

Day one-session II-Biospecimen/Biorepositories  
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**Investigator experience: Challenges and obstacles obtaining rare disease specimens and the use of registries**

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Abstract

A major obstacle to biomedical research in rare diseases is the lack of human biospecimens from patients with these diseases. Obstacles that investigators face in obtaining such specimens include the lack of contact with sufficient subjects to get an appropriate number of specimens, and the challenge of setting up multi-institutional collaborations to increase the number of subjects. The burden of complying with regulations at numerous institutions is a significant factor discouraging collaboration. Registries of people with rare diseases can lower many of these barriers by creating cohorts of subjects for study, and can often lower the burden of regulatory issues. Some registries are linked to biorepository activity and can serve as a pre-existing bank of specimens. Complexities of biospecimen procurement that include the lack of availability of fresh/frozen tissue and lack of standardized or even adequate biospecimen procurement infrastructure at many medical institutions are issues that are continuing challenges.



*Uniting Rare Diseases*

*Advancing Rare Disease Research:  
The Intersection of Patient Registries, Biospecimen Repositories  
and Clinical Data*

*Session II  
Biospecimens/Biorepositories*

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*Challenges and Obstacles Obtaining Rare Disease  
Specimens & and the Use of Registries*

# 2 broad themes in biospecimen research

## **Hereditary genetics:**

Finding genes responsible for the disease

Target specimens: blood, oral swabs

Major issues: recruiting familial cohorts; privacy

## Research Outcomes:

- Genetic animal models
- Molecular insights into mechanism

## Direct Clinical Outcomes:

- Predictive genetic tests

## **Disease phenotype:**

Understanding how the disease manifests itself in organs, tissue and biofluids

Target specimens: mostly tissue but could be anything

Major issues: complexity /difficulty of tissue collection

## Research Outcomes:

- Understanding of disease mechanism
- Candidate biomarkers of disease

## Direct Clinical Outcomes:

- Tests of disease state

## Ultimate Clinical Outcome:

- Therapies

# Challenge #1: Recruitment

- Issues
  - Rare diseases are rare
  - Limited number of investigators studying the disease
- Solutions
  - Networks of investigators/colleagues (ad hoc)
  - Advocacy groups/foundations
    - Pro-active targeting of physicians/clinics
    - Entry point for self-recruitment
  - Formal registries
  - Internet linking all of the above (self recruitment)

# Challenge #2: Regulation

- Well-intentioned regulation on many fronts
  - Human subjects research
  - Private health information
  - Clinical infectious agent
  - Animal research
  - Laboratory chemical, radiation and biohazards
  - Shipping of biohazards

# Challenge #2: Regulation

- Requirements
  - Training
  - Manuals and standard operating procedures
  - Review and approval of protocols
  - Documentation of training, review and protocol-specific events
  - Inspections of documents and facilities
  - Periodic retraining of personnel
  - Periodic resubmission of all protocol documents for review

# Challenge #2: Regulation

- The cumulative effects of regulation on an individual investigator or potential investigator may be daunting
  - Personal time
  - Expense of personnel required to comply with regulation
- Bureaucratic burdens are particularly high barriers to investigators new to human subjects research, institutions without robust research infrastructure and for rare disease research

# Challenge #3:

## Complexity of tissue collection

- Many molecular constituents of tissue that reflect the disease state are extremely labile
  - Ideally tissue should be frozen within minutes of blood supply disruption
  - Rapid tissue procurement is NOT standard clinical procedure
  - Many non-academic medical centers do not have facilities for deep freezing ( $< -70^{\circ}\text{C}$ ).
    - Hard to exclude non-academic centers when dealing with some rare disease types
- To obtain viable cells from tissue:
  - Tissue processed and stabilized in special media
  - Should reach research labs in  $<24$  hours

# Challenge #3:

## Complexity of tissue collection

- Very difficult to obtain tissue specifically for research purposes
  - Risk and expense of surgery or biopsy of internal organs is a high hurdle
- Most tissue comes from:
  - “left-overs” from clinically-required surgery
    - Cancer resection, organ explant
  - Autopsy
    - Most autopsy tissue is severely degraded due to post-mortem time
    - “Warm autopsy” programs are rare

# Challenge #3:

## Complexity of tissue collection

- Formalin-fixed paraffin-embedded (FFPE) tissue
  - A by-product of routine tissue processing in clinical diagnostic procedures
- Plus side
  - Available from most surgeries and autopsies
  - Usually archived by medical institutions for years
- Negative side
  - Biomolecules are highly degraded by processing
  - Number of analyses that can be performed on FFPE tissues more limited than on frozen samples

# Challenge #4:

## Timing of biospecimen collection

- Diseases manifest themselves over time
  - Different types & degrees of organ damage
  - Different clinical implications
- Obtaining biospecimens from early manifestations of disease is often difficult
- Obtaining samples of end-stage tissues and organs that are not usually surgically resected is also difficult
  - Metastatic, unresectable cancer
  - End-stage diseased organs not suitable for transplant
    - e.g. central nervous system

# Challenge #5:

## Obtaining clinical information

- It is difficult to anticipate all clinical data needed for biospecimens when collected prospectively
- Highly technical clinical data is time consuming and expensive to collect and may not be required for most studies
- Data collection may be hindered by regulatory issues

# Challenge #5:

## Obtaining clinical information

- Detailed medical information is often buried in dense and fragmented clinical records
  - No uniform standards for clinical data
  - Not all information is digital in nature
  - Some digital information (e.g. radiology) is highly technology intensive (proprietary formats and software, expensive hardware)
  - Getting physicians/medical centers to comply with requests is time consuming
- Patient/subject is best advocate for obtaining clinical records
  - Problem if requests are highly technical in nature
  - Problem if subject is deceased

# Summary

- Challenges
  - Rarity & recruitment of subjects
  - Regulatory burden
  - Availability & complexity of tissue procurement
  - Availability of detailed clinical data
- Solutions
  - Rare disease registries
  - National biospecimen/biorepository programs
- Questions for future directions
  - Coordination of existing resources
  - Creation of new national resources