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

SUMMARY

National Cancer Institute Biospecimen Best Practices Forum

The Conference Center at Harvard Medical
Boston, Massachusetts

November 5, 2007

Prepared by:
Rose Li and Associates, Inc.
January 2008

Table of Contents

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 heavily upon the quality and consistency of the biospecimens analyzed in the translational and validation research arenas.

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, as well as from patients, survivors, advocates, and authoritative sources and regulatory bodies, 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 the quality and consistency of biospecimens and their related data 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 Boston, MA. This forum was the second 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*.

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

II. PART 1: OVERVIEW AND DISCUSSION OF *NCI BEST PRACTICES*

NCI Best Practices for Biospecimen Resources

Why Do We Need Biospecimen Best Practices?

Carolyn C. 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 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*.

Dr. Compton opened the forum by stating that cancer research is at an inflection point as exponential technological advances enable new understanding of cancer biology. High-quality biospecimens are essential for taking full advantage of new techniques and moving into an era of personalized medicine. The dearth of large quantities of high-quality, clinically annotated biospecimens is the main roadblock to advances in translational medicine.

The biospecimen banking community faces significant challenges from varying processes and procedures that compromise molecular research:

- Methods of collection, processing, and storage can affect the physical or biologic state of the biospecimen.
- Biospecimen-associated data elements influence how much the researcher knows about the character and nature of the specimen.
- Clinical information determines what the researcher knows about the patient and, therefore, the biologic context of the biospecimen.
- Legal, ethical, and policy restrictions—such as those relating to informed consent documents—dictate what the researcher may do with the biospecimen or the data.

To address these issues, the NCI, in conjunction with the biospecimen research community, has identified key requirements for biospecimen resources.[3] These requirements include 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; state-of-the-art

[3] 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/.

informatics systems to track biospecimens, associated data (clinical, pathological, and quality control), and patient consents; and communication with the public.

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 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
Martin L. Ferguson, Ph.D., Pharmaceutical and Life Sciences Consultant

Dr. Ferguson served as Director of Bioinformatics at Axys Pharmaceuticals and Senior Vice President of Bioinformatics and Cofounder of Ardais Corporation, a company whose mission was to build and deploy annotated biospecimen collection systems. Dr. Ferguson is now an independent consultant to pharmaceutical and life science informatics companies and Federal agencies such as the NCI.

Dr. Ferguson used his experience with The Cancer Genome Atlas pilot project to illustrate real-world biospecimen issues. The pilot study was designed to comprehensively catalog the molecular changes associated with cancer through large-scale molecular analyses of brain, ovarian, and lung cancer tissues obtained from retrospective collections. 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. Sometimes half or more of the biospecimens lacked accompanying blood samples (needed as a source of germline DNA); others were of inadequate size, cellular composition, or molecular quality. Some biospecimens failed to meet the requirement of being treatment naïve due to prior chemotherapy or radiation. To have an adequate number of samples, investigators decided to obtain biospecimens from more than the anticipated two retrospective collections. In addition, they may collect some biospecimens prospectively.

Several lessons can be drawn from this example: (1) The quality of existing sample sets is typically overestimated by biospecimen resources, (2) the collection of control samples is not routine in existing protocols, (3) anatomic site-matched normal controls may be nonexistent, and (4) histological quality does not guarantee molecular quality. Data are lacking to define quality parameter delimiters accurately; for example, it is unknown how cellular composition and tumor necrosis affect genomics profiling and whether the DNA and RNA yields can be estimated by sample weight. Biospecimen research is needed to understand effects of biospecimen variables on analysis data from different platforms.

Dr. Ferguson concluded that the implementation of the *NCI Best Practices* can reduce such failure rates in future studies, and therefore, it is worth the upfront investment to handle biospecimens accordingly. Biospecimen banking, too often considered a sideline activity, is an exacting science requiring SOPs. Every biospecimen protocol should be treated with the rigor of a clinical trial, and participants should be tracked over time. Investigators ought to perform histopathology review and molecular quality control assessments prior to biospecimen deposition, categorizing biospecimens according to quality and discarding biospecimens as appropriate.

Overview of Ethical and Policy Best Practices

Ethical and Policy Implications of Using Human Biospecimens in Research: What You Need To Know

P. Pearl O'Rourke, M.D., Director, Human Research Affairs, Partners HealthCare System

Dr. O'Rourke is a pediatric critical care physician who has dedicated her recent career to public policy and healthcare. She is Director of Human Research Affairs at Partners HealthCare Systems and Associate Professor of Pediatrics at Harvard Medical School.

After a presentation of section C of the *NCI Best Practices* on informed consent, privacy protection, custodianship, intellectual property, and access, Dr. O'Rourke summarized some of the challenges related to the best practices and their implementation. Institutions are expected to voluntarily adopt the *NCI Best Practices*, but it is unclear what happens if an institution decides not to do so. Assuming they are adopted, an institution must then decide if these best practices will be applied to oncology tissue banking or all specimen banking. Institutions may also encounter logistical problems in following multiple sets of guidelines and best practices promoted by a variety of regulatory bodies, funding agencies, and professional societies. Custodianship challenges involve questions of what constitutes a "gift," contributors' expectations in terms of future access to the donated tissue and research results, and the effects of State-based court decisions on biospecimen ownership rights. Biospecimen sharing and intellectual property considerations present challenges in terms of standardization of access rules and questions of exclusivity.

Informed consent raises challenges including, among others, ethical and logistical questions about the timing and process of obtaining informed consent, how to handle consent from children, and managing the logistics of tiered consent. The lack of harmonization between the Health Insurance Portability and Accountability Act (HIPAA) and the Common Rule[4] presents an additional challenge.

Dr. O'Rourke focused on one specific element of the *NCI Best Practices*, discontinuation of participation, to illustrate the myriad challenges raised by a single issue. The Common Rule confers the right to discontinue participation in research. The *NCI Best Practices* recommends that following a request for discontinuation of participation, identifiable biospecimens and clinical data be withdrawn from the repository, with the exception of specimens that have already been transferred to recipient investigators as they cannot realistically be withdrawn. In

[4] Title 45, Code of Federal Regulations, Part 46 available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

direct conflict, the *NCI Best Practices* also recommends that biospecimen resources are ethically obligated to inform recipient investigators whenever permission has been withdrawn. It also recommends that those investigators determine how to handle relevant samples. This adds significant confusion. Dr. O'Rourke suggested that the *NCI Best Practices* should clearly state that investigators have the right to use any biospecimens and data they receive and that consent forms should indicate that discontinuation of participation only will apply to biospecimens that remain in the banking facility.

