The Ethics of Genetic Research with Stored Samples and Data

Sara Chandros Hull, Ph.D.
Office of the Clinical Director, NHGRI
and
Department of Bioethics
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

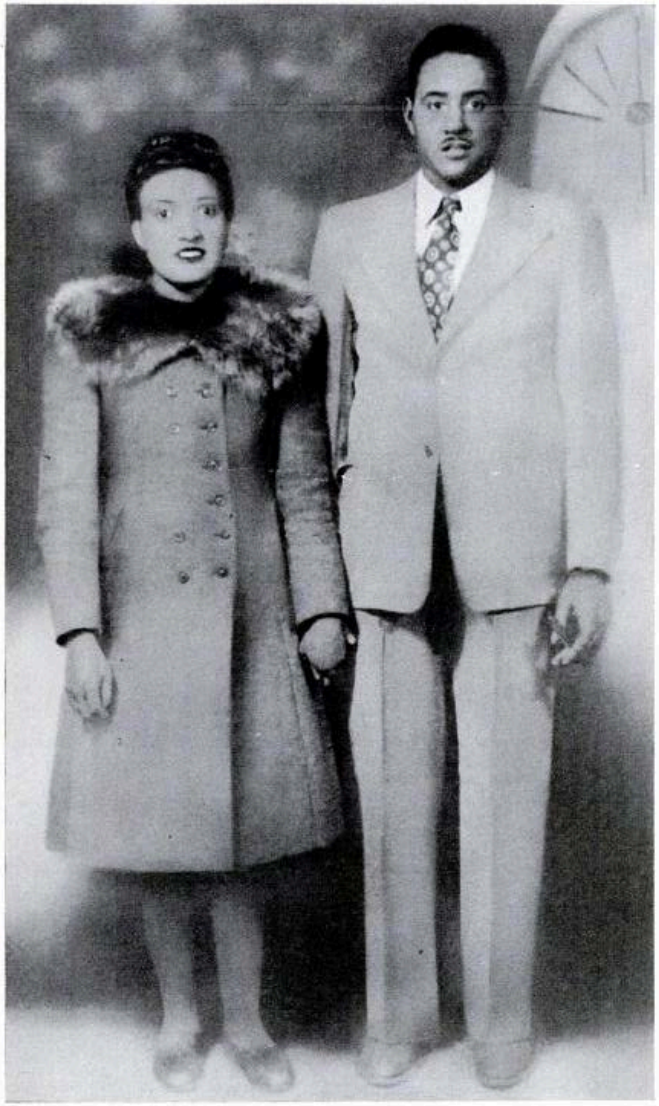
- Three cases
- Setting the stage
  - Large sample/data collections
  - Regulatory framework
- Informed consent for collection, storage, and future use of samples/data
  - Broad
  - Study-specific

Case 1: Consent, *circa 1951*

I hereby give consent to the staff of XXXXX Hospital to perform any operative procedures and under any anaesthetic either local or general that they may deem necessary in the proper surgical care and treatment of:

_____

THE MIRACLE OF 'HELA'



Mrs. Henrietta Lacks, who died of cancer in 1951, inspired the interest of medical researchers because the cells from her tumor have in some way survived and are contributing to cancer cure search. She is shown with her husband David at time of their marriage.

Tissue of a woman dead 25 years has strangely survived as a major tool in fight against cancer

AN OBSCURE black woman without training in medicine has ironically become one of the pivotal figures of the crusade against cancer. Mrs. Henrietta Lacks, the mother of five, died 25 years ago, but her cancerous cells are being studiously preserved as an important instrument of science.

Already her name, in contracted form, is invariably included in the journals and symposia of the fight against cancer. Her "HeLa" cells, say workers in the field, have yielded vital information about the causes of cancer and other problems of medicine. For it is the first time ever that human cancer tissue has been preserved so long.

The events of the story, one of the marvels of research, had a tragic beginning for the woman and her family.

One winter day, Mrs. Lacks, 31, paid a desperation visit to the gynecology clinic at Johns Hopkins University, complaining of vaginal bleeding. A sample of her tissue was immediately referred to Dr. George Gey of the Johns Hopkins faculty. Dr. Gey was a leader in tissue culture studies, a field of medicine in which tissues are preserved for experiments in laboratories.

