Tissue and Biobanking

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Agenda

• Promises: the importance of tissue banking

• Challenges
  – Access to tissue
    • What we do...and...what people know/think we do
  – How to obtain consent
  – Return of research results

• Warning: the US Regulations are scheduled to change
Fact:

- Tissue is/has always been an important resource for biomedical education and discovery
Fact:

• Genetic research has made tissue an even more valuable resource
  – The ultimate goal:
    • Large numbers of tissue specimens that are identifiable and updated in perpetuity with medical, social and environmental information that can be used for broad research uses
    • And support Personalized/Precision Medicine
Example:
Personalized Cancer Care

- Disease of Interest
- From all patients collect:
  - Tissue specimen/s
  - Demographics and longitudinal medical information that is continuously updated
    - Therapeutic response
    - Disease progression/regression
Example:
Personalized Cancer Care

• Sub-populations will emerge:
  – Demographics
  – Response to specific therapy/ies
  – Progression of the disease, co-morbidities
Example:

Personalized Cancer Care

• Sub-populations will emerge:
  – Demographics
  – Response to specific therapy/ies
  – Progression of the disease, co-morbidities

• Study sub-populations to find genetic markers, that relate to response to therapy and/or outcome

• Focus drug research on these distinct sub-populations

• As appropriate develop theranostic/s
Personalized Medicine: Reality?

• Yes
  – Herceptin (Trastuzumab) for HER-2/neu breast cancer
    • FDA in 1998 gave simultaneous approval for:
      – Herceptin and
      – Hercep Test - theragnostic
  – Metabolomics
    • Thiopurine-S-methyltransferase (TPMT): 10% have under-active version of this enzyme
      – Appropriate dosing could prevent drug-related morbidity and morality
Personalized Medicine: Caution

• Common, multi-factorial conditions; e.g., hypertension, asthma
  – Multiple subgroups
  – More subtle outcomes
  – Study will require thousands of subjects

• Cancer
  • Tumors are heterogeneous
  • Primary tumor and metastases may not have the same genetic signature
  • Genetic signature changes over time
    – Often in response to therapy

http://online.wsj.com/article/SB10001424052970203961204577267773582045562.html?mod=WSJ_article
Basics of a Biobank

Depositors → The Bank → Withdrawers
Basics of a Biobank

There must be ‘Rules of Engagement’
The Bank Itself

• Structure of the bank
  – Brick and mortar or virtual?
  – Single institution or many
• Type of tissue
  – Clinical vs research
  – Blood only?
• Broad use versus specific disease focus
• Is tissue in the bank: identifiable?
• Does the bank process the tissue?
  – E.g. extract DNA
• Who ‘owns’ the bank? Who is responsible if something goes wrong?
• How is the bank funded?
  – What happens if the bank loses funding?
• What are the rules for deposit and withdrawal?
The Depositors

- Who is allowed to deposit?
  - Affiliates of the bank?
  - Others?

- Is recruitment to the biobank
  - Free-standing request to join the biobank?
  - Added to ‘feeder’ studies

- Informed consent:
  - Whose form?
  - Who obtains consent for the bank?
The Withdrawers

- Who can access tissue?
  - Only those who deposit?
  - Only affiliates of the bank?
  - Other?

- What can they access?
  - Identifiable or de-identified tissue?

- Are withdrawers expected to return results to the bank?

- Is there a charge?
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How Tissue Gets into Research*

• Research oversight is driven by the Common Rule

• And the Common Rule is driven by definitions:
  – **Human Subject**: a living individual about whom an investigator conducting research obtains
    • Data through intervention or interaction with the individual, or
    • Identifiable private information.

• IRB action required if:
  – Data/sample obtained specifically for research
  – Existing data (clinical and/or research) is identifiable

* Obviously US-centric – but any analysis must begin with the details of the relevant regulations.
How tissue gets into Research

QUESTION:
Do donors know that their tissue is going into a bank?
Is consent from the donor required?

ANSWER:
Depends on local regulations.
How tissue gets into Research

• In the U.S., driven by Common Rule definition of a Human Subject
  – “a living individual about whom an investigator conducting research obtains”
    • Data through intervention or interaction with the individual, or
    • Identifiable private information”.

