

# **Partners HealthCare System Genetics Research Advisory Panel Report**

## **I. Preamble**

The Partners HealthCare System Genetics Research Advisory Panel was convened in June, 2000 for the purposes of examining the issues related to genetics research involving human subjects, and developing guidelines for researchers and members of the Human Research Committee (Partners' Institutional Review Board or IRB).

The goal of this advisory panel is to foster quality research and to strengthen the protection of people who volunteer to participate in genetic studies by improving the communication and understanding of genetic investigators and IRB members.

### **A. Charge to the Committee**

1. Review and summarize current Partners policies and procedures related to genetics research, within the context of other national and international guidelines.
2. Identify and analyze current problems and controversies about genetics research as it affects individuals and society. These include:
  1. Research use of archived specimens that carry identifiers
  2. Prospective collection of specimens for unspecified use in future genetic studies
  3. Use of genetic information obtained in a research setting for medical decision making
  4. Maintenance of privacy and confidentiality of genetic information
3. Recommend policies and procedures that will guide investigators, IRBs and institutions about how to conduct and oversee genetic research and its applications for clinical management.

### **B. Background**

Genetic research has resulted in important advances in medicine and public health. It has increased our understanding of how genetic changes can contribute to complex diseases such as cancer and heart disease, and has led to the development of tests that can identify individuals who may be at risk for certain conditions. The mapping of the human genome, completed April 2003, will no doubt accelerate the pace of this research.

But this progress has also created challenges, both for researchers and individuals who serve on IRBs. The field of genetics – along with its language and the possibilities for research – seems to expand daily. IRBs have suddenly been asked to consider a large number of genetic research protocols, yet IRB members may have little knowledge or expertise in this area. And these challenges will only grow in the future. We are entering an era where genetics and genomics are going to be at the center of both research and patient care.

Not surprisingly, this new field is also raising scientific, ethical, legal and social issues. People on the frontlines – whether in research laboratories or on IRB panels – are asking for guidance about how to make decisions about particular studies.

This document incorporates the HIPAA guidelines that became effective April 14<sup>th</sup>, 2003.

### **C. Areas of Concern**

The committee examined the following issues:

1. Subject recruitment policies and procedures
  - a. Participation of family members
  - b. Participation of children in genetic studies
2. Future use of stored/retained samples
3. Prospective epidemiological studies
4. Archived specimens
5. Reporting of results
6. Case reporting and research limited to medical records
7. Single patient diagnosis/clinical care of unusual genetic disorders

## II. Overview

### A. What This Document Does and Does Not Provide:

- **Guidelines, Not Hard and Fast Rules**

These guidelines are intended to provide a framework for individual researchers in the development of protocols and for the IRB in evaluating protocols. The guidelines are meant to be flexible. The field of genetics is advancing too rapidly to allow for rigid rules. The researchers and the IRB must exercise their judgment and discretion in making decisions about complex issues.

Application of the tools of genetics to clinical research is not new, but the increasing power of these tools has raised concerns about the protection of research participants. Public discussion of these issues has included some extreme statements, including extravagant promises of new discoveries and dire predictions of loss of autonomy and privacy. IRBs are being asked to review a rapidly increasing number of research proposals dealing with genetics and genomics. This report is intended to improve the quality of proposals and their review by increasing awareness of the issues in protection of research participants that are particular to genetic studies.

- **Guidelines for Genetic Analysis and Research Only – Not Genetic Therapy**

The genetic research covered in this document includes any analysis of DNA, RNA, genes and/or chromosomes in order to detect an inherited or acquired alteration that might increase the risk of a particular disease or condition. Many protocols submitted to the IRB involve such genetic research. This document does NOT cover any guidelines for experimental genetic therapy.

These guidelines have been developed after reviewing recommendations of key advisory bodies involved in the larger national discussion about ethical issues in biomedical research. Key panels include the National Bioethics Advisory Commission established in 1995 by President Clinton, the Secretary's Advisory Committee on Genetic Testing, chartered in 1998 by then Surgeon General David Satcher, and the President's Council on Bioethics established in 2001 by President Bush.

- **These Guidelines Are a Supplement**

The guidelines in this document are intended to supplement the instructions for protocol submission and the form templates already approved by the Partners HealthCare System hospitals (Brigham and Women's Hospital and Massachusetts General Hospital) and the Dana Farber Cancer Institute.

Additional information and forms are available on the Partners IRB web site at <http://healthcare.partners.org/phsirb/>. This site includes assurances, guidance

documents, policies and procedures, regulatory documents, investigator education, Partners' IRB forms, IRB meeting dates, IRB contact numbers and emails. Information about HIPAA and research can also be found on this site.

## **B. The Role of Genetics in Health and Disease**

The modern era of research on human genetics dates to the beginning of the twentieth century, when the first human traits that segregate in families in accordance with Mendel's laws were discovered. Much of the first half of the twentieth century was dedicated towards understanding how genes function, how they are organized on chromosomes, and how they segregate in cell division. The structure and function of DNA was discovered in the 1950s. Continuing advances in molecular genetics culminated in the sequencing of the human genome by the end of the twentieth century.

Medical applications began in the 1950s with the advent of techniques to study human chromosomes and the discovery of chromosome abnormalities such as trisomy 21, the cause of Down syndrome. During the 1960s, techniques of prenatal diagnosis were developed and newborn screening for inborn errors of metabolism were introduced. The ability to study genes at the molecular level, beginning in the 1970s, ushered in an era of molecular diagnosis, where genetic traits could be analyzed at the level of DNA.

The human genome consists of approximately 3 billion base pairs of DNA, comprising about 30,000 genes. Each gene contains a specific sequence of bases that encodes the amino acid sequence of one or several proteins. The highly regulated activation and repression of genes is responsible for both human development and the many ways that cells and tissues respond to the environment.

It is estimated that any two people share about 99.9% identity in their DNA base sequences. The 0.1% difference comprises about one change every few hundred bases. Some of these differences are silent, having no impact on gene function. Others are responsible for physical differences among people, such as hair or eye color or height. From a medical point of view, some of these changes have a profound impact on health, causing disorders such as sickle cell anemia or cystic fibrosis. Others affect health in a more subtle way, increasing vulnerability to developing disorders such as hypertension or asthma. Many of these disorders have very complex mechanisms that include multiple genes interacting with one another and with the environment to produce a specific disease.

It is likely that no disorder can be said to be entirely genetic in etiology or entirely environmental. Even single gene disorders such as cystic fibrosis are modified by the action of other genes and environmental factors. Similarly, even overwhelmingly environmental conditions such as trauma are influenced by genetics – perhaps in determining vulnerability to accident or ability to heal.

The overall goal of clinical research in genetics is to identify genes – and sequence variations in these genes – which underlie various medical conditions. The insights obtained from this effort

include improved ability to diagnose disease or predict those at risk, as well as insights into disease mechanisms that may lead to new treatments.

### **C. Major Approaches to Genetic Clinical Research**

There is no single pathway for clinical research in genetics; the approach depends on the nature and frequency of the disorder under study and may utilize various types of tools. Some of the major approaches include:

- 1. Determining the mode of genetic transmission:** Sometimes a pattern of inheritance, *e.g.*, dominant or recessive, is obvious from analysis of a single family. Even disorders that are generally due to multiple genetic and nongenetic factors may sometimes occur as single gene traits in rare families. Moreover, multifactorial traits can sometimes be modeled as being due to one or more major genes acting in a dominant or recessive manner, together with other genetic or environmental modifiers. These patterns are elucidated through studies of families, some small, some large, by examining relatives or simply collecting histories, with the goal of tracking the trait through the family. In some cases, DNA or tissue samples may be collected for this analysis
- 2. Gene Mapping:** If a trait appears to be determined in whole or in part by changes in a single gene, a gene mapping study may be done to localize that gene. This requires study of multiple family members, including both affected and unaffected individuals. It may require as few as one or as many as hundreds of families. DNA samples are tested in an effort to find genetic variation (a “polymorphism”) that tracks through the family(s) together with the trait. Such a variant is likely to reside near the disease gene on that chromosome and can serve as a marker to that gene in further studies. The map of the human genome is now very densely populated with variants that can be used for such mapping studies, making this a very productive approach if suitable large families can be identified.
- 3. Gene Identification:** There are various routes to finding genes that are responsible for clinical disorders. If linkage between a particular area of a chromosome and the disorder has been established, DNA from the region surrounding the gene can be examined to determine the site of mutation in affected individuals. In some cases, gene identification is aided by study of “candidate genes”— genes that have already been discovered and appear to be plausible candidates to cause the condition based on their location or function. The mapping and sequencing of the human genome has greatly facilitated gene identification studies, though many complexities remain. For example, a single clinical disorder may result from mutation in different genes in different people.
- 4. Genotype-Phenotype Studies:** Once a gene has been identified as playing a role in disease, it is necessary to correlate different mutations (genotype) with their clinical impact (phenotype). Mutations can vary widely in their impact on gene function – complete loss of function, altered function, or causing gain of function, for example. In many cases, these differences will be reflected in subtle, or major, differences in phenotype. Sometimes, distinct conditions will be caused by different mutations in the same gene. For example, some mutations in the *CFTR* gene can cause cystic fibrosis, while others cause congenital bilateral absence of the vas deferens leading to male infertility. Genotype-phenotype studies are generally done using DNA from

clinically affected individuals. In some instances, these studies enable genetic tests to be developed.

