The Ethics of Genetic Research with Stored Samples and Data

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- The speaker declares no financial conflicts of interest.

Roadmap

- A warm up case
- Setting the stage
  - Large sample/data collections
  - Regulatory framework
- Informed consent for collection, storage, and future use of samples/data
  - Broad
  - Study-specific
    - A contrasting case

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*

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

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

Then vs. Now

"Traditional" Genetic Research	"Next-Generation" Genomic Research
• Individual researcher/team	• Biobanks/repositories • Broad sharing
• One set of defined studies	• Many studies possible
• Future uses not anticipated	• Future uses encouraged
• One study/one consent	• More general/broad consent
• Targeted/candidate genes	• Exomes/genomes

Endorsement of Broad Consent

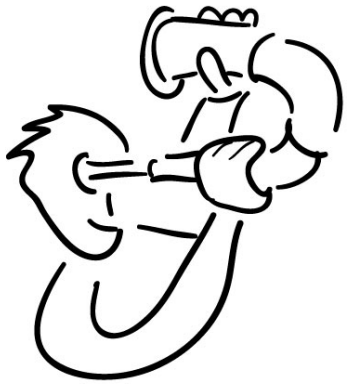
- ANPRM (2011)
  - Written consent for research use of specimens
  - Could be obtained via “brief standard consent form agreeing to generally permit future research”
- NIH Genomic Data Sharing Policy (2014)
  - “NIH expects that informed consent for future research use and broad data sharing will have been obtained even if the cell lines or clinical specimens are de-identified.”
  - “NIH recognizes that in some circumstances broad sharing may not be consistent with the informed consent of the research participants.”

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”



What is a human research subject?

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

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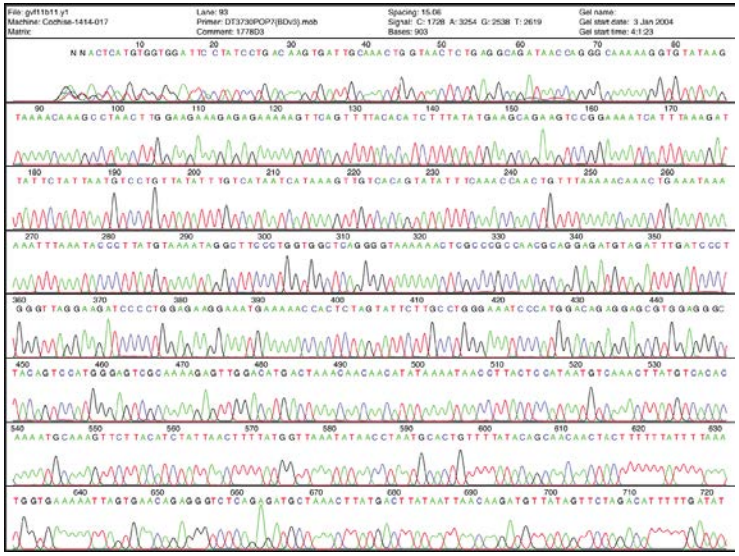


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Definition of Human Subject

(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

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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- ❑ *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)

