

## GENETIC/GENOMIC RESEARCH

*This guidance document is intended for researchers using participants' samples (blood, saliva, or other tissue), genetic or genomic data, and/or associated health information. Should you need additional assistance, please contact OPHS at 510-642-7461 or [ophs@berkeley.edu](mailto:ophs@berkeley.edu).*

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### **A. Introduction**

Human [genetic](#) or [genomic](#) research (sometimes called [DNA](#) research) involves the study of inherited human traits. (Note: Although often used interchangeably, “genetic” and “genomic” have somewhat different meanings: put simply, “genetic” testing examines specific DNA material that has a known function, while “genomic” testing looks for variations within large segments of genetic material, whether its function is known or not. For purposes of these guidelines, we use the above definitions. See article from NIH project on Genetics and Social Science, “[Genetics vs. Genomics](#),” for fuller explanation).

The use of human research subjects in both genetic and genomic research has facilitated significant scientific discoveries and achievements, by enabling scientists to study human genetic variation, to identify the genetic underpinnings of disease, and to research how genomic information more broadly can be applied clinically.

The expanding applicability of such research holds great promise for discoveries in the biomedical and social-behavioral sciences, but also raises challenging ethical and regulatory issues. These challenges include implications of sharing research findings for subjects and their family members, issues of confidentiality, types of testing, determining appropriate methods for providing genetic or genomic information to subjects, and ownership of DNA obtained from research samples.

## **B. Background**

DNA (or [RNA](#)) can be harvested directly from subject samples soon after their receipt, or it can be prepared from stored tissues, blood, serum, saliva, cytological preparations, and pathology specimens. Also, because DNA is an informational molecule, the sequence of DNA stored in a computer is subject to the same considerations as DNA itself. (Note that these guidelines may apply to protein sample analysis as well as DNA and RNA research, if such research falls under the purview of the CPHS.)

Many tissue and serum banks currently exist at UC and other institutions; some involve samples from thousands of subjects collected over several decades. With the advent of [Polymerase Chain Reaction \(PCR\)](#) (a laboratory technique used to amplify DNA sequences), all of these samples can now be used for DNA analyses. Policies are still evolving on how to deal with DNA and RNA studies of archived samples from individuals who, at the time of donation, had no idea that their specimens would later be used for any genomic analyses. Such proposals will be handled on a case-by-case basis (e.g., deciding whether or not the researcher must go back and obtain consent for DNA testing from subjects). However, the CPHS is primarily concerned with *ongoing and future studies* that utilize DNA sampling, storage, and/or analysis.

## **C. Types of Genomic Studies (any genetic or genomic testing as described above)**

Genomic studies usually fall into one of the following general categories:

1. *Anonymous donors, who are untraceable by any means.* This would include samples that have been collected or will be collected solely for non-research purposes, such as pathology samples, where only the samples and not any identifying information linking the samples to individuals will be provided to the researcher.
2. *Donors whose identity is known or traceable, but the investigator does not plan to track the individual.* An example would be a study where specimens are obtained, banked, and coded by the investigator, or the investigator obtains samples and associated data from a public, private or commercial repository (and there is a key linking these to the subject's name/identifying information), but no subject-related genomic analysis is planned at this time. (However, the investigator retains identifying information or ability to identify individual subjects should plans change in future.)
3. *Donors whose identity is known or traceable, where the investigator plans to link genomic analyses to other study data from the specific individual, but will not inform subjects of the results of the analyses.* An example would be a study about whether impulse control is hereditary, where the investigator would compare individual DNA data to behavioral assessment data, but would not inform the subject of these results.

4. *Donors who are the subjects of genomic studies. The identities of these subjects are traceable and the investigator intends to inform the subject about the results of the analysis.* An example would be a study of a cancer susceptibility gene, where it would be possible for the subject to learn the test results if they wished.
  - If the condition under study is very serious or emotionally charged, it may be important to offer counseling resources to individuals bearing a disease-related gene. Other issues, such as confidentiality protection, are also especially critical for this type of study. See below for further discussion.
5. *Donors who are the subjects of ongoing, prospective studies, where identities are traceable and the investigator intends to track the subjects through continuing contact for years into the future.*
  - Where tracking will occur, subjects have a much higher level of participation in the study (e.g., repeat visits, testing). When individuals consent to participate in such a study, this indicates initial and continuing consent; however, re-consenting may be needed during the course of a longitudinal study, especially if minors are involved and/or procedures change over time. Subjects in an ongoing study should be informed at the outset and reminded periodically that they always retain their right to withdraw from the research.

