



The Cancer Human Biobank (caHUB): Advancing the Vision of Personalized Medicine

Filling the Infrastructure Gap for Translational Research

Carolyn C. Compton, M.D., Ph.D.

**Director, Office of Biorepositories and Biospecimen Research
Acting Director, Office of Technology and Industrial Relations**

**2nd Annual Biospecimen Research Symposium
March 17, 2009**



What Is caHUB?

OBBR Office of Biorepositories
and Biospecimen Research

A unique, centralized, non-profit public resource that will ensure the adequate and continuous supply of human biospecimens and associated data of measurable, high quality acquired within an ethical framework.



Translational Research Promises to Realize the Vision of Personalized Medicine

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Molecular Data

Diagnosis / Therapy

Translational Research



PERSONALIZED CANCER CARE

Biospecimen Analysis

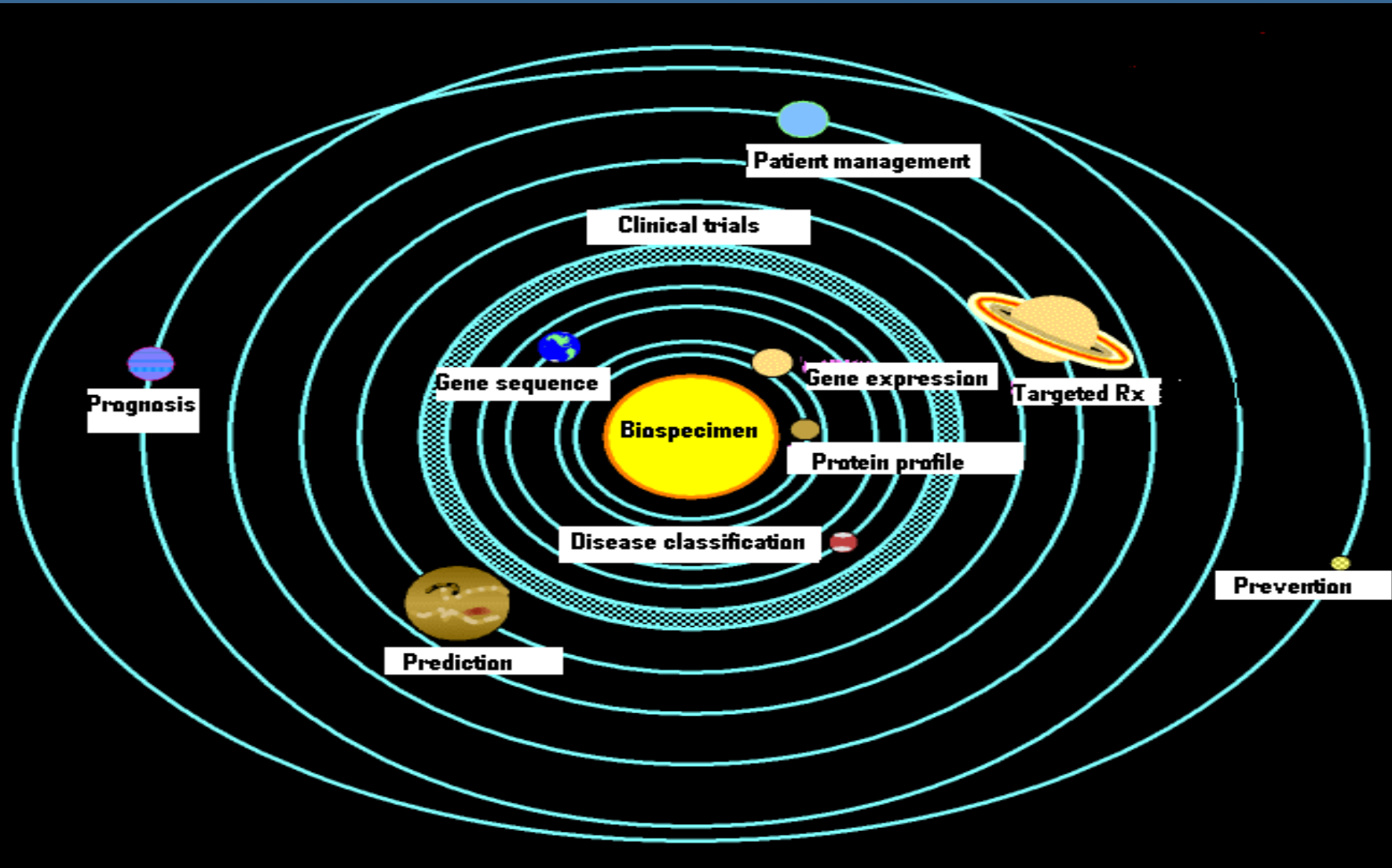
Biospecimen Collection



Biospecimen Processing and Banking

The Personalized Medicine Universe

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The Challenge for Translational Research: Biospecimen Resources in the USA Operate in Silos

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



The Step-Wise Process Towards a National Biospecimen Resource

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2008

- **NCI Executive Committee approves planning for caHUB**
- **OBBR begins concept development process for caHUB**
- **OBBR studies market; risk/benefits; organizational/funding models**
- **NCI Director asks OBBR to explore plans for a national resource**

2007

- **OBBR publishes the NCI Best Practices for Biospecimen Resources**

2006

- **Biospecimen Research Network (BRN) is formed**

2005

- **OBBR is formed**

2003

- **National Biospecimen Network (NBN) Blueprint published**

2002

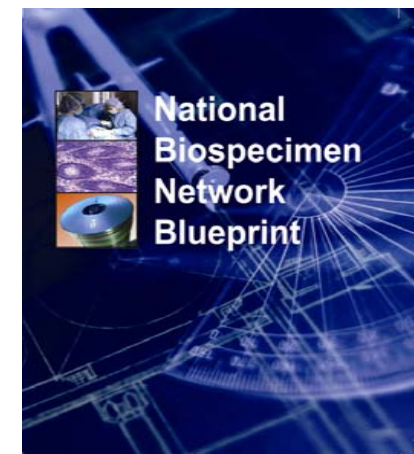
- **National Dialogue on Cancer identifies biospecimens as critically important to post-genomic cancer research**

The National Biospecimen Network Blueprint: The Principles on Which caHUB Is Founded

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Key principles for a national biobank:

- Standardized biospecimen collection and distribution procedures
- Standardized data sets and data vocabulary
- Integrated information technology system to support all functions
- Harmonized approached to ethical and legal issues
 - Standardized consent, MTAs
- Transparent governance and business models
 - Transparent access policies
- Large well-designed specimen sets





The Importance of Standardized Specimens and the Requirement for a National Biospecimen Resource Is Widely Cited

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- **Genomics and Personalized Medicine Act of 2007**
- **Institute Of Medicine Report: *Cancer Biomarkers*, 2007**
- **Dept. of Health and Human Services, *Personalized Health Care Report*, Sept. 2007**
- **President's Council of Advisors on Science and Technology: *Priorities for Personalized Medicine*, Sept. 2008**
- **President's Cancer Panel Report, *Maximizing Our Nation's Investment in Cancer*, Sept. 2008**
- **Kennedy-Hutchinson Cancer Bill ("War on Cancer, Part II"), 2008**
- **The NCI By-Pass Budget for FY2010**



The USA Lags Behind Other National Initiatives

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- ***Iceland DeCode Biobank***
 - National; Population-based
- ***Estonian Genome Project***
 - National; Population-based
- ***UK Biobank***
 - National; Population-based; Ages 45-69
- ***GenomEUtwin (Finland)***
 - International; Population-based; Twin cohorts
- ***Biobanking and Biomolecular Resources Research Infrastructure***
 - Pan-European; Network of new and existing biobanks (population, twin, case/control)
- ***Biobank Japan***
 - National; Hospital patient-based;
 - Focus on common diseases and pharmacogenomic research
- ***OnCore UK***
 - National; Cancer Tissue and Blood Repository for research
- ***Singapore Tissue Network***
 - National; Tissue and DNA Bank for translational and population research for Singapore
 - Collects, processes, and disseminates tissue samples for specific research projects



Can We Do This? The NCI Learns: caHUB-Relevant Pilot Experience

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- The caHUB vision: standardized specimen and data collections that optimize quality that is fit for the scientific purpose has been and is being piloted
 - The Prostate Cancer SPORE Biomarker Project
 - The Cancer Genome Atlas project
- Issues and solutions: experiences brought to the caHUB Planning Process
- Our answer: Yes, we can



