Ethical Issues in Genetic Research with Stored Samples and Data

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Disclaimers/Disclosures

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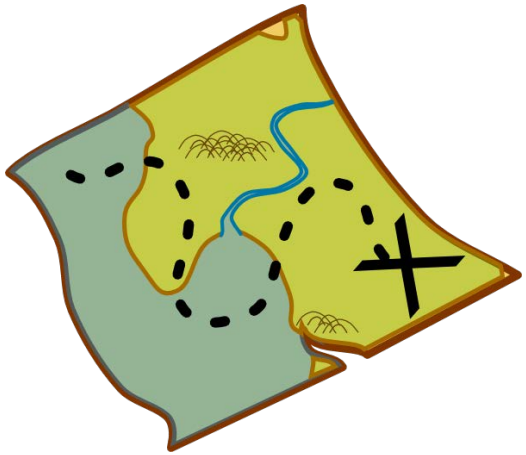
- The speaker declares no financial conflicts of interest.

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



PERSPECTIVE

doi:10.1038/nature09764

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green[1], Mark S. Guyer[1] & National Human Genome Research Institute*

There has been much progress in genomics in 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 harnessed to obtain robust foundational knowledge about the structure and function of the human genome and about the genetic contributions to human health and disease. Here we articulate a 2011 vision for the future of genomics research and describe the path towards 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[1,2], genomics has become a mainstay of biomedical research. The scientific community's foresight in launching this ambitious project[3] is evident in the broad range of scientific advances that the HGP has enabled, as shown in Fig. 1 (see rollfold). Optimism about the potential contributions of genomics for improving human health has been fuelled by new insights about cancer[4–7], the molecular basis of inherited diseases (http://www.ncbi.nlm.nih.gov/omim and http://www.genome.gov/GWAStudies) and the role of structural variation in disease[8], some of which have already led to new therapies[9–13]. Other advances have already changed medical practice (for example, microarrays are now used for clinical detection of genomic imbalances[14] and pharmacogenomic testing is routinely performed before administration of certain medications[15]). Together, these achievements (see accompanying paper[16]) document that genomics is contributing to a better understanding of human biology and to improving human health.

As it did eight years ago[17], 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 explore future directions and challenges for the field. These discussions have led to an updated vision that focuses on understanding human biology and the diagnosis, prevention and treatment of human disease, including consideration of the implications of those advances for society (but these discussions, intentionally did not address the role of genomics in agriculture, energy and other areas). Like the HGP, achieving this vision is broader than what any single organization or country can achieve—realizing the full benefits of genomics will be a global effort.

This 2011 vision for genomics is organized around five domains 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 (in this case, genome biology) as a basis for understanding disease biology, which then becomes the basis for improving health. At the same time, there are other connections among these domains. Genomics offers opportunities for improving health without a thorough understanding of disease (for example, cancer therapies can be selected based on genomic profiles that identify tumour subtypes[18,19]), and clinical discoveries can lead back to understanding disease or even basic biology.

The past decade has seen genomics contribute fundamental knowledge about biology and its perturbation in disease. Further deepening this understanding will accelerate the transition to genomic medicine (clinical care based on genomic information). But significant change rarely comes quickly. Although genomics has already begun to improve diagnostics and treatments in a few circumstances, profound improvements in the effectiveness of healthcare cannot realistically be expected for many years (Fig. 2). Achieving such progress will depend not only on research, but also on new policies, practices and other developments. We have illustrated the kinds of achievements that can be anticipated with a few examples (Box 2) where a confluence of need and opportunities should lead to major accomplishments in genomic medicine in the coming decade. Similarly, we note three cross-cutting areas that are broadly relevant and fundamental across the entire spectrum of genomics and genomic medicine: bioinformatics and computational biology (Box 3), education and training (Box 4), and genomics and society (Box 5).

Understanding the biology of genomes

Substantial progress in understanding the structure of genomes has revealed much about the complexity of genome biology. Continued acquisition of basic knowledge about genome structure and function will be needed to illuminate further those complexities (Fig. 2). The contribution of genomics will include more comprehensive sets (catalogues) of data and new research tools, which will enhance the capabilities of all researchers to reveal fundamental principles of biology.

