease Control and Prevention formed a multidisciplinary group to develop an informed consent approach for integrating genetic variation into population-based research. The group used expert opinion and federal regulations, the National Bioethics Advisory Commission's report on research involving human biological materials, existing consent forms, and literature on informed consent to create suggested language for informed consent documents and a supplemental brochure. This language reflects the premise that the probability and magnitude of harm, as well as possible personal benefits, are directly related to the meaning of the results for the health of the participant and that appropriate disclosures and processes for obtaining consent should be based on an assessment at the outset of the likelihood that the results will generate information that could lead directly to an evidence-based intervention. This informed consent approach is proposed to promote discussion about how best to enable potential participants to make informed decisions about population-based research involving genetics and to suggest issues for consideration by research sponsors, institutional review boards, and investigators.

JAMA. 2001;286:2315-2321 www.jama.com

THE HUMAN GENOME PROJECT HAS PRODUCED AN explosion of genetic information. Unfortunately, the gap is immense between gene discovery and our ability to use genetic information to improve health and prevent disease. Bridging this gap with population-based knowledge about the contribution of gene variants and gene-environment interactions to disease requires that genetics be integrated into the public health research agenda. The likely outcome of this research will be more effective and targeted medical and public health interventions.

A significant challenge in pursuing these scientific aims is satisfying the basic ethical principles of respect for persons, beneficence, and justice.[1] How these principles are best applied depends on the nature of the risks and potential benefits of a particular study. Genetic research is typically considered sensitive because much of it has been directed toward the investigation of highly predictive mutations in families with a heavy burden of disease. Investigating *BRCA1/2* mutations among families that have multiple members affected with breast or ovarian cancer, for example, arouses grave concerns about the psychological and social harms that could result from uncovering information that has significant implications for the health of family members. These concerns are intensified when only limited or unproven interventions are available. Thus, recommendations for the protection of genetic research participants typically call for close scrutiny by an institutional review board (IRB), detailed informed consent procedures, and professional genetic counseling, sometimes both before and after testing.[2]

Some highly penetrant gene variants should ideally also be studied in a population-based setting. Although *BRCA1/2* muta-

See also p 2326.

Author Affiliations are listed at the end of this article.
Corresponding Author: Laura M. Beskow, MPH, Office of Genetics and Disease Prevention, Centers for Disease Control and Prevention, 4770 Buford Hwy NE, MS K-28, Atlanta, GA 30341-3724 (e-mail: laura_beskow@unc.edu).
Reprints not available from the author.
Health Law and Ethics Section Editors: Lawrence O. Gostin, JD, the Georgetown/Johns Hopkins University Program in Law and Public Health, Washington, DC, and Baltimore, Md; Helene M. Cole, MD, Contributing Editor, *JAMA*.

tions are thought to account for less than 5% of all breast cancers,[3] ascertaining their impact in the general population could help scientists understand the risks and biological mechanisms of breast cancer in general. Nevertheless, the most important contribution of population-based research involving genetics will be to elucidate the interactions between lower-penetrance gene variants and environmental factors that increase the risk of disease. The interaction between genes and one's chemical, physical, infectious, nutritional, social, and behavioral environment plays a role in many, if not all, diseases, including the common chronic diseases of public health interest. Fulfilling the ultimate promise of the Human Genome Project to benefit human health requires population-based data about the prevalence of gene variants, their associations with disease, and their interactions with modifiable risk factors.[4]

Although much has been written about ethical issues in epidemiology,[5,6] ethical, legal, and social issues in genetic testing,[7,8] and informed consent for genetic research,[2,9] there is little or no guidance available specifically for population-based studies of low-penetrance gene variants. Recommendations developed for family-based research are not well suited to most population-based research because they generally fail to distinguish between studies expected to reveal clinically relevant information about participants and studies expected to have meaningful public health implications but that involve few physical, psychological, or social risks for individual participants. Uniform application of these recommendations to all genetic research could make some otherwise beneficial population-based studies difficult or impossible to conduct. As noted by Clayton et al,[10] the risks involved in identifying high-risk mutations must be distinguished from the risks of identifying "common alleles that are neither necessary nor sufficient for the development of disease."

In response to the urgent need for appropriate guidelines, the Centers for Disease Control and Prevention (CDC) formed a multidisciplinary group to develop an informed consent approach for integrating genetic variation into population-based research. This approach highlights similarities with other population-based research; indeed, many argue that genetic information is fundamentally similar to other kinds of health information.[11] However, society currently invests enormous power in the concept of genetics, and, considering the history of eugenics and other research abuses in the United States and around the world, clarifying the obligations of investigators to participants in population-based research involving genetics is important. We propose this approach to stimulate discussion about how best to enable individuals to make informed decisions about participation in population-based research involving genetics and to suggest issues for consideration by research sponsors, IRBs, and investigators.

METHODS

Our informed consent approach is based on federal policy for the protection of human research participants, as codified at title 45, part 46, of the Code of Federal Regulations (45 CFR §46). The approach closely follows the document Consent for CDC Research: A Reference for Developing Consent Forms and Oral Scripts.[12] We also considered literature on informed consent for human tissue research,[10,13-16] particularly the report of the National Bioethics Advisory Commission (NBAC).[17] In addition, we studied 10 existing consent forms for population-based research involving genetics from CDC and other major studies outside CDC. Although these forms were developed in the absence of specific guidance, they received IRB approval and thus provided useful ideas for appropriate wording and disclosures. Our purpose was not to critique or compare these documents, however, so we do not cite them herein.

Using these and other resources, one of us (L.M.B.) created an informed consent template that contained suggested language for the collection of new, coded specimens in population-based studies, a supplemental informational brochure to accompany consent documents, and a draft of this article. Following internal and external discussions, the CDC Office of Genetics and Disease Prevention formed an ad hoc group of nonfederal experts to review these materials. Members were invited based on their (1) expertise in genetics and/or research ethics; (2) representation of diverse backgrounds, including genetics, medicine, public health, epidemiology, law, ethics, and consumers; and (3) broad understanding of public health research. Draft versions of the template, brochure, and manuscript were circulated to group members electronically, providing a foundation for detailed comments and expert input via an extensive e-mail forum. Group members posed a number of questions for discussion and resolution, and documents were revised approximately 10 times in response to comments from group members and *JAMA* peer reviewers. Group members reviewed all new versions of the documents, and final versions were accomplished during an approximate 12-month period.

RESULTS

The informed consent template, summarized in TABLE 1 and found in its entirety on the *JAMA* Web site (http://jama.ama-assn.org/issues/v286n18/abs/jlm10008.html) as well as the CDC Web site (http://www.cdc.gov/genetics/info/reports/policy/consent.htm), contains suggested language for informed consent required by ethical considerations and federal regulations. The supplemental brochure, summarized in TABLE 2 and also available online at the same address, provides additional general information to prospective participants about population-based research involving genetics. The content and rationale for selected sections of the template are described here.

Why Is This Study Being Done?

Investigators must explain to prospective participants the purposes of their research (45 CFR §46.116[a][1]). Table 1 contains sample language that explains the research question involved in a gene-disease association study. None of

Table 1. Summary of Suggested Informed Consent Language*

Template Element	Excerpts of Sample Language
Introduction Identify the organizations conducting the research and the object of the study. Explain how prospective participants have been chosen.	The Centers for Disease Control and Prevention (CDC) and the Heart Alliance are doing a research study to find out more about how genes affect a person's risk of getting heart disease.
Why is this study being done? Summarize the problem and explain the research question(s) to be addressed.	Scientists have also found many genes that may be linked with heart disease and we expect they will find more in the future. The purpose of our study is to find out which genes are the most important for heart disease. This may help us begin to learn why some people get heart disease and others do not.
What is involved in the study? Describe how the biological sample will be obtained, any questionnaires or interviews, and whether participants will be asked to grant access to their medical records.	If you decide to provide a sample for this study, we will draw about 2 tbsp of blood from a vein in your arm. We will also ask you to fill out a survey about your health, diet, and exercise and your use of tobacco, alcohol, and medicines. There will be no medicines to take and no experimental treatments to undergo in this study.
How will information about me be kept private? Describe security measures and describe the extent to which confidentiality of records identifying the participant will be maintained.	Once we take your blood sample, we will assign it a code number. We will separate your name and any other information that points to you from your sample. We will keep files that link your name to the code number in a locked cabinet. Only the study staff will be allowed to look at these files. We will only release study information if it is ordered by a court of law.
What are the risks of the study? Describe relevant physical risks, informational risks, and potential group harms.	Although your name will not be with the sample, it will have other facts about you such as your race, ethnicity, and sex. These facts are important because they will help us learn if the factors that cause heart disease to occur or get worse are the same or different in men and women and in people of different racial or ethnic backgrounds. Thus, it is possible that study findings could one day help people of the same race, ethnicity, or sex as you. However, it is also possible through these kinds of studies that genetic traits might come to be associated with your group. In some cases, this could reinforce harmful stereotypes.
Are there benefits to taking part in the study? Reiterate the object of the study.	You will not get any direct benefit for providing a blood sample for this study, but you will help us learn more about genes and other factors that may lead to heart disease.
Are any costs or payments involved? Explain whether participants will be reimbursed for time or travel and what compensation or treatment is available if injury occurs. Explain arrangements regarding the development of products with commercial application.	The aim of our research is to improve the public health. Sometimes such research may result in findings or inventions that have value if they are made or sold. We may get a patent on these. We may also license these, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits from this may be paid back to the researchers and the organizations doing this study, but you would not receive any financial benefits.
How will I find out about the results of the study? Include description of any general communication (eg, newsletters) about the study.	The studies we do are to add to our knowledge of how genes and other factors affect health and heart disease. We are gathering this knowledge by studying groups of people, and the study is not meant to test your personal medical status. For these reasons, we will not give you the results of our research on your sample. However, you can choose to get a newsletter that will tell you in general about the research studies we are doing. If you have questions about whether any genetic tests would be useful to you, you should ask your doctor.
What will happen to my sample after the study is over? Describe how the samples will be stored, where, and for how long. Clarify plans for future research to the extent possible.	After our study is over, we would like to keep any unused blood left over for future research. We don't have specific research plans at this time, but we would like to use the sample for future studies of heart disease. An institutional review board, like the one that helps protect you during this research project, will review and approve all future projects.
What are my rights as a participant? Include provisions for withdrawal following storage for future research.	You may choose not to have your sample stored for future research and still be part of this study. Also, you may agree to have your sample stored and later decide that you want to withdraw it from storage. If so, you should call the study person and tell him or her to discard your sample. He or she will discard your sample, but any data from testing your sample until that point will remain part of the research.
Whom do I call if I have questions or problems? Provide contact information for questions, rights, and injury.	If you have any questions about how this study works, contact _____. If you have any concerns about your rights in the study, contact _____. If you think that being in this study injured you, contact _____.
Consents and signature Include separate section for consent to storage for future research. Offer option to receive general study communications.	My choice about having my sample stored and used for future research under the conditions described is (please check ONE box): ☐ I refuse to have my blood sample stored or used for studies of heart disease. ☐ It is OK to store my blood sample with a code number and to use it for studies of heart disease. I would like to receive a newsletter that will tell me about the research study and what researchers are learning in the future studies about genes and disease. Please circle ONE: Yes/No

*The examples used throughout the templates are fictitious and were not drawn from any actual research project. The right column contains only excerpts of sample language and does not necessarily include all of the elements listed in the left column. See http://jama.ama-assn.org/issues/v286n18/abs/jlm10008.html for complete template and sample language.

Table 2. Summary of Supplemental Brochure*

Element	Content Description
Introduction	This brochure gives facts that can help you decide whether or not to take part in a population-based genetic research project
What is population-based genetic research?	Purpose of genetic research, difference between family- and population-based research, role of institutional review boards
What is informed consent?	Purpose and process of informed consent
What are some of the benefits of population-based genetic research?	Purpose of population-based genetic research, societal benefits
What are some of the risks of participation in population-based genetic research?	Will anyone know that the sample is mine? How likely is it that someone other than the researchers could get facts that point to me? How likely is it that I will be harmed if someone other than the researchers gets facts that point to me?
Will my sample be used for other research?	Storage and future use of biological samples

*See http://jama.ama-assn.org/issues/v286n18/abs/jlm10008.html for complete text of supplemental brochure.

the 10 existing consent forms we reviewed explicitly identified the genes to be examined. For some broad, exploratory studies, the exact genes may not be known, and for still others, numerous genes and gene-environment interactions will be under investigation. Specifying certain genes may limit researchers to the study of only those genes even though others may be related to the same disease, and, conversely, naming one disease that will be studied (eg, heart disease) could be misleading if a gene under investigation is also linked to other diseases (eg, Alzheimer disease).[18] Focus group research could provide useful insight into the level of detail that has an impact on prospective participants' decision making. In any event, researchers should be prepared to answer all questions about the genes under investigation to the extent such information is known.

