National Institutes of Health
National Cancer Institute
Office of Biorepositories and Biospecimen Research

SUMMARY

National Cancer Institute Biospecimen Best Practices Forum

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I. INTRODUCTION

Cancer research in the 21st century is moving toward a vision of personalized medicine where clinical and molecular data are used to treat individual patients with greater specificity, reduce the frequency of adverse events, and determine disease predisposition to allow early detection and prevention. In today's cancer medicine, the analysis of human specimens supports diagnosis, staging, and prognosis. In addition, these materials provide a critical link between molecular and clinical information for the personalized medicine of the future. The collection of accurate molecular data to inform the development of personalized medicine depends upon the quality and consistency of the biospecimens analyzed.

Over the past several years, the National Cancer Institute (NCI) has undertaken an intensive due diligence process to understand the state of its funded biospecimen resources and the quality of biospecimens used in cancer research. Based on extensive input from cancer research experts including clinicians, scientists, ethicists, biotechnology and pharmaceutical professionals, patients, survivors, and advocates, the NCI developed the *NCI Best Practices for Biospecimen Resources*.[1] The purpose of the *NCI Best Practices* is to define state-of-the-science practices for acquiring tissues and fluids from research participants to promote biospecimen and data quality and to encourage adherence to the highest ethical and legal standards to support the development of new cancer interventions.

The purpose of this forum was to inform and obtain feedback about the *NCI Best Practices* from intramural and extramural research communities in and around Chicago, IL. This forum was the third in a series of public meetings to be held across the United States.[2] The forums were designed to address major areas of stakeholder concern and interest based on public comments received on an earlier draft of the document. The forum included NCI and non-NCI speakers to offer different perspectives on the practical impact of the *NCI Best Practices* on the cancer research and patient communities and provided time for questions and feedback from the audience. In addition to presenting external perspectives about the *NCI Best Practices* during the plenary presentations, non-NCI speakers had an opportunity to offer their opinions in response to questions and comments from the audience. The NCI intends to use feedback gathered from the non-NCI speakers and audience participants at these forums to inform, update, and plan for future versions of the *NCI Best Practices*.

II. Overview and Discussion of *NCI Best Practices for Biospecimen Resources*

NCI Best Practices for Biospecimen Resources
Why Do We Need Biospecimen Best Practices?
Carolyn Compton, M.D., Ph.D., Director, Office of Biorepositories and Biospecimen Research (OBBR), NCI

Dr. Carolyn Compton is the Director of the OBBR, with responsibility for developing a common biorepository infrastructure that promotes resource sharing and team science, and establishing biobanking as a new area of research. She came to the NCI from McGill University where she served as the Strathcona Professor and Chair of Pathology and the Pathologist-in-Chief of McGill University Health Center. Prior to this, she had been Professor of Pathology at Harvard

[1] http://biospecimens.cancer.gov/practices/
[2] http://www.nci-bestpractices-forum.com/meeting/obbr/

Medical School and Director of Gastrointestinal Pathology at Massachusetts General Hospital. Dr. Compton holds leadership positions in several professional organizations such as the College of American Pathologists, the Cancer and Leukemia Group B, the American Joint Committee on Cancer, and the American Society of Clinical Oncology. She is a member of the editorial boards of *Cancer*, *Cell Preservation Technology*, and *Clinical Proteomics*.

Cancer is the number one killer of people younger than 85 in the United States.[3] Research addressing that alarming statistic is at an inflection point: Exponential technological and analytical advances—such as genomic and proteomic arrays, which allow researchers to evaluate entire classes of molecules at one time—enable new targeted therapies and directed uses of older therapies. While past cancer treatments relied on morphologic diagnosis, phenotypic tumor classification, and therapeutic regimens with unpredictable and sometimes adverse effects, the future holds treatments tailored to individuals through therapies targeted to the molecular profile of the disease and drug regimens planned around host genetics. Biospecimens fuel this research.

Taking full advantage of this technological revolution will require significant advances in biospecimen science. Optimized biospecimen collections are essential for researchers to identify targets for treatment and prevention, validate new therapeutics, elucidate mechanisms of neoplasia, identify new biomarkers, and identify predictors of drug efficacy and toxicity. Biospecimen variability, from handling method to annotation, can adversely affect biospecimens' utility in cancer research as can variability in biospecimen-associated data, clinical data, and related restrictions (e.g., research participant consent).

