Guidelines for reviewing studies involving genetic research.

Washington University Institutional Review Board

New techniques present the research community with unprecedented opportunities to generate large amounts of genetic and genomic data, with the potential to significantly increase our understanding of the mechanism for many important diseases. These guidelines are developed recognizing the following points:

1. The research itself generates information that is individually identifiable.

2. The research may uncover information about the participant that has a direct bearing on the future health and welfare of the subject and/or individuals related to the subject.

3. The research may uncover unsuspected information about the information that has potentially harmful consequences to the individual, i.e., information about relatedness to other family members, criminal liability and some aspects future insurability that are not protected by the Genetic Information Nondiscrimination Act (GINA).

The IRB recognizes that genomic research has the potential for tremendous benefit to individual research participants, patients and society at large. Furthermore, the primary risks are informational, for which data protection strategies can provide effective mitigation. In addition, an evolving body of policy and law provides additional protection for individuals that contribute their samples for genomic research. Thus, the goal of the IRB is to facilitate the progress of these studies while adequately protecting the participant.

These guidelines apply to all research studies in which a sufficient amount of genetic information to uniquely identify an individual will be created or obtained. This includes, but is not limited to, Whole Genome Sequencing (WGS), Genome Wide Association Studies (GWAS), Single Nucleotide Polymorphism (SNP) arrays, exome sequencing and transcriptome sequencing. Privacy protections are not restricted to, but are of increased concern, when a link from the sample to the participants identity is maintained.

I. Prospectively collected specimens:

Consent is mandatory. Consent must include all of the following elements:

A. A statement that unique, individually identifiable genetic information may be generated as part of the research protocol. The significance of this should be explained in lay language.

B. Risks associated with genetic information, including re-identification.

C. A description of a plan with respect to return of research results.

D. Statement addressing the possibility of incidental findings

E. A statement describing plans for data sharing.

F. A statement describing a plan for sample sharing.

Version Date: 12.06.2011
Points for the IRB to consider in reviewing these studies:

A. The statement describing the research should be written such that the participant will understand what it is the researcher is examining (DNA, genes) and that the data generated is unique to him or her.

B. The statement of research should clearly specify the intent of the current studies, ie) what the genetic information will be used for (identify genes that cause cancer etc). If the investigator wishes to use the sample and/or data for future research, including not yet anticipated studies, this should be clearly indicated in the consent.

C. If there is a plan to inform subjects of findings from the research, the IRB will consider the following:
   a. Are subjects given the option to choose whether or not they receive research results (directly related or incidental)?
   b. Does the plan address what types of findings will be returned to the participant, ie) only those directly related to the research, or will participants be informed of unrelated incidental findings also?
   c. How will the investigator determine what findings merit disclosure to the participant?
   d. Who will provide the information to the participant, and will an opportunity for genetic counseling, if appropriate, provided?
   e. Will the investigator provide an opportunity for family members to be tested or counseled?

D. If there is no plan to inform participants of research findings, this should be stated in the consent.

E. If there is intent to share the data and/or sample, the nature of the sharing must be adequately described,? Will sharing be only with academic centers, industry partners, government databases? If there is sharing of data with a database, the controls that are placed on accessing the database should be described to the IRB.

F. If samples are to be collected from minors, the investigator must address what, if anything, will occur when the participant reaches age 18. The IRB recognizes the logistical difficulty that may accompany a requirement for reconsent at age 18. However current regulatory guidelines require that when the participant reaches the age of majority, if the use of that specimen still constitutes the regulatory definition of human subjects research, consent must be obtained from the subject, or the IRB must waive consent if the criteria for a waiver under 45 CFR 46.116(d). Alternatively, the investigator may either destroy all identifiers associated with the sample such that it is no longer considered human subjects research. In addition, for all studies that include minors, the option for a participant to have their remaining (if any) sample destroyed at age 18 should be available and stated in the consent.

II. Previously collected samples for which there is consent that addresses genetic research.
If the proposed research uses existing samples that were initially collected under a research protocol in which consent from the participant was obtained, and the consent addresses genetic research, the IRB will consider the following:

A. Does the consent under which the sample was collected provide an option for the participant to agree or not agree to participation in the genetic study. If participation was optional, only those that agreed to participate may be included.

B. The proposed studies must be consistent with what was described in the consent under which the specimen was collected.

C. If the proposed studies will share data with databases, the consent under which the sample was collected should have language consistent with the proposed sharing and use.
   a. If there is opt-in or opt-out language on data sharing, only those that opt in may have data shared.
   b. If the consent is silent on this issue, the IRB should weigh the risks and benefits of the sharing plan and may either require re-consent, or may approve sharing without re-consent if favorable. Assessment of risks will include consideration of the population from which the samples were obtained, implications for family members and members of the community.

D. If the consent under which the sample was collected described a plan for the return of research results or incidental findings, the proposed plan should be honored and included in the current research plan. If the consent was silent, the investigator must provide a plan that addresses whether and why they will return any research results or incidental findings, and how that will be done.

