ASU COMPLEX ADAPTIVE SYSTEMS INITIATIVE
ARIZONA STATE UNIVERSITY

Biospecimens: A Critical Resource for Advances in Molecular Diagnostics, Imaging and Therapeutics

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Keynote Presentation:
Annual Biospecimen Research Network (BRN) Symposium
Bethesda, MD 28 March 2011

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Slides available @ www.casi.asu.edu

Declared Interests:

- Board of Directors: Monsanto, Exelixis, Caris Life Sciences
- Scientific Advisory Board: Synthetic Genomics, Anacor
- I0M Forum on Global Infectious Diseases
- USG Activities: DoD, DHS

Key Themes

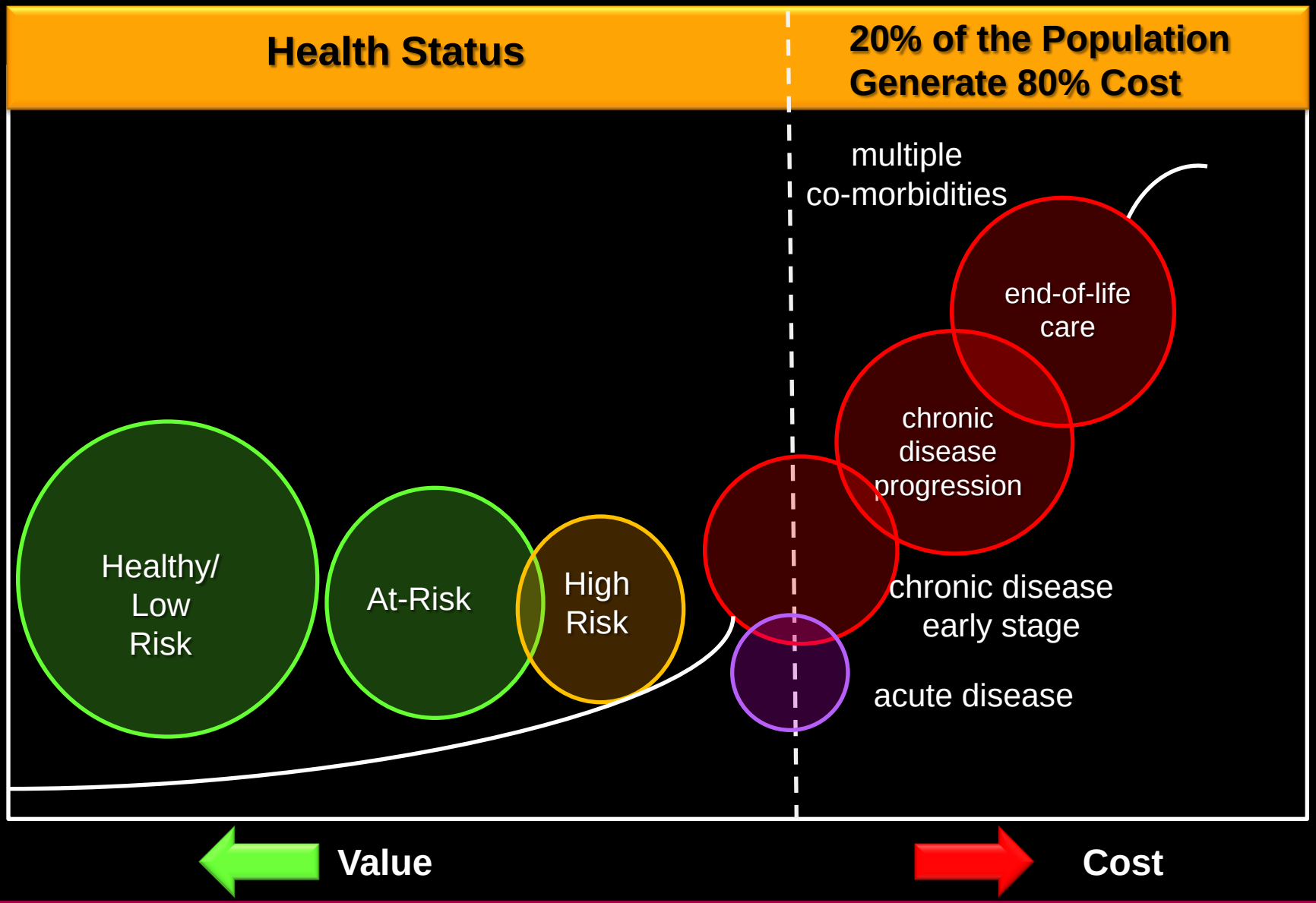
Sustaining Healthcare Innovation in an Era of Constraint