What Is Involved in This Study?

In addition to obtaining biological material, population-based research involving genetics often requires gathering information about participants' exposures to environmental factors and their health outcomes, for example, through questionnaires or interviews. Investigators and IRBs must consider the problems raised if information about family history will be elicited, including the potential need to obtain consent from all identifiable individuals.[19] This section of the consent form can also be used to notify participants that investigators would like to store remaining biological material for future testing if the material will be unlinked (or "anonymized").[12] Unlinking biological materials makes identifying the source difficult, if not impossible, and the potential for harm effectively disappears.[17] If stored materials will be coded or directly identified, a separate section is needed to describe such plans (see section "What Will Happen to My Sample After the Study Is Over?").

How Will Information About Me Be Kept Private?

One of the core ethical considerations of genetic research is the privacy of biological materials and any information derived from them.[20,21] Consent documents should affirm that participants' privacy will be protected and provide details about security measures and any legal protections that are available (eg, a Certificate of Confidentiality).

What Are the Risks of the Study?

The investigator's charge is to neither understate nor overstate the risks involved so that prospective participants can make informed choices about entering the study.[12] The risk of harm in genetic research is primarily related to the disclosure of information that could lead to insurance or employment discrimination, social stigmatization, familial disruption, or psychological distress. However, one important factor in assessing the probability and magnitude of these harms is the potential clinical relevance of the results. NBAC states that "most research using human biological materials is likely to be considered of minimal risk because much of it focuses on research that is not clinically relevant to the sample source."[17(p67)] Similarly, much population-based research involving genetics likely poses minimal risk because it focuses on questions expected to have meaningful public health implications but few clinical implications for individual participants. NBAC presents 4 questions for assessing the extent to which a source could be harmed, which may be useful for IRBs and investigators to consider when describing risks[17(p67)]:

- How easily identifiable is the source?
- What is the likelihood that the source will be traced?
- If the source is traced, what is the likelihood that persons other than the investigators will obtain information about the source?
- If noninvestigators obtain information regarding the source, what is the likelihood that harms will result, including adverse consequences arising from the reporting of uncertain or ambiguous clinical results?

Another potential risk is that of group harms.[22] Population-based research involving genetics may focus on particular groups because of differences in disease prevalence. When these groups are socially defined (eg, by race or ethnicity), research on genetic susceptibilities could perpetuate discrimination against or stigmatization of the group as a whole, even when the increase in disease risk for the individual is small. Current regulations for protecting research participants address risks and benefits to identifiable individuals. Institutional review boards may consider group harms and should consider consulting group members about cultural and other issues that may be raised by the research. How-

ever, the burden of considering group implications falls primarily on the participants themselves, and reasonably foreseeable risks to groups should be disclosed in consent documents (see Table 1 for possible language).

Are Any Costs or Payment Involved?

Some genetic studies may have the potential to result in a product with commercial value. When this possibility exists, it should be disclosed along with a statement about whether participants would share in any profits. Table 1 suggests language when profits will not be shared.

How Will I Find Out About the Results of the Study?

According to NBAC,[17(p72)] disclosure of research results to participants should be an exceptional circumstance and occur only when all of the following apply: (1) the findings are scientifically valid and confirmed, (2) the findings have significant implications for the participant's health concerns, and (3) a course of action to ameliorate or treat these concerns is readily available. The consent documents presented here reflect a policy of not disclosing individual research results to participants. The justification for this policy is discussed in the "Comment" section.

What Will Happen to My Sample After the Study Is Over?

Storing remaining biological material in a coded or directly identified form may enhance its research value in terms of the ability to link it with other clinical and epidemiologic data, but this practice raises issues that should be addressed in a separate section of the consent form.[12] This section should clarify who, or at least what types of individuals, will have access to research samples[20,23] and whether third parties (eg, outside investigators) will have access to the "key" that links coded samples to identifying information. As noted, the ease of identifying the source of a biological sample is an important part of assessing overall risk. Thus, any arrangements that either facilitate or block identification of participants should be disclosed in the consent form.

To assist collection, storage, and appropriate use of biological materials and to help prospective participants understand the decision they are being asked to make, NBAC recommends that consent forms be developed that provide a number of options, such as the following[17(p64)]:

- refusing use of their biological materials in research;
- permitting only unidentified or unlinked use;
- permitting coded or identified use for one particular study, but no further contact to seek permission for other studies;
- permitting coded or identified use for one particular study, with further contact allowed;
- permitting coded or identified use for any study relating to the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies;
- permitting coded use for any kind of future study.

In some situations, offering this number of relatively imprecise options may be prohibitively complex. Our consent documents suggest an alternative, which is to state that investigators would like to store remaining biological material for future research, describe plans for such research to the extent they are known, and offer participants the option of consenting or refusing. Storing biological materials for future research is essentially a separate project, and consent forms should expressly state the right to refuse to have one's material stored irrespective of the decision to participate in the immediate project.[12]

COMMENT

Much of the language in our consent materials is based on the distinction between genetic research that is expected to reveal clinically relevant information about individual participants and genetic research that is not. The probability and magnitude of harm, as well as possible personal benefits, arising from genetic research are directly related to the meaning of the results for the health of participants and their families. When the meaning of the results is not known or when they have only a small impact on the probability of disease, the risks are reduced.

Much population-based research involving genetics will not be expected to reveal clinically relevant information. We are in the infancy of the "genetic revolution" and much is unknown. Establishing associations between genes and disease in the general population begins with quantifying statistical relations, and even those that appear to be significant cannot be applied with any precision to particular individuals. As in other epidemiologic research, the interpretation of such data requires a chain of evidence substantiating the validity of the association and supporting a considered judgment as to cause and effect. Building this chain is neither simple nor straightforward, and any single study is but one component.

In addition, many population-based genetic studies will focus on lower-penetrance gene variants. Family-based studies provide a unique framework for investigating highly penetrant gene variants, ie, those that lead to disease expression most of the time and, thus, through inheritance, produce familial aggregation. Lower-penetrance gene variants by definition lead to smaller increases in relative risk for disease and a corresponding decrease in the probability of harms stemming from misuse of the information. Research on lower-penetrance gene variants may, however, allow better understanding of underlying disease mechanisms and the role of environmental exposures on a population level, providing significant opportunities for public health intervention.

There will be population-based studies for which the approach suggested here is not appropriate. At some point, the weight of existing evidence for a gene-disease association or gene-environment interaction will mean that the

next generation of epidemiologic studies will be confirmatory rather than exploratory. Furthermore, not all population-based studies will involve lower-penetrance gene variants, and in any event, drawing a dividing line between low and high penetrance would be difficult. When the risks identified in the study are both valid and associated with a proven intervention for risk reduction, disclosure may be appropriate. Thus, the decision to use the approach suggested here should be based on an assessment at the outset of the likelihood that research results will generate information that could lead directly to an evidence-based intervention. Our approach is intended for studies in which such results are not expected, as is currently typical of most population-based research involving genetics. This is the basis for our recommendation that individual results not be reported to participants, which merits further discussion.

Some IRBs have held that investigators are obligated to offer participants in genetic research their individual results. This stance, perhaps based in part on justifiable concerns arising in the context of family-based research, can create serious problems when applied to most population-based studies.

First, at this time, the objective of much population-based research involving genetics is to help establish clinical validity by characterizing gene-disease associations.[8] Until a chain of evidence regarding risk associations has been established, the results of such research will have no clinical interpretation or significance.

Second, without independent confirmation, the analytic validity of individual results may be in question. Federal regulations require that results given to patients be performed in a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA), which establish criteria for quality assurance. Many research laboratories are not certified, because CLIA contains an exemption for "research laboratories that test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease" (42 CFR §493.3[b][2]). This may create a quandary for investigators if they are expected to offer results. If a researcher discloses an individual's result in response to a request under the Privacy Act or other applicable law, this is generally not considered a "report for diagnosis" because it is disclosed to comply with the law and not for the medical purposes set out under the exemption. However, the quandary may remain with regard to any routine expectation that individual results be offered when the laboratory is not CLIA certified.

Third, when research involves existing biological materials and consent has been waived, offering results is especially problematic. Genetic information should never be given to a participant who does not want it. Therefore, results should not be returned unless a consent process is in place that includes the opportunity for an informed decision not to receive results.

Finally, creating an ethical or legal obligation to provide research results to participants could confuse the role of the researcher, especially if the researcher is not a physician. Physicians have an obligation to act in the best interest of their patients. To the extent that generalizable knowledge is generated and available for consideration of its relevance to the standard of care, the researcher's "obligation" to participants to conduct good science and disseminate findings widely is satisfied.

We believe that a reasonable means of addressing these dilemmas may be to apply the criterion proposed here: an assessment at the beginning of a research project of the likelihood that the results will generate information that could lead directly to an evidence-based intervention. If such an outcome is deemed likely on the basis of existing evidence and the aims of the study, the approach suggested here should not be used. The project should be established in connection with a CLIA-approved laboratory and participants should be informed about the specific genes to be studied. They should be counseled about the risks and benefits of clinically relevant genetic information and offered the option of receiving their individual results.

If such an outcome is deemed unlikely, the approach suggested here (or a derivative version; see "Conclusion" section) may be appropriate, including the statement that individual results will not be provided. Attempting to define certain exceptions under which an after-the-fact determination to offer results might be made could prove problematic. Informing participants about these exceptions would be extremely difficult, and researchers, IRBs, and participants are apt to disagree about what constitutes a finding sufficiently certain or significant to merit disclosure. Asking participants to consent after explaining clearly that individual results will not be provided may be the optimal ethical approach at this time to broad, exploratory genetic research.

Participants should, however, be given the option to receive an aggregate report of overall study results, for example, through a newsletter. In the rare event that results unexpectedly have clinical significance, participants could still receive through this mechanism any recommendation to be tested for a particular trait in a clinical laboratory, without revealing individual results. Participants who consent to storage and use of their biological material for future research should be given the option to receive aggregate reports about studies conducted using samples from the "bank" where their material is stored. One condition of obtaining samples from the bank could be an agreement by investigators to supply information about their studies and the overall results for dissemination to participants. The challenge will be to find ways of presenting research findings in lay language and to be clear about any clinical implications and their meanings in different populations.

Our consent approach may need to be modified in certain instances to meet applicable laws. For example, the Privacy Act provides individuals the right to review and get cop-

ies of their information (5 USC §552[a][d][1]). This act applies when records are maintained by a federal agency in a "system of records," a term that means a group of records under the control of a federal agency from which information is retrieved by the name of the individual, identifying number, or some other identifying factor. When research is subject to the Privacy Act, informed consent documents need to include the Privacy Act notification statement. In addition, individuals should be informed in advance of their right to see their information. However, although the Privacy Act permits individuals access to their records on request, it does not command affirmative steps to disclose results absent a request.

CONCLUSION

Federal regulations for the protection of human participants apply to both behavioral and biomedical research, but their articulation reflects an emphasis on clinical research,[24] eg, clinical trials or other research that involves manipulation or intervention. As NBAC noted, "Applied to non-clinical research, the regulatory requirements seem to be either irrelevant or insufficient to provide protection."[24] Dr Francis Collins, director of the National Human Genome Research Institute, made a similar observation when he stated, "The IRB guidebook is dusty and out of date for genetics research."[25]

We attempt herein to begin to meet the need for appropriate guidelines for population-based research that involves genetics, especially lower-penetrance gene variants. Our proposed informed consent approach and recommended issues for consideration are not fundamentally different from but an extension of existing guidance for other kinds of population-based research. The materials contain suggested language for use when the likelihood of generating information that is of clinical relevance to individual participants is small, as is currently typical of much population-based research that involves genetics. This language must be modified to address the specific issues that arise within any individual study. Further broad-based discussion will be important for refining this informed consent approach, as will focus group research among potential research participants. It will also be important to create alternate versions of these materials, for example, for research that involves anonymized or already existing specimens, different types of study designs, and different study populations, with culturally appropriate language and disclosures. As epidemiologic research in this area evolves, it will be important to continue reevaluating the optimal approach to obtaining informed consent.