5. **Gene Association Studies:** Association studies may be helpful to determine if a particular genetic variant is associated with increased risk of disease. This is often done by standard case-control methods, testing different groups of people for the presence or absence of a particular genetic variant. These variants are currently candidate genes, but may, in the future, be random variants tested as part of a whole genome search. As an alternative to a case-control approach, some investigators will sample an affected individual and both parents, or an affected individual and affected or unaffected siblings. These studies are designed to determine whether particular genetic variants are transmitted preferentially to affected individuals.

6. **Expression Studies:** Aside from detection of the role of specific genes in disease, investigators may examine tissues for overall patterns of gene expression. These experiments are becoming easier to perform using technologies that sample thousands of genes at a time on “gene chips.” Discerning patterns of specific gene expression in a diseased tissue can help identify genes that are involved in the pathological process and may be useful in identifying different disease subclasses.

7. **Genetic Outcomes Studies:** The identification of genetic variants that are correlated with disease requires validation and outcome studies in order to be incorporated into clinical use. Genetic tests, like other medical tests, vary in their analytic validity (likelihood that a result indicating presence or absence of a mutation is correct), clinical validity (predictive value of the test), and clinical utility (degree to which the test result guides clinical management). Studies of outcomes may be complicated by non-penetrance (lack of phenotype in person with the at-risk genotype) or age-dependent penetrance (delayed onset of phenotype). Other areas that may be studied are ethical issues, ability of tests to predict response to treatment, methods of reducing risk, *etc.*

#### **D. Risks Associated with Genetics Research**

There are probably no risks that are unique to genetic research, but there are a set of concerns that are more commonly raised by genetic studies, or that may be viewed in a unique light. No single study is likely to raise all of these issues. Examples include:

1. **Impact on Families:** Genetic traits are, for the most part (with the exception of new mutations), shared by multiple members of a family. This means that family members may be asked to participate in genetic studies and that results may have significance for multiple family members, not just the proband. Unexpected family relationships, such as misattributed parentage, may be inadvertently discovered. Relatives may feel coerced to participate in research. The investigator may learn about previously unsuspected risk of disease in a family member who participates in a study. Some individuals may blame family members who transmitted a trait, while others may feel guilty either for transmitting the trait or escaping its effects.

2. **Vagaries of Genetic Testing:** A genetic test result has the appearance of an ironclad objective finding, and, indeed, may stand as a “fact” about an individual for a lifetime. But a number of conditions about the test must be considered before assuming its clinical relevance. Errors of genotyping are possible, particularly in research laboratories that are not set up as clinical testing facilities. Some mutations may not be pathogenic, and may be erroneously assumed to predict disease. Conversely, failure to find a mutation may not rule out a particular disorder. Also, tests may be performed that do not guide clinical management, yet lead to anxiety and/or stigmatization. It should be noted that these issues are not always encountered. Some genetic tests give clear-cut results that can be instrumental in providing counseling or guiding care for an individual. The bottom line is that each test needs to be evaluated on its merits before being clinically implemented.

3. **Stigmatization:** Genetic testing often has the power of determining risk of disease well in advance of onset of signs or symptoms. This can be beneficial by permitting family planning, prenatal diagnosis, or medical surveillance. It can also expose individuals to risk of discrimination for employment, health, disability, or life insurance, or social stigmatization, and create emotional distress such as anxiety or guilt. But the risk/benefit consideration is seldom clear-cut. It should be recognized, for example, that sometimes testing can resolve issues for an individual who is at-risk based on family history, if the test shows that the individual himself or herself does not carry a particular gene. Similarly, some individuals are vulnerable to stigmatization by virtue of existing signs or symptoms of disease, and genetic testing may have little impact on this stigmatization. It should be noted that while federal and many state privacy laws restrict to some extent the disclosure of genetic test information, legal protections against discrimination by an employer or insurer based on such information vary.

4. **Group Stigmatization:** Genetic traits may be shared by groups of individuals with a common geographic or ethnic origin. Genetic studies of such groups may lead to a perception that the group is “genetically inferior” and may lead to group stigmatization and discrimination.

## **E. Potential Benefits of Genetic Research**

The great interest in genetic research is fueled by the impressive potential of this research for elucidating the basis of both rare and common disorders. To some extent, the promise may have been exaggerated by those who preach a tenet of “genetic determinism” – that a person’s fate is sealed in his or her genes. This extreme view is inaccurate, but this does not diminish the potential power of genetic research. From the point of view of a research participant there may be direct and/or indirect benefits of participation in research. These include:

1. **Diagnosis:** An individual may already be experiencing symptoms but may not know what the specific diagnosis or disease is. Many people in this situation, or their parents or relatives, may wish to determine a precise diagnosis; genetic testing may make this feasible. Learning the diagnosis may bring peace of mind, information about risk of recurrence in the family, knowledge of expected health outcomes, and may guide further clinical management. For predictive tests, surveillance or other risk reduction approaches may be feasible.

2. **Development of Therapies:** Discovery of genes that contribute to disease may reveal the cellular, tissue, and organ pathways that lead to the pathological process. These pathways

become targets for new therapeutic approaches, including new pharmaceuticals. Genetic approaches are revealing pathogenetic mechanisms that previously unknown are now opening doors to treatment of conditions that were previously considered to be intractable. Research participants may see hope of development of new treatments for themselves, their families, or future generations.



### **III. Subject Recruitment: Participation of Family Members**

#### **A. Purpose:**

- To provide guidelines for determining the circumstances under which relatives of the primary study subject (*proband*) would also be viewed as study subjects, and,
- To provide guidance regarding how to contact relatives to participate in a genetic study.

(Note: For guidelines on how to contact the proband, see the HRC Website at: <http://healthcare.partners.org/phsirb/recruit/htm>. The guidelines for contacting a proband to participate in a study are the same in genetic research as in other research, so they are not detailed here.)

#### **B. Background:**

Genetic research studies often involve collection of data from one or more family members in addition to the individual who is the primary study subject (proband).

Indirect collection of information about family members includes:

- Asking the proband about his/her family medical history
- Review of medical records that reveals the proband's family medical history

Direct collection of information includes:

- Direct contact of relatives for information
- Approaching family members for blood samples
- Review of family medical records

The practice of including information about relatives in a genetic study raises the question of whether relatives must themselves be considered to be study subjects. If so, before data or samples can be collected, the principal investigator must either obtain informed consent and authorization from each family member or obtain a waiver of informed consent and authorization. Whenever an informed consent and authorization are obtained, the PI must ensure that the family members have received a copy of the institution's Privacy Notice. (HRC HIPAA website for further discussion of HIPAA requirements as they relate to research. <http://healthcare.partners.org/phsirb/hrchipaa/htm>)

#### **C. Guiding Principle:**

The principal investigator needs to address the status of family members in the protocol for IRB review.

**D. Guidelines for Deciding Whether Family Members Are Subjects (Or Not):**

To determine whether or not a family member should be considered a human subject, consider the following:

1. If samples are to be obtained from relatives, the relative is considered to be a research subject, and informed consent and authorization need to be obtained.
2. If medical records of relatives are to be reviewed, the relative is considered to be a research subject, and informed consent and authorization or waiver of informed consent and authorization must be obtained before reviewing the records.
3. If information about a relative is obtained only from the proband, with no review of medical records, and the proband will be identified in the study, the family member is still considered a research subject but usually faces only minimal risk from the study. In this situation, informed consent and authorization from family members or waiver of informed consent and authorization may be required. An example would be if the proband were John Smith and the family member’s data was included as “mother of John Smith.”
4. If information about a relative is obtained only from the proband, with no review of medical records, and the proband will be de-identified in the study, it will not be possible to identify the relative, so he or she does not need to be viewed as a research subject. As an example, if the proband were identified only with a study number, (“Study Subject #5”), and the family member was listed as “mother of Study Subject #5.

| <b>What is obtained</b>                   | <b>Research Subject?</b> | <b>What is required</b>                              |
|---|--------------------------|--|
| Tissue or blood sample from family member | Yes                      | Informed consent and authorization                   |
| Review of family member’s medical record  | Yes                      | Informed consent and authorization or waiver of both |
| Data obtained from identifiable proband   | Yes                      | Usually waiver of informed consent and authorization |
| Data from de-identified proband           | No                       | Nothing  |

## **E. Guidelines for Recruitment of Family Members for Substantive Involvement in Genetic Research:**

### **1. Child as Proband:**

Both parents may be contacted by researchers, as long as the parent who was initially contacted has no reservations or concerns about contacting the other parent: i.e. a researcher may directly contact a father based upon verbal agreement from the mother that this is OK with her. Generally speaking, this contact is best made via the family's clinician rather than directly by the researcher.

### **2. Adult as Proband:**

Researchers may not directly contact any family members from a "list" provided by a proband. Instead, researchers must ask probands to initiate contact with family members about research studies. To help the probands communicate effectively, researchers should prepare an information sheet that briefly describes the study – this would typically be similar to a recruitment letter and provide details about purpose, procedures, important inclusion/exclusion criteria, time commitment and any compensation provided. Family members should then contact researchers directly to indicate their willingness to participate in the study. If possible, probands should not be informed regarding whether particular relatives have or have not agreed to participate. If this is not possible, the fact that such information will be provided to the proband must be indicated on the proband's consent form as well as on the letter of invitation to the family member.

