Ethical Issues in Genetic Research with Stored Samples and Data

Sara Chandros Hull, Ph.D.
Bioethics Core, NHGRI
and
Department of Bioethics, Clinical Center
National Institutes of Health
Disclaimers/Disclosures

• No statement in this presentation should be construed as an official position of the National Human Genome Research Institute, National Institutes of Health, or Department of Health and Human Services.

• The speaker declares no financial conflicts of interest.
Roadmap

• Setting the stage
• Two cases
• What is a human subject?
  – Large sample/data collections
  – U.S. regulatory framework
• Informed consent for collection, storage, and future use of samples/data
  – Broad
  – Study-specific
Charting a course for genomic medicine from base pairs to bedside

Eric D. Green*, Mark S. Clayton & National Human Genome Research Institute*

There has been much progress in genomics over the ten years since a draft sequence of the human genome was published. Opportunities for understanding health and disease are now unprecedented, as advances in genomics are harnessing efforts to retain constitutional knowledge about the structure and function of the human genome and the genetic contributions to human health and disease. Here we articulate a 2011 vision for the future of genomic research and describe the path toward an era of genomic medicine.

Since the end of the Human Genome Project (HGP) in 2003 and the publication of a reference human genome sequence, genomic medicine has become a reality of biomedical research. The scientific community’s foresight in launching this ambitious project is evident in the broad range of scientific advances and the HGP has enabled, as shown in Fig. 1 (see ref. 1). Optimism about the potential contributions of genomics for improving human health has been fuelled by new insights about cancer, the molecular basis of inherited diseases (http://www.ncbi.nlm.nih.gov/ omim and http://www.genome.gov/CWAStudiersand the role of genetic variation in disease, some of which have already led to new treatments (ref. 2). Other advances have already changed medical practice, for example, new tests are used for clinical detection of germ-cell neoplasia and pharmacogenomic testing is routinely performed before administration of certain medications (ref. 3). Together, these achievements (see accompanying paper) document that genomics is contributing to a better understanding of human biology and to improving human health.

As this decade begins, the National Human Genome Research Institute (NHGRI) has engaged the scientific community (http://www.genome.gov/Planning) to reflect on the key attributes of genomics (Box 1) and generate directions and challenges for the field. These discussions have led to an updated vision that focuses on understanding human biology and the diagnostic, prevention and treatment of human disease, including consideration of the implications of these advances for society (Box 1).

This 2011 vision for genomics is summarized over five themes extending from basic research to health applications (Fig. 2). It reflects the view that, over time, the most effective way to improve human health is to understand normal biology (this can, genome biology, as a basis for understanding disease biology, in which the disease is the basis for improving health). At the same time, these are other connections among these domains. Genomics offers opportunities for improving health through a thorough understanding of disease (for example, cancer therapeutics can be selected based on genomic profiles that identify tumour subtypes, and clinical decisions can be based on tumour subtypes), and clinical decisions can be based on tumour subtypes.

The past decade has seen a number of significant advances in our understanding of human biology and its perturbations in disease. Further deepening their understanding will require a new generation of genomics databases that will be able to capture the changes in genetic information that occur in disease.

The 2011 vision for genomics is summarized over five themes extending from basic research to health applications (Fig. 2). It reflects the view that, over time, the most effective way to improve human health is to understand normal biology (this can, genome biology, as a basis for understanding disease biology, in which the disease is the basis for improving health). At the same time, these are other connections among these domains. Genomics offers opportunities for improving health through a thorough understanding of disease (for example, cancer therapeutics can be selected based on genomic profiles that identify tumour subtypes, and clinical decisions can be based on tumour subtypes).

The past decade has seen a number of significant advances in our understanding of human biology and its perturbations in disease. Further deepening their understanding will require a new generation of genomics databases that will be able to capture the changes in genetic information that occur in disease.

The 2011 vision for genomics is summarized over five themes extending from basic research to health applications (Fig. 2). It reflects the view that, over time, the most effective way to improve human health is to understand normal biology (this can, genome biology, as a basis for understanding disease biology, in which the disease is the basis for improving health). At the same time, these are other connections among these domains. Genomics offers opportunities for improving health through a thorough understanding of disease (for example, cancer therapeutics can be selected based on genomic profiles that identify tumour subtypes, and clinical decisions can be based on tumour subtypes).

The past decade has seen a number of significant advances in our understanding of human biology and its perturbations in disease. Further deepening their understanding will require a new generation of genomics databases that will be able to capture the changes in genetic information that occur in disease.

The 2011 vision for genomics is summarized over five themes extending from basic research to health applications (Fig. 2). It reflects the view that, over time, the most effective way to improve human health is to understand normal biology (this can, genome biology, as a basis for understanding disease biology, in which the disease is the basis for improving health). At the same time, these are other connections among these domains. Genomics offers opportunities for improving health through a thorough understanding of disease (for example, cancer therapeutics can be selected based on genomic profiles that identify tumour subtypes, and clinical decisions can be based on tumour subtypes).

