

## Points to Consider in the Transition Toward Whole-Genome Sequencing in Human Subjects Research

*Developed by the NHGRI Intramural Research Bioethics Core*

When the field of genomics was in its infancy, the cost to sequence a single human genome was approximately \$1 billion. Sequencing technology has become progressively more efficient and less expensive in recent years, and the vision of a \$1,000 whole genome sequence soon will be a reality. An increasing number of research protocols are proposing to utilize whole-exome and whole-genome sequencing (WES/WGS), which are powerful new research tools to help identify the genetic variants/mutations responsible for a broad range of Mendelian disorders and complex genetic phenotypes. Traditional genetic research (i.e., candidate gene approaches) began with the study of single, relatively short segments of DNA and a single associated disease, giving rise to a range of ethical concerns. Research involving WES/WGS, while not necessarily raising novel ethical concerns, has amplified existing ones: theoretical concerns now are real, and previously uncommon situations are much more likely to occur. In large part, this is because WES/WGS represents a significant increase in the amount of data being gathered; WES/WGS research generates an extremely large volume of sequence data from at least all of the coding regions of genes, up to the majority of the genome. Accordingly, researchers are faced with an expanded set of ethical challenges related to the use of WES/WGS.

This document discusses three key ethical issues that research protocols involving WES/WGS should address: *the management of incidental findings, privacy and data sharing, and informed consent*. It does not recommend any specific actions or consent language; rather, it is intended to raise concerns that should be weighed in the context of each unique protocol.

### Issue 1: Management of Incidental\* Genetic Results

One of the most challenging issues in whole-genome sequencing relates to the level of responsibility a researcher has to inform participants about incidental (sometimes referred to as “secondary”) genetic findings that are unrelated to the disease being studied. In general, the guidance available on this subject emphasizes the importance of informed consent, sound clinical practices, and the balance between respecting a participant’s autonomous decision-making and potentially saving or improving a participant’s life. While a growing consensus leans towards returning certain genomic test results to participants, return of results may not be required in all circumstances or for all protocols. As discussed in more detail below, issues such as availability of monetary and personnel resources may have a significant impact on the feasibility of returning incidental findings to research participants.

**Genomic study protocols should address whether or not participants will be told about incidental genetic findings during the course of the study.** Some ethicists argue that an affirmative moral “duty” to disclose such information exists, particularly when a participant is

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\* There is a separate question about the point at which it is appropriate to return related (“primary”) results. Since we do not believe that WES/WGS research does not raise novel issues about return of related results, it will not be addressed in this document.

willing to be informed and/or when his or her life is in danger. Other scholars argue that the very nature of genomic research serves to sever any such ethical obligations, particularly when logistical barriers and costs to implement responsible disclosure mechanisms are high. When examining this threshold issue, consider:

- The level of relationship between researchers and participants. The closer the relationship (characterized, e.g., by more frequent communication, smaller study cohort, and/or involvement of entire families), the more likely it is that participants may expect to receive genetic information. Some ethicists suggest that similar expectations can arise when the research involves more invasive procedures or time-consuming duties.
- The expressed preference of each individual participant.
- Whether researchers have access to genetic counselors or other people who have been trained to deliver this kind of information and answer any foreseeable questions.

**If genetic findings will be communicated to participants, the protocol should describe the circumstances and method of disclosure.** Many scholars have argued that, at a minimum, any results offered to participants should be “scientifically valid, confirmed, and should have significant implications for the subject’s health and well-being.” Issues to consider when describing the circumstances and methods of disclosure:

- What kind of information will be disclosed? This may include:
  - The accuracy of both the genetic testing procedure and the subsequent data analysis, including whether the lab performing the test and analysis is CLIA-certified.
  - The level of correlation between genotype and phenotype for a particular disease or disease risk; that is, the chance that a particular phenotype will result from the presence of a particular allele or constellation of alleles.
  - The immediacy and seriousness of the risk.
  - Clinical utility: “the likelihood that a test will lead to an improved health outcome.” The concept of clinical utility includes genotype/phenotype correlation, but also takes into account “actionability” (available curative or palliative interventions) and the overall impact of the diagnosed condition or risk on a participant’s life and future decision-making.
- To whom will genetic information be disclosed?
  - Will a treating physician be notified of genetic information that is likely to become a part of the participant’s medical record?
  - Will there be exceptions or special protocols for participants who themselves lack the legal capacity to give informed consent?
  - Will family members be allowed to request or receive genetic data that may have an impact on them? In determining whether to disclose to any family members who may be at risk, remember that a family’s expectations could differ based on cultural norms or the level of familial involvement in the study. Some scholars have argued that the

permissibility of unauthorized disclosure to identifiable at-risk family members should hinge on clinical relevance of the information and the potential to avert or alleviate known health risks; others urge consideration of the availability of counseling/clinical resources for family members. Given the complexity of this issue, it is important to have clear guidelines for familial communications, and to ascertain participant preferences ahead of time if possible or relevant.

