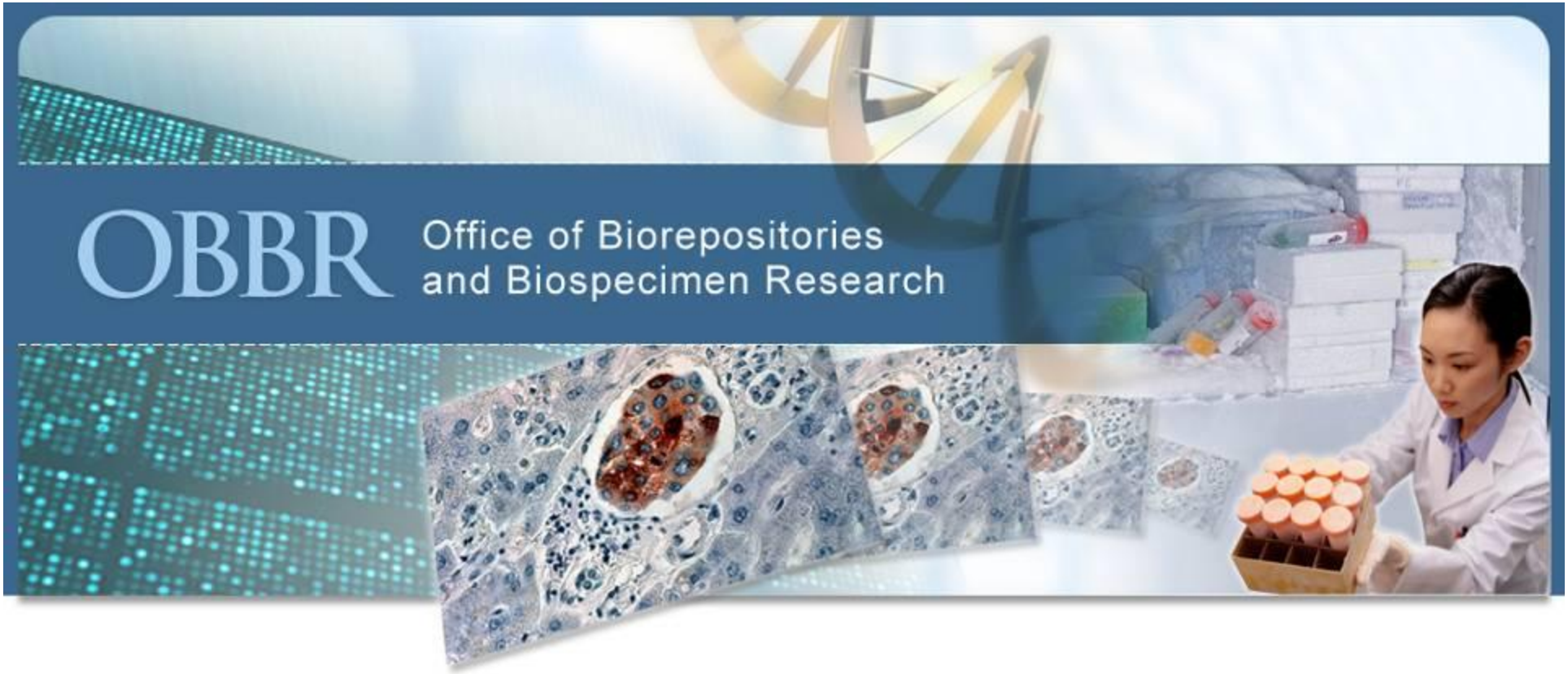

Developing Common Biorepository Infrastructures

Carolyn C. Compton, M.D., Ph.D.
Director, Office of Biorepositories and Biospecimen Research
Executive Director, The Cancer Human Biobank (caHUB)

IOM Workshop:
Developing Precompetitive Collaborations to Stimulate Genomics-Driven Drug Development
Washington, DC
July 22, 2010

NATIONAL CANCER INSTITUTE

Getting to Personalized Medicine

OBBR Office of Biorepositories and Biospecimen Research

Molecular Data → Diagnosis / Therapy

Translational Research

DETERMINES QUALITY HERE

PERSONALIZED CANCER CARE

Biospecimen Analysis

QUALITY HERE

Biospecimen Collection

Biospecimen Processing and Banking

The Demand for High Quality Human Specimens

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POWERFUL TECHNOLOGIES

Genomics Proteomics Metabolomics

Identification of targets for drug development, treatment and prevention

Identify biologic variations that determine drug efficacy and drug toxicity

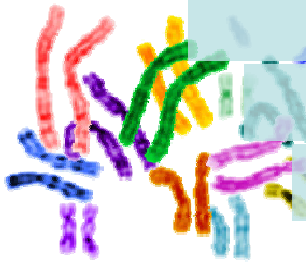
Defining markers for susceptibility, screening and reoccurrence

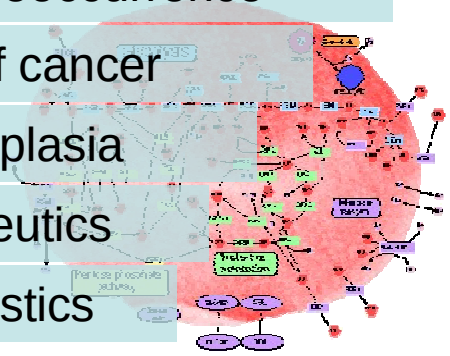
Development of molecular based taxonomy of cancer

Elucidation of molecular mechanisms of neoplasia

Development and validation of new therapeutics

Development and validation of new diagnostics





All Depend On High-Quality, Annotated Human Biospecimens

Quality Data Begins with Quality Analytes

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Garbage in…

…Garbage out

Diamonds in……

Modified from Jerry Thomas

High-Quality Specimens Are Needed

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The lack of high-quality, clinically annotated human specimens is the #1 limiting factor for translational cancer research.