The past decade has seen a number of significant advances in our understanding of human biology and its perturbations in disease. Further deepening their understanding will require a new generation of genomics databases that will be able to capture the changes in genetic information that occur in disease.
Future of Genomic Research

“Complete characterization of the genetics of complex diseases will require the identification of the full spectrum of human genomic variation in large, diverse sample sets.”

The Basic Challenge

How to get informed consent for future research that is not fully anticipated at the time of sample collection?
Related Challenges

• Was the consent process for existing collections of samples sufficient to permit new analyses, techniques, questions?

• When does a new use require specific consent?
  – Which, in some cases, might require re-contacting donors of samples for “re-consent”
Where are samples collected and stored?

$n > 282$ million in U.S., 20 mil new cases per year, NBAC (1999)

- **Clinical**
  - Pathology departments
  - Cord blood banks
  - Blood banks

- **Research**
  - Individual laboratories
  - Repositories/biobanks

- **Public Health/State**
  - Newborn screening programs
  - Military DNA collections
  - Forensic collections
Case 1: BRCA, Tamoxifen, and Consent

- BCPT (n>13,000): found that tamoxifen significantly reduced incidence of invasive breast cancer in high-risk women
  - Conducted 1992-1998, before BRCA1/2 cloned
  - Study did not show who would benefit most
- Investigators wanted to go back to DNA samples to test for BRCA1/2 mutations

Case 1: BRCA, Tamoxifen, and Consent

• Women had not given explicit consent for BRCA1/2 genetic testing
  – General consent for future genetic research
Case 1: BRCA, Tamoxifen, and Consent

• Women had not given explicit consent for BRCA1/2 genetic testing
  – General consent for future genetic research
• Subjects were informed about the new study
  – Given opportunity to “opt out” and withdraw DNA sample
• Samples were “anonymized”
  – No genetic results given
Case 1: BRCA, Tamoxifen, and Consent

• Appropriately or overly cautious approach?
  – Prior consent sufficient for breast cancer genetics
  – Little evidence of harms
    • From discrimination
    • From receipt of BRCA results
  – Reduced scientific utility of samples/data
  – Non-disclosure of potentially beneficial information
Case 1: BRCA, Tamoxifen, and Consent

- What if...
  - The researchers wanted to study genetics of cardiovascular disease using these samples?
  - The researchers wanted to sequence these samples
    - And deposit the data in a public repository?
What is a human research subject?
Current Definition of Human Subject

(f) A living individual from whom an investigator ... conducting research obtains:

(1) *information or biospecimens* through intervention or interaction with the individual

45 CFR 46.102
What is a Human Subject?
Current Definition of Human Subject

(f) A living individual from whom an investigator . . . conducting research obtains:

1. **information or biospecimens** through intervention or interaction with the individual
2. identifiable private information **or identifiable biospecimens**

45 CFR 46.102
Classification of Samples

identifiable

cannot be identified/de-identified
OHRP Interpretation:

*not identifiable = not readily ascertainable*

- “OHRP does not consider research involving only coded private information or specimens to involve human subjects . . . if the following conditions are both met:
  - (1) the private information or specimens were not collected specifically for the proposed research . . . and
  - (2) the investigators cannot readily ascertain the identity of the individual(s)”

OHRP Guidance, 2008
Addressing the Evolving Concept of “Identifiability”

• Federal agencies will collaborate at least every 4 years to:
  – Re-examine the meaning of identifiability
  – Identify analytic techniques capable of generating identifiable private information or biospecimens

§__.102(e)(5)-(7)
What information is needed for valid informed consent?

Consent for Specimen Collection
What information is needed for valid informed consent?

Consent for Sample Collection

- I consent to the donation of my tissues for research and education. If you wish to decline donation, indicate with your initials here_____.

What information is needed for valid informed consent?

- I consent to the donation of my tissues for research and education. If you wish to decline donation, indicate with your initials here_____.

  - Specific disease
  - Particular gene
  - Explicit methodology
  - Individual investigator
  - Distinct time


NBAC (1999)
Variable consent practices

• “We observed considerable variability in consent form content regarding the conditions under which secondary research might be conducted.” (n=258)
What information is needed for valid informed consent?

Consent for Sample Collection

- I consent to the donation of my tissues for research and education. If you wish to decline donation, indicate with your initials here_____.

