What About Privacy and Progress in Whole Genome Sequencing?

Amy L. McGuire, JD, PhD
Recommendation 3 - Consent

- Should be done at the outset of testing/research, and should include:
  - What is WGS?
  - How will data be analyzed, stored, and shared?
  - What types of results can the patient/participant expect to receive, if any?
  - Future uncertainty
Paths for Obtaining WGS
Need for Recommendation

- Current practice is variable!
  - Research consents: language about genetic analysis, sequencing and data storage not consistent; most legacy samples consented without mention of data sharing
  - Clinical consents: the majority (n=37) of states do not require specific informed consent to order a genetic test; often genetic testing is ordered by non-genetic specialist for diagnostic purposes under general consent to treat
Informed Consent Challenges

1. Length, complexity, and quality of informed consent documents and process
2. Patient/participant understanding
3. Incidental findings and the scope of informed consent
4. Unexpected findings
1. Length, Complexity, and Quality of IC

- Model consent documents
  - Long and complicated

- Consent process
  - Variable

NHGRI Consent Form Examples and Model Consent Language
http://www.genome.gov/27526660

Texas Cancer Research Biobank
http://txcrb.org

ANOTATED CONSENT DOCUMENT FOR THE
TEXAS CANCER RESEARCH BIOBANK

INTRODUCTION
The use of stored specimens in research is becoming increasingly more common as genomic research progresses. Consequently, there is a growing need for biobanks with collections of clinically annotated specimens for use in a variety of research endeavors. The banking of such specimens, though, presents unique challenges to the informed consent process. In particular, informed consent for biobanking is typically broad to allow for a wide range of potential downstream uses that are unspecified at the time consent is obtained.

Here we provide example consent language that we developed for our biobanking activities using language from publicly available models, guides, best practices, and current literature, and discuss the issues, challenges, and points to consider with regard to biobanking for each element of the consent form. We adopt a broad, forward-looking approach to maximize the utility of the specimens and associated data and minimize the need for consent in the future. Though we intend for this to be used as a template for those writing consent forms for their own biobanking projects, there are many ways in which biobanks can operate, making a one-size-fits-all approach impossible. As such, investigators should be sure to tailor their consent forms to their specific projects and institutional review board (IRB) requirements.

CONSENT FORM ELEMENTS

BACKGROUND
We use the background section of the consent form to introduce the project as a whole, including describing what a biobank is, how it works, and its general purpose. Since our biobank involves genetic research, we include a brief explanation of genetics and DNA sequencing. There is an inherent challenge in the need to discuss genetics and inform the participant that genetic analysis will be performed without being too specific about the types of technology that will be used, as they will likely change with advances in the field. There is currently controversy surrounding the question of whether or not whole genome sequencing should be addressed specifically in consent forms used for such research, as it is a distinct technology with associated risks. In this consent document we specifically mention whole genome sequencing, but that may not be deemed necessary by all IRBs.

We are asking you to take part in a research project. Please read this information and ask any questions before you decide if you want to take part.

For this project, we will collect, store, and use tissue samples and health information for research. Tissue samples are substances from the body, such as blood, or tumors that may be removed during surgery. If you agree, your samples and some of your health information will be put into a biobank.

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2. Patient/Participant Understanding

To share or not to share: A randomized trial of consent for data sharing in genome research

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- Randomized trial of consent for data sharing (n=335)
- Followed by interviews with participants to assess understanding, perspectives, and preferences (n=229)

\textit{R01 HG004333 (2007-2011)}
Participants’ Reported Understanding

<table>
<thead>
<tr>
<th>Reported Understanding</th>
<th>Agree/Strongly Agree % (n = 229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I felt sure about what to choose with regard to sharing my genetic information</td>
<td>85.1%</td>
</tr>
<tr>
<td>The decision to share my genetic information was easy for me to make</td>
<td>86.9%</td>
</tr>
<tr>
<td>I feel I have made an informed decision with regard to sharing my genetic information</td>
<td>91.2%</td>
</tr>
</tbody>
</table>
### Participants’ Actual Understanding

<table>
<thead>
<tr>
<th>Actual Understanding</th>
<th>“No” % (n = 224)</th>
<th>“I don’t know” % (n = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you know if you are participating in a research study?*</td>
<td>40.2%</td>
<td>NA</td>
</tr>
<tr>
<td>Have you ever heard of genetic studies?</td>
<td>28.1%</td>
<td>NA</td>
</tr>
<tr>
<td>Have you already given DNA to your doctor?</td>
<td>16.1%</td>
<td>36.6%</td>
</tr>
<tr>
<td>Do you remember signing a consent form to participate in a genetic study?*</td>
<td>25.9%</td>
<td>NA</td>
</tr>
</tbody>
</table>