To address these issues, the NCI, in conjunction with the biospecimen research community, has identified key requirements for cancer research biospecimen resources.[4] The latter includes best practice–based, data-driven technical and operational standards to ensure quality and enable reproducible molecular analysis; consistent, high-quality biospecimen annotation, encompassing pathological and clinical data; biospecimen access through a timely, centralized, peer-review process; ethical and privacy compliance through a well-defined chain of trust; and state-of-the-art informatics systems to track biospecimens, associated data (clinical, pathological, and quality control), and patient consents. Final requirements are communication with the public and outreach efforts that include research participants.

The *NCI Best Practices* was published with the dual objectives of unifying policies and procedures for NCI-supported biospecimen resources for cancer research and providing a baseline for operating standards on which to build as the state of the science evolves. It is a living document that will be updated in response to evidence-based recommendations. Periodic revision of the *NCI Best Practices* will occur with input from researchers, biospecimen resource managers, advocates, policymakers, and related stakeholders as changes in science, law, and policy occur. New tools and supplemental guidance in key areas will be added as appendices

[3] Each of the presentations in this summary is available electronically on the OBBR Web site at http://www.nci-bestpractices-forum.com/meeting/obbr/chicago2007/.

[4] The NCI defines biospecimen resource as "a collection of human specimens and associated data for research purposes, the physical entity where the collection is stored, and all relevant processes and policies." Source: *National Cancer Institute Best Practices for Biospecimen Resources* available at http://biospecimens.cancer.gov/practices/.

and/or posted to the OBBR Web site. Further, the NCI and, specifically, the OBBR are committed to developing biospecimen research as a valid area of scientific investigation worthy of funding and will be developing evidence-based standard operating procedures (SOPs).

Overview of Technical and Operational Best Practices
State-of-the-Science Biospecimen Handling: Real-World Perspective
Elizabeth Hammond, M.D., Professor of Pathology and Professor of Internal Medicine, University of Utah School of Medicine

Dr. Hammond is Professor of Pathology and Adjunct Professor of Internal Medicine at the University of Utah School of Medicine. She is past Chairman of the pathology department at LDS Hospital, Salt Lake City, and currently a member of the Intermountain Healthcare Board of Trustees. Dr. Hammond, an expert in transplantation pathology and predictive cancer factor evaluation, has worked with the NCI on a number of initiatives and was recognized by the College of American Pathologists (CAP) as the 2005 Pathologist of the Year.

Dr. Hammond began her presentation by explaining that qualified biospecimens can be difficult for researchers to obtain. Biospecimens within a resource often have been collected under a variety of protocols without standardization among collecting entities and without regard for defined end uses such as RNA extraction or proteomics. The Cancer Genome Atlas (TCGA) pilot project is a good example of real-world biospecimen issues. This pilot study was designed to catalog molecular changes associated with cancer through analyses of 1,500 cancer tissue samples. A sample failure rate of approximately 35 percent was anticipated, but in reality, only 2 to 7 percent of the frozen samples in the best available repositories were qualified for the project.

Dr. Hammond then emphasized the need to harmonize specimen handling across biospecimen collection sites. To do so, protocols must be clear, specific and flexible; clinical situations for biopsy consent issues anticipated; template documents and charts used to simplify understanding; and the uses of samples explained to ensure that the rationale for specimen handling is clear. Furthermore, specimen kits for biospecimen collectors should be customized to the protocol as they would facilitate specimen handling by providing all appropriate tube types, reagents, equipment, and instruction sheets. For example, blood collection kits or tissue excision kits would include everything necessary to process blood or tissue according to the *NCI Best Practices*. Information could be provided in a variety of formats including detailed instructional posters and videos, tables to fill in handling details such as time between collection and preservation, and space for each institution to fill in contact numbers for help and questions.

Dr. Hammond then reviewed the technical and operational best practices in section B of the *NCI Best Practices* that address biospecimen collection and processing, monitoring and storage, biosafety, packaging and shipping, collecting and managing clinical data, and recordkeeping. Success in obtaining qualified biospecimens requires careful preparation and planning, including incorporation of local and national regulations into the protocol before initiation; standardization of protocols, instructions, and personnel training; establishment of a helpline to answer questions, and flexible implementation to accommodate the needs of the specific institution. Incentives for biospecimen procurement personnel will help motivate adherence to the *NCI Best*

Practices. Finally, monitoring is required to evaluate the success of handling procedures, including quality assessments of the biospecimens, processes, and personnel training.

