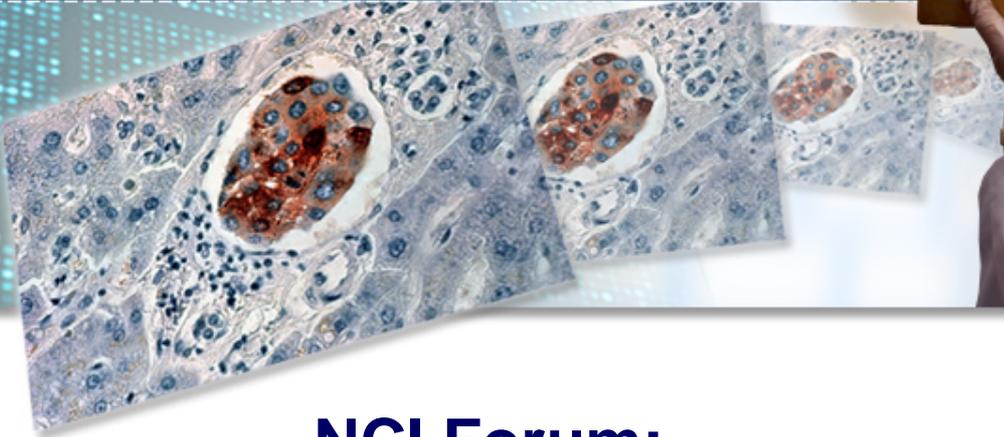


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NCI Forum: NCI Best Practices for Biospecimen Resources

Boston, MA
November 2007

Carolyn Compton, M.D., Ph.D.
Director, Office of Biorepositories and Biospecimen Research
Acting Director, Office of Technology and Industrial Relations
National Cancer Institute



Cancer: Our #1 Health Problem

- **Cancer is now the #1 killer of Americans under the age of 85**
- **1 American dies of cancer every minute**
- **Nearly 600,000 will die of cancer this year**
- **1.4 million will develop cancer this year**
- **1 of 3 females will develop cancer in their lifetime**
- **1 of 2 males will develop cancer in their lifetime**
- **\$189 billion/year on healthcare costs for cancer alone**

A New Era: Molecular Technology Promises to Transform Oncology

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MOLECULAR MEDICINE

Beating cancer

Oct 14th 2004
From *The Economist* print edition

The war on cancer is entering a new phase

"CANCER" is one of those words that sends shivers down the spine. The phrase "battle with cancer" is a headline writer's cliché. And the military metaphor was widened in 1971, when Richard Nixon, then president of the United States, announced an initiative that later became known as the "war on cancer". Cancer, however, has not been beaten. Indeed, by some measures the problem is worse than it was three decades ago. It is true that treatments have improved somewhat, and prognoses with them, and that a few forms of the disease, particularly in children, can be cleared up altogether. But the biggest success has been due to people giving up smoking, rather than to new treatments. And despite that success, the likelihood that a person will get cancer at some point in his life has actually risen since Nixon's speech.

In the past three decades of effort have seemed a disappointment, the next decade could prove to be one of rapid progress. The battle against cancer is at a turning point. Because of recent advances, it is becoming possible to imagine a time in the not-too-distant future when new medical treatments will be able to tame the disease, transforming it from a potent killer into something akin to a chronic complaint. The day when cancer no longer strikes terror in the heart of those diagnosed with it may not be far away (see article).

Researchers have unravelled much of the basic molecular biology of cancer and, aided by the outpouring of knowledge that the Human Genome Project has yielded over the past ten years, they have come to understand how the disease progresses. Indeed, they have come to understand far more clearly than before the term "cancer" properly refers not to a single disease, but rather to a whole class of diseases that have in common only the fact that they are caused by cells that do not know when to stop dividing. That understanding has now reached the point where it can be turned into action. The next few years should see an array of treatments that will add up to a big change in the way that cancer is viewed and dealt with by society.



