The Frontiers of Precision Medicine: You Are There!

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CMO, National Biomarker Development Alliance
CMO, Complex Adaptive Systems Institute

AAPA 42nd Annual Conference
San Diego, CA
September 13, 2016

Getting to Precision Medicine: Biomarkers Are the Driving Force

Vision of 21st Century Medicine: Greater Efficiency and Efficacy

- **Better understanding of the biology of disease**
- **Diagnosis based on molecular characterization of disease**
- **Rational treatment using molecularly targeted agents**
- **Connection of research and clinical practice in seamless feedback loop**

↑

ALL OF THESE ARE BIOMARKER-DRIVEN

Biomarkers and the Laboratory

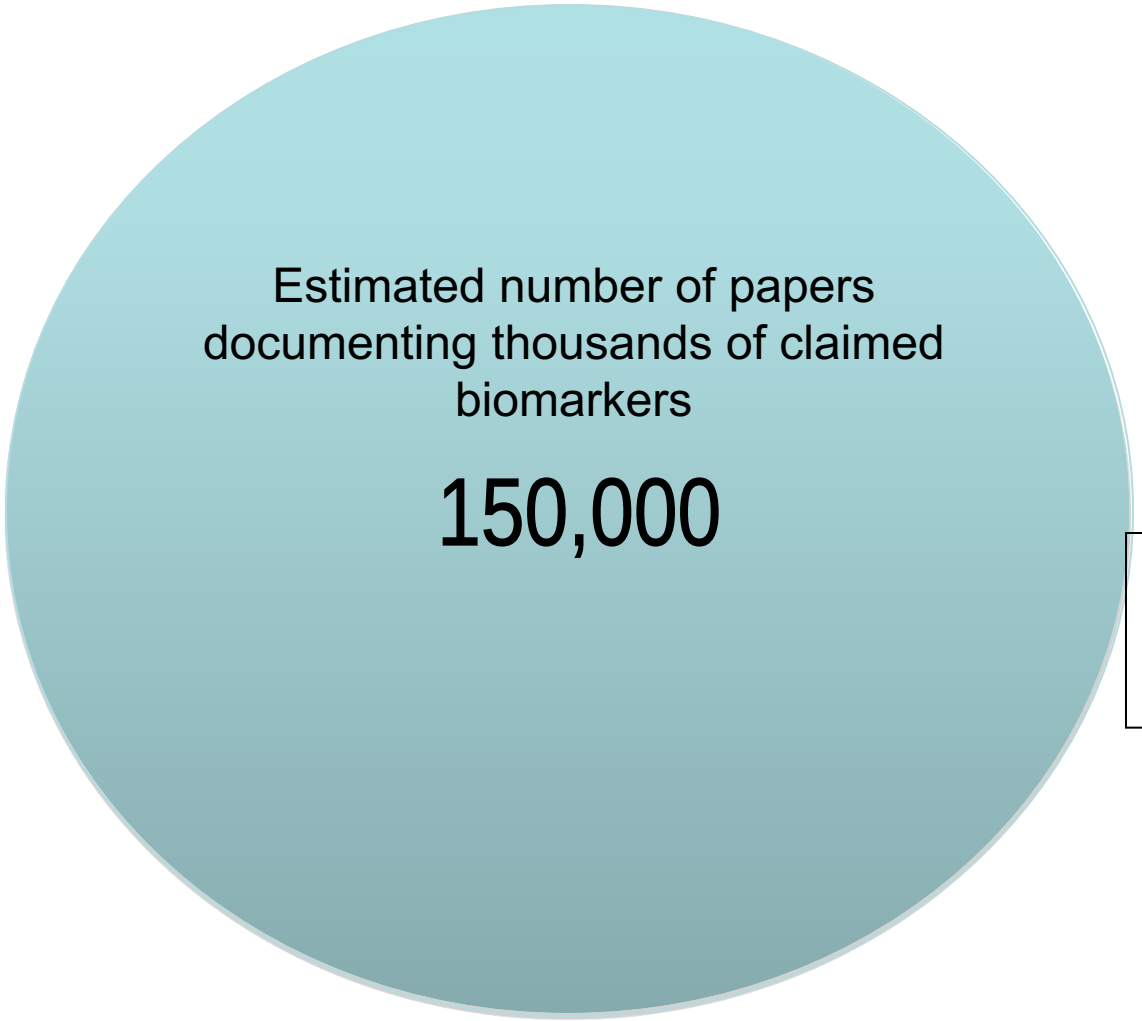
Biomarker: **A *measurable* characteristic used as an indicator of a biological state or condition**

Usually a protein or a set of proteins measured in cells, tissue, blood but may be any class of biomolecule – DNA, RNA, miRNA, other

Uses of Biomarkers in Precision Medicine

- Early detection, surveillance
- Prognosis, prediction
- Choice of treatment
- Monitoring of treatment
- Monitoring of disease
- Drug development – clinical trials:
  - patient selection
  - efficacy, toxicity
  - surrogate endpoints

Biomarkers: Many Are Reported, Few Are Qualified



100

Estimated number of biomarkers routinely used in the clinic

Source: Poste G. Nature 469, 156-157 13 Jan 2011

Consequences for Product Development - Massive Attrition, Long Duration, High Costs

The average drug developed by a major pharmaceutical company now costs at least $5 billion, and it can be as much as $11 billion.