## **F. Suggested Language for Consent Forms**

The following "standard language" regarding the recruitment of family members can, when appropriate, be placed in consent forms:

You may be asked if you are willing to tell other family members about this research study so that their samples can be obtained for analysis. If so, you will be given copies of a letter describing the study to give to your family members. Interested family members should contact the investigator and his/her staff for more information. You should not feel obligated in any way to recruit family members. If you do tell family members about this study, you should tell them to contact the investigator with any questions. You are free to choose not to tell other family members about this study. The investigators will not tell you or other family members who does, and who does not, agree to participate in the study.

## IV. Inclusion of Children as Participants in Genetics Studies

### A. Purpose:

To provide guidelines regarding the criteria that should be considered whenever including children in genetic studies

### B. Background

Federal regulations have specific criteria for the inclusion of children as participants in research of any kind. These regulations include a somewhat different approach to the risk-benefit consideration, and they require that whenever reasonably possible, the child be asked to give permission in the form of an assent. In addition to these general considerations, genetic studies may raise a set of distinct questions. For example, a child may be asked to contribute a sample to a family study in which the child is not the primary focus for study and will have no direct benefit. This document will address the types of issues that may arise and propose points to consider in the design of protocols.

Two basic principles should be kept in mind.

First, there must be a good reason to conduct a study involving children. In the protocol, the principal investigator must justify why it is necessary to involve children in the study. Remember that although a blood draw poses only minimal medical risk, it can be traumatic for young children. And, for the child as well as for the adult there are potential risks of discrimination and/or stigmatization for being part of a genetic study.

Second, if the study includes the return of study results to the subject (child), the investigator must recognize that the immediate and future impact of such information may be different for the child versus the adult.

### C. Types of Studies

Consider two major types of studies that may request the involvement of children:

#### **1. Genetic Studies in Which the Child Displays the Phenotype Under Study**

Many genetic studies are aimed at identification of genes that are linked to or associated with specific phenotypes. These studies may be designed to identify these genes, or to study the correlation of genotype with phenotype.

The issues here are for the most part similar to those in other studies in which children may be asked to participate, such as the ability of the child to assent to participate in the study. This kind of study is also governed by rules concerning the return of results to research subjects. (For further guidance on return of results in a genetic study, see pages in the section “Reporting of Results.” **Also see appendix 1: Issues Concerning Children Who Display a Specific Phenotype**)

## **2. Involvement of Unaffected Children in Family Studies**

A second type of study is one in which the child does not display the phenotype under study, but where the analysis of the child's DNA is required to permit a comprehensive study of a family. An example would be inclusion of an unaffected child in a linkage analysis, where the phenotype under study has an early age of onset and complete penetrance, and analysis of the unaffected sibling provides important data to contribute to a significant measure of linkage.

### **D. Issues to Consider when Enrolling a Child into a Genetic Study**

In these studies, the child may not be the direct subject of investigation, but may be providing information necessary for analysis of the family. It is essential that the principal investigator understand that children are different from adults, and their participation in such a study must be justified clearly. In the protocol, the following issues should be addressed by the investigator:

1. Is there a possibility that information will be discovered as a consequence of the study that may impact the health or future family planning of the child? If so, consult the section on reporting of results. Investigators should consider carefully if the risks, discomforts or burden of knowledge are different for the child versus the adult.
2. If the child does not display the phenotype under study, what is the likelihood that he/she will eventually develop this phenotype? If there is a reasonable possibility that the phenotype will eventually appear, follow-up genetic counseling and psychological counseling should be made readily available. Providers of genetic testing should be prepared to educate, counsel, and refer, as appropriate.
3. If the child does not display the phenotype, and is believed to be unaffected, why is it necessary to include the child in this family study? Justify in terms of power calculation for linkage or association study.
4. Is there any potential benefit to the family unit by having the child participate? If so, specify.
5. What types of tissue samples could be used to complete the study (i.e., cheek brushing vs. blood). If invasive sample (including blood drawing) is necessary, justify this in terms of the type of genetic testing to be done.
6. What efforts will be made to enlist the child's assent to participate in the study?

## **V. Future Use of Donated Samples**

### **A. Purpose:**

This section provides guidance about obtaining informed consent for research involving the future use of prospectively collected, identifiable specimens (blood, tissue, cells, DNA).

The discussion is divided into two parts:

- (1) Tissue obtained for a specific study and
- (2) Tissue obtained for a tissue bank.

The issue of “blanket” consent (the granting of consent for all future unspecified genetic research on any disease) is also discussed.

### **Part I:**

#### **The Individual Investigator Who Is Collecting Tissue Specimens For a Specific Study**

### **A. Background:**

Research is not static. An investigator's hypotheses often evolve in response to preliminary study results or other scientific advances. As a result, in the course of a specific study, a principal investigator may wish to narrow or broaden the subsequent research focus. In anticipation of such changes, investigators can write their protocols and informed consent documents to include likely potential changes.

But there are many situations in which the "new" findings are completely unanticipated, well beyond the scope of the original study question, and hence not included in the protocol or informed consent document. In these situations, the investigator must submit a separate protocol before proceeding. While this issue is not unique to genetics research, it may be more frequently encountered in genetics research. For example, a search for a specific disease-related mutation may well result in the discovery of a new relationship with another disease or a different mutation. When this occurs, the researcher may want to be able to expand his/her protocol to fully assess this new finding without having to go back to obtain a new informed consent from each of the participants.

IRB members are aware of these concerns, and as a result must decide what type of informed consent and authorization is necessary at the time the initial tissue sample is obtained, and under what circumstances investigators will be required to obtain a new consent and authorization from study participants. Investigators may request approval of a “blanket consent” that would allow them to use the specimen/information for any future unspecified research. As noted below, the use of “blanket consents” raises a number of issues that IRB members must carefully consider; for example, HIPAA prohibits the use of “blanket” authorizations and thus investigators may not request authorization to use or share identifiable information for future unspecified research.

A number of ethicists, medical societies and government panels have examined the issue of informed consent for future use of samples, including those stored in tissue banks. A brief summary of the major findings can be found in the addendum at the end of this document.

## **B. Guiding Principles:**

1. The purpose of informed consent is to provide individuals with accurate and understandable protocol-specific information that will allow them to make an informed decision about whether or not to participate in a study. A fundamental component of informed consent is a description of the risks and benefits and other factors that would be important to a reasonable person in deciding whether to participate in a study. A clear description of all potential uses of a person's tissue is a fundamental requirement for this type of research. If future, unspecified uses are intended, the informed consent should include:

Statement of this fact, and an attempt to outline the likely areas of research

Description of the process by which future use shall be determined

And if that process includes the possibility that an individual may be re-contacted for future studies, permission to be re-contacted must also be requested

In addition to the informed consent, an authorization is required by HIPAA/the Privacy Rule. HIPAA requires that the authorization be as specific as possible – and, in fact does not allow a “blanket” authorization for the use of identifiable health information in future unspecified research. (<http://healthcare.partners.org/phsirb/hrchippa/htm>)

2. Special care should be taken to prevent breaches of privacy that could lead to the identification and stigmatization of individuals, and to prevent discrimination against particular groups (such as ethnic groups) participating in genetic studies.

## **C. Recommendations**

While there are several possible approaches, we suggest the following approach to this issue:

The PI should consider building some flexibility into the protocol and informed consent and authorization document/s that would allow for future use of samples. One way to do this would be to specify that the research will encompass not only a single specific disease, but related diseases/conditions as well. For example, consider an investigator who plans to evaluate genes associated with the development of asthma. Rather than obtaining consent to study only those genes associated with asthma, the investigator may include consent for studies on asthma as well as other related lung and inflammatory-mediated diseases. The protocol and the consent form would have to include an explanation of the relevance of this broader group of diseases/disorders, in addition to the risks and benefits of such research and other required factors (refer to the addendum regarding required elements in an informed consent document). In the routine review, the IRB would consider each protocol and informed consent and authorization document to determine what constitutes reasonable flexibility for each situation.

If the focus of the research evolves beyond the defined area of investigation, then the investigator would have to re-approach the IRB to determine if: (1) new informed consents and authorizations must be obtained or (2) waiver criteria are met and the research could proceed without requiring new consent and authorization. One example of a situation that might trigger a request for new consent and authorization would be a new direction of research into disorders/diseases that are potentially stigmatizing.

In order to have the potential of doing future genetic research on identifiable stored samples, research participants would have to understand that genetic research may lead to unexpected findings, and that it is possible that investigators may want to re-examine a donated sample in the course of research. Study participants should be informed of this possibility at the outset, and should be given the opportunity to specify whether or not they are willing to be contacted in the future if a new area of research emerges.

To avoid potential problems (including harm to participants or ethical concerns regarding the research):

1. Be as specific as possible in the consent form and authorization, so that research participants can make an informed choice.
2. Write the protocol in a way that acknowledges the potential (if relevant) of conducting future genetic research on identifiable stored samples, and specify that if this occurs, a new protocol will be submitted for IRB review. This will enable the IRB to evaluate the future research and the adequacy or inadequacy of the existing informed consent and authorization forms.
3. The informed consent process and form should include all required elements as outlined in the appendix. Special consideration must be given to: **Appendix 2: sample informed consent and authorization**
  - Statement of whether or not the sample may be used for future research, and if so, what type of research.
  - Also if the sample may be used for future research, the process for review and consideration of whether or not a new consent and authorization may be required.
  - If there is the possibility of recontacting the individual for a new consent and authorization, the individual should be asked if they are willing to be recontacted.
4. Authorization:
  - All elements as required in the Privacy Rule must be included. (see <http://healthcare.partners.org/phsirb/hrchipaa/htm> )
  - Note that an authorization must state the specific purpose/s and cannot include unspecified future uses.