Question-and-Answer Session

A participant observed that in the *NCI Best Practices,* human specimens are considered a biological safety hazard, which exceeds the standards of the CAP. Dr. Hammond agreed that the *NCI Best Practices* ought not to exceed the standards of the CAP. Dr. Compton reminded participants that the *NCI Best Practices* is an evolving guidance document and encouraged them to continue to provide this sort of feedback to the OBBR.

Two discussants described in detail how they avoid problems with freezing and thawing of samples. One suggested that in cases where end users of a biospecimen resource are local, aliquots of large tissue pieces be avoided, a frozen section prepared to guide what is taken from a block, and samples derived from the block transferred from -80 °C to - 20 °C prior to a single freeze-thaw. The other participant suggested submitting to the pathology laboratory tissue adjacent to the one set aside for research purposes as a record investigators could tap into for comparison purposes. Dr. Hammond lauded their creative solutions and recommended detailing their instructions in their protocols so that everyone involved would know exactly what to do and understand why these additional steps are necessary.

Another participant noted that each investigator requesting biospecimens from her resource submits a unique protocol; these protocols often are extremely long with the necessary details dispersed throughout. She recommended that protocols have tissue collection requirements concisely delineated in one section and that a fill-in chart be included enumerating all biospecimen requirements. Dr. Hammond agreed with these recommendations and informed participants that the Group Banking Committee is working to standardize tissue collection protocols. As templates are generated, they will be widely shared with the research community.

Dr. Compton pointed out that many biospecimen resources do not perform quality assessment of biospecimens upon entry to the repository. In fact, the disparity in the estimated and actual number of qualifying biospecimens in TCGA pilot project was attributed to biospecimen resources not knowing the quality of the samples they were storing. A participant strongly recommended that protocols with stringent requirements only be applied to prospective biospecimen collections because retrospective collections are unlikely to meet such requirements.

In response to a concern regarding limited biospecimen sharing by private practice pathologists, Dr. Compton informed participants that the NCI has initiated the NCI Community Cancer Centers Program, which engages high-quality care facilities; one of the requisites for inclusion is biospecimen collection.

Overview of Ethical, Legal, and Policy Best Practices

Ethical, Legal, and Policy Implications of Using Human Specimens in Research: What You Need To Know

Lori Andrews, J.D., Distinguished Professor of Law, Chicago-Kent College of Law; Director, Institute for Science, Law, and Technology; and Associate Vice President, Illinois Institute of Technology

Ms. Andrews is an internationally recognized expert in biotechnology law. She is involved in setting policies and advising private and public clients in genetic technologies and was recently named one of the 100 most influential lawyers in America by the National Law Journal. She also has authored many professional texts and has written two novels on issues surrounding the use of human specimens.

Ms. Andrews opened her presentation by stating that although there are laws in place to protect human research participants, there is still a lack of legal consensus on the rules that should apply to research using human specimens, as highlighted by *Washington University* v. *Catalona*. In light of a growing recognition that research participants are interested in what happens to their specimens, the NCI and a number of professional organizations have published best practices on the use of human specimens in research. Specifically, the *NCI Best Practices* offers recommendations on custodianship, privacy, conflicts of interest, intellectual property, and informed consent.

Ms. Andrews lauded the document's level of detail on informed consent, particularly the recommendation to discuss future uses of biospecimens with the research participant. However, she suggested that participants should be allowed to place limits on the future use of their specimens (even if they are anonymized) based on religious or ideological beliefs. She also recommended further thought be given to discontinuation of participation in research, not only in terms of honoring how people want their specimens used in the future but also in terms of how patients' wishes are communicated to researchers to whom the samples already have been distributed. Ms. Andrews noted that Federal regulations permit research on anonymized biospecimens in certain circumstances. However, these regulations do not specifically endorse the deidentification of samples as a means of enabling their subsequent use against patients' expressed wishes.[5]

Ms. Andrews cautioned that not honoring research participants' wishes regarding what is done with their specimens will result in losing the trust of potential, future contributors; for example, several tribal nations have withdrawn en masse from research based on the perceived violation of Havasupai tribe members' wishes by Arizona State University researchers. In a positive development, studies are now being conducted on how people want their specimens to be used, with recent results showing that a large number of people are willing to give specimens for cancer research while fewer are willing to do so for pharmacogenomics research. Among the African-American community, distrust of researchers' motives still lingers decades after the Tuskegee scandal. Ms. Andrews emphasized that to ensure the realization of the personalized medicine era, the research community must not jeopardize the public's trust in the research enterprise and, in the case of some subpopulations, must earn it. As recent events attest, it is

[5] http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

particularly important that investigators honor research participants' wishes regarding how their specimens are to be used. Ms. Andrews concluded that the *NCI Best Practices* dovetail with current law and take a major step forward in addressing the most pressing ethical, legal, and policy issues today in research on human specimens.