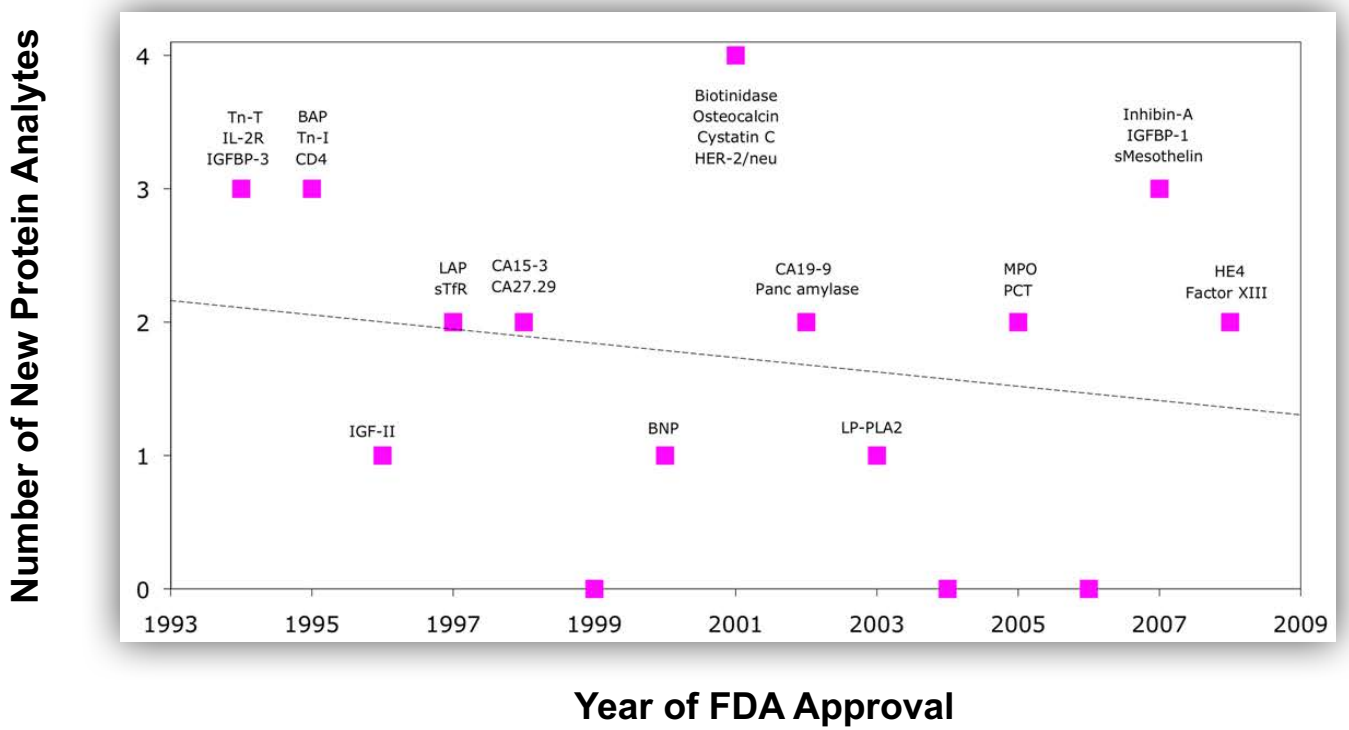
- *The Truly Staggering Cost of Inventing New Drugs*.
  Matthew Herper, Forbes 2/20/12
- *The Cost of Creating a New Drug Now $5 Billion, Pushing Big Pharma to Change.*
  Matthew Herper, Forbes 8/11/13

5-10,000:1 chance of success **12 Years** **~ US$ 1.6 B**

Time and attrition are both directly related to lack of validated biomarkers of efficacy and toxicity

Sad Status of Protein-Based Biomarkers

- Few biomarker candidates are being approved for clinical use by FDA/EMA
- Approval rate is steadily declining rate



- **Biggest problem is *non-reproducibility* across labs and studies**

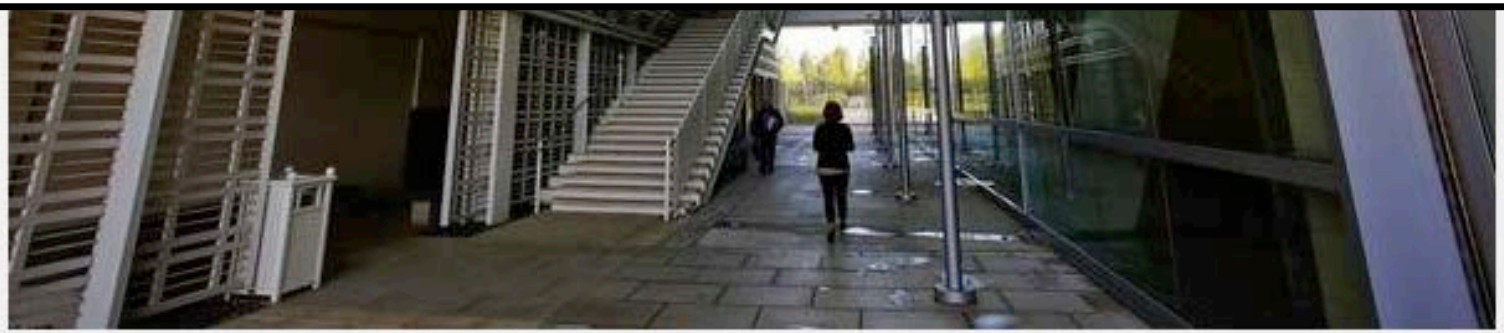
Source: Based on data from FDA and Plasma Proteome Institute

Science has lost its way, at a big cost to humanity

Researchers are rewarded for splashy findings, not for double-checking accuracy. So many scientists looking for cures to diseases have been building on ideas that aren't even true.

Los Angeles Times, October 27, 2013

Amgen attempts to verify results of 53 landmark studies in oncology and hematology;
Only 6 (11%) could be reproduced.



A few years ago, scientists at Amgen set out to double-check the results of 53 landmark papers in cancer research and blood biology. Only six could be proved valid. Above is an Amgen building in Thousand Oaks. (Anne Cusack, Los Angeles Times / April 25, 2013)

How Widespread Are Failures to Reproduce Published Biomedical Science?

- Mass spec diagnostic for ovarian cancer – results due to experimental artifact and bias – control and experimental groups run separately (Lancet, 2002)
- Five of 7 largest molecular epidemiology cancer studies did not classify patients better than chance (JNCI, 96:2004)
- Microarray drug sensitivity signatures – from cell lines – to predict patient response (named one of top100 breakthroughs in 2006) could not be reproduced in large clinical trial in 2009 (Nature Medicine, 2006)
- Of 18 published microarray studies, only 2 were reproducible (Science, 2011)
- Bayer scientists can reproduce only 20-25% of 67 key published experiments and halts 2/3 of its target validation projects as a result (*Nature Reviews Drug Discovery* 10, 712 doi:10.1038/nrd3439-c1, 2011)
- Amgen's team of 100 scientists could reproduce only 11% of 53 seminal studies published on reported drug targets or toxicity (*Nature* 483, 531-533 doi:10.1038/483531a, 2012)

Reproducibility Rate of 10-30% in Academic Biomedical Science

- For biomedical businesses relying on academic discovery to drive product development (like pharma), flipping a coin would be superior to reading *Science* or *Nature* in making business decisions.
- US government spends nearly $31 billion in science funding through the NIH every year, mainly for research grants to academic scientists
  - 10% reproducibility rate ➔ 90% of this money ($28 billion) is wasted
- Wasted money, wasted time, lost opportunities
- Pollution of the biomedical literature by bad studies and bad data:
  - What do we really know? What can we really trust?
- Why should patients and the public believe in what we do?