National Biospecimen Network Pilot Study

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- **Carried out in 2005-2006 among 11 prostate cancer SPORE sites around an inter-SPORE biomarker project in prostate biopsies**
- **Challenges posed by process variation among study sites:**
 - Different procedures for collecting tissues
 - Different procedures for obtaining informed consent
 - Different informatics systems that were not interoperable
 - Lack of information necessary to identify sources of variation
 - Lack of ability/authority of participants to institute procedural changes within their institutions that would be needed to harmonize across sites
- **Pilot terminated**
- **“Rule book” needed: *NCI’s Best Practices for Biospecimen Resources***
- **“Business model” inadequate: academic, collegial, bottom-up**



Case Study from The Cancer Genome Atlas (TCGA): Lessons in Biospecimen Challenges and Solutions

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- Large-scale team project to explore the full spectrum of cancer-associated genomic changes: coordinated, comprehensive approach
 - Data made available to the broad research community
 - Pilot phase 2006-2009
- Premise: Cancer is a disease of genomic alteration
 - Many alterations remain unknown
- Envisioned benefits (underpinnings for personalized medicine):
 - Elucidate etiologies
 - Provide bases for molecular classification, taxonomy
 - Reveal targets for therapy
 - Provide insights into clinical behavior; prediction, prognosis



Case Study from The Cancer Genome Atlas (TCGA): Lessons in Biospecimen Challenges and Solutions

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TCGA pilot project

- Three different cancers: brain, ovarian and lung
- Biospecimens obtained from a network of retrospective collections at multiple academic medical centers
- Centralized pathology and molecular QC of samples (caHUB model)
- Molecular analyses – 10 platforms
 - RNA and micro-RNA profiling
 - Copy number variation
 - Translocation analysis
 - Epigenetic (methylation) analysis
 - Sequencing
- Clinical data collected for clinical correlation



TCGA Specimen Requirements

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- Set by the technical demands of the molecular analysis platforms
- All 10 analysis centers would analyze exactly the same molecules from the same samples from the same patient - all data directly comparable
 - Sufficient quantity to satisfy all platforms
 - Sufficient quality to yield interpretable data on all platforms
- The target number of 500 cases per tumor type: defined depth of analysis and probability of finding genomic changes that occur infrequently (3% level)



TCGA Lessons Learned - Real Numbers

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- From responses to original RFI (2006), estimated that all 1500 cases could be acquired from 4-6 sites
- OBBR now working with 54 sites (and counting)
 - Several are outside the USA
- Impossible to reach accrual goals from retrospective collections alone
- Prospective collection instituted – relevant caHUB experience

TCGA Lessons Learned - Real Numbers

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- Biobank inventory drop-out rates as high as 95 – 99%
- Molecular QC failure rates for qualifying samples typically 30%

	Repository 1 (Major Academic Site)	Repository 2 (Major Academic Site)
# Frozen samples logged in collection	5000+	1200+
# Samples meeting spec upon detailed review of inventory	1392	120
# Samples meeting physical/pathological specs	174	18

← Before full
pathology
review



Case Study from The Cancer Genome Atlas (TCGA): Lessons in Biospecimen Challenges and Solutions

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- **Quality of existing samples is typically overestimated by biobanks**
- **Collection of normal control samples is not routine**
- **Histological quality does not guarantee molecular quality**
- **Other important factors:**
 - **Consent, IRB, HIPAA issues**
 - **Material Transfer Agreement, Intellectual Property, Authorship, Incentives issues**
 - **Governance and communication challenges**
 - **Informatics needs**
 - **Extraction and transfer of associated clinical data**
 - **Standards compliance (caBIG™)**
 - **Costs**



TCGA as a Pilot for caHUB - Specimen Collection and Processing

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Prospective patient consent and tissue collection instituted:

- Protocols designed to maximum qualification of samples
 - Handling appropriate for specimen type and study design
- Protocols started at the source
 - Surgical /OR staff, consent
- Learned that Standard Operating Procedures, training and education required for all aspects



Case Study from The Cancer Genome Atlas (TCGA): Lessons in Biospecimen Challenges and Solutions

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- TCGA is now a proven success
- First Nature paper published October 2008
 - Most comprehensive high-quality data set on GBM to date
- Recently approved by BSA for continuation/scale-up
- Specimen accrual recognized as the biggest challenge for the project
 - High-quality data dependent on high-quality analytes from high-quality specimens
 - Strong recommendation to adhere to specimen quality standards
- Bottom line: specimen challenges can be met and are worth the effort, but we don't already have what we need in our current system

Lessons learned/solutions developed directly applicable to caHUB



- What it is: a unique, centralized, non-profit public resource that will ensure the adequate and continuous supply of human biospecimens and associated data of measurable, high quality acquired within an ethical framework
- Do we need it?
- What will it do to advance progress?
- What are the next steps?



caHUB Key Concepts

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- Scientifically designed collection strategies
- 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 U.S. biospecimen resources

OBBR Has Developed a Vision in Preparation for Implementation Planning

caHUB Strategic Planning Process

STEP 1: MARKET RESEARCH

Project Organization

Market and Environmental Assessment

STEP 2: PROGRAM DESIGN

Program Direction and Strategies

Product and Service Development Plan

- Initial management team
- Process expectations
- Key planning questions
- Guiding principles
- Initial assumptions
- Requirements for success

• Internal Capabilities

• External Assessment

• Future environmental

• Scope of product

PLANNING PHASE

Step 1: Market research process already begun

Steps 2 and 3: Approval from NCAB 12/9/08

- Partner/collaborator /researcher relationships
- Organization structure
- Program leadership
- Business development
- Ethics, legal, privacy, policy frameworks

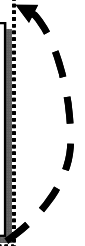
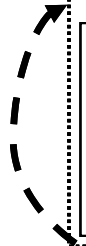
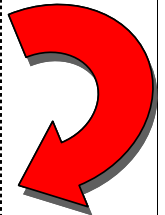
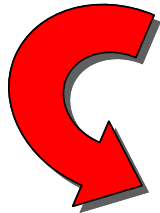
- Staffing
- Accessibility/policies
- Customer service
- Product acquisition oversight and management
- Program scale-up targets

- Key messages
- Key stakeholder groups
- Plan roll-out/timing
- Marketing objectives and strategies
- Web site development

- Capital investment
- Reimbursement models
- Operating *proforma* analysis
- ROI

- Milestones
- Actions
- Responsibilities
- Resource requirements
- Sequence/priority

Bioinformatics/IT Infrastructure





Step 1: Market Research Conducted for OBBR by NCI's Office of Market Research and Evaluation

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<u>Methods</u>	<u>Time Frame</u>	<u>Respondents</u>
In-depth Interviews	July/August 2008	22 (30 invited)
Online Survey	October 2008	727 (~5000 invited)

Types of Respondents

- Academia, NCI grantees (the majority of respondents)
- Federal agencies (NCI, NIH, other)
- Cancer/clinical centers
- Foundations and advocacy groups
- Industry (pharma, biotechnology)

Themes of Questions

- Need for quality biospecimens
- Barriers to access
- Consequences of poor access to quality specimens
- Response to the concept of a central biorepository resource



Initial Survey Findings: Researchers Are Working in Silos

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What percentage of your biospecimens come from each of these sources?

	% Get any from source	Mean % from each
My patients/volunteers	42%	25%
Other patients in my org	55%	31%
Other research institutions	41%	17%
Other medical care facilities	23%	8%
Commercial U.S. biobank	18%	6%
Non-profit biobank	12%	4%
NCI CHTN	12%	4%
Sources outside the U.S.	4%	1%
Other sources	1%	1%

56%

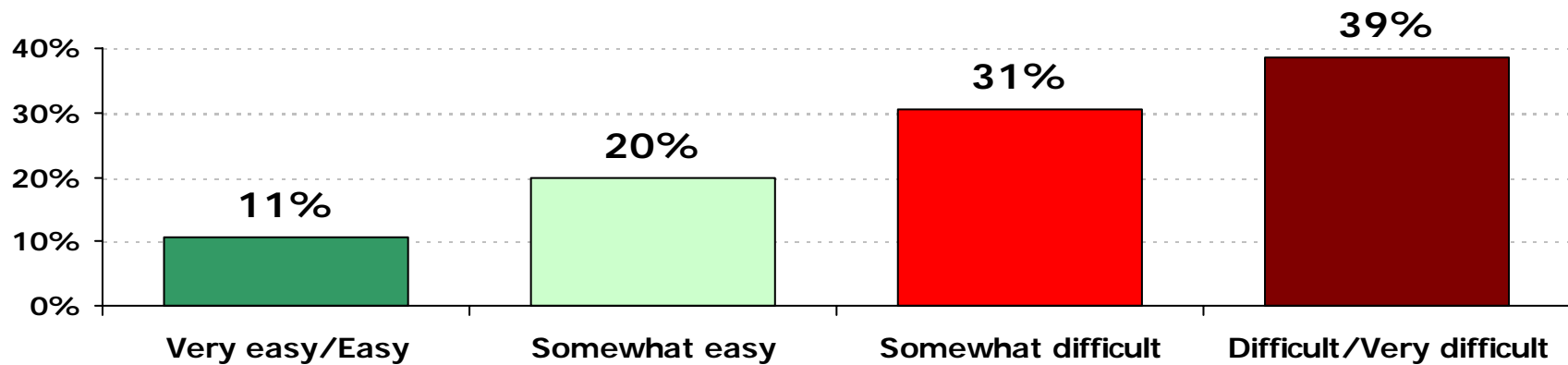
- **Collaborative agreements are not widespread**
55% None/Few (0-25%)
23% Some/Many (26-75%)
22% Most/All (76-100%)

What proportion of your biospecimens come from individuals or organizations who are your research collaborators?