#### **D. Risks of Participating in Genomic Research**

Unlike the physical risks presented by many biomedical research protocols, the primary risks involved in genomic research are those of social and psychological harm. Genomic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and/or compromise the subjects' future financial status.

Such risks include:

- Privacy breaches (e.g., previously unknown paternity information) due to possible re-identification or other losses of confidentiality;
- Disclosure of results that lack clinical utility, proven validity, or accuracy (e.g., false positives or false negatives);
- Emotional distress, anxiety, or guilt;
- Psychological or social risks through receiving information that is unexpected or unwanted;
- Effects of the knowledge that one has a disease-related gene that might alter one's life course, reproductive decisions, employability, or insurability; and
- Results which could cause stigmatization, discrimination, or psychosocial risks to the participant's family, ethnic community, or to isolated populations.

Investigators need to address factors that may affect the rights and welfare of their study subjects (as outlined above), explain their thoughts on these problems and how they plan to handle the issues, as well as how they plan to communicate them to subjects. This should be reflected in both the protocol and the consent documents.

## E. Informed Consent

Given that one's genome contains personal health and other information, its analysis as part of a research study raises a number of issues that the informed consent documents need to address. The informed consent process and consent document(s) must include: a description of the genomic research being conducted, the ways in which participants' samples, genomic data, and health information will be used and might be shared (including unspecified future uses), the risks and benefits of their participation, measures in place to protect their privacy, and circumstances under which information will be returned to them (if any). For more information, refer to [OPHS' Informed Consent Checklist for DNA/Genetic Testing](#).

Investigators should ensure that the consent process for their study is consistent with program or funding agency data-sharing expectations. In order to facilitate future research and increase the scientific value of the data, broad consent is generally more useful. For NIH-funded research, investigators are expected to obtain consent for future uses and broad sharing of genomic and [phenotypic](#) data (see "Sharing and Accessing Data through Databases" below). When considering the use of broad or specific consent approaches, investigators should balance the responsibility of protecting participants' interests with the potential loss of opportunities for public benefit due to limitations on future research uses.

### ***Broad consent:***

In addition to or in combination with obtaining specific consent for research in which genomic testing is the primary aim, participants can be asked to agree to storage of their samples/data and to the use of their samples/data in future unspecified research ("general research use").

### ***Specific consent:***

Sometimes it may be appropriate to seek consent for more narrowly defined research uses of participant samples and data. These consent approaches may increase participation of people who have concerns about privacy or do not want their samples and data used for research on certain topics. Researchers may include options for data use limitations in the consent form. Examples of such limitations on samples and data include:

- Use of the samples and data must be limited to health/medical/biomedical purposes; does not allow study of population origins or ancestry.
- Use of the samples and data must be related to a specified disease.
- Use of the samples and data must be for not-for-profit purposes or by non-commercial entities.

### ***Consent for Genomic Sub-Studies:***

For protocols in which genomic analysis is not an integral part of the overall research study, subjects should be given the option to decline participation in the genomic sub-study. A mechanism for tracking subjects' choices in this regard should be provided—often a separate section or entirely separate consent addendum for the genomic component is recommended.

### ***Child Assent and Parent Permission for Minors:***

When enrolling minors in a study which involves genomic research, all of the above criteria apply. In addition, children should be provided with an assent document containing age-appropriate language, if

applicable, and parent permission must also be obtained, unless criteria for waiver of assent or permission are met. Furthermore, the protocol and initial informed consent process should discuss plans for re-contact and/or re-consent for those minor participants who reach the age of majority while enrolled in an ongoing study.

### ***Discontinuing Study Participation:***

Participants have the right to withdraw from a research study at any time. However, there are likely to be practical limits on the ability of participants to withdraw samples, genomic data, or health information that have been contributed to a biorepository. The potential limitations of withdrawing samples and data from research should be discussed in the consent form and as part of the consent process.

For genomic studies that involve bio-banked samples and/or storage of associated data in unrestricted or controlled-access databases, complete withdrawal of samples and data may not be possible once samples or data have been distributed to other laboratories. However, it may be possible to withdraw samples or data from future distributions. In such circumstances, the consent document and the informed consent process should include a full explanation of the extent to which withdrawal of samples or data is possible and what the process is.