WIRED MAGAZINE

JUNE 2010

FEATURES 18.06

Libraries of Flesh: The Sorry State of Human Tissue Storage

By Steve Silberman | May 24, 2010 | 12:00 pm | Wired June 2010

Photo: Andrew Tingle

Of all the forms of woe that take root in the human genome, the cancer called *Glioblastoma multiforme* is one of the most merciless. It can infiltrate the brain's white matter for months before causing any symptoms. By the time memory loss and seizures reveal the presence of an invader, there's often little to do but minimize the patient's suffering. Most who are diagnosed with the disease—people like the late senator Edward Kennedy—are dead within two years.

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The Question Is Not Just…

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…. can I get existing biospecimens, but do I want them???

- **Key Issues:**
  - **What is the quality/consistency of available samples data?**
  - **Do we even have the "yardstick of truth" by which to benchmark existing samples??**

Sharing specimens and data of unknown, low, or variable quality is unlikely to accelerate progress.

Why Is It Difficult to Acquire High-Quality Human Biospecimens and Associated Data?

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- Collection, procession, storage procedures differ
- Degree and type of data annotation varies
- Scope and type of patient consent differs
- Materials transfer agreement conditions differ
- Supporting IT structures differ in capacity and functionality
- Access policies are lacking or unknown to potential users

→ **WIDE VARIATION IN QUALITY AND ACESSIBILITY OF SPECIMENS AND DATA**

Lessons Learned at the NCI in Acquiring Biospecimens For Strategic Initiatives (e.g., The Cancer Genome Atlas)

OBBR Office of Biorepositories and Biospecimen Research

- Quality of existing samples is typically overestimated by biobanks
- Collection of normal control samples is not routine
- Clinical data on specimen donors is not readily available
- Histological quality does not guarantee molecular quality
- Other important factors that challenge the scientific project:
  - Consent, IRB, privacy law (HIPAA) issues
  - Material transfer agreement, intellectual property, authorship issues
  - Informatics issues (that make data access and sharing problematic)
    - Lack of compliance with IT standards
  - Costs

Solutions That Can and Should Exist in Precompetitive Space

OBBR Office of Biorepositories and Biospecimen Research

Stepwise Approach:

- **Standards**
  - **The *NCI's Best Practices for Biospecimen Resources***
- **Biospecimen Science**
  - **NCI's Biospecimen Research Network**
- **Specimens and Service**
  - **The Cancer Human Biobank**

NCI's Best Practices for Biospecimen Resources: Rules of the Road

OBBR Office of Biorepositories and Biospecimen Research

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

- State-of-the-science baseline for operating standards on which to build as the state of the science evolves
- Unifying policies and procedures for biospecimen resources across the USA
- Web version 2009 capabilities:
  - Hyperlinks to outside resources and references
  - Internal links between various sections
  - Search functionality
- First step to improve the quality of human biospecimens used in cancer research
- Updated in 2009-10; release to Federal Register July 2010
- http://biospecimens.cancer.gov

The NCI Best Practices

OBBR Office of Biorepositories and Biospecimen Research

NCI Best Practices include recommendations for:

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

Solutions

OBBR Office of Biorepositories and Biospecimen Research

Stepwise Approach:

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Understanding the Biology of Biospecimens: The Goal of Biospecimen Science

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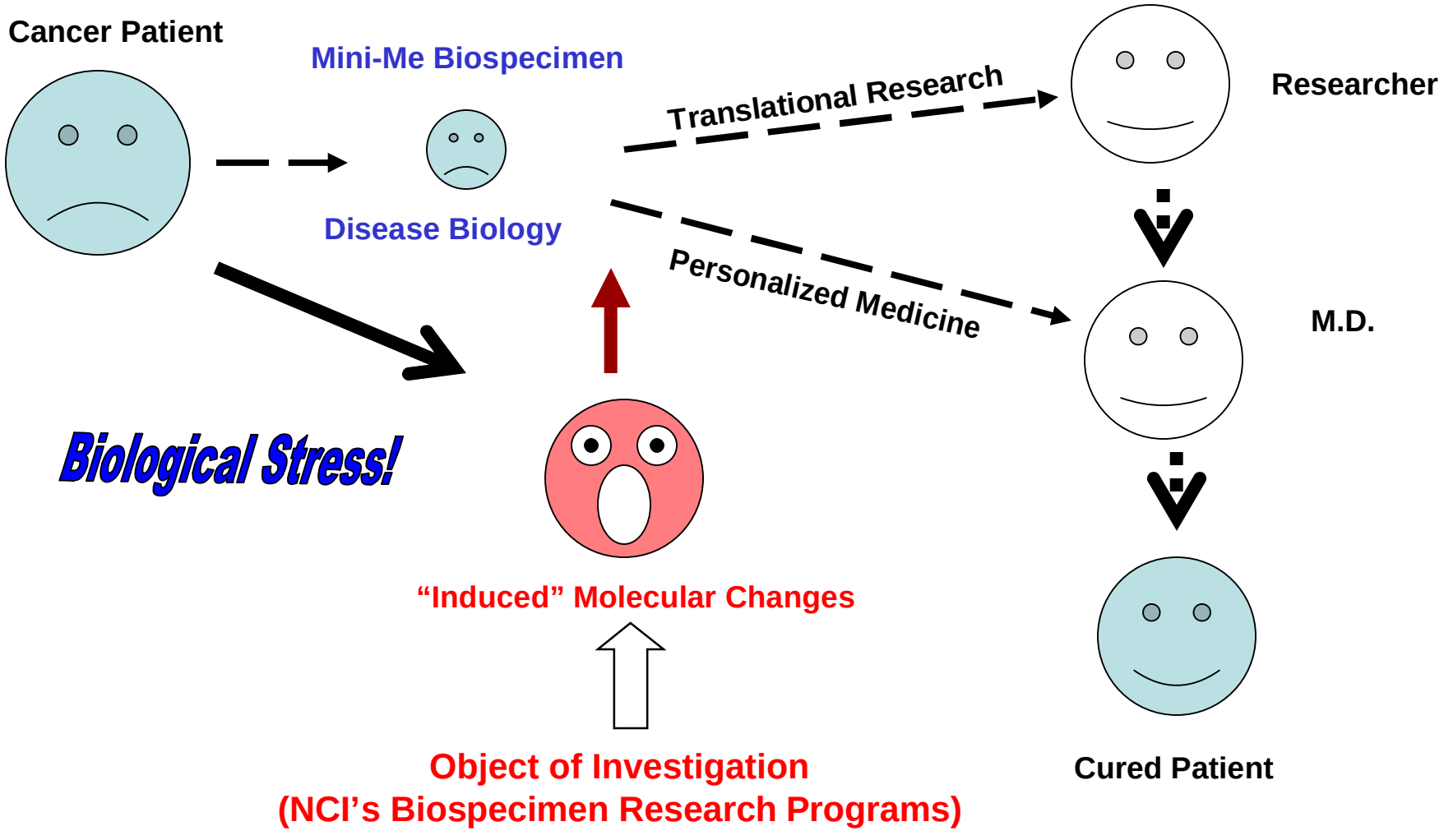