Dr. O'Rourke concluded by citing biospecimen banking as an invaluable resource for biomedical research and commended the NCI on its solicitation of feedback on the *NCI Best Practices* and its willingness to continue addressing these issues.

caBIG™, caTissue, and Achieving Silver-Level Compatibility
Informatics Solutions to Biospecimen Management: Finding the Right Tools for Your Resource
Ian Fore, D.Phil., Associate Director for Biospecimen and Pathology Informatics, NCI Center for Bioinformatics

Dr. Fore is Associate Director for Biospecimen 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.

Dr. Fore underscored the multiple applications of information technology (IT) in attaining the goals of the *NCI Best Practices*, from research participant registration to reporting. Key features of IT in biospecimen resources include its application to biospecimen tracking; the potential for integration with clinical data systems to connect clinical annotation with stored biospecimens; security, including physical access, system backups, and login protections; and support in implementing regulatory and sharing requirements.

Dr. Fore offered the following recommendations for resource managers aiming to build or buy biospecimen tracking software:

- Structured databases are preferable to free-text records.
- The true costs of system development, installation, and maintenance need to be evaluated.
- A plan must be established for the future, ensuring that the software platform is robust enough to last the lifetime of the biospecimen resource.
- Software developers ought to heavily involve end users, employing use cases to follow a system of development methodology (e.g., unified process) and strive for Capability Maturity Model® Integration Level 3.

Partially in synergy with development of the *NCI Best Practices*, the NCI engaged in building information systems to support the research community's IT needs. This endeavor, named the cancer Biomedical Informatics Grid (caBIG™), comprises a community of over 1,000 individuals working in the domains of clinical trial management systems, integrative cancer research, biospecimen banks and pathology tools, and *in vivo* imaging. CaBIG™ also is

developing vocabularies and common data elements and architecture to support other research domains.

In an effort to avoid penalizing systems based on size, the caBIG™ approach is intended to apply across the cancer research landscape, which ranges from institutions with integrated, IT staff-supported systems to those with informal or no information systems. The three prongs of the caBIG™ approach are the development of modules that address specific needs, connection through defined electronic interfaces, and use of international data standards. Dr. Fore emphasized that the focus of caBIG™ is not on the use of particular applications but rather on the boundaries and interfaces between them, with the assumption that the applications will be diverse and will change over time.

Within the area of biospecimen research, caBIG™ has a number of objectives, including creating virtual repositories and supporting multisite studies, among others.[5] Dr. Fore noted that institutions may follow any of multiple pathways to caBIG™ compatibility: Adopt caBIG™ tools, map an existing tool to caBIG™ tools, or make an existing tool caBIG™ compatible for standard reports only. Dr. Fore listed several benefits of caBIG™ to biospecimen resources:

- 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.
- Most importantly, 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 emphasized that just as the willingness of cancer patients to share their specimens is fundamental to cancer research, the willingness of researchers to share biospecimen-related data is critical to maintaining public trust.

Dr. Fore then briefly described three core caBIG™ biorepository and pathology tools:

- *caTissue Core*: Biorepository management infrastructure that supports the key functions of biospecimen resources; i.e., inventory management
- *cancer Text Information Extraction System (caTIES)*: Supports importing information from a hospital pathology system to a biospecimen resource system
- *caTissue Clinical Annotation Engine (CAE)*: Supports the addition of clinical information associated with biospecimens

Each of these tools is open-source software available as a free download at the caBIG™ portal under the Tissue Banks and Pathology Tools Workspace domain.[6] Some specialized IT skills are required to adopt caBIG™ tools or to make an existing tool caBIG™ compatible, but installation and use do not require hiring a full-time staff or investing in an IT laboratory.

[5] These caBIG objectives are further explained in biospecimen resource-specific materials available at. http://www.nci-bestpractices-forum.com/meeting/obbr/boston2007/webcast.asp#general.
[6] https://cabig.nci.nih.gov/workspaces/TBPT/

In closing, Dr. Fore described caBIG™ future efforts directed to developing a support network for caBIG™ users. He also invited participants to obtain background information about caBIG™ by visiting http://cabig.cancer.gov and to join the technical effort by visiting http://cabig.nci.nih.gov.

The Importance of Best Practices to Patients, Survivors, Advocates, and the General Public
It's All About the Patient: Putting Biospecimen Research in Perspective
Paula Kim, President and Chief Executive Officer, Translating Research Across Communities

As a long-time advocate for patients with pancreatic and other cancers, Ms. Kim has worked to coordinate the efforts of industry, science, and academia and in doing so has contributed to a number of initiatives, including C-Change and the FDA Patient Consultant Program.

Ms. Kim opened her presentation by pointing out that biospecimens cut across many domains: Physical, behavioral, social, cultural, economic, political, spiritual, and technological. The use of human specimens in research has been occurring for more than 100 years and predates many aspects of medicine, including oncology. Biospecimens are precious human resources that the research community is privileged to use, and this use comes with responsibility.

Ms. Kim noted that many cancers have a mortality rate greater than 45 percent while the development of new treatment products takes several years and a significant investment; no one is more interested in seeing these statistics change than patients. 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. Furthermore, when patients give their biospecimens to research, they believe that the biospecimens will be used in a manner that is appropriate, with free and open access to qualified investigators; therefore, patients likely would be disappointed at the limited sharing within the research community. Ms. Kim stated that the *NCI Best Practices* will help to earn patient trust and confidence, which is critical to their involvement in the research process, and she asked researchers to be incentivized by the patient benefit in all of their actions.

Ms. Kim proceeded to enumerate the consequences of poor biospecimen research practices, including eroding public confidence and impeding the accrual of benefits to patients. Appropriate infrastructure and a commitment of resources are needed in biospecimen research to produce data with integrity that ultimately will benefit patients. Publication of the *NCI Best Practices* represents a great opportunity to move this research agenda forward. In closing, Ms. Kim stated that patient advocates also are 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 and Panel Discussion

A pathologist in the audience asked how to handle a situation in which a research participant contacts the biospecimen resource requesting a newly available assay on his or her biospecimen, but the biospecimen already has been used in its entirety. Dr. O'Rourke replied that State laws currently dictate how long clinical biospecimens must be retained and wondered whether a new

standard of clinical care ought to be established in which some portion of tumor tissue is kept in perpetuity. That responsibility ought not to be migrated to the research biospecimen resource; biospecimens given for research must be those that are not needed for current or future clinical care. Ms. Kim emphasized the importance of developing infrastructure that acknowledges the importance of maintaining biospecimens and their associated clinical data.

A patient advocate asked how to ensure that good-quality biospecimens are used in studies if they are being collected at locations with varying standards. Ms. Kim responded that the obstacles are control and cost: Who has custodianship of the biospecimen, what protocols will be followed, and who will cover the costs? A system and process is needed by which consistent, high-quality biospecimen handling can be ensured.