Author Affiliations: Office of Genetics and Disease Prevention, Centers for Disease Control and Prevention, Atlanta, Ga (Ms Beskow and Drs Gwinn and Khoury); University of North Carolina at Chapel Hill School of Public Health (Ms Beskow); Department of Medical History and Ethics, University of Washington, Seattle (Dr Burke); Center for Bioethics, University of Pennsylvania, Philadelphia (Dr Merz); Genetic Alliance, Washington, DC (Ms Terry); PXE International Inc, Sharon, Mass (Ms Terry); Division of Medical Genetics, Beth Israel Medical Center, New York, NY (Dr Penchaszadeh); and the Center for Law and the Public's Health, Georgetown University and Johns Hopkins University, Baltimore, Md (Mr Gostin). Ms Barr was formerly with Barr, Sternberg, Moss, Lawrence, Silver, and Saltonstall PC, Bennington, Vt.

Funding/Support: This project was supported in part under a cooperative agreement from the CDC through the Association of Teachers of Preventive Medicine, Washington, DC.

Acknowledgment: We thank Janet McNicholl, MD, Deborah Tress, JD, Karen Steinberg, PhD, and Diane Wagener, PhD, for their input. We also thank the CDC scientists who brought attention to these issues.

REFERENCES

1. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, DC: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; 1979.
2. American Society of Human Genetics. Statement on informed consent for genetic research. *Am J Hum Genet*. 1996;59:471-474.
3. Coughlin SS, Khoury MJ, Steinberg KK. BRCA1 and BRCA2 gene mutations and risk of breast cancer: public health perspectives. *Am J Prev Med*. 1999;16:91-98.
4. Khoury MJ, Dorman JS. The Human Genome Epidemiology Network (HuGE Net). *Am J Epidemiol*. 1998;148:1-3.
5. Coughlin SS, Beauchamp TL, eds. *Ethics and Epidemiology*. New York, NY: Oxford University Press; 1996.
6. Council for International Organizations of Medical Sciences. International guidelines for ethical review of epidemiological studies. *Law Med Health Care*. 1991; 19:247-258.
7. Andrews LB, Fullarton JE, Holtzman NA, Motulsky AG, eds. *Assessing Genetic Risks: Implications for Health and Social Policy*. Washington, DC: National Academy Press; 1994.
8. Holtzman NA, Watson MS, eds. *Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing*. Baltimore, Md: Johns Hopkins University Press; 1998.
9. Human Genome Organization. Statement on the principled conduct of genetics research. 1996. Available at: http://www.hugo-international.org/hugo/conduct.htm. Accessed July 25, 2001.
10. Clayton EW, Steinberg KK, Khoury MJ, et al. Informed consent for genetic research on stored tissue samples. *JAMA*. 1995;274:1786-1792.
11. Gostin LO, Hodge JG. Genetic privacy and the law: an end to genetics exceptionalism. *Jurimetrics J*. 1999;40:21-58.
12. Centers for Disease Control and Prevention. Consent for CDC Research: A Reference for Developing Consent Forms and Oral Scripts. November 1998. Available at: http://www.cdc.gov/od/ads/hsrconsent.htm. Accessed July 25, 2001.
13. American College of Medical Genetics Storage of Genetics Materials Committee. Statement on storage and use of genetic materials. *Am J Hum Genet*. 1995; 57:1499-1500.
14. Office for Protection from Research Risks. Issues to consider in the research use of stored data or tissues. November 1997. Available at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm. Accessed July 25, 2001.
15. Grizzle W, Grody WW, Noll WW, et al, for the Ad Hoc Committee on Stored Tissue, College of American Pathologists. Recommended policies for uses of human tissue in research, education, and quality control. *Arch Pathol Lab Med*. 1999; 123:296-300.
16. Merz JF, Leonard DG, Miller ER. IRB review and consent in human tissue research. *Science*. 1999;283:1647-1648.
17. National Bioethics Advisory Commission. *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*. Vol 1. Rockville, Md: National Bioethics Advisory Commission; 1999.
18. Greely HT. Special issues in genetic testing for Alzheimer disease. *Genet Test*. 1999;3:115-119.
19. Botkin JR. Protecting the privacy of family members in survey and pedigree research. *JAMA*. 2001;285:207-211.
20. Weir RF, Horton JR. DNA banking and informed consent, part 2. *IRB*. 1995; 17:1-8.
21. Fuller BP, Ellis Kahn MJ, Barr PA, et al. Privacy in genetics research. *Science*. 1999;285:1360-1361.
22. Weijer C, Emanuel EJ. Protecting communities in biomedical research. *Science*. 2000;289:1142-1144.
23. National Action Plan on Breast Cancer. Executive summary: model consent form for biological tissue banking focus group report. December 1996. Available at: http://www.4woman.gov/napbc/napbc/model_consent.htm. Accessed July 25, 2001.
24. National Bioethics Advisory Commission. *Ethical and Policy Issues in Research Involving Human Participants*. Vol 1. Bethesda, Md: National Bioethics Advisory Commission; 2001:13.
25. Presentation by Francis Collins to the National Human Research Protections Advisory Committee, April 9, 2001. Available at: http://ohrp.osophs.dhhs.gov/nhrpac/mtg04-01/mtg04-01.htm. Accessed July 25, 2001.

INFORMED CONSENT TEMPLATE

Population-Based Research Involving Genetics

Study Title: _____

[A] are doing a research study on [B]. Please read the attached booklet, *Informed Consent: Taking Part in Population-Based Genetic Research*. We would like to include a sample of your _____ in this research study because [C]. We think that about _____ people will give samples for our study.

A. Identify the organizations conducting the research.
B. Identify the object of the study.
C. Explain how prospective participants have been chosen.

*Examples**

- The Centers for Disease Control and Prevention (CDC) and the Heart Alliance are doing a research study to find out more about how genes affect a person's risk of getting heart disease. Please read the attached booklet, *Informed Consent: Taking Part in Population-Based Genetic Research*. We are asking you to provide a blood sample for this study because you are one of about 5,000 people between the ages of 45 and 65 who we selected at random from the community.
- We are doing a research study to learn more about how genes and other factors lead to heart problems. This study is being done by the Centers for Disease Control and Prevention (CDC) and the Heart Alliance. Please read the attached booklet, *Informed Consent: Taking Part in Population-Based Genetic Research*. We are asking everyone who comes to this clinic with certain kinds of heart disease to give a blood sample for our study. We are also asking some people who do not have heart disease. We think about 500 people will take part.

Why Is This Study Being Done?

This study is being done because [D]. The purpose of this study is to [E].

D. Summarize the problem and/or explain the disease.
E. Explain the research question(s) to be addressed.

Example

Heart disease causes serious health problems for many people. We know that a person's risk for heart disease is related to factors like diet, exercise, and smoking. Scientists have also found many genes that may be linked with heart disease and we expect they will find more in the future. *[Add one of the following:]*

- *For gene prevalence studies:* The purpose of our study is to estimate how many people have some of the genes that may be related to heart disease. This is a first step in finding out how important these genes are for heart disease.
- *For gene-disease association studies:* The purpose of our study is to find out which genes are the most important for heart disease. This may help us begin to learn why some people get heart disease and others do not.
- *For gene-environment interaction studies:* The purpose of our study is to learn more about which genes are the most important for heart disease. We also want to know how factors like diet, exercise, and smoking affect people who have those genes. This will help decide if changing these factors can prevent heart disease or keep it from getting worse.

What Is Involved in the Study?

If you choose to provide a _____ sample for this study, we will [F]. This process will take approximately [G]. You will not need to [H].

[Add the following paragraph only if leftover specimens will be stored without identifiers (unlinked) for future testing. See "What will happen to my sample after the study is over?" below if specimens will be coded or identified.]

We would like to store any _____ that is left over after we do your test. We plan to use this sample for studies we will do in the future. We will store your sample with some data about you, such as your age, race, sex, and about your health problems. But we will not put your name on the sample and there will be no way for anyone, including us, to know it is yours. You can decide to not let us store your _____ and still be in this study.

F. Describe the procedure for obtaining a biological sample and what will be done with the sample. Describe also any questionnaires or interviews, and whether participants will be asked to grant full or partial access to their medical records.
G. Estimate the amount of time participation will entail.
H. Describe procedures that will *not* be done, if appropriate.

*The examples used throughout the template are completely fictitious and were not drawn from any past or present reserach project.

Examples

• If you decide to provide a sample for this study, we will draw about 30 ccs (2-2½ tablespoons) of blood from a vein in your arm. The blood will be sent to the CDC in Atlanta, Georgia to study genes that may play a role in why some people get heart disease.

We will also ask you to fill out a survey about your health, diet, and exercise, and your use of tobacco, alcohol, and medicines. It is all right to skip any question you don't want to answer.

We will need less than 5 minutes to take the blood sample. The survey will take about 30 minutes. There will be no medicines to take and no experimental treatments to undergo in this study.

• If you choose to be in this study, we will collect a sample of your cells by brushing the inside of your cheek with a cotton swab. This sample will be sent to the CDC in Atlanta, Georgia for processing.

We will also need to check with your doctors to confirm whether you have had any of the heart diseases we are studying. To do this, we will ask you to sign a form to let your doctor give us a copy of your medical record.

Nothing else is required. We will compare the results with tests on other people who have heart disease and on people who do not have heart disease. The only genetic testing performed on your cell sample will be for conditions associated with heart disease.

How Will Information About Me Be Kept Private?

Once we take your _____ sample, we will assign it a code number. We will separate your name and any other information that points to you from your sample. We will keep files that link your name to the code number [I]. [J]. No one who reads or hears a report about this study will be able to identify you because, before any facts are given out, we combine your facts with those of other people in this study.

I. Describe security measures.

J. Describe the extent to which confidentiality of records identifying the participant will be maintained.

Example

Once we take your blood sample, we will assign it a code number. We will separate your name and any other information that points to you from your sample. We will keep files that link your name to the code number in a locked cabinet. Only the study staff will be allowed to look at these files. *[Add one of the following:]*

• *For legally unprotected research:* We will keep private both the test results and the information you tell us in the survey. We will only release study information if it is ordered by a court of law. Your name or other facts that might point to you will not appear when we present this study or publish its results.

• *When a Certificate of Confidentiality has been obtained:* Records that identify you in this study are strictly private. No one other than study staff can ever look at them unless you agree to it. This is because the study has been granted a Certificate of Confidentiality under a federal law (Section 301(d) of the Public Health Service Act). This means that the records of this study may not be disclosed, even under federal, state, or local court order, without your OK. No one who reads or hears a report about this study will be able to identify you because, before any facts are given out, we combine your facts with those of other people in this study.

• *When an Assurance of Confidentiality has been obtained:* Your test results at CDC are kept private by an Assurance of Confidentiality under the Public Health Service Act (Section 308(d)). This means that CDC will not let results out with information that identifies you for any reason unless you agree. The records of what you tell us on the survey will be kept at the Heart Alliance here in Anytown. We will release them only if ordered to by a court of law. No one who reads or hears a report about this study will be able to identify you because we will combine your facts with those of other people in this study.

What Are the Risks of the Study?

The physical risks to you for providing a _____ sample for this study are [K]. [L]. [M].

K. Describe relevant physical risks.

L. Describe the informational risks based on the types of information expected and the identifiability of the sample.

M. Describe potential groups harms.

Example

The risks of drawing blood include brief pain, slight bruising, and rarely, infection where the needle went in. We take every precaution to prevent infection. Some people feel dizzy when they have blood drawn, but this goes away when the person lies down.

The kind of information we will look for in this study is not likely to tell you anything specific about your personal health. Even so, there is a risk that if people other than the researchers got your genetic facts they could misuse them. We think the chance of this ever happening to you is very small. To protect your information, we will not keep your name

and address with the sample, only a code number. As we said, files that link your name to the code number will be kept in a locked cabinet and only the study staff will be allowed to look at them. Although no one can absolutely guarantee confidentiality, using a code number greatly reduces the chance that someone other than the study staff will ever be able to link your name to your sample or to your test results.

Although your name will not be with the sample, it will have other facts about you such as your race, ethnicity, and sex. These facts are important because they will help us learn if the factors that cause heart disease to occur or get worse are the same or different in men and women, and in people of different racial or ethnic backgrounds. Thus, it is possible that study findings could one day help people of the same race, ethnicity, or sex as you. However, it is also possible through these kinds of studies that genetic traits might come to be associated with your group. In some cases, this could reinforce harmful stereotypes.

Are There Benefits to Taking Part in the Study?

You will not get any direct benefit for giving a _____ sample for this study. The major benefit of the study is [N].

