Legal and Ethical Issues in Uses of Stored Tissue in Human Subjects Research

Gail Javitt, JD, MPH

Outline

- Human specimens have become increasingly important to the conduct of scientific research
- Use of biospecimens has received increasing attention in recent years
- Several legal cases and highly-publicized controversies have raised issues regarding rights, expectations, and obligations of tissue contributors, researchers and institutions
- Legal/Ethical issues remain unresolved
- Policies to address ethical/legal concerns still evolving

Overview

- Importance of biospecimens
- Human subjects research oversight framework
- Cases and controversies
- Issues to consider

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What is a biospecimen?
Biospecimens are biological materials collected from human beings

Blood
Cells (e.g., tumor cells)
Plasma
Urine

Biospecimens contain DNA – source of genetic information

Sources of biospecimens

Diagnosis
E.g., Newborn screening, Biopsy of possible cancerous tissue

Treatment/Routine medical care
E.g., Surgical removal of tumor; examination of placenta after delivery

Research
E.g., Collection from subject participating in drug development

What is a biorepository (a.k.a. biobank)?

“Libraries” in which biospecimens are stored

Biospecimens frequently annotated with information e.g.,
• Demographics
• Clinical data

Considered critical to enabling modern molecular-based research (e.g., genomics, proteomics, molecular imaging) to drive the development of targeted diagnostics and therapies

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Biorepositories

- Academic medical centers, government research institutions, commercial enterprises have established biorepositories
- Collectively contain more than 300 million samples
- Biorepositories & Electronic medical information linkage can be used for both research and patient care
- Personalized healthcare - targeting tests & treatments based on individual genetic variations

Research uses of biospecimens

- Identify and validate ways to deliver drugs or agents to specific cells
- Identify genetic variants associated with disease
- Identify variants associated with drug response/adverse events
- Selection of human subjects for research based on genetic variants
- Develop screening tests to detect biomarkers that are associated with certain stages or sub-types of a disease

Legal/Ethical issues

- ‘The Immortal Life of Henrietta Lacks’ Rebecca Skloot
- As was typical at the time no informed consent for use was acquired
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**Legal/Ethical issues**
- What is the legal status of a biospecimen?
- Who gets to use it?
- Is the information that can be derived from the biospecimen (genetic information) protected?
- Is research with a biospecimen the same as "human subjects" research?
- If so, what do researchers need to do in order to use the specimen?

**Federal rules governing research with human subjects**
- First issued by Department of Health & Human Services in 1991
- Codified in Code of Federal Regulations, Volume 45, Part 46
- Known as the "Common Rule" - adopted by 15 departments & agencies & codified in their regulations
- Applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by the federal government

**Definitions**
- "Research": "A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge"
- "Human subject": "a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) data through intervention or interaction with the individual, or (2) identifiable private information"
Federal rules governing human subjects

- "Intervention" – both physical procedures by which data are gathered (for example, venipuncture) & manipulations of the subject or the subject’s environment that are performed for research purposes
- Interaction includes communication or interpersonal contact between
- **Private information** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record)
- Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects

Federal rules governing human subjects

Common Rule specifically exempts:

Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects

Rules governing human subjects: The Common Rule

- Key Common Rule requirements:
  - **Informed consent**
  - **Confidentiality protections**
  - **IRB review and oversight**
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Rules governing human subjects: The Common Rule

Informed consent must include

- Statement that the study involves research, explanation of research purposes, expected duration of subject’s participation, description of the procedures to be followed, and identification of any procedures that are experimental
- Description of any reasonably foreseeable risks or discomforts to the subject
- Description of any benefits to the subjects or to others which may reasonably be expected from the research
- Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject

Informed consent requirements

Consent document may not include “any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.”

Informed consent requirements

- Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled
Rules governing human subjects: The Common Rule

Institutional Review Board (IRB)

- Must review and approve all proposals to conduct research in humans
- Must ensure:
  - Risks to subjects are minimized
  - Risks to subjects are reasonable in relation to the anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result
  - Selection of subjects is equitable
  - Informed consent obtained and documented
  - Privacy protected
  - Vulnerable populations adequately protected

Is research with biospecimens subject to Common Rule?

