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# Yale University Institutional Review Boards

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## 400 PR.3 Use of Genetic Tests and Investigational Genetic Tests in Human Research

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### Overview

The guidance addresses protocols in which there is genetic testing, either through validated tests or via tests for which some aspect is investigational in nature. The term “investigational tests” includes tests for which the marker under investigation has not been verified to correlate with a disease or other phenotypic state, or for which some aspect of the test is experimental in itself. The guidance has developed out of concern about the individually identifying information that is available from genetic test results, and the potential risks related to inadvertent disclosure of the test results. The guidance is meant to apply to the various kinds of individually identifying tests and research that use biological materials, i.e., DNA, RNA, proteins, chromosomes, tissues, and cells (that contain DNA, etc.).

Both validated and investigational genetic tests performed in the context of a research study are subject to all of the standard requirements, including IRB review and exemption or approval under 45 CFR 46.111(a). The potential for participants to receive the results of a genetic or investigational genetic test should be anticipated and addressed when the protocol is submitted to the IRB for review. Further information on communicating individual research results to participants can be found within *IRB Policy 720: Findings with Possible Health and Safety Significance of Research Participants* and *720GD.1: Sharing Study Findings with Participants*.

The guidance also describes considerations in the areas of informed consent including a balanced and accurate description of the impact of the Genetic Information Nondiscrimination Act (GINA) in the areas of risk minimization and confidentiality, as appropriate.

The guidance should also be considered in projects that involve banking and future use of genetic materials. Biological materials provided for genetic tests should generally be retained for as long as they are deemed useful for research purposes according to the policies and procedures laid forth in the *IRB Policy 440: Biological Specimens and Repositories*.

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### Participant Concerns in Genetic Research

Unlike physically invasive forms of research, research studies that use genetic information have the potential to expose research participants to harms stemming from social and psychological injury rather than from physical injury. Studies that generate information about subjects’ personal health risks may possibly provoke anxiety and confusion, damage familial relationships, and compromise subjects’ insurability and employment opportunities. In some cases, the results of a genetic test may not provide a direct correlation to a specific risk, or the test may not have undergone the scrutiny of a carefully controlled research study to determine the value of the information generated. Nonetheless, the test results may raise concerns for participants, even when presented in an unbiased manner that reflects the investigational or non-diagnostic nature of the result. These concerns include:

1. Access to or retention of benefits or entitlements (e.g., health insurance, life or disability insurance, educational opportunity and employment)
2. Stigmatization: views of others, within or without the subject’s family, about the subject; possibility of altered family relationships and interactions.
3. Psychological responses to information: altered self-concept; possible feelings of depression, guilt and anger.
4. Detection of biological relationships within a family: paternity, maternity and adoption.

Some of these concerns are addressed in the Genetic Information Nondiscrimination Act of 2008 (GINA), a Federal law that prohibits discrimination in health coverage and employment based on genetic information, and thus decreases certain types of risks related to research participation in studies involving genetic tests. Critical to the use of genetic information in research is the recognition that researchers are

custodians of their subjects' genetic information and must respect the subjects' right to keep that information private, especially when a breach of this confidentiality could result in damage to the subjects' well being.

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## **The Genetic Information Nondiscrimination Act (GINA) of 2008**

GINA (H.R. 493) prohibits certain types of discrimination based on genetic information obtained through either a clinical or research-related interaction or intervention. In doing so, GINA addresses some of the real or perceived risks of genetic research and an individual's willingness to participate in such research, including disclosure risks of information obtained through genetic services such as genetic tests, genetic counseling and genetic education. The protections of GINA extend to the use of genetic information collected in the past.

GINA's protections against genetic discrimination and any limitations to the scope of these protections should be clearly presented in consent forms as appropriate. The IRB will consider whether the inadvertent disclosure risks are minimized and reasonable in relation to anticipated benefits and whether there are adequate provisions in place to protect the privacy of subjects and maintain the confidentiality of their data.