N. Insert the object of the study.

Examples

- You will not get any direct benefit for providing a blood sample for this study, but you will help us learn more about genes and other factors that may lead to heart disease.
- You will get no direct benefit from being part of this study. But the information and results from these kinds of studies may help prevent and treat heart disease in the future.

Are Any Costs or Payments Involved?

It does not cost you anything to provide a _____ sample for this study and you will not be charged for any research tests. [O]. In the unlikely event that you are physically hurt during the process of providing a _____ sample, [P].

The aim of our research is to improve the public health. [Q].

O. Explain whether participants will be reimbursed for things such as time, travel, and inconvenience.

P. Explain what compensation or medical treatment is available if injury occurs.

Q. Explain arrangements regarding the development of products with commercial application and value.

Examples

- It does not cost you anything to provide a blood sample for this study and you will not be charged for any research tests. You will not be paid for participation in this study. In the unlikely event that you are injured while giving a blood sample, we will give you first aid and direct you to proper health treatment. We have not set aside funds to pay for this care or to compensate you if a mishap occurs.

The aim of our research is to improve the public health. Your blood will never be used to develop a process or invention that will be sold or patented.

- There are no dollar costs to you for being in this study. We will give you $25 to reimburse you for your time and effort. If you are physically hurt because of this research project, we will help you to get medical care through your usual doctor. You or your health insurer will need to pay for any such care that you get.

The aim of our research is to improve the public health. Sometimes, such research may result in findings or inventions that have value if they are made or sold. We may get a patent on these. We may also license these, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits from this may be paid back to the researchers and the organizations doing this study, but you would not receive any financial benefits.

How Will I Find Out About the Results of the Study?

The studies we do on the samples we collect are to add to our knowledge of how genes and other factors affect health and disease. We are gathering this knowledge by studying groups of people, and the study is not meant to test your personal medical status. For these reasons, we will not give you the results of our research on your sample. However, [R]. We will also share what we learn with other health professionals through medical publications. If you have questions about whether any genetic tests would be useful to you, you should ask your doctor.

R. Describe any general communication (e.g., newsletters) about the study that will be provided.

Example

The studies we do on the samples we collect are to add to our knowledge of how genes and other factors affect health and heart disease. We are gathering this knowledge by studying groups of people, and the study is not meant to test your personal medical status. For these reasons, we will not give you the results of our research on your sample. However, you

can choose to get a newsletter that will tell you in general about the research studies we are doing. This newsletter will not announce your results or anyone else's, but it will tell you what we are learning about genes and heart disease. We will also publish what we learn in medical journals. If you have questions about whether any genetic tests would be useful to you, you should ask your doctor.

What Will Happen to My Sample After the Study Is Over?

After this study is over, we will throw away all the _____ samples.

[OR]

After our study is over, we would like to keep any unused _____ left over for future research. [S]. We don't have specific research plans at this time but we would like to use the samples for studies [T]. We will store the sample under a code number and we will keep the file that links the code number to your name private. We may share the samples with other researchers for [U], but we will not give other researchers any information that would allow them to identify you. We will always know which sample belongs to you, but other researchers will not.

An Institutional Review Board, like the one that helps protect you during this research project, will review and approve all future projects.

You can choose not to have your sample stored for future research and still be part of this study. You will have the chance to state your choice about this at the end of this form.

S. Describe how the samples will be stored, where, and for how long.

T. Clarify plans for future research to the extent possible.

U. Clarify the types of research that other investigators may be permitted to do.

Example

After our study is over, we would like to keep any unused blood left over for future research. *[Insert one of the following:]*

- *For frozen samples:* We will keep it frozen in a specimen bank at CDC and use it for as long as it lasts.
- *When cell lines will be created:* We will create a living tissue sample (called a "cell line") from which we can get an unlimited supply of genetic material in the future without the need to get more blood from you. Cell lines will be stored at CDC.

We don't have specific research plans at this time but we would like to use the samples for studies of heart disease as well as other diseases. We will store the sample under a code number and we will keep the file that links the code number to your name private. We may share the samples with other researchers for studies of genes and disease, but we will not give other researchers any information that would allow them to identify you. We will always know which sample belongs to you, but other researchers will not.

An Institutional Review Board, like the one that helps protect you during this research project will review and approve all future projects.

You can choose not to have your sample stored for future research and still be part of this study. You will have the chance to state your choice about this at the end of this form.

What Are My Rights as a Participant?

You are free to take part in this study or not. No penalties or loss of benefits will occur if you refuse to take part.

If you decide to take part in this study, you may withdraw at any time. You may choose not to have your sample stored for future research and still be part of this study. [V].

We will give you a copy of this consent form to keep for your records.

V. Describe withdrawal following storage for future research.

Example

You are free to take part in this study or not. No penalties or loss of benefits will occur if you refuse to take part. If you decide to take part in this study, you may withdraw at any time. You may choose not to have your sample stored for future research and still be part of this study. *[Add one of the following:]*

- *For unlinked storage:* If you agree to have your sample stored, you can change your mind up until the end of the study, when we store the remaining samples. At that time we will remove all information that identifies you. After that we will not be able to withdraw your sample because we will not know which one is yours.
- *For coded or identified storage:* Also, you may agree to have your sample stored and later decide that you want to withdraw it from storage. If so, you should call the study person listed in this consent form and tell her to discard your sample. She will discard your sample, but any data from testing your sample until that point will remain part of the research.

We will give you a copy of this consent form to keep for your records.

Whom Do I Call if I Have Questions or Problems?

If you have any questions about how this study works, contact _____ , the chief study person, at _____ .

If you have any concerns about your rights in the study, contact _____ , head of the _____ , at _____ .

If you think that being in this study injured you, contact _____ , the chief study person, at _____ .

Consents and Signature

I agree to give a _____ sample for this study. I have been given a chance to ask questions and feel that all of my questions have been answered. I know that giving a sample for this study is my choice. I understand that my individual results from the study will not be given to me. I have been given a copy of this consent form to keep.

I have read the part of this form about storing my sample for future research. My choice about having my sample stored and used for future research under the conditions described is (please check ONE box):

☐ I refuse to have my _____ sample stored or used for [W].

☐ It is OK to store my _____ sample with a code number and to use it for [W].

W. Summarize parameters of future research, e.g., "future research on genes and heart disease" or "any kind of future research."

I would like to receive a newsletter that will tell me about the research study and what researchers are learning in the future studies about genes and disease. Please circle one: Yes/No

Participant _____ Date _____

[Add the following if the signature will be witnessed:] I observed the process of consent. The prospective participant read this form, was given the chance to ask questions, appeared to accept the answers, and signed to enroll in the study.

Witness _____ Date _____

SUPPLEMENTAL BROCHURE

Informed Consent: Taking Part in Population-Based Genetic Research

Introduction

This brochure gives facts that can help you decide whether or not to take part in a population-based genetic research project.

What Is Population-Based Genetic Research?

Genetic research is an important way for us to learn about the role of genes in human health and disease. Every genetic research project has its own purpose. The purpose may be to discover genes, find out how genes work, or learn how to use what we know about genes to treat or prevent disease. The researcher should explain the specific purpose of the project to you before you decide to take part.

In order to learn how genes affect health, researchers sometimes study large groups of people. Usually, some of these people have the disease being studied or have a family member with the disease, and some do not. This way of looking at genes is often called "population-based research." Population-based research helps us find out more about the effect of common genetic traits on the risk for various diseases. It also helps us learn how genetic traits work with other factors, such as smoking or diet, to cause disease. This is the kind of research project that you have been asked to join.

Before a research project begins, a group called an Institutional Review Board or IRB usually reviews it. An IRB includes scientists and non-scientists, such as clergy, social workers, lawyers, nurses, and people from the community. This group makes sure that the researchers explain the project well and protect the people who take part. But, the decision to take part is yours to make. There is a process called "informed consent" to help you make your choice as freely as possible.

What Is Informed Consent?

When researchers ask for your consent, they are asking for your voluntary agreement to take part in a research study. Informed consent means more than signing a consent form. It means that you know about the benefits and risks of the study. You need to know how the study may affect you. You need to know that you are free to take part or not, and that your decision will not affect your health care now or in the future. The research team should give you the facts you need to make your own choice. Be sure to read any forms the researcher gives you to sign. If you think you do not have enough facts to make an informed choice, or there is something you do not understand, ask questions. You should give your consent only when you are sure you know what the study involves.

What Are Some of the Benefits of Population-Based Genetic Research?

Population-based genetic research adds to our knowledge about the role of genes in human diseases. The goal is to one day find better ways to prevent and treat disease. By taking part in a population-based genetic study, you will contribute to progress in science and medicine. However, you should not expect any direct personal benefits. Researchers will not give you your test results because they are studying groups, not individuals. The researchers should tell you the purpose of the study and how it might add to our knowledge of health and disease. They may also offer to give you the overall results of the study.

What Are Some of the Risks of Participation in Population-Based Genetic Research?

Researchers will need a sample of your tissue, usually a sample of your blood, to do genetic research. The risk that you will be injured giving a sample is very small. However, there is a risk that if someone other than the researchers got your genetic facts they could misuse them. You can learn about the risks in a particular genetic research project by asking the researcher:

Will Anyone Know That the Sample Is Mine?

In some studies, researchers will make the samples "anonymous." This means they will remove forever your name and all other facts that point to you. This greatly reduces the risk to you. No one will be able to link the genetic facts that come from research on an anonymous sample to you. Although your DNA is unique, like a fingerprint, not even the researchers will know that a sample is yours without getting another sample from you and then comparing the two.

There are disadvantages to anonymous samples. Although your name will be removed, researchers may have basic information such as your race, ethnic group, and sex. This information is useful because it helps researchers learn whether the factors that cause disease to occur or get worse are the same in different groups of people. However, it is possible that over time genetic traits might come to be associated with people of the same race, ethnicity, or sex as you. In some cases, this could reinforce harmful stereotypes.

For other kinds of genetic studies, researchers mark the samples with code numbers. One reason for doing this is so researchers can contact you if they discover they need additional information that will help the study. The study staff can use this code number to know which sample is yours, but no one else can. The disadvantage is that genetic facts will exist that could be linked to you. For that reason, you need to know how these facts will be kept private.

How Likely Is it That Someone Other Than the Researchers Could Get Facts That Point to Me?

If researchers make your sample anonymous, no one will know which sample is yours, not even the researchers. If researchers mark your sample with a code number that is linked to your name, at least one person on the study staff will have access to the files that tell which sample is yours. Researchers can take many steps to keep this and other study information safe. For instance, they can keep research materials in a locked file or on a secure computer so that only the study staff can look at them. But no one can completely guarantee that insurance companies, employers, or other people will never get this information.

How Likely Is it That I Will Be Harmed if Someone Other Than the Researchers Gets Facts That Point to Me?

If someone other than the researchers gets your information, concerns that it will be misused are greatest in studies where the results may have important meaning for your future health. It is not the aim of population-based genetic research to produce these kinds of results, but it is impossible to say now what researchers may learn in the future by studying genes.

Will My Sample be Used for Other Research?

Sometimes researchers want to store the left over part of your sample so that it is available for other studies or for more work on the first study. The researcher should tell you how long your sample would be stored, who would be able to use it, and what kinds of research it would be used for. You will get to choose whether you want your sample stored for future research. The risks of research using stored samples are the same as described above.

Future studies are important to learn about genes and to find new ways to prevent and treat disease. An IRB will review all the studies to make sure you are protected from most risks. But no one can tell you the exact risks and benefits of future studies that researchers have not yet planned. You should think through your choice carefully, and you should be able to do this without pressure and in a comfortable process where you receive answers to all your questions.

For general information about genetics and genetic research, you can call the Genetic Alliance Helpline at 1-800-336-GENE.

Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study

Rita McWilliams, MPH
Julie Hoover-Fong, MD
Ada Hamosh, MD, MPH
Suzanne Beck, MD
Terri Beaty, PhD
Garry Cutting, MD

Context Sequencing of the human genome provides an immense resource for studies correlating DNA variation and epidemiology. However, appropriately powered genetic epidemiology studies often require recruitment from multiple sites.

Objectives To document the burden imposed by review of multicenter studies and to determine the variability among local institutional review boards (IRBs) in the approval of a multicenter genetic epidemiology study.

Design A PubMed search was performed to determine the frequency of citations of multicenter studies by 5-year intervals from 1974 through 2002. A 7-question survey was sent to all participating study centers to obtain information on frequency of IRB meetings, dates for submission and approval, use/nonuse of a specific consent form, type of review performed, types of consent forms required, preparation time, and number of changes requested by the IRB at each center. Centers also provided a copy of all consent forms they generated and IRB correspondence regarding the study.