The same advocate pointed out that another patient frustration is the lack of biospecimen sharing due to informed consent limitations. She asked whether there is a way to get around consent limitations in HIPAA and Common Rule regulations. Dr. O'Rourke acknowledged that many people wish there was a way to authorize "universal permission," but others do not. For example, some research participants refuse to allow their biospecimens to be used for contraception research or in studies that involve fetal tissue. Ideally, guidance from the Department of Health and Human Services Office for Human Research Protections (OHRP) and the FDA, along with recommendations from the *NCI Best Practices*, would inform a template for informed consent regarding biospecimen banking. Dr. Compton added that several governmental agencies are examining how HIPAA regulations interfere with translational research.

Another participant asked about Dr. O'Rourke's suggestion that there may be overuse of certificates of confidentiality, noting that in many cases, such certificates are essential due to the sensitive nature of the research. She asked how one would protect the privacy of research participants involved in such studies and convince them that they are protected without certificates of confidentiality. Dr. O'Rourke assured her that there will always be instances in which the certificates are necessary. Dr. O'Rourke clarified that since the NIH includes collection of genetic information as an example of "sensitive research" that may necessitate a certificate of confidentiality, she is concerned that the prevalence of genomic technologies may lead any research involving biospecimens or genetic material to qualify for a certificate of confidentiality, which could diminish the effectiveness of a certificate of confidentiality. Dr. Compton added that although certificates of confidentiality are the strongest privacy protection currently in place, they do have limits; only a genetic privacy act could provide protection from criminal misuse of genetic data.

A pathologist asked about consent management in facilities that are not set up for obtaining consent from ambulatory outpatients. Dr. O'Rourke agreed that there is not a simple solution to this question; current healthcare providers are focused on moving patients through the system rapidly, which leaves little time for informed consent administration. Perhaps an informed consent kiosk could be made available to answer questions as patients self-administer consent forms. Another option to investigate is Web-based informed consent.

An epidemiologist inquired about support for choosing and interfacing a new informatics system with an aged retrospective collection. Dr. Fore indicated that the NCI will not dictate

biorepository software choices, but it does offer a process designed to help institutions identify software that will meet their needs; for example, by providing lists of functionality areas to help identify requirements and match them with various software options. Dr. Ferguson mentioned that several for-profit companies provide analysis and integration services.

The same participant expressed concern about the cost of such consultation and of upgrading biospecimen resource informatics. Dr. Compton agreed that cost concerns are significant. The NCI invested in developing caBIG™ to enable interoperability and thus serve the greater good of the research community. However, additional investments must come from several sources: Academic institutions, industry, and public organizations, as well as from tax dollars. Ms. Kim added that Federal and State governments have a tremendous responsibility to address this issue and urged attendees to ensure that their concerns about the importance of healthcare and biomedical research be heard in upcoming elections.

III. Part 2: Concurrent Breakout Sessions

Detailed summaries of the breakout session presentations and discussions are found in the appendix.

IV. Part 3: Closing and Adjournment

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

Elisa Eiseman, Ph.D., Senior Scientist, RAND Corporation

Dr. Elisa Eiseman joined the RAND Corporation in 1996 and collaborated with the NCI on a study of biorepository best practices and development of the National Biospecimen Network concept.[7] She most recently has been working with the OBBR to develop a searchable, Web-based tool for biospecimen research data.

Dr. Eiseman introduced the Biospecimen Research Database (BRD)[8], a searchable, Web-based curation tool designed to help investigators maximize the quality and utility of biospecimens by analyzing existing data on how biospecimens are affected by preanalytical handling variables such as acquisition, processing, storage, and distribution. While the BRD is being developed with the NCI OBBR to advance cancer research, it will have broad application to any research involving biospecimens.

Development of the database began with a comprehensive literature search for studies of the effects of preanalytical variables on the quality of biospecimens used to investigate genetic changes in cancer. Dr. Eiseman noted that few published studies specifically look at the effects of biospecimen handling variables; such investigation often is considered preliminary background research and might only appear as a line or two—if at all—in the final publication.

[7] For more information on the National Biospecimen Network, visit http://biospecimens.cancer.gov/biospecimen/network/.
[8] http://brd.nci.nih.gov/BRN/brnHome.seam

The data from the literature analysis were entered into the BRD. The tool's data collection fields include biospecimen type, the associated diagnosis, identity of the biomolecule of interest, analysis platform, and biospecimen handling variables. The tool also has fields for basic information about the publication such as the PubMed identification number, title, and author names as well as an open-text field to enter information about the publication's purpose and conclusion. For each publication several different studies of preanalytical variables may be described, and each one is entered into the BRD as a separate study. Over the past year, 65 papers describing 145 different studies have been reviewed.

The OBBR intends to make this tool publicly available on the OBBR Web site as a service to the research community. This is an ongoing project whose next steps are to continue populating the BRD with data from other studies, including information from procedures for clinical laboratory testing and from other potential sources of data such as OBBR-funded studies of preanalytical variables and unpublished drug-development studies by industry colleagues.

Dr. Eiseman concluded by stating that the BRD will be used by the OBBR in several ways: (1) To inform development and prioritization of Biospecimen Research Network (BRN) laboratory studies, (2) to identify new areas of research funding, and (3) to inform development of evidence-based SOPs. Researchers may search the BRD for the results of studies on the effects of preanalytical variables and use the information to inform the design of their research investigations and to interpret subsequent results.

Next Steps for NCI Best Practices: Biospecimen Research for Molecular Medicine
Carolyn Compton, M.D., Ph.D.

Dr. Compton stated that one of the OBBR's immediate goals is to facilitate personalized medicine by improving the evidence base for the *NCI Best Practices*. The OBBR further intends to legitimize biospecimen research as a scientific endeavor through focused funding and support. The multidisciplinary field of biospecimen research is aimed at developing experimentally tested and proven biospecimen handling procedures. Its premise is that quality is not a generic concept; many aspects of collection, processing, and storage can compromise quality. Thus, the OBBR intends to address physical and molecular biospecimen quality through a variety of approaches. Population of the BRD will facilitate an analysis of needed biospecimen research data that may be supplied by the intramural BRN and a new, extensive extramural research program. The OBBR also will support technology development and form strategic partnerships with organizations, such as the College of American Pathologists, with the goal of incorporating new biospecimen handling data into SOPs in laboratory accreditation programs.