The Challenge of Translation of Discovery Advances to Tangible Benefits for Patients and Society

Biomarkers and Diagnostic Technologies as Major Value Drivers in Improving Health Quality and Outcomes and Controlling Costs

Radical Reform of the Organization and Funding of Biomedical Research to Address Major Gaps in Scale, Standards, Education and Accountability

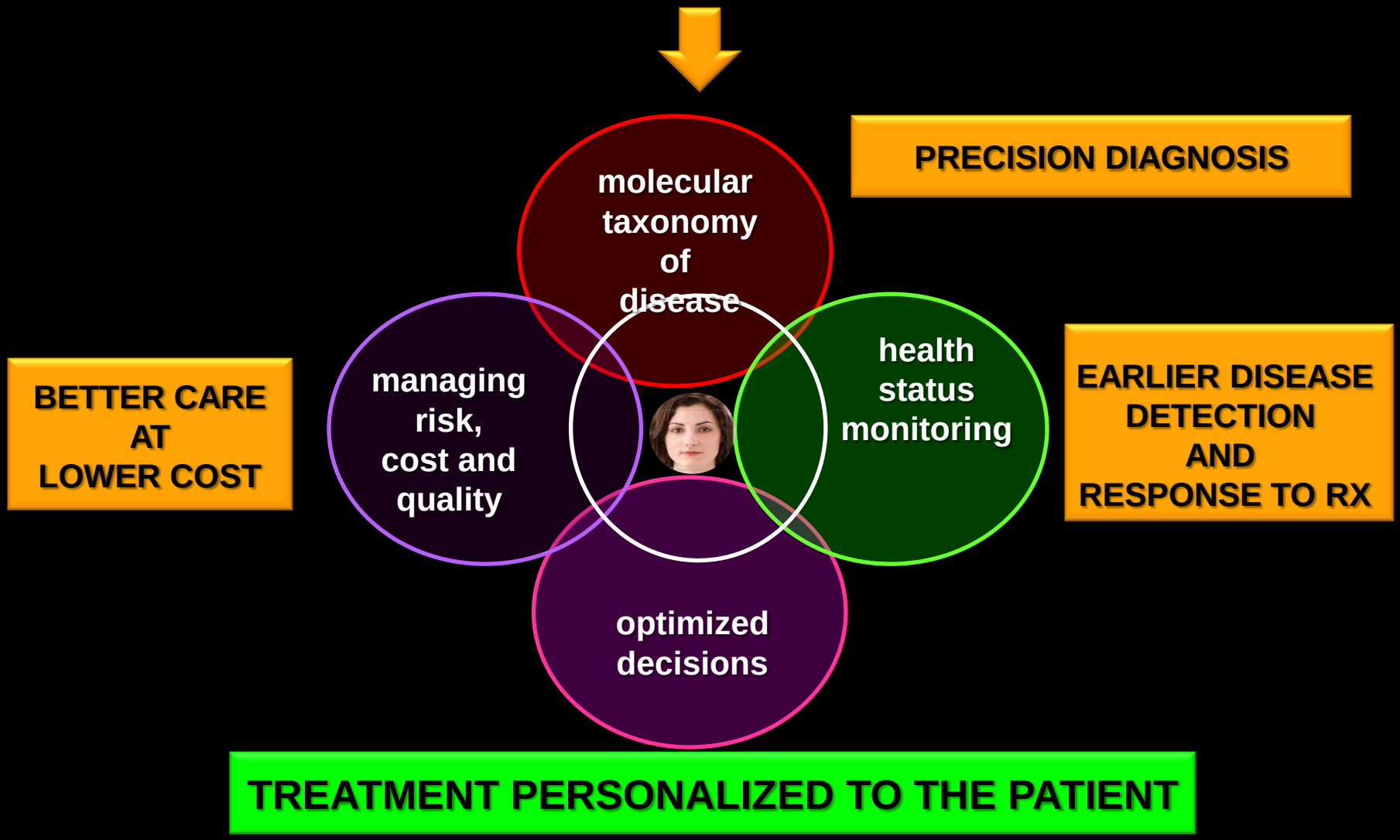
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities



New Value Propositions in Healthcare

- social and economic value of reducing disease burden will rise
  - earlier disease detection and mitigation
  - rational Rx and guaranteed outcomes
  - integrated care for complex chronic diseases
  - extension of working life
- progressive shift from ‘reactive’ medicine to ‘proactive’ care and ‘integrated’ delivery
  - prospering in an era of increasing constraints
  - managing the limit(s) of society’s willingness and ability to pay for innovation

Disruptive Innovation in Healthcare: Redefining the Value Equation in Healthcare



US Cancer Prevalence Estimates 2010 and 2020

Site	# People (thousands) 2010	2020	% change
Breast	3461	4538	31
Prostate	2311	3265	41
Colorectal	1216	1517	25
Melanoma	1225	1714	40
Lymphoma	639	812	27
Uterus	588	672	15
Bladder	514	629	22
Lung	374	457	22
Kidney	308	426	38
Leukemia	263	240	29
All Sites	13,772	18,071	32

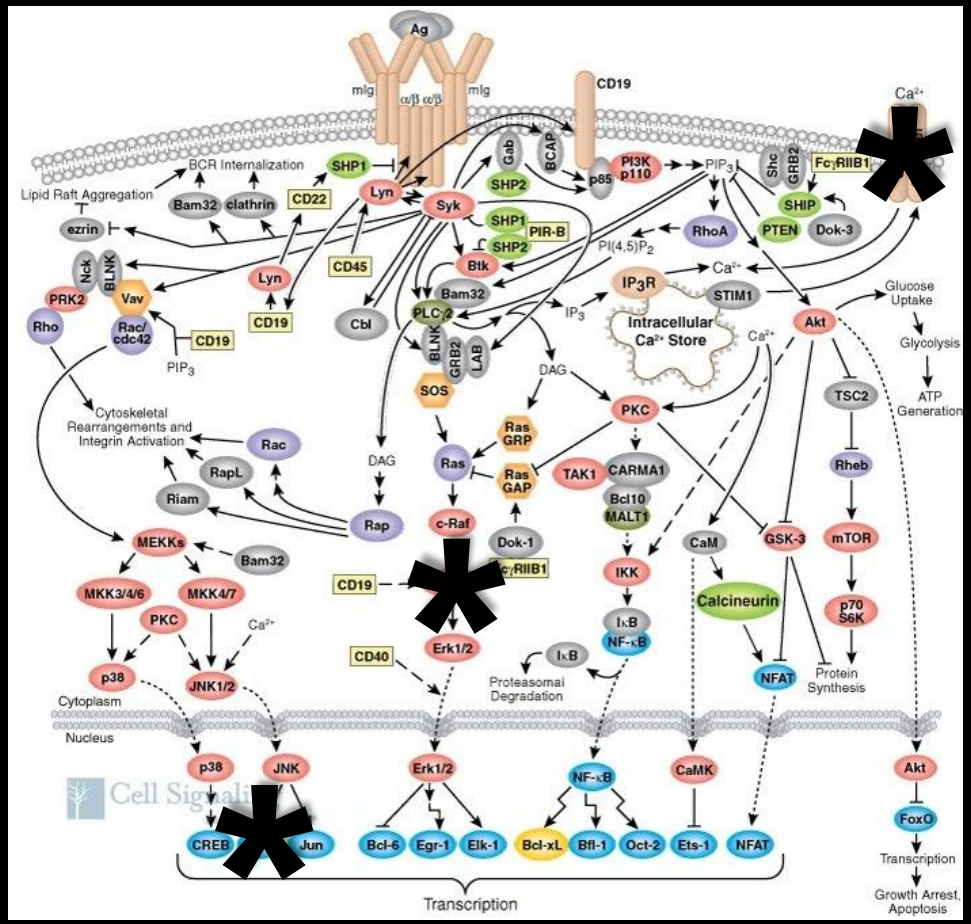
From: A.B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117

