Tissue Tug of War: Issues in tissue procurement for research and banking

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Tissue Tug of War

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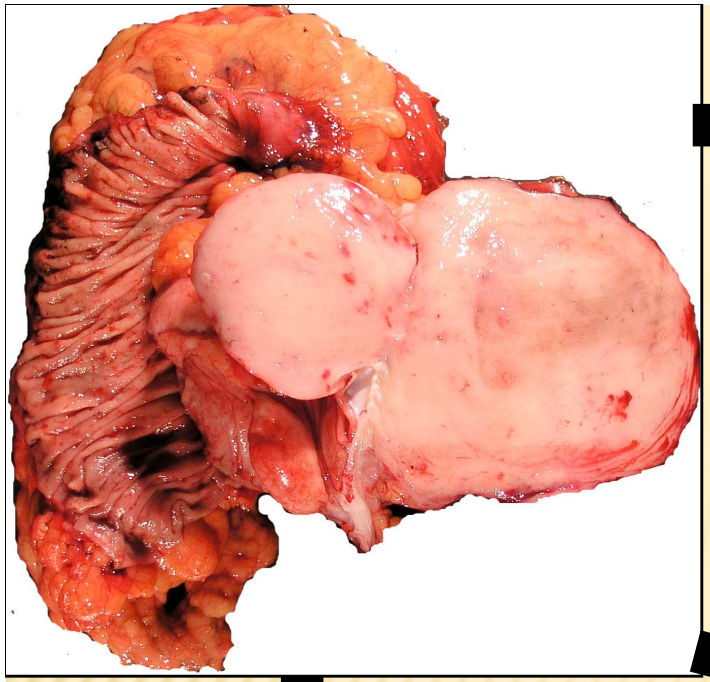


Fresh and/or frozen for special diagnostic studies

Frozen IHC/Immunofluorescence
Flow cytometry
Cytogenetics
Molecular diagnostics

Other procurement

Formalin-fixation
Paraffin-embedding

Paraffin block

Research

Transplantation/
Commercial uses

H&E histology
Special stains/IHC/FISH
Molecular diagnostics

The elephant in the room….

- Most tissue procurement is for research and is not part of my clinical responsibility
- I don't get reimbursed for tissue procurement
- Tissue procurement is a pain in the %*#!

Topics for today's talk

- Ethics of tissue procurement
- Laws governing tissue "ownership"
- Some of the logistics of tissue procurement

Tissue procurement: Ethical considerations

- Welfare ("risk/benefit")
  - Of the individual
  - Of society ("greater good")
- Autonomy of the individual
  - Decision to participate

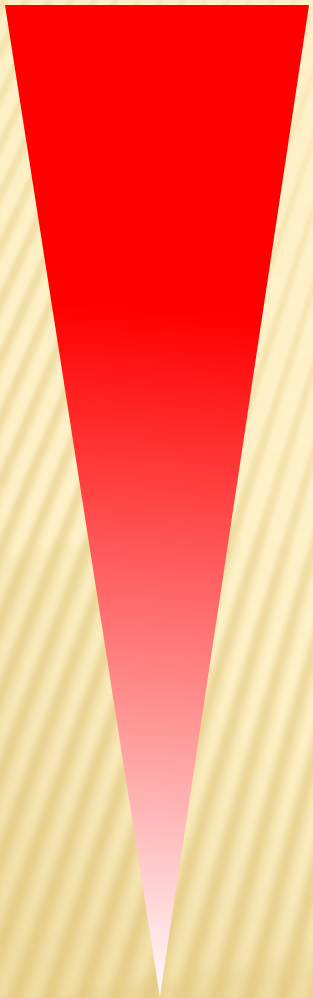
The values of welfare and autonomy are overlapping, vague, and contested.

Mark. S. Stein

Informed consent for tissue procurement in "minimal risk" medical research is one of the major flashpoints in bioethics today.