Dr. Compton underscored the need to develop evidence-based SOPs by describing the potential effects of variations in biospecimen quality. First, variable results in molecular analysis between and within laboratories are detrimental to technology development because it is unknown whether the variation stems from a poor-quality analyte, variation in technology, or both. Therefore, minimizing analyte variation will allow comparisons among existing technologies and support the development of new technologies. Second, biospecimen variation has the potential to effect adverse clinical outcomes, including misdiagnosis and incorrect treatment. Third, research outcomes are negatively affected by biospecimen variables when results are irreproducible and,

more importantly, when artifacts are misinterpreted as biomarkers. Thus, there needs to be an evidence base for SOPs that defines which variables need to be controlled and which do not impact biospecimen quality. In addition, Dr. Compton called for an elucidation of the effects of unmodifiable patient care factors (such as anesthesia) on biospecimen quality so that data analyses account for such factors appropriately.

Dr. Compton outlined the OBBR's work for the upcoming year:

- Holding a series of national forums to educate the scientific community about the *NCI Best Practices* and obtain feedback. This forum will be followed by meetings in Chicago and Seattle over the next 3 months.
- Hosting symposia on complex biospecimen issues, the next of which will cover custodianship; resulting white papers will be published on the OBBR Web site.
- Initiating an extramural biospecimen research program by publishing a Request for Information/Request for Proposals and a Broad Agency Announcement as well as a Request for Applications for technological solutions to biospecimens issues through the Innovative Molecular Analysis Technologies Program.
- Holding the second annual Biospecimen Research Symposium in early 2008 (details will be available on the OBBR Web site in the near future).
- Continuing collaboration on key NCI and international initiatives.

Dr. Compton closed by expressing her appreciation for attendee participation in this landmark effort of biospecimen resource standardization. She hailed it as a paradigm shift for researchers, patients, and efforts to cure disease.

APPENDIX:

BREAKOUT SESSION SUMMARIES

Overview of the Critical Importance of Biospecimens in Cancer Research
Carolyn C. Compton, M.D., Ph.D., and Paula Kim

Dr. Compton and Ms. Kim welcomed participants to the breakout session, which featured a diverse group of participants including patients, patient advocates, industry representatives, institutional review board (IRB) members, pathologists, and biospecimen resource managers. Participants were referred to several tools designed to educate patients about participating in research through biospecimen donation; namely, NCI-developed publications as well as publications by the Research Advocacy Network and the Coalition of National Cancer Cooperative Groups.[9] Dr. Compton and Ms. Kim noted that the purpose of this session was to provide background information on biospecimens—and thereby greater context about the *NCI Best Practices*—to patients, patient advocates, and the general public. However, given the diversity in attendance, a greater emphasis would be placed on making the session interactive.

Dr. Compton opened the breakout session by providing definitions for key concepts and explaining that the current "one-size-fits-all" approach to medicine does not acknowledge or address the great differences among patients; for example, over 30 percent of patients in general do not benefit from medicines for their conditions. Thus, the NCI is interested in supporting research into more targeted treatment to have an optimal effect on tumors and minimize detrimental effects on patients from excessive or inappropriate therapy.

The move toward personalized medicine is driven by genomics, proteomics, and metabolomics, powerful and relatively new research analysis approaches that require high-quality human specimens. Historically, researchers were limited to studying one gene or protein, but these new "array" technologies permit a single investigator to study all genes and proteins in real time, creating a fingerprint of a molecular complex. This spectacular advance generates vast amounts of data that are difficult to correlate with clinical outcomes, the step that will translate into improvements in patient care. However, these data will be misleading or unusable if they are generated from analysis of poor-quality biospecimens, which Dr. Compton cautioned would significantly hinder the search for treatments and cures.

Dr. Compton then reviewed the current system of biospecimen use that has existed in pathology departments for over 100 years. Millions of biospecimens residing in U.S. pathology departments comprise the largest repositories of human specimens today. However, the quality of many of these biospecimen is questionable due to the routine use of a formalin-fixing method and paraffin-embedding technique, the oldest technology still used in medicine. Although this process effectively preserves the structure of biospecimens indefinitely, it does not guarantee preservation of the molecular integrity of the specimen that is critical for more sophisticated analyses. In addition, there are no national standards in existence for collection and storage of biospecimens and no regulatory bodies overseeing resources for human tissue.

Dr. Compton next briefly traced the clinical and research paths a specimen takes after it leaves the human body. The focus of the clinical pathway is on diagnosis and treatment of an individual patient: The patient's specimen is processed and diagnosed by a pathologist, and the diagnosis and any other clinically relevant information is fed back to the patient through his or her primary

[9] All materials are available at http://www.nci-bestpractices-forum.com/meeting/obbr/boston2007/webcast.asp.

provider. The remainder of the specimen is stored for a certain number of years (as required by State laws, accrediting organizations, etc.), at which time resources are free to dispose of specimens, although some may choose to keep them. The second path for a biospecimen, the research pathway, typically begins with obtaining a patient's informed consent to participate in research. Investigators may gain access to the patient's biospecimen through the patient's physician, the pathology department or the biospecimen resource. The research enterprise culminates in investigation using the biospecimen that may lead to generation of new knowledge, publication of new data and/or, new treatments for patients.

Prior to opening the floor for discussion, Dr. Compton commented that in the research pathway, the potential loss of quality occurs upfront, as biospecimens may sit unprocessed for several days before being fixed, and there is no requirement to document how a biospecimen has been handled. Without this knowledge, a researcher has no way of determining the molecular integrity of a biospecimen prior to extraction.

Discussion

A pathologist in the audience asked whether there are ways to improve methods to extract RNA or DNA from samples so that partially degraded samples may be of some use. Dr. Compton responded that improving extraction methods will not advance research if all of the RNA has been degraded before the specimen is fixed. She stated that the change needs to occur a step back—in the preservation of the biospecimen's molecular integrity before stabilization occurs. One participant working in clinical trials research commented that her research group has overcome the quality issue somewhat by handling biospecimen collection in the operating room themselves. However, she acknowledged that this level of control becomes impossible in local, Phase II clinical trials. Dr. Compton responded that this is the reason why there is a need to standardize approaches to biospecimen collection and processing. Ideally, standard operating procedures (SOPs) based on scientific evidence should dictate biospecimen handling and annotation, patient consent, and material transfer because the procedures are proven to have optimal outcomes.

Another participant raised concerns about biospecimen collection and handling that compromise patient care in institutions with dual responsibilities for patients and research. Dr. Compton emphasized that ensuring patient care is the professional and legal responsibility of the pathologist. It was suggested by one participant that researchers can build personal relationships with physicians and pathologists to merge patient care with research goals, but Dr. Compton noted that this approach relies on the altruism of the parties involved, which would make it an unsuccessful approach on a large scale. She spoke to the need for incentivizing pathologists to change their behavior; for example, creating insurance billing codes that they can use to process biospecimens in such a way that preserves their molecular integrity. She concluded that it is pathologists who sit at the interface of patient care and research, and it is this workforce that needs to be educated, trained, and reimbursed to incorporate new demands on their time and expertise in an era of personalized medicine.

