173 ENCORE! Handling Patient Diagnostic Materials: Ethical, Social, and Legal Issues

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Thousands of archived diagnostic slides and paraffin blocks reside in individual pathology laboratories, each of which can be linked to an individual patient and potentially to a wide variety of patient specific data, while new federally funded research grants and projects encourage inter-institutional sharing of tissues. This session will help you understand critical ethical, legal, and social issues and implement protocols for efficient handling of requests for archived diagnostic materials. You will leave with the ability to:;;Understand the legal and ethical responsibilities surrounding the use of diagnostic archival blocks for current or anticipated clinical care and for research studies.;;Fulfill requests from outside institutions for diagnostic archived patient materials.;;Recognize emerging developments in federal attitudes about the use of tissues in research studies and the demands these will place on pathology labs.

- Understand pathologists' legal and ethical responsibilities surrounding the use of diagnostic archival blocks for current or anticipated clinical care (including clinical trials) and for research studies.
- Determine how to fulfill requests from outside institutions for diagnostic archived patient materials.
- Recognize emerging developments in Federal (NCI/NIH) attitudes towards use of tissues in research studies, especially inter-institutional tissue sharing, and the demands these will place on pathology labs.

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Entire Pathology Team
Laboratory/Business Management
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Patient Diagnostic Materials: The Reality

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www2.timesdispatch.com/lifestyles/2010/sep/11/i-tiss0802-ar-497721/

- Richmond Times-Dispatch, September 2010
- *"Tumor tissue an emerging issue in cancer research"*
- "All Niki Perry wanted were pieces of her own brain, and she got angrier by the day as she tried to get them."
- "… in March, she ran into weeks of red tape and a Catch-22 when the hospital balked at sending slides to another hospital until she was officially in a trial there, though she needed the tissue to even enter the trial. (The hospital mailed the slides at the end of May.)"
- "The 37-year-old ….wrote that she felt the hospital, which has said it will not comment on her case, got 'in the way of my trying to save my own life.'"

Why is this important to me?

- Biotech advances permit extraction of molecular, protein, genetic data from FFPE
- *Personalized medicine*
- Patient samples with unique rules
- Practicing pathologists are confused about how to handle requests for use of these materials in research
- Hint: Possession does not equal permission to distribute

Objectives

- 1. Understand pathologists' legal and ethical responsibilities surrounding the use of diagnostic archival blocks for current or anticipated clinical care (including clinical trials) and for research studies.
- 2. Determine how to fulfill requests from outside institutions for diagnostic archived patient materials.
- 3. Recognize emerging developments in Federal (NCI/NIH) attitudes towards use of tissues in research studies, especially inter-institutional tissue sharing, and the demands these will place on pathology labs.

Disclosures

- No financial conflicts of interest
- The opinions expressed here are those of the speakers and do not represent the official positions of our institutions

Case #1

- Mrs. Smith had a breast biopsy in 2006 at Main Street Medical Center (MSMC), and was diagnosed with benign fibrocystic change. In 2008, she contacts the Pathology Department at MSMC and asks for her tissue to be returned to her. The secretary begins asking Mrs. Smith where the tissue will be sent and for what purpose she is requesting it. Mrs. Smith asks, "Why are you asking these questions? This is my tissue, and I would like it back, period." What is the status of Mrs. Smith's tissue?
- A. The tissue belongs to the patient and she has the right to request it be returned to her.
- B. The tissue belongs to the Pathology Department. The Department has the right to choose if the tissue is returned to the patient or not.
- C. The tissue belongs to the patient, but the Pathology Department has the legal responsibility to see that it is used properly. Thus, the Department can ask questions of Mrs. Smith in order to ensure she will use the tissues properly.
- D. None of the above

Custodianship vs. Ownership

- *Tissues removed in the course of normal diagnosis and treatment do not have a designated "owner" under Federal or State law, or as the result of case law.*
- *Pathology Departments are the legal caretakers of such tissues, and must abide by all State laws regarding the care of these tissues.*

Custodianship

- Custodianship
  - Required to follow minimal legal standards
  - Duration and conditions of storage, ability to retrieve, how to discard
  - Protect patients' interest in later access
    - additional diagnostic testing
    - legal proceedings.
- Specifics vary by State
- Elements of Trust
- Elements of Trust
  - Transparency must exist within Repository SOP's
    - With Regard to storage/sharing of samples and data
  - SOP's should be submitted to IRB for Review