Unprecedented Potential for Progress

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- **Technological change is exponential, not linear**
 - “We won’t experience 100 years of progress in the 21st century – it will be more like 20,000 years of progress (at today’s rate).”
 - **Ray Kurzweil, *The Law of Accelerating Returns***
- **Scientific knowledge will double in the next 3 years**
- **Biologic knowledge will double in the next 5 years**
- **The sum of all human knowledge is just 1% of what it will be in the year 2050**



Cancer Research at an Inflection Point

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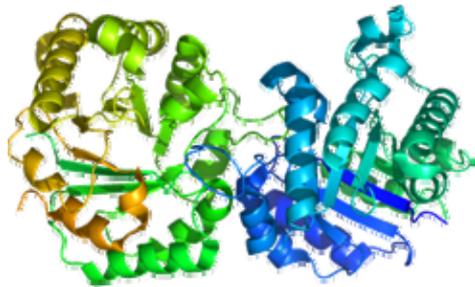
- **The goals of analysis are broadening**
- **The analysis tools are increasing in power**
- **The volume of relevant data is increasing**
- **The complexity of the analysis is escalating**
- **The context of medical application is changing**
 - New targeted therapies
 - Directed uses of old therapies

Understanding the Biologic Complexity of Cancer

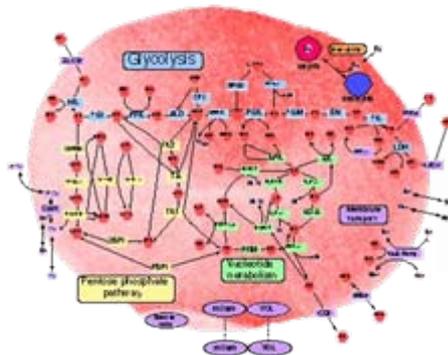
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Genomics



Proteomics



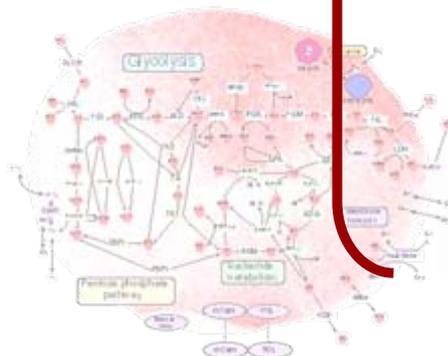
Metabolomics

Understanding the Biologic Complexity of Cancer

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All Depend
On High-Quality
Materials and
Technologies



Genomics

Proteomics

Metabolomics

Advances in Molecular Technologies and Research

Generic

Personalized

Morphologic diagnosis and phenotypic tumor classification

Generic therapeutic regimens with unpredictable effectiveness

Treatments with unpredictable adverse effects on patients

Molecular characterization of tumor pathways and processes

Targeted therapies tailored to the molecular profile of the disease

Drug regimens planned around host genetics that portend toxicity

Understanding Molecular Biology of Host and Disease



Biospecimens at the Center of the Evolution of Cancer Research

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- In the drive towards personalized molecular medicine, technology is the engine, but biospecimens are the fuel
- It's where the molecules are
 - **Normal specimens: molecular character of the host**
 - **Tumor specimens: molecular character of the disease**
 - **Serum, plasma, urine: circulating or excreted biomarkers, easily accessible**
- However, new technologies have raised the bar dramatically for specimen quality and standardization



The Critical Role of Biospecimen Resources in 21st Century Medicine

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Biospecimen resources encompassing large quantities of high-quality, clinically annotated biospecimens are urgently needed to:

- Identify targets for detection, diagnosis, treatment, and prevention
- Develop diagnostics that predict drug efficacy
- Validate new therapeutics
- Elucidate molecular mechanisms of neoplasia
- Develop a molecular-based taxonomy of cancer
- Identify biomarkers for susceptibility, screening, recurrence
- Identify biologic variations that determine drug efficacy
- Identify biologic variations leading to drug toxicity



Biospecimen Variation Compromises Molecular Research

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The challenges: All must be met, because all affect quality

- **Varying methods** of collection, processing, and storage can alter the physical/biologic state of the specimen
- **Varying associated specimen data** elements alter what the scientist knows about the character/nature of the specimen
- **Variable clinical information** alters what the scientist knows about the patient (biologic context of the specimen)
- **Variable restrictions** (patient consent; other ethical, legal, and policy issues) alter what the scientist may do with the specimen and/or data



