

Fred Hutchinson Cancer Research Center

Institutional Review Board

Genetic Research Guidelines

There is growing concern that ethical issues in characterizing people according to genetic traits in research studies need to be considered. Therefore, the FHCRC-IRB has developed the following recommendations and points of consideration to assure that the investigators designing research protocols and consent forms consider the ethical issues unique to the conduct of genetic research. Genetic research includes:

- **Testing of any biological material for genetic alterations or variations.**
- **Family (Pedigree) studies.**

The following recommendations and points of consideration, with few exceptions, are only guidelines and not rules that apply to every study.

- I. Recommendations for research activities in which subjects from previous studies need to be re-contacted because either stored specimens or other key data (e.g., family history) are being obtained, and genetic testing is part of the new research activity.*

These studies should, for the most part, be treated as if they were new investigations in which the participation of human subjects will be solicited and genetic tests performed. All subjects should give consent. All of the issues presented below, as well as others to be identified, should be addressed in the IRB application, and consent forms.

- II. Recommendations for research activities in which genetic testing was not part of the original protocol (and thus, not mentioned in the consent), but stored specimens exist that would permit such testing; what factors influence the need to obtain consent (e.g., through re-contact or subjects) to conduct such tests?*

A. Clinical Impact of Knowledge of Results

The need for consent for genetic testing of biologic specimens depends primarily on the degree to which the information that would be obtained would be important to the clinical care of the subject. If the results of a test for a gene or marker have clinical utility (e.g., counseling might be performed, effective treatment may be available), then the participant must provide informed consent before testing can be performed. If the test is not being used clinically, (e.g., it is not

even clear to what extent the gene or marker is related to the disease of interest), informed consent is not needed. If there is on-going debate about the clinical utility of the test, consent must be obtained. The definition of "clinical utility" is necessarily vague and would be expected to vary from test to test, etc. For this reason, investigators will need to provide sufficient background to permit the IRB to perform a fair review.

Points to consider when preparing the IRB application:

Briefly summarize the current status of the clinical utility of the results of the genetic tests proposed in this activity. For example, has the test been used to counsel or treat individuals? When is it likely results will be clinically useful? (If in the near future, please specify in the consent form the need for recontact for future studies and ask subjects if they would want their physician contacted about test results.) What mechanism has been established for subsequent testing and determining validity of test results?

B. Feasibility of Re-Contacting Subjects

Even in circumstances where the genetic test has clinical value, the need to obtain re-consent for genetic testing depends to some extent on the practical issue of re-contacting subjects. To the extent that it is infeasible to re-contact a substantial portion of the study population, re-consent could be waived. An extreme example of the latter is if the analyses are completely blind (i.e., it is not possible to link results to individuals).

Points to consider when preparing the IRB application:

Discuss the feasibility of re-contacting former study participants to obtain consent for performing the tests specified in the application. If former participants can be identified from study records, how would the need to re-contact subjects impact the ability to conduct the proposed tests and the validity of the results? Factors to consider include (but are not necessarily limited to) direct costs of locating and contacting individuals, and negative reactions from individuals who may view re-contact as an intrusion. How do these factors compare to the risks of not informing the participants that the specific tests are being performed?

III. *Recommendations applicable to studies in which participants have consented to some type of genetic testing.*

In addition to the usual elements of consent, the following elements must also be considered when conducting studies in which genetic tests will be performed.

A. Need for Participants in Genetic Studies to Remain Abreast of New Developments

Although many tests for genetic characteristics will have no immediate clinical relevance, scientific advances could lead to the use of such tests within the lifetime of the participant and/or his/her immediate family members. Investigators who have received consent to test for genetic characteristics should consider the extent to which they should be prepared to inform research participants of developments that could have clinical relevance. The degree to, and manner in, which this activity might be performed will depend on several factors, including (but not necessarily limited to): 1) the likelihood that use of the test in clinical settings would expand considerably during the life of the study, 2) the extent to which investigators have established a long-term relationship with the subjects (e.g., as in a cohort study or series of studies on the same population), 3) the feasibility of actively contacting participants vs. having information available should participants contact investigators.

Will the project have a role in providing information to participants regarding any expanded clinical relevance of the proposed test(s) that may occur? If not, explain. If so, what approach(es) would be used?

Points to consider when preparing the IRB application:

Describe plans in the study protocol to encourage participants to keep abreast of changes in knowledge regarding the clinical utility of specific genetic tests made as part of the proposed research.