The Common Rule:
Distilled down to two questions

1. Why was the tissue obtained?
   – For research purpose
   – For non-research purpose: e.g., clinical care

2. Regardless of how obtained - is the tissue identifiable?
How the Tissue Was Initially Obtained

IRB action: Informed Consent/waiver

Research

Clinical Care
How the Tissue Was Initially Obtained

- IRB action: Informed Consent/waiver

Research
- Is there excess tissue?
  - YES
  - IRB action: consent or waiver
  - NO
    - Is it identifiable?
      - YES
      - IRB action: consent or waiver
      - NO
        - STOP

Clinical Care
- STOP
Therefore...

• Existing* tissue/data, if not identifiable
  – Not a human subject
  – No worry about consent (Common Rule)
  – No worry about authorization (HIPAA)

• If identifiable
  – Voila! A human subject!
  – IRB must determine need for informed consent and possibly authorization (HIPAA)

* Either from clinical care or an earlier research protocol
Decision pivots on identifiability

- The current and Final Rule state:
  - Identifiable means that the “identity of the subject is or may readily be ascertained by the investigator” or associated with the information or biospecimen
The binary decision:

Identifiable?

YES
Therefore a human subject

NO
Therefore not a human subject
So if identifiability is so important...what elements should be considered?

- General demographics
- Health information
- Genetic information
Consistency Between IRBs/ERBs

• HA!
Reality

Identifiable

Not identifiable
Reality

Identifiable

Pretty much identifiable

‘Sorta’ identifiable

Could-be-perhaps

Not very identifiable

Pretty much not identifiable

Not identifiable
General Demographics
The Science of Re-identification

- Reliance on ‘auxiliary’ information and data sets
- From 1990 US census data*
  - Zip code + DOB + gender
    - Can identify 87% of the population
  - City + DOB + gender
    - Can identify 53% of the population
  - County + DOB + gender
    - Can identify 18% of the population

Common Rule:
How identifiability is defined

• Allows judgment
  – “the identity of the subject is or may readily be ascertained by the investigator or associated with the information”
Reality and the Common Rule

Human Subject
aka identifiable

Not Human Subject
aka not identifiable

IRB #1 Determination
Reality and the Common Rule

- Human Subject
  aka identifiable

- Not Human Subject
  aka not identifiable

IRB #2 Determination
Can the data be deidentified?

- Deleting key data points
- Obfuscating the data
- Coding
- Anonymizing
- Disguising
Reality and HIPAA

- Identifiable
- Limited Data Set
  (dates, town/city, state, zip code)
- De-identified
Enter HIPAA

• Identifiability defined by what is not de-identified
  – Two Safe Harbor Methods
    • Stripping of 18 HIPAA identifiers
    • “...a person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable.”
Identifiability: the 18 identifiers (1)

- Names
- Geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial 3 digits of the zip code if, according to the current policy available from the Bureau of the Census
  - The geographic unit formed by combining all zip codes with the same 3 initial digits contains more than 20,000 people; AND
  - The initial 3 digits of the zip code for all geographic units containing 20,000 or fewer people is changed to 000.
Identifiability: the 18 identifiers (2)

- Dates (except yr) directly related to an individual (e.g., DOB, discharge date, date of death) and all ages over 89 and all elements of dates (including yr) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
- Telephone numbers
- Fax numbers
- Electronic mail addresses
- Social Security Numbers
- Medical Record Numbers
- Health plan beneficiary numbers
- Account numbers
Identifiability: the 18 identifiers (3)

• Certificate/license numbers
• Vehicle identifiers and serial numbers, including license plate numbers
• Device identifiers and serial numbers
• Web Universal Resource Locators (URLs)
• Internet Protocol (IP) address numbers
• Biometric identifiers, including finger and voice prints
• Full face photographic images and any comparable images; and
• Any other unique identifying number, characteristic or code
Enter HIPAA
Health Insurance Portability and Accountability Act
An example of a privacy rule/law

• Identifiable
• Limited Data Set
  – Dates and limited geocodes
• De-identified
Genetic Data

• Unique
• But alone not sufficient to be identifiable
Genetic Information

• Single Nucleotide Pairs (SNPs)?
  – How many?
• Whole exome sequence?
• Whole genome sequence?
Think ‘fingerprints’

• You find my fingerprints on the murder weapon...can you identify me?