Setting and Participants Thirty-one of 42 cystic fibrosis care centers in this single US multicenter genetic epidemiology study of cystic fibrosis replied, yielding a 74% response rate.

Main Outcome Measures Frequency of published research studies and consistency among IRBs.

Results The number of all published single-center studies has increased 1.3-fold since 1985, while the number of published epidemiology and genetic epidemiology multicenter studies increased by 8- and 9-fold, respectively, during this same period. Evaluation of the risk of the same genetic epidemiology study by 31 IRBs ranged from minimal to high, resulting in 7 expedited reviews (23%) and 24 full reviews (77%). The number of consents required by the IRBs ranged from 1 to 4; 15 IRBs (48%) required 2 or more consents, while 10 (32%) did not require assent for children. The most common concern (52%) of IRBs pertained to the genetic aspects of the study.

Conclusions Review of a protocol for a multicenter genetic epidemiology study by local IRBs was highly variable. Lack of uniformity in the review process creates uneven human subjects protection and incurs considerable inefficiency. The need for reform, such as the proposed centralized review, is underscored by the ever increasing rate of genetic discoveries facilitated by the Human Genome Project and the unprecedented opportunity to assess the relevance of genetic variation to public health.

JAMA. 2003;290:360-366 www.jama.com

PROTECTION OF HUMAN SUBjects in research is an evolving process. The current system of institutional review board (IRB) assessment of human subjects protection was established in 1974 in response to highly publicized human research scandals in the 1960s and early 1970s.[1,2] Federal regulation of research conduct and IRB function was implemented in 1979. When IRBs were created, the common paradigm for human subjects research consisted of a single investigator at one institution enrolling local participants, with the major emphasis of regulation on the review of clinical trials.

Over the past 25 years, research strategies and technologies have changed, often bringing together investigators from multiple institutions to enroll geographically diverse pools of participants into epidemiological studies. However, IRB procedures and their federal underpinnings have not correspondingly kept pace.[2,3] Because of the focus of IRBs on clinical trials, others have asserted that IRBs "often have little insight into the needs of epidemiology."[4] Indeed, it is worth noting that one infamous human subjects re-

Author Affiliations: Bloomberg School of Public Health (Ms McWilliams and Dr Beaty) and McKusick-Nathans Institute of Genetic Medicine (Drs Hoover-Fong, Hamosh, and Cutting), Johns Hopkins Medical Institutions, Baltimore, Md; Department of Pediatrics, Drexel University College of Medicine, and St Christopher's Hospital for Children, Philadelphia, Pa (Dr Beck).
Financial Disclosure: Ms McWilliams owns stock in Johnson and Johnson, SciClone Pharmaceuticals, de Code, Discovery Labs, and Osteotech. Dr Cutting owns stock in Invitrogen and Life Technologies and has consulted for Roche Molecular Systems.
Corresponding Author and Reprints: Garry Cutting, MD, McKusick-Nathans Institute of Genetic Medicine, CMSC 1004, 600 N Wolfe St, Baltimore, MD 21287 (e-mail: gcutting@jhmi.edu).

search scandal—the Tuskegee Syphilis Study—involved an epidemiology study rather than a clinical trial.[1]

The incorporation of genetic information into clinical and epidemiological studies has raised additional problems for the current IRB system. There are few standards set by the Office for Human Research Protections for genetic studies, and substantial disagreement exists within the research community about what constitutes minimal risk in studies that are not clinical trials.[5] According to Greely,[6] "Research into human genetics has stretched current regulations of human subjects research beyond the breaking point." The inherent rarity of the outcome and the large number of subjects needed to unravel complex gene-gene and gene-environment relationships often require a multicenter study design to attain sufficient statistical power to generate meaningful results.

Although Silverman et al[7] have reported variability in the review of multicenter clinical trials, there have been no published reports examining IRB approval for sites involved in multicenter genetic epidemiological studies. In addition, current regulations are not well suited to the complex issues raised by genetic studies. According to Jamrozik, "The current systems of ethical oversight designed primarily to regulate intervention studies involving individual patients associated with single institutions have been completely overtaken by developments in clinical, molecular, and epidemiological research."[4] When IRB committees do not allow a consistent method of consent among the participants, "selection bias may be introduced and statistical power is certainly decreased."[4] Therefore, IRBs are largely without guidance in the review of studies that incorporate genetics.

The current method of multicenter review involves approval by each local IRB involved in the study. This results in variability in the type of review, type of consent form, time to approval, changes requested, and the quality of human subjects protection afforded.[7,8] Compounding the problem is the variability inherent in the interpretation of regulations by the estimated 3000 to 5000 IRBs in the United States.[2] To assess the burden imposed by review of all types of multicenter studies, we determined the yearly volume of single-center and multicenter studies published in the literature since 1974. One method of evaluating the impact on the current IRB multicenter process is to submit a common protocol to multiple IRBs.[7]

We are conducting a multicenter genetic epidemiology study to identify modifiers of cystic fibrosis (CF). Implementation of this study required the participation of CF care centers across the United States. Institutional review board review of the same study protocol varied considerably. Here, we present results of a survey of participating CF centers to document current IRB issues in conducting a multicenter genetic epidemiology study.

METHODS

A PubMed search was performed to assess the number of English-language human multicenter studies in the literature since 1974.[9] Abstracts, letters to the editor, review articles, and publication types not containing original results were excluded. In addition, collaborative studies of disease mechanism, disease treatment, or health care delivery were excluded. The frequencies of citations of published, multicenter, English-language human studies in PubMed from 1974 through 2002 were tabulated in 5-year increments. (The algorithm used in the PubMed search is available on request from the authors).

The CF Twin and Sibling Study is a multicenter genetic epidemiology study that was used as a case study to illustrate variability in IRB review. The study involved collection of medical record data along with a blood sample from CF patients who attended CF care centers throughout the United States. A study protocol and consent form developed by the researchers at Johns Hopkins Medical Institutions and approved by the Johns Hopkins University School of Medicine IRB, Baltimore, Md, was distributed to each center. This protocol and consent form was provided as a template for the IRB application at each center. Each center was provided with additional information that included the guidelines for genetic banking provided by the American Society of Human Genetics.[10]

To document the process of IRB approval, a 7-question survey (available on request from the authors) was sent to all participating CF centers asking the study staff to provide information on the following: frequency of IRB meetings, dates for submission and approval, use/nonuse of the Johns Hopkins University consent form, type of review performed, types of consent forms required, preparation time, and number of changes requested by the IRB at each CF center. Each center was also asked to provide a copy of all consent forms generated at their center and all IRB correspondence regarding the CF study. Variability among IRBs regarding approval of this study was derived from review of IRB correspondence and approved consent forms. Issues raised by centers and differences among consent forms were categorized and tabulated.

A matrix of consensus statements published from 1987 through 2001 was created to assess the most frequently cited guidelines for genetic studies and to illustrate variability in use of these statements in the consent forms. Data on number of beds, obtained from the American Hospital Association, were used as a proxy for the size of the institution.[11] Extramural research revenues obtained from the National Institutes of Health (NIH) were used as a surrogate for volume of research performed at each institution.[12] Number of beds and level of NIH extramural funding in centers that did and did not respond to the survey were compared by *t* test. *t* Tests were also performed to assess differences in number of days to approval between centers requiring full review vs those that used expedited review and between centers with children vs those with adults. $P<.05$ was considered statistically significant. A stepwise linear regression analysis was

Table 1. Frequency of Multicenter Studies in PubMed, 1974-2002*

	Multicenter Studies				Nonmulticenter Studies	
	All Studies					
Interval, mo/d/y	No.	No./y	Epidemiology Studies, No. (%)†	Genetic Epidemiology Studies, No. (%)†	No.	No./y
1/1/74-12/31/79	385	64	19 (4.9)	1 (0.2)	499 917	83 319
1/1/80-12/31/84	990	198	99 (10.0)	1 (0.1)	545 534	109 107
1/1/85-12/31/89	3016	603	245 (8.1)	17 (0.6)	680 170	136 034
1/1/90-12/31/94	5541	1108	789 (14.2)	39 (0.7)	777 493	155 499
1/1/95-12/31/99	8632	1726	2007 (23.2)	156 (1.8)	940 360	188 072
1/1/00-12/31/02	6521	2174	1904 (29.2)	154 (2.4)	634 443	211 481
1/1/00-12/31/04 (Projected)	10 870	NA	3173 (NA)	257 (NA)	1 057 405	NA

Abbreviation: NA, not applicable.
*Data compiled as of May 12, 2003.
†Percentage of all multicenter studies.

performed with number of days to approval as the outcome variable. All statistical analyses were performed using SAS software.[13]

RESULTS

The overall number of multicenter studies and the number of epidemiological and genetic epidemiological research multicenter studies published since the establishment of IRBs are presented in TABLE 1. The number of citations for multicenter studies increased by 1.6- to 3-fold for each of the 5-year periods from 1985 to 1999. However, the number of epidemiology and genetic epidemiology multicenter studies increased 4- to 5-fold every 5 years during the same period. Between 1985 and 1999, the number of multicenter epidemiology and multicenter genetic epidemiology studies increased approximately 8- and 9-fold, respectively, while the increase in single-site studies in the literature was 1.3-fold. Numbers for 2000 through 2002 are consistent with this trend continuing. Thus, multicenter studies of epidemiology and genetic epidemiology comprise an increasing fraction of the multicenter studies reviewed by IRBs.

Thirty-one of 42 CF care centers involved in a multicenter genetic epidemiology study replied to the survey of their IRB approval process, yielding a 74% response rate. Twenty-four (77%) of the 31 institutions required full IRB reviews, and 7 (23%) considered the blood draw and medical record review in the protocol to be of minimal risk and eligible for expedited review based on their interpretation of the federal regulations.[14] Twenty-nine centers (94%) required use of consent forms from their own institution. Three centers (10%) required 4 forms (adult, minor, parental, and assent). The number of centers requiring 2 or more consent forms was 15 (48%). Ten centers (32%) did not require an assent for children. Of the 21 centers that did require an assent, 10 (48%) provided a separate assent form that included an explanation of the study; the rest required a signature or initials of assent on a consent form written for an adult. The specific age range of patients for which assent was required varied considerably among centers. Ages specified for assent ranged from a minimum of 7 years to a variable maximum of 12 to 18 years. Nine assent forms (43%) did not specify age. There were no statistical differences between centers with children vs centers with adults. The number of consents required by a center was independent of whether the review was full or expedited. To assess the issue of response bias due to differences in the familiarity of centers with human subjects research, the number of beds and the level of NIH extramural funding in the centers were compared between the those who did and did not respond to the survey; no differences were found.

The mean time to obtain approval for an expedited review was 32.3 days (range, 9-72 days), and the mean time to obtain approval for a full review was 81.9 days (range, 13-252 days). The range of preparation time for the full review varied from 2 hours to as many as 40 hours. Predictably, the mean preparation time for an expedited review was shorter than that for a full review (5.8 vs 14.8 hours) and the mean number of changes requested was lower for an expedited review (5.7 vs 8.6). Preparation time was not separated into time to initial submission to the IRB and time to make changes and resubmit to the IRB. This information may be useful in future studies of this type. Prior to regression analysis, correlation analyses were conducted for all variables regardless of review type, all variables for centers using full review, and all variables for centers using expedited review.

Days to approval, an indicator of the difficulty of review, correlated with the number of changes requested when both review types were combined ($P=.004$) and with full review ($P=.01$) when the data were stratified by review type. No other significant correlations were observed. *t* Tests were performed for comparison of the full and expedited review groups. There were no significant differences between the groups except in preparation hours ($P=.01$). However, the paucity of numbers for the expedited review groups requires cautious interpretation of this result. Although the sample size was small, a stepwise regression analysis was performed with number of days to approval as the outcome variable. Num-

ber of changes required was the only variable that predicted number of days to approval.

The large variability in days to approval was not explained by the variability in meeting schedules, hours of preparation, number of consent forms, size of the institution, or volume of research dollars received by the institution. The large variability in the content of the consent forms and the number of changes requested was explained in part by differences in the amount of genetics-related information provided and the high percentage of questions regarding the genetic aspect of the study. Institutional review boards from smaller institutions with lower research revenues tended to ask more questions, which, in turn, led to longer preparation time.

Review of correspondence between the IRB and the study principal investigator at each center revealed that a substantial fraction (52%) of issues raised by local IRBs related to genetics. Most genetics questions related to DNA banking and risk-benefit analysis (TABLE 2). Questions related to nongenetic issues of confidentiality accounted for only 35%. There were also several questions that referred to clinical trial design tools that were not a part of this observational study. Only 2 centers (6%) explained that the study was observational and that there would be no treatment involved.