B. Providing Information to Subjects

If it has been determined that the genetic characteristic(s) being determined definitely has/have clinical utility, or if the clinical utility is under debate, each subject should be advised of this in the consent form. If the tests are performed by a certified diagnostic laboratory, each subject should be given the opportunity to receive or not receive results, or have results sent to his or her health care provider. The IRB application and consent form should describe the method(s) by which the results would be communicated. If the testing will not be done in a clinically certifiable manner, each subject should be so advised. In such instances, consider the extent to which the project should provide subjects with information on the availability of certified diagnostic testing.

Points to consider when preparing the IRB application:

Will the results of any of the genetic tests be made available to participants? If so, describe your plans for 1) confirming test results in a clinically certifiable manner, and 2) providing information about the results of these tests to the participants and/or their health care provider (e.g., drafts of letters, telephone scripts). What resources will be available, if any, for participants with no health care provider but who need assistance in understanding the meaning of the test results? If the proposed tests will not be certified for diagnostic use, what plans (if any) will be made to provide interested participants with information on the availability of certified diagnostic testing?

C. Setting in which Biologic Specimen is Obtained

The possible implications of the result of a genetic test for a participant's insurability may be affected by the setting in which the biologic specimen is obtained. In particular, if the specimen is obtained in such a way that an insurance company or other form of health plan (e.g., HMO) is charged for the procedure (e.g., an extra tube of blood drawn as part of a participant's routine blood work), it may be easier (legally) for the insurer to obtain the results than had the specimen been obtained entirely in a research setting. This issue is particularly important in studies in which collections of specimens by clinicians is the only way to obtain appropriate specimens (e.g., pre-treatment, fresh biopsy tissue).

Points to consider when preparing the IRB application:

Will any biologic specimens be obtained during the regular clinical care of the subject? If so, the consent form should state that there is a possibility that the results could be released to insurance companies.

IV. Recommendations specific to family studies.

A. Sharing of Information Among Family Members

Family studies sometimes involve sharing of information regarding disease status among family members (e.g., for validation or clarification). With increasing emphasis on gene-environment interactions, this could conceivably extend to other characteristics (e.g., smoking history, reproductive history, medication use). Sharing of such information, however, leads to a loss of confidentiality. It could also lead to stress among persons learning of the health status of relatives.

Points to consider when preparing the IRB application:

Does the protocol involve sharing information regarding the disease status of individuals among family members? If so, this fact should be included in the appropriate section of the applicable consent forms.

To what extent could such loss of confidentiality be stressful to either 1) persons receiving such previously unknown information, or 2) persons to whom the information applies?

B. Pedigree Publication

Publication of pedigrees allows a greater chance for individual research subjects, or entire families, to be identified. If there is a possibility that this may be done (even if not part of current plans for publications), consent forms that include traditional wording regarding "no individuals will be identified in the reporting of this study" are likely to be only partially correct. More accurate consent form wording must be used (e.g., "Individuals will only be identified by [gender, age] and their relationship to other family members. Names of families or individuals will not be reported." Demographic information and geographic location may allow identification of a specific individual or family group.).

Points to consider when preparing the IRB application:

There are two types of pedigree studies:

- 1) Population based studies which cannot be linked to an individual.
- 2) Studies involving several extended families which can be linked to specific families and disclosure of study results can be very damaging.

Will investigators publish pedigrees as part of the dissemination of their research findings? What steps will be taken by the investigators to minimize the possible identification of individual family members, or the family as a whole (e.g., deleting gender or age of family members when reporting pedigrees)?

V. *Recommendations for new studies in which testing for genetic susceptibility is not a focus of the specific aims.*

ISSUE. What if you store DNA and wish to test this sample five years later for a previously unconsented purpose and the subject is deceased? Is consent by a legal representative required in order to test this preexisting specimen?

Points to consider when preparing the IRB application:

There are a number of issues which one may want to consider prior to answering the question of whether having the consent of a legal representative of a deceased subject is required before testing a preexisting sample of the deceased person. Will the proposed testing permit identification of familial relationships (e.g., through pedigree or positional cloning studies)? To what extent could there be emotional or legal ramifications should new information about familial relationships (e.g., changes in paternity) be uncovered? How does the probability of these ramifications occurring relate to the need or feasibility of contacting next-of-kin or other legal representative?

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- Resources:
- 1) FHCRC - IRB 1994 Ad hoc Policy Board
 - 2) OPRR 1993 *IRB Guidebook*
 - 3) McKay, Charles R.: Points to Consider in Research Related to the Human Genome. *Human Gene Therapy* 1993; 4:477-495