The Ethics of Research with Stored Samples and Data

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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

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***."

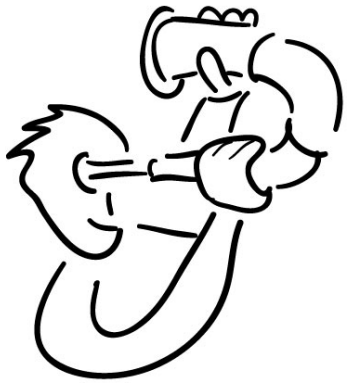
Green E, Guyer M, and NHGRI (2011) "Charting a course for genomic medicine from base pairs to bedside." Nature. 470: 204-13.

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

What Are the Risks?

- Informational risk/disclosure
  - To participants
    - Anxiety/uncertainty
    - Familial
  - To third parties
    - Stigmatization
    - Discrimination
    - Group harms

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

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) data through intervention or interaction with the individual

45 CFR 46.102

What is a Human Subject?


5199-3126
595-0322
595-1500
1-85-16635
1583-4617

Current Definition of Human Subject

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

(1) data through intervention or interaction with the individual

(2) identifiable private information

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, 8/10/04

A Moving Target

- NPRM (2015) proposal:
  - To expand the definition of human subjects to include research in which an investigator obtains, uses, studies, or analyzes a biospecimen
    - Regardless of the identifiability of the biospecimen
  - To create an exemption for secondary research using biospecimens or identifiable private information
    - With initial consent (broad or specific)

What information is needed for valid informed consent?

Consent for Specimen Collection

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_____.*

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

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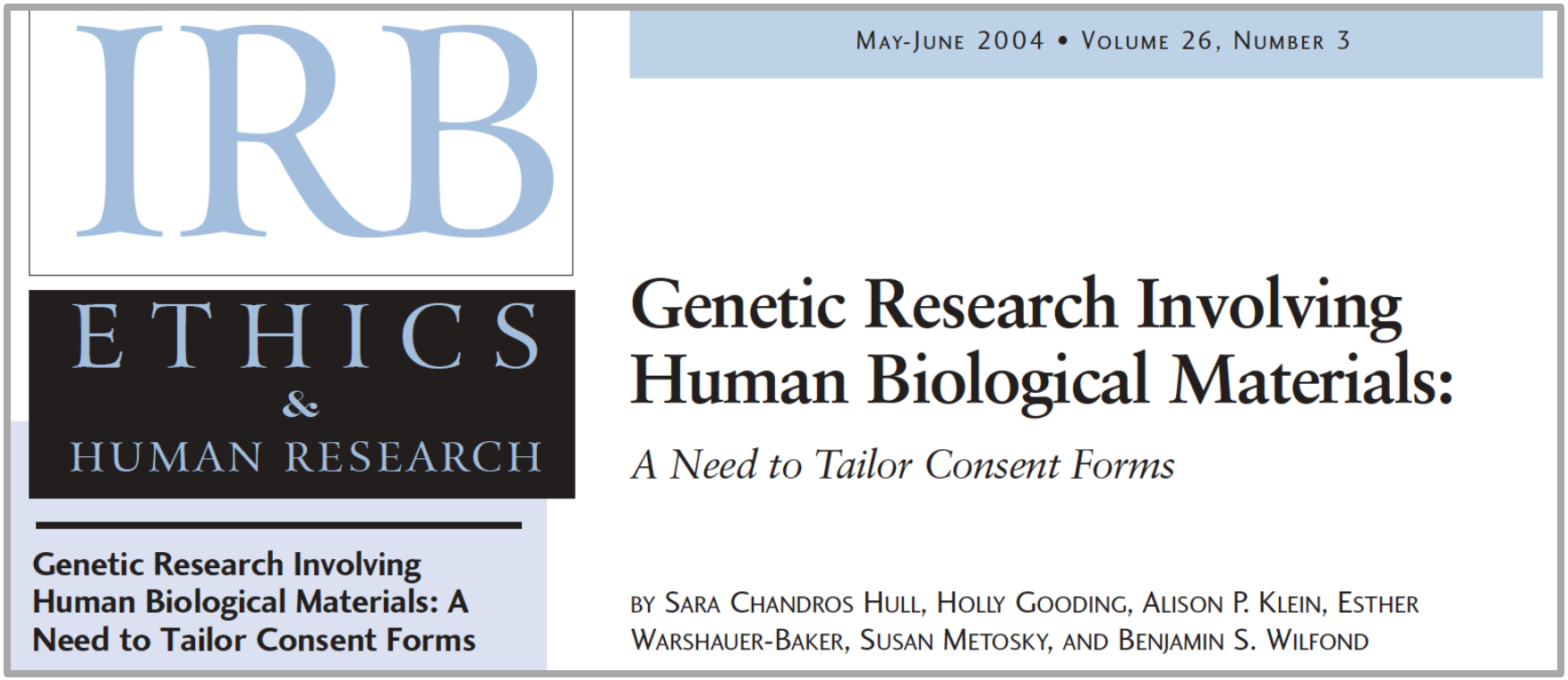
- ❑ *Specific disease*
- ❑ *Particular gene*
- ❑ *Explicit methodology*
- ❑ *Individual investigator*
- ❑ *Distinct time*

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)



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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)

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

Attitudinal Data

- The majority of individuals are willing to provide one-time broad consent and rely on independent ethics approval to determine the specific studies for which their samples are used
  - Regardless of disease, technology, etc.