• Maybe
  – NO:
    • If I have never had my fingerprints formally taken
  – YES:
    • If my fingerprints are on file
Genetic Analysis

• Do enough reference sets exist to allow for re-identification of most individuals?
• On what scale?
• Consider...
  – PI obtains 500 fully anonymized specimens: ICD9 codes-> asthma plus steroids
    • Recognizes two individuals from genetic pattern...
    • Both individuals had been in prior studies.
Reality and Geneticists

‘Genetic data’ should be considered identifiable

‘Genetic data’ unique – and only theoretically identifiable
So What’s an IRB/ERB to do?

- Reality
- Common Rule
- HIPAA
- Geneticists
- Other Geneticists
Identifiability of whom?

• Just the person donating the tissue?
• What about genetically related family members?
  – My brother has Huntington’s gene
  – Twin studies
• What about communities
  – BRCA1 and 2 and the Ashkenazi Jewish population
Participant Expectations

—De-identification of my tissue does not make any difference to me...I still want to control how it is used.
Questions:

• Is it possible to truly de-identify a biospecimen?
• Who ‘owns’ the answer?
• How to deal with conflicting definitions of identifiability?
• Should we just consider all tissue identifiable?
Summary

• Existing specimens (from clinical or research) that are de-identified are NOT considered human subjects.

• Hence not covered by the regulations.
  – Secondary use allowed without IRB approval.
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  – Secondary use allowed without IRB approval.

Do you agree with this approach?
An investigator has just finished a study of Diabetes and has samples from 500 participants left over.

- A colleague who is also studying diabetes asks for access to these specimens for a specific protocol.
- The biobank director asks that the specimens be placed into the biobank.

**Question:**

- Are both of these simple secondary research?
- Do they each require different consideration?
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  – How to obtain consent
  – Return of research results
Clinical Consent

THE PROCEDURE: I understand that I am about to have abdominal surgery for a horrible cancer. There are many risks involved, including for example, death from anesthesia or the surgery itself.

DISPOSITION OF EXCESS MATERIAL: I understand that blood or other specimens removed for necessary diagnostic or therapeutic reasons may later be disposed of by the hospital. These materials also may be used by the Hospital, or other academic or commercial entities, for research, educational purposes (including photographing), or other activity, if in furtherance of the Hospital’s missions.

My signature certifies that all of this is fine with me.

Signature ___________________________ P. Pearl O’ Rourke    Date ___7/12/15______
Clinical Consent

THE PROCEDURE: I understand that I am about to have abdominal surgery for a horrible cancer. There are many risks involved, including for example, death from anesthesia or the surgery itself.

DISPOSITION OF EXCESS MATERIAL: I understand that blood or other specimens removed for necessary diagnostic or therapeutic reasons may later be disposed of by the hospital. These materials also may be used by the Hospital, or other academic or commercial entities, for research, educational purposes (including photographing), or other activity, if in furtherance of the Hospital’s missions.

My signature certifies that all of this is fine with me.

Is this enough? What about banking?

Signature ____________________________ P. Pearl O’Rourke  Date ______ 7/12/15 ______
Broad Research Consent

By signing this consent, you agree to have your specimen (blood) placed in a research bio-repository for future research on anything by anyone.

Signature _______________________________ Date 7/12/15

P. Pearl O’ Rourke
Research Consent

By signing this consent, you agree to have your specimen (blood) placed in a research bio-repository for future research on anything by anyone.

Signature ___________________________ Date _____________

P. Pearl O’ Rourke

Does such a blanket statement cover the following?

- Full genome sequence
- Development of a chimera
- Creation of an immortalized cell line
- Creation of a pluripotent stem cell line

- Note that pluripotent stem cells can theoretically become any cell line in the body…including gametes
Specific Research Consent

By signing this consent, you agree to have your specimen (blood) used for Diabetes Research. Your tissue will also be placed into a Tissue Bank.

