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 biospecimens 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 the Greater Washington, DC, area. This forum was the first 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. PART 1: NCI BEST PRACTICES FOR BIOSPECIMEN RESOURCES

NCI Best Practices for Biospecimen Resources Rationale and Development
Dr. Carolyn Compton

Dr. Compton opened the forum by emphasizing the importance of biospecimens to 21st century medicine and the intensely collaborative process used to develop the *NCI Best Practices*.[3] The

[1] http://biospecimens.cancer.gov/practices/
[2] http://www.nci-bestpractices-forum.com/meeting/obbr/
[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/bethesda2007/.

document will evolve as the scientific evidence base in biospecimen research grows. The *NCI Best Practices* is based on several principles of operation for biospecimen resources[4]:

- Best practice–based, data-driven technical and operational standards to ensure quality and enable reproducible molecular analysis;
- High-quality biospecimen annotation with pathological and clinical data;
- Biospecimen access through a timely, centralized peer review process;
- Ethical and privacy compliance through a chain of trust with research participants;
- State-of-the-art informatics systems to track biospecimens, associated data, and research participant informed consents; and
- Communication and outreach efforts, particularly with investigators, to ensure greatest impact.

Technical and Operational Best Practices

Dr. Mark Sobel, Executive Officer, American Society for Investigative Pathology

Dr. Sobel is Executive Officer of the American Society for Investigative Pathology, the International Society for Biological and Environmental Repositories (ISBER), the Association of Molecular Pathology, the Association of Pathology Chairs, and several affiliated societies involved in pathology and tissue resources. Prior to that, he had a 25-year career as a pathologist at the NIH where his main interests were gene regulation, molecular basis of metastasis, and molecular diagnostics.

Dr. Sobel began his presentation by stating that several international groups have been working on establishing standards for biospecimen resources since the beginning of this decade. ISBER published the first standards for biospecimen resources in 2005, and subsequently, other international groups—including the Marble Arch Working Group on International Biobanking and the Public Population Project in Genomics—began efforts to harmonize international practices in biobanking.[5] The *NCI Best Practices* represent a consolidation of many of the ideas generated by these groups as well as the work of a trans-NIH group on biospecimen resources chaired by Dr. Roger Aamodt, which was established in the 1990s, that focused on developing common guidelines for all Institutes that support biospecimen resources.

He then reviewed the components and contents of the technical and operational best practices in Section B of the *NCI Best Practices*. This section covers the topics of biospecimen collection and processing, monitoring and storage, biosafety, packaging and shipping, collecting and managing clinical data, and recordkeeping.

Dr. Sobel concluded by reviewing several themes of biobanking in the 21st century. First, there is a search for international standards to promote harmony and sample sharing. Dr. Sobel identified the *NCI Best Practices* as a guide for institutions globally. Second, biospecimen-based research

[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/.

[5] International Society for Biological and Environmental Repositories. Best practices for repositories I: Collection, storage, and retrieval of human biological materials for research. *Cell Preserv Technol.* 2005; 3:5-48.

emphasizes respect for human rights and personal autonomy. Finally, continued improvements in technology will require flexibility and are expected to impact processing, storage, and retrieval of biological samples; datasets; and information technology (IT) both in terms of security and interoperability.

Questions and Comments

One participant inquired whether the *NCI Best Practices* recommend the inclusion of the medications a patient is taking as part of the clinical data related to his or her biospecimen. Dr. Sobel affirmed that it is important to know whether a patient has had treatment or exposure to environmental stimuli and commented that there often is a focus on collecting treatment data for what is being studied. He emphasized the need for good medical histories that include all relevant data.

The discussion turned to the impact of the *NCI Best Practices* in the international arena, with a participant asking if the *NCI Best Practices* are moving toward the level of the detail of International Society of Blood Transfusion Code 128 or ISBT 128, which sets a global standard for the identification, labeling, and information processing of human blood, tissue, and organ products across international borders and disparate healthcare systems. Dr. Sobel replied that a move toward this level of detail in the *NCI Best Practices* is likely premature given the need to coordinate what different groups are doing before reaching an agreement on international biospecimen resource practices. There also was a question about translating the *NCI Best Practices* in other languages for international use. Dr. Sobel stated there are no plans for translation at present, and such an effort may not be warranted given that English is the standard language of science. Furthermore, biospecimen resource standardization efforts are underway in both the European Union and Asia.