The Importance of Best Practices to Patients, Survivors, Advocates, and the General Public
It's All About the Patient: Putting Biospecimen Research in Perspective
Mary Lou Smith, J.D., Cofounder, Research Advocacy Network

Ms. Smith holds a J.D. with certification in health law and is a 21-year survivor of breast cancer. She is Cofounder of the Research Advocacy Network and has served on a number of national cancer committees representing patient interests. She also has developed patient care products for Blue Cross Blue Shield and served in multiple NCI clinical trial cooperative group committees.

Ms. Smith began her presentation by stating that many cancers have a mortality rate greater than 45 percent. Patients are eager to participate in research to speed the discovery of cancer prevention, treatment, and a cure. However, the dilemmas and decisions a patient faces are unlike those of the researcher who wishes to involve them in a study; patients may be overwhelmed simply by new terminology. When patients give specimens to research, they believe that the specimens are going to be freely used and openly accessed and would likely be disappointed at the limited sharing within the research community.

Biospecimens are precious resources; thus, the public expects that the research community will act as responsible stewards of these materials. The consequences of poor biospecimen research practices include eroding public confidence and impeding the accrual of benefits to patients. A commitment of resources is needed in biospecimen research to produce data that ultimately will benefit patients. The *NCI Best Practices* represents a great opportunity not just to advance research but to earn patients' trust, which is critical to their involvement in the research process. Patient advocates are also research advocates—from their involvement in clinical trial design to grant reviews—who assist by bringing the patient perspective to translational research.

Question-and-Answer Session

A patient advocate asked why the *NCI Best Practices* are not regulations if improved biobanking is the way to advance cancer research. Dr. Compton replied that the NCI does not develop regulations, but is working with the research community to encourage widespread adoption of the *NCI Best Practices*. At this time, the NCI is interested in forming partnerships to motivate biospecimen handlers by demonstrating the superior results that adopting the *NCI Best Practices* will engender.

An attendee asked about the definition of a "publicly available" biospecimen. He pointed out that to maximize sharing within the research community, it would be ideal if biospecimens are given to a research team or institution rather than an individual. Ms. Andrews agreed but responded that people will often impose conditions on gifts. Ms. Smith added that informed consent documents must make it clear where or to whom the donation is being made. While some

researchers are reluctant to share samples or information, the approach of the *NCI Best Practices* is to encourage sharing to ensure that each donation yields the greatest good.

A participant who works on a rare disease commented that only two or three relevant biospecimens might become available in a year, and each time the investigator must accommodate the expectations of the research participant's local institutional review board (IRB). A nationwide IRB would make obtaining such biospecimens less onerous. Ms. Smith commiserated about extensive IRB forms and mentioned the NCI's Central IRB Initiative in conjunction with the Office for Human Research Protections. Dr. Compton added that this is a complex issue encompassing sociological as well as legislative considerations. A past attempt at a centralized IRB complicated matters by adding rather than replacing a layer of review. The participant suggested that NCI-designated Cancer Centers could work toward IRB standardization. Another discussant recommended that attendees read the report produced by the Public Responsibility in Medicine and Research (PRIM&R) Human Tissue/Specimen Banking Working Group, which promotes IRB consistency.

One discussant objected to section c.2.2.9 of the *NCI Best Practices*, which states that if a research participant withdraws consent to use a biospecimen, the biospecimen resource has an obligation to notify any investigator who received samples derived from that individual. Ms. Andrews responded that this is an interpretation of the Federal regulation ensuring that research participants can withdraw consent at any time. Dr. Compton pointed out that because the *NCI Best Practices* comes from a Federal agency, it must maintain consistency with Federal regulations. As an evolving document, the *NCI Best Practices* will be adjusted to accommodate new developments, and between iterations of the document, revised guidances will be available on the OBBR Web site. Ms. Andrews emphasized that research participants must be educated about their choices; for example, the informed consent document must state that research participants have the right to withdraw consent and, if they do, what would become of their specimens, whether it be destruction or anonymization followed by continued use.