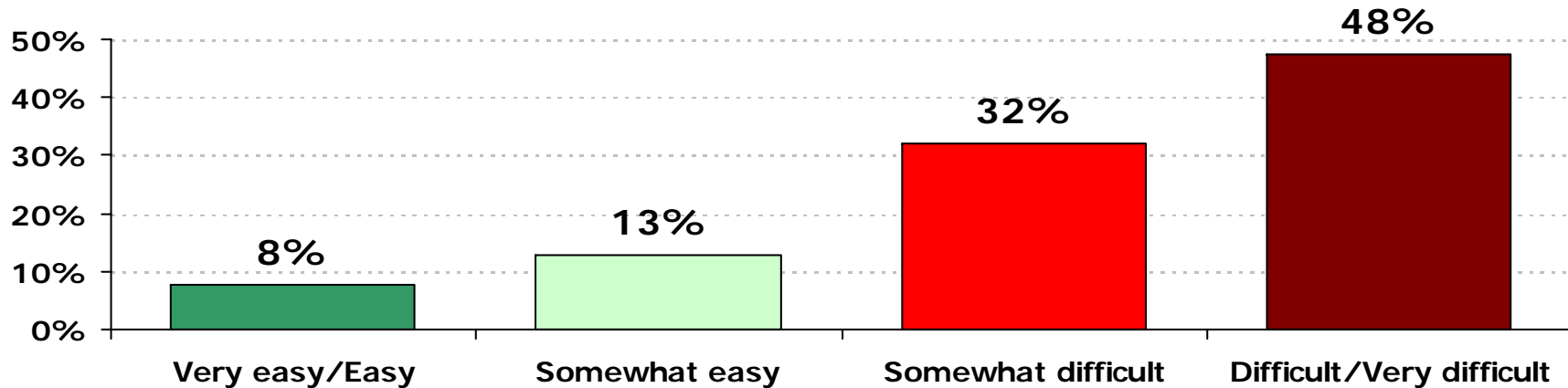
Silos Make It Difficult for Investigators to Get What They Need

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Ease of Acquiring the Quantity of Biospecimens Needed



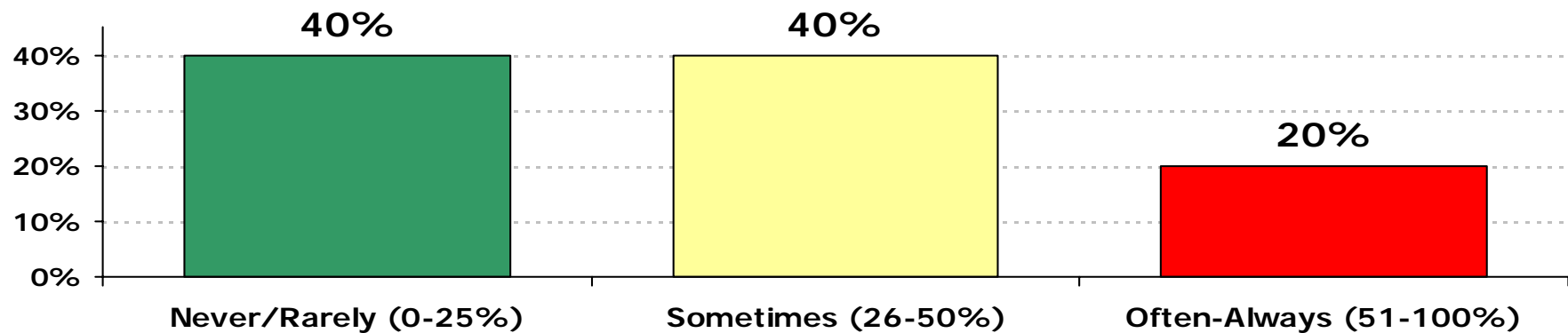
Ease of Acquiring the Quality of Biospecimens Needed



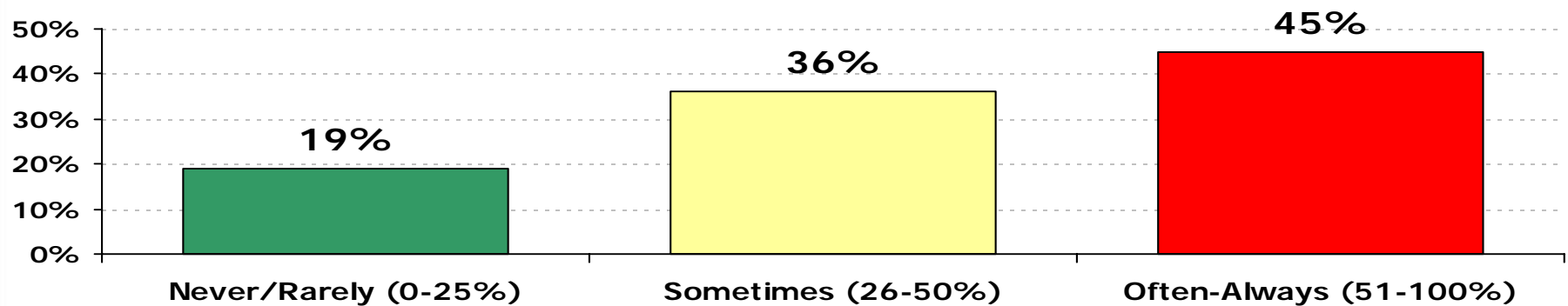
The Science Suffers: Consequences for Investigators

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Question Their Data Because of the Quality of Biospecimens



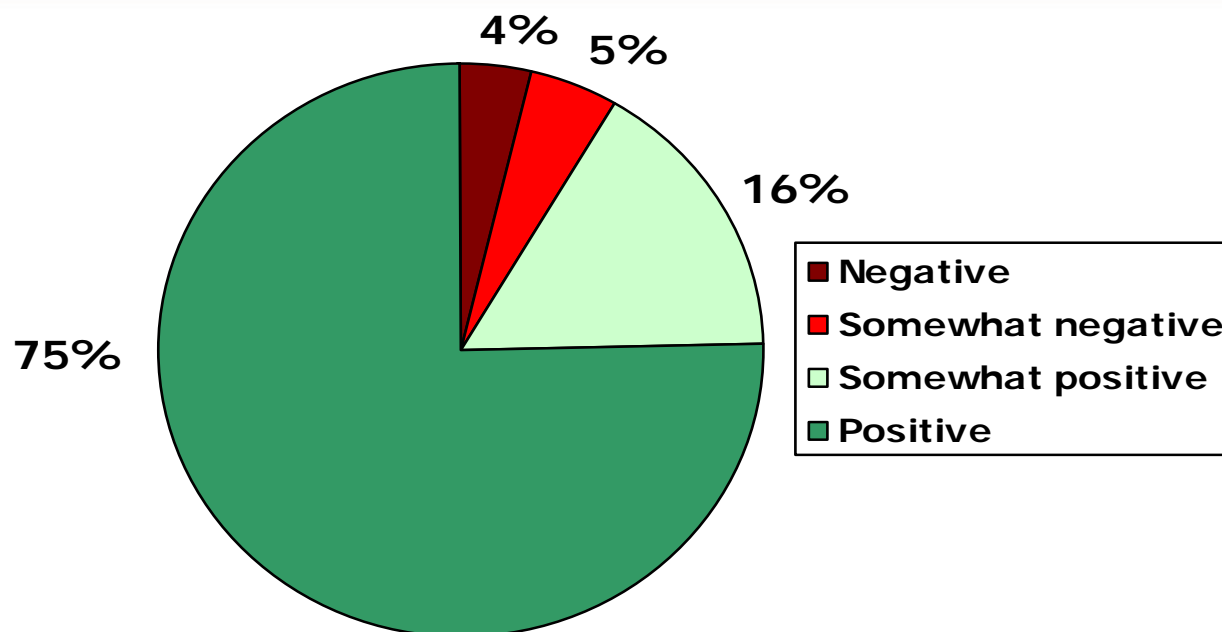
Limit Their Scope of Work Due to the Shortage of Quality Biospecimens





The Reaction to a National Biobank

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How likely would you be to obtain biospecimens from this repository?