E. If samples come from an institution other than WU, the PI is responsible for obtaining assurance from the source institution that the proposed research is consistent with the conditions set forth in the consent under which it was collected, and that all conditions as set forth above are met.

III. Previously collected samples for which there is no consent or consent is silent:

If the proposed research uses existing samples that were collected without consent, the IRB will consider the following in determining whether genetic research is permissible.

1) Samples collected for research in which there is consent, but the consent under which it was collected is silent with respect to genetic research.

A. The IRB will consider whether participants should be contacted and consent obtained for the proposed studies. If it is determined that there should be re-consent, all elements described in section I for prospective data collection should be addressed.

B. In unusual circumstances, the IRB may consider approving genetic research on samples in which the consent under which it was collected does not address genetic research. In making this determination, the IRB will consider whether the aims of the proposed research are sufficiently related to the original research, and the risks of the proposed research to the participant, family
members and any specific social/ethnic/cultural group. The IRB may determine that aims are sufficiently related to permit use of the specimens for genomic research. In such a case, the investigator must address:

a. A plan addressing whether or not there will be return of research results/incidental findings. Adequate justification must be provided to support the proposed plan.

b. A plan describing data and sample sharing. If there is to be data and sample sharing, adequate justification must be provided to support the plan. Additionally, a description of how privacy and confidentiality will be protected must be provided.

2) Samples collected for research under a waiver of consent. This is expected to be a rare circumstance and would typically have occurred in an emergency research setting in which neither the research subject nor the subject’s legally authorized representative was able to provide informed consent for the sample collection. This is a difficult area for which the IRB will need to carefully consider each study on an individual basis. Elements that the IRB will consider include whether the specimens are identifiable or anonymized, the population from which the samples were collected and the potential risks/benefits to that population, the conditions under which the IRB initially waived consent.

A. The IRB will consider whether participants can be and/or should be contacted and consent obtained for the proposed studies. If it is determined that there should be consent, all elements described in section I for prospective data collection should be addressed.

B. In very unusual circumstances the IRB may approve genetic studies on samples collected under a waiver of consent. In making such a determination, the IRB will consider the following:

a. Do the conditions under which the original waiver of consent was granted address the proposed use of the specimen?

b. Is there any information related to the sample that would suggest whether or not the proposed research might be of benefit to the subjects from which the sample was taken (e.g., using blood collected initially from subjects enrolled in an emergency research study on resuscitation with a proposed use in a secondary research study on heart disease)

c. Are the proposed studies likely to affect the rights of or have special significance to any specific social/ethnic/cultural group? If so, are there appropriate measures in place to protect the interests of these groups?

C. The investigator must provide the IRB with:

a. A plan addressing whether or not there will be return of research results/incidental findings. Adequate justification must be provided to support the proposed plan.

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b. A plan describing data and sample sharing. If there is to be data and sample sharing, adequate justification must be provided to support the plan. Additionally, a description of how privacy and confidentiality will be protected must be provided.

3) Samples collected for clinical purposes for which there is no consent.

A. The IRB will consider whether participants should be contacted and consent obtained for the proposed studies. If it is determined that consent should be obtained, all elements described in section I for prospective data collection should be addressed.

B. Rarely, the IRB may consider granting a waiver of consent for genetic studies on specimens collected for clinical purposes. In making this determination, in addition to the criteria for a waiver of consent found at 45 CFR 46.116(d), the IRB will consider the following in determining whether the research is permissible:

a. Are the proposed studies likely to benefit the population from which the samples were collected?

b. Are the proposed studies likely to affect the rights of or have special significance to any specific social/ethnic/cultural group? If so, are there appropriate measures in place to protect the interests of these groups?

c. Will the data be collected in a manner that links it to any identifiers?

C. The investigator must provide the IRB with:

a. A detailed plan addressing whether or not there will be return of research results/incidental findings. Adequate justification must be provided to support the proposed plan.

b. A plan describing data and sample sharing. If there is to be data and sample sharing, adequate justification must be provided to support the plan. Additionally, a description of how privacy and confidentiality will be protected must be provided.

IV. Samples from individuals that are now deceased.

If the proposed research uses samples from individuals that are now deceased, the IRB will consider the following in determining whether the proposed research is permissible.

1) Samples collected from now deceased individuals in which there was consent obtained at the time of the original sample collection.

A. The IRB considers that the conditions specified on the original consent document apply regardless of the vital status of the individual. Therefore, these will be considered in an identical manner as described in sections II and III above.
B. Does the use of the samples have implications for living family members, members of the same ethnic or racial groups or in any other way have the potential to violate religious beliefs, cultural or social values or norms?

2) Samples collected in research protocols under a waiver of consent or clinical samples for which there is no consent, from individuals now deceased.

A. Do the conditions under which the original waiver of consent was granted address the proposed use of the specimen?

B. Is there any information related to the sample that would suggest whether or not the proposed research might be of benefit to the subjects from which the sample was taken (ie, using colon cancer specimens collected at the time of surgery to study the genetic causes of colon cancer).

