Participation in the Cooperative Family Registry for Breast Cancer Studies: Issues of Informed Consent

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No universal surveillance system collects information on all cases of cancer in the United States. Instead, cancer data are assembled in a variety of ways. Several very good population-based registries collect data in a fairly uniform manner, but different hospital-based registries often have different formats for data reporting, collection, coding, and analysis. Outcomes of interest include estimates of incidence, prevalence, and mortality; the identification of risk factors through epidemiologic analyses; the evaluation of patterns of care; and financial and resource planning. Few of the registries, however, have any genetic information. The recent identification of genes associated with high penetrance for breast cancer has brought a new focus to the study of cancer genetics—one that emphasizes the identification of families with heritable patterns of cancer—and has created the need for the development of registries that are defined by familial cancers.

The Cooperative Family Registry for Breast Cancer Studies

The Cooperative Family Registry for Breast Cancer Studies (CFRBCS) is an international consortium established in 1995 as a resource for research on the epidemiologic, clinical, and genetic aspects of breast cancer. Funded by the National Cancer Institute (NCI), six sites (Northern California Cancer Center [Union City], Ontario Cancer Genetics Network, Cancer Care Ontario [Canada], University of Melbourne [Australia], Fox Chase Cancer Center [Cheltenham, PA], Metropolitan New York Registry, and Huntsman Cancer Research Center [Salt Lake City, UT]) collaborate to enroll a total of 5000 families at high risk for breast cancer into a family-based registry. The purpose of the CFRBCS is twofold: 1) to collect pedigree information, epidemiologic data, and related biologic specimens from patients with a family history of breast cancer in order to provide a registry resource for interdisciplinary studies on the etiology of and survival from breast cancer and to encourage translational research in this area and 2) to better characterize populations at high risk for breast cancer who could benefit from new preventive and therapeutic strategies.

Individuals with a personal or family history of breast cancer are identified according to a standardized set of eligibility guidelines. An attempt is made to enroll each proband, her first-degree relatives, and her affected second-degree relatives. Participants are asked to provide detailed family-history data as well as epidemiologic, medical, and lifestyle information. Blood samples are obtained from participating family members, and tumor specimens are requested from those with a cancer diagnosis. These resources are then made available to the research community for studies approved by an external advisory board of scientists and patient advocates.

The principal investigators from the participating sites and the leadership of the NCI recognized immediately the need to address the unique aspects of participation in a family-based registry with an emphasis on genetic research. The Informed Consent Working Group was created to identify issues of primary interest in the informed-consent process as it relates to involving families in an ongoing process of data collection, evaluation, and analysis and to develop a model informed-consent document. This commentary presents the results of its deliberations and discusses those issues of particular significance to registry participation.

History of the Consent Process

Beginning with the publication of the Nuremberg Code in 1949, the realization of the need to involve research participants in voluntary consent has been a growing and evolving process. Although written consent forms for therapeutic research were introduced at the National Institutes of Health (NIH) in 1953 (1), it was not until the 1970s that the research community, in partnership with the federal government, began to develop formal guidelines for the ethical conduct of medical research. The Code of Federal Regulations published in 1975 created the system of Institutional Review Boards (IRBs) that were charged with safeguarding the rights and well-being of research subjects and guaranteeing that appropriate informed consent is obtained (2). The purpose of the consent form is to apprise the prospective research subject of the nature of the study and to disclose the potential risks and benefits associated with participation. IRBs have become an integral part of the medical research environment, and the process of obtaining informed consent has become part of the standards and guidelines in the conduct of medical research involving human subjects.

General agreement has been reached about the required con-

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See “Notes” following “References.”
The members of the Informed Consent Working Group clearly identified the need to consider informed consent as a process that is based on a trusting relationship between study participants and investigators and reflected in both verbal and written formats. The goals of the consent process are to ensure respect for the participants, to guarantee participant autonomy, and to facilitate informed decision-making. As a first step, the group identified seven core content items necessary for inclusion in the consent form.

1) Study purpose: The rationale for the collection of information and biospecimens from a cohort of defined-risk families into a multisite registry should be stated as clearly as possible. This is particularly important, since the registry is a resource for future research projects and not a research project itself. While the individual research projects that will use these resources will, at the time of informed consent, be undefined, the general categories of research (e.g., new gene discovery, risk factor identification, and gene–environment interactions) can be described to emphasize the potential value of the resource being developed. The rationale for including data from multiple sites should also be explained. It is important that participants be made aware that the outcome of research is always uncertain but that knowledge may be gained as a result of their participation in the registry.

2) Eligibility: Individuals agreeing to participate in a family-based cancer registry should have a clear understanding as to what role they play in the potential research and what personal and family characteristics make them eligible for participation. This information helps to explain the need to enroll the family as a whole, rather than isolated individuals within the family, and fosters a sense of community and common goals with other participating families.