Part 2: Informatics Best Practices and Economic Issues for Biospecimen Resources

caBIG™, caTissue, and Achieving Silver-Level Compatibility

Informatics Solutions to Biospecimen Management: Finding the Right Tools

Warren Kibbe, Ph.D., Associate Professor and Director of Bioinformatics, Robert H. Lurie Comprehensive Cancer Center and Associate Director, Northwestern University Biomedical Informatics Center

Dr. Kibbe is Principal Investigator at the Northwestern University site for the cancer Biomedical Informatics Grid (caBIG™), an NCI initiative that supports the development of interoperable software tools designed to facilitate translational research. He helped develop the caBIG™ Tissue Bank and Pathology Tools (TBPT) Workspace designed to address the technological challenges of managing biospecimens and associated data.[6] Dr. Kibbe received a Ph.D. in chemistry from the California Institute of Technology and served as a visiting professor at the Max Planck Institute before joining Northwestern University, where he directs a

[6] https://cabig.nci.nih.gov/workspaces/TBPT/

multidisciplinary team of computational biologists, bioinformaticians, and information technology (IT) specialists.

Dr. Kibbe began by noting the potential of caBIG™ to advance personalized medicine. The software tools developed within the caBIG™ have been designed to enable effective management of biomedical research. Additionally, the caBIG™ team is developing common vocabularies, data elements, and architecture to enable virtual repositories and multisite studies.

IT can facilitate implementation of many recommendations of the *NCI Best Practices*. A resource's IT platform can integrate with clinical data systems to link clinical annotation to stored biospecimens. Security—physical access, system backups, and login protections—remains a staple of IT support. IT aids resources in serving as an honest broker and implementing regulatory requirements. Finally, it is essential to biospecimen resources' ability to track biospecimens: Assigning each distinct entity a unique identifier; tracking the parent-child relationships between biospecimens and resultant samples, extracts, and aliquots; linking biospecimens to physical labeling; and supporting barcoded containers and processes. Software modules developed within the TBPT Workspace integrate these functions and enable custom solutions to meet each resource's needs.

When resource managers aim to build or purchase biospecimen tracking software, Dr. Kibbe recommended that the true costs of system development, installation, and maintenance be evaluated; a plan for the future be established, ensuring that the software platform is robust enough to last the lifetime of the biospecimen resource; and a system of development methodology (e.g., unified process) be used.

Dr. Kibbe then listed several benefits of caBIG™ to biospecimen resources, researchers, and advocates:

- Software development costs may be reduced.
- Even small biospecimen resources may advertise their biospecimen and data availability as well as learn what others have to offer.
- Researchers can choose what data to share.
- Built-in security and privacy considerations can enhance patient confidence.
- The increased data sharing facilitated by caBIG™ improves the effectiveness and efficiency of cancer research, helping individual scientists, the cancer research community, and, ultimately, the cancer patient.

He explained that there are multiple pathways to caBIG™ compatibility[7]: Adopting caBIG™ tools, mapping an existing tool to caBIG™ tools, or making an existing tool caBIG™ compatible for standard reports only. Three core caBIG™ biorepository and pathology tools have been developed, and together these modules comprise caTissue Suite. They are:

- *caTissue Core* is a biorepository management infrastructure that supports the key functions of biospecimen resources; i.e., inventory management.

[7] Visit *Informatics* at http://www.nci-bestpractices-forum.com/meeting/obbr/boston2007/webcast.asp#general

- *cancer Text Information Extraction System (caTIES)* imports information from a prose-based hospital pathology system to a biospecimen resource database.
- *caTissue Clinical Annotation Engine (CAE)* supports the addition of clinical annotation associated with biospecimens.

Each module is open source and has been carefully structured for interoperability with every other. Some specialized IT skills are required to adopt caBIG™ tools or make an existing tool caBIG™ compatible, but installation and use do not require hiring a full-time staff or investing in an IT laboratory. Dr. Kibbe concluded by affirming that now is the time to adopt caBIG™ because the new caBIG™ Enterprise Support Network is available to help deploy the system. [8]

Demonstration of caBIG™ Biospecimen Resource Management Tools
Warren Kibbe, Ph.D.

Using screen shots, Dr. Kibbe walked attendees through the main features of caTissue Core version 4.0, which was designed to coordinate the workflow around biospecimen collection, annotation, and distribution. The software has multiple information entry and access points. After logging in, users can register participants, designate specimen collection groups and protocols, add biospecimens, enter collection events, and extract data reports. Users can click on a record to access information, from participant demographics to the locations of related aliquots. The software also has the ability to merge data—such as patient clinical data—from other systems and has the flexibility to enter multiple biospecimens at one time, run queries and reports, and accept microarray data. Graded access levels help protect system security and participant privacy, determining how much information a user may view or whether he or she can define protocols and create reports. caBIG™ tools are available as free downloads at the caBIG™ portal under the TBPT Workspace.[9]