Pre-analytical Variables Can Affect Molecular Composition and Integrity

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Variables (examples):

- Antibiotics
- Other drugs
- Type of anesthesia
- Duration of anesthesia
- Arterial clamp time

Time 0

Variables (examples):

- Time at room temperature
- Temperature of room
- Type of fixative
- Time in fixative
- Rate of freezing
- Size of aliquots

Patient	Medical/ Surgical Procedures	Acquisition	Handling/ Processing	Storage	Distribution	Scientific Analysis	Restocking Unused Sample

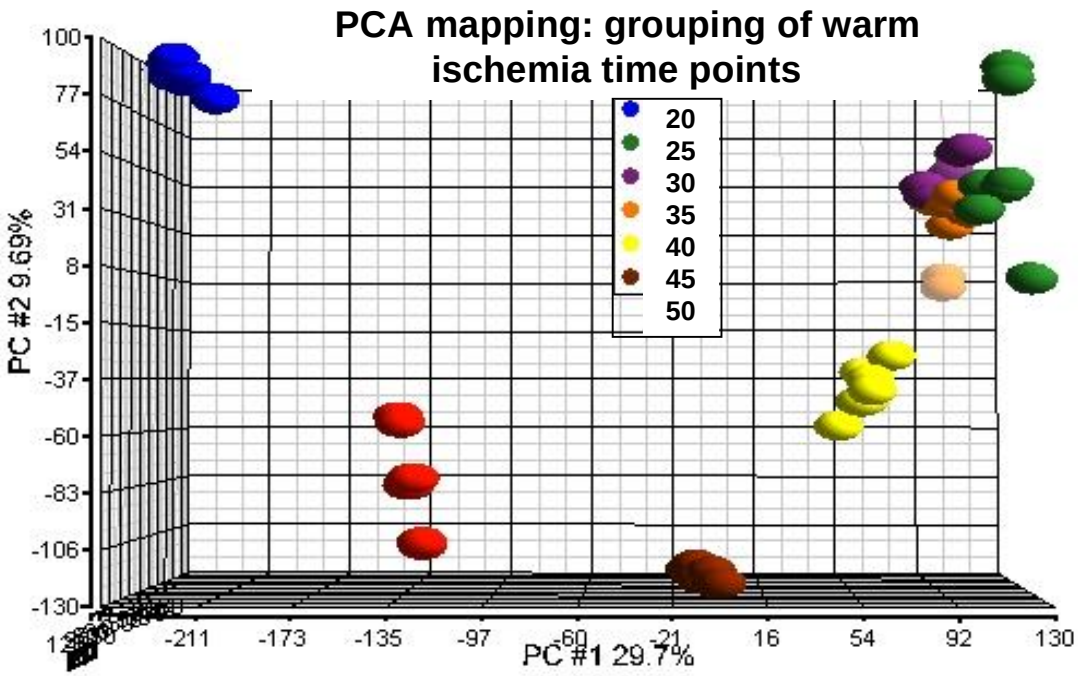
Pre-acquisition

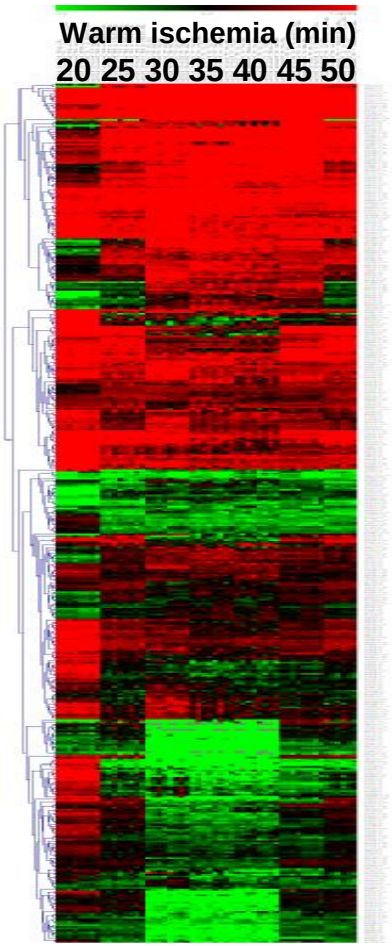
Post-acquisition

Intrasurgical Ischemia (Time from Artery Ligation to Tumor Resection) Affects Gene Expression In Colon Cancer