Chris Moskaluk

Risk of tissue procurement: a gradient



Biopsy/surgical procedure procedure carried out *specifically* for the research to collect tissue

Tissue collection from clinically-indicated procedure *prior* to Pathology assessment

Remnant ("left-over") tissue collected from clinically-indicated procedure

Risk of tissue procurement: a gradient

- Most would agree that tissue obtained specifically for research and tissue obtained from clinical specimens *prior* to pathologic examination constitutes greater than "minimal risk" and the subject must be asked for consent

Risk of tissue procurement: a gradient

- Much research carried out on remnant tissue confers “minimal risk” to the subject
  - Risk is loss of privacy
  - The debate is whether such research can be carried out with waiver of informed consent

Informed consent: the cornerstone of autonomy in medical research

- All agree that informed consent for every use of tissue obtained conforms to the highest possible ethical standards for individual autonomy
- There are many practical and financial issues that impede the implementation of this principle, thus potentially delaying research for the benefit of the greater society

Issues that impact informed consent for using human tissue

- Most tissue research is on remnant tissue and is “minimal risk”
  - Most tissue research does not impact the subject’s clinical care
  - Most tissue research does not involve data that would be prejudicial to the subject

Issues that impact informed consent for using human tissue

- It is *impractical* to obtain consent for many studies
  - Most research is carried out by investigators that do not have a relationship with the subject
    - Difficult access for research personnel to subjects at point of medical care
    - Clinical personnel may not be motivated or too busy to effectively obtain consent for research they are not directly involved with

Issues that impact informed consent for using human tissue

- Pre-existing samples in clinical archives and tissue banks
  - Generally not consented for a specific research project
  - Obtaining specific informed consent retrospectively is problematic

Waiver of informed consent

- Under current Federal law, an IRB may grant waiver of informed consent if:
  - The specimens are already present
  - The research is of minimal risk to the subject
  - The research could not practically be performed without the waiver
- There are no proscribed criteria for “minimal risk” and “practicality”
  - Interpretation at the discretion of the IRB

Tissue associated data that may confer more than “minimal risk”

- Experimental diagnostic or prognostic tests that could be used to in therapeutic decision-making
- Prognostic data on disease severity/recurrence
- Genetic data of disease risk
- Diagnosis is associated with prejudicial activity

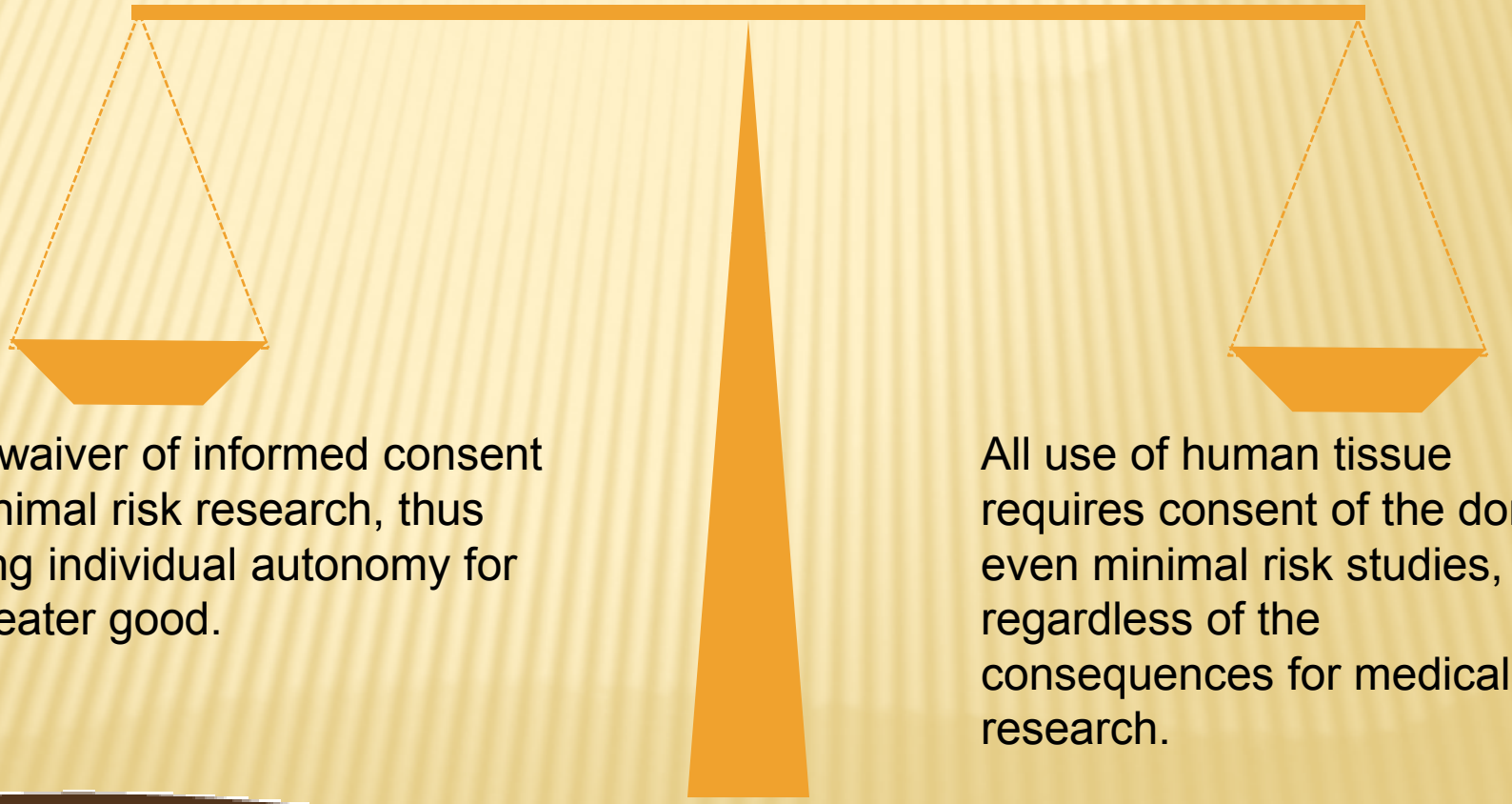
Who decides what is minimal risk?