- Specific disease
- Particular gene
- Explicit methodology
- Individual investigator
- Distinct time


NBAC (1999)
One-time general consent for research on biological samples

David Wendler

Summary points

It is now recognised that people should give informed consent for the use of their biological samples in research

The types of consent needed and when consent should be obtained have not been defined

Studies have collected data on the views of more than 33,000 people on this issue

These data support one-time general consent
### Approaches to Consent for Future Research with Biospecimens

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>No consent</td>
<td>Do not obtain donor consent</td>
</tr>
<tr>
<td>Blanket</td>
<td>Consent to future research with no limitations</td>
</tr>
<tr>
<td>Broad*</td>
<td>Consent to future research with specified limitations</td>
</tr>
<tr>
<td>Checklist</td>
<td>Donor and/or family types of future studies allowed</td>
</tr>
<tr>
<td>Study specific</td>
<td>Consent for each specific future study</td>
</tr>
</tbody>
</table>

*Framework proposed here couples initial broad consent with oversight and the possibility of ongoing communication*
Components of “Broad” Consent

1. Initial broad consent
2. Process of oversight and approval for future research activities
3. Wherever feasible, an ongoing process of providing information/communicating with donors

Christine Grady et al. (2015)
American Journal of Bioethics
Human Subjects Research

Is it research?
- No or Activities deemed not to be research

Yes
Does it involve human subjects?
- Yes

Is it exempt?
- No
Non-exempt HS research that requires IRB review

Yes - Does it involve exemptions 2(iii), 3(i)(C), 7, or 8?
- No

Yes
Require limited IRB review that exemption conditions are satisfied

Legend: New to the revised Common Rule

from Yvonne Lau, OHRP
Elements of Broad Consent per Final Common Rule

- Risks/discomforts
- Benefits
- Maintenance of confidentiality
- Voluntary
- Commercial profit
- Whole genome sequencing
- Types of research

- Description of samples and data, whether shared, who might use
- Time period for storage and maintenance
- How much information about future studies
- Whether results will be disclosed
- Contact information

§__.116(d)-(f)
What about the minority of individuals who are unwilling to give broad consent?

- One-time broad consent provides opportunity to say “no”
- However, concern that this approach excludes/alienates certain populations
  - If, for example, they object to specific downstream uses
- Mechanisms for soliciting preferences?
- Role for oversight
  - To limit uses in particular ways
Genetic Research as a Double-Edged Sword

• Non-European populations are persistently underrepresented in genomic research/databases
  – “Data collection should be extended to as many diverse populations as possible.”
    Rotimi and Jorde (2010) *NEJM*

• Some underrepresented populations are reluctant to participate in open-ended genomic research with broad sharing of samples and data
  – Genetic/genomic research poses risks to groups
  – Historical stigmatization, discrimination, failure to obtain/respect informed consent
Case 2: Havasupai Tribe

Indian Tribe Wins Fight to Limit Research of Its DNA

Edmond Tilousi, 56, who can climb the eight miles to the rim of the Grand Canyon in three hours. More Photos »

By AMY HARMON
Published: April 21, 2010
Case 2: Havasupai Timeline

• **1990-1994** Havasupai DNA samples collected for genetic studies on T2D by ASU researchers

• **2003** Discovery that samples also used for research on schizophrenia, migration, inbreeding

• **2004** *Havasupai Tribe of the Havasupai Reservation v. Arizona Board of Regents and Therese Ann Markow*

• **2010** Settlement ($770K, funds for clinic and school, return of DNA samples to Tribe)
Case 2: What are the lessons?

- Two common explanations:
  - Individual researchers making bad choices
  - Communities exerting inappropriate control over otherwise good research
- “[A] profound disconnect exists between common academic research practices and legitimate community expectations, and justice requires that this gap be bridged.”

Requirements for Ethical Research

1. Collaborative partnership
2. Social value
3. Scientific validity
4. Fair selection of study population
5. Favorable risk-benefit ratio
6. Independent review
7. Informed consent
8. Respect for recruited participants and study communities

Emanuel, Wendler, Killen, Grady (2004) JID
A Role for Empirical Data & Consultation

- To identify approaches that are consistent with the views and preferences of individuals and communities
- To examine clinical and social factors associated with particular opinions (e.g., cultural/population divides)
- To study the outcome of different consent approaches
  - e.g., rates of enrollment, cost and burden, facilitating more research
Native Hawaiian Views

Discussion groups (n=92) with Native Hawaiians

– “If I’m going to give my tissue to anyone for any cause, I want to know what the purpose of that is for. I don’t feel comfortable giving a generic sample and willy-nilly let people do what they want with that.”

– “[D]on’t just take my tissue and use it for diabetes; take my tissue and use it for diabetes to help the Native Hawaiians. That I can agree to...because we don’t have enough studies on us, the Native Hawaiians, so that we can get medicines that complement us.”

Alaska Area Specimen Bank

• Working Group
  – A resource of the Alaska Native people held in trust to be used to benefit the health and well-being of Alaska Native people
  – Individual specimens are property of the study participant who provided consent to have that specimen banked for future study; participant can request to have the specimen removed at any time.

• CDC + Alaska Area IRB approval

Parkinson et al (2013) *Int J Circumpolar Health*
Thank you!