A review of consent forms consistently revealed language required by each individual IRB for all studies at their institution. In general, the required templates were not well suited to a genetic epidemiology study.[15] For example, most consent templates provide information regarding data and safety monitoring boards. An IRB in this study requested that this information be included in its consent form despite the fact that this study did not contain an intervention for it to monitor. In addition, items necessary for genetic studies are not found in the templates, such as assurances of confidentiality for family members, since families are a unit of research in genetics. Finally, although each center was provided with DNA banking guidelines[10] and other guidelines were available, few consent forms contained information relating to purpose/advantage, location, use, and confidentiality procedures or withdrawal procedures (TABLE 3).

COMMENT

Since the early 1980s, the growth of multicenter studies in the scientific literature has been dramatic. This increase has raised researchers' concerns about the adequacy of human subjects protection.[17,18] In 1998, the deputy inspector general issued a report calling for the reform of IRBs. The report noted the inability of IRBs to cope with rapid advances in biomedical research and changes in the research environment, from conduct of small single-institution studies to larger multi-

Table 2. Issues Raised During Local Institutional Review Board Review

Issue Category	No. (%) of Centers	No. of Items	Mean No. of Items per Center (Range)
Administrative/grammar/spelling/punctuation*	12 (39)	41	3.4 (1-6)
Language level	7 (22)	10	1.4 (1-5)
Total DNA/genetic	16 (52)	68	4.2 (1-12)
Banking	11 (69)	30	2.7 (1-8)
Risk-benefit/privacy	10 (62)	23	2.3 (1-4)
Results†	6 (38)	6	1.0
Miscellaneous‡	7 (44)	9	1.3 (0-2)
Confidentiality	11 (35)	23	2.1 (1-8)
All other§	18 (58)	77	4.3 (0-11)
Check-boxes‖	13 (42)	31	2.4 (1-7)
Genetic	10 (77)	16	1.6 (1-3)
Other	7 (54)	15	2.1 (1-4)

*An example of administrative issues is verification of human subjects training.
†Issues concerning results of genetic studies (eg, who should receive results).
‡Other genetic issues (eg, need to list all candidate genes to be investigated).
§For example, need to submit written assent.
‖Provision of check-boxes on consent form to opt in or out of various aspects of the study (eg, for genetic studies: "I agree that my anonymized DNA may be used by other researchers"; for other studies: "I verify that my participation is voluntary").

Table 3. Use of DNA Banking Guidelines by IRBs

Guidelines	Source of Guidelines, Reference No.	No. (%) of IRBs
Right to and procedure for withdrawal	10, 22, 25, 27, 30	8 (26)
Certificate of confidentiality	16, 25, 28, 30	0
Anonymous storage (coded)	16, 29, 30	14 (45)
Description of genetic risk	10, 22, 25, 28	11 (35)
Commercial development	22, 27, 30	7 (22)
Right to refuse genetic results	22, 26, 30	6 (19)
Duration of bank	10, 22, 25, 30	5 (16)
Operation and quality assurance of bank	10, 22, 25, 28	1 (3)
Benefit of bank	10, 16, 25, 27	1 (3)
Location of bank	10, 25, 30	10 (32)
Oversight of sample access	16, 22	4 (13)
Ownership of DNA	10, 25, 26	2 (6)
Rules for release to researchers	10, 22, 25	1 (3)
Research limitations on samples	10, 25	24 (77)
Obtaining results	30	20 (64)
Purpose of bank	29	3 (10)
Procedure for unexpected findings	10, 25	3 (10)
Sample reidentification	30	3 (10)
Depositor communication with bank	10, 25	1 (3)

Abbreviation: IRB, institutional review board.

institution studies, and inadequacy of reviews due to increased workload, due in part to an increase in multicenter studies, lack of resources, and insufficient scientific expertise, with many IRBs spending "only 1 to 2 minutes of review per study."[19]

The dramatic increase in the number of all multicenter research studies supports previous reports of the impact of this research strategy on review of clinical trials.[17,19-21] The number of multicenter genetic epidemiology studies found by our search of the PubMed database may be underestimated because of the infrequency of the term *genetic epidemiology* in the database during the early years. This limitation was in part overcome by use of a series of Medical Subject Heading terms that describe epidemiological studies (eg, case-control) and by combining them with multiple genetic descriptors (eg, hereditary). Indeed, a review of 10% of the results of the search strategy yielded a maximum of 8% false-positive results.

It was not possible to differentiate between multicenter studies with separate IRB approval and studies in which review was performed only at the originating center. Because of the nature of the PubMed database, publication bias may also reduce the number of genetic epidemiology studies found in our search. However, this would result in an underestimate of the numbers, thus implying stronger results. Although the number of multicenter studies constitutes a small fraction of all research studies, the amount of work involved in the multiple reviews of a multicenter study imposes a disproportionate burden on the IRB system. Thus, the rapid increase in use of the multicenter research strategy underscores the urgency for changing the current process of IRB review of multicenter studies.

Using a single multicenter genetic epidemiology study as a case study, we observed considerable variability in local IRB assessment of type of review required. There were differences among local IRBs as to what constituted minimal risk when coded rather than anonymous data were involved and when any genetic information was involved. The definition of minimal risk in research has been a source of debate during the last decade.[5,7] Many IRBs struggle with the ideas of risk and benefit in nonintervention studies. Researchers and ethicists are divided as to whether genetic studies should always be considered to be of higher risk than other forms of research.[22]

All participants in this study were patients with a well-defined genetic disorder, CF. However, IRBs seemed confused about what risk information they needed to provide the participants. It has been noted that IRBs lack experience in finding the equipoise in a risk-benefit analysis in which the risk is psychosocial and any benefit is solely scientific knowledge and, hence, indirect.[23] Genetics introduces probabilistic risk information that incorporates the concepts of penetrance and variable expressivity[24] and, often, unconfirmed estimates of risk perception, which further complicates determining risk-benefit ratios. These issues were illustrated by considerable variability in how IRBs dealt with DNA banking within their consent forms.

As shown in Table 3, guidelines for consent for genetic studies have been issued by several organizations.[10,25-30] However, these guidelines are not consistent. Sometimes conflicting guidance has been offered, which, we speculate, contributes to the observed inconsistency among the IRBs. As noted by Francis Collins, "Many groups have made recommendations; researchers and IRBs are still confused. The IRB Guidebook is dusty and out of date for genetics research."[31]

The National Bioethics Advisory Commission found considerable disagreement across IRBs regarding "when informed consent should be required, and what constitutes proper consent."[32] Variability in IRB review was also revealed in this study by the types and numbers of consent forms required and the content of the consent forms. In this study, the lack of consensus among IRBs regarding assent was exemplified by variability in the assent requirement. Institutional review boards are required to set ages of minority and majority based on local laws and their own judgment, taking age, maturity, and psychological state into consideration.[14] State definitions of minority age range from at least 12 years to at least 17 years, while age of majority ranges from 18 to 21 years.[33] Most IRBs appear to apply the local legal definition when preparing assents.

We observed that some IRBs prepared an assent form with a grade 2 to grade 4 reading level, while others only furnish a space for a signature on a consent form requiring greater reading skills. This practice introduces considerable variability in the level of protection afforded to children participating in the same research. Thus, variability in multiple local IRB reviews uncovered differences in review criteria that could lead to uneven protection of human subjects. In addition, the inefficiency of multiple and variable IRB reviews of a single research protocol postponed the time to study initiation and resulted in redundant allocation of valuable IRB resources without adding substantially to the protection of human subjects.

A possible solution would be the creation of an independent national multicenter IRB review system overseen by the Office for Human Research Protections. An independent but federally accredited central multidisciplinary IRB program for multicenter studies could obviate concerns regarding inadequate staffing and education of IRBs, the burden multicenter review places on local IRBs, variability among IRB reviews, continuity of human subjects protections among all participating institutions, IRB availability at smaller institutions, and institutional conflict of interest.[34] Membership could be drawn from a pool of qualified individuals with various levels and types of expertise. To ensure the quality of the review, membership should be recognized within the scientific community with the same level of recognition attributed to membership in a study section at the NIH.

Local IRBs would review multicenter research approved by a federally accredited, independent central IRB in an expedited fashion. Full local IRB review would be undertaken only if the expedited review revealed a potential for adverse effects on a community within their catchment area, conflict with local or state regulations, or overlap with ongoing studies within their institution. Cooperation would be essential to make it work.[35]

Several other solutions to the multicenter dilemma have been proposed and implemented to greater or lesser effect.[5,18,20,21,34,36-39] The NIH is currently considering establishing regional multicenter IRBs. Although this approach may decrease the burden on the local IRBs, it does not address the issue of variability among IRBs, does not deal with the issue of indemnification, and would require a centralized system for resolving conflicts among regions.[34]

The debut of the new Health Insurance Portability and Accountability Act (HIPAA) privacy regulations, written with an emphasis on single-institution clinical trials, could cause review of multicenter research to be even more prone to variation in human subjects protection and inefficiency. This is particularly true for genetic epidemiology studies, which often require the participation of many centers. The requirement for detailed disclosure documentation has raised apprehension that "this is a very complicated and expensive task, and some healthcare organizations will simply choose instead to deny researchers access to the information."[40] Concerns regarding a criterion for minimal privacy risk seem to echo those previously expressed, and unanswered, regarding minimal risk in federal research regulations.[41] No attempt has been made to create a standard individual privacy authorization or data use agreement. This leaves the regulation and the language to interpretation at each institution. Based on our experience with IRB review in this study, we anticipate that local IRBs will differ in their interpretation of the HIPAA, thus adding another layer of variability in the review of multicenter studies and further complicating the execution of studies evaluating the contribution of genetic variation to common disease.

CONCLUSION

In summary, the dramatic increase in multicenter studies has substantially increased the workload of local IRBs. A result of the Human Genome Project has been an increased interest in the application of epidemiological techniques to genetic research, which will lead to continued increases in the number of multicenter genetic epidemiology studies. However, the current multicenter approval process is onerous because of inexperience with new technologies and science, outdated regulations, and a lack of unified comprehensive national standards. The current approval process results in variability in the review of multicenter research. The observed variability is due to an absence of uniform standards to protect subjects in studies addressing disease etiology. The HIPAA will very likely add more variability. A centralized review board for multicenter studies, particularly genetic epidemiology studies, could reduce the variability in human subjects protection among medical centers, ensure that proper expertise is applied to each study, decrease the time required for review, and lessen the burden on local review boards. The need for reform appears necessary if we are to reap the full potential of the Human Genome Project.

Author Contributions: *Study concept and design:* McWilliams, Cutting.
Acquisition of data: McWilliams, Hoover-Fong, Beck.
Analysis and interpretation of data: McWilliams, Hamosh, Beaty, Cutting.
Drafting of the manuscript: McWilliams, Beaty, Cutting.
Critical revision of the manuscript for important intellectual content: Hoover-Fong, Hamosh, Beck, Cutting.
Statistical expertise: McWilliams, Beaty.
Obtained funding: Cutting.
Administrative, technical, or material support: Beck.
Study supervision: Cutting.
Funding/Support: This work was supported by grants CUTTIN00A0 from the Cystic Fibrosis Foundation, HL68927 from the National Heart, Lung, and Blood Institute, and R01 DK44003 from the National Institute of Diabetes and Digestive and Kidney Diseases.
Acknowledgment: We thank the research coordinators at the CF centers for their participation, Sharon Krag, PhD, for critical review of an early version of the manuscript, Adele Gilpin, PhD, JD, for guidance on ethics, Holly Harden at the Welch Medical Library, Baltimore, Md, for assistance with PubMed, and Tricia Cornwall for secretarial assistance.