62% Very likely
25% Somewhat likely
7% Somewhat unlikely
6% Very unlikely

How willing would you be to contribute biospecimens to it?

53% Very willing
31% Somewhat willing
11% Somewhat unwilling
5% Very unwilling



Comments about Biospecimen Needs and a National Oncology Repository

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- “While it remains an ideal goal at this point, I firmly believe that **high quality specimens are required for all uses** - mine specifically include: identification and validation of biomarkers, establishing clinical cut-offs for test values, establishing normative data for test values, determining predictive value of tests, validating test methods [new and modified], etc.”
- “We don’t know [if high-quality biospecimens are necessary or desirable] because **we aren’t sure how variable our current specimens are and how much this is affecting our outcome.**”
- “It would be great to always have ‘high quality biospecimens’, but **we often have to make do with what we have.**”
- “As basic researchers in a cancer center, **we rely on others to obtain ANY samples, whether high quality or not.** A centralized source for high-quality biospecimens (QA/QC SOPs established and monitored by NCI, for example) would be absolutely ideal.”



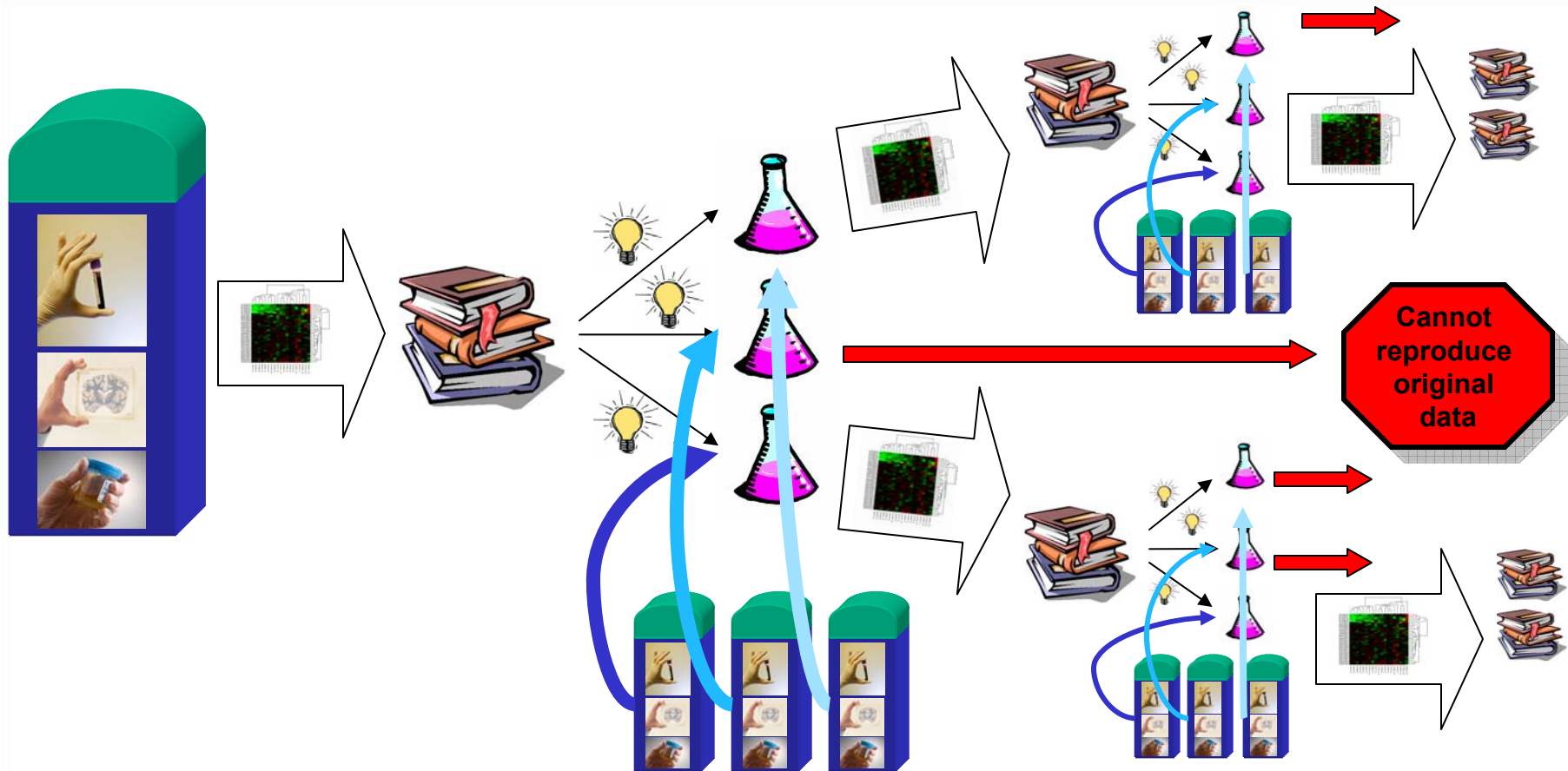
Salts Biorepositories: A Critical Bedrock for the Advancement of Science and Medicine

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- Builds on NCI's experiences to date and NBN principles
- Links cancer institutions, researchers, and scientific initiatives
- Benefits (not competes with) other biobanking programs
- Facilitates rapid development and regulatory approval of medical products
- Facilitates standardization and medical implementation of approved products
- Allows direct performance comparisons of different technologies
- Increases efficiency of scientific innovation and knowledge maturation

Silos: Biospecimen Variation Thwarts Innovation in Medical Science

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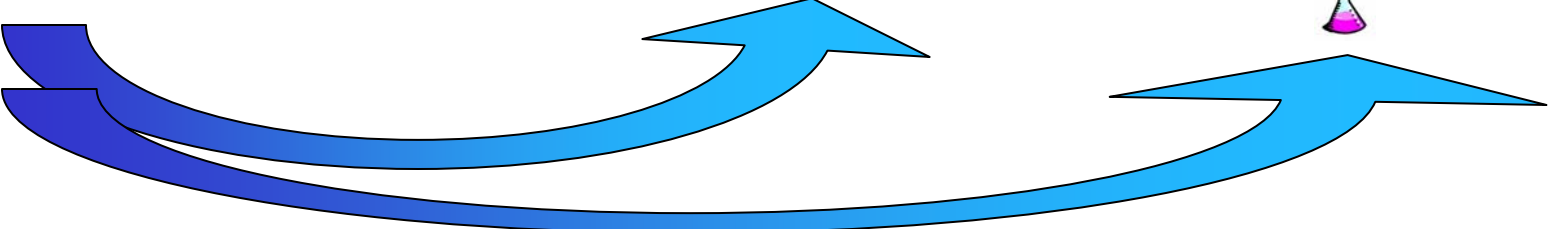
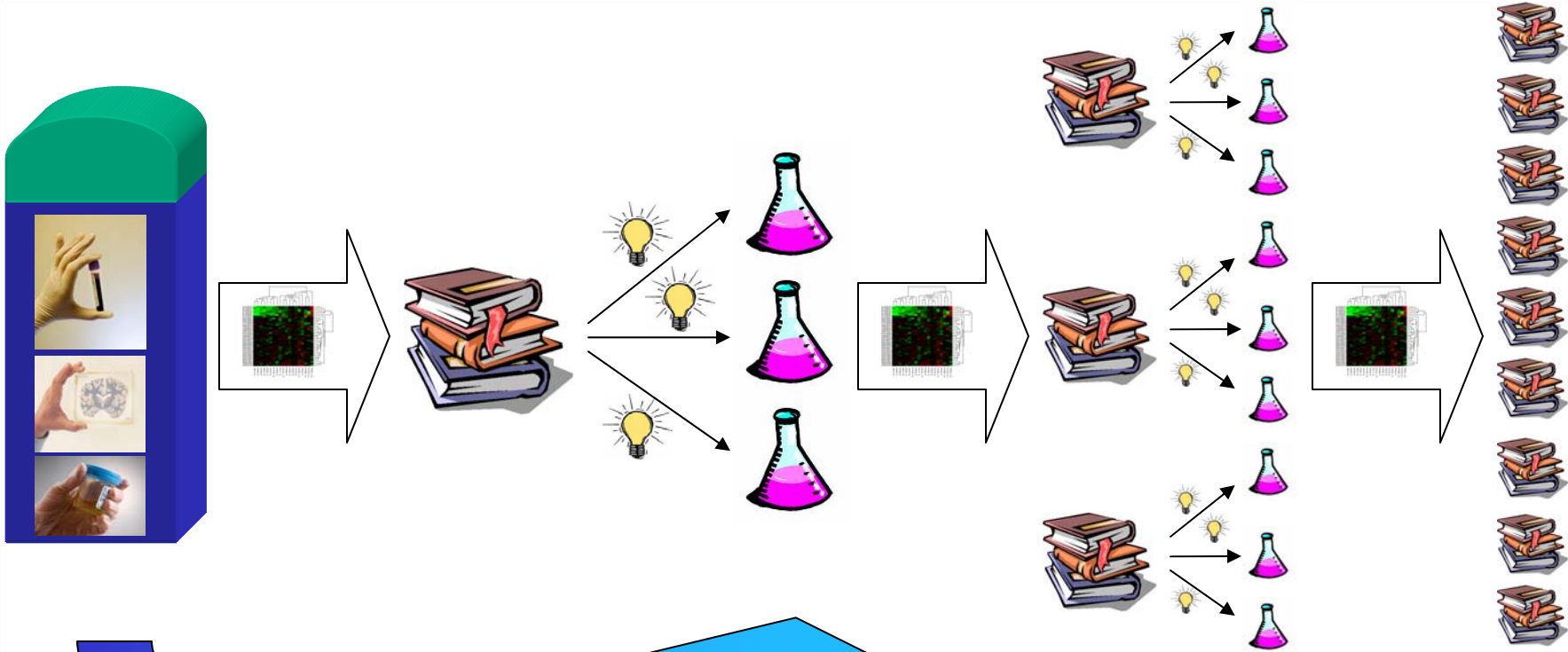