Comprehensive catalogues of genomic data

Comprehensive genomic catalogues have been uniquely valuable and widely used. There is a compelling need to improve existing catalogues and to generate new ones, such as complete collections of genetic variation, functional genomic elements, RNAs, proteins, and other biological molecules, for both human and model organisms.

Genomic studies of the genes and pathways associated with disease-related traits require comprehensive catalogues of genetic variation, which provide both genetic markers for association studies and variants for identifying candidate genes. Developing a detailed catalogue of variation in the human genome has been an international effort that began with The SNP Consortium[20] and the International HapMap Project[21] (http://hapmap.ncbi.nlm.nih.gov), and is ongoing with the 1000 Genomes Project[22] (http://www.1000genomes.org).

Over the past decade, these catalogues have been critical in the discovery of the specific genes for roughly 3,000 Mendelian (monogenic) diseases

Figure 1 | Genomic achievements since the Human Genome Project (see accompanying rollfold). ▶

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*Lists of participants and their affiliations appear at the end of the paper.

2/2011: NHGRI published new "vision" for genomics

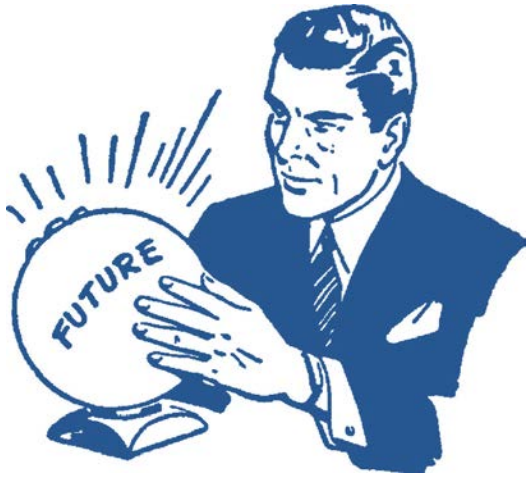
Future of Genomic Research

"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***."

Green E, Guyer M, and NHGRI (2011) "Charting a course for genomic medicine from base pairs to bedside." Nature. 470: 204-13.

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

Fisher *et al.* 1998, *J Natl Cancer Inst*; MC King *et al*., 2001, *JAMA*

Case 1: BRCA, Tamoxifen, and Consent

- Women had not given explicit consent for BRCA1/2 genetic testing
  - General consent for future genetic research

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  - 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?


5199-3126
595-0322
595 997 #1R
596-1800
5199-3093
595-0025
595-0068
593-1678
1-86-9020
595- 897 A
5199-3700
1-85-16635
98-1281-2
98-1281-1
98-513
1582-7483
1583-4617

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

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

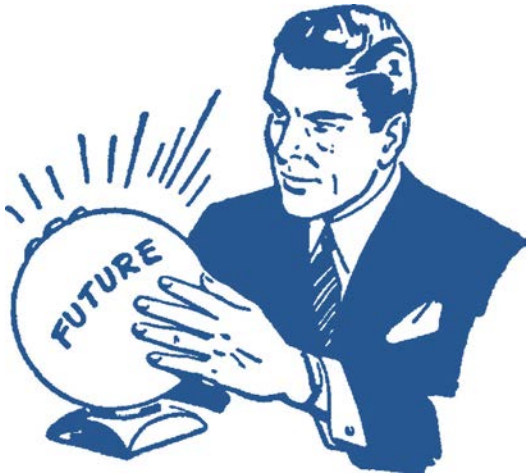
Addressing the Evolving Concept of "Identifiability"

