

## Ethical Issues in the Use of Stored Samples

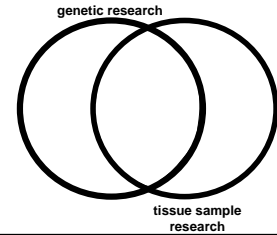
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## Disclaimers/Disclosures



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## Overlap with genetic research

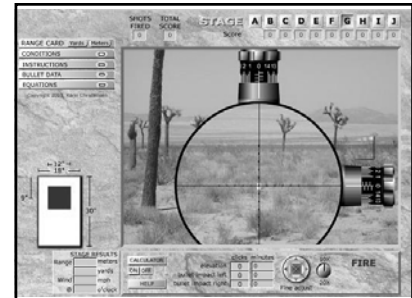


## A Note about Terminology "blood" samples"

"tissues"  
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*samples √ genotypic and phenotypic data*



## Where are stored samples?

n>282 million in U.S., 20 mil new cases per year  
NBAC, 1999

- Individual laboratories
- Multi-center trials
- Pathology departments
- Newborn screening programs
- "Biobanks"
- Military DNA collections
- Forensic collections



## Definition of Human Subject

- (f) A living individual from whom an investigator . . . conducting research obtains:  
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45 CFR 46.102



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- (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

## What is *not* research with human subjects?

Collection and study of:

- Samples from deceased individuals
- Samples taken for diagnostic purposes only
- Specimens or data that are available from commercial or public repositories or registries
- Established cell lines that are publicly available to qualified scientific investigators...

From OHSR Information Sheet #14

## Ethical Issues in the Use of Stored Samples

- Research design
  - Collection of new samples vs. use of existing samples
  - Plans for linking samples to medical records, identifiable information
  - Use/disclosure of research results
- Informed consent
  - Adequate disclosure
    - Prospective
    - Existing, stored samples

## Case 1 HCV “Look-Back” Study

- Problem
  - Need for research on long-term outcomes for young, healthy persons with hepatitis C infection
- Potential Solutions
  - Prospective studies
  - Retrospective cohort study using stored samples

L. Seeff et al., 2000, *Ann. Int. Med.*

## HCV Study Procedures

- Serum specimens (n=8568) collected between 1948-1954 from military recruits for group A strep and acute rheumatic fever
  - Tested for presence of HCV antibodies
  - Names and military service numbers matched to SS#s + demographics
  - Morbidity and mortality data collected from VA and HCFA records

## HCV Findings

- Historical significance
  - HCV in US prior to 1968
- Healthy HCV+ individuals may be at less risk for progressive liver disease than was previously thought
  - 2/17 (12%) HCV+ and 205/8551 (2%) HCV+ individuals had developed liver disease

## HCV Study: Questions

- When should subjects be asked to “re-consent” prior to new research on samples?
  - Military vs. other contexts
- When is it appropriate to inform individuals regarding + results?
  - Potential benefits vs. risks to subjects
  - Additional scientific knowledge to be gained
  - 7/10 HCV+ individuals still living were recontacted

## 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*

### BRCA1/2 Testing: 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

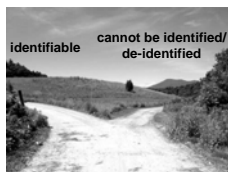
### Scaling Up

- Biobanks
- Whole genome sequencing

### "Traditional" Research with Samples vs. Biobanks

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• Individual researcher/team</li> <li>• One set of defined studies</li> <li>• Future uses not anticipated</li> <li>• One study/one consent</li> <li>• Individual genes</li> </ul> | <ul style="list-style-type: none"> <li>• Broker/intermediary supplies samples</li> <li>• Many studies possible</li> <li>• Future uses anticipated</li> <li>• More general ("blanket") consent?</li> <li>• Exomes/Genomes</li> </ul> |
|--|---|

### 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

### But isn't the human genome uniquely identifiable??\*\*\*

- Whole exome/genome research
- Genome-Wide Association Studies (GWAS)
  - Assessing up to a million single nucleotide polymorphisms (SNPs) per sample
  - SNP pattern provides information unique to individuals
    - 30 to 80 SNPs to uniquely identify a single person (Lin et al. 2004)
  - SNPs vary among ethnic groups
    - Determination of ethnicity of participant is possible
    - Risk of "group harm"

\*\*\*If you have a reference sample

### But isn't the human genome uniquely identifiable??



### Risks of Using Identifiable Samples

#### Disclosure

- To third parties ("erroneous or malicious," Lowrance and Collins, *Science*, 2007)
  - Embarrassment
  - Legal or financial ramifications
  - Stigmatization
  - Discrimination (theoretical, in research context)
- To patients/subjects
  - Privacy intrusion from undesired contact
  - Harm from disclosure of results (anxiety)

### 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)
  - Data placed on computers not linked to the Internet
- Legal
  - Data Use Certificates/Agreements
  - Certificates of Confidentiality
  - GINA 2008/HIPAA/ADA/state laws



### Explicit Consent Possible Options ("Menu Approach")

- 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)

### A Role for Empirical Data?

- Subject attitudes and informational needs
- Subject consent "behaviors"

### 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)

	Anonymous	Identifiable
Clinically-derived	72%	81%

Hull et al (2008) AJOB

### Subject Attitudes: Need for Informed Consent, II

Proportion of patients who would require informed consent for research with tissue samples (n=504)

	Anonymous	Identifiable
Clinically-derived	27%	66%
Research-derived	12%	29%

Wendler and Emanuel (2002) Arch Intern Med

### Subject Attitudes: Willingness to Give Blood to Genetics Researcher

Very Willing	58%
Moderately Willing	26%
Somewhat Hesitant	11%
Very Hesitant	1%
Unwilling	3%

(n=1193)

Sobolski et al., submitted



### Scope of Consent: Future Use of Stored Samples

Okay to study different diseases	79%
Willing to sign one-time release	73%
Okay for different researchers to use sample	61%

phone patient survey, n=1193, Sharp, Willford, Hull, in process

Prefer to give blanket consent	48%
Prefer being asked about new project	42%

online public survey, n=8735, Murphy et al (2009) AJPH

### Subject Behaviors: The NHANES Experience

- National survey that collects specimens from representative sample of US population
- Of people surveyed in 1999-2000, 84-85% consented to collection of DNA specimen
  - Females and black participants least likely to consent (73-84%, depending on year)

McQuillan et al., 2003, Genet Med

### Unresolved Issues Regarding Biobanks

- Acceptability of "blanket" consent approaches (one time vs. every time)
- Reconsent for use of old samples/data
- Provision of results (research, incidental)
- Right/ability to withdraw
- Enrollment of minors
- Ownership/commercial aspects
- Evolving definitions of "identifiable"
- Oversight and governance

### New Paradigm Needed?

- Old paradigms may no longer preserve public trust
  - Burden on consent procedures
  - Reliance on open access
  - Group harms possible
- New model of "stewardship"
  - Responsible use of resources
  - In service to common good
  - Accountability to uphold commitments

Fryer-Edwards (2008) as presented at ASBH