### **What GINA does and does not cover**

1. GINA applies to genetic testing or collection of genetic information. The term "genetic information" is defined by GINA as information about 1) an individual's genetic tests; 2) genetic tests of an individual's family members; 3) genetic tests of a fetus or legally-held embryo; 4) an individual's family medical history; or 5) requests for, or receipts of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling or education) by an individual or an individual's family members. "Genetic tests" under GINA are defined as an analysis of human DNA, RNA, chromosomes, proteins or metabolites that detect genotypes, mutations or chromosomal changes. Routine blood tests such as those that analyze proteins or metabolites directly related to a manifested disease, disorder or pathological condition are not protected under GINA.
2. GINA prohibits discrimination in either health coverage or employment based on genetic information. Together with the Health Insurance Portability and Accountability Act (HIPAA), GINA provides protection against health insurers or health plan administrators requesting or requiring genetic information for an individual or their family members, or using it for decisions regarding coverage, rates and pre-existing conditions. An exception is that health plans engaged in research can request but not require an individual undergo a genetic test. The exception requires, in part, that the activities comply with HHS regulations at 45 CFR 46 and other applicable laws, that the results will not be used for insurance underwriting purposes and the Federal government is notified in writing about the activities.
3. GINA prohibits employers with at least 15 employees from using genetic information for any decisions regarding employment including those of hiring, firing, promotion or terms of employment.
4. GINA does not prohibit discrimination in matters of life insurance, disability insurance or long-term care insurance, and does not mandate coverage for any particular test or treatment and allows health insurers to obtain genetic test results in making health insurance payment determinations.

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## **Communicating the Results of an Genetic Test**

Genetic tests may be done on anonymous or identifiable samples, and may involve tests with substantiated clinical value or be investigational with regards to the meaning of the information generated. The following considerations apply when determining whether it is appropriate to return the results of a genetic test to participants or third parties.

### **1. Communicating the results to the participant.**

- a. Participants should be informed when a given genetic test is investigational in nature and told that the investigational genetic test is not approved under Clinical Laboratory Improvement Amendments (CLIA) of the Food and Drug Administration (FDA) or by state laboratory authorities

of appropriate jurisdiction and therefore should not be regarded as definitive, established or validated.

b. Genetic tests performed on anonymous samples in which the samples have been de-identified to HIPAA standards and no link to identifiers is retained would not be able to return the test results to participants. Participants should be informed that the test results can not be returned to them for this reason.

c. Genetic test results yielding information without major clinical impact derived from coded samples for which a link to the identifiers has been retained can be shared with the participants only with IRB approval of the planned communication.

d. Genetic test results assaying for a marker with a known major impact on clinical care require consideration by the investigator and IRB regarding the meaningfulness of the anticipated test results and whether notification of the participant would allow changes to their care or health related behaviors to mitigate the impact of the genetic status. The consent form should clearly explain whether or not the study will provide the test results. If test results will not be provided, then participants should be informed that those interested in learning whether they carry a certain genetic marker should contact their clinician for the testing.

e. In all cases, participants should be encouraged to follow-up with their clinician for more information or additional testing if they are interested.

In cases where contacting the participant is possible, and the IRB decides that re-contact is in the best interest of participants, the content of the message or information conveyed to the subject must have been pre-approved by the IRB. The IRB and the investigator(s) will favor communications suggesting that the person contact his or her regular health care provider for established, validated testing in cases where such testing is available and would likely yield the same or similar information. In all cases, such communications to participants must be scrupulously correct and unbiased.

## **2. Communicating the results to others.**

a. The results of any genetic test shall not be released to family members, individuals not named on the informed consent, or any third person or organization without specific authorization from the individual subject of the test or the subject's legally authorized representative.

b. The results of genetic tests conducted within a research study can not be placed in a subject's medical record without specific consent from the subject.