In response to a question regarding the use of formalin-fixed, paraffin-embedded blocks that are discarded by pathology departments every year, Dr. Compton pointed out that although it is permissible to use such biospecimens in research under current regulation as long as they have

been stripped of all patient identifiers, the larger issue is the questionable quality of the biospecimen. Unless comprehensive annotation of biospecimen handling and patient clinical information are available, using such specimens in research would not be advisable as the data generated may not be accurate. Dr. Compton added that biospecimen quality is an overriding issue for the pharmaceutical industry as its business decisions are based on the data yielded by biospecimen-based research.

A patient advocate recognized the need for better quantitation of the effects of biospecimen handing variables and inquired if the NCI is funding research in this area. Dr. Compton replied that although much of this type of research remains to be conducted, some studies have been published in the scientific literature. In collaboration with the RAND Corporation, the NCI is developing a searchable Web-based tool that will be populated with such data. Ultimately, researchers will be able to search the biospecimen research database to find SOPs for specimen handling that will yield consistent, optimal results. The NCI OBBR also has established the Biospecimen Research Network and will be funding research in which the biospecimen is the object of the study.

To achieve personalized medicine, evidence-based SOPs must become part of the standard of care in pathology departments across the Nation. Some of the challenges that currently impede this development are best illustrated by the biomarkers study conducted by the Prostate Cancer Specialized Programs of Research Excellence (SPOREs). Collaborating pathologists discovered that two parameters varied by an order of magnitude across SPORES: (1) Length of time of prostate specimen fixation and (2) the temperature of paraffin in which the tissue was embedded. Recognizing that biomarker immunohistochemistry results would not be comparable under these varying conditions, pathologists attempted to harmonize procedures for this study across SPORE sites. However, because hospitals administer pathology laboratories and controlling these parameters would change the laboratory workflow, turnaround time for specimens, and even the length of stay for patients, these changes were not put in place.

The final topic of discussion was biospecimen “hoarding” and how it represents an impediment to research. A participant explained that there is a sense of biospecimen ownership among pathologists but that they are willing to share specimens as long as the researcher has a good track record and the specimen will be used in valid research. Another discussant added that malpractice (i.e., that something may have been missed or misdiagnosed by the pathologist at the institution where the specimen is stored) is also a concern and felt that incentives to share biospecimens more broadly were lacking. Dr. Compton recognized the need to address this issue.

In closing, Dr. Compton summarized the session by enumerating the five key issues comprising this breakout group’s discussion.

- Improvement of biomolecule extraction techniques will not advance research if poor or variable biospecimen quality persists.
- Involvement of pathologists in the quality control of biospecimen collection is essential, as pathologists are responsible for making real-time decisions regarding what tissue needs to be preserved for diagnosis and what can be allotted to research without compromising patient care.

- There may be some value in salvaging biospecimens that would typically be discarded by pathologists after a period of time prescribed by state law or an accrediting agency. However, there needs to be quality indicators to help determine whether these biospecimens will be useful for research. Perhaps seeking IRB approval to deidentify rather than destroy biospecimens could aid research.
- As highlighted by the Prostate Cancer SPOREs, pathology departments vary widely in routine biospecimen processing. However, even the most highly motivated pathologists may not be able to reduce such variation because the laboratories are owned and operated by the institutions, not the pathologists.
- Biospecimen "hoarding," in which researchers limit others' access to biospecimens, was identified as an impediment to research. Thus, a challenge for the NCI is to find ways to ensure that biospecimens are used for research in an equitable and efficacious manner.

Dr. Compton thanked attendees for their participation and invited them to submit further questions and/or provide additional input to the OBBR on the *NCI Best Practices* via e-mail to biospecimens@mail.nih.gov.

Demonstration of caBIG™ Biospecimen Resource Management Tools
Ian Fore, D.Phil.

Dr. Fore opened the demonstration session by informing participants that three versions of caTissue Core have been released to date, with the most recent (version 1.2) released in June 2007. This version, which was developed by Washington University in St. Louis, underwent testing at 4 funded "adopter" universities, and is now in use at approximately 20 institutions. Enhancements from the previous version are primarily around usability and include easy access to edit data from search screens, support for a study calendar, the ability to propagate collection values for all biospecimens in a group, and a more intelligent storage system.

Before beginning a step-by-step demonstration of caTissue Core using mock data, Dr. Fore explained its general organization. A patient will be entered into the system then registered to a protocol and a biospecimen collection group—one patient might be part of many collection groups. From there, biospecimen data can be entered. Biospecimen events (e.g., centrifugation or slicing) are recorded by the software such that the parent-child relationships of each biospecimen are maintained for the resultant units. The software also will track the physical location in which the biospecimen is stored and the transfer of biospecimens to other researchers.

Dr. Fore explained that caTissue Core is a Web-based application; the software runs on a central server at the institution and can be accessed by registered users at their personal computers with usernames and passwords. He then initiated a step-by-step caTissue demonstration. Each user logs in to the system and will have access to different system parameters depending on user status. Administrators, for example, are super users; they are able to define collection protocols and the types of biospecimens and processing events that will be logged for a particular study. Data entry personnel would not have access rights to define protocols but would be able to enter information about individual patients, biospecimens, and events. Screen by screen, Dr. Fore showed participants the vast array of biospecimen data that can be recorded and tracked with caTissue Core.

Dr. Fore concluded that caTissue version 1.2 is user friendly and practical for managing day-to-day operations at a biospecimen resource. He then mentioned several caTissue Suite features, which will be available in late 2007 or early 2008, including informed consent tracking; advanced methods for saving routine queries; the ability to add data entry fields; integration with cancer Text Information Extraction System (caTIES); and tracking of biospecimen ordering, shipping, and receiving.

Questions and Answers

In response to several specific software operation questions throughout the presentation, Dr. Fore demonstrated tracking the physical transfer of samples or boxes of samples to different storage units; clicking on a sample in the software specimen location map to access information on a particular biospecimen; illustrating biospecimen storage information in three dimensions (e.g. which freezer shelf and the position in X-Y coordinates on that shelf); entering several biospecimens at one time; and accessing information (amount and type) based on user role and responsibility.

A participant asked about the origin of the drop-down list of anatomic biospecimen source sites (breast, prostate, lung, etc.). Dr. Fore responded that the list was generated from the NCI Thesaurus.

