Published in final edited form as:
Am J Clin Pathol. 2011 November ; 136(5): 679–684. doi:10.1309/AJCP7DWCQ1SWJTWU.

A New Paradigm for Biospecimen Banking in the Personalized Medicine Era

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Abstract

Banking of high-quality, appropriately consented human tissue is crucial for the understanding of disease pathogenesis and translation of such knowledge into improvements in patient care. Traditionally, tissue banking has been thought of as primarily an academic research activity, but tissue and biospecimen banking is increasingly assuming clinical importance, especially with the advent of genetic and proteomic testing approaches that rely on fresh or fresh frozen tissue. These approaches are part of the revolution in personalized medicine. This revolution's impact on biorepositories—their mission and day-to-day function—will be profound. Direct patient care will require structuring tissue procurement to become a routine part of patient care. Accordingly tissue banking will expand from its traditional research role in large academic medical centers into the everyday practice of surgical pathology. Successful implementation of this model will require consideration of several financial, medicolegal, and administrative issues.

Keywords

Biobanking; Personalized medicine; Reimbursement; Surgical pathology; Tissue procurement; Biorepository

The Personalized Medicine Revolution and Its Impact on Biospecimen Banking

Banking of high-quality, appropriately consented human tissue is crucial for the understanding of disease pathogenesis and translation of such knowledge into improvements in patient care. Traditionally, tissue banking has been thought of as primarily an academic research activity, but tissue and biospecimen banking is increasingly assuming clinical importance, especially with the advent of genetic and proteomic testing approaches that rely

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on fresh or fresh frozen tissue. These approaches are part of the revolution in personalized medicine, namely, the objective of adapting treatment specifically to the genetic or metabolic profile of an individual person's disease.

This revolution's impact on biorepositories—their mission and day-to-day function—will be profound. Direct patient care will require structuring tissue procurement to become a routine part of patient care. Accordingly, tissue banking will expand from its traditional research role in large academic medical centers into the everyday practice of surgical pathology at all hospitals. The new paradigm is not just about the *banking* part itself—the actual storage of a sample on a freezer shelf—but also the *realignments* needed in priorities among clinicians, pathologists, and hospitals. This new focus on biospecimen banking constitutes a fundamental additional role of pathologists in laboratory evaluation: We bank specimens *now* because we expect they will be useful *later*, reflecting the fact that disease pathogenesis and medical knowledge evolve over time. No longer will laboratory samples be thought of simply as tissues to be processed, diagnosed, and discarded, but rather as patient samples that have potential prospective and retrospective value in an evolving and highly complex molecular world of multistage pathogenesis, where they will support patient care in ways not previously feasible.

As changes occur, institutions with previous biorepository experience must provide leadership in the new paradigm (along with their peers in pathology organizations and other professional groups) to hospitals and third-party payers, educating them about the need for banking practices to support the evolving patient care standards and emerging genome-wide testing approaches. Although a major focus is on tissue banking specifically because it allows molecular analysis of diseased tissue in comparison with germline DNA and/or surrounding nondiseased tissue, other patient samples will also have increased importance, including biofluids (eg, DNA from leukocytes or from effusions), thus the broader term *biobanking* is often used for more general discussion. Many best practices of successful research biobanking, as summarized by the Office of Biorepositories and Biospecimen Research[1] and the International Society for Biological and Environmental Repositories,[2] will form a useful cornerstone as biobanking assumes a more clinical, patient-centered role.

Implementation

Traditionally, many institutions, particularly larger research-oriented centers, derive a high proportion of their banked specimens from the surgical pathology service. Typically, samples come from surgical resections (from sites of the tissue specimen not needed for diagnostic evaluation), after patient consent is obtained via institutional review board (IRB)-approved protocols, and are available for research performed under other IRB-approved protocols. However, as a direct result of emerging genomic, proteomic, and metabolomic (and other) techniques, tissue banking is evolving from a primarily research activity to a direct clinical activity required to support individualized therapy based on the information provided by the new technologies.[3,4] In addition, banked samples may help resolve clinical questions that were not necessarily present at the time of the original procurement. Because these new "omic assays" often require or work best on fresh frozen tissue[5,6] (also known as snap-frozen tissue), demand for banked tissues of this type will grow, especially for samples obtained under rigorous protocols that minimize the elapsed ischemic time between surgical resection and processing.