- 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



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

Grizzle et al (1999) *Arch Pathol Lab Med*

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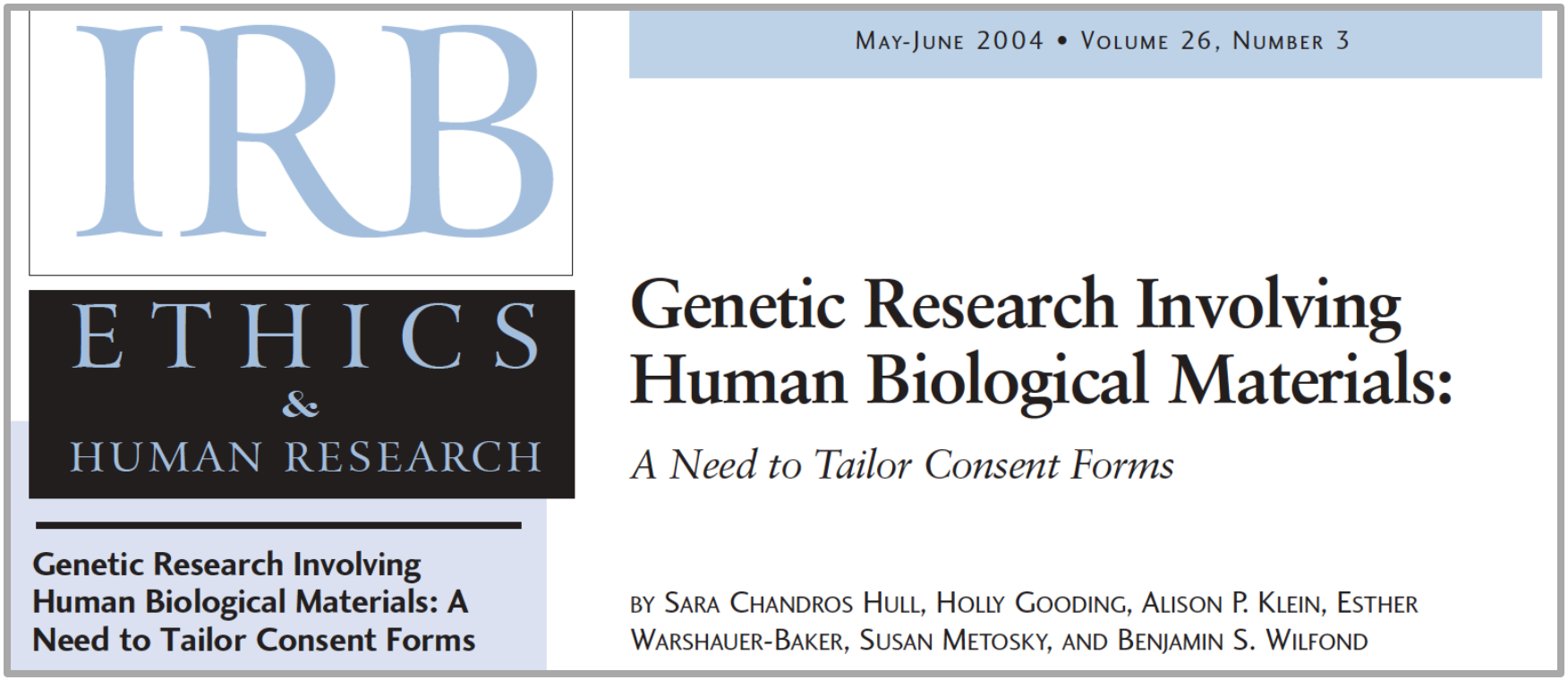
- ❑ *Specific disease*
- ❑ *Particular gene*
- ❑ *Explicit methodology*
- ❑ *Individual investigator*
- ❑ *Distinct time*

Grizzle et al (1999) *Arch Pathol Lab Med*

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)



IRB

ETHICS & HUMAN RESEARCH

Genetic Research Involving Human Biological Materials: A Need to Tailor Consent Forms

MAY-JUNE 2004 • VOLUME 26, NUMBER 3

Genetic Research Involving Human Biological Materials:

A Need to Tailor Consent Forms

BY SARA CHANDROS HULL, HOLLY GOODING, ALISON P. KLEIN, ESTHER WARSHAUER-BAKER, SUSAN METOSKY, AND BENJAMIN S. WILFOND

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NBAC (1999)

One-time general consent for research on biological samples

BMJ VOLUME 332 4 MARCH 2006

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

Less burden, less control

More burden, more control

TYPE	DESCRIPTION
No consent	Do not obtain donor consent
Blanket	Consent to future research with no limitations
Broad*	Consent to future research with specified limitations
Checklist	[illegible] types of future studies allowed
Study specific	Consent for each specific future study