Question-and-Answer Session

A participant asked for whom caBIG™ is intended: Protocol designers, biospecimen collectors, patient registrars, individuals obtaining a patient's informed consent, etc. Dr. Kibbe replied that anyone with a role in biospecimen processing would be able to use the software, with each entering the data he or she collected. Dr. Ian Fore (Associate Director for Biorepository and Pathology Informatics, NCI Center for Bioinformatics) added that caTissue was designed for biorepository use, and consent coverage is limited to purposes of querying, not the range of consent tracking that might be seen in a clinical trial. However, an application program interface may be used to integrate patients registered in another system into caTissue, precluding the necessity of manually reentering the information. The participant then asked how caTissue would handle biospecimens derived during a single surgery that were used in different research projects. Dr. Fore answered that caTissue allows registration of one patient for multiple protocols. Because caTissue is a Web-based application, it is possible for distributed sites conducting portions of a study to enter information about a single patient.

[8] http://cabig.nci.nih.gov/esn
[9] http://cabig.nci.nih.gov/workspaces/TBPT

The manager of a small biospecimen resource asked what computer hardware is necessary to run caBIG™. Dr. Kibbe and Dr. Fore explained that a server-class machine, running Linux or Windows, is required to deploy the system, but users can access the software from any personal computer running a modern Web browser on any operating system.

Another participant inquired whether caBIG™ software is specific to cancer samples. Dr. Kibbe replied that users could enter data about any biospecimen type, and although many of the drop-down menus are cancer specific, it is possible to extend fields to accommodate other needs. If this were done using NCI vocabulary, the software would remain caBIG™ compatible. In response to a followup question, Dr. Fore replied that the system is easily extended to add variables and images. caTissue can house uniform resource locators; thus, it is possible to enter images with a Web address. Finally, caTissue Suite, which is in the final testing stages, includes more dynamic extensions to enable users to add to the system.

Cost Recovery Models and Other Economic Issues Involved in the Implementation of the *NCI Best Practices*

Julie Schneider, D.Phil., Technology Program Manager, OBBR
Lisa Miranda, Technical Director, Tumor Tissue and Biospecimen Bank (TTAB), University of Pennsylvania (U Penn)

Dr. Schneider earned a D.Phil. from Oxford in human molecular genetics. Since joining the OBBR, she has co-led an initiative to study the economics of biobanking with Dr. Jim Vaught, Deputy Director of OBBR. Lisa Miranda is Technical Director of the U Penn TTAB. In this position, she developed a detailed cost recovery model successfully implemented at the TTAB.

Background and Overview

Dr. Schneider began by stating that several economic areas of interest to the NCI OBBR have emerged from public comments and conversations with area experts, as follows: Understanding the overall economic value of biospecimen resources, supporting the NCI leadership in efforts to control the costs of biospecimen resources in an era of NIH budget limitations, and determining the associated costs of implementing the *NCI Best Practices*. The OBBR has recently become aware of work by economists on measuring the value of biological resource centers (BRCs), defined as institutions that preserve materials over long periods of time and provide the community with broad access to these materials (the prototype BRC being the American Type Culture Collection).[10] BRCs have an important economic role in that they amplify the impact of scientific progress by enabling future generations of researchers to build on past discoveries. In addition, BRCs function to authenticate the quality of materials, preserve materials that may have future value over a long period of time, provide broad access to the research community, and exploit economies of scale. Despite data to support the macrolevel economic value of BRCs, economists recognize that it can be costly and challenging for individual institutions to maintain such resources.

In light of these discoveries, the NCI has been exploring the potential for cost recovery to supplement other support mechanisms for biospecimen resources. References to a cost recovery

[10] See Jeffrey L. Furman and Scott Stern, "Climbing Atop the Shoulders of Giants: The Impact of Institutions on Cumulative Research," NBER Working Paper 12523, September 2006.

model in the *NCI Best Practices* emphasize developing user fees that do not exceed cost recovery and ensuring that user fees do not become prohibitive and thereby impede research. Dr. Schneider acknowledged that despite the practicality of a cost recovery model, there are challenges associated with it because of the diversity of biospecimen resource and funding models.