The resources and processes needed to support biobanking as an integral component of direct patient care are not trivial. Our medical center (Barnes-Jewish Hospital [BJH] and Washington University School of Medicine, St Louis, MO) recently reorganized the tissue procurement practices in support of this goal, and the infrastructure and funding mechanisms

needed for the project's success provide some insight into the scope of the endeavor. In general, successful implementation was critically dependent on several factors, including the following: (1) close partnerships and effective communication among the Department of Pathology, Department of Surgery, Siteman Cancer Center (of BJH and Washington University School of Medicine), and the BJH administration; (2) demonstration of value to the BJH administration; (3) technical support (pathologist assistants); (4) tissue bank; (5) dedicated transport personnel; and (6) education of gross room personnel, trainees, and attending pathologists Table 1.

Implementation of the new process was successful for several reasons, which are illustrative. First, our medical center already had an active biobank (already containing approximately 400,000 diseased and normal specimens, derived from basic science, translational, and clinical research protocols and programs focused on oncology), which greatly simplified banking focused on direct patient care. Second, there was early recognition and support of the need for real-time fresh specimen transport to ensure that specimens reached the pathology laboratory from the operating room in 30 minutes or less. Timely transport required 2 dedicated personnel and development of novel chain-of-custody documentation to ensure that specimens were processed within the target time frame (including time-updated listing of all specimen containers generated from a procedure, which itself required custom software applications and computer hardware within the operating rooms). Third, multiple institutions within the medical center were eager and willing to provide funding for biobanking focused on direct patient care, including BJH, the Siteman Cancer Center, and the Department of Pathology. Without the financial support (necessary for software development and computer hardware in the operating rooms, hiring transport personnel, and hiring pathologist assistants to support tissue processing in the frozen section area), the initiative would not have been possible.

Needs

Infrastructure

Clinical biobanking requires money for new infrastructure, support personnel, and operation of the tissue bank itself. Support for clinical biobanking through academic or research funds is inappropriate because the activity is focused on direct patient care. However, philanthropic sources of support should be considered, and business process flow diagrams can be valuable in promoting the program and implementing it successfully.[7] However, in our opinion, financial support from the hospital administration is appropriate and critical for 2 reasons. First, biobanking itself (although performed under the oversight of pathologists) is becoming an integral part of the hospital infrastructure required to support all clinical departments. Second, as personalized medicine's advantages become more clear to providers and the lay community, the hospital will stand to benefit greatly from an institutional biobank. Specimen procurement and biobanking capabilities should be viewed as any other new technology or emerging patient care paradigm that requires new infrastructure and additional staff (not unlike outpatient surgical suites, ambulatory care centers, advanced cardiac care units, and so on).

CLIA Certification and CAP Accreditation

Tissue banking in support of direct patient care will require a certification process for Clinical Laboratory Improvement Amendments of 1988 (CLIA) and an accreditation program that attains and maintains standards, resulting in enhanced confidence in biospecimen quality. The available best practices for biorepositories[1,2] serve as a useful starting template, and, as of this writing, a draft accreditation program based on industry best practices is due to be released from the College of American Pathologists (CAP) in late

2011. Besides enabling use of banked samples for clinical patient management (which is not feasible in a research-only, non–CLIA-certified biobanking environment), certification and accreditation standards will increase patient and physician confidence in the overall enterprise and the individual repositories they use. Also, it will help ensure procedural consistency on which patient outcomes are based. The frequency of CAP accreditation will be every 3 years. CLIA certification enables the laboratory to report patient test results and to bill for patient services. The responsibilities conferred by CLIA certification are clearly defined in applicable law and regulation.

Parallels With Existing Banking Paradigms

Comparison of the emerging clinical biobanking model with umbilical cord blood banking provides some clues as to how tissue banking might evolve Table 2. Cord blood—a limited, but available, material that might otherwise be discarded—is collected and stored for possible later use; although there is an uncertain likelihood that the material will be used, there is a potentially high-impact benefit when needed, and future uses may not necessarily be envisioned at the time of procurement. Education is key to utilization; physicians and cord blood bank directors must discuss the potential uses and limitations of cord blood banking to new parents to gain consent. Education also helps the practice become more widely used, which not only enhances patient care but also lowers the marginal cost. Private cord blood bank samples are linked to patient identity, and cord blood banking is formally regulated. Besides US Food and Drug Administration regulations, accreditation programs for private cord blood banks exist through the American Association of Blood Banks, the Foundation for the Accreditation of Cellular Therapy, and the CAP.[8]