Ownership of Samples: Case Law

- Moore v. Regents of University of California 793 P2d 479 (Cal 1990)
  - John Moore treated for Hairy Cell Leukemia
  - MD continued to collect samples from Moore after surgery
    - Bone marrow, sperm, blood skin – looking for T-lymphocytes
  - MD Patented cell line from Moore's tissue
  - Must show "interference with his **ownership** or right of possession"
- Greenberg v. Miami Children's Hospital 264 F.Supp2d 1064 (S.D. Fla 2003)
  - Group of patients (children) with Canavan Disease
  - Donated to help develop Diagnostic Test
  - Researchers Obtained Exclusive Rights (Restrictive Cost)

Underlying Themes Patient Ownership or "Financial Interest" Cases

- No specific written law on point
- Case law considered clear that patients cannot derive financial benefits from studies on their tissues UNLESS they agreed to specific terms prior to providing their tissues for research
- Investigators/Institutions accept Risk in Conducting Research
- Research adds value to samples – Property Right might unnecessarily hinder medical research
- Benefit of society outweighs benefit to individual
- Patients Need to show expectation of continued control
- Review Relationship and Review Consent
- Open Issue? In Greenberg the Court held that a trial was need to determine whether Dr. Matalon and MCH had unjustly obtained a financial benefit using the resources provided by the families (Case Settled before trial)

Case Law cont.

- Washington U. v Catalona (2006) 490 F3d 667 (8th Cir 2007)
  - M.D. was developer of PSA test for prostate cancer
  - Instrumental in Developing Biorepository for research
  - Transferred to Northwestern
  - Sent letters to Patients asking them to request transfer of samples from Wash. U. to Northwestern (6000/10000 did)
  - Court: Confirmed right of University to

This is Great News …Right?

- No Specific Laws on Excised/Donated Samples
- Case law says Patients Typically have no Financial/Proprietary Interest in products derived/discovered
- Lack of Legislative Mandates creates Opportunity
  - To Create a Relationship of Trust with Patients
  - Do Not Breach the Trust – **Bad Cases Create Bad Law!**
  - Develop Ethical Guidance and Standards within

NCI Best Practices -Custodianship

- The following issues should be addressed in the governance plan:
- (1) How does the biospecimen resource propose to ensure the physical integrity of biospecimens?
- (2) How does the biospecimen resource propose to ensure the integrity of the human research participant data that accompany the biospecimens?
- (3) What plans and protocols are in place for the distribution of samples to investigators? and
- (4) What are the roles and responsibilities of the biospecimen resource director and his or her institution?

Case #2

- Mr. Johnson had nephrectomy for a 7 cm renal cell carcinoma at Main Street Medical Center. One year later, MSMC Pathology receives a faxed request for one paraffin block of tumor for a research project being conducted at the state university academic medical center. The fax contains a valid university IRB approval for the project and an informed consent form signed by Mr. Johnson. The 2007 slides are reviewed, including 6 blocks of tumor. The diagnosis is confirmed. Assuming Mr. Johnson signs a Departmental release form, what should MSMC Pathology do?
- A. Release a block as requested. The patient wants to participate in the research project and the appropriate documents have been completed.
- B. Refuse to release any materials for research, due to MSMC's custodian responsibilities for the tissue
- C. Discuss the request with the study Principal Investigator, to determine if other materials (ie, H&E recuts, unstained recuts) can meet the research requirements of the project to avoid releasing blocks
- D. Ask Mr. Johnson to sign additional forms from MSMC legal counsel that acknowledge: 1. his wish to send his diagnostic material for research; 2. his release of MSMC's responsibility to care for the block properly
- E. Several of the above (which?)