Irreproducibility in Biomedical (Biomarker) Research: A Crisis in Confidence (Public View)

The Economist | World politics | Business & finance | Economics

Unreliable research

Trouble at the lab

Scientists like to think of science as self-correcting. To an ala

Oct 19th 2013 | From the print edition

the Atlantic November 2010

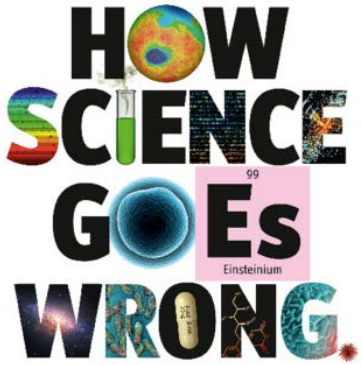
Lies, Damned Lies, and Medical Science

MUCH OF WHAT MEDICAL RESEARCHERS CONCLUDE IN THEIR STUDIES IS MISLEADING, EXAGGERATED, OR FLAT-OUT WRONG. SO WHY ARE DOCTORS—TO A STRIKING EXTENT—STILL DRAWING UPON MISINFORMATION IN THEIR EVERYDAY PRACTICE? DR. JOHN IOANNIDIS HAS SPENT HIS CAREER CHALLENGING HIS PEERS BY EXPOSING THEIR BAD SCIENCE.

By David H. Freedman

The Economist

Washington's lawyer surplus
How to do a nuclear deal with Iran
Investment tips from Nobel economists
Junk bonds are back
The meaning of Sachin Tendulkar



THE NEW YORKER

ANNALS OF SCIENCE

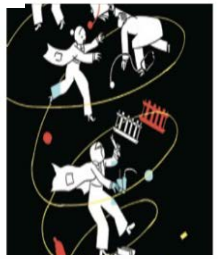
THE TRUTH WEARS OFF

Is there something wrong with the scientific method?

BY JONAH LEHRER

DECEMBER 13, 2010

On September 18, 2007, a few dozen neuroscientists, psychiatrists, and drug-company executives gathered in a hotel conference room in Brussels to hear some startling news. It had to do with a class of drugs known as atypical or second-generation antipsychotics, which came on the market in the early nineties. The drugs, sold under brand names such as Abilify, Seroquel, and Zyprexa, had



PLOS | MEDICINE

Why Most Published Research Findings Are False

John P. A. Ioannidis

Published: August 30, 2005 • DOI: 10.1371/journal.pmed.0020124

Abstract

Summary

There is increasing concern that most current published research findings are false. The probabili
the number of other studies on the same question, and, importantly, the ratio of true to no relation
framework, a research finding is less likely to be true when the studies conducted in a field are sm
and lesser preselection of tested relationships; where there is greater flexibility in designs, definiti
and other interest and prejudice; and when more teams are involved in a scientific field in chase o
designs and settings, it is more likely for a research claim to be false than true. Moreover, for man
simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these

December 2011

THE WALL STREET JOURNAL.

WSJ.com

HEALTH INDUSTRY | DECEMBER 2, 2011

Scientists' Elusive Goal: Reproducing Study Results

By GAUTAM NAIK

Two years ago, a group of Boston researchers published a study describing how they had destroy
targeting a protein called STK33. Scientists at biotechnology firm Amgen Inc. quickly pounced o
dozen researchers to try to repeat the experiment with a goal of turning the findings into a drug.

"This is one of medicine's dirty secrets: Most results, including those that appear in top-flight peer-reviewed journals, can't be reproduced"

Irreproducibility in Biomedical (Biomarker) Research: Cultural Contributing Factors

In science, irreproducible research is a quiet crisis

The Boston Globe

- Few scientists attempt to repeat their own studies
- Publications often based on the one time out of multiple attempts that it actually worked
- External validation (by another lab) is extremely rare
- **Few, if any analyses, focus on the quality and consistency of the biological materials that are the test subjects**
- **Shockingly, this is also true in clinical medicine**

PATRIC SANDRI FOR THE B

By Carolyn Johnson | GLOBE STAFF MARCH 19, 2015

Quality Data Begins with Quality Analytes

Purgamentum init,
exit purgamentum.