In an almost identical way to cord blood banking, biobanking of tissue samples supports direct patient care—specimens are banked *now* because they are expected to be useful *later.* And even though there is an uncertain probability of the tissue being used, it has a potentially high impact when needed. Given the rapid evolution in molecular diagnostics, clinical biobanking can almost be viewed as an insurance policy of sorts in that current specimens are preserved for future testing to support treatment approaches we cannot envision now. Education will also be key: Pathologists, oncologists, and surgeons (at the least) will need to commit to ongoing discussion and promotion of the advantages of tissue banking to ensure integration of the practice further into the mainstream of care; the health care benefits of clinical biobanking will be realized only with widespread acceptance. Recent patient-centered federal legislation should help ensure acceptance of a clinical tissue banking model, especially as centered on molecular science, and will be a key part of the educational process for physicians and patients. Notably, the Genetic Information Nondiscrimination Act of 2008 prohibits the improper use of genetic information for employment and health insurance purposes,[9] and the Patient Protection and Affordable Care Act of 2010 prohibits health insurers from denying coverage or charging higher premiums because of preexisting conditions.[10] These types of legislation should help reduce the concerns of patients and facilitate their informed consent with regard to the types of information that will be generated as a result of the molecular analysis of banked tissue samples.

Updated Consent Process

Consent and IRB requirements, cornerstones of successful tissue banking programs for academic and research programs, need to be reevaluated. For research biobanks, in which samples are derived from the areas of tissue specimens not required for diagnosis, anonymization of patient origin is of fundamental importance. In contrast, biobanks designed to support direct patient care will require a different sampling focus and, of course, will need to preserve and certify the accuracy of the specimen’s link with the patient’s

identity. Similarly, the form and content of patient consent will need to change, from an IRB-approved process to a purely clinical process analogous to, or as a mere component of, routine patient consent to diagnosis and treatment. Patients will need to understand and consent to the banking of their tissues and subsequent molecular studies done for their clinical management as another component of appropriate pathologic evaluation. The need for patient consent to release tissues will also need to be considered, just as existing permissions are followed to release radiographic and other clinical records outside of the treating institution. Patients will also need to appreciate the *time* dimension of banking—that proactive storage of their tissue may turn out to be useful for their clinical management in the future in ways neither they nor their physicians can currently foresee. As in other new paradigms, communication is important—in this instance with local IRBs and on a national level such as the New England IRB and the National Cancer Institute Central IRB Initiative—to achieve common understanding and cooperation to develop an appropriate consent process.

Reimbursement

Hospitals and pathology departments should establish appropriate Current Procedural Terminology (CPT) codes because, as with any value-added activity in the clinical arena, clinical tissue banking should be compensated in a way consistent with its value to patient care. However, there are many issues to be addressed Table 3. What is a fair level of reimbursement? What cost components of tissue banking (eg, specimen handling, quality assurance evaluation, informatics, and storage) should be included in the CPT code reimbursement, and would different CPT codes need to be established for different cost components? Which components of the process fall under the technical component of the CPT codes vs the professional component? How best should the value of clinical tissue banking be communicated to the American Medical Association and third-party payers? To address these issues, we recommend that a working group of stakeholders from biorepositories, hospitals, and pathology professional societies be formed to devise best-practice recommendations for tissue banking, apply to the relevant American Medical Association panel for development of appropriate CPT code(s), and secure the endorsement of third-party payers.

Alternatively, the costs and revenues associated with clinical tissue banking could merely be folded into the general infrastructure costs borne by hospitals. There is no doubt that clinical biobanking will become part of the general hospital infrastructure required to support best patient care and that many aspects of the process, such as the specimen transport procedures from surgery to laboratory, might best fit this model. However, there are clear value-added steps in clinical biobanking that require the hands-on involvement of pathologists, including selection of appropriate tissue samples at the gross level from surgical specimens,[11] answering requests for consultation from clinicians about the best use of a banked specimen,[12] microscopic review of banked samples to select appropriate areas of molecular testing, and implementation of quality assurance practices. Some of these activities have counterparts in the current use of archival formalin-fixed paraffin blocks from surgical pathology; thus, it could be said that clinical biobanking has always existed in the much more limited form provided by these paraffin block archives. However, as mentioned, the advent of molecular techniques and the concomitant increased storage and use of frozen tissues greatly raise the scale, complexity, and potential benefit of clinical biobanking. Because several relevant activities in this process require a pathologist, it is appropriate that whatever infrastructure provided by the hospital, CPT codes should reflect the professional involvement of pathologists.