3) Procedures: The nature and extent of commitment to the registry should be understood before a potential participant agrees to participate. It is especially important that the proband understand that she will be responsible for providing access to and encouraging participation by other eligible family members. The type and quantity of data to be collected must be clearly specified. The following items should be included: the number, content, and frequency of the study questionnaires; the frequency of follow-up contact; and the frequency of blood collection and amount of blood typically collected. When appropriate, the need to obtain tumor specimens and pathology reports should be explained, and consent should be obtained. The possibility of recontact for specific study needs and the need to identify proxy informants to supply information for family members who are deceased should also be made explicit.

4) Use of registry data: The consent form should describe how investigators apply to use registry resources and explain that their requests are peer-reviewed. Participants should be aware of the nature of prospective research results and when and how they will be reported and shared, how new research findings will be added to the registry database, and the process to be followed when research findings appear to have potential clinical benefit. (Of particular relevance here is the mechanism by which clinical benefit is determined.) The estimated duration of DNA banking should be stated.

5) Property rights: Biospecimens and any products thereof are the property of the registry. Participants are assured, however, that the specimens they provide will be used only for the purposes described in approved study projects. Participants may be rightly concerned about the fate of biosamples that they provided when the original project is completed and funding ends. In most registries, specimens are saved indefinitely, since one of the goals is to be responsive to new research directions, but participants retain the right to withdraw from the registry and to request that their samples be destroyed and deleted from the registry database.

6) Risks, benefits, and costs: Risks referred to in traditional consent forms usually pertain to physical effects associated with different treatment modalities. In the case of participation in a family cancer registry, however, risks are more likely to be psychological or social and may involve changes in established family dynamics. Participants should be informed that they or other family members may discover things about themselves that they did not really want to know or are unsure how to react to. The risk of genetic discrimination by virtue of participation in a cancer family registry, particularly by insurers or employers, should be mentioned as a possibility, albeit a remote one. The benefits to society of each individual’s participation (education and information received, the benefit to future generations, etc.) should also be stated.

7) Confidentiality: Participants should be informed how the data and biosamples that they provide will be protected from violations of confidentiality. Methods of coding, encryption, physical storage and security, and transmittal of data, especially electronic information transfer, should be described. Biosamples stored in a central repository should be coded

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with identifiers removed prior to storage so that the ability to identify samples is left only with the site from which they originated.

The Informed Consent Working Group agreed that all information should be conveyed to potential participants in language that is clear and suitable to their ages, educational levels, and cultural backgrounds. They recognized that many research subjects are interested in receiving even generalized or preliminary research project results, and another decision emerging from these discussions was the commitment to publish a regular newsletter to keep participants informed about the development of the registry, about ongoing research projects, and about general research results as they are reported.

**CONTENT AREAS OF PARTICULAR SIGNIFICANCE FOR REGISTRY PARTICIPATION**

Some aspects of consent to participate in a family-based registry for the purpose of genetic research deviate from the more traditional individual-focused clinical research protocols and require special consideration. The communication of data from multiple, international sites to a central data repository requires special safeguards. Uncertainty about the nature of the research projects that will be conducted by use of the registry’s resources is common. The extent to which other family members may be affected by either registry participation or registry research findings is also unclear. And finally, the delicate distinction between research results and clinically significant findings may be especially difficult to define in the case of genetic data.

**Privacy and Confidentiality**

At the core of the ethical issues associated with the involvement of human subjects in medical research are the issues of privacy and confidentiality. Privacy pertains to the extent to which others can gain access to information about an individual. Privacy issues may arise in research when information is obtained about individuals without their specific consent to divulge or to disseminate that information. Of particular significance is the case of family-based studies, where one person often provides information about the medical histories of family members without their explicit consent. The creation of a family pedigree may reveal previously unknown relatives or may uncover patterns of disease of which the family was unaware.

It has been suggested that publishing family pedigrees poses the risk of invasion of privacy (3). Individuals may experience pressure from other family members to provide information so that the pedigree is complete. While recognizing that there is no clear consensus on this issue, the Office for Protection from Research Risks (OPRR) of the U.S. Department of Health and Human Services has stated that IRBs can consider the collection of pedigree information to be acceptable as long as the nature of the risks involved is defined (4).

Although the identification of the size of the family by the proband is a necessary first step in the creation of a pedigree, the subsequent recruitment of additional family members to a family cancer registry should be done without coercion and with sensitivity to the needs and concerns of each family member. The strategy taken by the Informed Consent Working Group was to request specific written permission from the proband for the registry’s staff to contact each additional family member. This policy gives the proband the opportunity to consult with other family members to decide whether withholding permission to contact some family members is in their best interests. At the same time, it removes the burden of actual recruitment from the proband and allows individuals contacted by registry staff to decline to participate without fear of recriminations from family members.