Case #2, continued

- Review of the IRB and informed consent form reveals that Mr. Johnson will be participating in a clinical trial.
- A telephone call to the study PI reveals that the block is being requested for testing to determine whether or not Mr. Johnson qualifies for the clinical trial.
- Should this information change how MSMC Pathology handles the request?
- Is Local MSMC IRB Review Required?
  - Is MSMC "engaged in research"

Case #2 - issues

- Ethical and legal differences between testing for clinical trials and for research
  - Patient care; affects treatment options
  - If Clinical Trial office exists, may help if involved
- Balance between legal custodial responsibilities and patient wishes
  - Not discussed in law or case law
  - As MDs, responsibility to try to act in best wishes of patient
  - Still need to protect materials for possible future clinical or medical/legal use
  - Is there an exception in treating Cancer Patients under a Protocol
  - What is the status of Therapeutic Misconception when SOC is not a cure ?

Case #2 issues, cont

- What is an IRB?
  - Group appointed to review research proposals involving human subjects at an institution
  - Interpret federal, state, institutional laws
  - Protection of human subjects
  - "human subject" by Federal Law (CFR 41)
    - Living
    - Identifiable
- Types of IRB approval
  - Exemption, expedited, full committee

Informed Consent

- Are/Were samples collected for research purposes or
- Are Samples associated with identifying information
- Then -Informed consent must be obtained from the donor unless appropriately waived by the IRB
- Basic Elements
  - Statement of research, purpose, duration, procedures
  - Risk/discomforts and Benefits
  - Alternatives
  - Plan to protect Privacy/Confidentiality
  - Costs and/or compensation including compensation for injury
  - Whom to contact if injury or questions
  - Participation is Voluntary

Informed Consent: Other Considerations

- A statement regarding secondary uses of the samples. For example,
  - there will be secondary use only after the banked samples have been stripped of identifiers,
  - there will be no secondary use,
  - subjects have option of allowing secondary use, or
  - subjects will be contacted for additional consent in the future for secondary use.
  - When and if samples will be destroyed
  - OHRP recommends that a Certificate of Confidentiality be obtained to protect confidentiality of human cell repository specimens

Case #2 informed consent

- Types of Risk
  - Exposure of PHI
  - Personal identification in publications
  - Review of confidential medical records
  - Mental or physical injury
  - Financial (including employability/insurability)
  - Civil/Criminal Liability, Harm to Reputation
- IRB approved "waiver of informed consent"
  - Research poses no more than "minimal risk" OR
  - Research cannot practically be done without waiver
- How Does HIPAA come into play
  - IRB as Privacy Board –Waiver of HIPAA Authorization

Case #3

- A MSMC Oncologist requests that Pathology send 10 blocks of colon carcinoma, to a local academic research institution for collaborative research she is doing with a doctor there. She provides valid MSMC IRB approval for this project. Are any additional documents required?

- A. Signed MSMC informed consent from each patient
- B. Material Transfer Agreement (MTA)
- C. Universal MTA
- D. Intellectual Property Office approval
- E. Clinical Trials office approval
- F. More than one of above

Case #3, continued

- Review of the MSMC IRB reveals that this research project is sponsored by a pharmaceutical company.
- Could this change the documentation needed for Pathology to release the blocks?
- What if Pathologist is not intending to publish and is only sending samples to help validate a test?

Issues in Case #3

- MTAs
- IP
- For profit vs academia/non-profit
  - Federal initiatives to encourage/require tissue sharing among academics - UBMTA
  - For profit raises unique ethical, patient relations issues
- Unique approval process, concerns by institution
  - Is there a gatekeeper for other reviews?
- Understand the process in your institution
  - Ensures compliance with rules
  - Clarifies role of Pathology

What is an MTA?

- Contract covering the exchange of research materials (and, possibly related data) for promises regarding use of those materials and/or information

Why do we need MTA's

- Research material exchanges require MTAs
- Agreements require institutional signatures
- Institutions are concerned about academic issues, liability, and proprietary material - and money.
- Faculty are concerned about science and academic issues - as well as money.

What may an MTA do?

- Restrict use of and further distribution of the material
- Dictate how the results from using the materials can be used
- Protect provider from liability resulting from recipient's use of material
- Protect proprietary material
- Other terms as agreed

MTA Legal Issues

- Restrictions on publication
- Definition of Material (including modifications and derivatives)
- Restrictions on ownership and/or use of data and inventions
- Indemnification/Liability

What is Intellectual Property?