## **Part II:**

### **Tissue Banks**

The Policies and Procedures for tissue banking continue to evolve. The reader is advised to review the material available on the HRC website at <http://healthcare.partners.org/phsirb/>.

#### **A. Background:**



Part I addresses the situation in which tissue is initially being obtained for the purposes of a specific study. Tissue banks or repositories deserve separate comment. It is important to first understand that one of the primary reasons for creating tissue banks is to provide a tissue resource for a variety of studies - to bank tissue for future use.

While some repositories focus on specific types of diseases, others have been developed as a resource for research on any and all diseases. The feature that all have in common is the fact that at the time of tissue donation, it is virtually impossible to state with certainty what all of the potential uses of that tissue may be.

There has been new guidance from OHRP regarding tissue banks. This is summarized in appendix 5. OHRP has stated that tissue repositories that retain any identifiers (including coded samples) are themselves research studies that require IRB review and approval. The IRB should consider the specifics of the bank itself: how will specimens be obtained, how the repository will handle the specimens, how confidentiality will be protected, how tissue samples will be made available to researchers. OHRP has recently supported different requirements for the release of unidentifiable or coded specimens and directly identifiable specimens, as described below:

If an investigator requests unidentifiable or coded samples from the repository and the code is kept by the repository, then that investigator does NOT need to have an IRB approved protocol for that specific study. BUT, that investigator must sign an agreement that he or she will not try to identify any individuals from the information provided.

If the investigator is obtaining specimens with identifiers, then the recipient investigator must have an IRB approved protocol - and the IRB will determine whether a new informed consent and authorization is required, or whether the requirement of informed consent and authorization can be waived.

OHRP requires that individuals who are asked to provide a specimen to a tissue repository must provide informed consent and authorization. The informed consent form must include: a description of the repository and how it is run; a description of what type of research the tissue will be used for; and a description of the various ways in which researchers will obtain samples (as described above).

OHRP prefers that informed consent documents be as specific as possible in terms of the potential uses of the tissue. And it prefers that if any non-specified uses are considered, before providing tissue for such a use, an IRB will review the proposed new uses and determine whether or not a new consent and authorization are required. It is important to note that in this situation, the initial consent form would have to include permission to re-contact the individual as necessary.

Despite the fact that OHRP prefers that consent describe specific uses of the tissue, it does understand that for some tissue banks, the tissue may be used for virtually any type of research. In these latter cases, broad unspecified future use must be clearly stated in the informed consent form.

In contrast, it is important to note that HIPAA requires that an authorization be as specific as possible and does not allow "blanket" authorization for the use of identifiable health information for future, unspecified research. If future unspecified research can be done with de-identified

specimens (including coded specimens *where the investigator cannot link to individuals (SS)*) or with a limited data set, it is not necessary to obtain a new authorization or a waiver of authorization. But, if future unspecified research requires the use of identifiable specimens or data, then the researcher must apply to the IRB for a new authorization or a waiver of authorization.

## **B. Sample Language for Consent to a Particular Study**

Your blood will be tested for the presence of a gene that may be associated with the development of asthma. Your blood will also be tested for mutations that may be associated with other kinds of diseases related to asthma. These include other lung diseases, such as emphysema and bronchitis, and diseases caused by allergy or inflammation, such as eczema, psoriasis, and inflammatory bowel disease. Testing for these related diseases/disorders may provide information that will improve our understanding of asthma and these other related diseases.

It is also possible that this research may provide information on diseases/conditions that previously have not been thought to be related to asthma. Before beginning any research on diseases/conditions other than asthma, other lung diseases or diseases caused by allergy or inflammation, we would first discuss the new research with the Institutional Review Board (IRB). The IRB is the committee responsible for reviewing research that involves human subjects. The IRB follows federal laws in order to determine that the welfare of study participants such as you are protected.

The IRB may find that a new proposed direction of research effort does not change any potential risks to study participants or the overall risk/benefit ratio. In such cases, the IRB could allow the new research to continue without obtaining new consent from you.

But there may be some areas of new research for which the IRB or legal rules will require that every research subject have the opportunity to have the new research explained and then be asked to provide new consent before the research proceeds. If this happens, we would like to re-contact you to explain this new area of research to request your consent. But we would only re-contact you if you gave us permission to re-contact you. Please let us know your decision about being re-contacted by checking one of the following:

I would like to be contacted about future research projects that require additional consent.

I do not want to be contacted again for participation in additional research.

In the event that you do not want to be contacted again, or in the event that we are unable to contact you, your specimen will not be used for research that the IRB believes poses risks to you beyond those described in this protocol or otherwise requires new informed consent.

## VI. Epidemiological Studies

**A. Purpose:** To provide guidance to principal investigators who are either already conducting large ongoing epidemiological studies, such as the Nurses Health Study, or who are designing such a study.

### B. Definitions:

**Epidemiological Genetic Research:** Studies of patterns in large populations of people to determine what contribution genes and environmental factors make to the development of disease. Epidemiologists analyze such details as age, gender, weight, and lifestyle choices (i.e., diet and exercise) to determine what people who develop a particular disease (i.e., heart disease, cancer) have in common. Because epidemiologists study large populations and are looking for associations and patterns, their research cannot predict a particular individual's risk of developing a disease. Epidemiologists may not have personal contact with individual study participants in the same way as investigators in other types of research do. In some studies, participants complete written surveys and mail them in to the investigator, sometimes with blood samples or tissue samples. In other cases, though, epidemiologists will meet periodically with participants to interview them and assess their health. However, even in these cases, the epidemiologist will not become a participant's primary caregiver.

**Identified Samples/Data:** Samples or data labeled with personal identifiers, such as name or social security number. Samples and data are not considered "identified" if the only identifier is a clinical trial subject number. Refer to the HIPAA definition of identifiable (Appendix 6).

**Coded Samples/Data:** Samples that do not carry any personal identifiers, but are labeled with a clinical trial subject number that can be traced or linked back to the subject only by the investigator. (Although HIPAA/the Privacy Rule considers coded information to be de-identified if the investigator does not have access to the code, the Common Rule considers coded information as indirectly identifiable.)

**Anonymous Samples Data:** Samples and data that are not and cannot be linked to personal identifiers – there is no code that can be used to identify an individual from specific data. Anonymous samples may have population information (e.g., the samples may come from patients with diabetes), but contain no identifying clinical data. See appendix for detailed information regarding de-identifying data.

### C. Background:

Epidemiological studies are large, often involving thousands of participants. In general, epidemiological studies can be characterized as follows:

1. There is limited contact between the principal investigator and study participants.

2. Epidemiological studies involving genetics generally are interested in discovering gene-environment interactions.
3. Epidemiological studies generally look at common diseases (such as heart disease, breast cancer, colon cancer) and common genetic variations. The expectation is that if particular genes or gene mutations are identified, they will not present a high relative risk for a particular condition.
4. Because epidemiological studies involve many participants (often thousands), it is cumbersome and expensive to contact all participants, hence whenever possible, review of existing medical records is used.
5. The level of risk posed to an individual by epidemiological studies is relatively small. The risk of obtaining specimens for epidemiological studies is minimal. Risk of loss of privacy or confidentiality can be addressed by taking the proper precautions.
6. There may be risks to particular groups of people or “communities” (defined by ethnic origin, race, geography, sexual orientation, etc.). Members of such communities may fear that participating in genetic studies may produce findings that stereotype, stigmatize, or result in discrimination. These risks need to be acknowledged and addressed by the investigator. (For more information on this issue, see information from the NIH at: [http://www.nih.gov/sigs/bioethics/named\\_populations.html](http://www.nih.gov/sigs/bioethics/named_populations.html))
7. Blood and tissue samples may be analyzed in research laboratories that are not CLIA approved. Any data that is communicated back to participants for providing any sort of medical care or genetic counseling must be performed in a CLIA approved lab.

#### **D. Guidelines**

If you are involved in an epidemiological study that is already underway, see guidelines for archived specimens. If you are about to start an epidemiological study, see guidelines for prospective studies.

#### **E. Guidelines for Use of Archived Specimens**

Thousands of archived specimens are currently stored from ongoing epidemiological studies. Many of these studies began 15 to 25 years ago, prior to the revolution in genetics. Even those that began only 5 years ago did not anticipate the rapid advances in genetic knowledge.

As a result, the informed consent process that was in place when these studies began may not meet current consent standards for genetic studies. In some cases, consent was never formally obtained; rather, consent was implied by the fact that individuals actively participated in the studies (by answering questionnaires or submitting blood samples or tissue).

The future use of these existing specimens for new studies must take into consideration the new paradigm for the review of genetic research as well as the new HIPAA/Privacy Rule requirements. In many cases, waiver of informed consent and authorization is the most appropriate way to handle use of retrospectively collected data, as long as certain criteria are met. The Common Rule has four criteria for the approval of a waiver of informed consent. Specific genetic concerns that must be addressed when considering these four criteria are listed below:

### **Criteria for Waiver of informed consent**

#### **1. The Research Involves No More Than Minimal Risk to the Subjects.**

Breach of confidentiality is the risk associated with the use of archived specimens. This can be minimized if there will be no disclosure of any patient specific genetic data except as required by regulatory agencies. In your protocol you should list the relevant agencies that have the right to review data from your study (i.e., NIH, FDA, OHRP).