Conclusions

As tissue banking moves from a primarily research endeavor to a clinical activity, a host of issues must be addressed by medical centers, including infrastructure refinements, an appropriate consent process, reimbursement mechanisms, and CLIA certification. Successfully addressing these challenges is an absolute requirement for biobanking so that it can evolve to directly support enhanced patient care for personalized medicine. Many best practices that have contributed to successful research tissue banking at large academic institutions (histologic and molecular quality assurance, informatics applications, governance, and workflow models) should be useful as foundations for the new clinical biobanking paradigm. Based on the experience at our medical center, a tissue banking program based on clinical objectives is feasible but requires broad institutional cooperation and support for implementation.

Acknowledgments

Supported by grant P30 CA91842 from the Siteman Cancer Center and grant UL1RR024992 from the Institute for Clinical and Translational Science, Washington University Medical Center, which has partially funded the biorepository at Washington University School of Medicine.

We acknowledge the College of American Pathologists, Accreditation Programs Office, for useful input into this article.

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Table 1

Requirements for a Successful Procurement Program for Clinical Tissue Banking

Requirement	Justification
Close partnerships among pathologists, surgeons, and hospital administrators	As in all complex enterprises with multiple stakeholders, efficient partnerships are crucial to leveraging the expertise of the various participants and ensuring that they perceive a common benefit.
Demonstration of solid clinical value to hospital administration	As with any new enterprise with significant initial costs, demonstration of short- and long-term value is essential.
PAs with good knowledge of gross evaluation techniques	PAs help ensure a good working relationship between tissue banking and surgical pathology that confers advantages for patient care and the biobanking process; PAs save time, increase efficiency, and help prioritize key specimens for quick dissection and banking.
Knowledgeable tissue bank staff and pathologists who understand key aspects of the process	These staff members and pathologists help ensure efficiency and development of good working relationships with customers and stakeholders, as noted above.
Transport personnel between operating rooms and pathology laboratory	Transport personnel are required for prompt banking to ensure adequate specimen preservation; they preserve chain-of-custody throughout.
Instruction/education process	Gross room personnel, technologists, trainees, and pathologists need to understand the process and its importance; development of standardized procedures (documented in the laboratory policy and procedure manual) is critical; education is especially important in environments with a high degree of personnel turnover, eg, departments with residency training programs.

PA, pathologist assistant.

Table 2

Comparison Between Umbilical Cord Blood Banking and Clinical Tissue Banking

Issue	Comparison	Comments
Time dimension of the biobanking process	In both fields, specimens are banked in the present for uncertain but potentially high-impact use in the future; can be used to benefit patients in ways not necessarily envisioned at the time of procurement.	Education of users is required because stakeholders often tend to value only things that offer immediate benefits.
Promotion of advantages of the procedure to physicians and patients	Communication and education are central components of cord blood banking to increase use of the procedure; this is also likely true of clinical tissue banking.	Helps overcome expectation and cost barriers and helps the practice become more widely used; recent protective federal legislation (see main text) should be a key item communicated to patients.
Link to patient identity	Private (although not public) cord bank specimens linked to patient identity; required for clinical tissue banking	Will require a consent process different from that used for biospecimen repositories focused on research
Accreditation	Besides US Food and Drug Administration regulations, accreditation programs for private cord blood banks exist through the American Association of Blood Banks, College of American Pathologists (CAP), and the Foundation for the Accreditation of Cellular Therapy; accreditation program for tissue banks is pending release in late 2011 from the CAP.	Certification standards and accreditation programs enhance patient care; they will also increase patient and physician confidence in the overall enterprise and the individual repositories they use.

Table 3

Establishing CPT Codes for Clinical Tissue Banking

Issue	Possible Approach
What is a fair level of reimbursement?	Pathologists need to actively promote their value in the clinical biobanking process and the advantages conferred by their experience; reimbursement should reflect the inherent clinical value of the procedure and the costs of providing the service.
What cost components of tissue banking should be included in the CPT code for reimbursement?	Components of tissue banking that require the most hands-on involvement by pathologists are the best candidates for a pathology-generated CPT code charge; general institutional tissue banking processes (such as specimen transport) could more readily be included in hospital infrastructure costs.
What is the best way to justify the proposed code(s) to the American Medical Association?	College of American Pathologists standards for tissue bank accreditation, when available, will help justify the need for CPT codes because they will demonstrate the clinical value of the activity; working groups consisting of stakeholders from pathology and hospital administration should devise a consensus approach.

CPT, Current Procedural Terminology.