Garbage in…

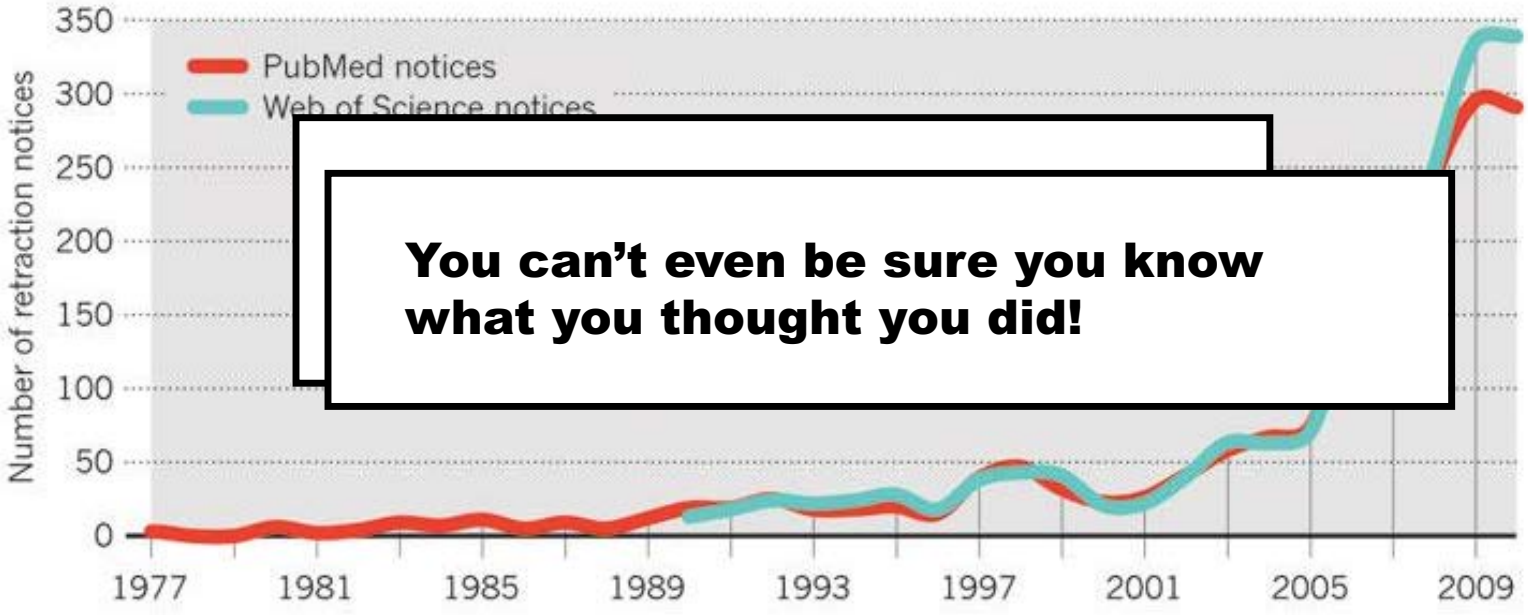
…Garbage out

Diamonds in……

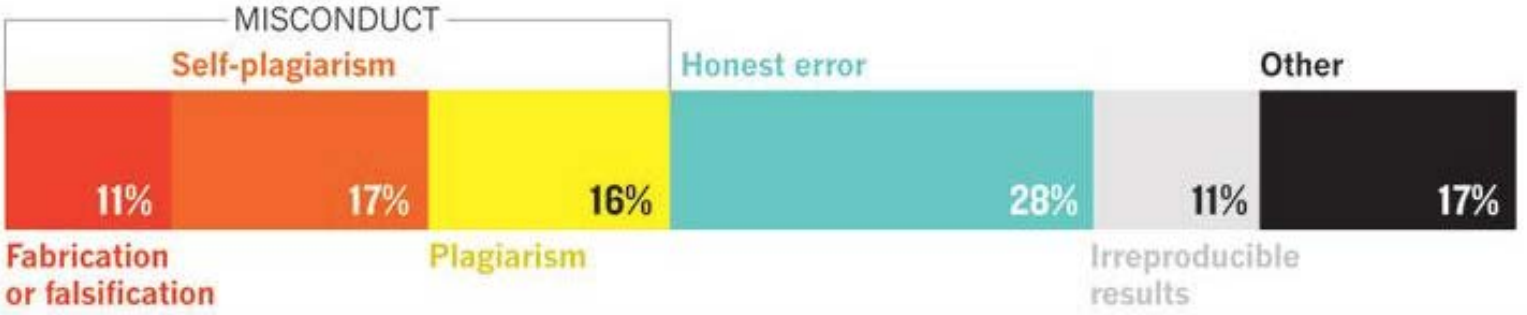
Modified from Jerry Thomas

Here Today, Gone Tomorrow

In the early 2000s, only about 30 retraction notices appeared annually. This year, the Web of Science is on track to index more than 400 (see 'Rise of the retractions') — even though the total number of papers published has risen by only 44% over the past decade.



You can't even be sure you know what you thought you did!



White House Takes Notice of Irreproducibility in Science and Seeks Public Input

August 21, 2014

- Federal Register:
- The Office of Science and Technology Policy and the National Economic Council request public comments to provide input into an upcoming update of the *Strategy for American Innovation…….*
- “Given recent evidence of the irreproducibility of a surprising number of published scientific findings, how can the Federal Government leverage its role as a significant funder of scientific research to most effectively address the problem?”

Taking Action in the Public Sector

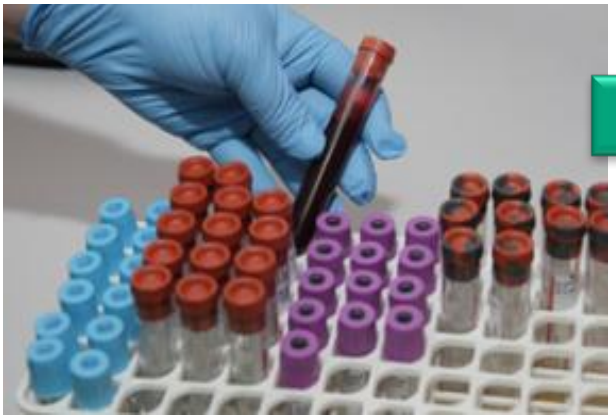
- **National Institutes of Health: Rigor and Reproducibility Workshop, 2014**
  - Joint meeting with Science and Nature publishing groups
  - Principles and Guidelines for Reporting published
    - "Sufficient information about sample collection must be provided to distinguish between independent biological data points and technical replicates"
  - Refers to rigor in use/description of biological reagents (antibodies), cell lines and animals, but **omits reference to human biological materials**!
    - NOT because it is unimportant
    - **Complex for the NIH and publishers to approach because this issue is embedded in the world of clinical medicine and its requirements, standards and legal restrictions**

Where is the Variability Causing Non-Reproducibility and How Is it Controlled?

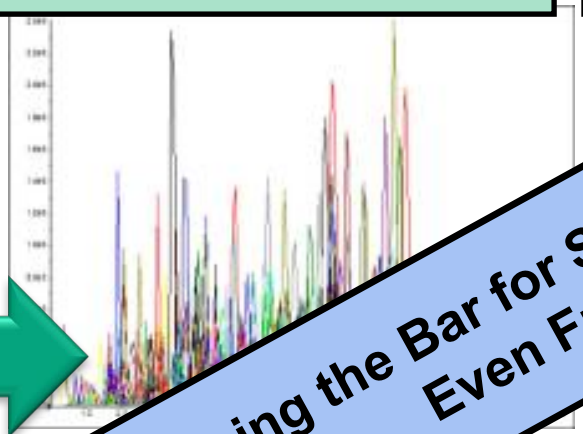
- Place where test is done
  - CLIA/CAP laboratory accreditation
- People doing the test
  - Education
  - Proficiency testing
  - Licensure
- Platforms used for testing
  - CDRH approved devices
- Processes followed for testing
  - SOPs
  - Quality management
- Patient samples to be tested
  - WILD WEST

Evolution of Biomarker Testing

Unianalyte Tests



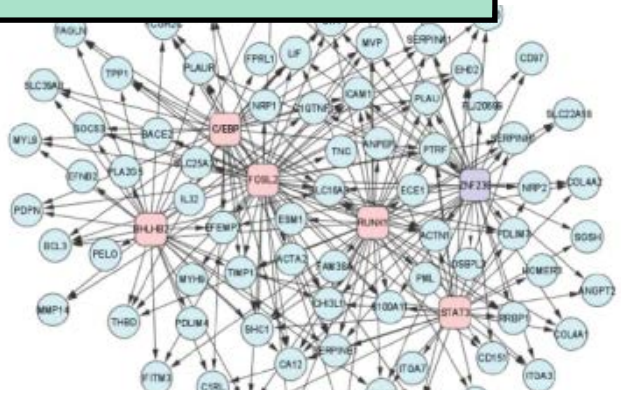
Multianalyte Tests



Omics Analyses

Raising the Bar for Specimen Quality Even Further!