Common rule defines “research” as involving only identifiable information; exempts research where subjects cannot be identified

When are/not biospecimens “identifiable”?

Guidance on research involving coded private information or biological specimens (2008)

Individually identifiable specimens - can be linked, directly/indirectly, to specific individuals by the investigator(s) through coding systems

Non individually identifiable specimens - cannot be linked, directly/indirectly, to specific individuals by the investigator(s) through coding systems

E.g. if both following conditions are met

- Specimens not collected specifically for currently proposed research project through an interaction or intervention with living individuals
- Investigator(s) cannot readily ascertain identity of individual(s) to whom specimens pertain
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Rules governing human subjects: FDA

Rules for Human Subjects (21 C.F.R. Parts 50 and 56):

- Very similar to Common Rule
- Governs clinical investigation of unapproved drugs/devices and clinical investigations to support marketing applications for FDA-regulated products
- Differs from Common Rule with respect to research with deidentified specimens

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FDA regulations for research with investigational devices define “human subject”:

Individual OR Individual’s specimen

“A human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.”

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Informed consent for in vitro diagnostic device studies using leftover human specimens that are not individually identifiable (2008)

FDA will not require consent for use of human specimens for diagnostic device investigation provided certain criteria are met, including:

- Use of “leftover” specimens, i.e., remnants from clinical care, obtained from biorepository, or collected for other clinical research
- Specimens must not be individually identifiable. “Identity of the subject is not known to and may not readily be ascertained by the investigator or any other individual associated with the investigation, including the sponsor”
- Study has been reviewed by an IRB

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Biospecimen lawsuits

There are instances where the common rule and FDA regulations do not apply

Non federally funded research

Not to be submitted to FDA

Moore v. Regents of the University of California
(Cal. 1990)

Tissues samples used by

Dr. Golde, Moore’s treating physician, and Dr. Quan, a researcher

Gave many blood and tissue samples

Financially beneficial to the parties and done without Mr. Moore’s knowledge

Developed cell line + filed a patent, which listed Golde and Quan as the inventors

Moore argued that the unauthorized use of his cells constituted “conversion” (technical term for interference with ownership or right to possess property)

Moore v. Regents of the University of California

Mr. Moore, hairy cell leukemia patient

Filed lawsuit

Aske to return several times as physicians needed more samples for research, once more without informing Mr. Moore of the purpose
Moore v. Regents of the University of California

Court cites line of cases holding that:

1. Individual has right to determine whether or not to submit to medical treatment
2. Consent must be informed in order to be effective
3. Physician has a duty to disclose "all information material to a patient’s decision"

Moore v. Regents of the University of California

- No conversion claim
  - Moore’s situation would require an extension of conversion theory. Court declined to extend because:
    - Patient autonomy can be protected through other means, including adequate disclosure of financial conflicts of interest
    - Extending conversion theory would hinder research
    - Extending conversion theory is a job for the legislature

Moore v. Regents of the University of California

- Two Justices Dissent
  - Patients have right to determine before tissue is removed what will happen to it after removal
  - Patients have legally protectable property interest in their body parts and products derived therefrom
  - Disclosure of economic interests through informed consent is inadequate substitute for conversion
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Moore v. Regents of the University of California

Dissent (Broussard, J.)
- Question is not about ownership following removal, but about right to determine before removal what use will be after removal
- Majority does not demonstrate that patient does not have this right. Majority does not acknowledge patient’s economic interest in his/her own body parts. Nor does it demonstrate that application of conversion will hinder research
- Prohibiting conversion does not eliminate profit potential, just keeps the patient from being included
- The “fortuitous nature of the economic value does not justify the creation of a novel exception from conversion liability which sanctions the intentional misappropriation of that value from the patient”

Moore v. Regents of the University of California

Dissent (Mosk, J.)
- “Whatever merit the majority’s single policy consideration may have is outweighed by two contrary considerations, i.e., policies that are promoted by recognizing that every individual has a legally protectible property interest in his own body and its products”
- Disclosure is an inadequate substitute for conversion. Patients are unlikely to refuse treatment even after disclosure. Furthermore, it gives the patient the right to refuse, but not to condition consent on sharing in commercial proceeds


Plaintiffs: Subjects and subjects’ families

Defendants: Researchers + Institute

Plaintiffs worked with researcher to identify gene for Canavan disease and develop test, raising money, donating tissue, and developing a patient registry
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Greenberg v. Miami Children’s Hospital Research Institute

Informed consent claim
- Court finds there is a duty (under state law) to obtain informed consent for medical treatment but not necessarily for medical research
- Consent does not need to include researcher’s financial interests
- Chilling effect on medical research
- Plaintiffs are donors, not objects of human experimentation

Donors or subjects?