In genetic research, issues of confidentiality equal privacy issues in importance. Confidentiality pertains to the handling and use of data provided by an individual for the purpose of scientific research. Appropriate mechanisms must be in place to prevent the improper disclosure of information and to limit the use of the data to the purposes prescribed in the consent process. Special confidentiality concerns arise in family studies because of the unique nature of genetic data and the implications that information about one family member may have for other family members.

The assurance of confidentiality in genetic studies has two components. First, participants in the registry should be clearly informed as to the physical security of their data and biospecimens, including methods of coding and removal of identifiers, encryption techniques, and quality-assurance policies. Second, participants should be informed about the process of releasing data to future investigators as it relates to maintaining confidentiality. To address the latter issue, the CFRBCS has been constructed as a functionally anonymous data bank that uses an informatics structure that maintains linkages to personal identifiers for the purposes of long-term follow-up but blinds individual investigators to these identifiers.

**Use of Data and Biospecimens by Investigators Outside the CFRBCS**

Storage of biospecimens in a tissue repository for the purpose of future research creates an archive of biologic samples. The use and reuse of archived tissues are areas of growing debate, particularly when they involve the banking of genetic material. IRB guidelines developed in 1993 by OPRR indicate that investigators should attempt to disclose plans for subsequent use or reuse of data or biospecimens at the time of consent. The dilemma is knowing how to disclose to prospective registry participants the potential risks resulting from research when the nature of future research projects is unknown, and the current pace of genetic research challenges our ability to adhere to the OPRR’s recommendation.

The Informed Consent Working Group considered under what circumstances the investigator should be required to obtain a new consent for use of the specimens stored as part of registry participation, a process that may put undue burden on the research subjects or compromise the research effort. Several documents address this issue.

By federal regulation (5), research using stored tissue samples is exempt from IRB review if the tissue samples already exist when the research is proposed and the ability to identify the research subjects is not available to the research team. In cases where samples can be linked to individuals, renewal of consent may be waived when 1) it is judged that there is minimum risk to the subjects, 2) the rights or welfare of the subjects will not be jeopardized, 3) the research could not feasibly be carried out without the waiver, and 4) subjects will receive information about their role in the research when appropriate (4,6,7).
The Genetic Privacy Act, a proposal for federal legislation, recommends a stringent set of consent mechanisms for genetic research, including the restriction of access to DNA samples to persons clearly authorized by the subject at the time of consent and the requirement to destroy the sample upon completion of the specifically authorized genetic analyses unless retention is clearly authorized or the specimens are made anonymous (8). This proposal is based on the premise that genetic information is qualitatively different from other types of medical information, since it provides information about the health of the individual’s family and has, historically, served as a means of discrimination.

A workshop convened by the NIH and the CDC in 1994 determined that all investigators, including those not directly involved in the participant’s care, should be bound, in most cases, by the limits of the original consent and that, given the potential for risk involved in genetic research, individuals have the right to determine how their samples are used. This principle implies that renewal of consent would be necessary for research projects that are not described in the original consent form. The workshop participants made an exception for samples that were made irretrievably anonymous, since renewal of consent would be impossible (9).

The ASHG, on the other hand, takes a somewhat more flexible view regarding samples that are identifiable. Its statement maintains that subjects providing samples for prospective studies should be informed about the nature of the research proposed, its possible limitations and outcomes (including the possibility of unexpected findings), and the steps that will be taken to assure confidentiality. The ASHG supports renewing consent by subjects for new studies but offers criteria that allow recontact to be waived and that are based on the level of risk involved and the practical constraints imposed by the process of renewing consent (10).

All of the statements and guidelines published to date recognize the uncertainty of many issues pertinent to genetic research and recommend continued debate both within the scientific community and within society at large. Given these limitations, the Informed Consent Working Group recognized the need for an oversight body to monitor the use of the resources stored in the CFRBCS. With the agreement of the entire steering committee, it was decided to expand the advisory committee to include individuals with expertise in the legal and bioethical aspects of genetic research and to give the committee the responsibility to include the issue of renewing consent in their evaluation of research projects. The existence and function of this Research Ethics and Monitoring Panel (REMP) are made explicit in the consent form so that potential registry participants are made aware of the nature of the decision-making process as it relates to their biosamples.