#### **2. The Waiver or Consent Alteration Will Not Adversely Affect the Rights and Welfare of the Subject.**

Issues of rights and welfare include the possibility of a breach of confidentiality; the possibility of discovering a diagnostic test that can help some (or all) participants; ownership and intellectual property issues related to gene discovery; and possible commercialization of discoveries.

Perhaps the most difficult of these issues is what to do when a discovery would likely provide direct benefit to individuals. In general, because epidemiological research seeks evidence of gene-gene and gene-environment interaction, the effects of the gene being studied are often modest in size.

However, it is always possible that researchers may discover a causal gene that does place people at high risk of a particular disease (such as the relationship between BRCA and the development of breast cancer). If working with anonymized samples, there is no dilemma regarding the return of information to individuals. But if anonymization is not possible, the principal investigator should prepare for a situation in which a high-risk gene is identified. This is a particular concern when research is done pursuant to a waiver of informed consent and authorization. The specific subject does not know that she is in a study, hence any communication regarding her results would be a complete surprise. In view of this the PI should never contact a subject without asking the IRB for guidance. If the IRB determines that participants should be informed of the discovery, the investigator should outline a proposed procedure that could be used for contacting and informing them. (This is probably best accomplished through a newsletter or letter to participants, advising them to talk with their own physician if they are concerned, and to get retested in a CLIA approved laboratory.) The protocol should include this plan for seeking the IRB's guidance in such situations.

### 3. The Research Could Not Practicably Be Carried Out without Waiver or Alteration.

Many large epidemiological studies were established long before the possibility of genetic studies was anticipated. These existing large studies may involve thousands of participants distributed over a wide geographic region. Moreover, in many cases the original consent form was broad, and there was no anticipation that investigators would ever re-contact the participants. In such studies recontact of participants to request consent to do genetic studies may be impractical.

### 4. Whenever Appropriate, the Subjects Will Be Provided with Additional Pertinent Information after Participation.

Except for the situation discussed in #2 above, any information provided should ordinarily be provided in the aggregate. It should discuss the study results as a whole and should be sent to all participants (rather than providing participant-specific information individually).

One option for communicating this information is through a newsletter (or letter), sent to all participants.

#### **Criteria for Waiver of authorization:**

A waiver of authorization must also be obtained. There are three criteria for the waiver of an authorization. Note that there is overlap between the Common Rule and the HIPAA waiver criteria.

1. The research involves no more than minimal risk to the privacy of the subjects. The protocol must include, at a minimum, the following elements:
  - a. An adequate plan to protect identifiers from improper use and disclosure
  - b. An adequate plan to destroy the identifiers at the earliest opportunity. Identifiers can be maintained if there is a health or research justification or if retention is required by law. The investigator must document such justification.
  - c. Adequate written assurance that the identifiable information will not be reused or disclosed except:
    - i. As required by law
    - ii. For authorized oversight of the research project
    - iii. For other research for which the use or disclosure would be permitted
2. The research could not practicably be carried out without the waiver
3. The research could not practicably be conducted without access to and use of this identifiable information.

If a waiver of authorization is approved:

- Any disclosure of subjects' identifiable health information outside of the Partners system must be tracked in accordance with the accounting requirements of the

Privacy Rule. (Please see HRC website for specifics regarding tracking of disclosures.)

- Only the minimum necessary amount of information may be used or disclosed

–The IRB submission form for a waiver includes all of the HIPAA/Privacy Rule as well as the Common Rule waiver criteria. More information on applying for a waiver can be found on the HRC website – submission forms and instructions are available at this site. Please see **Appendix 7**.

## **F. Guidelines for Prospective Studies**

The assumption is that any prospective study will have an informed consent and authorization. In these documents consider the following:

### 1. Define the Study Broadly If Appropriate

In order to build in flexibility to study unanticipated associations, and yet to fully inform participants of the intent of the study, describe the study in a way that focuses on broad disease categories rather than specific types of disorders. For example:

- Heart disease
- Cancer
- Asthma and chronic obstructive airways disease

### 2. Specify the Long-Term Nature of the Study

Principal investigators must inform participants that tissue samples and possibly identifiable data will be stored for a long time, and that it is possible that these samples will be used to study other diseases, genes, or conditions that cannot be predicted now. Investigators should include a description of any and all areas of anticipated research. The reason for being as inclusive as possible is the fact that HIPAA requires the authorization to be as specific as possible about potential future studies, and it disallows “blanket” authorization for the use of identifiable health information for unspecified future studies.

### 3. Document That the Research Involves No More Than Minimal Risk To the Subjects.

There are two primary risks involved in epidemiological research: that related to sample acquisition (i.e., fainting when blood is drawn), and that related to breach of confidentiality.

Sample acquisition poses minimal risk to participants.

In comparison, breach of confidentiality poses a greater risk, but this can be minimized if there will be no disclosure of any patient specific genetic data except as required by regulatory agencies. *Also* list any regulatory agencies that may review data from your study; i.e., NIH, FDA, OHRP.) Document the steps that will be taken to ensure participant confidentiality (E.g., explain whether samples will be identified, coded, or

anonymous, as explained in definitions; also provide any additional information about steps to ensure confidentiality). Define terms, using the definitions above.

#### 4. Document That the Research Will Not Adversely Affect the Rights and Welfare of the Subject.

Issues of rights and welfare include the possibility of a breach of confidentiality; the possibility of discovering a diagnostic test that can help some (or all) participants; ownership and intellectual property issues related to gene discovery; and possible commercialization of discoveries.

Perhaps the most difficult of these issues is what to do when a discovery would likely provide direct benefit to individuals. In general, because epidemiological research seeks evidence of gene-gene and gene-environment interaction, the effects of the gene being studied are often modest in size. However, it is always possible that researchers may discover a causal gene that does place people at high risk of a particular disease (such as the relationship between BRCA and the development of breast cancer). The informed consent form should clearly describe what would be done if such a discovery were made. If all specimens obtained are anonymized samples, obviously no results can be returned to individual participants. But if anonymization is not possible, the principal investigator should prepare for a situation in which a high-risk gene is identified. The PI should specify that he or she will ask the IRB for guidance. If the IRB determines that participants should be informed of the discovery, the investigator should outline a proposed procedure that could be used for contacting and informing them. (This may be accomplished through a newsletter or letter to participants, advising them to talk with their own physician if they are concerned, and to get retested in a CLIA-approved laboratory.)

#### 5. Specify That the Research Will Not Involve Clinical Counseling or Return of Individual Information to any Participant.

For studies that will be conducted in a setting such as a research laboratory or done in such a way that the principal investigator has minimal personal contact with participants, explain that it will be inappropriate for the principal investigator (or a designee) to provide clinical counseling. Specify that there are no plans to return participant-specific information to any participant or reported to any third party besides those that conduct reviews as required by regulatory agencies. (List any regulatory agencies that may review data from your study.)

While the study plan may be to NOT proactively return research results to the participant, it is important to note that HIPAA/the Privacy Rule gives an individual the right to access any identifiable health information that is part of a “designated record set.” A designated record set is any information upon which a medical treatment or a billing decision may be made. Therefore, for genetic research a research participant has the right to access any research information that may be used in their clinical care. The PI would have to determine if any of the research information meets this standard.



6. Specify That Whenever Appropriate, Subjects Will Be Provided With Additional Pertinent Information After Participation.

Any information provided should be provided in the aggregate. It should present the study results as a whole and should be sent to all participants (rather than providing participant-specific information individually).

One option for communicating is through a newsletter (or letter), sent to all participants.

7. Provide Instructions on How Participants Can Obtain More Information.

Participants in the study may have questions. Provide specific information (preferably a name and phone number) about how they can ask questions at any time during the study.

8. Specify How to Withdraw from the Study.

If it is possible for participants to withdraw from the study, they should be given explicit instructions on how to withdraw, and should be advised that they may withdraw at any time. They should always be allowed to withdraw if samples are identifiable. However, withdrawal may not be possible if the samples are anonymous – and participants should be advised as such. Please also refer to HRC HIPAA website for more information regarding the withdrawal of an authorization.

9. Include the Consent/Authorization Form as Part of the Questionnaire.

Since epidemiological studies involving mailed-in surveys are so large in scale, it is impractical to ask the principal investigators first to send out a consent form and later to send out a questionnaire to collect data. Instead, the consent form should be included with the initial questionnaire; the consent should include contact numbers for any questions. It should be designed in such a way that the participant understands it is a consent form, and knows where to sign it. This form must also include authorization language as required by HIPAA/the Privacy Rule.

## G. Sample Consent Form – Large Epidemiological Studies

NOTE: This **brief consent form** is intended for large-scale epidemiological studies such as the Nurses Health Study or Physician's Health Study, in which subjects are not typically followed at Partners' hospitals. Medical information obtained from these subjects is usually forwarded from the subjects at regular intervals via questionnaires or surveys.

### SAMPLE LANGUAGE

You are being asked to participate in a research study because (or about): (investigator fill in).

