

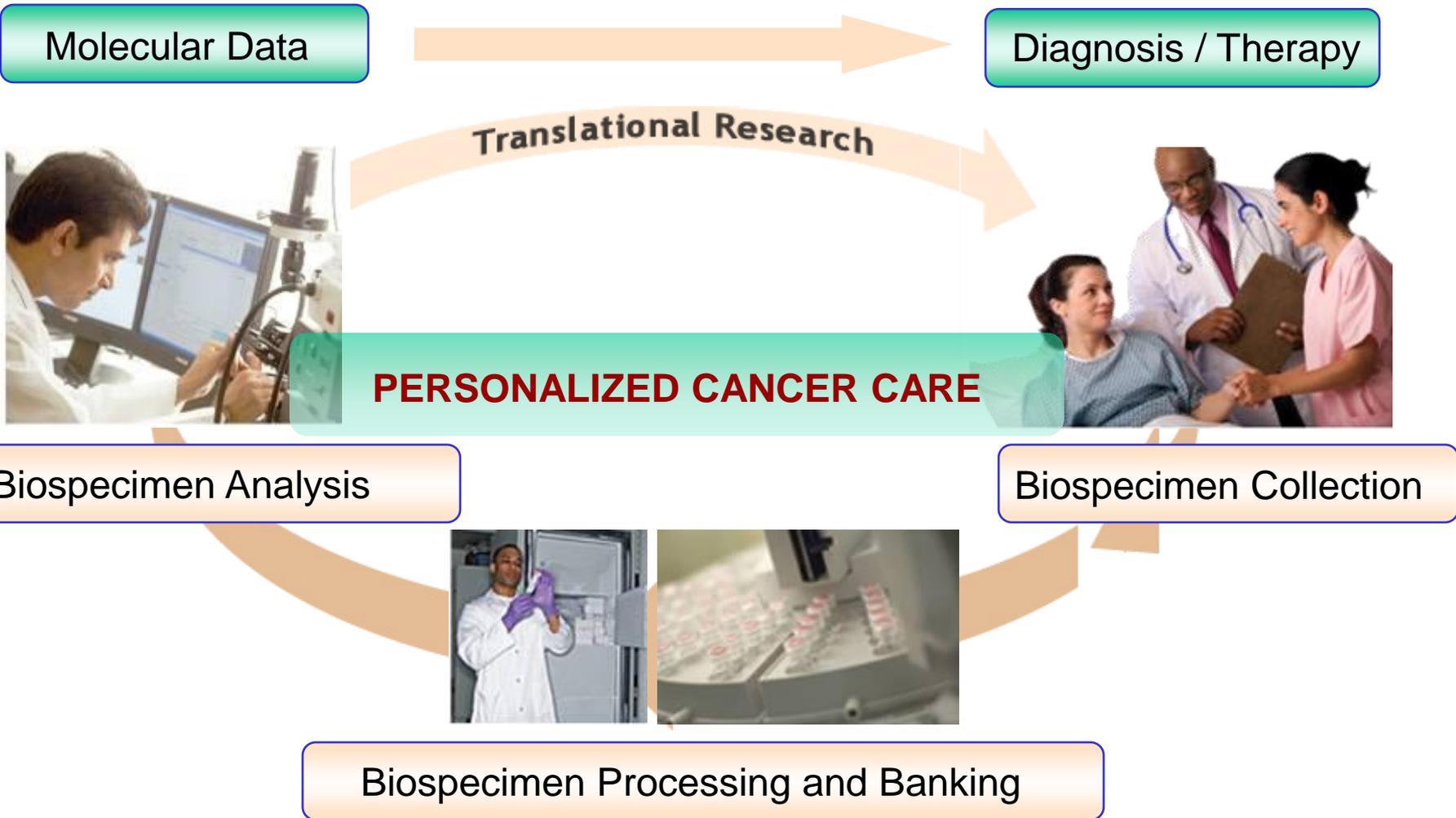
# **Biospecimen Handling: Impact on Cancer Research and Molecular Diagnostics**

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

**NIH Biospecimens Interest Group**  
**May 26, 2009**

# Translational Research Promises to Realize the Vision of Personalized Medicine

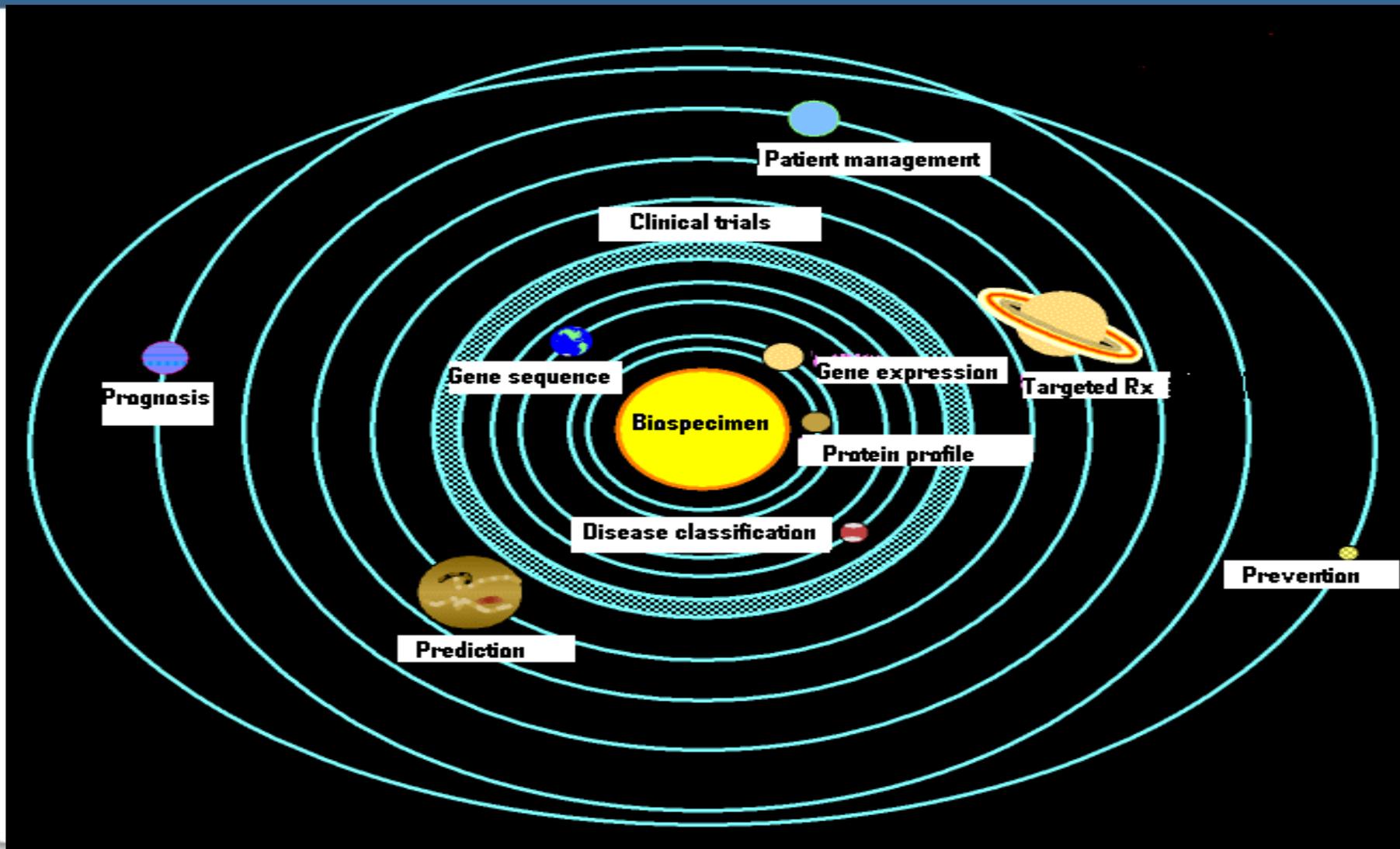
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# The Personalized Medicine Universe