OBBR Office of Biorepositories and Biospecimen Research

Intrasurgical Ischemia



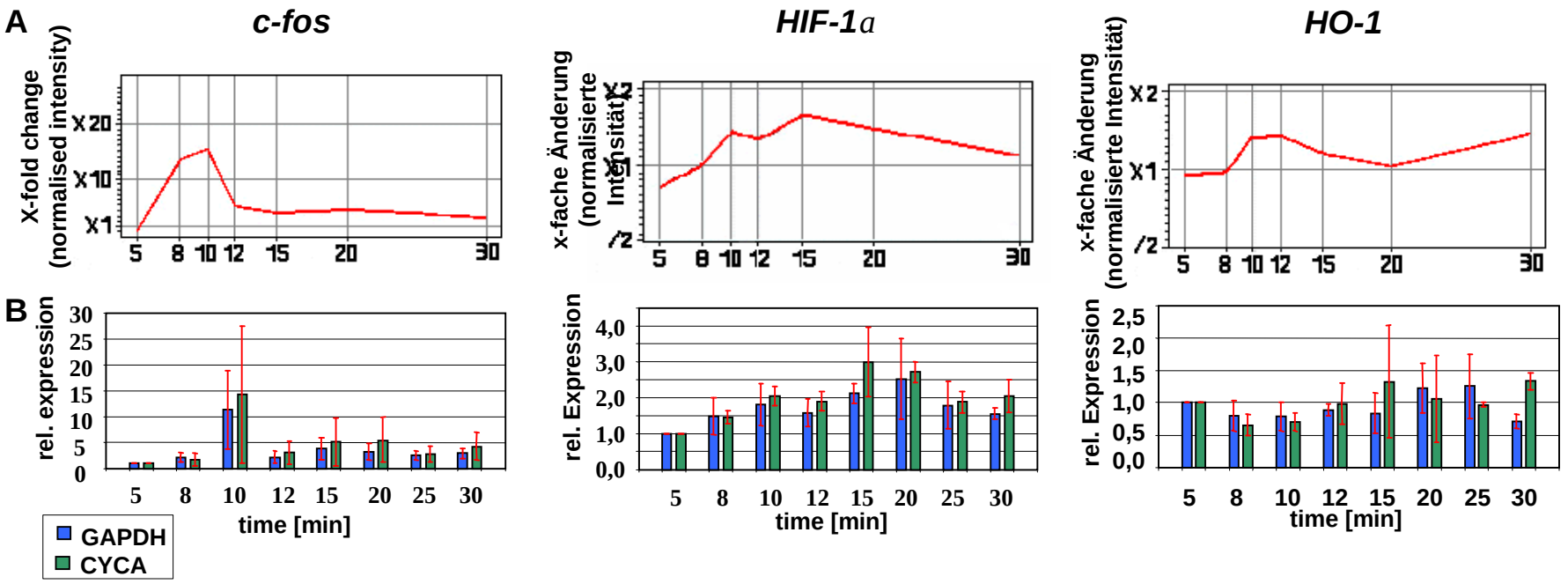


Indivumed-NCI Study

Postsurgical Ischemia and Gene Expresion

OBBR Office of Biorepositories and Biospecimen Research

Ischemia regulated genes c-fos, HIF-alpha and HO-1



Tissue ischemia and gene expression profiling

(Comparison Affymetrix data and real-time RT-PCR)

Slide Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg

Sprüssel et al, BioTechniques 2004

Postsurgical Ischemia and Gene Expresion

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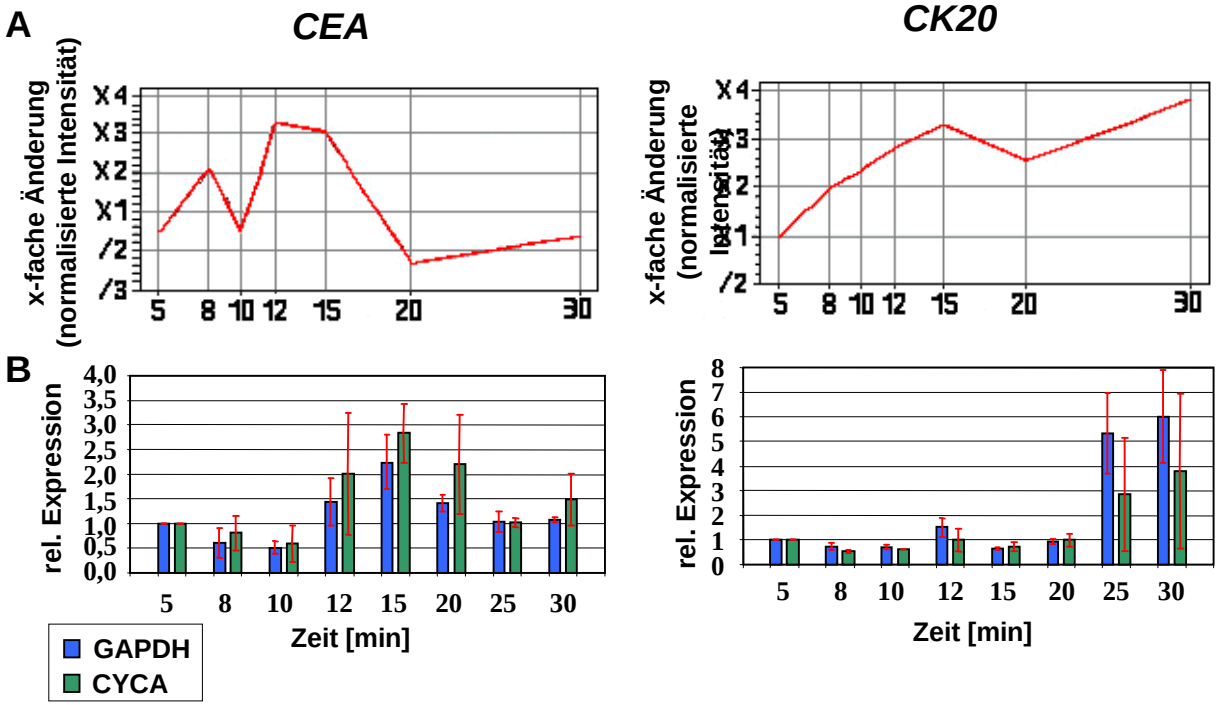
Common colorectal tumor markers *CEA* and cytokeratin *CK20*



