

Research on Human Biological Materials

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Disclaimer

The following presentation does not necessarily represent the official views of the men pictured below nor the organizations they lead.



Where are stored tissues? (n>282 mil.)

- Individual laboratories
- Multi-center trials
- Pathology departments
- Newborn screening programs
- Collections such as Coriell, CEPH
- Military DNA collections
- Forensic collections



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

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

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

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 is currently 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*

What should investigators do?

- 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

Tissue Issues

- Research design decisions
 - 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

Classification of samples

- Not identified
 - No “human subject” if truly not identified
 - Question of how much clinical and demographic data can be retained
- Identified
 - Directly (name/ID)
 - Coded/linkable

Historical interpretation:

not identified = anonymous

- “Even if the researcher cannot identify the source of tissue, the samples are **not anonymous** if some other individual or institution has this ability.”

Clayton et al, *JAMA*, 1995

Current 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 researchand
 - (2) the investigators cannot readily ascertain the identity of the individual(s)”

Confused ?

Anonymous

Anonymised

Anonymously coded

Unidentified

De-identified

De-linked

Permanently de-linked

Irreversiblement anonymisé

Not traceable

Irretrievably unlinked to an identifiable person (UNESCO)

Completely anonymised

Unlinked anonymised

Traceable

Réversiblement anonymisé

Coded

Identifiably linked

Pseudonomised

Unlinked

Unlinked to an identifiable person (UNESCO)

Encoded

Encrypted

Identified (NBAC)

Nominative

Directly identified (Clayton et al 1995)

Fully identifiable

Confidential (NHS Confidentiality Strategy)

Linked to an identifiable person (UNESCO)

Identifiable

Personal data

Risks of using identified data

Disclosure

- To third parties
 - Potential for breach of privacy and confidentiality
- To patients/subjects
 - Privacy intrusion from undesired contact
 - Harm from disclosure of results

Research design measures to reduce these risks

- Maximize confidentiality
 - The “least necessary” or “least identifiable” dataset
 - Use of intermediary to hold link between code and identifiers
 - Obtaining maximal legal and practical protections
 - e.g., data placed on computers not linked to the Internet
- Develop approach for re-contacting subjects
 - Clinical relevance or value
 - Adequate counseling

What role
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consent
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What role does informed consent play?



Late at night, and without permission, Reuben would often enter the nursery and conduct experiments in static electricity.

Informed consent for research on human biological materials

- If/when?
 - For prospective collection
 - Maybe for existing samples, depending on:
 - Identifiability
 - Adequacy of prior consent
 - Setting in which collected (research vs. clinical)
- How?
 - Extent of detail
 - Frequency

“identifiable, private information”

vs.

“cannot be identified”



Informed Consent Guidance

- “Research conducted with *unidentified samples* is not human subjects research and is not regulated by the Common Rule.”
- “Research using *coded or identified samples* requires the consent of the source, unless the criteria for a consent waiver have been satisfied.”

NBAC (1999)

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NBAC (1999)

Waiver of informed consent for use of existing samples (see 45 CFR 46.116)

- Protocol must pose minimal risk
 - Determination of whether it might be desirable to communicate directly with patients
 - If yes, then $>$ minimal risk, and consent should be obtained
- Cannot adversely affect rights and welfare
- Impracticability of obtaining consent
 - From some or all participants

Why make this distinction?

- Right to avoid risks
- Right to control research that has the potential to affect them

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, *Arch Intern Med* 2002

Arch Intern Med

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Arch Intern Med

Proportion of Jewish adults who would require informed consent for research with tissue samples (n=273)

	Anonymous	Identifiable
Clinically-derived	60-75%	
Research-derived		

Schwartz *et al*, *Amer J Med Gen* 2001

Arch Intern Med

Public Attitudes about Genetic Research with Tissue Samples

- 30 minute phone interviews (n = 1193)
 - Duke University
 - Univ. of Arizona
 - Univ. of Utah
 - Johns Hopkins Univ.
 - UNC Chapel Hill
- Recruited from
 - General internal medicine
 - Oncology
 - Thoracic surgery
 - NIEHS population study at UNC

Hull, *et al.*, in progress

Vignette

“We want you to suppose that a medical researcher wants to do genetic research with some blood of yours left over from a doctor visit, together with some information from your medical records. We will be asking about two different situations.”