A lengthy discussion on funding to support implementation of the *NCI Best Practices* ensued as participants sought more information on this topic from the OBBR. Dr. Compton first acknowledged that this is a contentious issue surrounding the *NCI Best Practices*. She clearly stated that adherence to the *NCI Best Practices* is voluntary. Nevertheless, the Institute does have a vested interest in seeing that these best practices are carried out. Furthermore, investigators cannot afford not to follow best practices, as it is an investment not only in the quality of biospecimens but, ultimately, in the research and data derived from their use. Thus, the drive for implementation should be based on the desire to conduct good science.

The OBBR also plans to address economic issues relevant to biospecimen resources in the near future. Dr. Compton described the challenges to determining the true cost of initiating and/or maintaining a high-quality resource as follows:

- Cost is dependent on the size, mission, and scope of each resource.
- The expense for most resources is “hidden” in other funding mechanisms.

Identification of costs depends on analyzing “modular” costs that comprise high-quality resources and applying these metrics to particular resources to determine their actual costs. Once these costs are realized, the NCI will need to recognize that this is research infrastructure that deserves investment commensurate with the quality of the work to be produced. Dr. Compton

also informed participants that while the NCI does not approve of profitmaking from biospecimens, it does approve of cost recovery as stated in the *NCI Best Practices*. The economic analysis described above also will be useful in helping a resource develop a business plan to subsidize its cost. She concluded that even though it is certain that implementing the *NCI Best Practices* is an expensive undertaking, it costs just as much and maybe more to conduct biospecimen research poorly as to do it properly.

One participant emphasized the importance of educating investigators about the complexities involved in establishing a biospecimen resource. Dr. Sobel commented that investment in personnel infrastructure often is the largest expense in establishing or improving a biospecimen resource. Because the quantity of time needed for these activities can represent a significant expense, ISBER is planning to make resources available to facilitate sharing of information. For example, previously established procedures can be customized to the needs of individual institutions, ultimately effecting tremendous time savings for personnel.

A final question was raised about how the NCI is reaching out to other Government agencies with the *NCI Best Practices*. Dr. Sobel responded that the main impact will be made through broad dissemination of the *NCI Best Practices* (i.e., through forums to be held nationwide and in the literature). He also noted that the *NCI Best Practices*, particularly the technical and operational components, will be useful to other Federal agencies that collect specimens of any kind; e.g., the Environmental Protection Agency and the U.S. Department of Agriculture.

Overview of Ethical, Legal, and Policy Best Practices
Dr. Karen Thiel, Patton Boggs, LLP

Ethical, legal, and policy practices in biomedical research are evolving and may be the most challenging aspect of the *NCI Best Practices*. Consequently, the NCI is committed to maintaining the currency of the *NCI Best Practices* as these practices evolve. Dr. Thiel, an attorney and formerly an academic researcher, policy consultant, and Federal policy analyst, has dedicated her recent career to public policy and healthcare.

After a presentation of the *NCI Best Practices* on informed consent, privacy protection, custodianship, intellectual property, and access (found in section C of the *NCI Best Practices*), Dr. Thiel provided some history on how the U.S. courts have interpreted Federal regulations and guidelines on issues surrounding biospecimens. Most importantly, from the landmark *Moore* v. *The Regents of the University of California* to the recent and highly publicized *Washington University* v. *Catalona* cases, the courts have denied claims of biospecimen ownership based on common law property theories, essentially applying laws of personal property possession or gifting to biospecimens. On the topic of informed consent, the courts ruled in *Perry* v. *St. Francis Hospital* that informed consent is not a contract but a memorialization of consent. Aside from these and a few other examples, there is little case law to guide the courts on biospecimen issues. Dr. Thiel concluded that courts often do not address the issues directly because of the lack of clear guidance in the Federal regulations. In addition, courts are protective of the research process, want to avoid bringing harm to biomedical research, and view biospecimen donation as an altruistic process. While the *NCI Best Practices* are not a regulation

and thus do not have the force of law, they may serve as a policy framework for the courts to use in deciding biospecimen-related cases.