Key Requirements for Biospecimen Resources for Cancer Research

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- Best practice-based, data-driven technical and operational standards to ensure quality and enable reproducible molecular analysis
- High-quality specimen annotation (pathology and clinical data)
- Specimen access through a timely, centralized, peer-review process
- Ethical and privacy compliance through a chain of trust
- State-of-the-art informatics systems to track specimens, associated data (clinical, pathological, and quality control), and patient consents
- Communication and outreach efforts to ensure greatest impact



Key Requirements Found Wanting

Heterogeneity in practices among NCI-supported biospecimen resources with a resultant lack of:

- **Common procedures, standards, and management principles**
- **Common definitions**
- **Common computerized access to information on specimens**
- **Common approaches to ethical, legal, and policy issues**



A Call To Action

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For NCI's biospecimen resources, the need for standardization and quality management is critical and long overdue.

The Evolution of NCI's Efforts

2007

- FGGs revised based on public comments and renamed **NCI Best Practices for Biospecimen Resources**

2006

- **First-Generation Guidelines for NCI-Supported Biorepositories (FGGs) published in Federal Register**

2005

- **First International Summit on Harmonization of biorepositories conducted**
- **caBIG™ software tools for biorepositories developed**

2004

- **Analysis of NCI-supported biospecimen resources conducted**
- **Trans-NCI Biorepository Coordinating Committee formed**

2003

- **Case Studies of Existing Human Tissue Repositories published**
- **National Biospecimen Network (NBN) Blueprint published**

2002

- **Internal and external review process begun**
- **Biospecimen resources identified as critically important to post-genomics cancer research**

NCI Best Practices Development Process

First-Generation Guidelines (FGGs) for NCI-Supported Biorepositories were reviewed by:

- NIH Office of Science Policy
- DHHS Office for Human Research Protections
- NIH Office of Intramural Research
- NIH Office of Extramural Research
- NIH Office of Technology Transfer
- NIH Office of the General Counsel

FGGs were published in the Federal Register

- Open public comment period, April-July 3, 2006
- Approximately 60 comments received on topics including:
 - biospecimen resource economics
 - informed consent requirements
 - biospecimen resources affected by the FGGs

NCI Best Practices for Biospecimen Resources were published in April 2007

- Consideration and response to public comments
- Reviewed by NIH and DHHS offices listed above
- Reviewed and approved by the NCAB



National Cancer Institute Best Practices for Biospecimen Resources

June 2007

Prepared by:
National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

Objectives:

- **Unify policies and procedures for NCI-supported biospecimen resources for cancer research**
- **Provide a baseline for operating standards on which to build as the state of the science evolves**



What Is a Biospecimen Resource?

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NCI defines a 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.

The NCI Best Practices include recommendations for:

- **Common technical, operational and safety best practices**
- **Quality assurance and quality control programs**
- **Implementation of enabling informatics systems**
- **Establishing reporting mechanisms**
- **Providing administration and management structure**
- **Addressing ethical, legal, and policy issues**
- **Definitions of key terms**



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NCI Best Practices for Biospecimen Resources

Technical and Operational Guidelines

<http://biospecimens.cancer.gov>





Specimen Collection, Processing, Storage, Retrieval, and Dissemination

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- Handle specimens as appropriate for specimen type and study design.
- Develop SOPs for all protocols and a training program for all appropriate personnel.
- Minimize collection/processing time as appropriate.
- Develop a comprehensive quality management system.
- Annotate specimens with key collection, processing, and storage data.
- Monitor specimen inventory with a tracking system.
- Store specimens in a stabilized state without unnecessary thawing/refreezing.
- Dispose of specimens according to clear rules.
- Review and document storage equipment performance on regular basis.
- Follow specimen-appropriate biosafety, packaging, and shipping procedures.

Collecting/Managing Clinical Data/QA/QC

Collecting and Managing Clinical Data

- Collect and store relevant clinical and epidemiologic data associated with a specimen, including longitudinal data, if applicable.
- Use an informatics system that tracks all aspects of collection, processing, and distribution.
- Comply with applicable privacy rules and human subjects regulations.