No significant difference based on consent type

*Study type significantly associated with knowing they are participating in research study and remember signing consent form
General Understanding of Research Participation

  - 27 patients enrolled in a phase I clinical trial: Only 33% were able to state the purpose of the trial in which they were participating

  - Most participants considered themselves to be well informed, but many did not understand that they may receive non-standard treatment (74%), the potential for incremental risk from participation (63%), the unproven nature of the treatment (70%), the uncertainty of benefits to self (29%), or that trials are done mainly to benefit future patients (25%)

  - 77 patients enrolled in randomized phase II or phase III clinical trial: 38% did not understand the purpose and nature of the trial they were participating in; 56% did not understand the study procedures, and only 40% correctly listed at least one of the major risks or complications related to their participation in the trial

- Flory and Emanuel, JAMA (2004); Tamariz et al, JGIM (2012)
  - Efforts to improve understanding have had only limited success
  - Most effective intervention: one-on-one education
3. Incidental Findings and Scope of IC

The Incidentalome: A Threat to Genomic Medicine

Incidental findings, which are often discovered as a result of medical imaging or other diagnostic testing, can have significant implications for patient care. However, the management of incidental findings poses several challenges for healthcare providers.

Diagnostic Testing and Incidentals

Incidental findings are often discovered during routine medical testing. However, the management of incidental findings poses several challenges for healthcare providers.

American College of Medical Genetics and Genomics

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

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Keywords: secondary findings, incidental findings, genome, genomic medicine, personalized medicine, whole-exome, whole-genome, sequencing.
4. Unexpected Findings

Identifying Consanguinity through Routine Genomic Analysis: Reporting Requirements

Amy L. McGuire, Melody J. Wung, and Frank J. Probst

Introduction
Increasingly, genomic analysis is being utilized to diagnose children with developmental delay or dysmorphic facial features suggestive of a congenital disorder. Genetic testing has rapidly evolved, and as the genome-wide tests that we use today are significantly different from the more targeted single-gene tests of the last decade. Chromosomal microarray analysis (CMA) is now a first-line test for children with multiple birth defects, children with intellectual impairment (including autism), and children with an unusual constellation of symptoms that do not fit with a known disease. There are three types of CMA that are currently clinically available. CMA by oligonucleotide array-based comparative genomic hybridization (aCGH) compares the hybridization signal from the patient’s DNA to that of a reference DNA sample for each oligonucleotide on the array. Depending on the specific array, there can range from tens of thousands to hundreds of thousands of oligonucleotides. A relative loss of signal from the patient's DNA is interpreted as a deletion, whereas a relative gain is interpreted as a duplication (or, in rare cases, a triplication or quadruplication). aCGH can detect very small losses or gains of DNA and typically uncover genetic abnormalities in about 10-20% of cases. CMA by single nucleotide polymorphism (SNP) analysis uses a complex different technologies to genotype the individual at hundreds of thousands to millions of single nucleotides that are commonly polymorphic in the genome. Gains and losses of DNA are detected by relative increases or decreases of the signal at each SNP relative to the other SNPs on the array, as well as by the specific genotypes seen at SNPs that are located in tandem in the genome. Unlike aCGH, SNP analysis will detect losses or gains of DNA, but it will sometimes miss very small changes that aCGH can detect. However, SNP analysis, unlike aCGH, can also detect areas where chromosome pairs or parts of the chromosome pairs are identical to one another. Most recently, hybrid arrays have been developed that combine both technologies into a single test. Since one copy of each pair of chromosomes is inherited from the mother and the other pair of each chromosome is inherited from the father, when pairs of chromosome pairs are identical (i.e., there is an absence of heterozygosity (AOD)), there are two possibilities. If only one chromosome is involved, then the cause could either be uniparental isodisomy (meaning the child inherited two identical copies of a chromosome from one parent and no copy of the same chromosome from the other parent), or discordant consanguinity (meaning the parents are discordant blood relatives). If multiple chromosomes are involved, then the parents must be blood relatives of one another. The closure of the relationship between the parents.