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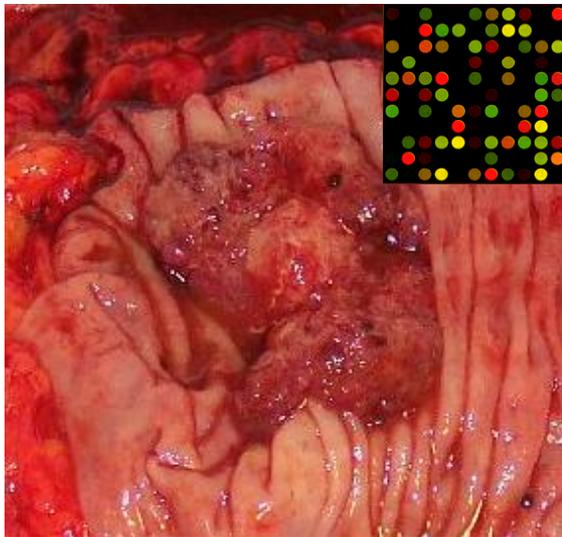




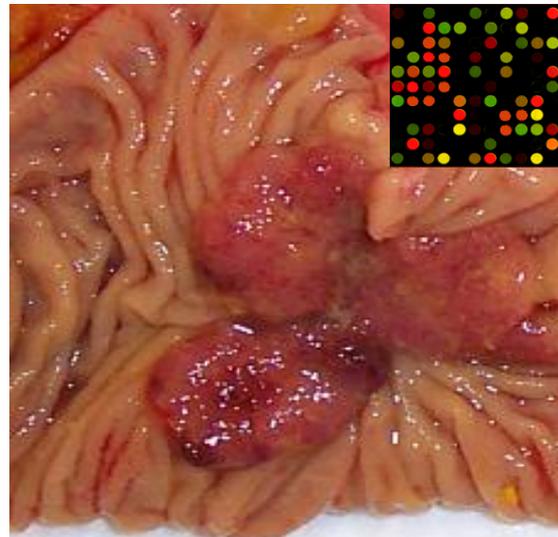
# Personalized Medicine: Individualized Medical Management Based on the Specific Biology of the Patient and His/Her Disease

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and Biospecimen Research

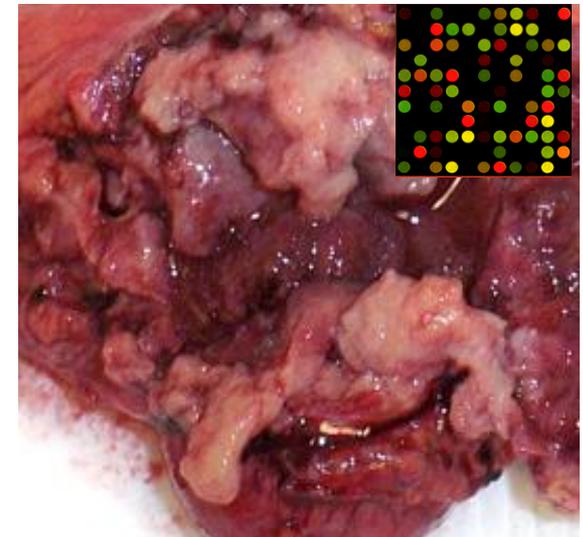
Patient 1



Patient 2



Patient 3



> 1000 different genomic changes in various combination may be involved

=

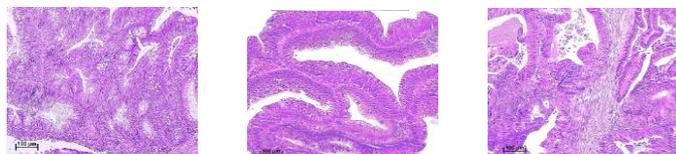
Each patient differs with respect to the molecular character of his/her cancer

Compliments of Dr. Hartmut Juhl, Individumed GmbH, Hamburg

# Today

# Future

of Biorepositories  
specimen Research



Tumor 1

Tumor 2

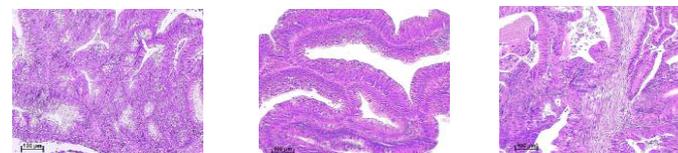
Tumor 3



Standard Therapy



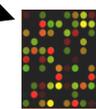
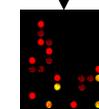
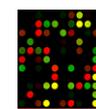
In 2001, only one of three patients benefited from cancer drug treatment  
(Spear et al. (2001) Trends Molec. Med. 7, 201-203)



Tumor 1

Tumor 2

Tumor 3

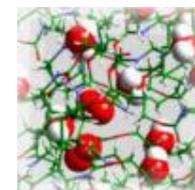


Molecular diagnosis

Therapy 1

Therapy 2

Therapy 3



More effective  
Less toxic  
Less costly

- Biospecimens are the basis of:
  - **Molecular characterization of the disease**
    - Molecular classification of tumor
    - Characterization of tumor heterogeneity/therapeutic targets
  - **Molecular characterization of the host**
    - Disease susceptibility
    - Treatment efficacy (e.g., pharmacogenomics)
  - Personalized medicine will depend on accurate, reproducible data derived from patient samples in the clinical setting

# Biospecimen Quality Impacts Clinical and Research Outcomes

## – Effects on Clinical Outcomes

- **Potential for incorrect diagnosis**

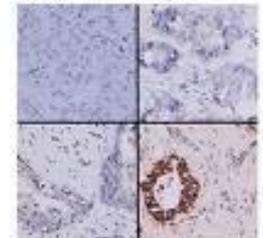
- Morphological/immunostaining artifact
- Skewed clinical chemistry results

- **Potential for incorrect treatment**

- Therapy linked to a diagnostic test on a biospecimen (e.g., HER2 in breast cancer)



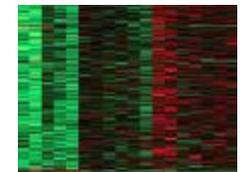
HER-2 as assessed by IHC



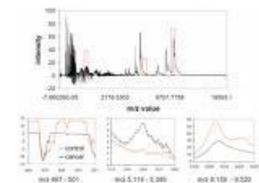
## – Effects on Research Outcomes

- **Irreproducible results**

- Variations in gene expression data
- Variations in post-translational modification data



- **Misinterpretation of artifacts as biomarkers**





# A New Era: Molecular Technology Promises to Transform Oncology

**OBBR** Office of Biorepositories and Biospecimen Research



## 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 new treatments that will add up to a big change in the way that cancer is viewed and dealt with by society.