## **F. Confidentiality and Privacy in Genomic Research**

Each person's DNA sequence includes health and other information about them and their families. Technological advances mean that it is now cheaper and easier than ever to sequence and interpret genomic information. It is important to consider how best to ensure that the individual's privacy is respected. While laws and policies exist that serve to protect the privacy of individual's genomic information, there is ongoing debate as to whether further measures are needed.

### ***Identifiable Populations:***

Ethnically, geographically, and linguistically identifiable populations present particular concerns with regard to privacy, stigmatization, and discrimination, since the ability to protect the privacy of these individuals or groups participating in research is diminished. For small communities or groups, relatively few numbers of family lines may make it especially challenging to protect participants' privacy, even if research samples are de-identified. Depending on the community that the researcher aims to work in, approval to conduct the research from the authorized representative(s) of the community and/or group may need to be obtained prior to consenting individual subjects.

### ***Involvement of Family Members:***

Genomic research may reveal new information about the research subject's health; in addition, the heritable nature of genetic information raises implications for the subject's relatives. Information about family members not involved in the study may be indirectly obtained through the research subject. Furthermore, genomic research using family pedigrees that can trace disease history may reveal family members who are carriers of a disease or will be affected themselves. These indirect results pose an ethical conflict between a possible duty to warn research subjects' family members and the protection of subjects' privacy.

If an investigator intends to obtain identifiable private information about the subject's family members, the family members may be considered human research subjects. In such instances, the CPHS will consider the necessity and/or appropriateness of a consent process for these "secondary subjects." Also, if the subject will be given genetic or genomic test results, the subject's consent to contact family members may be required.

### ***Protections for Subjects:***

- a. *Genetic Information Nondiscrimination Act:* The Genetic Information Nondiscrimination Act (GINA) prohibits health insurers and employers from requesting or requiring genetic information from an individual or an individual's family members, and further provides legal protection against discrimination on the basis of a person's genetic information.
- b. *HIPAA:* The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule establishes protections to maintain the confidentiality of patients' individually identifiable health information. In 2013, as required by the Genetic Information Nondiscrimination Act, the Privacy Rule was modified to establish that genetic information is health information protected by the Privacy Rule to the extent that such information is individually identifiable, and that HIPAA covered entities may not use or disclose protected health information that is genetic information for underwriting purposes. For more information, see the [CPHS HIPAA Guidelines](#).
- c. *Certificates of Confidentiality:* When dealing with sensitive data, the CPHS may require that the investigator obtain a "[Certificate of Confidentiality](#)" ("[CoC](#)"). Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. CoC's allow the investigator and others who have access to research records to refuse to disclose identifying information on research subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. However, there are limitations to this protection (e.g., it does not apply to any state requirement to report certain communicable diseases, or to legal or ethical requirements for researchers to report child abuse to appropriate authorities, etc.)

## **G. Disclosure of Individual Research Results and Incidental Findings**

The return of individual research results (IRRs) and incidental findings (IFs) from genomic research is an issue of interest among researchers, ethicists, sponsors, policy makers, research subjects, and others. As indicated above, when conducting clinical research studies, scientists may discover new health-related information about volunteers who have chosen to participate in the studies. This raises the question of when and how it is appropriate for the scientists to share such research findings.

IRRs are the results for a specific study subject from a scientific investigation. For example, in genomic research, an IRR could indicate whether a research subject possesses a particular gene variant under study. IFs are a subset of IRRs, findings that are not related to the objectives of an investigation. An example of an IF in genomic research would be finding that a subject in a study of heart disease possesses a gene variant related to Alzheimer's disease.

Currently, the only federal law regarding return of individual genetic testing research results and incidental findings is the [Clinical Laboratory Improvement Amendments of 1988 \(CLIA\)](#), which sets quality standards for all laboratories performing clinical testing. [CLIA](#) prohibits the return of individual research results to study subjects unless the tests were physician-ordered and the results were obtained in a CLIA-certified laboratory. For more information, refer to CPHS' [CLIA Guidelines](#).