Networks and Systems



Biospecimens – A Likely Source of Biomarker Irreproducibility at Every Level

Molecular Data → Diagnosis / Therapy

DETERMINES QUALITY HERE

PERSONALIZED CANCER CARE

Biospecimen Analysis

Biospecimen Collection

QUALITY HERE

Biospecimen Processing and Banking

Pre-analytical Factors Affect Both Molecular Composition and Molecular Quality

Specimen is viable and biologically reactive → Molecular composition subject to further alteration/degradation

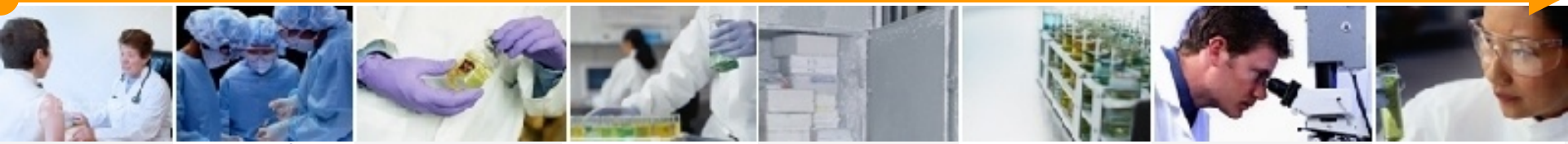
Factors (examples):

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

Time 0

Factors (examples):

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



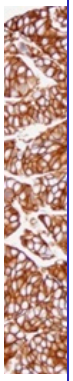
Patient | Medical/ Surgical Procedures | Acquisition | Handling/ Processing | Storage | Distribution | Scientific Analysis | Restocking Unused Sample

Pre-acquisition | **Post-acquisition**

Cold Ischemia and Molecular Assay Results

HER2 IHC and FISH in Breast Cancer:
Loss

pMAPK IHC of Colon Cancer :
to



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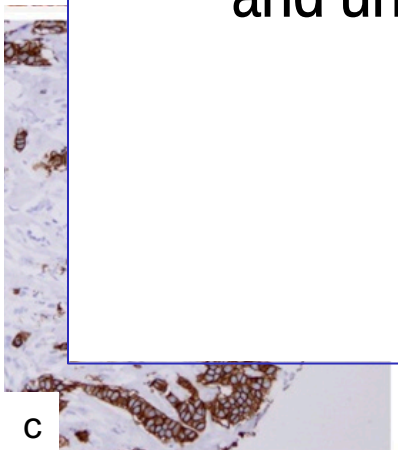

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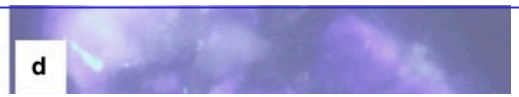

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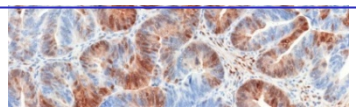


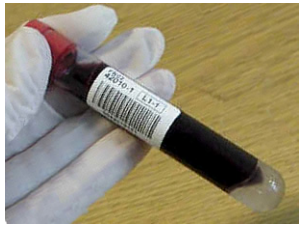
Without knowledge about tissue processing methods and assurance of rapid tissue fixation, protein expression data are unreliable, and understanding of pathway activity is impossible.

- Hartmut Juhl, CEO Indivumed

Khoury T, et al., Mod Pathol. 2009 Nov;22(11):1457-67

Hartmut Juhl, Indivumed GmbH, BRN

Blood Collection and Plasma Processing: Biomarkers and Circulating Tumor Cells



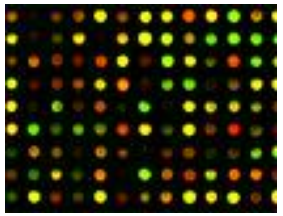
Collection Tubes and Order of draw

Processing Procedure, Temperature and Time

Distribution & Storage

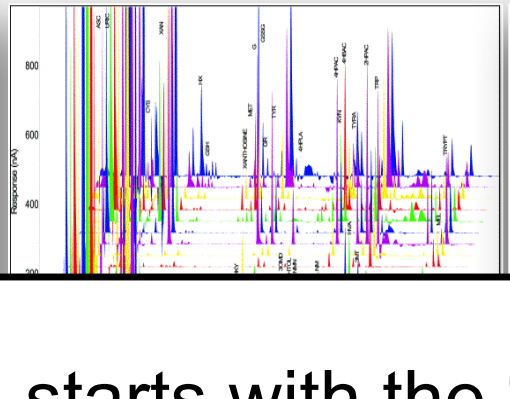
Blood Draw Procedure

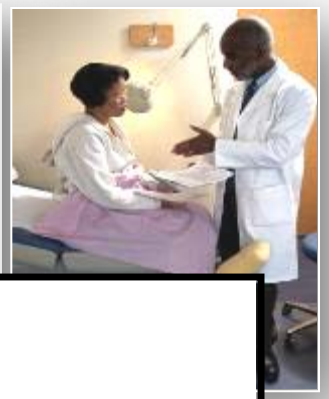
Patient Consent and Preparation



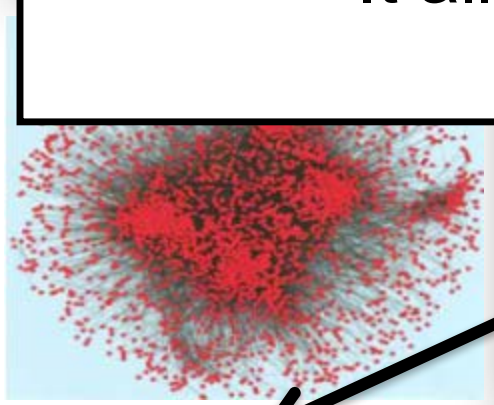
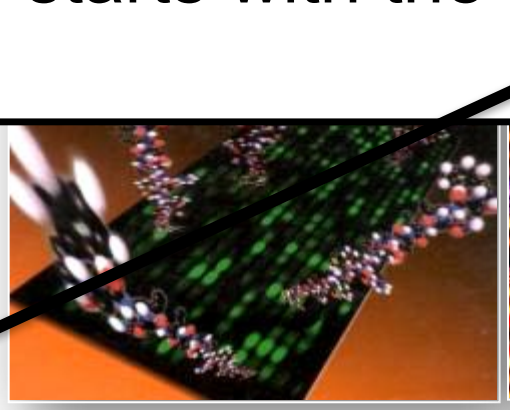
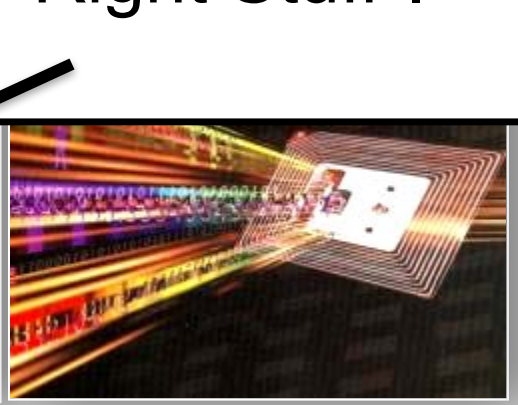
Molecular Analysis

And It's Getting Far More Challenging



It all starts with the "Right Stuff".