## Technology Development and Today's Unprecedented Potential for Progress

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- Technological change is exponential, not linear
  - “We won’t experience 100 years of progress in the 21<sup>st</sup> century – it will be more like 20,000 years of progress (at today’s rate).”
    - » Ray Kurzweil, *The Law of Accelerating Returns*
- Technology accelerates data production → knowledge
- Scientific knowledge will double in the next 3 years
- Biologic knowledge will double in the next 5 years



## Powerful Tools: Powerful Risks

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and Biospecimen Research

- The technological capacity exists to produce low-quality data from low-quality analytes with unprecedented efficiency
- We now have the ability to get the wrong answers with unprecedented speed
- Unraveling the massive matrix of misleading data is compromising progress in unprecedented ways

# An Inconvenient Truth.....

Garbage in...



...Garbage out



Diamonds in.....

Modified from Jerry Thomas





# NCI's Investments in the Future: Molecular Research Using Human Analytes

**OBBR** Office of Biorepositories  
and Biospecimen Research

**The Cancer Genome Atlas (TCGA)**

**National Community Cancer Centers Program (NCCCP)**

**Genomics**

**Proteomics**

**Metabolomics**

**Clinical Proteomic Technologies Assessment for Cancer (CPTAC)**

**Innovative Molecular Analysis Technologies (IMAT)**

**Alliance for Nanotechnology in Cancer**

**Cancer Genetic Markers of Susceptibility (CGEMS)**

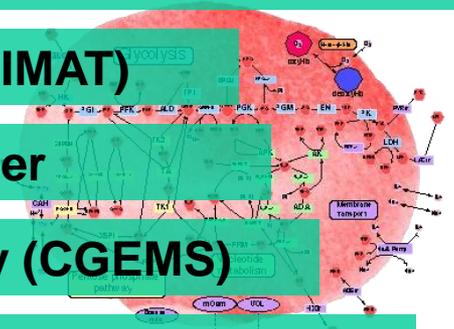
**Clinical trials correlative science**

**Molecular epidemiology programs**

**All Depend  
On High-Quality  
Human Biospecimens**

**SPORE programs**

**R01 Research**





# Market Research Conducted for OBBR by NCI's Office of Market Research and Evaluation



<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)