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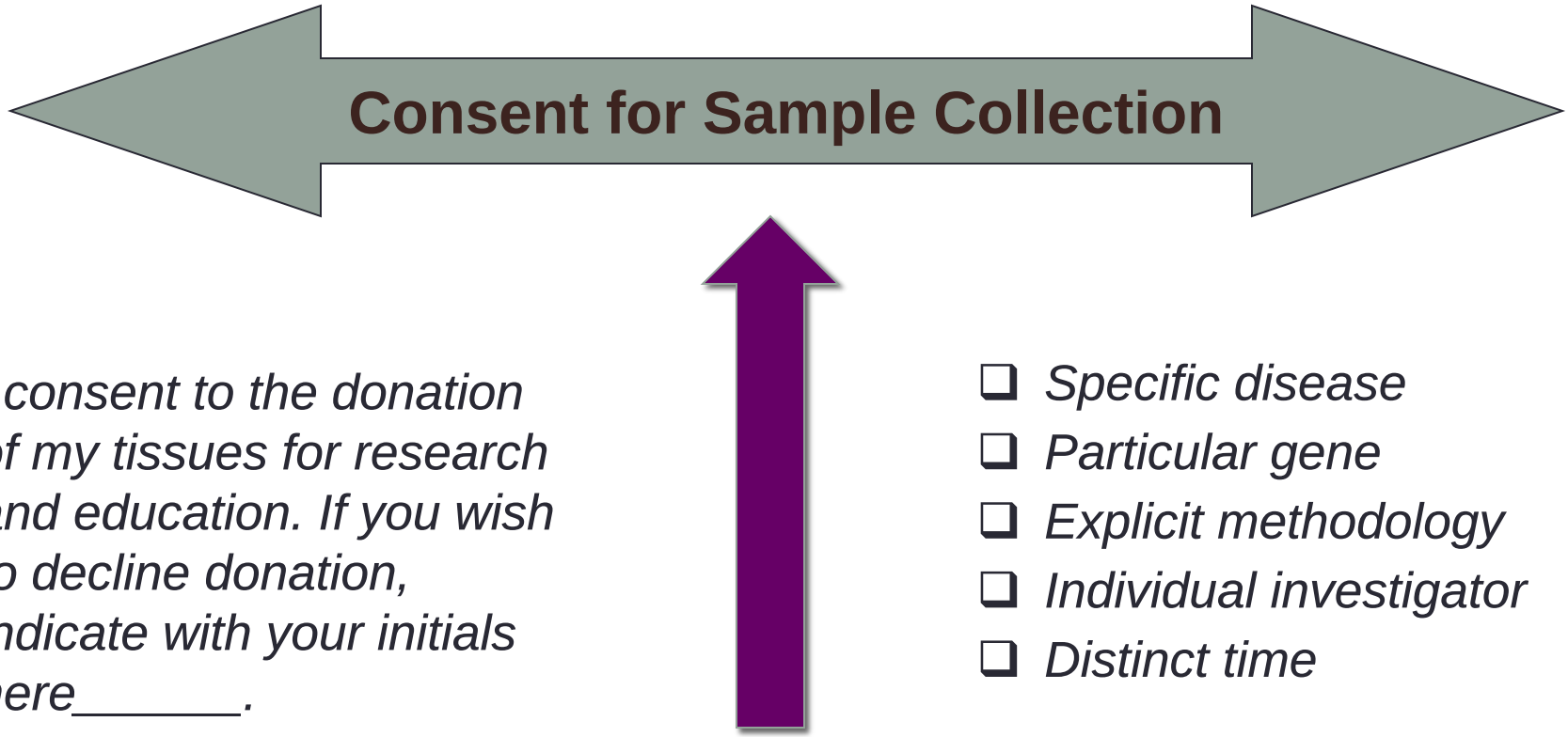

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Approaches to Consent for Future Research with Biospecimens

Less burden, less control

More burden, more control

TYPE OF CONSENT	DESCRIPTION
No consent	Do not inform, do not obtain donor consent
Blanket	Consent to future research with no limitations
Broad*	Consent to future research with specified limitations
Checklist	Donors choose which types of future studies allowed
Study specific	Consent for each specific future study

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

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

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Havasupai Case

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

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)

BCPT vs. Havasupai Cases

Awareness and Impact of Havasupai Case

- IRB Chairs and Researchers (n=26)
  - Able to articulate (some) ethical issues
  - Do not think issues translate to their own work

"It's an issue that I was aware of outside of the case, and I recently read the book about Henrietta Lacks, and so forth. So I did, I think, pass along an article about the Havasupai case to my study coordinator to make sure she's aware of these issues, but I can't say that the case in particular changed my thinking a lot."

Garrison and Cho (2013) *AJOB Primary Research*

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*

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

What Makes Clinical Research Ethical?

1. Collaborative partnership
2. Value
3. Scientific validity
4. Fair subject selection
5. Favorable risk-benefit ratio
6. Independent review
7. Informed consent
8. Respect for enrolled subjects and communities

Emanuel, Wendler, Killen, & Grady (2004) *JID*

BIOETHICS AT THE NIH

Thank you!

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