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## **Use of Genetic Tests in Pediatric Research**

The sensitive and enduring nature of genetic information makes it critical that special care be taken when genetic testing involves minor subjects. The investigator must consider the following specific issues in the research proposal when minors are to be included in a study involving a genetic test:

1. The form of assent that will be used and whether meaningful assent can be obtained from the minor subjects for the study;
2. Whether the minor, upon reaching majority, should be afforded the option of agreeing to or declining continued retention by the institution of his/her biologic materials for future possible genetic testing; and
3. Whether the choice by parents or other legally authorized representatives in regard to the option of being re-contacted for additional data, biological material donations, or receipt of clinically meaningful information generated during a research study will continue when the child reaches the age of majority, or whether such subjects should be re-contacted at the time of majority, or at any other time, to be given the option of re-contact or declination of re-contact;
4. Whether, for subjects who reach majority, the investigator might request that the IRB grant a waiver of informed consent and HIPAA authorization under applicable standards which will depend on the specific circumstances of the research.

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## Special Informed Consent Considerations for Studies Using Genetic Tests

The informed consent document providing information regarding a genetic test must include all the key elements of consent required by IRB Policy 200, Informed Consent and also address the following elements as applicable, unless specifically waived or altered by the IRB under 45 CFR 46.116(c) or (d).

1. A statement that the biological sample and data will not be used or tested for purposes other than those authorized and that the sample shall be retained for as long as it is deemed useful for research purposes, unless consent for retaining the specimen has been withdrawn. It should be noted that widespread sharing of the sample and/or data may occur. A description (this can be broad) of the types of research that may use the sample in the future should be included; if applicable, describe methods of analysis such as immortalization of cell lines, whole exome or genome sequencing, genome wide association studies (GWAS), injection of human cells into animals.
2. A statement of the risks of participating in the research, including the risks related to inadvertent disclosure of the results of the genetic test, and including the relevant protections offered by GINA if applicable. *(For research involving genetic or related testing, subjects must be informed of any risks associated with the genetic information that may result. Such risks could include reduced access to or retention of benefits or entitlements (e.g., insurance, educational opportunities, employment, etc.); stigmatization; psychological distress in response to information; or detection of biological relationships within a family).*
3. A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained. This is generally accomplished by stripping identifiers and establishing a code that links the de-identified samples/data back to identifiers. The key to the code is generally maintained locally while the shared data/samples are sent de-identified.
4. If appropriate for the study, a statement regarding whether or not the individual will receive the results of the genetic test from either the primary research project or future projects. In some cases, the IRB may authorize re-contact even without consent by the participant to the future re-contact, based on compelling medical or humanitarian reason for notifying the participant;
5. A statement that the participant may withdraw his/her sample or data from future use, or a statement that the participant may request that his or her sample or data be only used anonymously in the future. Any statement must be consistent with the Yale IRB policy and required forms for tissue and data banking. If there has been data derived from the samples (or initially collected data), the investigator shall inform participants that derived data will continue to be used as part of the approved research or, alternatively, would be destroyed;
6. If the test is investigational in nature, a statement that the efficacy, accuracy or diagnostic value of the test itself is unknown or being investigated, and that a test result may not be an indication that the individual is predisposed to or may have the specific disease or condition targeted by the test;
7. If the test is investigational in nature and an established, validated genetic test may already be used in clinical practice to detect the same genetic variation that the investigational genetic test is designed to detect, the consent document should inform the subject about the existing validated test. The consent document may also recommend that the individual consider pursuing genetic counseling and consider testing using the established, validated technology outside of the research study if the subject desires testing outcomes;
8. If appropriate for the study, a request (which must be agreed to or rejected by the participant) that the investigators or their designees be allowed to contact family members of the individual to obtain additional data or biological materials.
9. A statement about the potential for commercialization of products, stating that the *[Tissue/Specimen/Data]* obtained from the individual may be used to establish a *[product or information]* that could be patented and licensed by Yale University. If materials from the bank were shared with other investigators, the research and patenting might reach outside Yale University. In either case, there are no plans to provide financial compensation to the individual should this occur. The *[Tissue/Specimen/Data]* will not be sold.