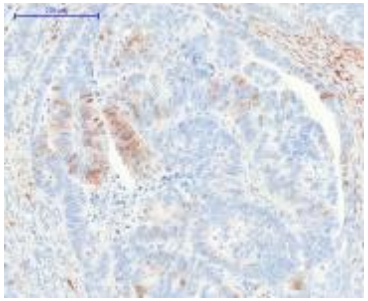
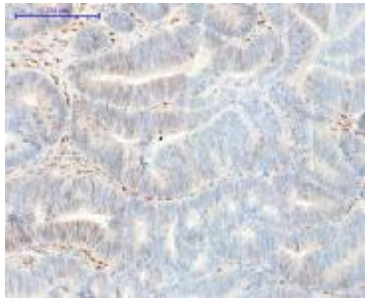
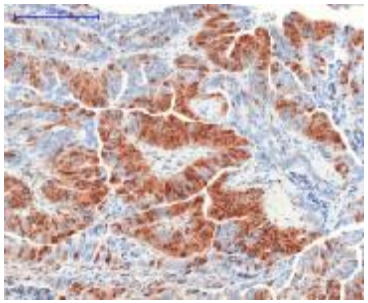
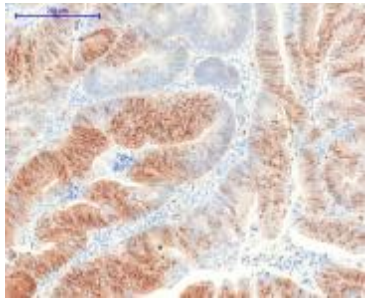
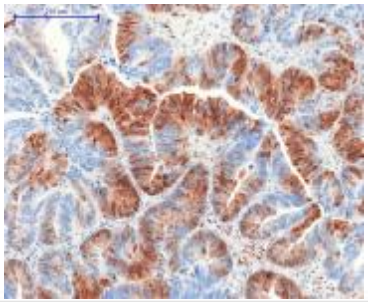
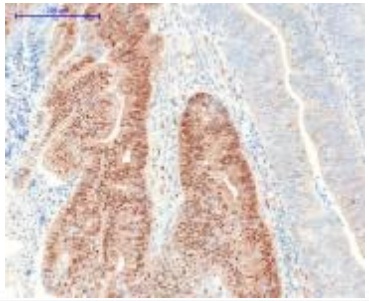
Tissue ischemia and gene expression profiling

(Comparison Affymetrix data and real-time RT-PCR)

Slide Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg

Phosphoprotein Expression and Postsurgical Ischemia: pMAPK Immunostaining (Ventana)

OBBR Office of Biorepositories and Biospecimen Research

	Case A	Case B
10 min		
20 min		
60 min		

Change of pMAPK expression after 10-20 min cold ischemia

Slide Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg

Plasma Biomarkers: Collection Protocol Variations with Known Effects on Analyte Assays

OBBR Office of Biorepositories and Biospecimen Research

Procedure	Variations
Venipuncture	Needle gauge Priming volumes
Phlebotomy	Patient position (seated / reclining) Tourniquet time Tube orders Venipuncture sites
Collection device	Tube types
Blood derivatives and processing	Anticoagulant types Temperatures Centrifugation speeds Processing time
Time between collection and storage	Variable or unknown times
Storage and shipping	Temperature Duration

How Can Changes in Biospecimens Affect Molecular Readout?

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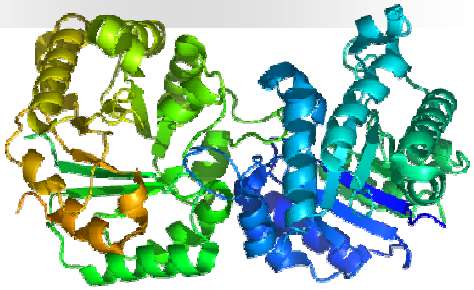
Genomics

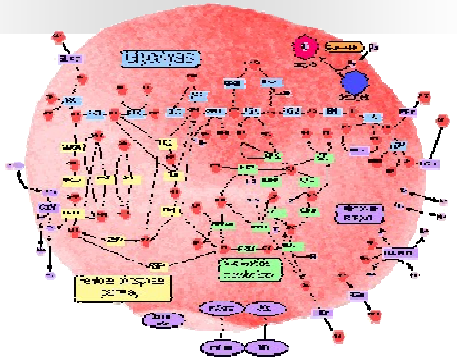
- Changes in specific transcript levels based on handling variables, not disease
- Changes in RNA levels with frozen storage time or freeze-thaw cycles