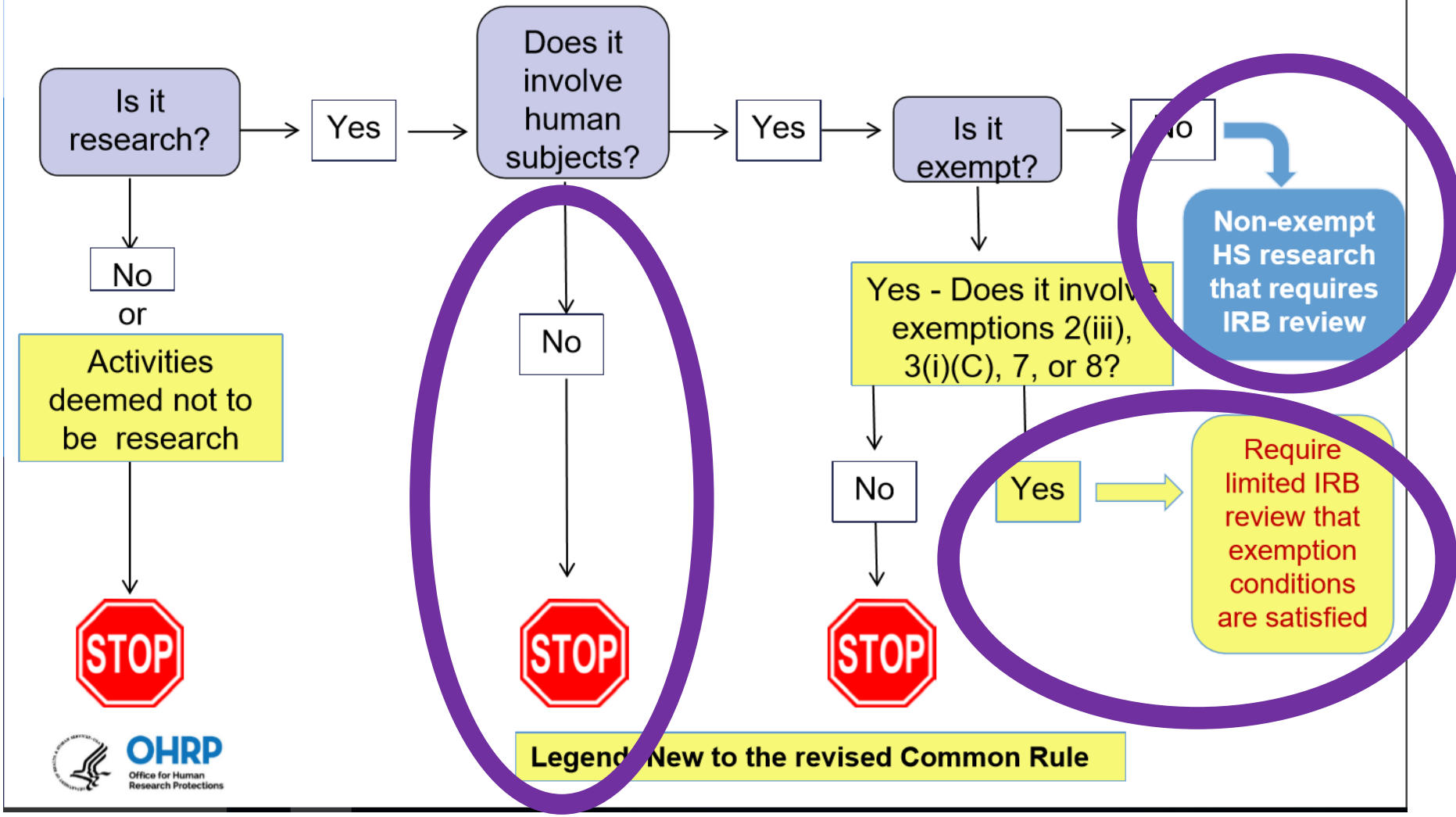
*Framework proposed here couples initial broad consent with oversight and the possibility of ongoing communication

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



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

Jim Wilson/The New York Times

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."

Goering, Holland, and Fryer-Edwards (2008) *HCR*

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."

Tauali`I et al (2014) *Journal of Cancer Education*

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*

Albuquerque, New Mexico
August 30 - Sept 1, 2017

http://206.192.150.42/tcs/#page:recordingList&pageNumber:1

Thank you!