*When results will be reported to individual subjects or their physicians.* For diagnostic or health-related uses, the tests must be physician-ordered and performed at a CLIA-certified laboratory. The CPHS application should include the fact that testing will be conducted consistently with CLIA requirements. Additionally, the Risks and Benefits sections of the protocol should discuss how the benefits of providing the results outweigh the associated risks, and what efforts will be taken to minimize such risks.

*When results will be withheld from individual subjects.* When research subjects are asked to give biological samples for laboratory testing, they frequently expect that test results will be provided to them. It is important to clarify with subjects from the outset that the tests are research-related, and that the results will not be shared. Accordingly, the consent documents should include language such as: "The requested laboratory tests are research-related tests only. We will not pass the results of the test on to you, as the results may not be clinically meaningful."

The CPHS generally recommends that individual research results of genetic or other genomic testing for research purposes rather than clinical reasons should *not* be shared with subjects or their families. For such studies, the fact that this information will not be passed on to subjects must be made clear in the protocol *and* consent form(s). However, if the investigator does intend to share results of genetic or other genomic testing with subjects, s/he will need to provide ethical and scientific justification for passing on such information to the subjects or family members. The CPHS will determine if disclosing genetic or other genomic testing results is appropriate, considering factors including:

- Clinical relevance and implications of the genetic or other genomic testing results.
- Reliability of genetic or other genomic testing results.

In addition to presenting justification for sharing results, the investigator must provide:

- A plan in the protocol outlining how such disclosure will be managed, including methods by which subjects will be informed of their results, qualifications of individuals who will disclose results (e.g., training and experience in discussing social, psychological and other non-physical risks); whether counseling will be offered, and if so, the qualifications of the counselors and who will pay such costs. This plan should also include how the investigator will minimize the risks of such disclosure and preserve confidentiality of test results.
- A consent process and document(s) giving subjects the option of receiving test results (e.g., by initialing boxes in the signature block), and providing information about plans for minimizing risks, preserving confidentiality, etc.



**Subjects' "Right Not to Know":** Subjects generally retain the right *not* to receive information about the results of a study that reveals their genetic status. A possible exception occurs where early treatment of a genetically linked disease could improve the individual's prognosis. In such circumstances, investigators may have a duty to inform the subject about the existence of the genetic defect and advise her/him to seek medical advice. As legal opinion and policies in this regard are still evolving, an investigator should consult with the CPHS if such a situation arises; these situations will be handled on a case-by-case basis by the CPHS.

## H. Sharing or Accessing Data through Databases

In 2008, NIH implemented the Genome-Wide Association Studies ([GWAS](#)) Policy. A genome-wide association study is an approach used in genetics research to associate specific genetic variations with particular diseases. This policy requires data from NIH-funded GWAS to be shared with the research community in a central data repository maintained by NIH, the database of [Genotypes](#) and [Phenotypes](#) ([dbGaP](#)). To protect research subjects' privacy, access to sensitive data in dbGaP is through a controlled access policy.

To further expand genomic data sharing of all types, NIH released a [Genomic Data Sharing Policy](#) that went into effect on January 25, 2015. This policy applies to all NIH-funded research that generates large-scale human or non-human genomic data, regardless of the funding level, as well as the use of these data for subsequent research. Large-scale data include whole genome, single nucleotide polymorphisms (SNP) arrays, whole genome sequence (DNA), gene expression (RNA), and other specified data. This policy states that NIH expects investigators to obtain consent for subjects' data to be used for future research purposes and to be shared broadly through databases. If researchers plan to use existing samples, documentation of consent to allow the samples and associated data to be deposited into a shared database must be furnished. If consent did not include language to explicitly allow the sharing of samples and data, subjects must be re-consented.

When depositing specimens into an NIH repository, there are strict standards for IRB review and informed consent before inclusion in the database will be considered. For more detailed information see: [NIH Points to Consider for IRBs and Institutions in Their Review of Data Submission Plans for Institutional Certifications under NIH's Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies \(GWAS\)](#). For every new data submission to NIH, the CPHS is required to determine that submission of data to the NIH GWAS data repository and subsequent sharing for research purposes received appropriate CPHS review and approval. The CPHS must also certify that the informed consent that was obtained from subjects is consistent with NIH requirements. Finally, when researchers are ready to submit data to NIH for GWAS, the CPHS will provide a signed data submission certification letter to the investigator.