The local IRB, on a case by case basis.

Informed consent for minimal risk tissue research: The ethical balance

Social welfare

Individual autonomy



Allow waiver of informed consent for minimal risk research, thus denying individual autonomy for the greater good.

All use of human tissue requires consent of the donor, even minimal risk studies, regardless of the consequences for medical research.

Proposed changes to Federal human subjects research laws

- Changes may eliminate waiver of informed consent for ANY tissue sample (clinical or research)
  - This includes archival paraffin blocks
- Public comment period closed Oct. 26, 2011
- Draft revisions to be later disclosed for additional public comment period

http://www.hhs.gov/ohrp/humansubjects/anprm2011page.html

Who "owns" surgically-resected tissue?

- The patient's view
  - "it is part of my body – I own it"
- The surgeon's view
  - "I took it out didn't I?"
- The pathologist's view
  - "as soon as it's out of the patient, it's mine"
- The medical institution's view
  - "we own everything"

“Ownership” is a relative concept for tissue specimens

- Overlapping purview, rights and responsibilities for tissue specimens
  - Legal restrictions in place for many uses of tissue
- Shared between patients/research subjects, scientific investigators, pathologists and medical institutions
  - Surgeons have no inherent ownership rights to the tissues that they resect

Who has purview over tissue specimens?

- The patient retains certain rights to tissue specimens in the clinical and research realm
  - Patient may request clinically-archived tissue sent to other health professionals/entities
  - Research subject may withdraw from research project and have remaining tissue samples destroyed

Who has purview over tissue specimens?

- The Pathologist makes independent judgments on the sampling, retention and discarding of resected tissue for clinical purposes
  - Documented and enforced by accrediting agencies (JCAHO, CAP)

Joint Commission on Accreditation of Healthcare Organizations

Standard QSA.13.01.01
Elements of Performance:

1.Surgical specimens are sent to a pathologist for evaluation unless exceptions are identified by the clinical staff.

2. The clinical staff, in consultation with a pathologist, decides when an exception to the submission of surgical specimens to pathology should be made using the following criteria:

- The quality of care has not been compromised.
- The surgical specimen removal is routinely verified by another clinically acceptable means.
- The removal of the specimen is documented in an authenticated operative or other official report.
- The exception is authorized by law, the requirements of a training program, or the clinical staff laws or rules and regulations.

Who has purview over tissue specimens?

- A researcher receiving tissue may make independent decisions on its use within the bounds of reviewed research protocols and retains intellectual property rights to discoveries made with the tissue

Who has purview over tissue specimens?