1. In the first situation, suppose that your name is removed from both the blood sample and from the information from your medical records so you cannot be identified by any of the researchers or anyone else. [*“anonymous scenario”*]

2. Suppose the researchers need to be able to identify the leftover blood sample as your blood and they also need some more detailed information from your medical records in order to do the research. To protect your confidentiality, your name will be replaced with a unique identification number that could be traced back to you and your medical records, if the researcher needs to do so. [*“identifiable scenario”*]

How important to know about research with previously collected samples? (n=1193)

	anonymous scenario	identifiable scenario
“Moderately/ very important”	850 (71%)	971 (81%)
“not very/not at all important”	312 (26%)	190 (16%)

Consistency between scenarios (n=1159)

	Moderately or very important for Knowing about IDENTIFIABLE SCENARIO	Not very or not at all important for Knowing about IDENTIFIABLE SCENARIO
Moderately or very important for Knowing about ANONYMOUS SCENARIO	773	75
Not very or not at all important for Knowing about ANONYMOUS SCENARIO	196	115

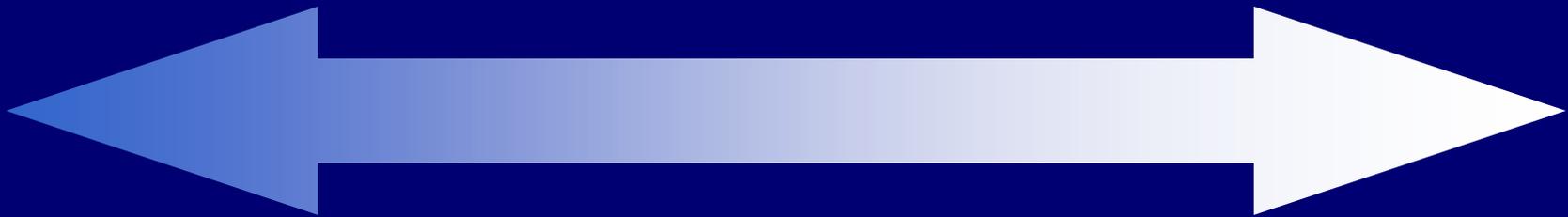
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Notification vs. permission

	anonymous scenario	identifiable scenario
notification required	365 (43%)	412 (42%)
permission required	475 (56%)	554 (57%)

What information is necessary to disclose for informed consent to be “valid”?



Any genetic research

Specific disease

Particular gene

Explicit methodology

Individual investigator

Distinct time

Unspecified Consent Forms

“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 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 Consent

Possible Options

- 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

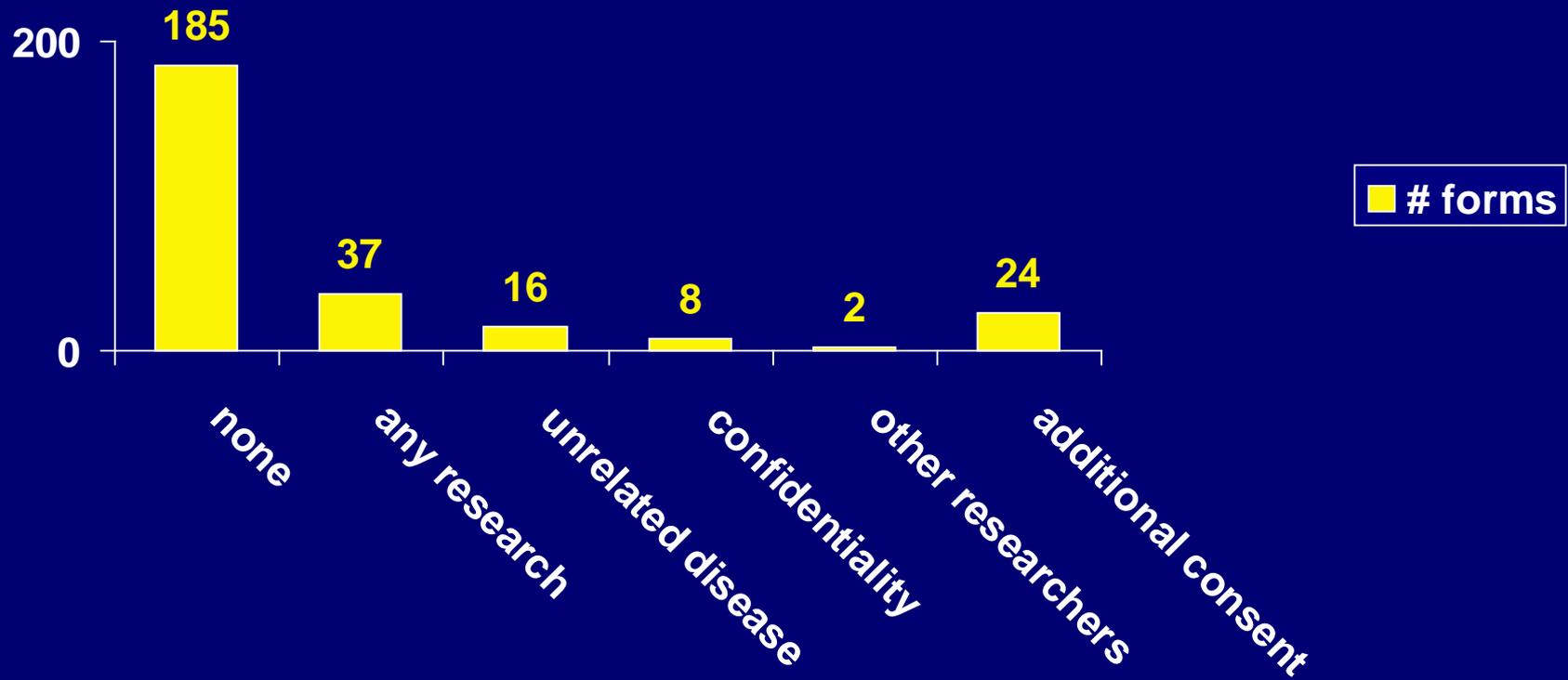
NBAC Report (1999)