REFERENCES

1. Reilly PR. Rethinking risks to human subjects in genetic research. *Am J Hum Genet*. 1998;63:682-685.
2. Brown J. Protecting human research subjects: status of recommendations. Report OEI-01-97-00197. April 2000. Available at: http://oig.hhs.gov/oei/reports/oei-01-97-00197.pdf. Accessibility verified June 2, 2003.
3. Grob G. Protecting human subjects: status of recommendations. Statement to Congress. May 3, 2000. Available at: http://www.house.gov/reform/cj/hearings/00.05.03/Grob.htm. Accessibility verified June 2, 2003.
4. Jamrozik K. The case for a new system for oversight of research on human subjects. *J Med Ethics*. 2000;26:334-339.
5. Institute of Medicine Committee on Assessing the System for Protecting Human Research Participants. *Responsible Research: A Systems Approach to Protecting Human Research Participants*. Washington, DC: National Academies Press; 2003.
6. Greely HT. Human genomics research: new challenges for research ethics. *Perspect Biol Med*. 2001; 44:221-229.
7. Silverman H, Hull SC, Sugarman J. Variability among institutional review boards' decisions within the context of a multicenter trial. *Crit Care Med*. 2001;29: 235-241.
8. Stair TO, Reed CR, Radeos MS, Koski G, Camargo CA, for the MARC Investigators. Variation in institutional review board responses to a standard protocol for a multicenter clinical trial. *Acad Emerg Med*. 2001;8:636-641.
9. PubMed home page. Available at: http://www.ncbi.nlm.nih.gov/PubMed. Accessibility verified June 2, 2003.
10. American Society of Human Genetics Ad Hoc Committee on DNA Technology. DNA banking and DNA analysis: points to consider. 1987. Available at: http://www.faseb.org/genetics/ashg/policy/pol-02.htm. Accessibility verified June 2, 2003.
11. American Hospital Directory. Data from AHA annual survey database. Available at: http://www.ahd.com/freesearch.php3. Accessibility verified June 2, 2003.
12. National Institutes of Health Office of Extramural Research. NIH extramural awards by state and foreign site. 2001. Available at: http://grants2.nih.gov/grants/award/state/state.htm. Accessibility verified June 2, 2003.
13. *SAS for Windows, Release 8.02* [computer program]. Cary, NC: SAS Institute Inc; 2001.
14. Department of Health and Human Services. Protection of human subjects. 1991. Codified at 45 CFR §46. Revised November 13, 2001. Available at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm. Accessibility verified June 16, 2003.
15. MacFadyen U. Electronic rapid response to: Lux AL, Edwards SW, Osborne JP. Responses of local research ethics committees to a study with approval from a multicentre research ethics committee. *BMJ*. 2000; 320:1182-1183. Available at: http://www.bmj.com/cgi/eletters/320/7243/1182. Accessibility verified June 16, 2003.
16. Office for Protection From Research Risks. Issues to consider in the research use of stored data or tissues. November 7, 1997. Available at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm. Accessibility verified June 2, 2003.

17. Levine RJ, Lasagna L. Demystifying central review boards: current options and future directions. *IRB*. 2000;22(6):1-9.
18. Morse MA, Califf RM, Sugarman J. Monitoring and ensuring safety during clinical research. *JAMA*. 2001;285:1201-1205.
19. US Department of Health and Human Services Office of Inspector General. Institutional review boards: a time for reform. Report OEI-01-97-00193. June 1998. Available at: http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf. Accessibility verified June 2, 2003.
20. Burman WJ, Reves RR, Cohn DL, Schooley RT. Breaking the camel's back: multicenter clinical trials and local institutional review boards. *Ann Intern Med*. 2001;134:152-157.
21. Christian MC, Goldberg JL, Killen J, et al. A central institutional review board for multi-institutional trials. *N Engl J Med*. 2002;346:1405-1408.
22. Beskow LM, Burke W, Merz JF, et al. Informed consent for population-based research involving genetics. *JAMA*. 2001;286:2315-2321.
23. American Association of University Professors. Protecting human beings: institutional review boards and social science research. 2000. Available at: http://www.aaup.org/statements/redbook/repirb.htm. Accessibility verified June 16, 2003.
24. Vastag B. Experts wrestle with social, ethical implications of human genome research. *JAMA*. 2001;285:721-722.
25. American Society of Human Genetics. Statement on informed consent for genetic research. *Am J Hum Genet*. 1996;59:471-474.
26. Office for Protection from Research Risks. Institutional review board guidebook: human genetic research. 1993. Available at: http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm. Accessibility verified June 16, 2003.
27. American College of Medical Genetics Storage of Genetics Materials Committee. Statement on storage and use of genetics materials. 1995. Available at: http://www.faseb.org/genetics/acmg/pol-17.htm. Accessibility verified June 2, 2003.
28. National Human Genome Research Institute. Institutional review board: investigators guide: section II: informed consent and assent. Available at: http://www.genome.gov/page.cfm?pageID=10005224. Accessibility verified June 2, 2003.
29. National Institute of General Medical Sciences Human Genetic Cell Repository. Model informed consent form. Available at: http://locus.umdnj.edu/nigms/comm/submit/model.pdf. Accessibility verified June 2, 2003.
30. Centers for Disease Control and Prevention. Consent for CDC research: a reference for developing consent forms. November 1998. Available at: http://www.cdc.gov/od/ads/hsrconsent.pdf. Accessibility verified June 16, 2003.
31. Department of Health and Human Services. The human genome project. 2001. Available at: http://ohrp.osophs.dhhs.gov/nhrpac/mtg04-01/franciscollins.pdf. Accessibility verified June 20, 2003.
32. National Bioethics Advisory Commission. *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*. Vol 1. Rockville, Md: National Bioethics Advisory Commission; 1999.
33. Boonstra H, Nash E. Minors and the right to consent to health care. In: *The Guttmacher Report on Public Policy*. August 2000. Available at: http://www.guttmacher.org/pubs/journals/gr030404.pdf.
34. National Bioethics Advisory Commission. *Ethical and Policy Issues in Research Involving Human Participants*. Vol 1. Rockville, Md: National Bioethics Advisory Commission; 2001.
35. Steinbrook R. Improving protection for research subjects. *N Engl J Med*. 2002;346:1425-1430.
36. Micetich K. Reflections of an IRB chair. *Camb Q Healthc Ethics*. 1994;3:506-509.
37. Alberti K. Local research ethics committees: time to grab several bulls by the horns. *BMJ*. 1995;311:639-640.
38. Slater EE. IRB reform. *N Engl J Med*. 2002;346:1402-1404.
39. Lemmens T, Thompson A. Noninstitutional commercial review boards in North America: a critical appraisal and comparison with IRBs. *IRB*. 2001;23(2):1-12.
40. Durham M. How research will adapt to HIPAA: a view from within the healthcare delivery system. *Am J Law Med*. 2002;28:491-502.
41. Sarraille W, Spenser A. Assembling the HIPAA privacy puzzle. *Healthc Financ Manage*. 2003;57:46-52.

The soul of man is divided into three parts, intelligence, reason, and passion. Intelligence and passion are possessed by other animals, but reason by man alone.

—Pythagoras (fl sixth century BC)

From http://www.cdc.gov/genomics/population/publications/consent.htm#Involved, see Beskow et al, Beskow et al JAMA 2001;286(18):2315-2321 (used with permission.)

Informed Consent Template for Population-Based Research Involving Genetics

CDC Genomics and Disease Prevention

Please Note: The examples used throughout the template are fictitious and were not drawn from any actual research project.

STUDY TITLE:

[A] are doing a research study on [B]. Please read the attached booklet, Informed Consent: Taking Part in Population-Based Genetic Research. We would like to include a sample of your _____ in this research study because [C]. We think that about _____ people will give samples for our study.

A. Identify the organizations conducting the research.

B. Identify the object of the study.

C. Explain how prospective participants have been chosen.

Examples:

- The Centers for Disease Control and Prevention (CDC) and the Heart Alliance are doing a research study to find out more about how genes affect a person's risk of getting heart disease. Please read the attached booklet, Informed Consent: Taking

Part in Population-Based Genetic Research. We are asking you to provide a blood sample for this study because you are one of about 5,000 people between the ages of 45 and 65 who we selected at random from the community.

- We are doing a research study to learn more about how genes and other factors lead to heart problems. This study is being done by the Centers for Disease Control and Prevention (CDC) and the Heart Alliance. Please read the attached booklet, Informed Consent: Taking Part in Population-Based Genetic Research. We are asking everyone who comes to this clinic with certain kinds of heart disease to give a blood sample for our study. We are also asking some people who do not have heart disease. We think about 500 people will take part.

Why is this Study being Done?

This study is being done because [D]. The purpose of this study is to [E].

D. Summarize the problem and/or explain the disease.

E. Explain the research question(s) to be addressed.

Example: Heart disease causes serious health problems for many people. We know that a person's risk for heart disease is related to factors like diet, exercise, and smoking. Scientists have also found many genes that may be linked with heart disease and we expect they will find more in the future. [Add one of the following:]

- For gene prevalence studies: The purpose of our study is to estimate how many people have some of the genes that may be related to heart disease. This is a first step in finding out how important these genes are for heart disease.

- For gene-disease association studies: The purpose of our study is to find out which genes are the most important for heart disease. This may help us begin to learn why some people get heart disease and others do not.
- For gene-environment interaction studies: The purpose of our study is to learn more about which genes are the most important for heart disease. We also want to know how factors like diet, exercise, and smoking affect people who have those genes. This will help decide if changing these factors can prevent heart disease or keep it from getting worse.

What is Involved in the Study?

If you choose to provide a _____ sample for this study, we will [F]. This process will take approximately [G]. You will not need to [H].

[Add the following paragraph only if leftover specimens will be stored without identifiers (unlinked) for future testing. See "What will happen to my sample after the study is over?" below if specimens will be coded or identified.] We would like to store any _____ that is left over after we do your test. We plan to use this sample for studies we will do in the future. We will store your sample with

some data about you, such as your age, race, sex, and about your health problems. But we will not put your name on the sample and there will be no way for anyone, including us, to know it is yours. You can decide to not let us store your _____ and still be in this study.

F. Describe the procedure for obtaining a biological sample and what will be done with the sample. Describe also any questionnaires or interviews, and whether participants will be asked to grant full or partial access to their medical records.

G. Estimate the amount of time participation will entail.

H. Describe procedures that will not be done, if appropriate.

Examples:

- If you decide to provide a sample for this study, we will draw about 30 ccs (2 to 2-1/2 tablespoons) of blood from a vein in your arm. The blood will be sent to the CDC in Atlanta, Georgia to study genes that may play a role in why some people get heart disease.

We will also ask you to fill out a survey about your health, diet, and exercise, and your use of tobacco, alcohol, and medicines. It is all right to skip any question you don't want to answer.

We will need less than 5 minutes to take the blood sample. The survey will take about 30 minutes. There will be no medicines to take and no experimental treatments to undergo in this study.

- If you choose to be in this study, we will collect a sample of your cells by brushing the inside of your cheek with a cotton swab. This sample will be sent to the CDC in Atlanta, Georgia for processing.

We will also need to check with your doctors to confirm whether you have had any of the heart diseases we are studying. To do this, we will ask you to sign a form to let your doctor give us a copy of your medical record.

Nothing else is required. We will compare the results with tests on other people who have heart disease and on people who do not have heart disease. The only genetic testing performed on your cell sample will be for conditions associated with heart disease.

How will Information about me be Kept Private?

Once we take your _____ sample, we will assign it a code number. We will separate your name and any other information that points to you from your sample. We will keep files that link your

name to the code number [I]. [J]. No one who reads or hears a report about this study will be able to identify you because, before any facts are given out, we combine your facts with those of other people in this study.

I. Describe security measures.

J. Describe the extent to which confidentiality of records identifying the participant will be maintained.

Example: Once we take your blood sample, we will assign it a code number. We will separate your name and any other information that points to you from your sample. We will keep files that link your name to the code number in a locked cabinet. Only the study staff will be allowed to look at these files. [Add one of the following:]

- For legally unprotected research: We will keep private both the test results and the information you tell us in the survey. We will only release study information if ordered to by a court of law. Your name or other facts that might point to you will not appear when we present this study or publish its results.

- When a Certificate of Confidentiality has been obtained: Records that identify you in this study are strictly private. No one other than study staff can ever look at them unless you agree to it. This is because the study has been granted a Certificate of Confidentiality under a federal law (Section 301(d) of the Public Health Service Act). This means that the records of this study may not be disclosed, even under federal, state, or local court order, without your OK. No one who reads or hears a report about this study will be able to identify you because, before any facts are given out, we combine your facts with those of other people in this study.
- When an Assurance of Confidentiality has been obtained: Your test results at CDC are kept private by an Assurance of Confidentiality under the Public Health Service Act (Section 308(d)). This means that CDC will not let results out with information that identifies you for any reason unless you agree. The records of what you tell us on the survey will be kept at the Heart Alliance here in Anytown. We will release them only if it is ordered by a court of law. No one who reads or hears a report about this study will be able to identify you because we will combine your facts with those of other people in this study.

What are the Risks of the Study?

The physical risks to you for providing a _____ sample for this study are [K]. [L]. [M].