- Inventions
- Discoveries
- Research results
- Data
- Know-how
- Trade secrets
- Technology
- Scientific developments
- Technical information
- Processes
- Procedures
- Techniques
- Compositions
- Devices
- Methods
- Protocols
- Software
- Literary works
- Artistic works
- Illustrations
- Photos
- Designs
- Videos
- Audio recordings

Intellectual Property Protection

- Patents
- Copyrights
- Trademarks
- Trade secrets

Subject Matter of Patents

- Patents cover “anything under the sun that is made by man.”
- Methods, compositions of matter, devices, processes, software, machines, articles of manufacture.
- Patents do not cover
  - laws of nature
  - ideas

Bayh-Dole Act (1980)

- Grantees own inventions made with government funds and the patents on those inventions
- Grantees are permitted/encouraged to license inventions to promote commercialization
- Changing role of U.S. universities in the marketplace
- Dramatic increase in human tissue patent applications

- Court decisions allowed patents for broad range of biotechnology innovations
  - *Diamond v. Chakrabarty* 447 US 303 (1980)
  - Genetically engineered organisms are patentable

Question on Patents

- Do Human tissue patents impede scientific research
- Evolving Recognition that Open Sharing of knowledge outweighs potential financial value
  - Isolated gene sequences needed to carry out genetic tests
  - Cell lines
  - Diagnostics

Should pathologists benefit financially/otherwise from providing access to archived diagnostic blocks?

- Reality: high quality clinically annotated samples are very valuable

- Once custodianship period terminates, archived blocks can be discarded
- Only can recover actual costs of human sample procurement, handling and shipping
  - Procurement/storage costs - ??recoverable
  - Could recover costs to identify and ship materials
- Don't forget TRUST!

Case #4

- A MSMC researcher asks MSMC Pathology to provide unstained slides on 10 cases of prostate carcinoma. He can receive the cases anonymously. What documents must he provide?
- Valid IRB approval
- Informed consent from the patients
- Both of the above
- None of the above
- It depends on institutional rules

Issues in Case #4

- Anonymous (no link) vs coded (link available)
- Anonymously labeled slides do not contain PHI and cannot be linked back to PHI
  - Does not constitute "human subjects" under federal laws
  - Institutional IRB may still choose to require review
  - Informed consent would only expose subjects further –definitely NOT required
- Coded slides require IRB review
- If there is institutional informed consent for use of remnant tissues in research, should confirm patients have signed prior to release of materials (ethical, possibly legal)

Issues Case #4, cont

- Does the source of the samples matter?
  - Archived pathological samples
  - Tissue Repository
  - Left over samples from a completed Clinical trial (Pharma?)

Case #4a, further request..

- The researcher forgot to ask if certain clinical data can be attached to the samples. Which of the below may require IRB approval?
- Age at diagnosis
- Social Security number
- Race and sex
  - Tilousi v Ariz. State Bd. of Regents
- Treating physicians' names
- Pathologic diagnosis
- Treatment received

Case #4a, continued

- Regarding the clinical data the researcher wants attached to the samples, can Pathology search the medical record to get this information?
- Can the researcher search the medical record to get this information?

Medical record searches

- HIPAA
- Tissues are not "anonymous" if the researcher can search the medical record for data.
- IRB-approved "Honest Broker"
  - Intermediary between PHI and researchers
  - Can be electronic or human (can't be PI)
  - Can search medical record and provide data to researchers
  - Data linked to samples, but samples coded or anonymous
  - Many biorepositories are set up in this way.
- If Pathology does not have an IRB-approved "Honest Broker" arrangement, medical record searches may not be allowed. Contact the IRB office.

Case #4a - Clinical data

- Rules different for existing versus prospective collections. Diagnostic tissues are existing.
- Most institutions require IRB to determine if data requested constitutes human subjects research or exemption from HSR
- Non-identifying data
  - Generally can be attached to samples
  - Examples: age (usually range), sex, race, pathologic diagnosis
- Identifying data – 18 HIPAA identifiers
  - Constitute PHI and would require IRB approval, and possibly informed consent, for release
  - Examples: Medical record numbers, pathology accession numbers, social security numbers, phone and address
- Definition of additional "identifying" data may depend on facility and on study.