Quality Assurance/ Quality Control

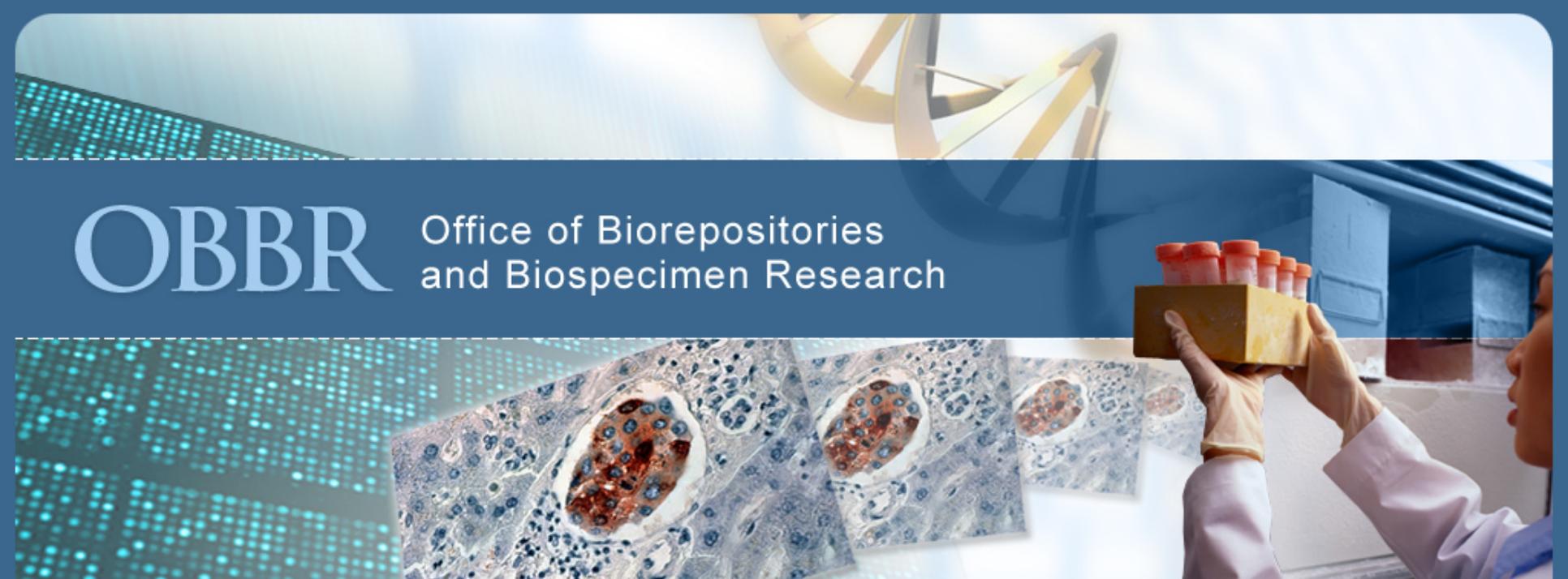
- Have a quality management system that describes QA and QC procedures.
- Maintain QA/QC training records for personnel.
- Adhere to and periodically review SOPs.
- Have security systems in place, including alarms and backup power.
- Include a computerized inventory tracking system in the data management plan.
- Develop a facility disaster plan.
- Maintain all equipment properly according to SOPs.