Questions and Answers

One participant asked for clarification of the *Perry* v. *St. Francis Hospital* case law regarding informed consent. Dr. Thiel explained that it means that once an institution has a biospecimen, they control it and it is up to the institutional review board (IRB) and research community to determine what is done with the biospecimen. However, she cautioned that it is not a well-settled issue and, in fact, this is the only case that has addressed the subject of informed consent.

In the course of discussion, Dr. Thiel clarified the following points:

- There is no case law on the ownership of clinical specimens that later may be used in research.
- Once an individual donates a specimen, he or she has no right to profit from research using that biospecimen. The *NCI Best Practices* call for clearly informing contributors that their specimen may be used for research from which products that have monetary value may be derived.
- To date, courts have upheld use of archived samples for secondary uses not specified in the original consent. However, a decision is pending in the *Tilousi* v. *Arizona Board of Regents* case brought by members of the Havasupai Tribe, who allege that blood samples collected by Arizona State University researchers for diabetes research were used for additional unauthorized research on schizophrenia, inbreeding, and population migration. Dr. Thiel reminded participants that if research is subject to the Privacy Rule, it requires authorization that pertains only to a specific study, not to nonspecific research or to future, unspecified projects.

A forum participant clarified that data associated with biospecimens are subject to the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule rather than the biospecimens themselves. Dr. Compton replied that while this comment is strictly true, State laws can take precedence over the HIPAA Privacy Rule, and some States have claimed that DNA is a patient identifier. By extrapolation, this means that there is a possibility of human specimens becoming identifiers. The participant added that the NCI has published a report on the State laws applicable in this area, which may be of interest to forum attendees.[6]

The Importance of Best Practices to Patients and Advocates
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 U.S. Food and Drug Administration Patient Consultant Program.

[6] Hakimian, R. , Taube, S. , Bledsoe, M. & Aamodt, R. *50-State Survey of Laws Regulating the Collection, Storage and Use of Human Tissue Specimens and Associated Data for Research* (U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, publication no.05.5628, November 2004).

Ms. Kim opened her presentation with the statement that 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 resources; thus, patients, survivors, advocates and the general public expect that the research community will act as responsible stewards of these materials.

Ms. Kim then shared her perspective about how patients encounter the research enterprise and highlighted how this interaction differs from a researcher's experience. Ms. Kim also noted how a patient's understanding of participation in research is shaped by mainstream media. Recently, the media has focused significant attention on commercially available tests based on analysis of biospecimens (i.e., for genetic profiling); this has increased patients' interest in future access to their specimens. Furthermore, when patients give specimens to research, they believe that they are going to be freely used and openly accessed and would likely 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. She further asked researchers to remember the critical importance of their work to improving the lives of patients.

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. The *NCI Best Practices* represent a great opportunity to move this research agenda forward, and patients are willing to participate in the research process to speed the discovery of prevention, treatment, and a cure. 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.

III. Part 2: Bioinformatics and Evidence-Based Best Practices for Biospecimen Resources

Tools for Tracking and Accessing High-Quality Biospecimens: caBIG™, caTISSUE, and Achieving Silver-Level Compatibility

Dr. Kenneth Buetow, Director, NCI Center for Bioinformatics (NCICB)

Dr. Buetow is the NCI Associate Director for Bioinformatics and Information Technology, Director of the NCI Center for Bioinformatics (NCICB), and Chief of the NCI Laboratory of Population Genetics. As NCICB Director, he oversees, coordinates, and deploys bioinformatics in support of NCI research initiatives and the NCICB's participation in the evaluation and prioritization of the biomedical informatics research portfolio. Dr. Buetow spearheaded the Genetics Annotation Initiative, an attempt to identify various forms of cancer genes identified by NCI Cancer Genome Anatomy Project, and initiated the caBIG™ pilot project, which he currently oversees.