Defining A New Taxonomy for the Diagnosis and Classification of Disease

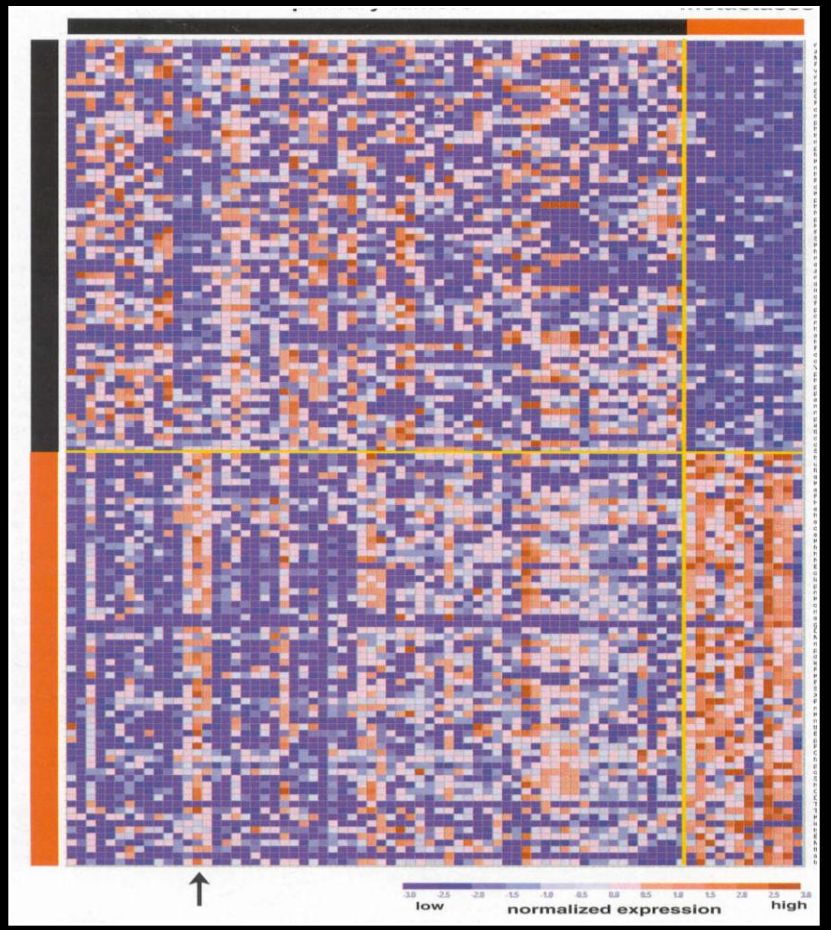
- redefining pathology as the deregulation/dysregulation of specific biological pathways
- disease with similar symptoms can arise in the same cell type via different patterns of pathway dysregulation
  - different points in the same biological pathway
  - multiple points in connected biological pathways
- molecular profiling of disease subtypes as the intellectual foundation for rational drug discovery and Rx treatment selection
  - “targeted therapeutics”
  - “personalized medicine”

From Pharmaceuticals to Pharmasuitables: Right Rx for the Right Disease (Subtype)

ID Molecular Targets for Rx Action



Disease Profiling to Identify Subtypes (+ or - Rx Target)



K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy

Vectibix® (panitumumab)