Case #5

- MSMC Pathology receives a faxed request for a paraffin block from Mrs. Smith's recent D&C for a spontaneous miscarriage for a research project being conducted at the university academic medical center in the neighboring state. The fax includes a valid IRB approval for the project and signed informed consent. Mrs. Smith's slides are reviewed. The diagnosis of fetal and maternal tissues with no specific pathologic change is confirmed. Mrs. Smith signs the MSMC release form for the blocks. What should MSMC do?
- A. Release the requested materials.
- B. Send only maternal tissues. No fetal tissues should be sent.
- C. Contact the PI to see if unstained slides or H&E recuts will suffice.
- D. Tissues potentially can be sent for this research project, but may require approval of other offices within MSMC.
- E. Refuse to release materials for this project.
- F. More than one of the above

Issues in Case #5

- *State laws on research use of fetal tissues*
- *Informed consent technically not required, as fetus not living.*
- *Permission from the mother to use the tissues may be recommended or required, depending on institutional and State policies.*

Case #6a

- Dr. Wong requires fresh, non-diseased human cardiac muscle for his experiments. The only possible source is autopsy material. He also would like to know the age and sex of the patient, pertinent past medical history, results of certain laboratory tests (liver and cardiac function, serum lipid panels, CBC results and data if present on Hemoglobin A1C) and cause of death. He contacts you. What should you do?
- A. Provide the tissue without further documents. Under federal guidelines, deceased individuals do not constitute "human subjects" and tissues can be distributed for research use.
- B. Since he wants medical record data as well, Dr. Wong needs IRB approval.
- C. Do not provide the tissue without approval of next-of-kin.
- D. Do not provide the tissue unless the patient, before death, gave informed consent for the research project or gave informed consent for his/her tissues to be used in research.

Case #6a, continued

- Dr. Wong's research discloses that people with both high HDL cholesterol *and* high hemoglobin A1C have an increased risk of abnormal myocyte function. He is concerned this could cause death in some patients, but requires further study.
- Is Dr. Wong obligated to inform the next of kin of these results? Why or why not?

Case #6b

- Dr. Fine is an expert in hereditary cancer syndromes, specifically BRCA1 cancers. For a hospital QA program, she was asked to review the charts of patients under 40 who died of cancer in the past year. She notes about 15 patients who fit the clinical picture of BRCA1 mutations, but sees no mention of this in the case notes. Dr. Fine thinks it would be very interesting to test the cancer and normal tissues on file for the BRCA1 mutation. She comes to you for tissues. What should you do?
- A. Provide the tissue. Under federal guidelines, deceased individuals do not constitute "human subjects" and tissues can be distributed for research use.
- B. Dr. Fine first needs IRB approval. She identified these patients during a non-related institutional clinical activity (QA). She needs IRB approval for this research project.
- C. Do not provide the tissue without approval of next-of-kin.
- D. Do not provide the tissue unless the patient, before death, gave informed consent for the research project or gave informed consent for his/her tissues to be used in research.

Case #6b

- Dr. Fine discovers that 12/15 patients clinically suspicious for BRCA1 mutations do in fact have mutations.
- Is Dr. Fine obligated to inform the next of kin of these results? Why or why not?

Case #6 issues

- Dead patients not "human subjects" by federal regulations.
  - No IRB review required by federal law.
  - Individual institutions may require review.
- Exception: research may reveal data that will impact living persons.
  - **HIPAA – protects PHI even after death if it impacts the living**
  - BRCA1 mutations are inherited. If a patient after death is found to have had this mutation, family members may want to be tested. If positive, they may want additional testing or treatment. Alternatively, family may NOT want any testing done.
  - The cardiac muscle data is too preliminary to be actionable. Furthermore, the risk factors (HgA1C and HDL) are tested routinely and most abnormalities are not inherited.
- Medical record review and linkage of clinical data to samples from dead patients

Emerging National Trends

- UBMTA
- Personalized medicine
- Increasing grants available for inter-institutional research studies
- Increasing grants for population-specific studies only feasible by multi-institutional cooperation
- We will see increased requests for our archived diagnostic materials!

Conclusions

- Custodianship vs. ownership
- Clinical trials vs. research
- IRB and types of IRB approval
- Informed consent/authorization and waiver of
- HIPAA
- MTA, IP
- For profit vs. not for profit
- Financial benefit (patient and pathologist)
- Data linked to samples and medical record searches
- Fetal tissues
- Deceased patients