Scientific Progress?



Biospecimen Standardization Advances Innovation in Medical Science

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Scientific Progress



The Value Proposition: Biobanks Are Institutions that Amplify Knowledge

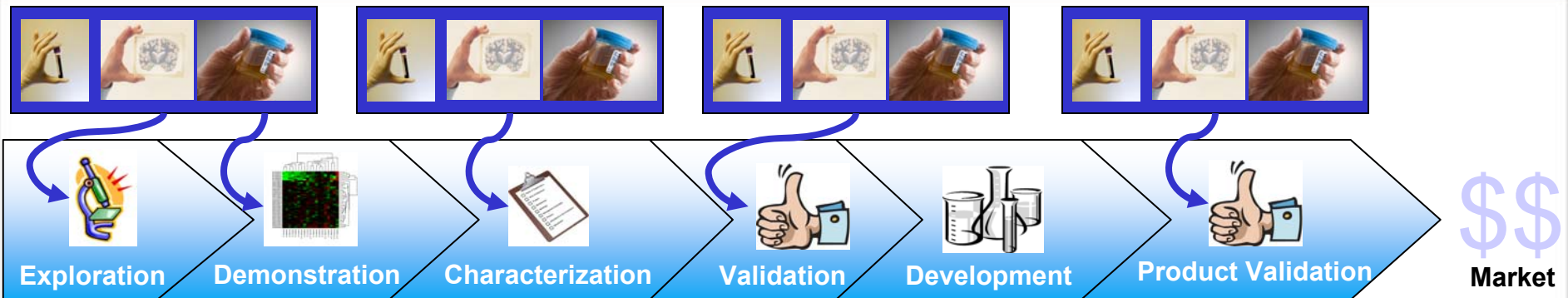
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- **Biological Resource Centers amplify the impact of scientific progress by enabling future generations to build on past discoveries**
- **Biological Resource Centers fulfill several key functions, including:**
 - *Authenticating* materials to ensure quality
 - *Preserving* materials having future value over long periods of time
 - *Providing Access* to materials for the research community
 - *Creating Economies of Scale*

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

Developing Cancer Solutions with High-Quality Biospecimens

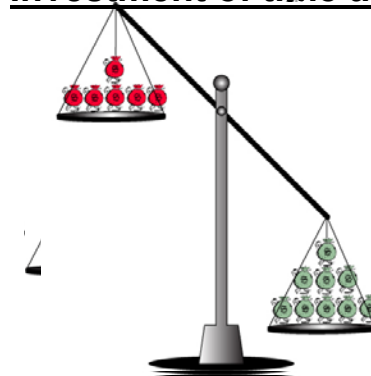
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Any ~~US or Japan~~ **US or Japan** with specific features, sample size, age, etc., outcome?

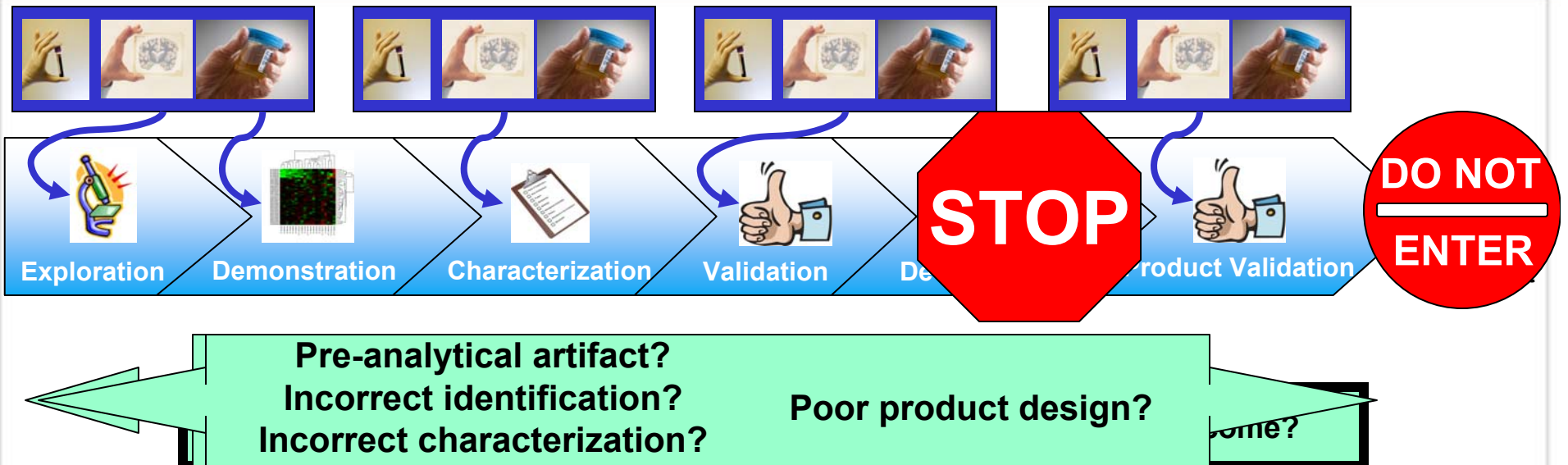
- Analysis of Molecular Features: Hypothesis Generation
- Demonstration of Linkage: Marker of Disease/Disease Feature
- Biomarker Validation
 - Milestone: Confirmation of Disease Biomarker*
- Product Development
 - Diagnostic test (clinical, pathologic)
 - Therapeutic drug
 - Molecular imaging tool
- Product Validation

Investment of time and money



Developing Cancer Solutions with Biospecimens of Unknown Quality

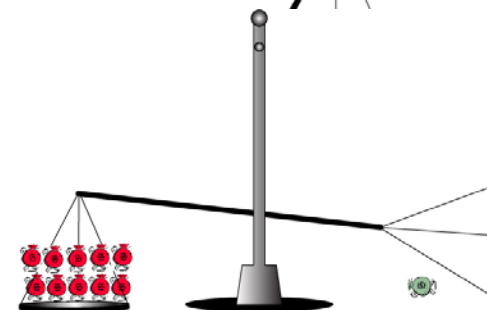
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- Analysis of Molecular Features
- Identification: Marker of Disease/Disease Feature
- Biomarker Validation
 - Milestone: Confirmation of Disease Marker*
- Product Development
 - Diagnostic (chemical, pathologic)
 - Therapeutic drug
 - Molecular imaging tool
- Product Validation

CANNOT REPRODUCE ORIGINAL RESULTS

Investment of time and money





The FDA Perspective on Developing Cancer Solutions with High-Quality Biospecimens

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- The **number one problem** that companies face in putting together submissions for new diagnostic tests is access to well-annotated human tissue samples that have been properly collected.
 - » Steven Gutman, M.D., M.B.A., Director, Office of In Vitro Diagnostics, FDA
- When it comes to the regulatory process, ... unified and standardized samples would make it much easier to move through the approval process. **You simply cannot have proper sample testing and comparative analysis without standardized samples.**
 - » Samir Khleif, M.D., Chief, Cancer Vaccine Section, NCI. Special Assistant to the Commissioner, FDA
- **If samples were collected in ways that are not determined**, it is a challenge for FDA to know what to allow the company to say about sample preparation. If the label is silent on this, **how will we know if the data are really reproducible?**
 - » Larry Kessler, Sc.D., Director, Office of Science and Engineering Laboratories CDRH, FDA



On the Road to Molecular Medicine.....