Proteomics



- Lack of reproducibility of protein biomarkers in discovery research
- Inconsistent IHC results in research and clinical labs

Metabolomics



Inconsistencies in small molecule readouts that may point to the wrong pathways

Solutions

OBBR Office of Biorepositories and Biospecimen Research

Stepwise Approach:

- **Standards**
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- **Specimens and Service**
  - **The Cancer Human Biobank**

Providing Resources for the Research Community: The Cancer Human Biobank (caHUB)

OBBR Office of Biorepositories and Biospecimen Research

The vision:

- **unique, centralized, non-profit public resource**
- **source of adequate and continuous supplies of human biospecimens and associated data of *measurable, high quality* acquired within an ethical framework**
- **source of high-quality biobanking services for the community**

caHUB The Cancer Human Biobank

caHUB Key Concepts

OBBR Office of Biorepositories and Biospecimen Research

- Scientifically designed collection strategies (including rare diseases)
- Multiple aliquots of every specimen
- Standardized, annotated collection, processing of all specimens
- Centralized QC and pathology analysis of every specimen
- Rich, standardized data profile for each sample
- Centralized source of normal human specimens
- Provision of tools, resources, training for biospecimen resources

caHUB Collection Design: Informed by User Need

OBBR Office of Biorepositories and Biospecimen Research

In high demand and short supply:

- **Benchmark samples**
  - **Collected through standardized methods with strict QC and metrics**
  - **Data associated with process variables**
- **Cases with multiple aliquots**
  - **Confirmation of prior studies**
  - **Opportunity to extend prior studies based on new technologies / analyses**
- **Statistically valid numbers of biospecimen sets**
- **Fully defined "patient case sets"**
  - **Tumor**
  - **Adjacent normal tissue**
  - **Tumor periphery (invasive border)**
  - **Pre- and post operative blood samples**
  - **Urine**
  - **Rich clinical data and outcome information for patients**
- **Non-surgical samples: normal tissues; metastases; pre-malignancy**

caHUB: High-Quality Specimens and Data from Patients Who Receive High-Quality Care

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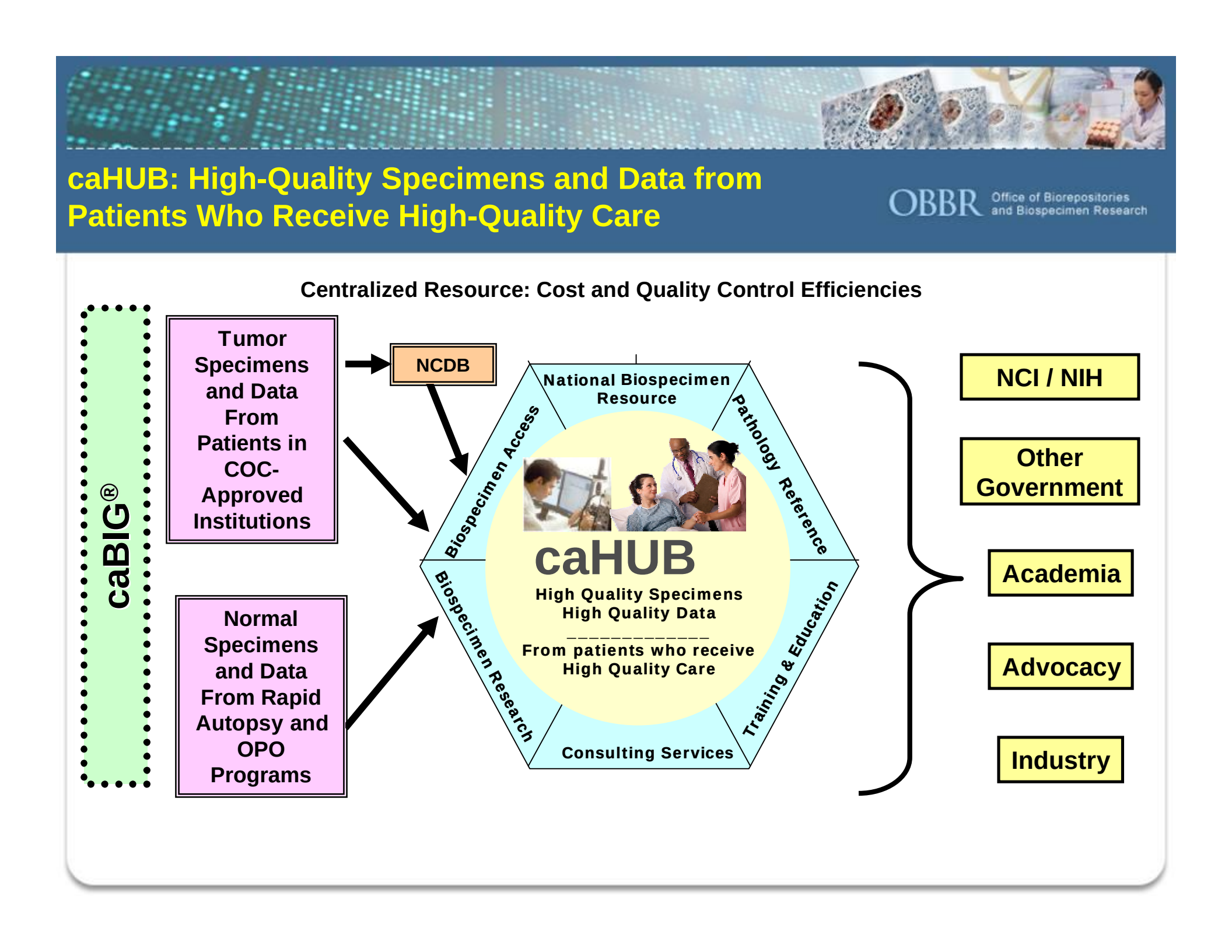
Centralized Resource: Cost and Quality Control Efficiencies