**Communication of Registry Research Results**

Traditionally, data from studies in research laboratories have not been communicated to the individuals who provided samples for the project. This policy is based on the assumption that results generated in a research laboratory may be subject to less stringent reliability criteria than those originating from a clinical laboratory that is subject to the strict quality-control conditions set by the Clinical Laboratories Improvement Act. Even under the conditions set by this act, many people have questioned the clinical utility of genetic tests that predict the probability of future diseases for which there are no efficacious protective interventions. Although the specific purpose of enrolling families into the CFRBCS was not to perform genetic tests on individual family members, the Informed Consent Working Group appreciated the likelihood that many proposed research projects would include mutation analyses for the major genes associated with breast and ovarian cancers, thereby creating a dilemma regarding the communication of these test results. If results were not communicated to CFRBCS participants, they might be deprived of the potential benefits of knowing their carrier status and taking (or not taking) preventive actions indicated by the results of their tests. On the other hand, giving research results to individuals who had not specifically consented to be tested for a particular mutation—and who may not want the information—raises many other ethical problems.

After much deliberation, it was decided that the consent form would indicate that, when information of potential clinical benefit was obtained as a result of research performed with CFRBCS resources, participants would be notified collectively and offered the opportunity to seek individual genetic testing in a clinically approved laboratory. The definition of clinical benefit would be determined by the full advisory committee, including the members of the REMP, and would be based on the accuracy of the test results, the magnitude of the potential threat posed to the research subject, and the magnitude of the potential benefit to be derived from receiving the information. While this compromise was thought to be reasonable, it was appreciated that it does not address the financial barriers to genetic testing in the clinical setting.

**Process Issues**

In the process of developing a model consent form, the Informed Consent Working Group identified two process issues that could affect the final form and style of the consent document at each site: 1) legal and regulatory issues for multiple sites and 2) geographic and cultural issues.

**Legal and regulatory issues for multiple sites.** IRB approval of research protocols remains a local prerogative and is subject to the history, philosophy, and legal constraints of each board. The Informed Consent Working Group recognized the possibility that individual state laws may jeopardize the acceptance of its model consent form and would necessitate local modifications. New York State law does not, for example, allow genetic test results generated in a research setting to be used to inform individuals, because an informed-consent process specific to the exact test being performed is required, and testing must be performed in a state-approved clinical laboratory.

**Geographic and cultural issues.** The ability to study diverse populations in different countries served by different health care systems is a tremendous strength for the CFRBCS in terms of research opportunities. It provides some challenges, however, with regard to standardization of the informed-consent process. Although there is international agreement on the basic principles of the process, there is also a need to respect the community milieu and the cultural context in which the research is conducted. For example, scientists and identified social leaders within a Native-American tribe collaborated to develop a protocol for genetic research that relies on communal decision-making as opposed to individual determinism (11). And geneticists in China are far more supportive than scientists in the United States of enforced government-initiated genetic-screening programs (12).
WITH reference to CFRBCS members, one of the major differences between the U.S. sites and sites in Canada and Australia is the organization of health care. While there are millions of uninsured and underinsured individuals in the United States, where health care is a complex mixture of private and public programs, both Canada and Australia have National Health Services that guarantee basic health care to all citizens. This situation translates into major differences in the litigious climate and in individuals’ perceived and real levels of vulnerability with regard to confidentiality and how it affects the availability of health care to them. In the United States, one of the major reasons cited for not participating in genetic testing research protocols is fear of discrimination by insurance companies (13). Residents of Canada and Australia, in contrast, do not share that risk and are likely to view genetic research with less concern. [Although in Canada the lack of a common law tort of discrimination precludes civil action against an insurer for discrimination, human rights legislation may provide limited protection from the use of genetic tests in underwriting insurance policies (14).]

**Impact of Other Regulatory and Advisory Bodies**

A growing number of academic, governmental, and political bodies are attempting to set policy with regard to genetic research and privacy, confidentiality, and discrimination issues. Their goals and agendas differ and change repeatedly to try to keep pace with the speed of genetic discovery and application. This changing environment makes it particularly difficult to address the concerns of all these organizations while developing and maintaining guidelines for informed consent for participation in the CFRBCS.

**CONCLUSION**

In order to promote and to preserve the public trust, which is essential to the success of genetics-based research, it is imperative that investigators maintain the highest ethical standards regarding informed consent and, at the same time, remain sensitive to cultural and social norms of scientific research. Genetic research in the current environment emphasizes the tension between the preservation of individual autonomy and the potential reward to the individual of contributing to genetic discovery. We recognize that the balance achieved and represented while explaining the CFRBCS to potential participants must reflect societal values and must strive to maximize benefit and minimize risk. The Informed Consent Working Group has extended the debate on informed consent by 1) considering the competing needs of the individual, the family, and the public; 2) recognizing the need for special expertise in ethics and law in the guidance of the CFRBCS; 3) anticipating the need for flexibility in the consent process as genetic knowledge moves ahead at unprecedented speed; and 4) acknowledging the responsibility of the investigators to include research participants in the dissemination of research results. It is hoped that these efforts may have relevance to others in the field of genetic research.

**REFERENCES**


**NOTES**

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