We will ask you to provide information about your health and medical history (by answering questions on a mail-in questionnaire or during an interview) and a blood sample to (name of PI or other contact). Data from the questionnaire/interview will be coded and stored in a database. Your blood sample will be divided into several parts, and frozen in a research collection or "bank." We will isolate DNA (your genetic, inherited material) from the cells in your blood. Your DNA and other parts of your blood sample will be used to study biochemicals (for example cholesterol, or vitamin levels) or genes (specific DNA sequences), which may contribute to: (fill in relevant investigative goal).

Examples of the problems and diseases we are studying include: (investigator fill in specifics). Because your sample will be stored for a long time, it is possible that it may be used to study other diseases, genes, or problems that we cannot predict now. Before any new studies can be undertaken, the investigator must receive approval from a hospital committee charged with the responsible conduct of medical research (the Institutional Review Board or IRB). The IRB will decide whether additional permission from you is needed or not.

One risk of participating in this study is the loss of confidentiality about your medical information. We will take steps to protect your privacy. The new Federal Medical Privacy rule outlines some specific ways that identifiable health information must be protected. A comprehensive notice of the Partners privacy protections can be found at (website). If you are interested in seeing this privacy Notice and cannot access it on the website, please contact us and we can send you a copy.

The basic steps taken to protect your privacy include:

- Your blood samples will not be labeled with names or other easily identified numbers like social security numbers.
- Your samples will be coded (assigned a unique study number), which will allow the researchers to link your sample to the other information that you provide through questionnaires or other study activities.
- The key to the code linking you to your blood and DNA samples will be maintained in confidential files with standard security precautions.

- The key is used only to connect other unidentified information you provide to your blood samples. The key to the code will not be given to researchers who are using the samples.
- Some of the tests performed on your samples may be done by research partners or laboratories outside the (BWH/MGH/DFCI), but they will never know who you are and never have access to the code linking the samples to you.
- Information gathered through this research may be reviewed by state or federal government agencies (for example the Food and Drug Administration), hospital accrediting agencies, or companies that sponsor (pay for) the research, as they fulfill their duties to agencies that oversee research. If this occurs, we will ask them to make reasonable efforts to protect your privacy.

Your samples will be stored in our laboratory indefinitely. **(Optional: Your sample will not be sold.)** You may withdraw your sample and your identifiable information from further study by contacting (\_\_\_\_\_). If you withdraw your permission, no further studies will be done using your blood sample or your identifiable information. But if your blood sample and/or information have already been used for analyses and studies, these results and the underlying information will be retained. Information obtained from this study will be used for medical statistical purposes only. In other words, your test results will only be studied as part of a large group. We will not return any individual results to you or to your doctor. Information from this study will not be placed in your medical records. *(We recommend the following optional statement in longitudinal studies, in an effort to share benefits of research with the subjects and keep them informed of new research directions: We will tell study subjects about our research results in a general way, without providing any individual results, through newsletters).* If medical advances are developed from this research and the research tests become part of routine care, you will need to be re-tested through your own doctor.

You will not benefit directly as a result of participation. Others may benefit in the future if we find useful new tests or treatments for \_\_\_\_\_.

You do not have to participate; your participation is voluntary. If you choose not to participate you will not lose any benefits to which you are otherwise entitled. Your health care at \_\_\_\_\_ will not be affected if you decide not to participate. This study does not involve medical treatment. Your alternative to participation is to not participate.

Blood drawing may cause pain, bruising and occasionally fainting. Rarely, an infection may develop, which can be treated.

The sample you provide may be used to develop new medical tests or treatments. It is possible that the researchers or hospitals might benefit financially if the tests or treatments can be patented or commercialized. There are no plans to provide you with payments or royalties, should this occur.

If you have any questions about this study or consent form, you may contact: (\_\_\_\_\_). If you think that your confidentiality has been violated or you have been

injured during this research study, you should contact the investigators. You may also contact the Human Research Committee at 617-724-5151 to seek independent assistance in addressing your concerns.

## **H. Secondary Use of Research Data**

At times, an investigator may want to use existing, prospectively collected research samples for research that was not envisioned at the time the samples were collected. Hence, this would be research that was not included in the informed consent process. In these situations, the IRB will carefully consider the best way for such research to proceed and whether or not this research can be done without recontacting the participants for a new informed consent and authorization.

An IRB may waive consent and authorization, or may alter or waive certain elements of informed consent if certain conditions described in federal regulations are met.

It is important for investigators to provide written specifics about the proposed research and carefully address potential risks to human subjects. Information to provide in the request for a waiver of written informed consent and authorization from the IRB for the use of samples already collected and stored from another study includes:

- Describe the study under which the samples were initially collected
- Who were the subjects?
- When did the study start?
- How many participants were involved?
- How were samples been collected?
- Do you contact the participants, in an ongoing fashion, and if so, how?
- Under what consent form or provisions were the samples originally collected? (*Enclose a copy of consent form.*)

You may request a waiver of authorization if all of the elements required by the Common Rule and HIPAA/the Privacy Rule are met. See appendix regarding waiver criteria.

Requests must be submitted formally in writing as amendments to existing protocols or formal new protocol submissions. Contact the IRB offices to determine which mechanism (amendment or new protocol) is best. Typically if two or three of the following—the population, purpose, or procedures—are altered, a new protocol rather than an amendment is required.

## VII. Reporting of Results to Subjects, Physicians, or Other Health Care Providers

**A. Purpose:** Genetic research may yield results that are relevant to a study participant's health. This document provides principal investigators with guidelines about how and when to report clinically relevant results from genetic studies.

### **B. Background:**

This section focuses on the planned voluntary reporting of research results to participants. The reader is reminded that even if the plan is to NOT return results, the participant independently has the rights to request access to some of their identifiable research information.

Research to identify genes or their variants may sometimes reveal findings that can affect a subject's health. The types of studies that could yield such results include for example:

- Study of inherited/inborn genetic changes (*germline changes*).
- Study of genetic changes that have occurred over time, which can be associated with cancer (*somatic changes*).
- Identification of genes that cause disorders or diseases within particular families. In some cases, the gene may already be known; in other cases, a gene responsible for a disorder is found by accident, while studying that gene's contribution to another type of condition.
- Correlation between the type of gene a person has (*genotype*) and the physical manifestations or symptoms that that gene causes (*phenotype*).
- Role of a gene that is known to be associated with particular physical characteristics in causing other disorders.
- The identification of patterns of gene expression or variation in particular tumors.

### **C. Issues to Consider**

#### *Clinical Implications of the Genetic Information:*

1. Identification of an inherited/inborn change may: confirm a suspected genetic diagnosis, determine whether someone is at risk for developing a particular disorder, or may suggest to participants that they undergo carrier or prenatal testing.
2. Identification of an acquired genetic change in a tumor may help to refine a diagnosis or influence a person's choice of therapies.

3. Investigators may face the dilemma of knowing something about a participant's risk for a condition unrelated to the original purpose of the study.
4. If the gene mutation found to cause a particular disease was previously unidentified, its discovery may come as an unwelcome surprise to the participant involved. This is especially true if the mutation is unique to that individual or his/her family.
5. The result may indicate risk for a disorder that may not manifest until some time in the future.
6. If the gene's penetrance is incomplete, a mutation may never cause symptoms.
7. Accurate data regarding penetrance may be unavailable.
8. A test may reveal risk for a condition for which no medical intervention – be it treatment or prevention – is available.

*Issues regarding the quality of the results:*

1. Mistakes happen, even in the best of laboratories. A mix-up of samples or laboratory error, which can be an annoyance in a research study, may have devastating impact clinically.
2. Test results that will be used as the basis for clinical decision-making should be performed in a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA). Most research laboratories are not certified. In some instances, the laboratory may need to share the results of research with a study participant, but unless that laboratory is CLIA certified, the results should be noted as being research results that should not be used for clinical decision-making. If the laboratory intends to share results for clinical purposes, it should either obtain CLIA certification or arrange for samples to be sent for testing to a CLIA-certified laboratory.

*Participants Vary in their Desire to Know:*

It is important to remember that different people have different opinions on whether they want to learn test results. When giving their consent to participate, some people may not have thought about the relevance of the genetic study to their personal health.

Some participants will expect to be informed of the results of their genetic tests. That is part of the reason they decided to participate: to receive information about their own diagnosis, or to gain access to prenatal testing. In many cases, especially for people with rare disorders, routine clinical testing is not yet available commercially, so the only way they can gain access to such testing is by participating in research.

Some people have an unrealistic expectation that genetic diagnosis will bring effective new therapies, if not cures.

At the other extreme, participants may not be aware that the results of genetic research might indicate that they are at risk for developing a disorder. This is especially true if they are not yet manifesting any symptoms.

### *Children Require Special Consideration*

If the study involves children who display a specific phenotype under investigation, there are additional concerns that need to be addressed. Can a young child or teenager adequately understand the risks and benefits of knowing the results of a genetic test? (See appendix 2.)

## **D. Guidelines for Principal Investigators**

Given the concerns outlined above, the following issues must be addressed in the study protocol, and, as appropriate, in the informed consent process. Please note that the standards for reporting results are very high, and a principal investigator must consider carefully whether he or she is able to meet them.

### 1. Criteria that the IRB will consider for Determining the Clinical Reporting of Genetic Test Results

The PI should specify the anticipated results of this research in the protocol

- Which gene or genes will be studied.
- How they will be studied.
- What kinds of genetic changes might be detected.