Dr. Buetow began his presentation by stating that IT supports multiple functionalities needed to attain the goals of the *NCI Best Practices*, from research participant registration to reporting. One key feature of IT in biospecimen resources is its usefulness in capturing the information associated with specimen tracking. Another is the potential for a resource's IT platform to integrate with clinical data systems to provide useful clinical annotation of stored biospecimens. Finally, security, including physical access, system backups, and login protections, remains a staple of IT support for biospecimen resources.

Partially in synergy with development of the *NCI Best Practices*, the NCI established the caBIG™ project to support the development of information systems based on input from a community of over 1,000 individuals working in the domains of clinical trial management systems, integrative cancer research, tissue banks and pathology tools, and *in vivo* imaging. caBIG™ also is developing vocabularies and common data elements and architecture to support other research domains. The caBIG™ project is engaging a variety of stakeholders ranging from institutions with integrated, IT-staff supported systems (in which the institution has heavily invested) to those with informal or no information systems. The caBIG™ approach is to develop modules that address specific needs, connect through defined electronic interfaces, and use international data standards. Dr. Buetow emphasized that caBIG™ focuses on the boundaries and interfaces between applications rather than the use of specific types of applications.

Within the area of biospecimen research, caBIG™ has a number of objectives, including creating virtual repositories and supporting multisite studies. These are explained in biospecimen resource–specific materials provided to forum participants. One provides an overview of caBIG™ for the layperson and is intended for use by decisionmakers, while a more technical, detailed document describes the road to caBIG™ compatibility. Dr. Buetow noted that there are multiple pathways to caBIG™ compatibility for an institution: To adopt caBIG™ tools, to map an existing tool to caBIG™ tools, or to make an existing tool caBIG™ compatible for standard reports only. Dr. Buetow 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 domain workspace (https://cabig.nci.nih.gov/workspaces/TBPT/). Some specialized IT skills are required to adopt caBIG™ tools or to make an existing tool caBIG™ compatible, but installation and use do not necessarily require hiring a full-time staff member or investing in an IT laboratory.

In closing, Dr. Buetow described caBIG™ future efforts directed to developing a support network for caBIG™ users that includes service providers, commercial vendors, other institutions that are accredited caBIG™ service providers, knowledge centers, program offices of institute-specific support, and enterprise adopters. Dr. Buetow concluded by inviting participants

to learn more about caBIG™ by visiting http://caBIG.cancer.gov for background information and http://caBIG.nci.nih.gov to join the caBIG™ technical effort.

Questions and Answers

One participant asked whether caBIG™ is planning to integrate its work with regional health information networks that are being adopted by many States and communities. Dr. Buetow affirmed that caBIG™ is involved with the Department of Health and Human Services Office of the National Coordinator for Health Information Technology. The NCICB also is involved in Federal health architecture activities to support cross-Government information exchange.

A participant commented that detailed input from the scientific community is required to ensure the development of useful informatics systems. Dr. Buetow agreed that software developers need detailed interaction with prospective users and explained that caBIG™ continues to extend an open invitation to anyone who is interested in joining a workspace and participating in its development.

In response to a request from Dr. Compton, Dr. Buetow clarified that caBIG™ silver-level compatibility, the level recommended by the *NCI Best Practices,* describes a biospecimen resource informatics system that has the capacity to share information via a set of Internet protocols.

Demonstration of caTISSUE
Dr. Ian Fore, Associate Director for Biospecimen and Pathology Informatics, NCICB

Dr. Fore is the NCICB Director of Biorepository and Pathology Informatics and a member of the OBBR team. Prior to joining the NCI, he worked on drug discovery informatics at Wyeth Pharmaceuticals and Johnson and Johnson. More recently, Dr. Fore was Product Manager at Celera Genomics where he was responsible for integrating the company's customer bioinformatics system.