- The institution has stewardship responsibilities and rights to tissue in both clinical archives and research banks
  - The institution has ultimate physical claim to resected tissue specimens
  - The Pathology Dept. is usually ceded day to day control and decision-making over clinical tissue specimens

Laws concerning tissue ownership

- Federal regulations
  - There is no overarching Federal legislation dealing with this specific issue
  - "The Common Rule" (45 CFR part 46) deals with tissue as part of human subjects research
  - HIPAA Privacy Rules (45 CFR parts 160 & 164) impacts release of medical information that affects tissue use
  - CLIA regulations (42 CFR 493) cover clinical archival tissue specimens

Laws concerning tissue ownership

- Federal regulations (cont.)
  - The National Organ Transplant Act (1984 Pub.L. 98-507) explicitly outlaws the sale of human organs
    - Reasonable fees for procurement can be assessed to cover costs

Tissue banking for transplantation and the Law

- Covered by Federal law and statutes
  - 1984 Pub.L. 98-507
  - 21CFR Parts 16 & 1270
- Regulated by the FDA
- Accreditation through several organizations

Excellent review:
Eisenbrey & Frizo, Clin Lab Med 25:487-498, 2005

Laws concerning tissue ownership

- State law
  - Most States have legislation dealing with human subjects research, but not biospecimen ownership
    - New York state law allows remnant biospecimens to be used without informed consent

cancerdiagnosis.nci.nih.gov/pdf/50StateSurvey.pdf

Laws concerning tissue ownership

- Some case law exists regarding tissue used in human subjects research
- Many issues have not been challenged in court to resolve priority of overlapping claims (clinical use vs. research use)

Tissue ownership: case law

- Moore vs. Regents of the U. of California
  - Excised tissue is no longer the property of the patient
  - There was a fiduciary breach because informed consent was not sought
- Greenberg vs. Miami Children's Hospital Research Institute
  - Donated tissue is no longer the property of the research subject
- In both cases it was found that research subjects do not have property rights to discoveries or reagents created from their biospecimens.

Tissue ownership: case law

- Catalona vs. Washington University
  - Biospecimens collected by a researcher at an institution belong to the institution, even if a subject expresses a wish to have the specimens move to another institution with the researcher.
  - My characterizations:
    - If you want to own your tissue you should keep it in your body
    - “Once you make a gift, you can’t take it back”
    - “The institution does indeed own everything”

Tissue “ownership”: the Pathologist’s role

- Case law suggests a patient no longer has “ownership” over clinically-resected tissue in the absence of a specific contractual agreement
  - Most medical institutions cede oversight of tissue to their Pathologists
- A specific informed consent document probably serves as a contractual agreement
  - If the surgical/biopsy procedure is specifically for research, the Pathologist may acquiesce normal procedures
  - If the document specifies “remnant” tissue, it is the Pathologist’s call as to what remnant is

Just because you own it, doesn't mean you can do whatever you want with it

- "Standard of care" for your clinical purview (tissue diagnosis) must be followed
- You can't sell it
- Research with tissue that is identifiable to a specific individual *is* human subjects research and is covered by "The Common Rule" (45 CFR part 46) and *must* be subjected to IRB review

The IRB decides if you can use it for research, not you.

Uses of human tissue allowable under the Common Rule

- Tissue that is identified (including coded-linked specimens) can be used in research if:
  - The patient consents and the IRB approves
  - The IRB approves waiver of consent
- If the tissue is completely stripped of all identifiers (including codes) it is not now considered human subjects research and is considered exempt research
  - Pending revisions to the law may change this

Activities not covered by the Common Rule

- Anything that is not research
  - Definition of "research": *a systematic investigation designed to develop or contribute to generalizable knowledge.*
    - Thus, research must involve:
      - more than one individual
      - creation of new knowledge

Activities not covered by the Common Rule

- Exempt activities
  - Case studies
  - Use of tissue in education
  - Use of tissue to set up a clinical assay
  - Use of tissue as controls for clinical assays

What about archival paraffin blocks?