Another participant asked whether anyone has integrated clinical patient registration with caTissue Core. Dr. Fore answered that he is not aware of the software being used in that manner but that an application programming interface (API) could be written to extract patient information at the time of clinical registration and add it to the caTissue Core database.

An attendee asked whether users have the ability to add fields in caTissue Core. Dr. Fore replied that they cannot but that caTissue Suite does have that capability. He emphasized, however, that to maintain interoperability with other biospecimen resources, any added data elements would need to be defined in a centralized dictionary.

A participant asked about the definition of the term “investigator” and how that field should be filled for biospecimens that routinely get distributed to several laboratories. Dr. Fore replied that for the purposes of this software, “investigator” refers to the person responsible for biospecimen collection and that it is possible to add information about the individuals to whom samples are distributed on a subsequent data entry screen.

Another attendee asked how to handle fields that prepopulate when a particular biospecimen lacks an accompanying blood sample, for example. Dr. Fore replied that users have the option to delete empty fields. In response to another question on unique identifiers, Dr. Fore indicated that everything in the database, from the freezers to the containers to the biospecimens, has a unique identifier.

Other questions concerned barcoding of biospecimen storage tubes. Dr. Fore explained that caTissue Core has the ability to print barcodes. However, he was not certain how the software would interact with a system that involved tubes that are prebarcoded.

Regarding the underlying database language, Structured Query Language (SQL), and performing queries, Dr. Fore responded that users with high-level access rights could access all information in the database and generate custom reports on relational databases, with the caveat that such custom reports lack user-defined data access restrictions. When queries are written using an API, which is recommended over writing custom reports in SQL, caTissue Core can enact user access controls on the report information generated. Another participant asked whether caTissue Core offers the full functionality of SQL. Dr. Fore replied that the intention was to make caTissue Core non-database specific; the version of SQL used is the lowest common denominator, avoiding use of specialized sequences to allow greater applicability. A discussant asked whether that makes APIs more difficult to define and was informed that it does not, as the API runs on the same server as the application.

Other questions addressed patient anonymity and inclusion of names in the database. Dr. Fore replied that users with no access to patient names might define the protocol without name fields, choose to delete name fields, or enter dummy information in name fields. Some of the early adopters have chosen to keep such proprietary information behind a firewall when they post their data to the Internet.

Other attendees asked about how caTissue Core compares to commercially available products such as Freezerworks. Dr. Fore replied that, while it is hoped that such commercial applications will become caBIG™ compatible, caTissue Suite is not intended to replace them. Rather, caTissue Core meets the needs of some institutions for a mature, robust biospecimen resource management tool to replace simpler systems such as a Microsoft Access database or an Excel spreadsheet. With respect to Freezerworks, his experience is with the free version, compared to which caTissue Core offers more extensive types of event tracking. Another participant volunteered that his site recently chose caTissue over Freezerworks because caTissue offers many predefined fields, while in Freezerworks, each field must be defined.

A discussant expressed concern that institutional review board (IRB) restrictions would not allow her site to share information. Dr. Fore replied that although the NCI would like to see information sharing, caTissue is a useful tool even within individual institutions, and using it does not require opening the system outside a firewall. Sometimes institutions or IRBs express concern about system hacking as a reason to avoid sharing data online. Dr. Fore pointed out that this is not a significant concern; financial institutions, for example, have their data online, and the caBIG™ infrastructure includes a complex security system.

In response to a question about the time necessary to download and install caTissue Core, Dr. Fore estimated download time to be about 0.5 hours and installation to be about 2 hours for someone who is familiar with Web servers and Java technology. He suggested the user ask the institutional information technology (IT) department what sort of support it could provide. He went on to describe a unique opportunity for free installation assistance: caBIG™ is looking for more applicants for the enterprise adopter program in which the adopter institution provides the necessary hardware and caBIG™ personnel help set up the system.

In closing, Dr. Fore stated that caTissue Suite will address many of the concerns raised by participants; for example, it will permit local customization and the addition of unique data fields

to a system without compromising caBIG™ compatibility. CaTissue Core also allows the user to load information from a delimited file (i.e., Excel spreadsheet or other legacy system) as well as automatically load information into the biobanking application when patients are registered to a linked clinical trial system.

Discussion of Cost Recovery Models and Other Economic Issues Involved in Implementing the NCI Best Practices

Jim Vaught, Ph.D., Deputy Director, OBBR; Martin Ferguson, Ph.D.; Jeff Furman, Ph.D., Boston University School of Management and the National Bureau of Economic Research;, and Lisa Miranda, Technical Director, Tumor Tissue and Biospecimen Bank, University of Pennsylvania

Dr. Vaught welcomed participants, introduced each of the speakers, and briefly framed key issues related to economics and cost recovery for biospecimen resources for discussion during the breakout session.

Dr. Vaught explained that the OBBR is exploring various economic and cost issues related to biospecimen resources based on public comments received about the *NCI Best Practices*. In addition to concerns from the scientific research community about possible additional costs associated with implementing the *NCI Best Practices*, Dr. Vaught mentioned that current National Institutes of Health budget limitations are encouraging the NCI leadership to employ a more comprehensive approach for controlling costs for intramural and extramural biospecimen resources. The heightened need to control costs is balanced with the value of preserving biospecimen collections with mature annotation over long periods of time.

Dr. Vaught mentioned several questions related to economics and cost recovery for biospecimen resources that the NCI is exploring:

- What funding models exist for biospecimen resources?
- Is it possible and/or desirable to fully recover costs? How does cost recovery affect access to biospecimens?
- What additional costs are associated with implementing the *NCI Best Practices*? How do implementation costs vary depending upon the size of a biospecimen resource?
- Does consolidation of small biospecimen resources into centralized facilities offer operational and/or economic advantages? Would a central resource be acceptable to organizations?
- Is it possible to quantify the economic impact of a biospecimen resource?
- Are there newer technologies available that can reduce costs now or in the near future?

In closing, Dr. Vaught emphasized the NCI's strong interest in receiving input from the research community about economics and cost recovery issues for biospecimen resources.

Biobanking Cost Recovery
Lisa B. Miranda, Technical Director, Tumor Tissue and Biospecimen Bank, University of Pennsylvania

Ms. Miranda introduced herself as the technical director of a new core biospecimen facility located at the University of Pennsylvania (U Penn), the Tumor Tissue and Biospecimen Bank (TTAB). Development of the TTAB began in May 2005, and the bank was approved in July 2006 as a School of Medicine Core Service Center to harmonize biospecimen banking activities, which were historically managed by a large number of investigators. Formal operations began in October 2006.