caBIG®

Tumor Specimens and Data From Patients in COC-Approved Institutions

Normal Specimens and Data From Rapid Autopsy and OPO Programs

NCDB



NCI / NIH

Other Government

Academia

Advocacy

Industry

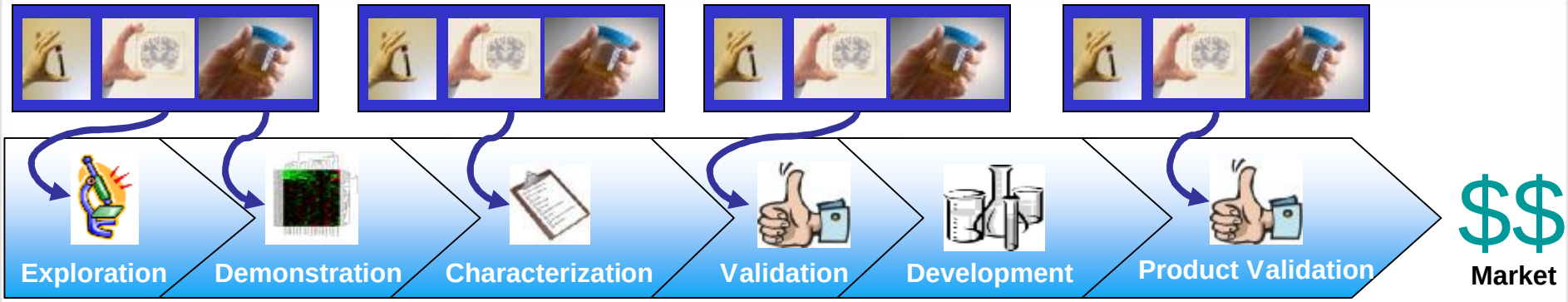
The caHUB as a Resource for Users

OBBR Office of Biorepositories and Biospecimen Research

- **Data available through the system:**
  - **Specimen type, amount, diagnosis, pathological characteristics, macro- and microscopic appearance**
  - **Collection, processing, storage, distribution**
  - **Quality control metrics**
  - **Clinical information about patient at multiple time-points**
  - **Molecular analysis results from different platforms**
- **The comprehensive data base may, with maturation over time, become more useful to the scientific community than the specimens themselves (in silico research)**
- **caHUB's policies and procedures will be publicly available and may serve as standards for the biobanking community**

Products for Patients: Developing Drugs with High-Quality Biospecimens

OBBR Office of Biorepositories and Biospecimen Research

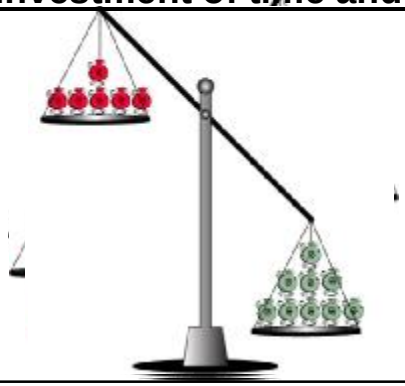


Any association with specific molecular type, stage, grade, outcome?

- Analysis of Molecular Features: Hypothesis Generation
- Demonstration of Linkage: Marker of Disease/Disease Feature
- Biomarker Validation

  Milestone: Confirmation of Disease Biomarker
- Product Development
  - Diagnostic test (clinical, pathologic)
  - Therapeutic drug
  - Molecular imaging tool
- Product Validation

Investment of time and money



Developing Drugs with Biospecimens of Unknown Quality

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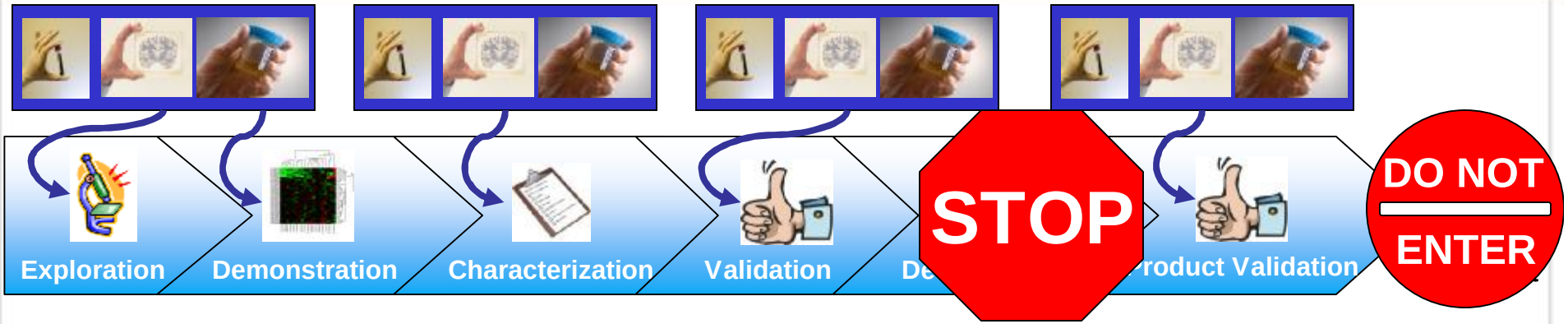


Pre-analytical artifact?
Incorrect identification?
Incorrect characterization?

Poor product design?