- Tissue blocks are recognized parts of the patient's medical record
  - In general, medical records are the property of those who prepare them, not the property of the patient
    - The patient has rights to review and share their medical records
  - Federal regulations (CLIA) requires block retention for 2 years and slide retention for 10 years
    - Implicit in this is the control of the tissue block by the institution that made it
  - Accrediting organizations (JCAHO & CAP) require block retention for 10 years

What about archival paraffin blocks?

- Conflict: Patient requests archival tissue blocks to be sent to research centers.
  - No definitive case law (that I am aware of), but existing Federal statutes suggest an institution is in its rights to deny such a request.

What about archival paraffin blocks?

- Remedies
  - If part of a clinical trial that includes a prospective surgical procedure, the trial design should include research tissue procurement
  - The subjects wishes should be honored whenever possible without exhausting the archival tissue
    - Unstained slides or a core sampling of tissue at the institution's discretion
    - Release of redundant block

If Pathologists have a large role in the "ownership" of tissue, what else do we own?

- Tissue procurement
  - Any tissue specimen not specifically exempted from pathologic review is the responsibility of the clinical Anatomic Pathology service
  - Thus non-clinical tissue procurement *must* interact with this service

Tissue procurement: Our choices

- Minimal changes in practice pattern, with no ownership of the service
  - "We'll let you know when we're through with it"
- Integration of procurement into service, with professional component for quality control
  - Embrace it and do it well

Tissue procurement logistics: The ideal case

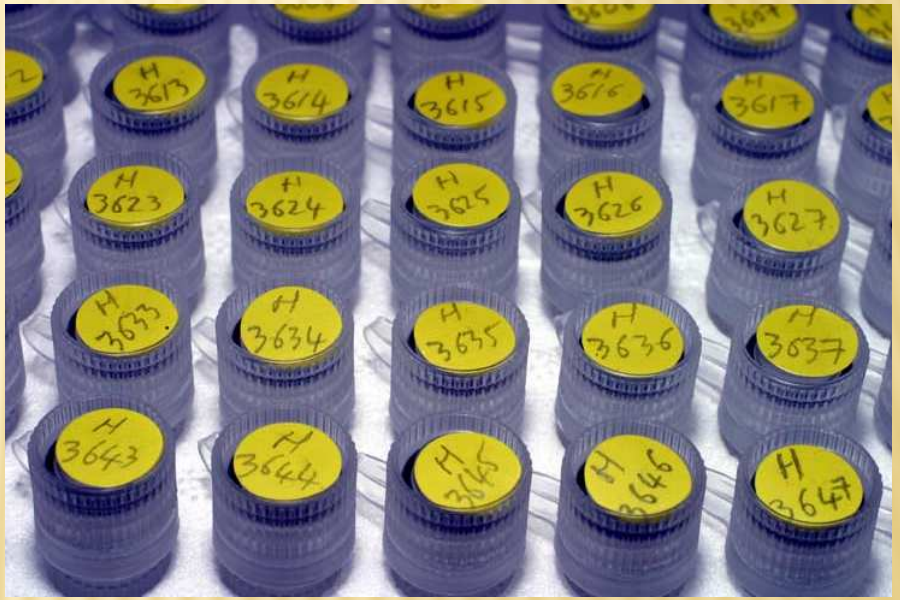
- Tissue procurement & tissue/biospecimen bank under one roof (Biorepository)
  - Staff prescreens procurement requests for IRB status and level of sample identification
  - Staff handles regulatory issues, procurement, sample processing, banking and data annotation

Tissue procurement logistics: The ideal case

- Requests are matched to surgery schedule and to unanticipated samples arriving in surgical pathology
- Samples are obtained from specimens in as short a time frame as possible, working closely with clinical staff
  - "Remnant" status can and should be decided while case is in process