Variability in approaching secondary research

- Options provided on consent forms
- Offer of additional consent

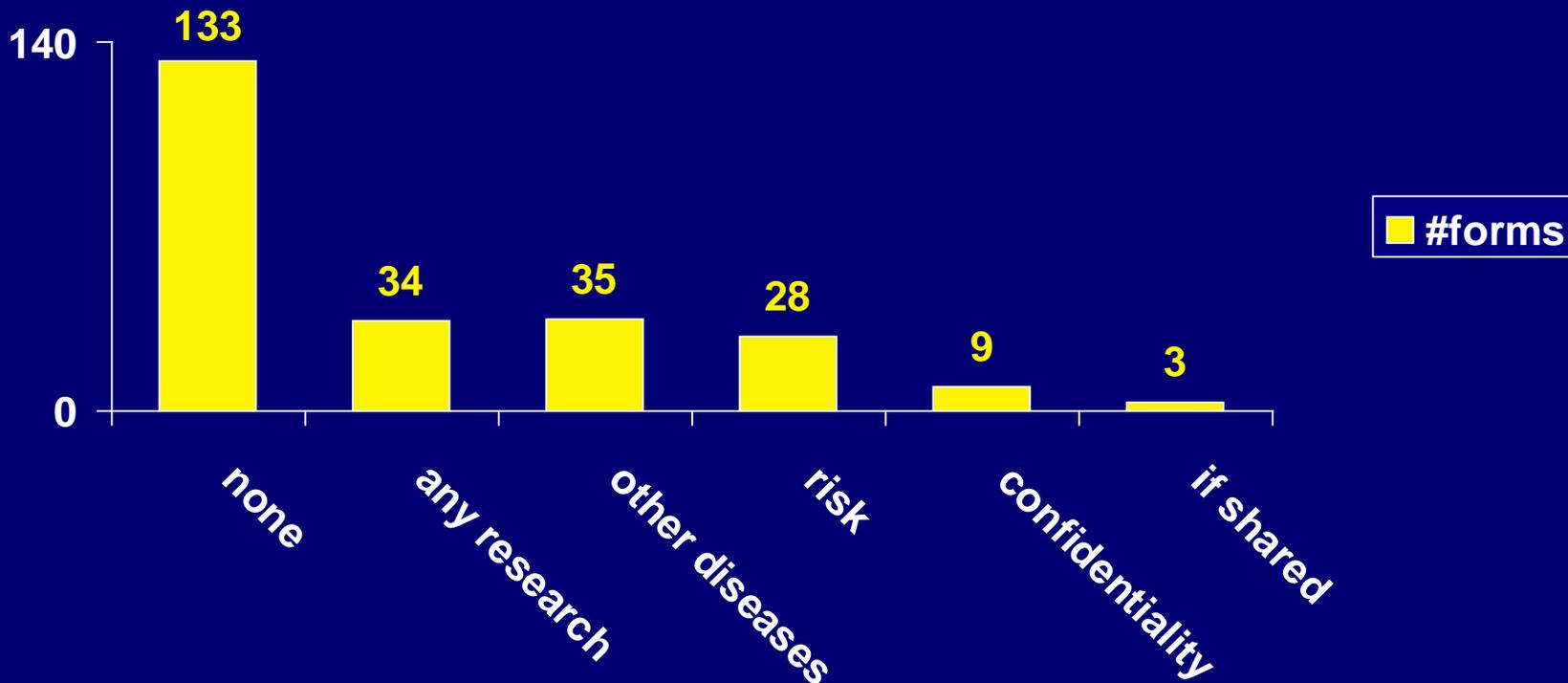
Hull *et al.*, *IRB*, 2004

Options for secondary research (n=230)



45 (20%) in 9 different combinations

Additional consent for secondary research (n=230)



97 (42%) in 11 different combinations

#1 thing participants want to know before giving blood sample

1. Goals of the research	33%	} 50%
2. What disease is being studied	17%	
3. How confidentiality is protected	16%	} 38%
4. What the risks are	12%	
5. Receipt of results/personal benefit	12%	
6. Who is doing research	6%	
7. Societal/general benefits	3%	
8. Who profits from research	0.5%	
9. How sample is being stored	0.5%	
10. Inclusion of certain race/class groups	0.2%	

Hull, *et al.*, in progress

Future use of collected samples

Okay to study different diseases 79%

Willing to sign one-time release 73%

Okay for different researchers
to use sample to study original disease 61%

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*

Boiling it down

- Does this research involve human subjects?
 - Are samples individually identifiable?
- Is this research exempt from IRB review?
 - Are samples existing at time of research?
 - How is information about samples recorded?
 - Will researchers have access to identifying information (or links)?
- Is prior informed consent adequate?
- Can informed consent requirement be waived?

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