C. Are the proposed studies likely to affect the rights of or have special significance to any specific social/ethnic/cultural group? If so, are there appropriate measures in place to protect the interests of these groups?

D. Does the use of the sample have implications for living family members?

E. The investigator must provide a plan that addresses data and sample sharing as described in above sections.

V. Additional considerations with regard to genomic research on previously collected specimens.

The IRB recognizes that research performed on specimens that were previously collected for other purposes than the proposed study and in which the specimens are coded such that the identity of the subject cannot be readily ascertained, according to the current interpretation of the regulations at 45 CFR 46 and outlined in the 2008 policy guidance from the Office of Human Research Protections entitled “Guidance on Research Involving Coded Private Information and/or Biological Specimens” (http://www.hhs.gov/ohrp/policy/cdebiol.html) may not constitute human subjects research. However, given the unique nature of these studies, their potential for uncovering sensitive information coupled with the possibility of re-identification of individuals and/or family members and implications for communities, the IRB will review all proposals for genomic research to assure that the proposal is consistent with current regulatory and institutional guidelines and ethical norms.

VI. Standards for data sharing

Given that the greatest risks of genomic research involve protection of privacy and confidentiality, researchers must clearly outline the proposed plan for data sharing. The IRB considers the standards outlined by the NIH for submission to dbGaP to represent the current accepted norm

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within the research community. All plans for data sharing must conform to these standards, as outlined in the following document (http://gwas.nih.gov/pdf/GWAS_points_to_consider_A.pdf). Approval for data sharing with databases will not be granted for studies in which the samples were not collected in accordance with the guidelines, as set forth in the aforementioned document. Plans for data sharing with other to other investigators both within and outside of Washington University, will be assessed for appropriate protections to the privacy and confidentiality of the research subject.

VII. Considerations for return of research results and incidental findings.

The IRB recognizes that plans for returning results either directly related to the research or incidental findings revealed during the course of the research will by necessity vary between individual studies, therefore uniform requirements are neither appropriate nor desirable. Nonetheless, there are several important points that investigators should consider in making the decision to return results and in the devising and implementing plans to return results.

Unless it is an obligatory part of the research design, participants should be provided with the option to choose whether or not they wish to be informed of the results of the study or of incidental findings. This should be clearly indicated as an opt-in or opt-out selection on the informed consent document.

A. Determining what results to return to participants.

If it is decided to return research results or incidental findings, the investigator must determine what results they will give back to the participant. In making this determination, the investigator should consider the following:

i. The strength of the evidence linking the mutation (or other genetic finding) to a disease phenotype. What is the penetrance of the phenotype? Is there consensus among experts in the field that the finding is linked to disease?

ii. Whether there is a clinically validated, independent test that can be used to verify the results.

iii. Whether there is an action that the individual can take as a result of learning this information that will modify their risk. Are there other important actions that might be taken a result of learning this information, e.g., family planning?

iv. Whether there are serious consequences to the individual of not learning and/or acting on the information.

The strongest case for returning results or incidental findings would be a mutation that was indisputably disease causing, had 100% penetrance, could be independently verified and for which an action would prevent serious health consequences. On the opposite end of the spectrum are findings for which the evidence of disease association is weak, there is no independent test and...
there is no action to be taken to modify risk. Most fall in between these extremes, and there is no clear consensus as to what mutations would be considered most reportable. Furthermore, as more studies are conducted new mutations will be found, new tests and therapies will be developed and the evidence for particular associations may strengthen or weaken Therefore, the reportability of specific findings is a moving target.

B. Plans for returning results.

Should an investigator deem it appropriate to return either research results or incidental findings to a participant, the plan must provide for adequate counseling and access to resources such that the person is fully informed as to the implication of the findings. In general, this will depend on the expertise of the investigator and the research team. If the results being returned are outside the expertise of the investigator, it may be desirable to include additional persons with expertise. If there are significant implications for family members, or for family planning on the part of the participant, the use of a professionally trained genetic counselor may be an important and desirable part of the plan. The investigator should also consider whether they will provide additional confirmatory testing to the participants, whether they are willing to test family members, and how the cost for such testing and counseling will be covered.

C. Secondary data obtained from banked specimens.

Returning results from specimens that were obtained from biobanks adds additional layer of complexity. Secondary users of banked specimens have no relationship with the participant, and the participant is almost certainly not aware of the details of the study for which the specimen is now being used. For the primary investigator (the one that collected the specimen) to assume responsibility for reporting back to the participant the findings of other, secondary users would be not only extremely burdensome, but problematic. In that instance, the researcher would be vouching for the validity of another researcher’s results. Therefore, unless the finding is thought to represent a serious and preventable threat to the health and welfare of the individual, the most appropriate plan may be to not return any findings.

Studies will be reviewed by fully convened committee or by expedited review procedures based on the particular risk profile of the study.