Biospecimens and Analysis of Molecular Pathway/ Network Perturbations

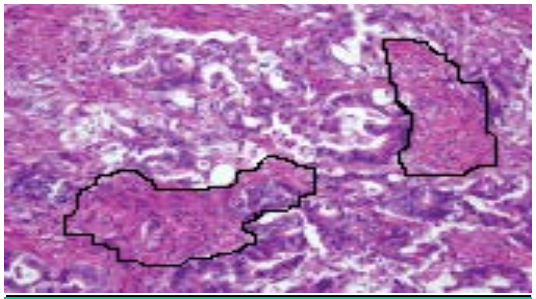
Multiplex Assays and Complex Signal Deconvolution Algorithms

Novel Instrumentation, Automation and Large Scale Informatics

Patient Profiling, Rational Rx and Health Monitoring

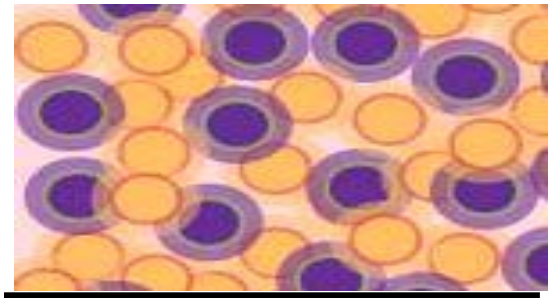
Courtesy of G. Poste

The Right Answers Depend on the Right Stuff: Challenges for DNA Sequencing Tests



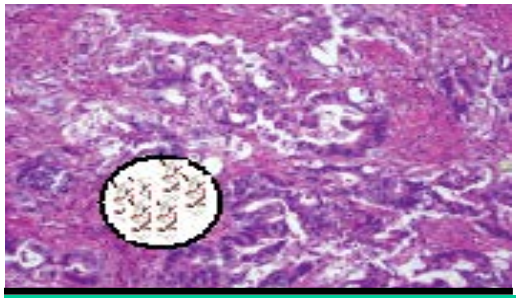
% Tumor content

- Tumor cells are mixed with normal cells
- Tumor content may be enriched by micro-dissection



% Mutant copies

- Tumors have background of normal wild-type DNA
- Challenge to detect low % mutant alleles