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“There is an opportunity for the NIH to be the ‘Statue of Liberty’ in creating a vision for how to collect, annotate, store and distribute samples in a standardized way.”

- Steve Gutman, FDA

caHUB Program Design - Functional Areas

Oversight and Governance

Communication and Outreach

- Partnerships Management
- Education and Outreach
- TSS Relations Management
- End User Relations Management

Services/Tools

- Best Practices
- Biospecimen Science Training
- Biospecimen Resource Evaluation Tools
- Specimen Locator Tool
- Biospecimen Research Database (BRD)

Administration

- Finance - Funding Model (Public-Private)
- Personnel
- Technical and Administrative Operations
- Quality Management
- Policies and Procedures
- Reporting

Data Repository

- IT Infrastructure and caBIG
- Clinical Data from NCDB
- Research Data from R&D
- Molecular Analysis Data from Users

Pathology Reference Center

- Sample receiving / quality control
- Sample accessioning – case file / labeling / inventory
- Sample profiling / processing
- Diagnostic confirmation
- Extensive pathology review and reporting
- Sample annotation (data to data repository)
- Sample storage and end user distribution

Ethical / Legal / Policy

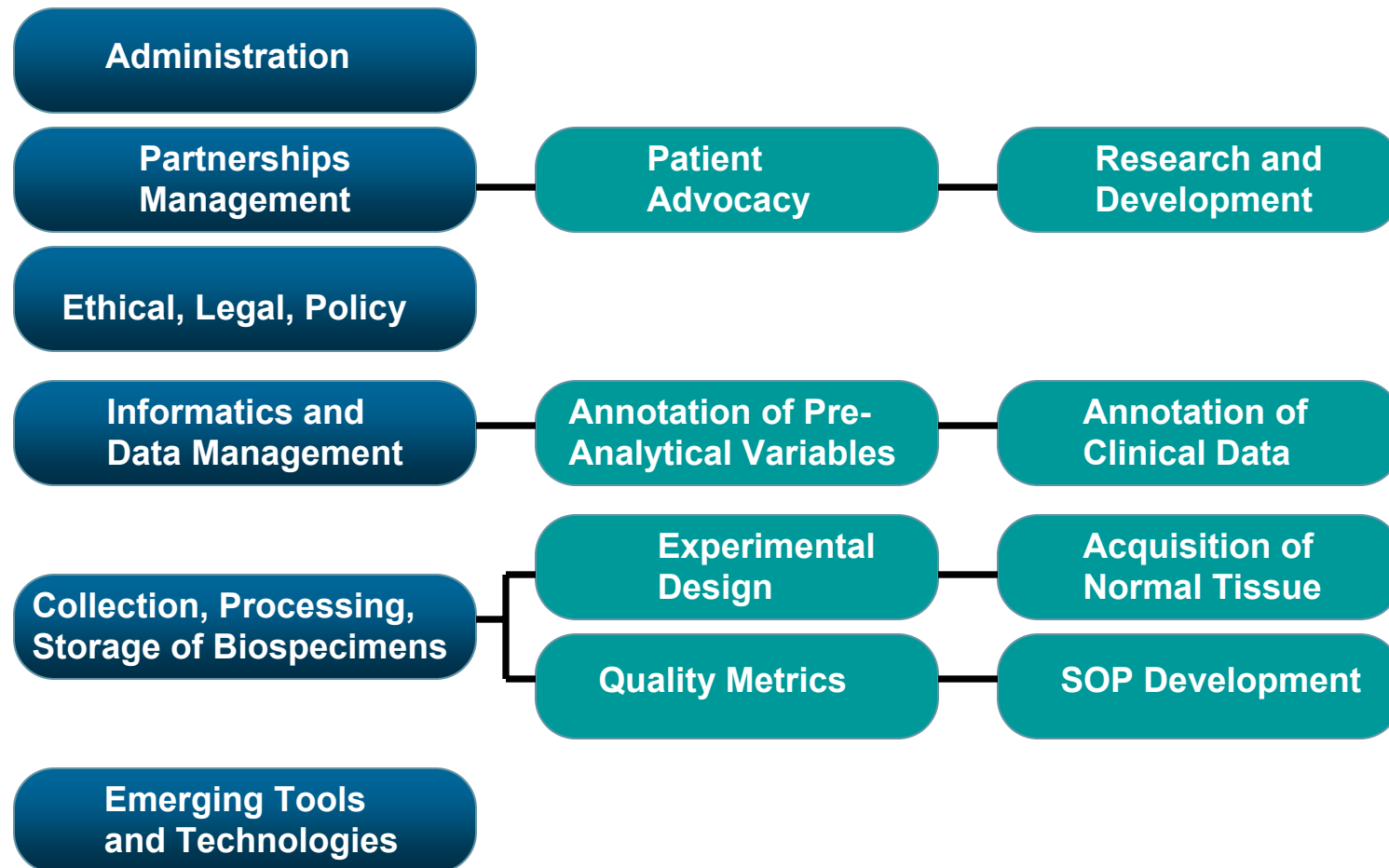
- Federal, State, Local Regulations
- DHHS policies
- NIH / NCI policies
- caHUB policies
 - Access
 - Protection
 - Consent

R&D

- Evidence-based Best Practices and Quality metrics (BRN)
- Technology development / validation (IMAT)
- Technology integration

Planning Phase Working Groups to Support Development of Functional Areas

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Sustainable Funding Models for caHUB

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- For caHUB to be **cost-effective**, **efficient** and **sustainable** over the long-term, it must have a funding model that:
 - Engages the resources of private industry and philanthropy through a public-private partnership
 - Minimizes or eliminates reliance on external funding through a sound cost-recovery program
 - Maintains efficiency and effectiveness through process automation, virtual networking, and technical innovation



A Sustainable Funding Model for caHUB: Public-Private Partnership

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- Consulting firm engaged to develop a sustainable, cost-recovery funding model
- Public-private partnership envisioned during or following demonstration phase
 - OBBR working with NIH Public-Private Partnerships Office
 - OBBR working with Foundation for the NIH (FNIH)
- Public-Private Partnership
 - Government and non-government (industry, advocacy, academic) represented
 - Governance and decision-making includes government, but not limited to government
 - NCI gives up some ownership (negotiated)

PHASE 1: Planning

PHASE 2: Implementation

PHASE 3: Ramp-Up/Maturation

Year 1

Year 2

Year 3

Year 4

Year 5

Year 6

On

Oct. Jan. July Sep. Oct.

Estab. of evaluation plan

Project Management Team

Estab. of PRC

Working Groups

Initiation of specimen collection

PRC implementation
• Specimen acquisition
• Processing
• Distribution

Subcontracts
• Specimen collection
• Consultant services

Monitoring

Formal program evaluation and report

External Advisory Board



Public-private partnerships, cost recovery, outside funding



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Filling the Infrastructure Gap for Translational Research

Carolyn C. Compton, M.D., Ph.D.

**Director, Office of Biorepositories and Biospecimen Research
Acting Director, Office of Technology and Industrial Relations**

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The Cancer Human Biobank (caHUB): Additional Information

Carolyn C. Compton, M.D., Ph.D.
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**Acting Director, Office of
Technology and Industrial Relations**



Lessons Learned from TCGA - Top 5 Sources of GBM Failure

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- Matched normal germline DNA controls (blood or other) lacking
- Insufficient tumor cellularity in samples
 - Tumor cellular composition too low
 - % necrosis too high
- Specimen size too small
 - Insufficient for minimum required DNA/RNA for all analyses
- Molecular quality insufficient
 - QC failure of DNA or RNA
 - Insufficient amount
- Clinical data incorrect: Tumor not primary disease
 - Samples derived from recurrent, i.e. previously treated GBMs (confounding issue: Rx-related effects)