Dr. Fore informed 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 the Washington University in St. Louis, underwent testing at four funded "adopter" universities. Enhancements from the previous version are primarily around usability and include easy access to edit from any search, support for a study calendar, the ability to propagate collection values for all biospecimens in a group, and a more intelligent storage system.
Dr. Fore then showed screen shots from three modules of caTISSUE and highlighted key functions and features in each.

- *Administrative Data*: In this module, resource managers can add users, specify storage container types, and add collection protocols defined at the patient level; i.e., name of principal investigator, the IRB number, and protocol events.
- *Biospecimen Data*: This module allows selection of biospecimens by protocol, with a specimen details screen organized by collection and clinical event timeline (i.e., initial visit, followup, surgery). In the new version, specimen data fields are prepopulated with collection protocol requirements, and electronic aliquots are easily created.

- *Search*: This module allows specification of multiple search criteria and returns data in an exportable table.

At the close of his demonstration, Dr. Fore concluded that caTISSUE version 1.2 is user-friendly and practical for managing day-to-day operations at a biospecimen resource.

Questions and Answers

In response to participant questions, Dr. Fore clarified the following points:

- caTISSUE is free, open-source software available for downloading at the caBIG™ Web site.
- caTISSUE likely will be most valuable to researchers who need software to support establishment of a biospecimen resource.
- caTISSUE Core is caBIG™ silver-level compatible. As long as caTISSUE is broadcasting to the Internet from its home institution, other sites will be able to query it using Web services; in this way, it facilitates development of a virtual biospecimen resource.
- Institutions are responsible for validating their data in caTISSUE and the data they make available to researchers at other sites. Limited control over data quality is provided by the standard terminology in the application's dropdrown menus, which contributes to the use of consistent terminology across sites that use caTISSUE.

Updating the NCI Best Practices for Biospecimen Resources
Dr. Compton

Importance of Stakeholder Participation in Updating the NCI Best Practices for Biospecimen Resources

Dr. Compton informed participants that the most current version of the *NCI Best Practices* is available on the OBBR Web site in portable document format.[7] Distribution will continue through the *NCI Best Practices* educational outreach program, which features regional forums in areas with high concentrations of NCI-designated Cancer Centers and Specialized Programs of Research Excellence. Meetings will be during late 2007 and early 2008 at dates and times to be posted on the OBBR Web site. Other biospecimen-related activities at the OBBR include formulating a frequently asked questions document regarding caBIG™ and developing self-evaluation tools based on the *NCI Best Practices*.

Toward Evidence-Based Best Practices

Genomics, proteomics, and metabolomics depend on high-quality human specimens. The OBBR intends to use the life cycle of a biospecimen to define all the possible biospecimen variables. To stimulate the field of biospecimen science, the NCI is launching a Biospecimen Research Network (BRN) to study preacquisition and postacquisition variables that affect molecular profiles. The BRN has initiated several intramural studies, and OBBR plans to issue extramural

[7] http://biospecimens.cancer.gov/

funding mechanisms to support biospecimen research in the next several months. The data generated by these studies will be used to inform the development of a set of publicly available biospecimen research standard operating procedures (SOPs) that will augment the *NCI Best Practices*.

In addition to this ambitious undertaking, the OBBR is engaged in other biospecimen-related activities. One is populating a searchable, Web-accessible database with literature related to biospecimens and the effects of handling and processing on them. The goal is to launch this tool by December 2007. The OBBR also is integrating with and supporting other large NCI strategic initiatives that require high-quality biospecimens (e.g., The Cancer Genome Atlas), forging external partnerships for expertise and implementation opportunities, harmonizing biobanking practices in NCI enterprises such as the clinical trials group, and facilitating NIH and international efforts to harmonize biobanking practices.

To summarize, Dr. Compton distilled the central themes of the OBBR's proposed biospecimen research program as (1) bridging the gap between existing clinical practice for biospecimens and emerging technologies for personalized diagnostics and therapies; (2) defining the most significant variables for prospective collection of tissues, blood, and body fluids; and (3) developing evidence-based biospecimen quality indicators for specific analytical platforms.

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