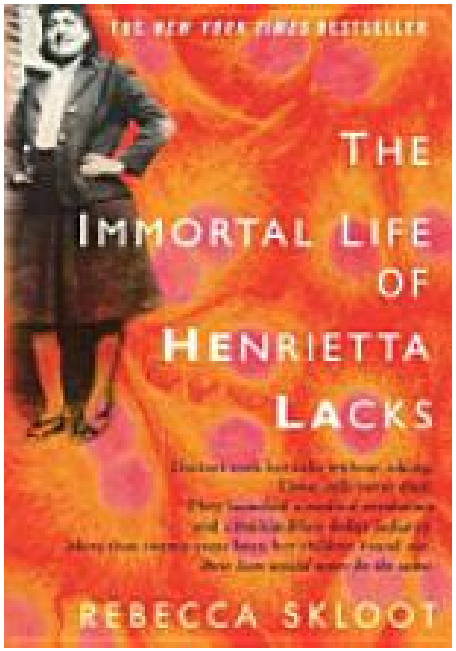
Most of the tissues that he studied were of animal origin, since human cancer tissue had been impossible to preserve. But the HeLa cells, as they were soon to be known, were very different in behavior.

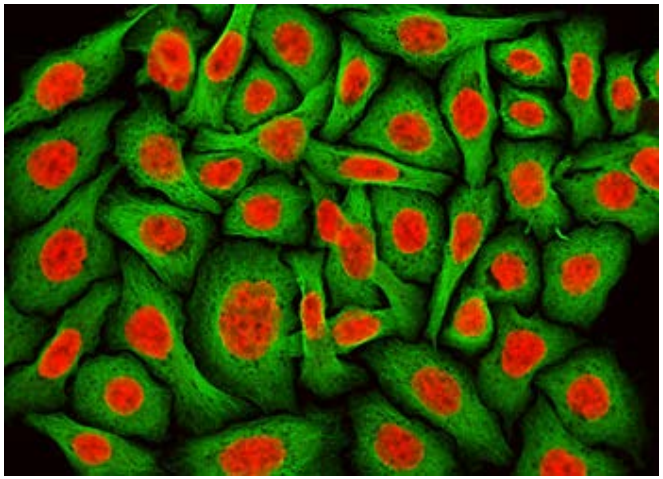
Mrs. Lacks did not recover; she died ten months later. But her tissue lived on. The cancer cells went right on multiplying, dividing about once in every 24 hours. Cancerous cells have a curious ability to invade other tissue and condition its behavior, leaving their imprint on the chromosomal structures of the colonized cells. Soon the HeLa cells were invading the nuclei of other laboratory tissue. And since tissue samples are regularly exchanged among centers of research, HeLa cells began turning up everywhere, contaminating the vials of medical researchers all over the world.

Aside from this inadvertent spread of HeLa, samples of the cells were regularly sent to other research centers, where their value has been inestimable.

As Dr. Jack E. White, who directs the Cancer Research Center at Howard University, explains: "We've been able to grow animal cells in the laboratory, but it has been far more difficult to squeeze out human cells from

Continued on Next Page





Ethical Themes in TILoHL

- Informed consent (84%)
- Compensation, benefit, profit-sharing (72%)
- Welfare of vulnerable (54%)
- Scientific/societal progress (34%)
- Accountability, regulation, oversight (26%)
- Patient control, data access, patenting (23%)
- Privacy, discrimination, disclosure (13%)
- Public education and consultation (8%)
- Advocacy, activism (5%)

Nisbet MC and Fahy D (2013) *BMC Medical Ethics*

Case 2: 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 2: BRCA, Tamoxifen, and Consent

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

Case 2: 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 2: 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 2: 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?

Case 3: 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 3: 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 3: Awareness and Impact

- 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*

Case 3: 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*

Then vs. Now

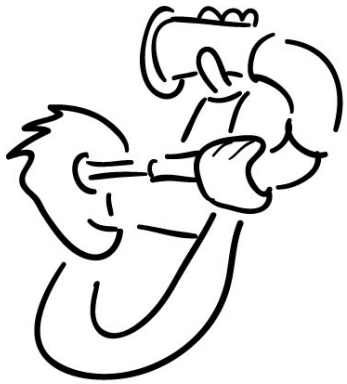
"Traditional" Genetic Research	"Next-Generation" Genomic Research
• Individual researcher/team	• Biobanks/repositories • Broad sharing
• One set of defined studies	• Many studies possible
• Future uses not anticipated	• Future uses encouraged
• One study/one consent	• More general/broad consent
• Targeted/candidate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

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?