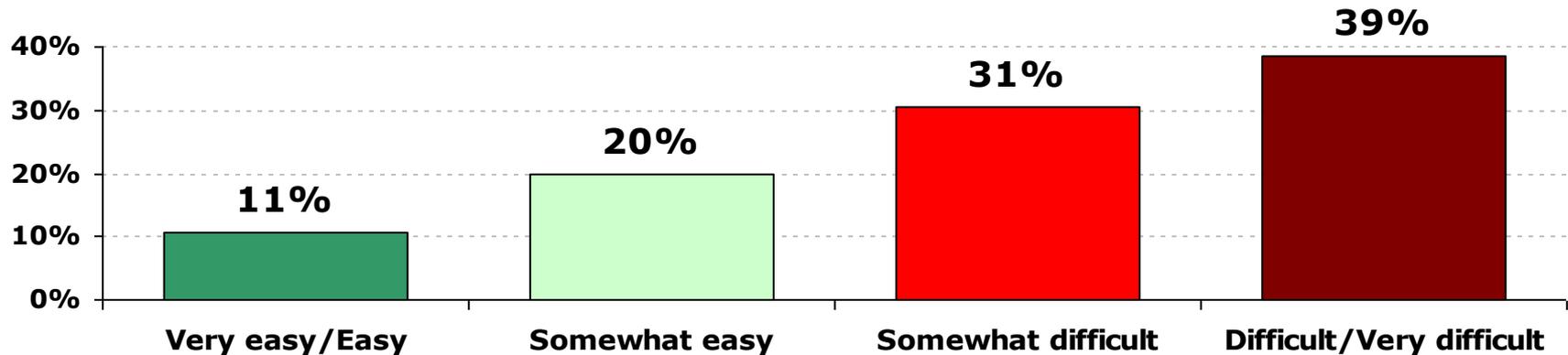
## Themes of Questions

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

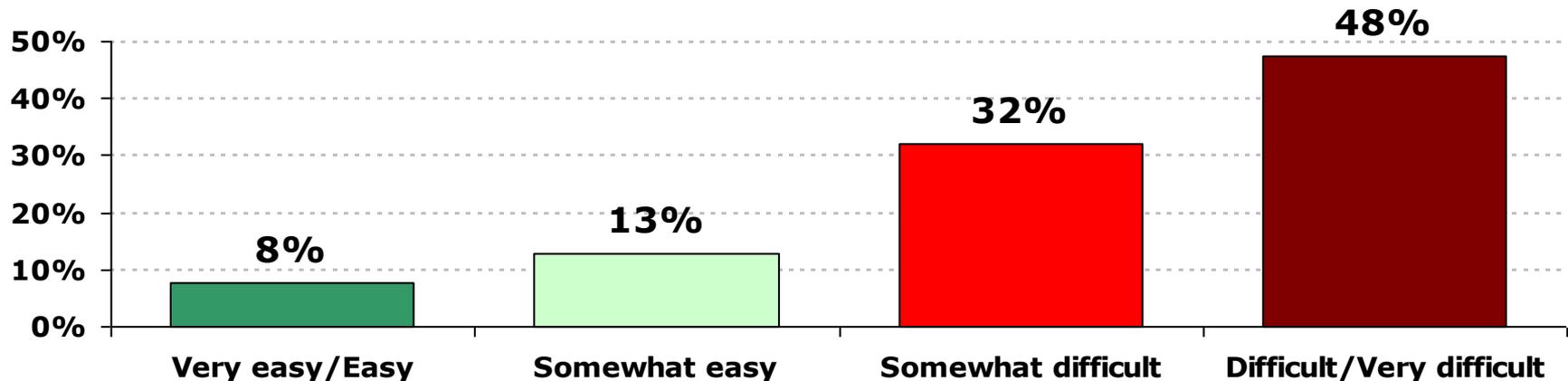


# Can Investigators Get What They Need?

## Ease of Acquiring the Quantity of Biospecimens Needed



## Ease of Acquiring the Quality of Biospecimens Needed

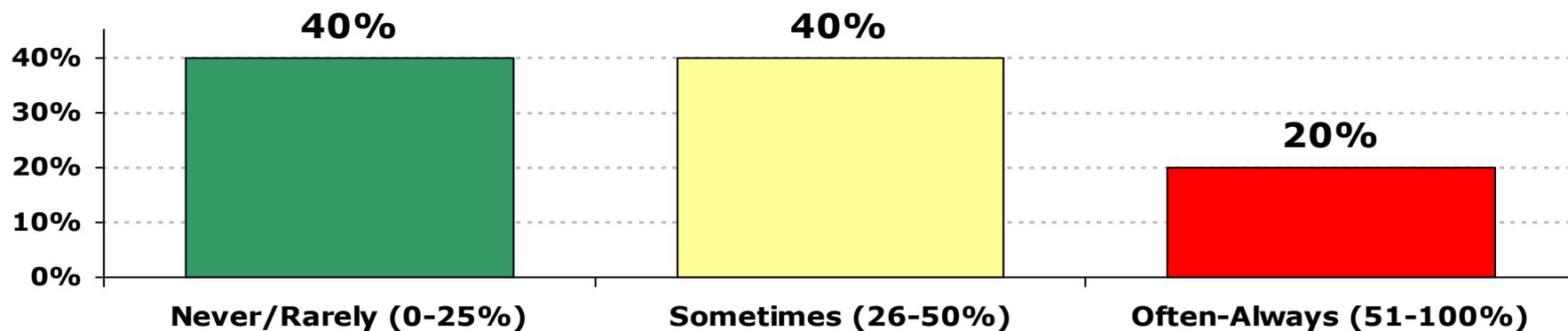




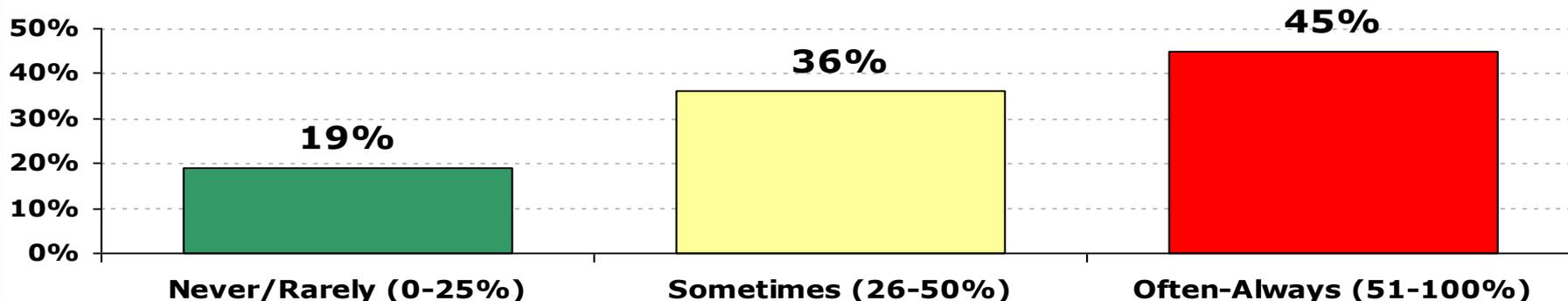
# Consequences for Investigators (and NCI): The Science Suffers

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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





## Comments about Biospecimen Needs

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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.”



## Why Is It Difficult to Acquire High-Quality Specimens and Data?

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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**

## Molecular Analysis and Human Analytes

**Challenge for the NCI:** Lack of standardization of human biospecimens compromises the quality and utility of molecular research dependent on them.

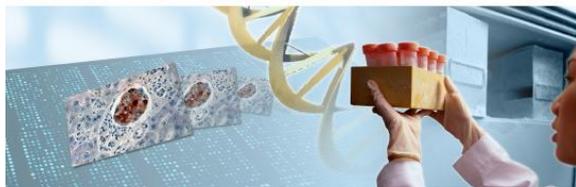
**Consensus of the Broad Scientific Community:** The lack of high-quality human specimens has become the limiting factor for post-genomic biomedical science.

- ***The #1 roadblock to translational research in cancer!!***



# NCI Best Practices for Biospecimen Resources: The State of the Science Guidebook

OBBR Office of Biorepositories  
and Biospecimen Research



## National Cancer Institute Best Practices for Biospecimen Resources

June 2007

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

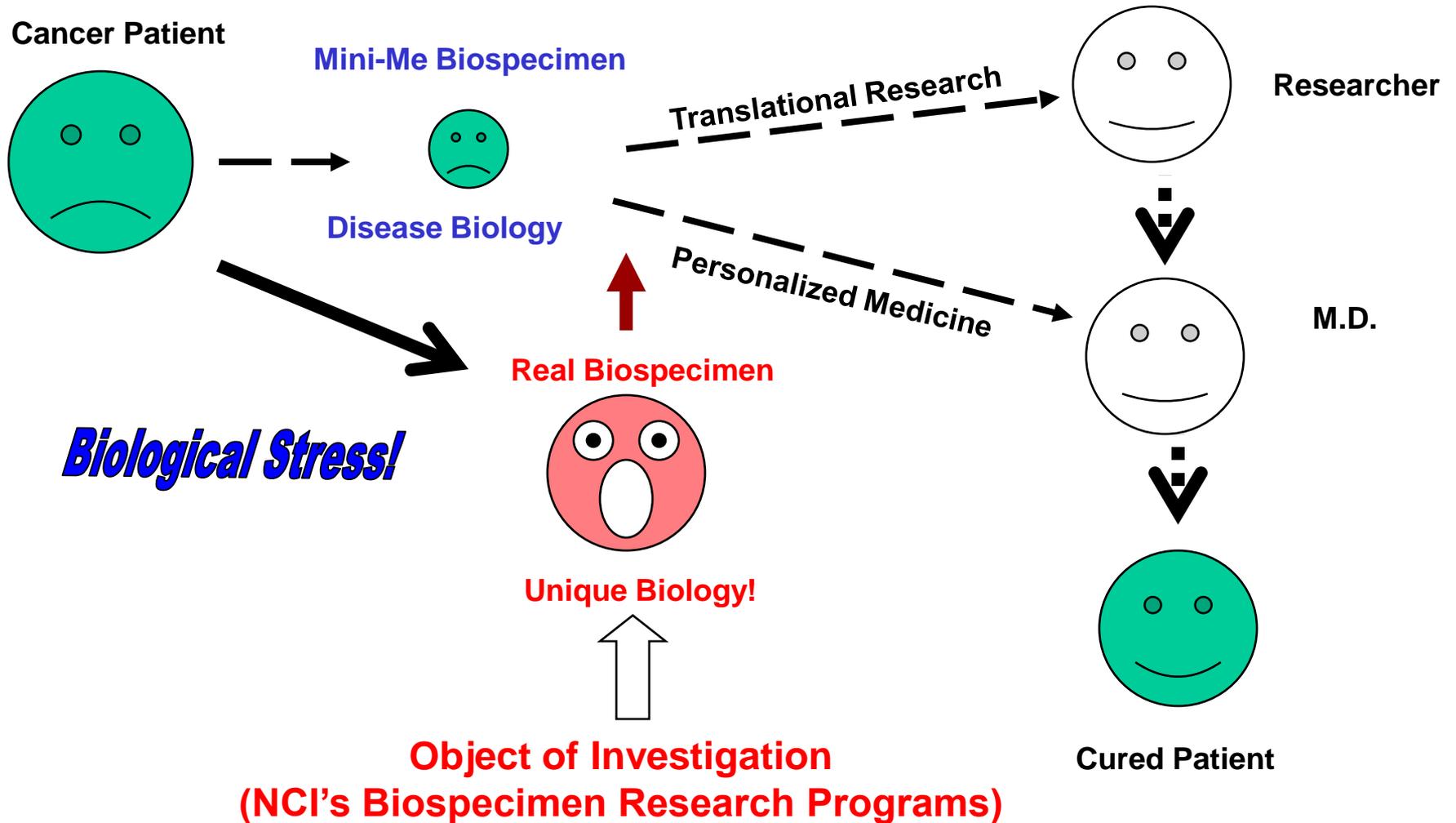
### Objectives:

- 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
- Update in progress: scheduled for completion December 2009
- <http://biospecimens.cancer.gov>

**Parallel Challenge:** Data-driven  
standard operating procedures



# Understanding Biospecimens: The Goal of Biospecimen Science



# Biospecimen Science

Time 0

Specimen is viable and biologically reactive

Molecular composition subject to further alteration/degradation



Pre-acquisition

Post-acquisition



## Variables for Study

### Pre-acquisition variables:

- Antibiotics
- Other drugs
- Type of anesthesia
- Duration of anesthesia
- Arterial clamp time
- Blood pressure variations
- Intra-op blood loss
- Intra-op blood administration
- Intra-op fluid administration
- Pre-existing medical conditions
- Patient gender

### Post-acquisition variables:

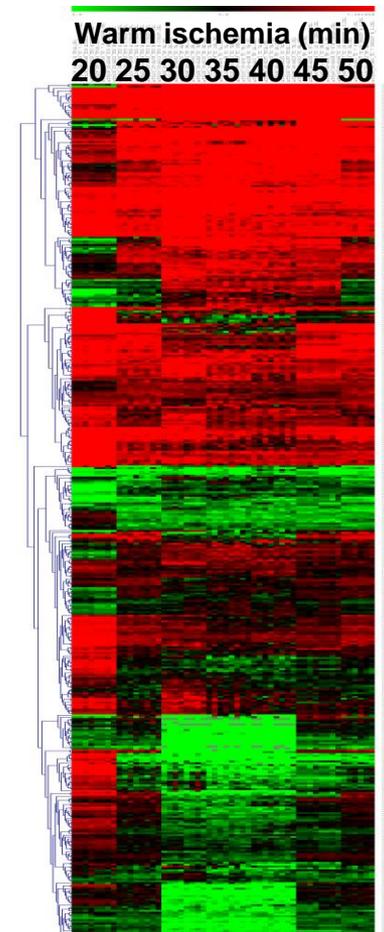
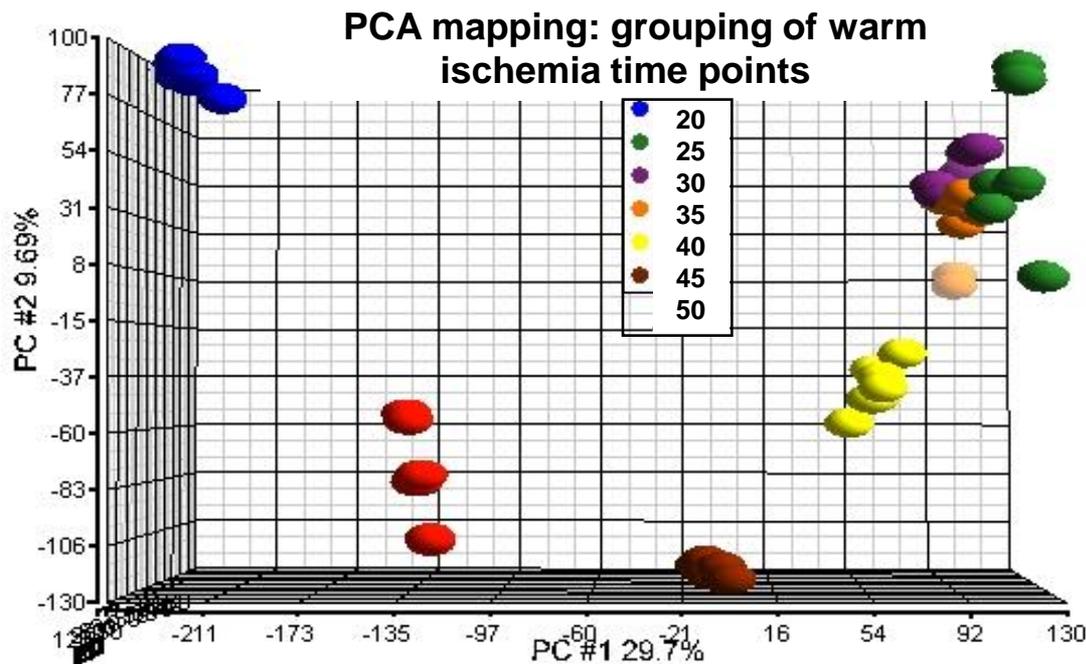
- Time at room temperature
- Temperature of room
- Type of fixative
- Time in fixative
- Rate of freezing
- Size of aliquots
- Type of collection container
- Biomolecule extraction method
- Storage temperature
- Storage duration
- Storage in vacuum



# Time Between Ligation Of Main Artery And Tumor Resection (Intrasurgical Ischemia) Affects Gene Expression In Colon Cancer (NCI-Indivumed study)