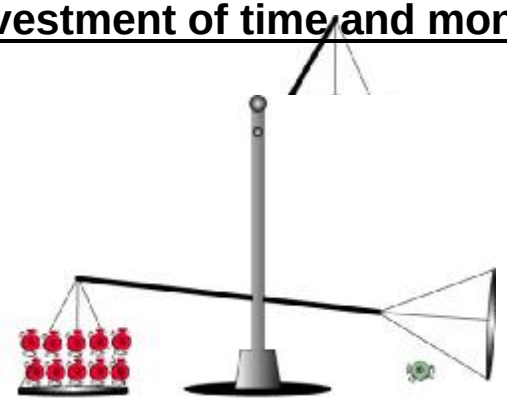
- Analysis of Molecular Features
- Identification: Marker of Disease/Disease Feature
- Biomarker Validation

Milestone: Confirmation of Disease Marker

- Product Development
  - Diagnostic (clinical, pathologic)
  - Therapeutic drug
  - Molecular imaging tool
- Product Validation

CANNOT REPRODUCE ORIGINAL RESULTS

Investment of time and money



Biospecimens: An Investment in the Future

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"If you don't have the time (or money) to do it right, when will you have the time (money) to do it over?"

- **John Wooden, Coach Extraordinaire**

Standards Are Required If Biospecimen Sharing Is to Enable Success

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1. What are the unique issues in sharing biospecimens (and data) that need to be considered in a sharing framework?

   Standards are lacking that ensure comparability and fitness for specific use.

   New types of data (about the specimen) are required.

2. What have you learned from your initiative that could be used to define 'best practices' for specimen and data sharing?

   Best practices need to be data-driven and standardized but are not.

3. What should motivate industry stakeholders to share specimens and data with each other and with the broader investigator community?

   Positive: huge opportunity for exposing unfit samples, promoting quality samples and increasing product development efficiency

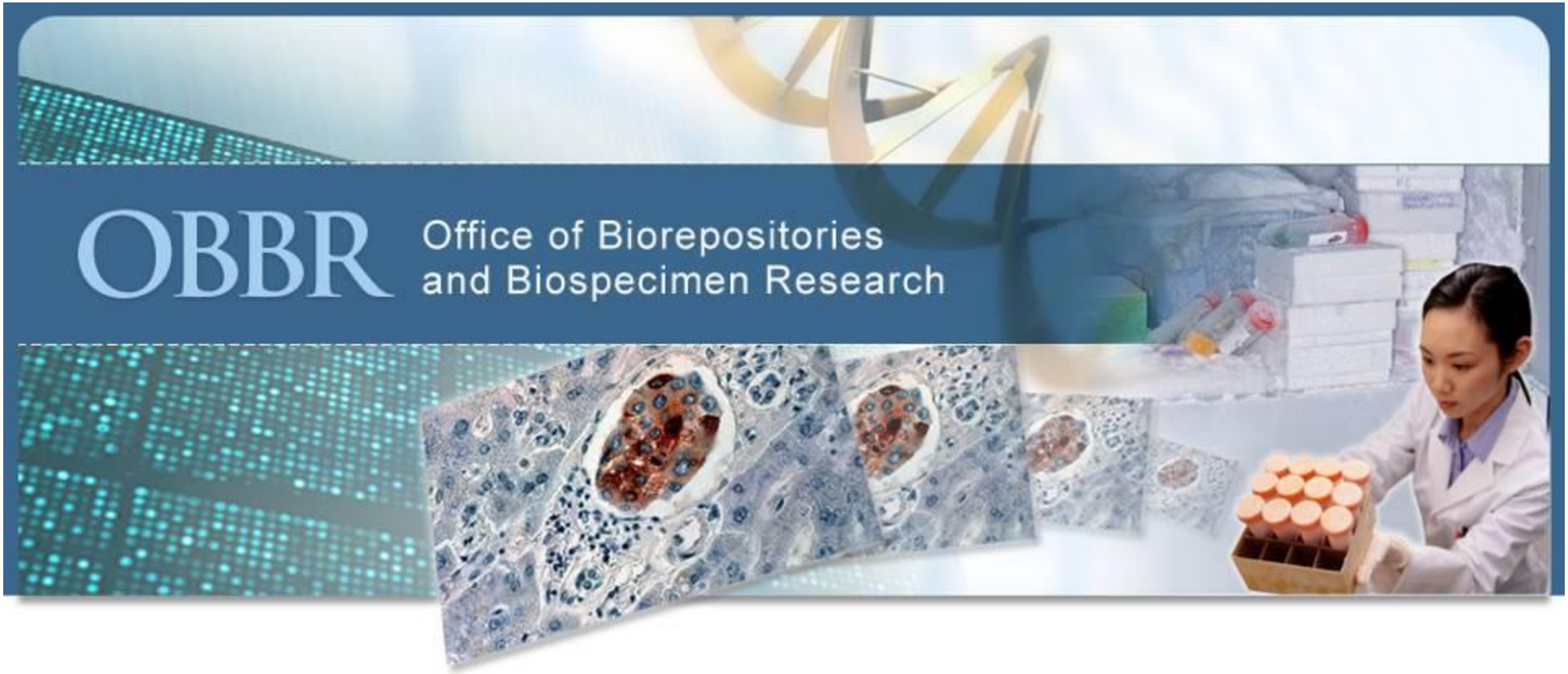
   Negative: things will stay the same -$1.2 billion and 10 years per drug

4. What incentives should or need to be in place to encourage sharing of biospecimens and data?

   Government requirement to do so if public funds contribute to creation of either/both.

5. What key structures and/or rules do you think are required for a framework of sharing biospecimens and data?

   A national biobank that can set the standards (with FDA and NIST) and supply benchmark samples for QA of specimens from any source



Developing Common Biorepository Infrastructures

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