Specify if the clinical reporting may:

- be limited to specific predetermined mutations
- include mutations yet to be discovered – in this situation, the PI must specify what criteria will be used to determine whether or not the results will be clinically reported.

If the results are to be reported, the investigator must address the following issues in the protocol:

- analytical validity of a test (how reliable does the test detect the mutation, or absence of a mutation)
- clinical validity (how accurately does the test detect or exclude the clinical disorder or genetic risk in question)
- clinical utility (how useful is the test in guiding clinical management)
- ethical, legal, and social implications of the test result



Generally speaking, only those results with a high degree of clinical relevance, and that are associated with an acceptable risk/benefit ratio should be communicated.

## 2. Informed Consent

Sometime during the informed consent process, a study participant must learn whether or not there is a plan to return research results to the participant/s.

## 3. Laboratory Testing

Any genetic tests the investigator intends to report to study participants, and that potentially could be used for clinical decision-making, must be performed in a laboratory that is certified under CLIA. (However, an individual can ask for study results simply for his or her own information, and as long as the information is not used for clinical decision making, it does not have to be from a CLIA laboratory.)

Note that HIPAA/the Privacy Rule gives individuals the right to access any research information that may be used for treatment or billing decisions. This generally limits accessible information to that obtained from a CLIA lab.

If a CLIA-certified laboratory is required, it might be the same one that is performing the research, or it might be a separate clinical laboratory, in the same institution or outside the institution. Follow these guidelines:

- If the original clinical sample was not obtained in a CLIA certified laboratory, a new sample must be obtained.
- If this is not possible (e.g., with tissue biopsies obtained through an invasive procedure), then the protocol should be designed so that initial samples are received in an established CLIA-approved clinical laboratory (such as a clinical pathology laboratory).
- If the genetic change is identified in a non-CLIA-certified research laboratory, the result must be verified in a CLIA-certified laboratory before the results can be reported to a subject who will use the information for clinical decision making.

## E. Genetic Counseling

There must be a mechanism for reporting results to participants that is appropriate to the nature of the test and the clinical disorder. The qualifications of the individuals who will report the results and provide counseling must be stated. These individuals can include professionals with substantial experience in the clinical reporting of genetic test results for the disorder in question, and/or board certified medical geneticists or genetic counselors. Test results and counseling should be documented in writing to the participant and the relevance of the results to other family members addressed with the participant.

## **F. Levels of Genetic Testing with regard to “Return of Results”**

To aid principal investigators, the flow chart below describes different scenarios concerning reporting of results, as well as suggested language for the informed consent documents and protocol.

Level 1. Return of results will occur (clinically validated information from CLIA-approved laboratory)

- A. Diagnostic
- B. Predictive

Level 2. Anticipated return of results possible (could attain Level 1 status or be less definitive)

Level 3. Anticipated return of general information only through newsletter

Level 4. No anticipated return of any kind of information, including no newsletter anticipated

## **G. Sample language for informed consent documents:**

### **Level 1(A & B) – Return of Results Expected**

Clinically or diagnostically relevant genetic information **is** likely to be obtained if you participate in this genetics research study. You may wish to get this information or not – it is your choice. If you wish to get these results, we will review the information and its medical importance with you, and provide you with the necessary counseling to help you understand the results. It is possible that additional samples may be needed to confirm test results. We can give the medically relevant information to your doctor or place it in your medical record if you wish. Both of these releases of information would require separate written permission from you.

#### **Level 1A      Diagnostic Only**

The results of the genetic testing may either confirm or exclude the diagnosis of \_\_\_\_\_. It is also possible that the genetic studies may not provide a definite answer. The importance and reliability of the results of testing can be discussed with you when the studies are completed. Learning the results of the genetic studies may be beneficial to you and help you and your doctor make medical decisions, but learning the results may also make you upset or anxious. Because genes are inherited, your genetic information may be relevant to other family members.

#### **Level 1B      Predictive Only**

You should be aware that there are many different forms of genes in different people. Genes are not the only determinants of your health. Other factors like diet, for example, can be important. Exact predictions about you or your family’s future health may not be possible. It may or may not be possible to use the genetic information from this study to suggest ways to improve your

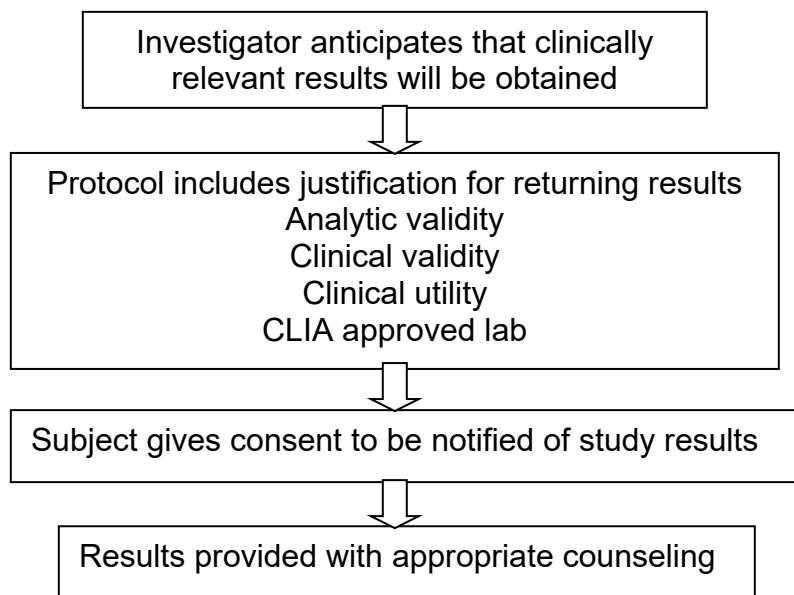
health or reduce your risk of illness. Study doctors will review with you the level of reliability about the genetic information obtained as a result of your participation. Learning the results of the genetic studies may be beneficial to you and help you and your doctor make medical decisions, but it may also make you upset or anxious. Because genes are inherited, your genetic information may be relevant to other family members.

### Level 1(A & B)

Would you like to be informed about medically important genetic information obtained during this study?

- Yes
- No

Please note: You should update the study doctors with changes to your address and phone number if you wish to be contacted. Research study staff cannot seek you out to update and maintain current addresses and phone numbers. If you receive ongoing medical care through BWH/MGH, the investigators can obtain that information from your hospital or clinic records.

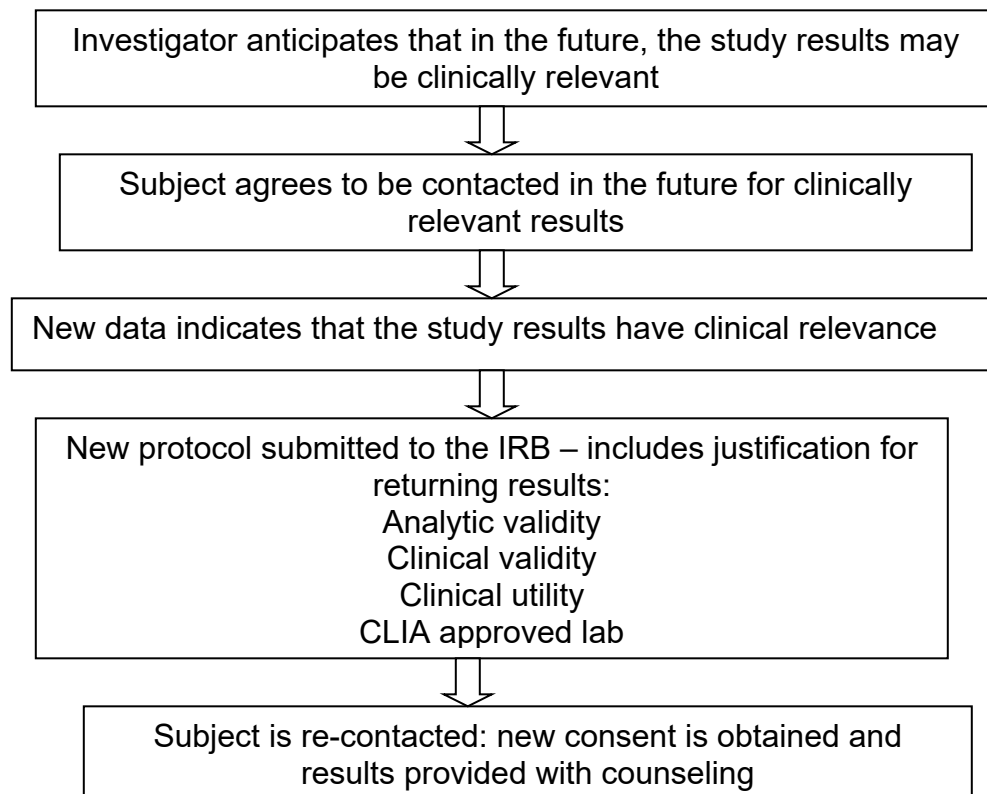


## Level 2: Possibility of Return of Results

Although no clinically or diagnostically relevant information can be learned from this research at this time, it is possible that medical information directly relevant to you and/or your family may be obtained in the future. If relevant information does become available from this study, we need to know if you would be interested in getting it. If you are interested, we will keep your name and contact information so that we can contact you. The decision to be recontacted is your choice. If this research does identify important information, it is likely that we will need to obtain an additional (blood) sample so that we can confirm the test results. Would you like us to contact you in the future if information relevant to you or to your family is obtained?