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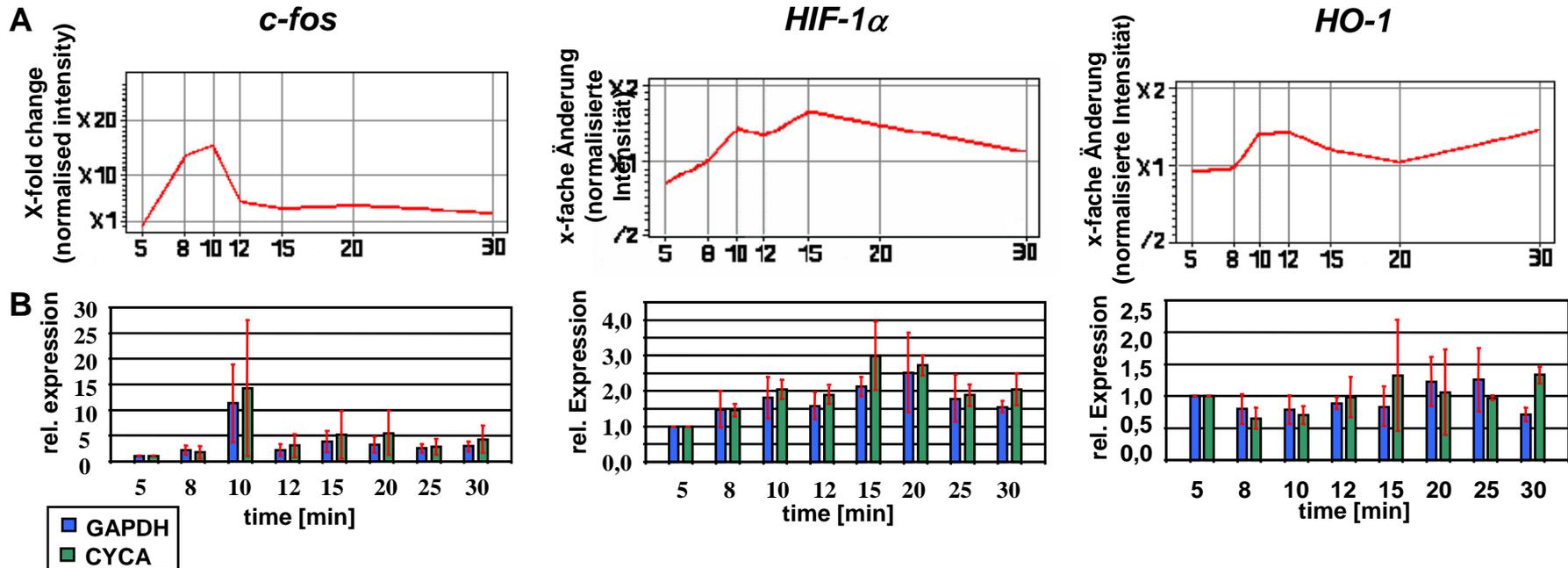
## Intrasurgical Ischemia



A prospective trial collecting tissue during surgery has been initiated

# Postsurgical Ischemia and Gene Expression

## Ischemia regulated genes *c-fos*, HIF- $\alpha$ and HO-1

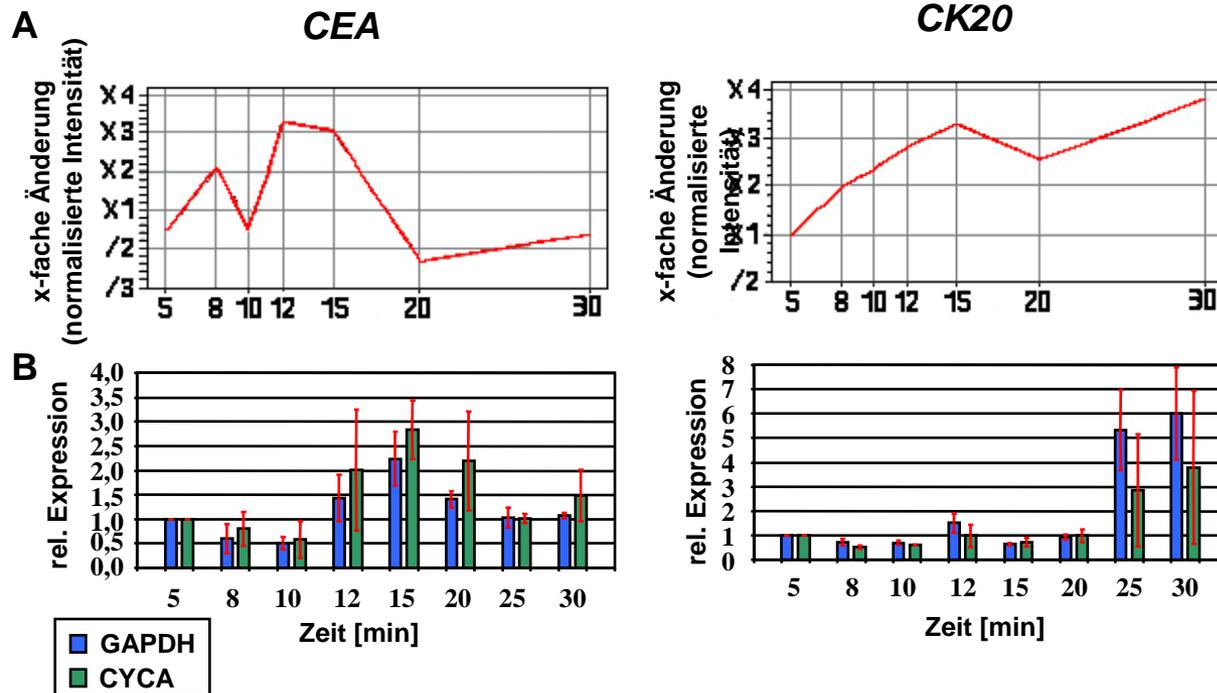


## Tissue ischemia and gene expression profiling

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

# Postsurgical Ischemia and Gene Expression

## Tumor marker *CEA* (colorectal cancer biomarker) and cytokeratin *CK20*



## Tissue ischemia and gene expression profiling

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



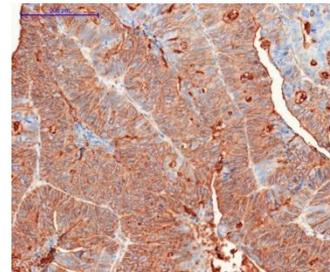
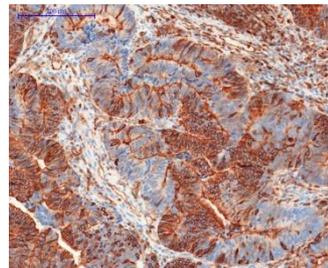
# Phosphoprotein Expression and Postsurgical Ischemia: pTyr100 Immunostaining (Ventana)

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and Biospecimen Research

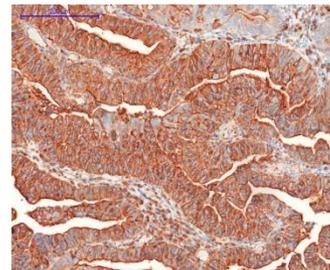
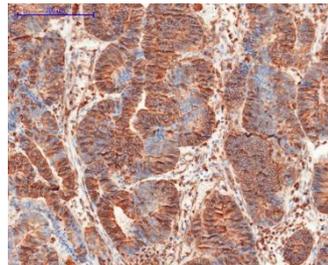
**Case A**

**Case B**

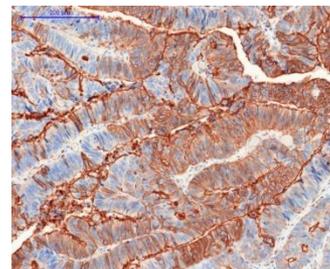
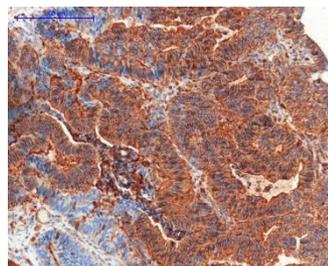
**10 min**