- Anyone who submits a marketing application of any drug, biological product, or device to submit certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies covered by the rule
- FDA’s device regulations define “subject” as a “human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control.” 21 C.F.R. § 812.3(p)

Greenberg v. Miami Children’s Hospital Research Institute

- Fiduciary Duty Claim
  - Plaintiffs argued that trust was placed in researcher and that the trust was accepted
  - Court found that there was insufficient evidence of acceptance of trust
- Fraudulent Concealment Claim
  - Court found that it was not adequately pleaded
  - Insufficient specificity as to acts constituting fraudulent concealment
- Misappropriate of Trade Secrets Claim
  - Plaintiffs alleged that the registry was a trade secret
  - Court held that requirements to be considered a trade secret were not met
    - Registry did not derive economic value from not being generally known to others
  - Even if it is, no evidence of misappropriation

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Greenberg v. Miami Children’s Hospital Research Institute

- Conversion Claim
  - No property interest here, since materials voluntarily given for research
  - Florida genetic testing statute not applicable
    - “Results of DNA analysis . . . exclusive property of person tested . . . ”
  - Researchers patented fruits of the donated tissue; distinguishable from the tissue itself
- Unjust Enrichment Claim
  - Requires that benefit is conferred and accepted, and that retention would be inequitable absent payment
  - Court found that the plaintiffs stated a claim for relief based upon the facts alleged

So, what happened?

- Parties reached a confidential settlement
- MCH can continue to license and collect royalty fees for clinical testing for the relevant gene mutation
- MCH permits royalty free research by institutions, doctors, and scientists searching for a cure for Canavan disease
- Plaintiffs agreed not to further challenge MCH ownership and licensing of the patent

Catalona v. University of Washington

Developed a biorepository for prostate cancer research

Patients/volunteers were invited to participate in genetic research
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Catalona v. University of Washington

- Informed consent required
  - Informed that biological samples might be used by many different entities for research
  - Included right to withdraw/right to destruction of the biological materials
  - As a part of the informed consent, participants waived any claims to the donated tissues or things derived from them

Catalona v. University of Washington

- Dr. Catalona Urologist
- Washington University Biorepository
- Northwestern University

- Without notice or approval from the IRBs at Washington University and Northwestern, obtained release forms from research participants indicating that they sought transfer of their samples to him
- Washington University sought declaration of its ownership of the biorepository and the biological samples

Catalona v. University of Washington

- Owner of the samples
- Washington University

Court of appeals framed the question as follows:

“[D]o individuals who make an informed decision to contribute their biological materials voluntarily to a particular research institution for the purpose of medical research retain an ownership interest allowing the individuals to direct or authorize the transfer of such materials to a third party?”

No

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Catalona v. University of Washington

- Biological samples were *inter vivos* gifts
  (fancy way of saying gift given while person still alive)
  - Donative intent
  - Delivery of property by donor to donee
  - Acceptance of gift by donee
    - Donor’s right to revoke/destroy does not negate gift status

As donors they do not have the same protection as human subjects

Catalona v. University of Washington

- As a part of the informed consent, participants waived any claims to the donated tissues or things derived from them
  - Is this acceptable under federal Human Subjects Protections rules?