TTAB provides U Penn researchers with the option to obtain support for a range of biospecimen banking services including biospecimen collection and banking support; pathology and case review; histology services and inventory management; and quality management, training, and education. Ms. Miranda summarized TTAB's three major types of users:

- Basic science researchers and/or clinical researchers who maintain private collections
- Departmental biospecimen banks
- External institutions that are developing virtual biospecimen resources

Ms. Miranda noted that TTAB is expected to operate using a full cost recovery model to recoup direct and overhead costs and must be fully revenue neutral at the end of a 3-year grace period. Ms. Miranda stated that when biospecimen resources employ a full cost recovery model, end users may enjoy a wide range of benefits including assistance with and support for resource, budgetary, and grant planning activities. In addition, the cost recovery model helps present a sound economic justification to the U Penn leadership for maintaining TTAB.

Ms. Miranda explained that she initiated the TTAB cost analysis by analyzing the specific services provided and corresponding user fees for 30 biospecimen resources, including 28 based in the United States, 1 in Canada, and 1 in Australia. She mentioned that key elements for consideration in developing user fees included labor (direct and general and administrative), direct materials, general laboratory supply fees, service contract fees, and capital depreciation.

She next reviewed key steps employed to conduct the TTAB cost analysis:

- Developing a narrative overview of the purpose and goals of the biospecimen resource;
- Creating an organizational chart for the biospecimen resource;
- Conducting a needs assessments for the TTAB facility;
- Estimating projected billable hours for all facility employees;
- Developing metrics for all services;
- Determining the service contract rate for the facility (i.e., freezer maintenance);
- Estimating capital depreciation rates for major equipment;
- Developing user fees and pricing for all services;
- Conducting financial projections to aid budgetary planning and assess revenue neutrality; and
- Implementing user fees and billing.

Ms. Miranda emphasized the importance of establishing transparent pricing structure and billing procedures so that users are prepared to pay for services rendered and referred participants to the detailed TTAB pricing list.[10] She explained that because many users are not accustomed to paying fees for biospecimen-related services, it is important to establish regular customer billing to prevent surprises about the true costs associated with providing biospecimen banking services.

Questions and Answers

One participant asked about how TTAB maintains a full cost recovery model when many clients pay with "soft" grant money. Ms. Miranda responded that TTAB carefully tracks the funding sources of each client to preempt possible funding issues. Another participant asked if TTAB provides a "layaway" program for investigators who are expected to obtain funding in the near future. Ms. Miranda replied that TTAB would consider this approach. However, they attempt to minimize offering pro bono services because of the need to maintain a full cost recovery model.

Another participant inquired how TTAB will plan for costs associated with the need to secure additional storage space over time. Ms. Miranda said that storage space is not yet an issue for TTAB. However, she agreed that it could become an issue as TTAB supports greater numbers of users. Ms. Miranda explained that TTAB is currently housed in empty space available in the hospital and that the TTAB staff are actively involved in designing the formal laboratory space. U Penn plans to reassess space for TTAB in approximately 5 years based on user demand and revenues obtained by the resource. Ms. Miranda did not have the exact number of samples accessioned by TTAB last year but confirmed that a significant number of samples had been added to the collection. She also indicated that TTAB plans to increase the intake rate next year.

Another participant inquired whether TTAB encourages users to share biospecimens. Ms. Miranda replied that investigators use TTAB on a voluntary basis; therefore, TTAB cannot obligate investigators to share biospecimens. However, TTAB does encourage sharing, and one of its goals is to increase biospecimen and biospecimen research data sharing. She anticipated that with the support of caTissue, this process will be expedited.

Another participant asked whether TTAB collects biospecimens prospectively in addition to providing services for funded investigators. Ms. Miranda clarified that TTAB established an umbrella protocol for biospecimen banking and mentioned the challenge of defining a minimal associated data set for this collection. She stated that TTAB is adopting caBIG™ software; therefore, prospective TTAB users can view available biospecimens online. TTAB is an early adopter of caTissue and has expended substantial time and effort to install this system. She mentioned that TTAB charges investigators a fee to recover costs of data entry and management associated with biospecimen banking support. In addition, TTAB is considering charging investigators a fee for accessing caTissue (e.g., conducting searches) to recover costs associated with using this software.

Ms. Miranda explained that TTAB employs formal, written SOPs for banking and collects tumor/normal pairs (i.e., matched tissue and/or blood specimens) and any other associated biospecimens as per individual project or protocol. She then mentioned that TTAB is currently

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

working to establish tissue utilization committees by organ group to assist in disseminating biospecimens collected under their umbrella protocol.

Another participant inquired how TTAB collects informed consent from research participants. Ms. Miranda replied that she is available to obtain consent for their umbrella protocol and is in the process of training the staff to do this as well. She noted that the numbers for TTAB consented collections are still low due to minimal staff at the current time. Thus, she is looking for additional staff to support this time-consuming task. She noted that TTAB charges recruitment and consenting fees, a practice that received substantial resistance from users. For projects, TTAB also charges a project management fee when applicable, and they are considering approaches for quantifying a quality assurance fee.

In summary, the group concluded that the appropriateness of a full or partial cost recovery system depends on the resource model. For example, certain institutions may want to support creation of a biospecimen resource for investigators who are not fully funded. Dr. Ferguson, who has experience in commercial biobanking, suggested that obtaining funding from several sources, including public-private partnerships, may be appropriate for some biospecimen resources. Participants agreed that regular communication with resource customers is essential for any cost recovery system to be effective. Significant interest was expressed in case studies of biospecimen resource cost recovery, general funding, and financial support for the implementation of the *NCI Best Practices*. The OBBR Web site was suggested as a logical place for these case studies to be made available.

Cost Recovery Models: Industry Perspective
Martin L. Ferguson, Ph.D., Pharmaceutical and Life Sciences Consultant and Cofounder of Ardais Corporation

Dr. Ferguson explained that his presentation would focus on his experience as a cofounder of Ardais Corporation, which operated from 1999–2006. Dr. Ferguson noted that a diversity of biospecimen cost recovery models exist in the private sector and explained that many large pharmaceutical companies establish arrangements with individual clinical sites where biospecimens are exchanged for money and/or resources.

Ardais operated as a “middleman” for biospecimens rather than an end user. Ardais intended to be a profit-making institution; however, this goal was not realized. Ardais collected biospecimens with extensive annotation and IT support from multiple clinical sites. Biospecimens obtained were divided into three “pools”: One available only to the collecting institution, a second available across the biospecimen collection sites, and a third available for licensing to private companies. In contrast to biospecimen collection activities supported through grant mechanisms, the Ardais model transferred biospecimens outside of the original clinical collection site. Dr. Ferguson highlighted the critical importance of addressing ethical and communication issues for models in which biospecimens are transferred outside of the collecting institution. Ardais worked with prominent bioethicists and patient advocates for 2 years before any samples left participating collection sites. To help manage conflicts of interest, surgeons at the participating institutions were not aware whether an individual patient consented to provide tissue to the Ardais bank at the time of surgery. Despite Ardais’s extensive work on ethical and

communication issues, many institutions were reluctant to partner with a for-profit entity focusing on biospecimen collection.