- Yes
- No

Please note: You should update the study doctors with changes to your address and phone number if you wish to be contacted. Research study staff cannot seek you out to update and maintain current addresses and phone numbers. If you receive ongoing medical care through BWH/MGH/DFCI, the investigators can obtain that information from your hospital or clinic records.



### **Level 3: No Return of Results but Offer Newsletter**

Although no clinically or diagnostically relevant information can be learned from this research now, it is possible that general medical information can be learned that you or your family may find helpful. A newsletter may be available in the future describing the findings of the research in general terms. No individual information will be reported in the newsletter. Would you like to receive a copy of such a newsletter, if one becomes available?

- Yes
- No

There is no plan to return individual information to you or to your doctor during this research. None of the research results will be placed in your medical record. It is possible that the results of this research may lead to medical advances such as new tests for diagnosing or treating \_\_\_\_\_. If such tests become available, you may be able to have them performed through your doctor and clinical laboratories as part of your regular medical care.

Please note: If you wish to be contacted, you should inform the study doctors with any changes to your address and phone number. Research study staff cannot seek you out to update and maintain current addresses and phone numbers. If you receive ongoing medical care through BWH/MGH/DFCI, the investigators can obtain that information from your hospital or clinic records.

### **Level 4: No Return of Results**

This research is only useful as a stepping-stone in advancing medical knowledge about \_\_\_\_\_. It is not intended to provide clinically or diagnostically relevant information. There is no plan to return any research results to you or to your doctor during this research. None of the research results will be placed in your medical record. It is possible that the results of this research may lead to medical advances, such as new tests for diagnosing or treating \_\_\_\_\_. If such tests become available, you may be able to have them performed through your own doctor and clinical laboratories as part of your regular medical care.

## **VIII. “Case Reporting” and Research Limited To Medical Records**

### **A. Purpose**

- To provide guidelines for appropriate oversight of medical case reporting
- To provide guidelines for appropriate oversight of medical records research.

### **B. Background and Rationale**

Clinical experiences are often the genesis of research questions and can influence the design and development of clinical research protocols. In an academic medical center it is not unusual for unique and interesting clinical cases to be written up as case reports for publication in medical journals or presentation at medical or scientific meetings. This policy is designed to provide guidance on when publication/presentation of case report(s) constitutes human-subjects research and when it requires prospective IRB approval.

### **Medical Case Reporting**

The Federal Policy for the Protection of Human Subjects (45 CFR 46.102(d)) defines “research” as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to general knowledge. In general, the review of medical records for publication of "case reports" of typically three or fewer patients is NOT considered human-subject research and does NOT typically require IRB review and approval. This is because case reporting on a small series of patients does not involve the formulation of a research hypothesis that is subsequently investigated prospectively and systematically for publication or presentation. Reporting or publication is not typically envisioned when one interacts clinically with the subject. Although case reports are not considered research, it is important to consider HIPAA/the Privacy Rule implications. All efforts should be made to de-identify the subject of the case report. If this can be accomplished, then there are no further requirements. But, if the patient is identified in the case report, an authorization must be obtained prior to publication of the report.

When larger series of patients are being reported, investigators usually begin to ask specific research questions and formal systematic collection of data occurs, moving these activities closer to prospectively designed research. The boundaries between case reporting and formal medical records research may be unclear for a series of one’s own patients. Researchers are advised to consult with the IRB or submit larger case series reports for IRB review when uncertainty exists about whether formal and systematic collection of human subjects research is occurring.

It should also be noted that teaching, and soliciting colleagues’ advice on clinical care of a specific patient or groups of patients during presentation of a case at departmental conferences, DO NOT require IRB review and DO NOT require an authorization. These activities are allowed as part of patient care and teaching under HIPAA. Generalized commentary by a clinician on the outcome of their clinical care of patients in accepted venues for discussion of clinical management is also not considered research requiring IRB review, if there is no prospective research plan and no formal, systematic and prospective collection of information. This type of communication may occur at hospital or practice meetings, in continuing education

venues, or in editorials, where the comments are explicitly identified as personal experience and not formal clinical research.

### **Formal Prospective Research Involving Retrospective Review of Medical Records**

Formal, prospective medical records review to answer specific research questions DOES constitute systematic, prospective medical records research on identifiable human subjects, and does require IRB review and approval (submit Medical Records form obtained at: <http://healthcare.partners.org/phsirb/>). Federal regulations state that if data is abstracted without retaining *any link* to specific individuals, some medical records research may be considered exempt from IRB review. The IRB, not the investigator, must make this determination. The IRB will consider the HIPAA requirements for specific research. See HRC HIPAA page. At MGH and BWH, institutional policy mandates that ALL systematic, prospective, formal records review requests are reviewed and approved, ordinarily by expedited IRB review mechanisms; such review requests are NOT “exempted.”

Investigators are reminded that they should abstract and retain only the minimum relevant identifiable clinical information. Investigators should discard links to human subjects when the research has been completed and published, or when relevant research goals or oversight requiring links to individuals are concluded. Institutional and governmental policies on the duration of retention of research records vary and are discussed in a separate policy. (HRC Website for Policies and Procedures) Links to identifiable subjects may be maintained, but should not, in general, be retained indefinitely.

**Confidentiality:** Patient/subject confidentiality should be respected in all clinical situations involving identifiable medical information from patients and subjects. All clinicians are reminded of the following points:

- Names, dates of birth, social security numbers, and other "codes" or combinations of identifiers, which might easily allow someone to identify a subject, should never be used in publications or external presentations. Remember that any dates relating to the person are considered to be identifiers under HIPAA.
- Unique family trees or pedigrees should be masked or disguised when such information could identify individuals or kindreds.
- Photographs should be appropriately masked to preclude identification of subjects.
- Partners’ Office of General Counsel strongly recommends that patients provide written consent to allow publication or electronic dissemination of pictures or other information (e.g. videos, voice recordings, transcripts), which might in any way identify them. Contact the Human Research or Public Affairs office, as appropriate, for sample research and non-

research consent forms for use of identifiable material. When photographs will ONLY be used in confidential medical records or as part of direct clinical care of the patient (for example, photograph of a characteristic rash which would be retained in a record for documentation or shown to colleagues in the provision of clinical care), it is appropriate and acceptable to obtain and document verbal consent.

- Clinicians should be sensitive to the "small cell problem": the existence of individuals with such unique or unusual diagnoses or illnesses, that it might be possible for others (or patients and families themselves) to identify the individuals in case reports or medical text books based upon limited information, such as state of residence, age and diagnosis.



## **IX. Single patient diagnosis / Clinical care of unusual genetic disorders in specialized academic laboratories**

### **A. Purpose:**

Provides guidance for sending a genetic sample to a non-Partners academic research laboratory for the diagnosis of a single patient, or for the clinical care of an individual/s with unusual genetic disorders.

### **B. Background:**

Clinical care of individual patients or counseling of their parents or family members may benefit when their biological samples are sent to academic centers or laboratories which have specialized expertise in a particular genetic disorder. Often, such laboratories only provide their services as part of a formal research protocol and are interested in collecting samples from relevant patients/families from around the world. An example is testing for the rare disorder Holt-Oram syndrome, which includes cardiovascular and limb anomalies. There are several laboratories listed in the GeneTests database ([www.genetests.org](http://www.genetests.org)) that offer research-based testing for this disorder, and such testing may be helpful in confirming a clinical diagnosis and serving as a basis for genetic counseling of a family. Although these research results may be confirmatory, or clinically useful to patients, physicians and families, there may never be enough clinical need for these highly specialized tests to become routine diagnostic procedures at any site.

Because such testing can have a significant research component, Partners' IRB expects these outside academic laboratories to have IRB review and approval at their sites. Hence, if a Partners care provider wants to send a biologic sample to such a research lab, patients should review and sign an IRB-approved consent form from that outside academic institution. The consent form (or an accompanying document) should clearly state that this is outside research, with which the treating provider and hospital are not involved. The referring Partners practitioner serves as a phlebotomist and collaborative clinician for return of relevant genetic information and counseling as he or she sees best clinically. If the test is being done for clinical purposes, HIPAA does not require specific authorization.

### **Guidelines:**

Partners' IRB does not find it reasonable to formally and fully review each of these single patient enrollments into outside studies, when the primary goal of such procedures is the clinical practice of genetics. The IRB does have an appropriate approval mechanism for this type of single patient study referral which clinician investigators may elect to use. This mechanism is the Innovative Diagnosis and Therapy (IDT) submission. (See separate policy at <http://healthcare.partners.org/phsirb/>). The IRB recommends submission and approval of an application via this mechanism when there is a prospective research plan on the part of the Partners investigator: e.g. publication is

expected, additional biological samples are anticipated, or family members beyond a child/parent triad is studied. The IRB will review *any* submission upon investigator request. Investigators are encouraged to seek guidance for determinations about need for review or problematic studies (contact Maria Sundquist at 726-3493 for advice if needed). When appropriate, clinicians should submit the information requested on page 2 of the IDT submission form AND the research consent form from the outside institution for review. These will then be reviewed in an expedited manner by an IRB chair.

It is important to emphasize that any Partners investigator who is actively recruiting multiple patients prospectively as a co-investigator, or actively identifying patients retrospectively by medical record review, for patient contact purposes, must submit a formal protocol for consideration by the IRB. Similarly, any Partners laboratories that accept referral specimens for research protocols, must have formal, IRB-approved protocols.