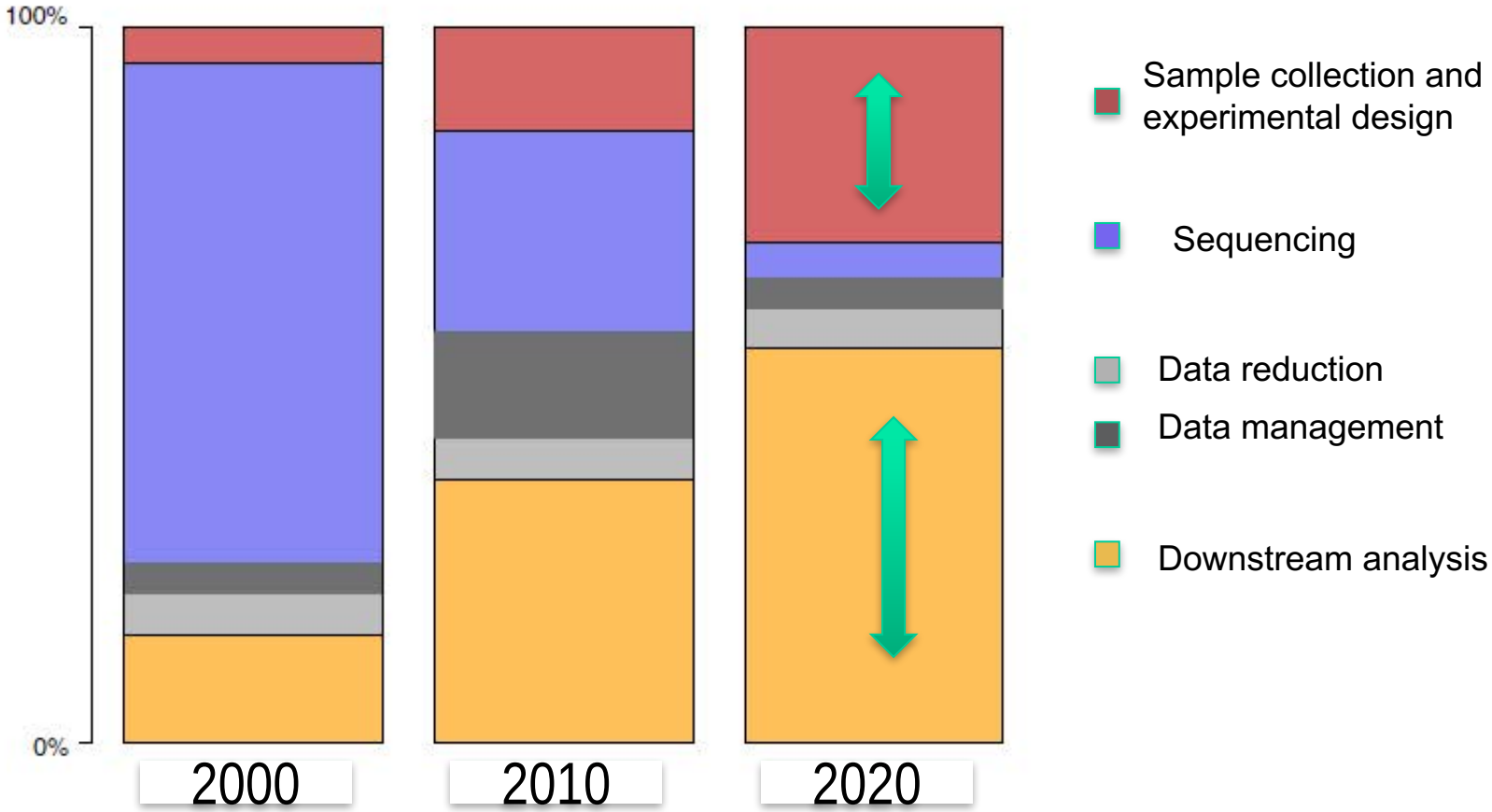
% Amplifiable DNA

- Tissue fixation damages DNA
- Necrotic cells may not have amplifiable DNA

FFPET = formalin-fixed, paraffin-embedded tissue

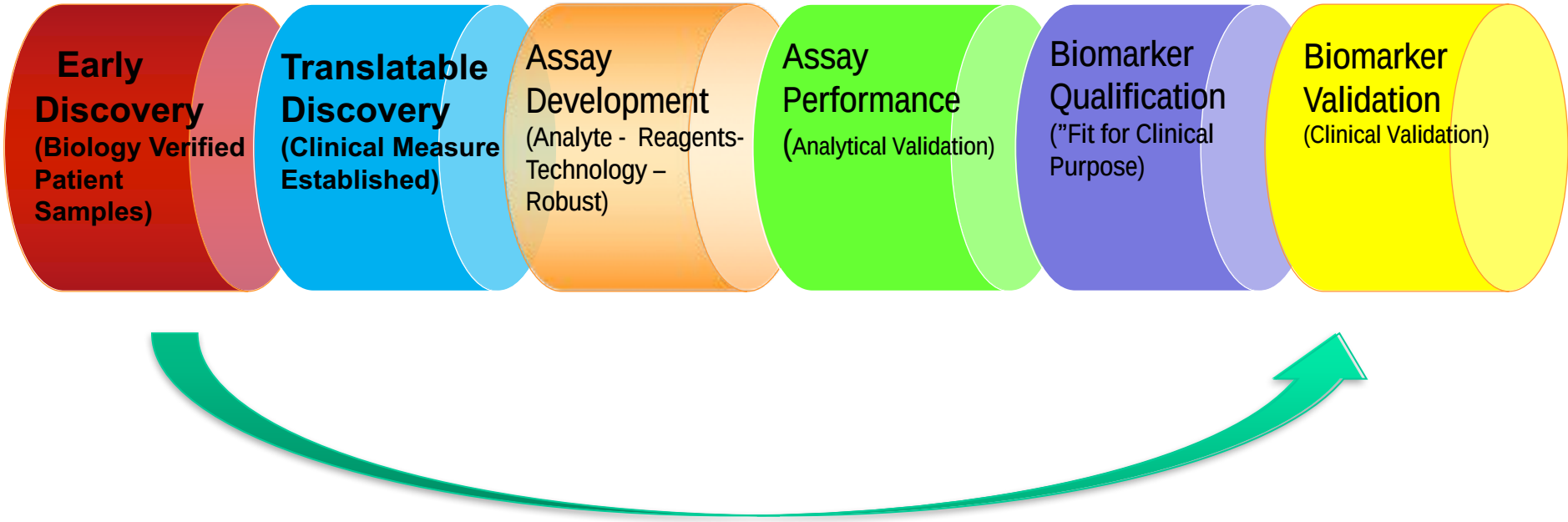
Estimating the Changing Aspects of NGS

Is Pathology prepared for what's coming?
More sample collection upfront; more data analysis downstream!!



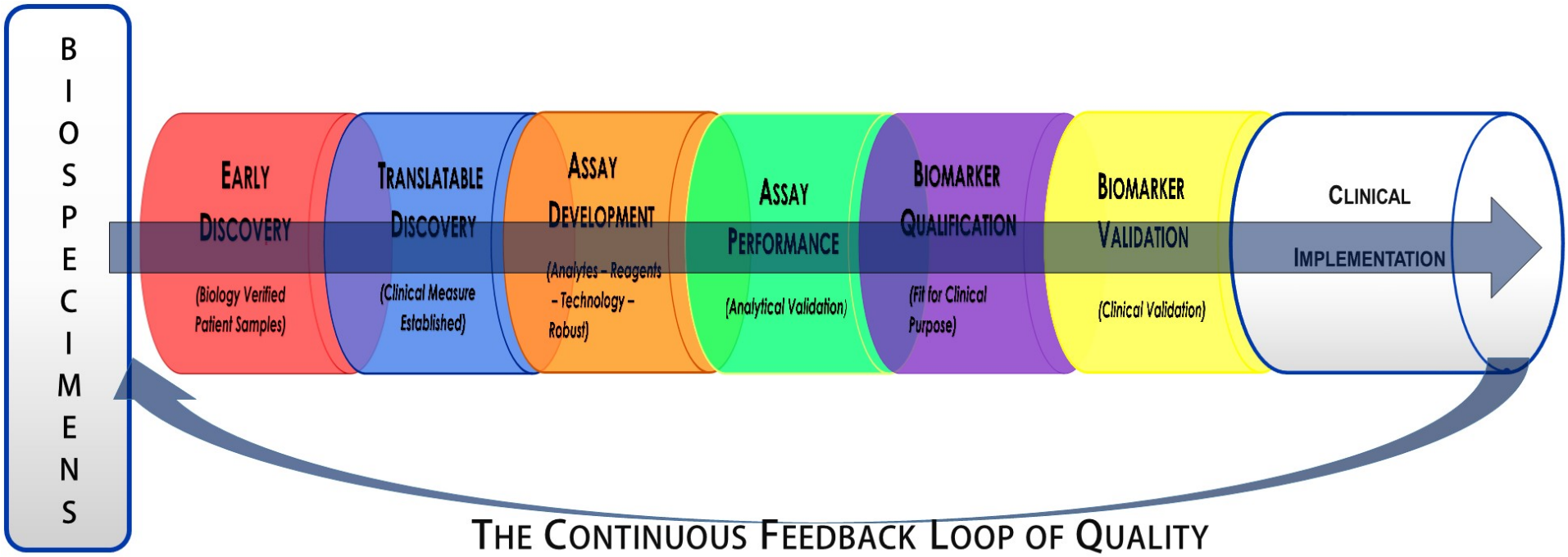
From Ken Bloom, MD, GE Healthcare, June 2014

