The Ethics of Research with Stored Samples and Data

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- The speaker declares no financial conflicts of interest.

Roadmap

- Background/setting the stage
- Key ethical challenges
  - Informed consent
  - Informational risk

  } *cases/open questions*
- Attitudinal data/policy developments

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.

Shifting Norms

"Traditional" Genetic Research	"Next-Generation" Genomic Research
Individual researcher/team	Biobank/repository Broad sharing
One set of defined studies	Many studies possible
Future uses not anticipated	Future uses anticipated
One study/one consent	More general ("blanket") consent?
Individual genes	Exomes/Genomes

Where are stored samples?

n>282 million in U.S., 20 mil new cases per year
National Bioethics Advisory Commission (1999)

- Individual laboratories
- Pathology departments
- Newborn screening programs
- "Biobanks"
- Cord blood banks
- Military DNA collections
- Forensic collections

…and data?

- Research databases
  - Government (dbGaP)
  - University-based
  - Private sector (23 and me?)
- Electronic health record (EHP)

What does a research subject look like?

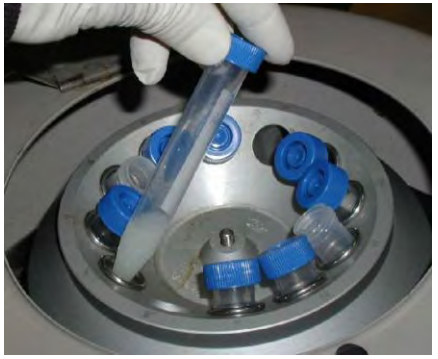
Definition of Human Subject

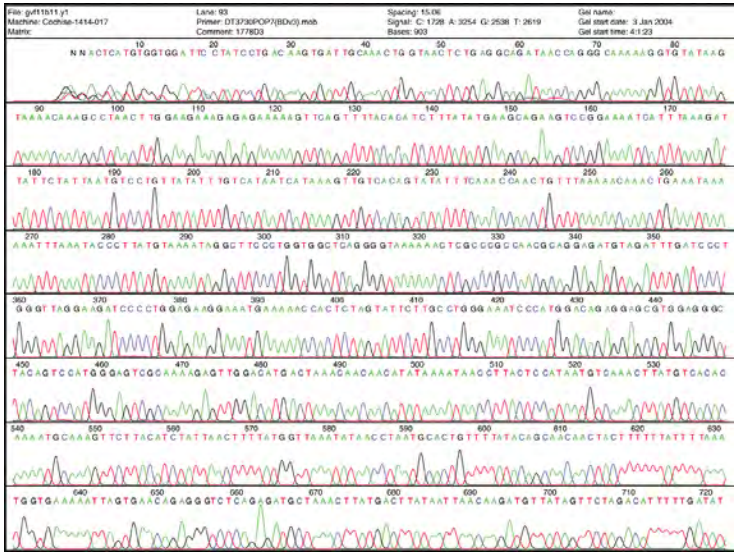
(f) A living individual from whom an investigator . . . conducting research obtains:

(1) data through intervention or interaction with the individual

45 CFR 46.102

What is a Human Subject?



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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

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

Classification of Samples

Key ethical challenges

Informed Consent

- Challenge of consent for future research that is not fully anticipated at the time of sample collection
  - Opt in vs. opt out
  - Broad vs. specific

Sample/Data Sharing

- Risks associated with sharing potentially identifiable information with third parties

Informed Consent

Broad Open-Ended Consent

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

CAP consensus statement (1999)

Explicit (Tiered) Consent

Recommendation 9:

> . . . to provide potential subjects with a sufficient number of options to help them understand clearly the nature of the decision they are about to make.

NBAC Report (1999)

Explicit (Tiered) Consent

- Only unidentified or unlinked use
- Use in one study only, no further contact
- Use in one study, with possible further contact
- Use in any related study, with possible further contact
- Use in any kind of study

NBAC Report (1999)

What information is needed for "valid" informed consent?