Biosafety

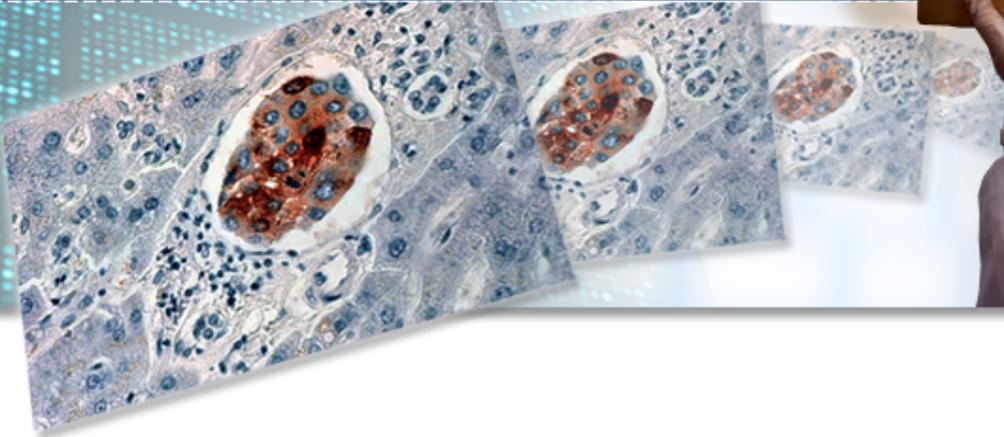
- Assume that all specimens are potentially infectious – provide appropriate vaccines.
- Adhere to governmental and accrediting agency requirements.
- Identify and address biosafety risks.
- Record exposure incidents and provide personnel with appropriate treatment.
- Establish indemnification agreements with users of biospecimens.
- Develop policies and procedures as appropriate for chemical, electrical, fire, occupational, and radiological safety.

Biospecimen Resource Informatics: Data Management, Inventory Control, and Tracking

- Assign a unique identifier (number and/or barcode) to each specimen.
- Update the database each time the specimen is moved or modified.
- Use informatics systems that support the linking of specimens with associated data and protect the health information of patients.
- Adhere to or initiate review of NCI Center for Bioinformatics guidelines and tools; caBIG™ “silver-level” compatibility is recommended.



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NCI Best Practices for Biospecimen Resources

Ethical, Legal, and Policy Guidelines

<http://biospecimens.cancer.gov>





Informed Consent

- Consider allowing research participants to specify the types of research for which their specimens may be used.
- Develop policies for handling specimens for which consent has been withdrawn.
- Develop policies for obtaining consent for studies involving children.
- Consider special U.S. Food & Drug Administration regulations.
- Establish and document transparent policies to govern the retention of records and specimens.



Access to Biospecimens and Data

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- Develop clear policies for specimen and data access.
- Develop clear guidelines for sample distribution and clinical data sharing (Protocol-specific requirements to be met before other access is considered).
- Ensure that investigators have timely, equitable, and appropriate access, without undue administrative burden.
- Charge for samples only to recover costs.
- If a resource needs to close, announce the availability of specimens for transfer.
- Restrict access to subjects' identities and medical, genetic, social, and personal histories via data access system with defined privilege levels.



Privacy Protection/Custodianship

Privacy Protection

- Protect the privacy of information and follow applicable regulations.
- Follow documented policies on employee access to data or specimens.
- Provide levels of security appropriate to the type of biospecimen resource.