NBDA: Realizing an End-To-End, Standards-Based Approach to Biomarker Development

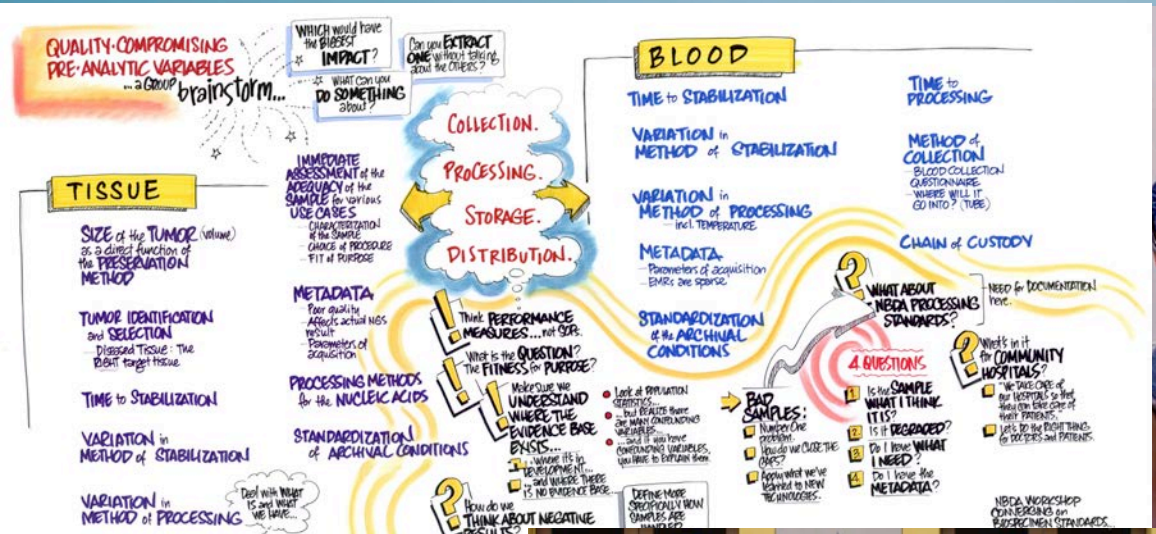


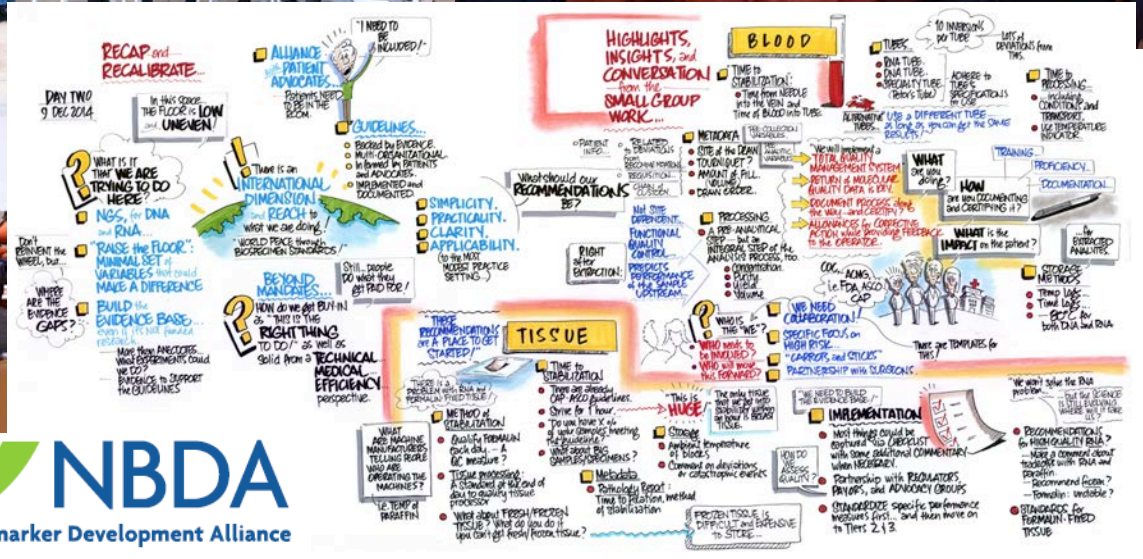
Standards are needed at every step and across the continuum

Biospecimens Flank End-To- End Biomarker Development



NBDA: Understanding The Issues - Building Towards Solutions





NBDA
National Biomarker Development Alliance

NBDA Convergence Conference

Goal:

•Converge (agree) on the pre-analytical steps in the biospecimen lifecycle that MOST compromise the quality of tissue and blood for cutting edge molecular analysis: NGS and proteomics

- **"Top 10 List"**

•Identify where the greatest value can be delivered in the control of pre-analytical variation (*biggest quality bang for the buck*)

- **"Top 5 List"**

NBDA Genomics Convergence Conference: Defining a Benchmark for Patient Biospecimens

Think: Pareto Principle (20/80 rule)

For many events 80% of the effects come from 20% of the causes

Top 5 Lists

Tissue

1. Time to stabilization
   - Cold ischemia time
2. Method of processing
   - Section thickness
   - Mass/volume ratio
   - Temperature
3. Method of stabilization
   - Type of fixative
   - Time in fixative
4. Tissue processor variables
   - Quality of processing fluids
   - Paraffin type
   - Paraffin temperature
5. Storage conditions
6. (Metadata to be collected]

Blood/Serum

1. Time to processing
2. Method of acquisition
   - Tube type
   - Draw order
   - Draw parameters (needle, vein vs. line)
   - Volume of tube fill
3. Method of stabilization
   - Tube type (stabilizer preset or not)
   - Tube inversions
4. Method of processing
   - Centrifugation speed/time
   - Temperature
5. Storage conditions
   - Freeze/thaw cycles
6. (Metadata to be collected]

Actions In Progress

- Pre-analytics for Precision Medicine Project Team: College of American Pathologists
- Establish performance metrics around the Top 5
  - **DATA-DRIVEN**: Validated from primary literature review and verification of guidelines from CLSI, NCI and ISBER
  - **PRACTICA**L
- Develop a Top 5 for cytology specimens
- Educate pathology workforce (pathologists, pathology assistants, medical laboratory technicians, phlebotomists)
- Implement and enforce performance metrics through the CAP Laboratory Accreditation Program checklists
- Seek new reimbursements codes, if needed
- Seek reinforcement through FDA guidance, research funder requirements

Envisioned Result

Historic transformation of practice with far-reaching impact:

•Variably variable and unknown quality ➔ uniform, known quality that is consistent with molecular analysis

•Simultaneous impact on both clinical and research results

•“Convenience samples” for research become fit for purpose!

•A “bar” is established that may be electively raised as needed to meet requirements of specific analysis types/platforms

- There will, at last, BE a bar to raise
- It’s about time

Specimen Quality Is A Front-loaded Issue

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

- John Wooden, Coach UCLA

The Ultimate Lab Revolution

Garbage in…

…Garbage out

The Frontiers of Precision Medicine: You Are There!

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