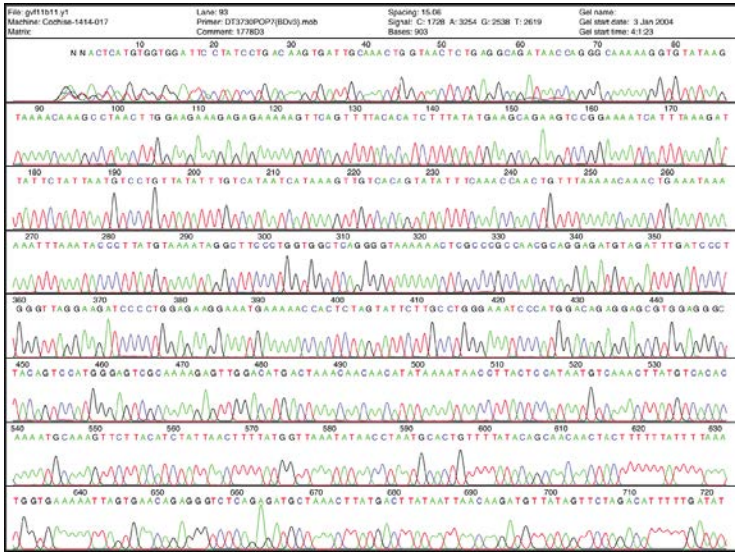
Current Definition of Human Subject

(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?




S199-3126
S95-0322
S99-2670
S95 997 #1R
S96-1300
S99-3093
S95-6025
S95-0068
S93-1678
S92-1509
1-86-9020
S95-897 A
S199-3900
1-85-16625
1582-7483
1583-4617
98-513
98 1281-2
98-1281-1

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*

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*

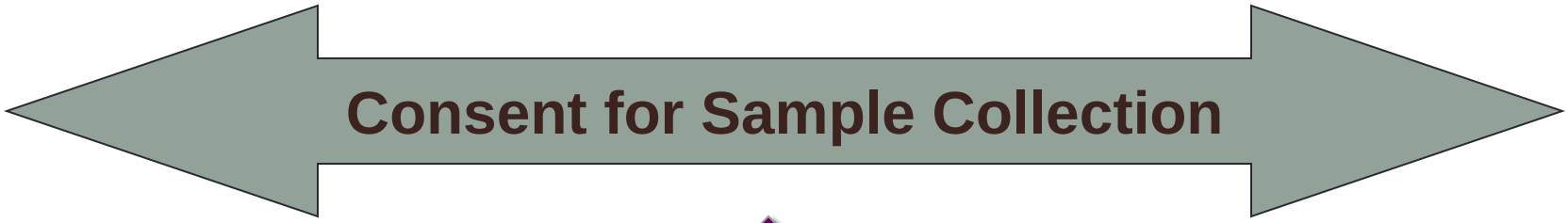
- ❑ *Specific disease*
- ❑ *Particular gene*
- ❑ *Explicit methodology*
- ❑ *Individual investigator*
- ❑ *Distinct time*

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?



- *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*

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

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

Christine Grady *et al.* (2015)
American Journal of Bioethics

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

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

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

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.”
- GREAT Research Framework
  - Governance
  - Re-consent
  - Education
  - Accountability
  - Transparency
  - Research Priorities

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

Rare Disease Populations

- Surveys with LD patients (46) and relatives (149)
  - “Sharing data with a lot of researchers in different countries is a plus to improve research”
  - “It is necessary to multiply, federate and pool research”
- Broad consent approach + ongoing information & oversight
- Initial consent content domains:
    - Nature of data collected and purposes of the database
    - Data security and confidentiality
    - Length of storage
    - Database ownership and governance
    - Conditions governing academic and pharma-industry partnerships
    - Commitment to give ongoing information
    - Existence of an ethics steering committee

Darquy *et al (*2015) *European Journal of Human Genetics*

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

BIOETHICS AT THE NIH

Thank you!

Sara Chandros Hull, PhD
shull@mail.nih.gov