“No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights”

45 C.F.R. § 46.116

OHRP letter (1989)

“[R]egulations [prohibiting waiver of rights] are not intended to prohibit the informed subject from making a legitimate donation of his or her [material] . . . an individual human subject of research may waive his or her rights, if any, in the commercial development of biological materials . . .”
Office of Human Research Protection (OHRP) and FDA
Draft Guidance (Sept. 2011)

- Would alter long-standing interpretation of Common Rule
to prohibit waiver of rights to biospecimens
  - In effect redefines regulatory definition of "exculpatory" language:
    - Common rule: Consent document may not include "any exculpatory
      language through which the subject or the representative is made to
      waive or appear to waive any of the subject's legal rights, or releases
      or appears to release the investigator, the sponsor, the institution
      or its agents from liability for negligence."
    - Draft guidance: "Exculpatory" = language which has the general
      effect of freeing or appearing to free an individual or entity from
      malpractice, negligence, blame, fault, or guilt

Office of Human Research Protection (OHRP) and FDA
Draft Guidance (Sept. 2011)

- Draft guidance - permissible to include in informed consent document
  language by which subject waives "any rights he or she may have with
  respect to a biospecimen obtained by investigators for research purposes"
- Impermissible to include in informed consent document language
  by which a subject waives right to be compensated for injuries
  arising from participation in research
  - OHRP and FDA "understand" that it has "long been common practice"
    for investigators and sponsors not to compensate research subjects
    who agree to provide biospecimens for research purposes even if those
    biospecimens are later used for commercial purposes
  - Thus, not exculpatory to include language that informs subjects that by agreeing
    to allow the use of their biospecimens for research purposes, they are giving up
    any legal right to be compensated for the use of their biospecimens

Office of Human Research Protection (OHRP) and FDA
Draft Guidance (Aug. 2011)

- Examples of acceptable exculpatory language:
  - "Although future research that uses your samples may lead to the development
    of new products, you will not receive any payments for these new products"
  - "By agreeing to this use, you are giving up all claims to any money obtained
    by the researchers from commercial or other use of these specimens"
  - "I voluntarily and freely donate any and all blood, urine, and tissue samples to
    the [name of research institution] and hereby relinquish all property rights, title,
    and interest I may have in those samples"
  - "By consenting to participate in this research, I give up any property rights I may
    have in bodily fluids or tissue samples collected during this research"
  - "Tissue obtained from you in this research may be used to establish a cell line
    that could be patented and licensed. No financial compensation will be provided
    to you should this occur"
Summary

- Ambiguity of the status of the tissue contributors and the tissue itself
- Courts did not give the contributors any rights to share in the proceeds from their tissues, or direct the usage once samples given
- In all these cases court defined the tissue contributors not as human subjects but as donors
  - Therefore, some of the traditional protections did not apply
  - There are inconsistencies in the decisions but some of the requirements have been re-interpreted for the case of biospecimens

Havasupai Tribe v. Arizona Board of Regents

- Allegations: tribe members were told that the samples would be used for diabetes research, but that they were actually used without permission in unrelated studies of schizophrenia, inbreeding, and theories of migration that ran contrary to the tribe’s beliefs regarding their origin
- Complaint alleged the following claims: lack of informed consent, breach of fiduciary duty, fraudulent concealment, emotional distress, conversion, violation of civil rights, and negligence

- Trial court granted summary judgment to the Arizona Board of Regents on procedural grounds, concluding that the Tribe had not complied with the Arizona notice-of-claim statute, A.R.S. 12-821.01
- Arizona Court of Appeals reversed, holding that the Tribe complied with the notice-of-claim statute, and remanded to the trial court for further proceedings
- In April 2010, the parties announced that they had reached a settlement in the case
Havasupai Tribe v. Arizona Board of Regents

- As part of the settlement, the Arizona Board of Regents reportedly agreed to:
  - Formally apologize to the Havasupai Tribe
  - Pay $700,000 to 41 of the Tribe’s members
  - Return the blood samples to the Tribe
  - Collaborate with the Havasupai Tribe on issues such as health, education, economic development, and engineering planning, e.g., assisting the Tribe in seeking third party funding to build a new health clinic and high school
  - Create scholarships for Havasupai Tribe members at Arizona State University, the University of Arizona, and Northern Arizona University