Biobanking Cost Recovery

Ms. Miranda opened her presentation with a brief description of TTAB at U Penn, a newly established core facility created with the intention to centralize the institution's biospecimen resources. After 2.5 years of existence, the facility is servicing approximately 20 protocols, a number that will expand with the opening of a new laboratory space, anticipated in February/March 2008. Ms. Miranda explained that to become a core facility, the resource must prove financial viability; thus, with only modest startup funding, cost recovery is vital to the resource's continued existence. The resource provides a full range of services with more than 90 percent of its costs recovered in user fees. Resource user types are individual investigators, departmental banks, and external institutions for which TTAB functions as a virtual resource. TTAB is using NCI's caTissue as its primary biospecimen inventory system to support these users.

After reviewing the basic elements and value of cost recovery as a business tool for biospecimen resources, Ms. Miranda described the TTAB's 12-step pathway to cost recovery. She began the process by comparing user fees at 30 institutions, exploring user fee issues and potential questions, using the resource's scientific advisory committee as a focus group to gauge the research community's reaction to a fee-for-service model. Next, she determined the services that would be offered and developed and standardized labor metrics for each procedure. User fees then were developed from the cost analysis and quotes built for customer planning purposes. Final steps included implementation of the billing process followed by reanalysis to fine-tune the model. Ms. Miranda recognized that cost analysis is labor intensive but argued that the time demands will only increase if the cost analysis is delayed. She also acknowledged challenges in billing and described success with transparent invoicing, building quality assurance into the price structure, and providing mechanisms for collaborators to continue funding activities that the resource otherwise would be unable to do. Ms. Miranda closed by endorsing cost recovery as a form of sustainable development as well as a method to achieve financial security for biospecimen resources in uncertain economic times.

Question-and-Answer Session

A number of participants' questions revolved around specific costs and charging practices at TTAB and how biospecimen resources interested in a cost recovery model could benefit from Ms. Miranda's experience. In response, she directed participants to the TTAB's Web site where a document containing the resource's costs per basic service can be downloaded in PDF. She indicated that a narrative description of each service is included in this document.[11] In addition, she is developing a "how-to" manual for managers interested in implementing a cost recovery system at their resource. The TTAB is an early adopter of NCI's caTissue, which at this time does not have a built-in cost recovery feature or link to a local billing system. Ms. Miranda

[11] http://www.med.upenn.edu/bmcrc/tumor/index.shtml?tumor

explained that some of the costs associated with caTissue (e.g., data entry) are incorporated into user fees.

The discussion turned to more philosophical considerations related to a cost recovery model; for example, how capturing costs can be balanced with not inhibiting future unspecified research. Ms. Miranda acknowledged that it is challenging to balance a resource's and investigators' needs. She said that the TTAB encourages unfunded investigators to find a sponsor, and they do not charge an investigator until services are rendered. A participant commented that the biospecimen resource he directs is partially funded and does not charge surgeons or surgical pathologists for services. This approach has boosted surgeon and pathologist cooperation in a cost recovery model. Ms. Miranda indicated that TTAB hopes to implement a similar strategy once it obtains partial subsidization.

In closing, Dr. Compton remarked that a fee-for-service model at biospecimen resources will indirectly help defer costs back to the NCI because applicants will be able to include anticipated charges for specimens in their grant budgets. Besides the obvious benefits to investigators, such a practice will help the NCI (1) gauge its investment in biobanking activities as they would be linked to funded research and (2) eliminate the problem of poorly maintained biospecimens being used in the research it supports.

Part 3: Next Steps and Closing Remarks

Assessing the Effects of Preanalytical Variables on Molecular Research: The Biospecimen Research *Network*

Helen Moore, Ph.D., Administrative Director, Biospecimen Research Network (BRN), OBBR, NCI

Dr. Moore is Director of the BRN, a new NCI research program whose goal is to sponsor, conduct, and collaborate on scientific studies of how biospecimen collection, processing, and storage variables influence the molecular integrity of those biospecimens. Dr. Moore has a broad background in research and product development and worked on the Human Genome Project at Celera Genomics before joining the NCI.

Dr. Moore asserted that translational research will advance molecular medicine and lead to personalized patient care. High-throughput technologies critical to translational research, such as genomics and proteomics, require high-quality, well-annotated human biospecimens. The BRN takes a comprehensive approach to improving biospecimen quality by developing, promoting and implementing evidence-based best practices. The BRN is improving accessibility to existing evidence on how biospecimen variables affect molecular analyses through the Biospecimen Research Database and the upcoming 2008 BRN symposium, Advancing Cancer Research Through Biospecimen Science.[12, 13] In addition, the BRN is identifying biospecimen research needs for new extramural programs and conducting associated research in the BRN intramural laboratory. Molecular analysis technology development also is being supported by the NCI Innovative Molecular Analysis Technologies, or IMAT, Program via a request for applications

[12] http://brd.nci.nih.gov/BRN/brnHome.seam
[13] http://www.brnsymposium.com

on innovative technologic solutions for cancer sample preparation. Finally, the BRN is establishing strategic partnerships with organizations such as the CAP to develop data-driven, specimen-specific, platform-appropriate standard operating practices (SOPs) that will be incorporated into the CAP's laboratory accreditation programs.