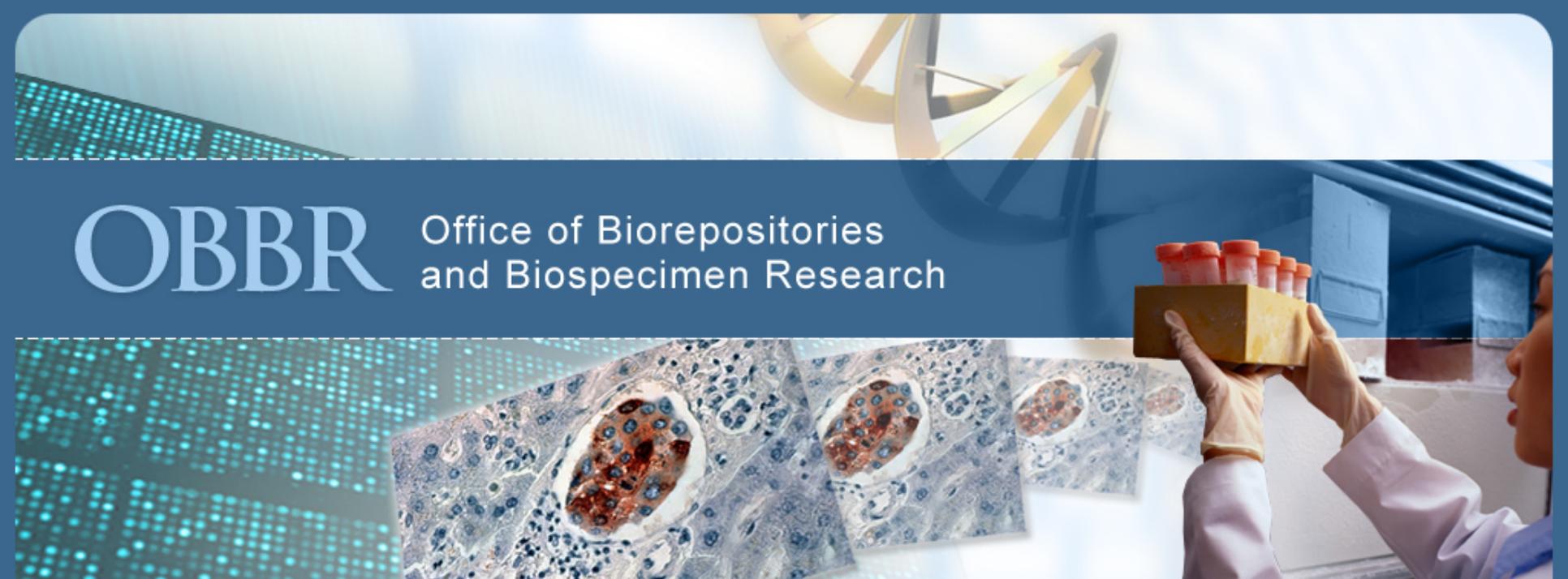
Custodianship

- Include plans for custodianship of collected specimens and associated data in biospecimen resource protocols.
- Develop plans to handle/dispose of specimens and associated data:
 - At end of the budget period of the grant
 - At completion of the specific research objectives of the study
- Identify and disclose financial conflicts of interest.
- In informed consent language, disclose that specimens may help to develop products, tests, or discoveries that may have commercial value.



Intellectual Property

- Use a material transfer agreement (MTA), such as the NIH Simple Letter of Agreement, to transfer materials.
- Specify in MTAs that research data obtained through the use of biospecimen resource specimens and/or associated data should be made available to the research community.



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Next Steps





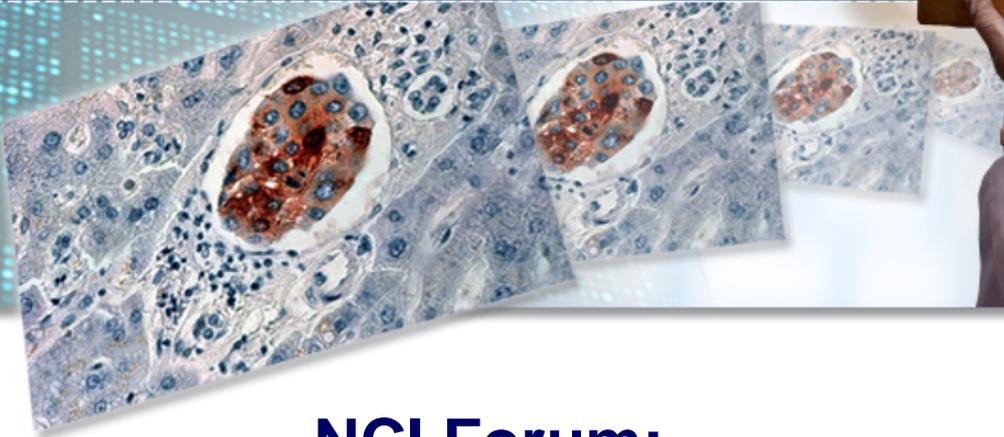
The NCI Best Practices: A Living Document

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- Periodic revision of the 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 to be added as appendices and/or posted to the OBBR web site:
 - Informatics and caBIG compatibility - available
 - Custodianship – in preparation based on recent symposium
 - QA/QC
 - Economics
 - Biospecimen resource evaluation (self-evaluation)
 - Biospecimen science and evidence-based SOPs!



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Public Comments – Major Issues

- Technical and operational guidelines perceived to be beyond the capability of smaller biospecimen resources in terms of both technical expertise and cost of compliance.
- Informatics requirements related to tools, particularly NCI's caBIG™, that have not yet been fully developed or made available for widespread adoption.
- Informed consent recommendations went beyond current regulations and were not clearly related to biospecimen collection and usage.



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