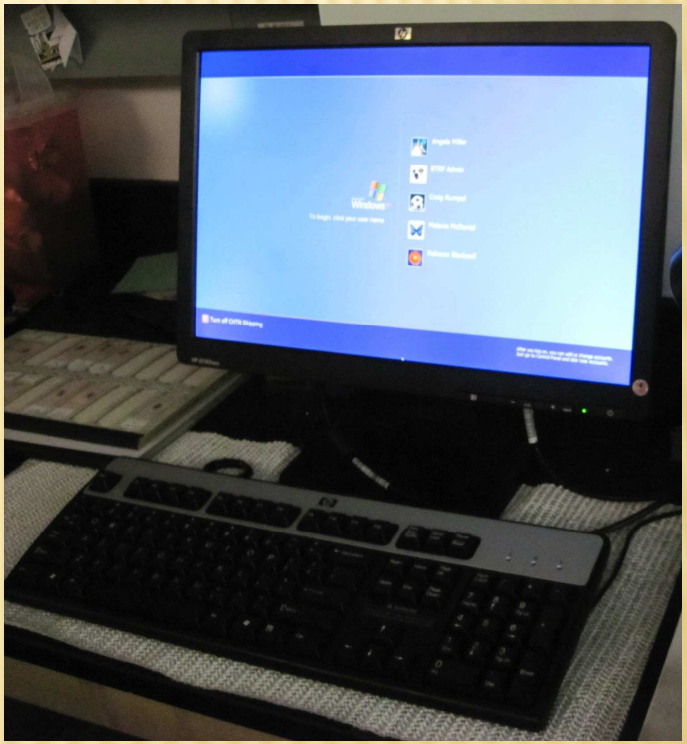
Tissue procurement logistics: The ideal case

- Samples are placed in containers labeled with coded designation ONLY.
  - Most common error as this research “best practice” deviates from clinical “best practice”.



Tissue procurement logistics: The ideal case

- Code, subject information and sample data (procurement time, weight, etc) are recorded
  - Digital database better than paper records
    - Digital databases should conform to HIPAA security standards



Tissue procurement logistics: The ideal case

- Several sources of information for Biorepository "best practices"
  - NCI Best Practices document
  - NCI Office of Biorepositories & Biospecimen Research (OBBR)
    - http://biospecimens.cancer.gov/default.asp
  - International Society for Biological and Environmental Repositories (ISBER)
    - http://www.isber.org/

Should Pathologists be reimbursed for tissue procurement and archival block retrieval?

- Yes

Can Pathologists be reimbursed for tissue procurement and archival block retrieval?

- The answer is up to you.
  - Educating investigators
  - Lobbying administration

Precedents and examples

- CPT 2011 allows reimbursement for examination and selection of archived material for molecular analysis
  - 88363, ~$38 Medicare recovery
- Tissue procurement fees at academic medical centers
  - $25-$40
- NIH-sponsored national programs
  - Cooperative Human Tissue Network: $40
  - National Disease Research Interchange: $125

How quickly do we need to procure tissue?

- How long can you hold your breath?
  - Anoxia will cause significant changes in signal transduction pathways in seconds to minutes
    - Post-translational modifications (phosphorylation, etc.)
  - Labile biomolecules will degrade in minutes to hours
- No such thing as a “pristine” sample
  - Intraoperative “warm ischemia” time already has significantly altered some biochemical tissue attributes before reaching Pathology

How quickly do we need to procure tissue?

- Conflicting studies/conclusions on rate of degradation of biomolecules “on the bench”
  - Greatly depends on specific biomolecule
- In general, faster is better
  - <1/2 hour from leaving subject’s body is great
    - “frozen section” speed
  - <1 hour from leaving subject’s body is good
  - <2 hours from leaving subject’s body may be acceptable
  - “overnight” even with refrigeration is NOT acceptable

How quickly do we need to procure tissue?

- DO NOT EQUATE HISTOLOGIC QUALITY WITH BIOMOLECULAR INTEGRITY
  - "Good-looking" histology may have badly degraded RNA / protein content
- Tissue obtained for molecular studies must be acquired on a faster time frame than histology
  - Optimal transport from Surgery to Pathology
  - Rapid specimen assessment in Pathology
  - "Remnant" status should be decided before case is blocked in

Bottom lines

- The disposition of tissue depends on the specifics of the approved research protocol and the degree of informed consent
- Tissue procurement of “remnant” tissue are at the discretion (and mercy) of the Pathologist who has been designated to the specimen

Bottom lines

- Having been given guardianship of clinical tissue specimens, Pathologists should not divorce themselves from research tissue procurement
  - Resources should be provided or charges should be expected for such services
  - Best practices should be followed
    - Procure as quickly as possible!

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