TCGA Components – Genome Characterization Centers

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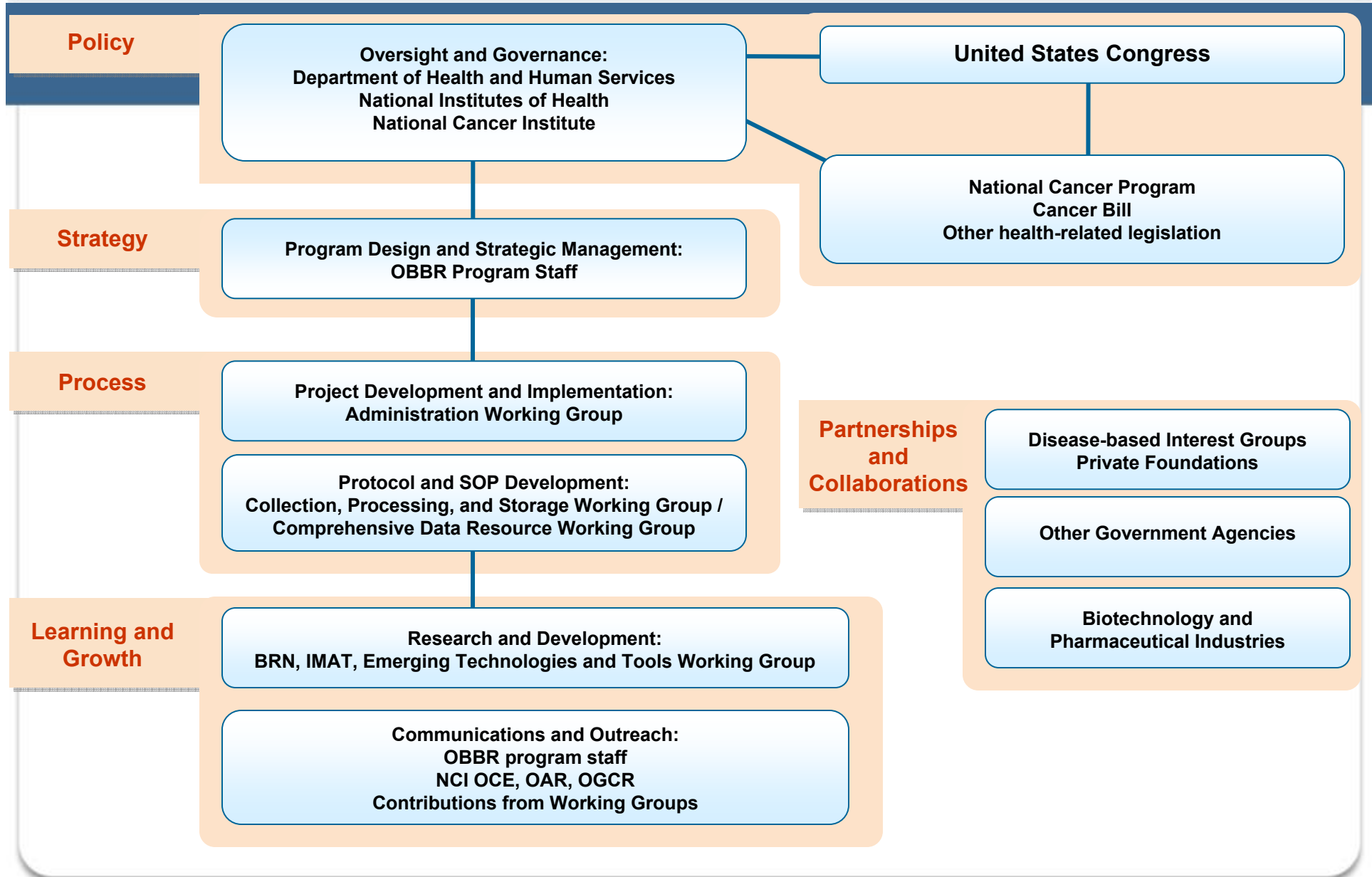
Institute	PI	Platform(s)	Other
Broad Institute of MIT and Harvard	Meyerson	Affymetrix U133 A HTS: transcription; SNP 6.0: copy number alteration	
Lawrence Berkeley National Laboratory	Gray	Affymetrix Exon 1.0 ST: transcription profiling	
Memorial Sloan-Kettering	Ladanyi	Agilent 244K “oligo” array: chromosomal copy number alteration	Custom Agilent array: chromosome translocations
U. of North Carolina	Perou	Agilent 244K “oligo” and microRNA arrays: transcription profiling	
Harvard	Kucherlapati	Agilent 244K “oligo” array: copy number alteration	Development of polony-based serial analysis of gene expression
Stanford	Richard Myers, PhD	Illumina 550k Infinium SNP chip array: copy number alteration	
Johns Hopkins	Baylin	Epigenetic analyses: Illumina Golden Gate platform: methylation	

TCGA Components – Genome Sequencing Centers

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Institute	PI	Platform(s)	Other
Baylor College of Medicine Sequencing Center	Richard Gibbs, PhD	Sanger sequencing of PCR amplified fragments	Illumina Inc, 454 Life Sciences
Broad Institute of MIT and Harvard, Cambridge, MA	Eric Lander, PhD	Sanger sequencing of PCR amplified fragments	Illumina Inc, others
Washington University School of Medicine Sequencing Center	Richard Wilson, PhD	Sanger sequencing of PCR amplified fragments	Illumina Inc, 454 Life Sciences

caHUB – ORGANIZATIONAL STRUCTURE





National Biospecimen Network Pilot Study

OBBR Office of Biorepositories
and Biospecimen Research

- Carried out in 2005-2006 among 11 prostate cancer SPORE sites
- Challenges posed by process variation among study sites:
 - Different procedures for collecting tissues
 - Different procedures for obtaining informed consent
 - Different informatics systems that were not interoperable
 - Lack of information necessary to identify sources of variation
 - Lack of ability/authority of participants to institute procedural changes within their institutions that would be needed to harmonize across sites
- Pilot terminated
- “Rule book” developed: *NCI’s Best Practices for Biospecimen Resources*



caHUB Biospecimen Access: Policy to Be Developed in Planning Phase

OBBR Office of Biorepositories
and Biospecimen Research

caHUB access policies will be:


- Guided by the principles outlined in the *NCI Best Practices for Biospecimen Resources*
- Based on merit and nature of the scientific investigation
- Adapted to meet the needs of the research community
- Developed to ensure compliance with all applicable Federal and State privacy and human subjects regulations and statutes
- Developed to ensure transparent, timely, equitable, and appropriate access
- Transparent and publically available



caHUB Vision: Progress Enabled in Unprecedented Ways

OBBR Office of Biorepositories
and Biospecimen Research

- Centralized source of standardized human samples
 - **Duplicate samples allow direct comparisons of data from different scientific initiatives / oncology product development steps**
 - **“Big science” data linked through the specimens (envision genomic, epigenomic, transcriptomic, and proteomic data linkage)**
 - **Product (therapeutic; diagnostic) and technology development /standardization/regulatory approval all streamlined**
 - **Direct product-to-product performance comparisons enabled**
 - **Standardized reference specimens (“yardstick of truth”) for FDA approval / medical implementation**
- Leverage NCI’s investment in other programs, create unprecedented return on investment and rapid acceleration of scientific knowledge



caHUB Goals: Accelerating the Vision of Personalized Medicine

OBBR Office of Biorepositories
and Biospecimen Research

- Develop and disseminate evidence-based standard operating procedures
- Document and evaluate the current status and quality of human specimens available for research through extensive market research
- Identify strengths in existing specimen demand-supply chain and identify areas of opportunity for further development
- Engage in contractual relationships with tissue source sites to acquire needed biospecimen types
- Support and sponsor research in biospecimen science to further refine and improve standard biobanking practices
- Support and sponsor innovative technology development in biobanking and integration of new and existing technologies into current biobanking practice
- Develop and disseminate tools and resources to support new and existing biospecimen resources
- Engage in public education awareness activities, and support the development of training programs in biospecimen science

Life After Regulatory Approval: Biospecimens Throughout a Product's Lifespan

OBBR Office of Biorepositories
and Biospecimen Research

Diagnostic Tests / Laboratory Assays

High-Quality Standardized Biospecimens

Define standards

- Test execution
- Tolerance for variation
- Test performance

Daily execution

- Quality Assessment
- Quality Control
- Calibration

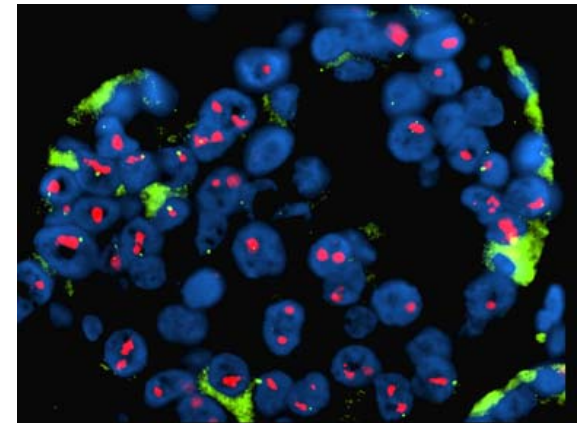
- Decreased false negatives and false positives
- Improved Standard of Care



Diagnostic Tests and Standardization: Consequences in HER2 Testing

OBBR Office of Biorepositories
and Biospecimen Research

- HER2 (ERBB2) gene is amplified in ~ 20% of breast cancers
- HER2 over-expression (“positive” status): important measure of clinical outcome and recommended therapy
- Clinical testing for HER2 status:
 - Formalin-fixed paraffin-embedded cancer tissue*:
 - Immunohistochemical test (0-3+)
 - 2+ cases: FISH
 - Pathologist uses scoring system to report status
- Positive result triggers therapy: ~\$55K/year
- False-positive: risk of cardiotoxicity, no clinical benefit
- False-negative: missing potentially beneficial treatment
- Genentech estimated 5,000 false positives and 7,000 false negatives per year: problem not the assay but where (proficiency) and on what (specimen quality) the assay is performed.
- Standards for specimen handling (type of fixative; length of fixation) not standardized by CAP until 2008



Biological Therapeutics and Standardization: Operating Procedures Have Dire Consequences

OBBR Office of Biorepositories
and Biospecimen Research

- Stem cells harvested from patient → frozen → reintroduced after chemotherapy
- SOP altered by lab director to shorten freeze time
- New SOP not validated
- **Result: > 20% mortality rate**
- **Lawsuit alleges negligence in quality control of stem cells in the biorepository**

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Stem-Cell Transplants Go Awry | Lawsuits allege fraud and negligence: ...