- Timing of and timeline for disclosure:
  - There is recognition among ethicists that it would be unduly burdensome for researchers to remain indefinitely obliged to return genetic results to participants. Temporal boundaries around the period for return of results should be established in the research protocol and communicated to participants.
  - If the participant is a child or otherwise legally incapable of independent decision-making, consider whether this will affect the timing, content, or other aspects of information disclosure.
- The potential for disclosed information to confuse the participant; cause severe psychological distress, social harm, or familial upheaval; or lull a subject into a false sense of security regarding disease risk.

## Issue 2: Privacy and Data Sharing

The issue of privacy is ubiquitous in discussions regarding the risks of genomic sequencing and data banking. Genomic data are (relatively) immutable, and many people view it as exceptionally personal. It potentially affects not only an individual's health, insurance coverage, and potential for discrimination, but also the collective identity and social/health status of the family or ethnic group to which the studied individual belongs. Consequently, research participants may be particularly sensitive about maintaining "genetic privacy."

The amount of data collected in WES/WGS research increases the possibility that a research participant's identity can be determined. This is particularly true when phenotypic, familial, or other information is collected alongside the genotypic data; the more data available about a participant, the more likely it is that he or she can be re-identified and linked to his or her genetic information.

**It is important to find a balance between making the best use of genomic information and protecting participant privacy;** in some instances, if this additional information is necessary to achieve the goals of the study, an accompanying increase in privacy risk may be justifiable. When striking this balance, issues to consider include:

- Traditional privacy concerns stem from basic security issues (e.g., who will have access to the data, the extent to which data are de-identified or anonymized, the size and type of database, etc.). While these topics remain relevant, an additional challenge for genomic research lies in the fact that an "anonymous" individual is at a statistically greater risk of identification as the amount of information about him/her increases.

- Any data-sharing or storage of information in biobanks makes it more difficult to remove a participant's genetic information if he or she withdraws from the study.
- It is possible that preserved WES/WGS data could be used for studies that are beyond the original scope of use to which the participant agreed. It is important to find a balance between honoring a participant's preferences (as well as the boundaries of his/her informed consent), protecting his or her privacy, and the scope of utility of the collected data. Consider the necessity of any additional steps needed (e.g., re-consent, limitations on data sharing) to maintain this balance.

### Issue 3: Informed Consent

The complexity of research on a participant's genomic sequence raises important challenges for his or her informed consent process. **A first step is to determine whether prior informed consent (if applicable) is sufficient, or whether new, prospective consent (or in some cases re-consent) is required.** Ideally, a consent form should address the following WES/WGS-specific issues:

- A description of the nature of the research (current and foreseeable in the future). Remember that tissue used for WES/WGS is likely to have its resultant data used for several different studies, some of which could be objectionable to the participant. Because future uses may vary considerably, consider a decision-making process in which re-consent may be obtained if necessary.
- Plans for data sharing and associated confidentiality protections/risks.
- Conditions under which incidental results will be disclosed. It is possible that these could vary within the same study or participant cohort.
- Description of any limitations on subjects' ability to withdraw data. Withdrawal of consent is much more challenging in WES/WGS studies, largely because of the potential for data dispersal. When determining how to structure the procedure for consent withdrawal, consider the possibility of providing options for partial withdrawal, and whether complete withdrawal (e.g., of all further participation, all previously collected data, and all analyses of previously collected data) is feasible given existing lab resources, data-sharing practices, and study progress.

**Approaches to consent and re-consent may differ among WES/WGS protocols based on the particular circumstances of each study.** The initial consent document may be broad or narrow, and the broader the original consent form, the less likely it will be that participant re-consent will be required. If a consent form is drafted too broadly, however, it may not provide enough information to help a potential subject make an informed decision.

- Given the increased risks associated with WES/WGS data, consider options that are flexible enough to suit a larger proportion of the participant pool.

- Given the proposed use of WES/WGS data, is one-time consent sufficient? (If not, what circumstances will trigger re-consent – e.g., radical changes in use or storage of data, etc.?) Is re-consent a necessary and practical option? If so, how will the re-consent be effectuated? What happens if the participant is unavailable? Is a waiver of re-consent appropriate?

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