Dr. Ferguson explained that Ardais was primarily supported by venture funding after securing letters of intent from prospective collection institutions. All charges to Ardais from the collecting institutions were based on cost recovery. Although cost recovery was an acceptable approach for the Ardais model, it was not for officials with decisionmaking roles in the collecting institutions. To address this problem, some partner collecting institutions transferred funds obtained from Ardais to nonprofit foundations affiliated with their institution.

Questions and Answers

One participant asked Dr. Ferguson to comment on why the Ardais business plan failed. Dr. Ferguson responded that the company brought in several millions of dollars of venture funding over 5 years and generated millions in revenue. He clarified that Ardais had profitable quarters but never a profitable year. In contrast to other biospecimen acquisition companies such as Asterand (which employ a lighter weight infrastructure), Ardais expended large amounts of capital to collect and maintain biospecimens. For example, Ardais performed molecular and histopathology quality control on every sample before depositing into its bank, including analysis of frozen samples using a bioanalyzer. Furthermore, Ardais collected structured clinical data that could be compared across samples.

Dr. Ferguson commented that Ardais could have been an extremely successful nonprofit. He noted that Ardais was several years ahead of its competitors in developing SOPs and IT to support biospecimen banking. Ultimately, many institutions were concerned about working with a for-profit entity collecting human specimens. In response to these concerns, Ardais shifted its business model during its final 2 years to become a biospecimen banking service provider that did not take physical custody of biospecimens.

Another participant asked about which individuals in the collecting institutions had the authority to sign agreements with Ardais. Dr. Ferguson answered that this varied substantially among institutions and noted the highly distributed authority over biospecimen banks. He emphasized the importance of establishing tissue utilization committees to ensure biospecimen use and remarked that patient advocates desire that biospecimens are used for research rather than stored indefinitely.

Another participant inquired about what ultimately happened to the thousands of samples collected by Ardais. Dr. Ferguson mentioned that parts of the collection moved into different entities. He also remarked that the repository was considered an asset with substantial economic value when the company dissolved.

Another participant asked about the types of institutions that licensed Ardais samples. Dr. Ferguson replied that the primary users were pharmaceutical and biotechnology companies conducting early-stage discovery research. Substantial revenues came in from the top five pharmaceutical companies.

Another participant asked about the impact of Ardais's closure on the participating collecting institutions. Dr. Ferguson commented that many of the participating institutions continue to benefit from their previous relationship with Ardais. For example, some of the former partners developed a detailed understanding of how patients enter the system as a result of the Ardais collaboration. In addition, several of these institutions developed new tissue banking infrastructure, such as frozen section rooms. Some of the collecting institutions still use the Ardais system. However, Dr. Ferguson also noted the dissatisfaction of some participating institutions in losing the substantial revenues generated from the Ardais partnership.

Toward the end of the discussion of Dr. Ferguson's remarks, Dr. Vaught requested that the audience comment on economic issues relating to attempting to implement the *NCI Best Practices*. One participant praised the *NCI Best Practices* as an important "philosophical step" toward improving the quality of biospecimen resources. He suggested that the OBBR develop case studies to address how specific institutions are implementing the *NCI Best Practices* for posting on the OBBR Web site to assist implementation efforts of other institutions.
Dr. Ferguson suggested that the NCI clarify a preferred approach in sections where the *NCI Best Practices* presents multiple options. For example, it is extremely inefficient for institutions to employ multiple "homegrown" informatics systems for biospecimen management.

A Penny for Your Quotes? Accessing the Impact of Biological Resource Centers on Life Sciences Research
Jeff Furman, Ph.D., Boston University School of Management and the National Bureau of Economic Research

Dr. Furman introduced himself as a social scientist who has conducted research on the economic impact of biological resource centers (BRCs), which provide the research community with broad access to biospecimens and other biological materials. Dr. Furman explained that economists are interested in institutions such as BRCs because of their role in knowledge generation, preservation, and diffusion. Such institutions are particularly important as long-term economic growth depends on the ability to draw upon a growing body of scientific and technical knowledge. BRCs can amplify the impact of scientific knowledge by enabling future generations to build on past discoveries at costs lower than the costs of rediscovery or reinvention.

Dr. Furman described the maintenance of BRCs as a "public goods problem" because individual scientists may not have incentives to preserve materials for broad dissemination. During his talk, Dr. Furman highlighted four important roles of BRCs as economic institutions:

- *Authentication*. BRCs certify the quality of materials to prevent costly errors, such as the contamination of multiple cell lines by HeLa cells at many elite U.S. research institutions in the past.
- *Long-term preservation*. BRCs preserve materials that may become extremely valuable for future research. It is difficult to predict which materials will become most valuable over time. For example, the archiving of *Thermus Aquaticus* as an extremophile in the American Type Culture Collection (ATCC) provided the basis for developing Taq DNA polymerase.

- *Independent access*. BRCs provide broad access to materials across the research community to enable follow-on research discoveries. “Special collections” stored at individual institutions are generally less accessible to the research community.
- *Economies of scale*. It is likely to be more cost efficient to maintain biospecimens in centralized BRCs rather than in thousands of small, distributed special collections.

During the final part of his talk, Dr. Furman described the results of his empirical research on BRCs, was conducted jointly with Scott Stern of Northwestern University’s Kellogg School of Management. In this research, Furman and Stern analyzed citation patterns associated with materials that were deposited without advance warning at the ATCC, the United States’ largest BRC. Their analysis showed that the accession of materials to ATCC led to a statistically and economically significant boost in the number of citations associated with the papers that initially characterized those materials. This finding suggests that depositing materials in BRCs has a positive impact on the diffusion of knowledge associated with those materials. Dr. Furman also described a “back of the envelope” analysis showing that supporting BRC deposits is a more cost-effective way to promote additional publication citations than supporting new, independent research projects. He emphasized, though, that such a calculation is quite preliminary and should be interpreted with caution.

In summary, the group concluded that centralized biospecimen resources are cost effective in a quantifiable way and can lead to a larger number of high-impact publications. Dr. Vaught suggested that the research presented above should prompt the NCI to consider the value of small, independent resources versus large, centralized resources and mechanisms for funding different biospecimen resource models.