Newborn blood spot litigation

- All 50 states and D.C. mandate newborn screening for specified diseases
- Residual dried “blood spots” left over after testing may be retained or discarded, depending on the state
- Some states permit research use of samples – policies for use of deidentified specimens vary – some require parental consent, others permit parents to request destruction of samples, many state laws do not address at all
- Beleno v. Texas Dept. of State Health Serv. (2009)
  - Class action on behalf of parents, arguing retention and use of sample unconstitutional under “search and seizure” provision of U.S. Constitution (prohibiting “unreasonable” searches and seizures by government)
  - State settled w/ plaintiffs; agreed to destroy all blood spots collected prior to May 2009
    - During pendency of litigation, Texas enacted “opt out” program applicable to specimens collected after May 2009
  - Texas thereafter developed policy on allowable uses of newborn blood spots; website lists studies undertaken prior to policy
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Higgins v. Texas Department of State Health Services (2010):
- Revelation from the Beleno case that 800 dried blood spots were given to the US Armed Forces Pathology Laboratory for use in a forensics database
- Prompting additional lawsuit claiming that the department “sold, traded, bartered, and distributed” DBS without parental permission for “undisclosed purposes” unrelated to the purpose for which the blood was drawn
- Court held parents lacked standing to seek injunctive relief requiring Department to destroy released samples

- 9 families sued the state Department of Health, claiming the retention of newborn dried blood spots without explicit parental consent violated the state’s Genetic Privacy Act, which requires written consent for collection and storage of genetic information
- Lower court ruled the state’s Genetic Privacy Act did not apply to the newborn screening program
- On appeal, state Supreme Court held that Genetic Privacy Act did apply, as blood samples are “genetic information” within meaning of law
  - Law defined “genetic information” to include “medical or biological information collected from an individual” and blood samples fit within the common understanding of “medical or biological information collected from an individual”
- As with Texas, state of Minnesota destroyed blood spots for which consent not obtained for research use

Case law – take home message
No uniform or coherent legal approach to questions of ownership of/control over human specimens and rights to products of research

Some cases, courts favored interests of researchers/institutions over those of tissue contributors
Disputes can nevertheless result in “bad press” for researchers, which may provide impetus for settlement
Recent developments

- Lacks family granted more control over use of HeLa cells
  - In 2013, NIH created HeLa Genome Data Access Working Group in response to strong reactions from the public and from the Lacks family when the full genome sequence of a HeLa cell line was posted in a public database (later removed)
  - The new rules from the National Institutes of Health allow Henrietta Lacks’s family members to have representation to help determine, on a case-by-case basis, the granting of access to the HeLa genomic data

Recent developments

- Major overhaul of Common Rule
  - Goal of refining framework to better address risks in context of modern research environment
  - Issued Advance Notice of Proposed Rulemaking in July 2011 proposing many changes to Common Rule, including:
    - Mandatory data security and information protection standards for identifiable information and rules protecting against inappropriate re-identification of de-identified information
    - Require “written general consent” for research use of pre-existing data originally collected for research purposes and all biospecimens, including de-identified specimens

Recent developments

- Upshot of proposal:
  - Consent would be required whether or not biospecimens “deidentified”
  - ANPRM takes position that eventually all DNA-containing specimens will be “identifiable”
  - IRB review of research w/ deidentified specimens not required, since risks are informational
  - Informational risks best dealt with through enhanced data security protections – to be developed through harmonization of Common Rule and HIPAA requirements
  - Consent can be for future unspecified research
  - For certain “controversial” research, consent may be study-specific with opt-out/opt-in for specific categories of research
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Recent developments
- Study published in 2015 found wide variation in IRB biobanking policies
  - Administrative Directors from 60 institutions regarding:
    1. Consent for future use of biospecimens
    2. Risk assignment for studies using biobanked specimens
    3. Sharing of biospecimens/data
- Study concluded that unclear or divergent policies regarding biospecimen research among IRBs may constitute a barrier to advancing genetic studies and to inter-institutional collaboration

Wrap-Up
- Increasing use of biospecimens for wide range of research
- Mismatch between laws and policies and participant expectations... with sometimes unfortunate consequences (e.g., destruction of samples)
- Continuing areas of ambiguity and inconsistency
- Revision of Common Rule by NIH would create uniform standard for federally-funded/supported research