Signature ___________________________ Date __________

P. Pearl O’ Rourke

7/12/15
Specific Research Consent

By signing this consent, you agree to have your specimen (blood) used for Diabetes Research. Your tissue will also be placed into a biobank.

Signature ____________________________ Date __________

Did you know that….

• Your specimen could be stripped of identifiers
• Then shared with another researcher and used for other research; e.g.,
  • Schizophrenia
  • Reproductive research
  • Stem cell derivation
What should be in the consent form?

• Purpose of the research
  – What is biobanking
  – How specimens will be stored and used

• What is required of you
  – Sample acquisition
  – Access to data

• Potential benefits
  – Few direct benefits - Return of results?
What are the risks?

• Tissue acquisition – rarely a risk
• Loss of privacy with potential discriminatory uses of the data
  – Is the risk elevated with genetic research?
• Return of Results: Burden of information
  – For yourself
  – For your family members
  – For your ‘community’
But remember:
There is often no consent

Is this a problem?
But remember:
There is often no consent

- The regulations clearly allow the use of tissue without the consent of the individual
  - Left-over clinical tissue that has no identifiers
  - Secondary use of tissue that has been rendered de-identified
  - Identifiable tissue pursuant to a waiver of informed consent
But remember:
There is often no consent

• The regulations clearly allow the use of tissue without the consent of the individual
  – Left-over clinical tissue that has no identifiers
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• How does this play out with the growing sentiment regarding an individual’s control over their own data and tissue?
The Immortal Life of Henrietta Lacks
Rebecca Skloot

- The origin of the HeLa cell line
- Extra biopsies taken for research purposes – without consent or knowledge of the patient or her family
- Biopsies taken in the 1950s – prior to the creation of IRBs
Newborn Blood Spots (NBS)

- State-specific programs for diagnosis of specific diseases in neonatal period
- In some states the NBSs were kept and made available for research purposes
- Fact:
  - These NBSs are an invaluable research resource
  - Status of consent/knowledge of – at best variable
Ownership of Data and Tissue

- Havasupai Indians and Arizona State University
  - 1990-1994 100 tribe members provided blood samples pursuant to an informed consent
    - Consent “to study the causes of behavioral/medical disorders”
    - Presumption was Diabetes research
  - Years later – secondary use for schizophrenia and migration studies
HAVASUPAI
BLOODCASE
VICTORY

PLEASE ATTEND A 10:00AM MEETING
ON FRIDAY, MARCH 12TH AT THE
COMMUNITY CENTER FOR MORE
INFORMATION
Havasupai Indians and Arizona State University

– Settlement:
  • $700,000 to 41 tribe members
  • Return or remaining specimens to the tribe for burial
  • Other forms of assistance to the community

– Arizona State University
  • $1,700,000 in legal fees

– Compensation for unauthorized use of DNA
So, what to do?

– Maintain the status quo: specimens with and without consent
  • Educate and notify all patients and research participants

– Obtain consent from any person whose tissue will be used in research *(note: some new proposals)*
  • Logistical challenge
  • Potential bias of specimen collection

– Allow people to opt-out
  • Logistical challenge
  • How reliable can an opt-out be?

– Other???
Final comments

• Tissue is needed for research
• A lot of tissue is needed for research
• Genetics highlights existing challenges that have never been well addressed
  – E.g., what is identifiable? Who is a subject? Community risk? Return of research results?
• Public needs and expectations must be addressed
The Perfect Storm?
The Perfect Storm?
The Perfect Storm?
The End
Changes to the US Regulations
The Common Rule

– A few highlights relevant to Tissue Banking

• Definition of human subject
  – Now includes biospecimens as well as information
  – Functionally no real change

• Plans for reassessing the determination of what is identifiable
  – Possible future determination could determine biospecimens to be identifiable.

• Expansion of exempt categories re: identifiable tissue and information
  – Will allow for additional ways to get identifiable tissue into research
Existing identifiable material – Final

Can Exemption #4 be used?

YES

NO

Publicly available

De-ID’d

Identifiable

HIPAA

‘Routine IRB review’

Broad consent given?

YES

Limited IRB review c/w use?

YES

NO

Secondary research

STOP