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

Broad Consent in Policies (Min. Std)

- NIH Genomic Data Sharing Policy
  - "NIH expects investigators to obtain participants' consent for their genomic and phenotypic data to be used for future research purposes and to be shared broadly."
- NPRM (Common Rule)
  - Requires broad consent for all use of stored biospecimens in secondary research, including de-identified
  - Establishment DHHS broad consent templates

What about the minority of individuals who are unwilling to give broad consent?

- 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

Genetic Research as a Double-Edged Sword

- Non-European populations are persistently underrepresented in genomic research/databases
  - "GWAS funded by the NIH and other sources are continuing to miss a vast portion of the world's genetic variation"

    Popejoy and Fullerton (2016) *Nature*

Genetic Research as a Double-Edged Sword

- 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*

Consonance with Community-Based Participatory Research

- Move from standard “principle” ethics to community dialogue and negotiations
- Room for innovative arrangements
- Assist in building cross-cultural equitable relationships between communities and researchers

Quigley (2006) *Health Education and Behavior*

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*

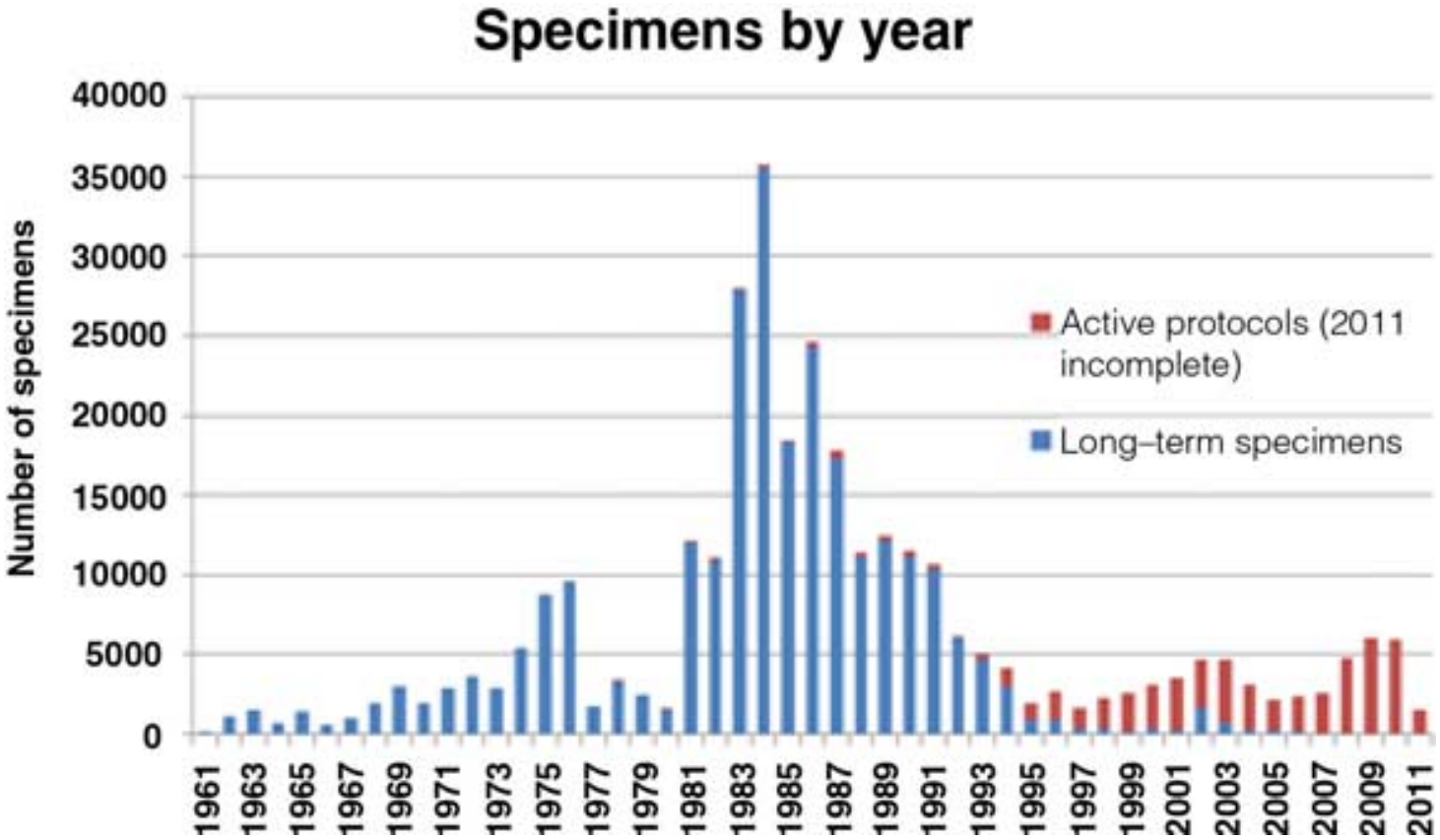
Alaska Area Specimen Bank

- 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*

Alaska Area Specimen Bank

266,353 specimens



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Thank you!