**20 min**



**60 min**

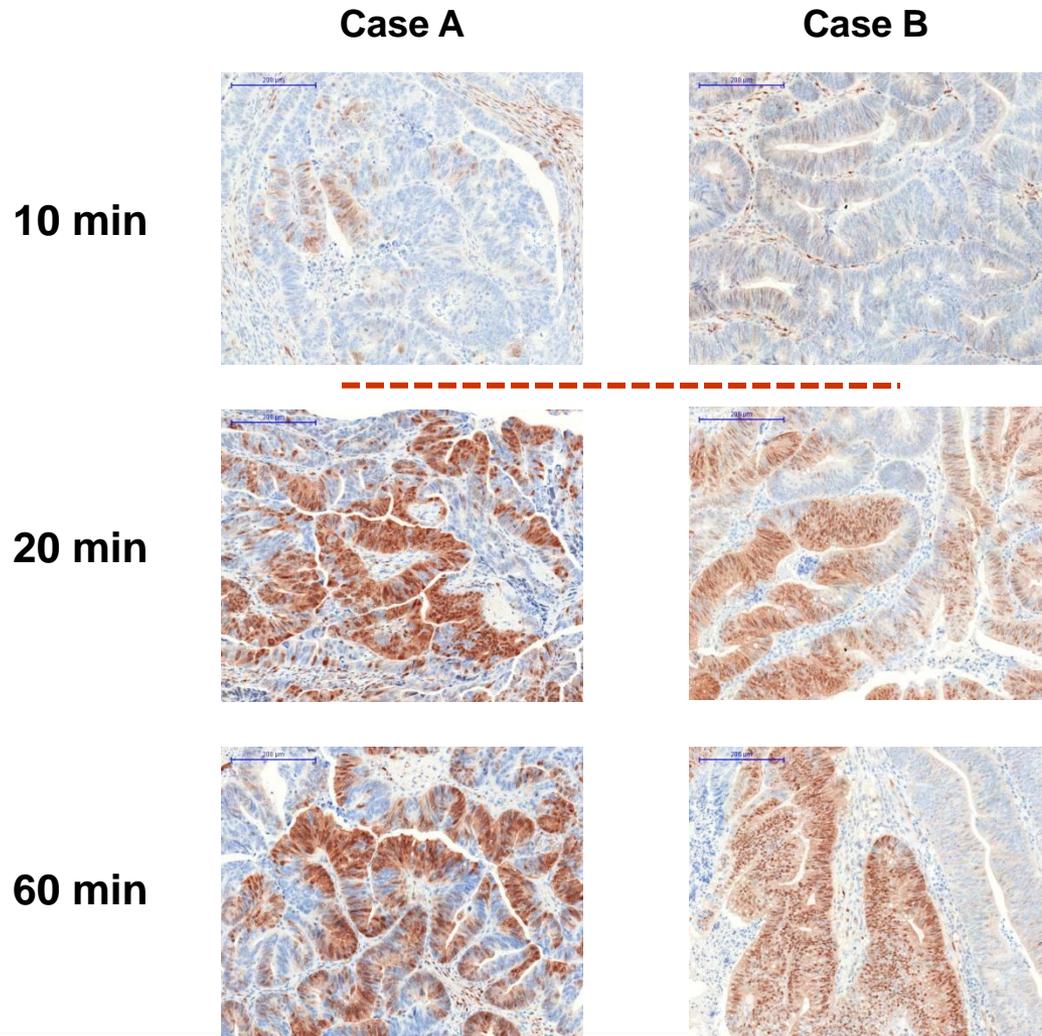


**No clear trend of  
pTyr100 expression  
within  
60 min of cold ischemia**

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



# Phosphoprotein Expression and Postsurgical Ischemia: pMAPK Immunostaining (Ventana)



↑ Change of pMAPK expression after 10-20 min cold ischemia ↓

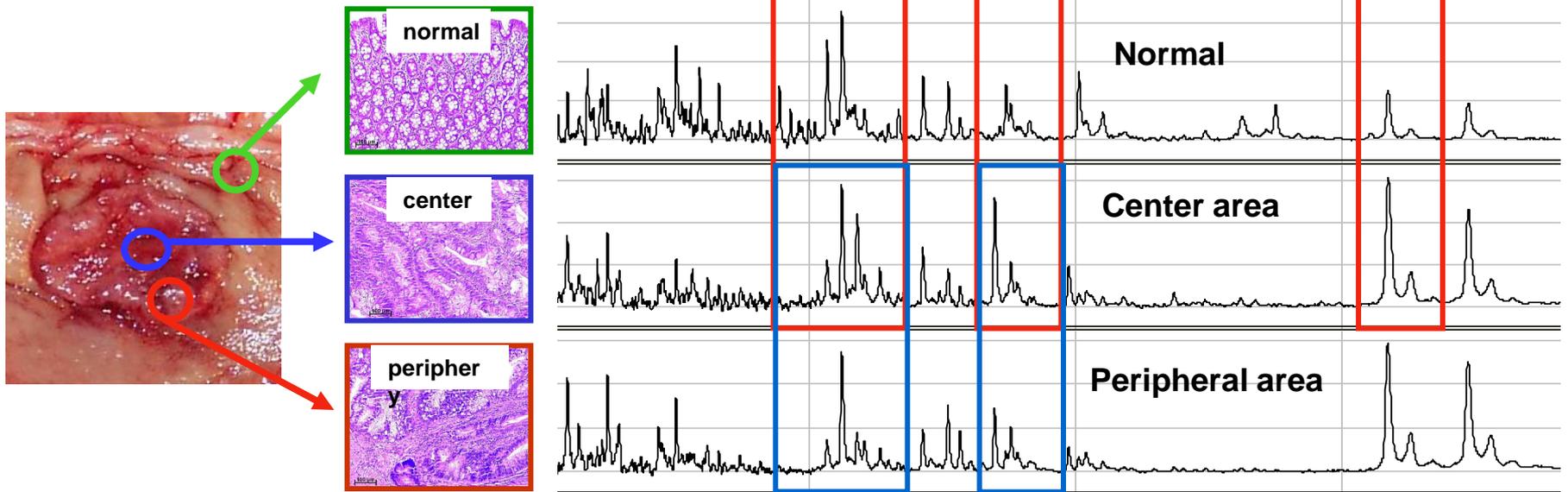


Slide Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg



# Biopsy Location and Protein Expression

## (Mass-spectroscopy analysis; SELDI-TOF MS)

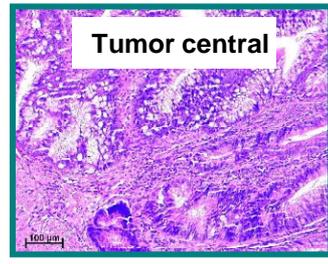
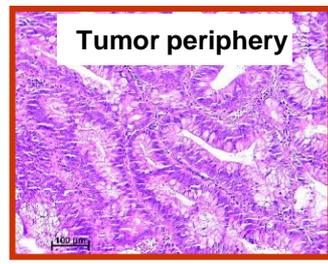
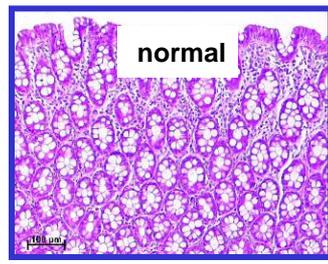
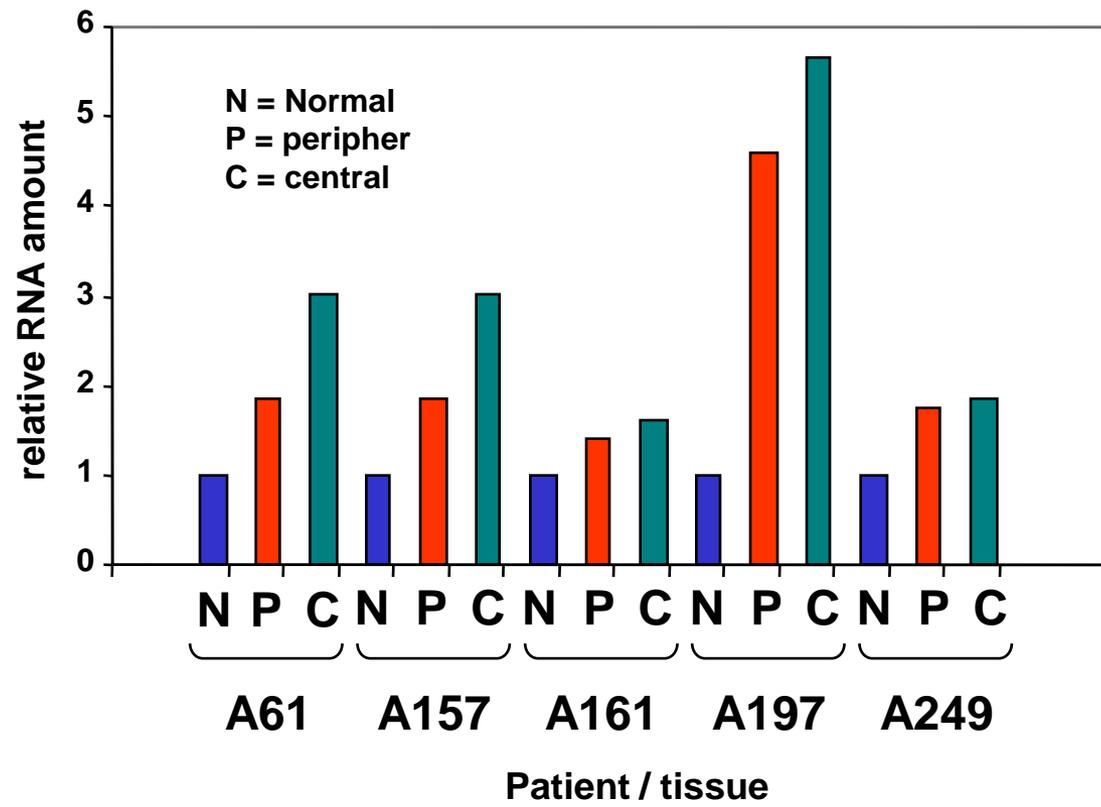


Approx. 40% of proteins are differentially expressed between peripheral and central tumor regions



# Biopsy Location and VEGF Expression in Colon Cancer

Expression of VEGF in different tissues:  
normal - periphery – central (real-time RT-PCR)





# The Biospecimen Research Network: Supporting Collaborative Research

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and Biospecimen Research

- **Provide a forum for research results on how biospecimen variables affect molecular analysis:**
  - **The Biospecimen Research Database: Make existing and emerging biospecimen research data more accessible**
  - **Annual symposium: “Advancing Cancer Research through Biospecimen Science” *March 16-19, 2009, MD***
- **Collaborate with other programs, e.g.:**
  - **Clinical Proteomics Technologies Assessment for Cancer (CPTAC)**
  - **The Cancer Genome Atlas (TCGA)**
- **Generate new research data:**
  - **IMAT Program – “Innovative and Applied Emerging Technologies in Biospecimen Science” (RFA)**
  - **New Extramural Research Programs**

# Biospecimen Research Network: Progress Report

## - Extramural research program, "Biospecimen Research for Molecular Medicine"

### Program aims:

(1) Develop innovative approaches to the control, monitoring and assessment of biospecimen quality.

- RFP issued 10/08, award decisions have been made

(2) Systematically define the impact of key pre-analytical variables in human biospecimens of specific type on downstream molecular data generated from specific molecular analysis platforms.

- Series of RFPs in preparation

## - Challenge Grant Topics on Biospecimen Research and Biobanking

- Sponsor, collaborate, and promote research on biospecimen science both intramurally and extramurally:

- **The Biospecimen Research Interest Group**



## OBBR's Most Recent Undertaking

OBBR Office of Biorepositories  