The BRN will conduct comprehensive studies to identify the impact of tissue preservation variables on a biospecimen's molecular profile. To improve prospective biospecimen collections, the BRN aims to define the most significant variables for the collection of tissues, blood, and body fluids. One such study, conducted in collaboration with the NCI Clinical Proteomic Technology Assessment for Cancer program, will address issues involved in prospective blood collection and plasma processing as well as the development of evidence-based biospecimen quality indicators to assess the usability of archival plasma collections.

Dr. Moore concluded by stating that the BRN contributes to the evolution of biospecimen resources by developing and implementing state-of-the-science processes that ensure the molecular integrity and clinical relevance of human biospecimens used in cancer research and clinical medicine. She also invited attendees to respond to an upcoming request for information regarding tissue preservation variables.

Biospecimen Research Database
Ian Fore, D.Phil., Associate Director for Biorepository and Pathology Informatics, NCI Center for Bioinformatics

Dr. Fore is Associate Director for Biorepository and Pathology Informatics at the NCI Center for Bioinformatics and a full member of the OBBR team. He has worked in drug discovery at Wyeth Pharmaceuticals and Johnson and Johnson and as a product manager at Celera Genomics, where he was responsible for integrating customer bioinformatics systems.

The Biospecimen Research Database is a Web-based tool that tabulates information regarding the effect of biospecimen handling factors on experimental results within various analytical platforms. The database is being populated with evidence that has been expertly curated from published studies, unpublished results, and ongoing BRN experimentation. Future steps for the database include meta-analyses of biospecimen handling data to help define the state of the science in biospecimen research, development of evidence-based SOPs, and an online library of biospecimen protocols.

The Biospecimen Research Database matrix comprises specimen types on one axis and analysis platforms on the other. Cells at the intersection of these two axes show the number of pertinent studies that have been entered in the database to date. By clicking on a cell, researchers can access citation information and PubMed links to the relevant publications, structured study data, and free-text entries about the purpose and conclusions of the study as well as individual study findings. Users can also locate data by searching the structured values in the database for particular terms.

Dr. Fore requested input from the audience on the level of interactivity of the database. One possibility would be to enable Web 2.0 mechanisms (i.e., open-access Wiki- or forum-like input

capability with minimal oversight). Another option would be controlled access to data entry, which would provide more concise analyses of the evidence. He requested that participants contact the OBBR to recommend key scientific papers and protocols and/or to volunteer their assistance.

Question-and-Answer Session

A participant lauded the development of the Biospecimen Research Database and urged anyone with pertinent data to publish in peer-reviewed journals.

In response to an inquiry, Dr. Compton commented that negative results are particularly important to biospecimen science. In addition to awareness of the factors that will adversely affect biospecimen quality, it is important for researchers to know which factors they can disregard. Consequently, she encouraged members of editorial boards to value the publication of negative findings.

A participant suggested that one way to ensure that protocol data are published would be to use material transfer agreements (MTAs) requiring companies to provide their protocol optimization data. Dr. Compton agreed, saying that the *NCI Best Practices* encourages the use of MTAs. On the same topic, another participant asserted that many Government agencies such as the FDA's Center for Biologics Evaluation and Research and the Centers for Disease Control and Prevention must have a great deal of data relevant to biospecimen handling; he asked whether these data could be deidentified and made public. Dr. Compton replied that confidentiality agreements preclude divulging proprietary information, but such information could be made available directly from pharmaceutical and device manufacturers, some of whom seem enthusiastic about doing so. She assured the audience that the NCI is aware of problems arising from different requirements between institutions; collaborations with the FDA, the Centers for Medicare and Medicaid Services, the American Association for Cancer Research, academia, and industry are aimed at coordination.

Closing Remarks
Carolyn Compton, M.D., Ph.D.

In closing, Dr. Compton assured participants that these forums represent the beginning of a partnership with the research community to address biospecimen-related issues. The NCI is providing tools for improving biospecimen resources; in turn, members of the research community are encouraged to provide feedback on the programs in development. Finally, she expressed her appreciation for attendee participation in this landmark effort of biospecimen resource standardization.