- Any (genetic) research

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

Case 1: Consent, *circa 1951*

- "I hereby give consent to the staff of ------ 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

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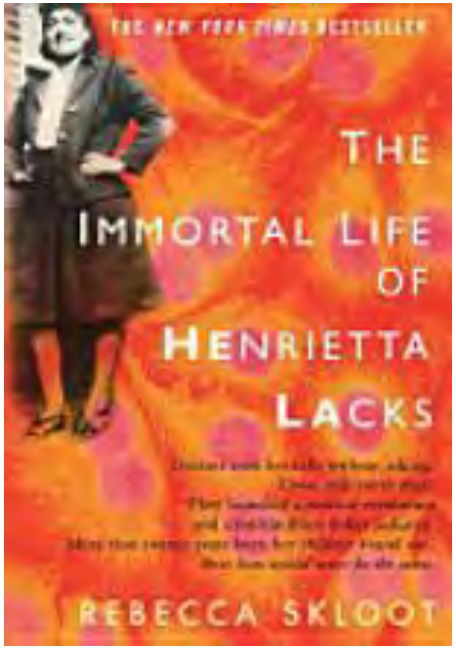

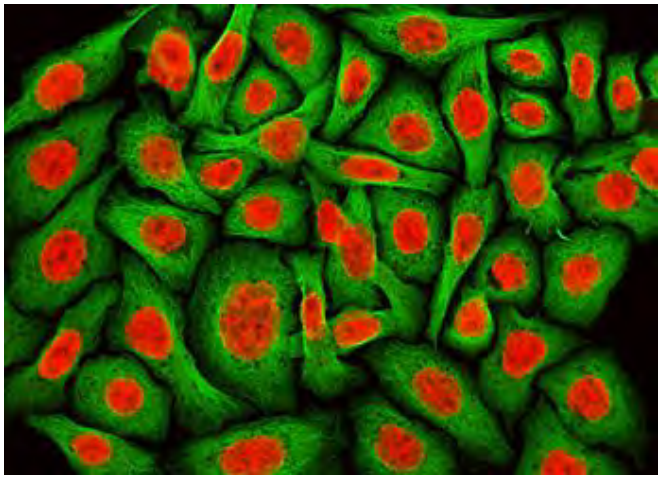

Case 1: Consent, *circa 2004*

- *The information collected for this study will be kept indefinitely…*

- *(Y/N) I agree to allow my genetic/DNA samples to be released, for research purposes, to:*
  - *Researchers from private or non-profit organizations who wish to develop diagnostic laboratory tests, medications, or other therapies that could benefit many people.*
    - *Note: Neither you nor your heirs will benefit financially from this…*

Case 1: What if…

- …Henrietta Lacks had signed the 2004 consent form?
  - Would that satisfy the questions that have been raised about the creation and use of the HeLa cell line?
- What if she had declined?
  - Tension between scientific progress and individual rights

Case 2: BRCA1/2 and Tamoxifen

- BCPT (n>13,000) - 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 1/2 & Consent

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

Case 2: BRCA 1/2 & 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: Implications

- Broad consent
  - More likely to interpret prior consent as sufficient/still applicable to THAT study
    - Open questions about scale and scope
      - next generation sequencing
      - induced pluripotent stem (iPS) cells
- BRCA1/2: more routinely disclosed
  - Open questions about obligations to disclose individual research results

Some Open Questions

Sharing of Samples and Data

NIH and Data Sharing

"We believe that data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health. The NIH endorses the sharing of final research data to serve these and other important scientific goals."

- NIH 2003 Data Sharing Policy

Informational Risk

- Disclosure of personal information
  - To research participants
    - Privacy intrusion from undesired contact
    - Pyschosocial harm from disclosure of results
  - To third parties
    - Embarrassment
    - Stigmatization
    - Legal or financial ramifications
    - Discrimination
      - theoretical, in research context

Research Design Measures to Reduce These Risks

- Technological
  - Anonymization/coding/encryption
  - Use of intermediary to hold link between code and identifiers (e.g., “honest broker”, “charitable trust” models)
- Legal
  - Data Use Certificates/Agreements
  - Certificates of Confidentiality
  - GINA 2008/HIPAA/ADA/state laws

Case 3:
Data Sharing and Identifiability

- Centralized GWAS Data Repository
  - "The NIH is interested in advancing genome-wide association studies (GWAS) to identify common genetic factors that influence health and disease."
    - Maximize availability of resources
    - Ensure consistency and quality control
    - Long-term commitment to storage and access

Case 3:
Data Sharing and Identifiability

- Investigators who receive NIH support for GWAS must deposit:
  - "Aggregated" descriptive data
    - Open access
  - Coded "individual level" data
    - Controlled access

Fed Reg, 72 (166), 11/28/07

Case 3:
Data Sharing and Identifiability

GWAS Data Sharing Policy – Footnote

- OHRP: GWAS repository does not currently involve human subjects research
- IRB review not required