American College of Medical Genetics and Genomics: standards and guidelines for documenting suspected consanguinity as an incidental finding of genomic testing

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Many genomic microarray platforms use a combination of probes designed to assay copy number and probe to genome single-nucleotide polymorphisms. In addition to copy-number changes (i.e., deletions, duplications), these array platforms can identify genomic regions that display an absence of heterozygosity often in the form of one or more long contiguous stretches of homozygosity. Large regions of homogygosity, when observed on a single chromosome, can indicate an uniparental origin of the chromosome. However, these regions are distributed throughout the genome, they usually represent segments of autosome or regions that are identical by descent (IBD). These segments are often long enough to intersect four or more segments of homogygosity per genome and can indicate a consanguous relationship between the proband’s parents. The health impact of consanguinity has been extensively studied.

The guidelines presented here are designed to assist clinical laboratories in the management of microarray and exome/genome sequencing results that suggest parental consanguinity, with a primary focus on detection and reporting results back to the ordering clinicians.

DETECTION OF CONSANGUINITY

Genomic regions that are IBD or IGE from a common ancestor, with the proportion of the genome that is IBD in the offspring of related parents is given by the coefficient of inbreeding (F). For example, on average, 0.25% of all IBD regions are estimated to be IBD. Although the number of regions that are IBD increases, the amount of IBD per genome will be present, although both the number and the sites of homogygosity segments are known to be highly variable. When long contiguous stretches of homogygosity involving multiple chromosomes are present, the proportion of the genome that is IBD can be estimated by the sum of the IBD regions divided by the total autosomal genomic length. (0.25%) for IBD=2.88×10^9. The sex chromosomes are typically excluded from the calculation because males have only one X chromosome and therefore cannot have homogygosity at any locus outside of the pseudoautosomal regions. This calculation is likely an underestimate of the actual proportion of the genome that is IBD because only those segments of homogygosity meeting the threshold set by the laboratory will be flagged for inclusion in the calculation. This percentage can then be compared with the theoretical value derived from the coefficient of inbreeding for any given parental relationship. These theoretical values are found in many genetics tests and resources.

About This Column
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Informed Consent
SCIENCE AND SOCIETY

From patients to partners: participant-centric initiatives in biomedical research


Abstract | Advances in computing technology are increasingly characterised by large volumes of data and the emergence of a number of challenges for obtaining consent and maintaining public trust. Participant-centric initiatives and the use of social media technologies to address these imperatives provide the basis for long-term interactive and collaborative communications. This overview of this rapidly moving field by provides an insight into the current practices, as well as the benefits and challenges.

Recent advances in digital technologies have led to increasing concern about the use of personal data, in particular about the amount of control that individuals have over their information and who may have access to it. At the same time, the ways in which individuals can choose to share personal data are exploding through the use of user-friendly tools such as social networking sites. In the medical research domain, this ‘user-centric’ approach is becoming increasingly important. The potential of personal data in research and the ability of participants to control the use of their data mean that new models of patient- and public-informed research are emerging. This model has the potential to harness the power of online communities to facilitate the recruitment of participants and engage them in the research process. However, this also gives rise to ethical, legal, and social challenges that need to be addressed.

Table 1 | **Key functions of participant-centric initiatives**

<table>
<thead>
<tr>
<th>Function</th>
<th>Characteristics</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matchmaking</td>
<td>• Brings together participants and researchers by either promoting communication or facilitating recruitment</td>
<td>• PrivateAccess (USA)</td>
</tr>
<tr>
<td>Direct-to-consumer services</td>
<td>• Provides participants with services as well as social-networking capabilities</td>
<td>• 23andWe (USA)</td>
</tr>
<tr>
<td></td>
<td>• Provides opportunities for involvement in research</td>
<td></td>
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<tr>
<td>Dynamic negotiation</td>
<td>• Enables an ongoing discourse and negotiation between researchers and participants</td>
<td>• CuraRata and String of Pearls Initiative (Netherlands)</td>
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<tr>
<td></td>
<td>• Enables participants to manage their preferences for personal data sharing while facilitating more accountable research governance</td>
<td>• CHRIS — Cooperative Health Research in South Tyrol (Italy)</td>
</tr>
<tr>
<td>Citizen science</td>
<td>• Allows participants to provide and to control the samples and data and, in so doing, to have an active involvement in facilitating research</td>
<td>• EnCoRe and the Oxford Radcliffe Biobank (UK)</td>
</tr>
<tr>
<td></td>
<td>• Allows participants to drive the research agenda and to carry out their own research projects</td>
<td>• PatientsLikeMe (USA)</td>
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<td></td>
<td></td>
<td>• TuAnalyze (USA)</td>
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<td></td>
<td></td>
<td>• Genomes Unzipped (UK)</td>
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<td>• Genomera (USA)</td>
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