Similarly, when researchers wish to access samples and data stored in NIH databases, the CPHS must review and approve the appropriate IRB application. Once approved, the CPHS will provide a signed certification letter to the investigator. Researchers should contact CPHS/OPHS directly if they intend to access data from an NIH database.



## I. Storage of Samples

Information must also be included in the protocol regarding how, where, and by whom genetic samples obtained for the study will be stored. Within the eProtocol Biomedical application, in the General Checklist, investigators need to answer the relevant questions as to whether they "*intend to use human blood, body fluids, tissues, or cells (including cell lines) in the course of [their] research, by drawing samples, accepting samples already drawn, receiving samples from any source, or in any other way,*" and whether "*biological specimens [will] be stored for future research projects.*" The lab location and [BUA](#) (Biological Use Authorization) number must be provided if applicable. (See UCB's EH&S website for further information about [CLEB \[Committee on Laboratory & Environmental Biosafety\]](#) and [BUA \[Biological Use Authorization\]](#) requirements).

## J. Financial Reimbursement, Costs, and Commercialization

In keeping with current University of California policy, subjects must be informed that while there may be future commercial use of their samples or genomic data, or production and distribution of derivatives such as cell lines, subjects will not receive any future profits if the research results in products that are eventually developed and sold for commercial purposes.

Consent forms for studies which utilize genomic samples/data are required by UC Office of the President (UCOP) policy to include language conveying this information, also known as the "[Moore Clause](#)," e.g.:

“Biospecimens (such as blood, tissue, or saliva) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research, and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.”\*

\*For more information on Moore Clause language, see UCOP's [Standard Language in Research Informed Consent Forms for Research](#) and OHRP's draft [Guidance on Exculpatory Language in Informed Consent](#) (2011).

## K. GLOSSARY

- *BUA*: Biological Use Authorization
- *CLEB*: Committee on Laboratory & Environmental Biosafety (UCB's Biosafety Committee)
- *CLIA*: Clinical Laboratory Improvement Amendments of 1988
- *CoC*: Certificate of Confidentiality
- *DNA*: Deoxyribonucleic acid. The material inside the nucleus of cells that carries genetic information.

*Example of lay language for DNA*: "The genetic material inside your cells."

- *Genetic(s)*: "Genetic" testing examines specific DNA material that has a known function. (For expanded explanation on differences between "genetic" and "genomic," see article from NIH project on Genetics and Social Science, "[Genetics vs. Genomics](#)").
- *Genomic(s)*: "Genomic" testing looks for variations within large segments of genetic material, regardless of whether its function is known or not. (For expanded explanation on differences between "genetic" and "genomic," see article from NIH project on Genetics and Social Science, "[Genetics vs. Genomics](#)").
- *Genotype*: An individual's collection of genes. The genotype is expressed when the information encoded in the genes' DNA is used to make protein and RNA molecules. The expression of the genotype contributes to the individual's observable traits, called the phenotype.
- *HIPAA*: Health Insurance Portability and Accountability Act
- *Moore Clause*: Statement in a consent form to reflect finding in the 1990 case of John Moore v. The Regents of the University of California, where the California Supreme Court ruled that cell lines established from a donated sample are not the property of the person who donated the sample.
- *PCR*: Polymerase chain reaction. A molecular biology technique that is a rapid, cheap, simple means for producing large numbers of copies of DNA molecules from minute quantities of source DNA.
- *Phenotype*: The observable physical and/or biochemical characteristics of the expression of a gene (e.g., height, eye color, and blood type). The genetic contribution to the phenotype is called the genotype. Some traits are largely determined by the genotype, while others are largely determined by environmental factors.
- *RNA*: Ribonucleic acid. A nucleic acid present in all living cells. Its principal role is to act as a messenger carrying instructions from DNA for controlling the synthesis of proteins.

## **L. REFERENCES**

- National Institute of Health Office for Protection from Research Risks (OPRR) 1993 Institutional Review Board Guidebook, "[Human Genetic Research](#)"
- National Human Genome Research Institute: Issues in Genetics, "[Human Subjects Research in Genomics](#)"
- National Human Genome Research Institute: Issues in Genetics, "[Informed Consent for Genomics Research](#)"
- National Human Genome Research Institute: Issues in Genetics, "[Privacy in Genomics](#)"
- UC San Diego, Human Research Protections Program, "[Issues on DNA and Informed Consent](#)"