and Biospecimen Research

Development of key infrastructure for  
translational research:

The Cancer HUman Biobank (caHUB)



## 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.



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

**OBBR** Office of Biorepositories  
and Biospecimen Research

- **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**



## 8. Biobanks

By ALICE PARK

**OBBR** Office of Biorepositories and Biospecimen Research



Inside Huntsman Cancer Institute's vaults: Pancreatic tumors on ice. Lance W. Clayton for TIME

Folks at the National Cancer Institute (NCI) are heading up an effort to establish the U.S.'s first national biobank — a safe house for tissue samples, tumor cells, DNA and, yes, even blood — that would be used for research into new treatments for diseases.... By fall, the group hopes to have mapped out a plan for a national biobank; the recent stimulus showered on the government by the Obama Administration might even accelerate that timetable.



## 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 U.S. biospecimen resources



# daHkiB c Biobanks through Beh @ts for the Standard of Science and Medicine

OBBR Office of Biorepositories  
and Biospecimen Research

- 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



## caHUB Vision: Progress Enabled in Unprecedented Ways

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- 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**
  - **Standardized samples can be compared to “standard of care” samples for assay development and FDA approval**
  - **Direct product-to-product performance comparisons enabled**
  - **Standardized reference specimens (“yardstick of truth”) for FDA approval / medical implementation/calibration/proficiency testing**
- Leverage NCI’s investment in other programs, create unprecedented return on investment and rapid acceleration of scientific knowledge



## On the Road to Molecular Medicine.....

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and Biospecimen Research

**“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**



# Who Are We?

OBBR Office of Biorepositories  
and Biospecimen Research



# **Biospecimen Handling: Impact on Cancer Research and Molecular Diagnostics**

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

**NIH Biospecimens Interest Group**  
**May 26, 2009**



## Initial Survey Findings: Researchers Are Working in Silos

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

	% Get <b>any</b> 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?