Kansas City Star
October 08, 2006

When doctors diagnosed Dedra Copeland with cancer in 1998, they prescribed an aggressive treatment: high-dose chemotherapy coupled with a stem-cell transplant.

“ I will never again not question ”

First, technicians would filter stem cells from her blood and freeze them. The chemo would kill her cancer. The stem cells would be thawed and pumped back in her body to resume making healthy blood cells.

But when the Kansas City Blood and Marrow Transplant Program collected Copeland's stem cells in April 1999, program leaders knew something she didn't.

Too many patients were dying soon after their transplants. Many others took weeks longer than normal to recover.

The program struggled with the kinds of problems that patients rely on their doctors to warn them about.

But that didn't stop it from taking on more unsuspecting patients like Copeland.

Eventually, an outside expert pointed to a simple change in the stem-cell freezing process in the summer of 1998. To save time and increase efficiency, a lab director had ordered a quicker freeze than was usually used. The stem cells died before they were given back to patients.

From August 1998 to June 1999, the program treated 40 adult patients whose stem cells were processed while the faster freezing method was being used.

About a fourth of these patients died within 100 days of their transplant from complications such as hemorrhages, infections or the return of their cancer, the program's internal documents show. Within two years, half the patients were dead.



National Cancer Database (NCDB)

OBBR Office of Biorepositories
and Biospecimen Research

- Joint program of Commission on Cancer (COC) of the American College of Surgeons and the American Cancer Society
 - Main goal: Assessment of quality of cancer care
- Collects data from 75% of newly diagnosed cancer cases
 - >1400 COC approved cancer programs, 80% community/other
 - Data: Patient characteristics, Pathology, Staging, Treatment, Outcome, Co-morbidity
- Significant data collection and reporting infrastructure
 - Requirement to follow up on care outside reporting institution
 - Standardized data (Facility Oncology Registry Data Standards [FORDS] manual)
 - Data managed by trained registrars
 - Quality control mechanisms
- Known issues
 - Data access agreements would need revision for HUB sources
 - Completeness of data on adjuvant therapy
 - caHUB adds additional impetus for follow-up
 - Partnering with NCDB on plan to address issues

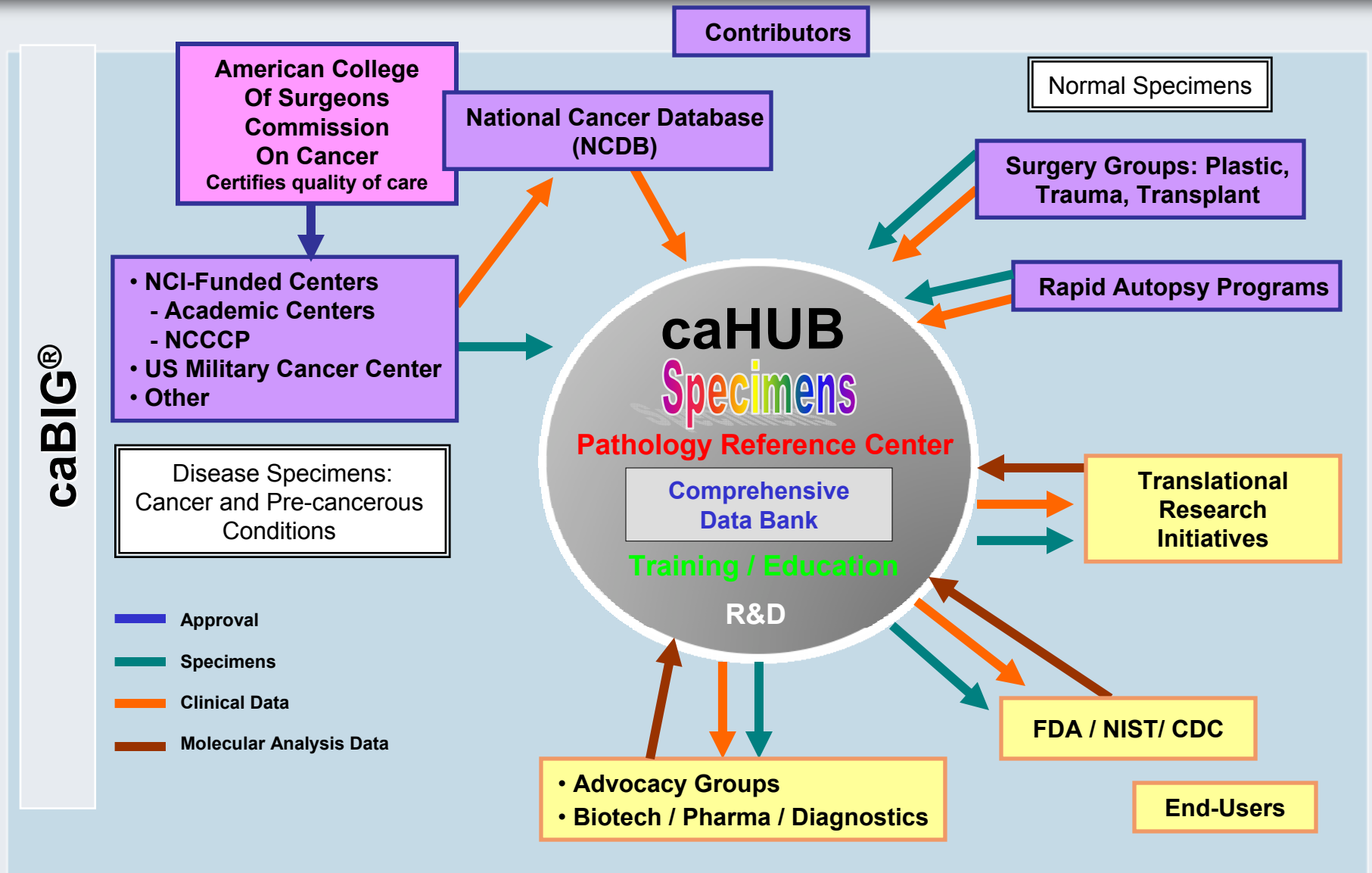


Comments about Biospecimen Standards and a National Oncology Repository

OBBR Office of Biorepositories and Biospecimen Research

- “We are wasting a lot of resources with low quality biospecimens. For example, in a project measuring various phospho-proteins by IHC, only 1/29 specimens was of sufficient quality (as judged by internal controls). In another project 1/6 specimens was satisfactory. The quality is very problematic and highly variable and absolutely differs according to the biomarkers of interest. For examples, all these specimens are adequate for RNA measurements, but are NOT adequate”
- “We perform advanced technology development on specimens and have no use for samples where the integrity of the DNA or the RNA or the protein in them is unknown before we start. Since such information is almost never known or even spot-checked for banked specimens, we inevitably perform such QC analysis on our own, since frankly, the quality of most biorepository materials we are aware of in the US is highly suspect.”
- “I am developing biomarkers. For detection I need disease vs. healthy; for diagnosis I need disease AND confounding diseases; for prediction of outcome I need follow-up; for prediction of response I need treatment data. It is a shame that an established procedure PLUS an appropriate bioinformatics package PLUS SOPs for biobank management has not yet been developed, so everyone has to design his own (e.g., Northwestern U, Fox Chase, Fred Hutch, etc.)”

caHUB (Cancer Human Biobank)



caHUB: **UNIQUE** • **HIGH QUALITY SPECIMENS** • **HIGH QUALITY DATA** • FROM PTS WHO RECEIVED **HIGH QUALITY CARE**



What Is caHUB?

OBBR Office of Biorepositories
and Biospecimen Research

A unique, centralized, non-profit public resource that will ensure the adequate and continuous supply of human biospecimens and associated data of measurable, high quality acquired within an ethical framework.