K. Describe relevant physical risks.

L. Describe the informational risks based on the types of information expected and the identifiability of the sample.

M. Describe potential groups harms.

Example: The risks of drawing blood include brief pain, slight bruising, and rarely, infection where the needle went in. We take every precaution to prevent infection. Some people feel dizzy when they have blood drawn, but this goes away when the person lies down.

The kind of information we will look for in this study is not likely to tell you anything specific about your personal health. Even so, there is a risk that if people other than the researchers got your genetic facts they could misuse them. We think the chance of this ever happening to you is very small. To protect your information, we will not keep your name and address with the sample, only a code number. As we said, files that link your name to the code number will be kept in a locked cabinet and only the study staff will be allowed to look at them. Although no one can absolutely guarantee confidentiality, using a code number greatly reduces the chance that someone other than the study staff will ever be able to link your name to your sample or to your test results.

Although your name will not be with the sample, it will have other facts about you such as your race, ethnicity, and sex. These facts are important because they will help us learn if the factors that cause heart disease to occur or get worse are the same or different in men and women, and in people of different racial or ethnic backgrounds. Thus, it is possible that study findings could one day help people of the same race, ethnicity, or sex as you. However, it is also possible through these kinds of studies that genetic traits might come to be associated with your group. In some cases, this could reinforce harmful stereotypes.

Are there Benefits to Taking Part in the Study?

You will not get any direct benefit for giving a _____ sample for this study. The major benefit of the study is [N].

N. Insert the object of the study.

Examples:

- You will not get any direct benefit for providing a blood sample for this study, but you will help us learn more about genes and other factors that may lead to heart disease.

- You will get no direct benefit from being part of this study. But the information and results from these kinds of studies may help prevent and treat heart disease in the future.

Are any Costs or Payments Involved?

It does not cost you anything to provide a _____ sample for this study and you will not be charged for any research tests. [O]. In the unlikely event that you are physically hurt during the process of providing a _____ sample, [P].

The aim of our research is to improve the public health. [Q].

O. Explain whether participants will be reimbursed for things such as time, travel, and inconvenience.

P. Explain what compensation or medical treatment is available if injury occurs.

Q. Explain arrangements regarding the development of products with commercial application and value.

Examples:

- It does not cost you anything to provide a blood sample for this study and you will not be charged for any research tests. You will not be paid for participation in this study. In the unlikely event that you are injured while giving a blood sample, we will give you first aid and direct you to proper health treatment. We have not set aside funds to pay for this care or to compensate you if a mishap occurs.

The aim of our research is to improve the public health. Your blood will never be used to develop a process or invention that will be sold or patented.

- There are no dollar costs to you for being in this study. We will give you $25 to reimburse you for your time and effort. If you are physically hurt because of this research project, we will help you to get medical care through your usual doctor. You or your health insurer will need to pay for any such care that you get.

The aim of our research is to improve the public health. Sometimes, such research may result in findings or inventions that have value if they are made or sold. We may get a patent on these. We may also license these, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits from this may be paid back to the researchers and the organizations doing this study, but you would not receive any financial benefits.

How will I find out the Results of the Study?

The studies we do on the samples we collect are to add to our knowledge of how genes and other factors affect health and disease. We are gathering this knowledge by studying groups of people,

and the study is not meant to test your personal medical status. For these reasons, we will not give you the results of our research on your sample. However, [R]. We will also share what we learn with other health professionals through medical publications. If you have questions about whether any genetic tests would be useful to you, you should ask your doctor.

R. Describe any general communication (e.g., newsletters) about the study that will be provided.

Example: The studies we do on the samples we collect are to add to our knowledge of how genes and other factors affect health and heart disease. We are gathering this knowledge by studying groups of people, and the study is not meant to test your personal medical status. For these reasons, we will not give you the results of our research on your sample. However, you can choose to get a newsletter that will tell you in general about the research studies we are doing. This newsletter will not announce your results or anyone else's, but it will tell you what we are learning about genes and heart disease. We will also publish what we learn in health journals. If you have questions about whether any genetic tests would be useful to you, you should ask your doctor.

What will Happen to my Sample after the Study is Over?

After this study is over, we will throw away all the _____ samples.

[OR]

After our study is over, we would like to keep any unused _____ left over for future research. [S]. We don't have specific research plans at this time but we would like to use the samples for studies [T]. We will store the sample under a code number and we will keep the file that links the code number to your name private. We may share the samples with other researchers for [U], but we will not give other researchers any information that would allow them to identify you. We will always know which sample belongs to you, but other researchers will not.

An Institutional Review Board, like the one that helps protect you during this research project, will review and approve all future projects.

You can choose not to have your sample stored for future research and still be part of this study. You will have the chance to state your choice about this at the end of this form.

S. Describe how the samples will be stored, where, and for how long.

T. Clarify plans for future research to the extent possible.

U. Clarify the types of research that other investigators may be permitted to do.

Example: After our study is over, we would like to keep any unused blood left over for future research. [Insert one of the following:]

- For frozen samples: We will keep it frozen in a specimen bank at CDC and use it for as long as it lasts.

- When cell lines will be created: We will create a living tissue sample (called a "cell line") from which we can get an unlimited supply of genetic material in the future without the need to get more blood from you. Cell lines will be stored at CDC.

We don't have specific research plans at this time but we would like to use the samples for studies of heart disease as well as other diseases. We will store the sample under a code number and we will keep the file that links the code number to your name private. We may share the samples with other researchers for studies of genes and disease, but we will not give other researchers any information that would allow them to identify you. We will always know which sample belongs to you, but other researchers will not.

An Institutional Review Board, like the one that helps protect you during this research project will review and approve all future projects.

You can choose not to have your sample stored for future research and still be part of this study. You will have the chance to state your choice about this at the end of this form.

What are my Rights as a Participant?

You are free to take part in this study or not. No penalties or loss of benefits will occur if you refuse to take part.

If you decide to take part in this study, you may withdraw at any time. You may choose not to have your sample stored for future research and still be part of this study. [V].

We will give you a copy of this consent form to keep for your records.

V. Describe withdrawal following storage for future research.

Example: You are free to take part in this study or not. No penalties or loss of benefits will occur if you refuse to take part. If you decide to take part in this study, you may withdraw at any time. You may choose not to have your sample stored for future research and still be part of this study. [Add one of the following:]

- For unlinked storage: If you agree to have your sample stored, you can change your mind up until the end of the study, when we store the remaining samples. At that time we will remove all information that identifies you. After that we will not be able to withdraw your sample because we will not know which one is yours.

- For coded or identified storage: Also, you may agree to have your sample stored and later decide that you want to withdraw it from storage. If so, you should call the study person listed in this consent form and tell her to discard your sample. She will discard your sample, but any data from testing your sample until that point will remain part of the research.

We will give you a copy of this consent form to keep for your records.

Whom do I Call if I have Questions or Problems?

If you have any questions about how this study works, contact _____, the chief study person, at _____.

If you have any concerns about your rights in the study, contact _____, head of the _____, at _____.

If you think that being in this study injured you, contact _____, the chief study person, at _____.

Consents and Signature

I agree to give a _____ sample for this study. I have been given a chance to ask questions and feel that all of my questions have been answered. I know that giving a sample for this study is my choice. I understand that my individual results from the study will not be given to me. I have been given a copy of this consent form to keep.

I have read the part of this form about storing my sample for future research. My choice about having my sample stored and used for future research under the conditions described is (please check ONE box):

_____ I refuse to have my _____ sample stored or used for [W].

_____ It is OK to store my _____ sample with a code number and to use it for [W].

W. Summarize parameters of future research, e.g., "future research on genes and heart disease" or "any kind of future research."

I would like to receive a newsletter that will tell me about the research study and what researchers are learning in the future studies about genes and disease. Please circle ONE: Yes / No

Participant_____ Date_____

[Add the following if the signature will be witnessed:] I observed the process of consent. The prospective participant read this form, was given the chance to ask questions, appeared to accept the answers, and signed to enroll in the study.

Witness_____ Date_____

DRAFT

Suggested elements for Population Genomics Studies consent forms:

Consistent with and in addition to those elements required by 45CFR46, the following elements specifically apply to Population Genomics Studies and may be considered.

These elements are included in part, and some, verbatim, from Beskow et al JAMA 2001;286(18):2315-2321 with additions based on the specific goals of public posting of genotypic and phenotypic data and sharing with both academics and commercial entities. Additional draft language is highlighted in yellow.

Element	Sample Language	Comment
Introduction	The (*Institution)* is doing a research study to learn about how genes may influence the risk of getting (*disease*).	Identify organization conducting research, objective of study, how participants will be chosen.
Why is this study being done?	Scientists have found genes that may be linked to health and disease and hope that more will be found in the future. The purpose of this study is to find out which genes impact the risk of (*disease*). This may help us to learn why some people get certain diseases while others do not.	
How many people will be participating in this study?	In this particular study, X people will be included, Y who have (*disease*) and Z who do not, for comparison. Because the information from this study may be combined with that collected via other studies, the approximate total number of subjects in studies where this data may be used is not possible to predict.	
What is involved in the study?	If you decide to participate in the study, we will draw about 2 tbsp of blood from a vein in your arm. We will also ask questions *(about…)* and do a brief physical *(including…)*	Describe how the sample and phenotypic data will be collected.
How will information be kept private?	Your blood sample will be given a code number that is different from your birth date, medical record number, or any other number that could be used to identify you. only (name of PI, collaborators) will be able to link your identify with the code. No information that can be used to identify you will be made public or shared outside of the study itself. Genetic information that is unique to you will be available publicly. If another blood sample were drawn from you, and used for genetic analysis, and if it were also associated with your identity by the party that you donated it to, it could be used to identify your in the public database.	Should additional language be included regarding how a database may protect privacy, i.e., such as requiring a password?
What are the risks of the study? • Medical • Genetic	The risk of having your blood drawn, from a vein, is minimal. You may experience discomfort or bruising at the site where the blood is drawn. Although your name and any medical information that may identify you will not be kept with the sample, other facts such as age, sex, ethnicity, and diagnoses in you and that run in your family will be associated with the sample. Additionally, genetic information that is unique to you will be associated with the sample. The risks of this information,	The particular use of genotyping data on a publicly accessed website may have risks that are currently unforeseeable.

	which will be available publicly, may have future risks which we believe are minimal but are unknown.	
Will the study identify genes that can predict who will get a disease?	Genes that may be discovered are expected to increase or decrease the risk for (*disease*) but not to cause it. (*Disease*) has many causes, which include genes. Even though we believe there may be genetic risk factors in (*disease*), the fact that you have this disorder does not mean your children will or will not get this.	Many subjects (as well as IRB members) may be confused regarding the difference between causal (Mendelian) genes and genetic risk factors.
Are there benefits to taking part in the study?	You will not get any direct benefit for providing a blood sample for this study, but you will help us learn more about genes and other factors that may lead to (*disease*). *(Beskow et al 2001).* This study will not directly impact your health.	
Are there costs or payments involved?	(Cite any compensation for participants). Sometimes research such as this results in findings or inventions that may have value if they are made or sold. These would not result in your receiving financial benefits. Additionally, there may be costs in sharing your sample and the de-identified data and the repository that stores these may charge a fee to help offset costs of that banking and sharing.	Per the First generation Guidelines for NCI Biorepositories (4-06), "for profit" was felt to be inappropriate for repositories, other than to cover costs. See http://biospecimens.cancer.gov/biorepositories/guidelines_overview.asp
How will I find out about the results of the study?	The studies we are doing we hope will add to our knowledge of how genes and other factors that affect health and disease. We are gathering this knowledge by studying groups of people, and the study is not meant to test your personal medical status. No personal feedback on results will be given to you. This study also does not predict the risk for any of your relatives. This study does not do genetic testing for any disease. (*if the study will have a newsletter, mention here*).	Some investigators provide a newsletter, others do not.
What will happen after the study is over?	After our study is over, we would like to keep any unused blood left over for future research. We don't know specifically now what those research projects may be. The blood sample and the de-identified information (such as age, gender, ethnicity, diagnosis) will be kept indefinitely for future studies.	
What if I want to have my sample or the information I gave you removed from the study or the public database?	If you wish to have your sample removed from the study, let (*Investigator*) know. However, because the information you're your sample have had all identifying information removed, it may not be possible to track your sample and data in order to remove it from a public data source. Additionally, since the information and the sample may be shared with other researchers anonymously, it may not be possible to track those who have used the information or have the sample and are using it for their study. Despite this, (Investigator) will make every effort to comply with your request.	
Whom do I call if I have questions or problems?	If you have questions about this study, contact_____. If you have concerns about your rights in the study, contract _____. If you think that being in the study injured your, contact _____.	