OPEN ACCESS Freely available online

PLoS GENETICS

Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex Mixtures Using High-Density SNP Genotyping Microarrays

Nils Homer[1,2], Szabolcs Szelinger[1], Margot Redman[1], David Duggan[1], Waibhav Tembe[1], Jill Muehling[1], John V. Pearson[1], Dietrich A. Stephan[1], Stanley F. Nelson[2], David W. Craig[1]*

1 Translational Genomics Research Institute (TGen), Phoenix, Arizona, United States of America, 2 University of California Los Angeles, Los Angeles, California, United States of America

August 2008 | Volume 4 | Issue 8 | e1000167

"[I]t is now clear that further research is needed to determine how to best share data while fully masking identity of individual participants."

"While in hindsight this conclusion seems obvious, it represents a fundamental paradigm shift in thinking..."

Case 3:
Data Sharing and Identifiability

11/18/08 Revision to the Policy

- NIH removed aggregate genotype data for GWAS studies from public access
  - available only through controlled access

Some Open Questions About Informational Risk

- When are data in a database considered to be "anonymized"?
- How significant are the consequences of removing identifying information from data for the value of scientific analyses of the remaining data?
- How real are the risks to subjects of re-identification and disclosure of potentially harmful data?
- What kinds of privacy protections should be put in place for removing identifying information from data, or for limiting access to data in some way?

-from charge to SACHRP panel

Importance of Consent for Data Sharing

POLICYFORUM

Specifically, we recommend a stratified consent process in which all subjects who participate in future genomic sequencing studies are fully informed about how their DNA data may be broadcast and have the authority to decide with whom they want their data shared.

are adding DNA banking and analysis to research protocols, resulting in new disease-specific DNA databases. A major ethical and policy question will be whether and how much information about a particular individual's DNA sequence ought to be publicly accessible

there are genetic variances associated with Parkinson's disease. Dr. A obtains IRB approval for her study and recruits subjects from her clinic. She explains to potential subjects that she is conducting a genetic study of Parkinson's disease. Subjects are presented with a consent form, which explains that they will be asked to give a blood sample and to fill out a health survey. They are told the risks associated with the blood draw, warned

Although some might fear a negative impact on subject participation in genomic research, stratified consent merely restricts the ability to release sequenced data publicly. If anything, it may boost enrollment by providing an opportunity for even the most risk-averse members of society to participate in research, while ensuring optimal privacy protection.

genetic data while purportedly protecting privacy (*3*–*6*). We believe that minimizing risks to subjects through new developments in data and database structures is crucial and should continue to be explored, but that additional safeguards are required.

Dr. C, at Datamine University, is interested in studying whether patients who have a particular genetic marker for Parkinson's disease also have genetic markers for Alzheimer's-type dementia. Dr. C accesses the public Web site and searches and analyzes the published DNA sequences, looking for associations.

Science, 2006

A Role for Empirical Data?

Prevailing Regulatory Paradigm

- ***Identifiable*** = IRB review, informed consent
- ***De-identified*** = not human subjects research, no IRB review

Public Attitudes

- Patients may have preferences regarding the research projects to which they contribute, *independent of* risks to privacy and confidentiality. (*e.g.*, Wendler 2002)

One-time general consent for research on biological samples

David Wendler

BMJ VOLUME 332 4 MARCH 2006

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

Subject Attitudes: Need for Informed Consent, I

Proportion of patients who feel it is "important to know about" genetic research with tissue samples (n=1193)

	De-Identified	Identifiable
Clinically-derived	72%	81%

Hull et al (2008) *AJOB*

Patients' Attitudes about Biobanking and Genetic Research

Summary

- Patients want to be told about research with their clinical samples
- Preferences do not align with consent paradigm that depends on identifiability
- Notification (vs. written permission) might be acceptable

ANPRM/Common Rule
Enhanced Protections for Specimens and Data

- Written consent required (specimens)
  - Whether coded or not
    - Essentially treats biospecimens as identifiable
  - Standardized consent form
    - Allowing open-ended use in future research
    - Very succinct
      - Will this be sufficient?
  - Applied prospectively

Emanuel and Menikoff (2011) *NEJM*

ANPRM/Common Rule
Enhanced Protections for Specimens and Data

Confidentiality/security protections (data)

- Uniform standards
- Modeled on HIPAA
  - e.g., use of encryption, audit trails
- Enforced through periodic audits
  - rather than IRB review

Emanuel and Menikoff (2011) *NEJM*