ERBITUX® CETUXIMAB

NCCN

ASCO®

clinical guidelines

- higher response in patients with K-RAS versus mutant-K-RAS
- estimated $604 million/year savings (ASCO)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

- regulatory endorsement in product labeling

Molecular Profiling of Chemotherapy-Refractory Metastatic CRC and Resistance to EGFR-Targeted Therapy
W. DeRook et al. (2010) Lancet 11, 753

- 900 patients profiled for K-RAS, BRAF, NRAS, PIK3CA and response to cetuximab
- all wild-type genes
  - 41.3% response rate (RR)
- wild-type K-RAS
  - 36.3%RR
- K-RAS mutants
  - 6.3%
- BRAF mutants
  - 8.3% of RR
- N-RAS mutants
  - 7.7%
- PIK3CA mutants (exon 20)
  - 0%

Rethinking Approaches to Cancer

Is There a Fundamental Imbalance in Investment in Diagnostics Versus Therapeutics?

Cancer Therapeutics: Some Perplexing Questions

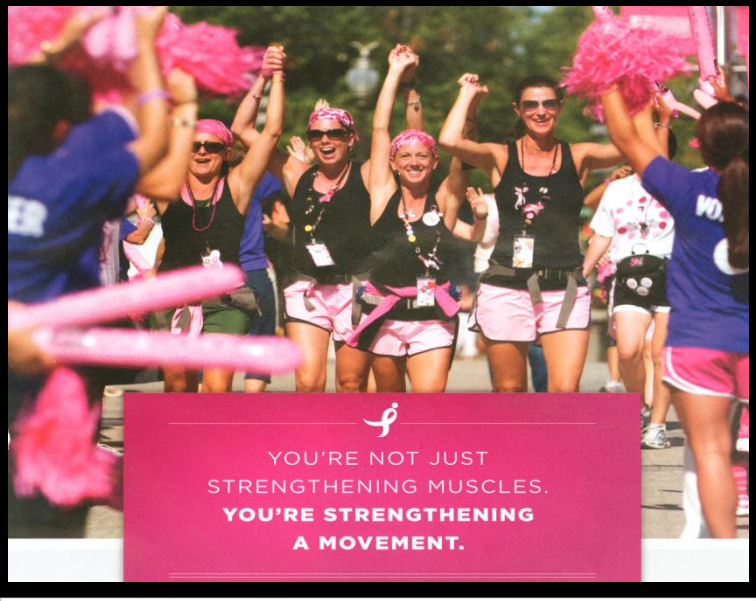
- have next-generation ‘targeted therapies’ (versus cytotoxic agents) resulted in improved OS and QOL?
- can ‘all comer’ cancer trials without stratification of patients on molecular profiling be afforded or ethically justified?
- can the high cost of targeted therapeutics ($40-100K) be justified for disease control of a few weeks or at most months?

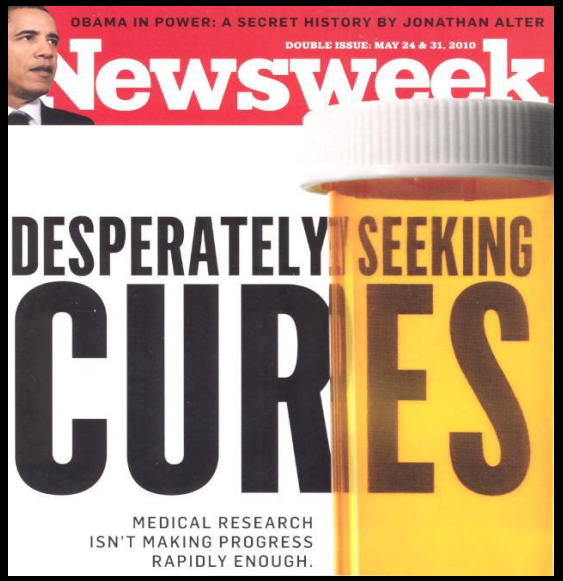
UK National Institute for Health and Clinical Excellence (NICE)

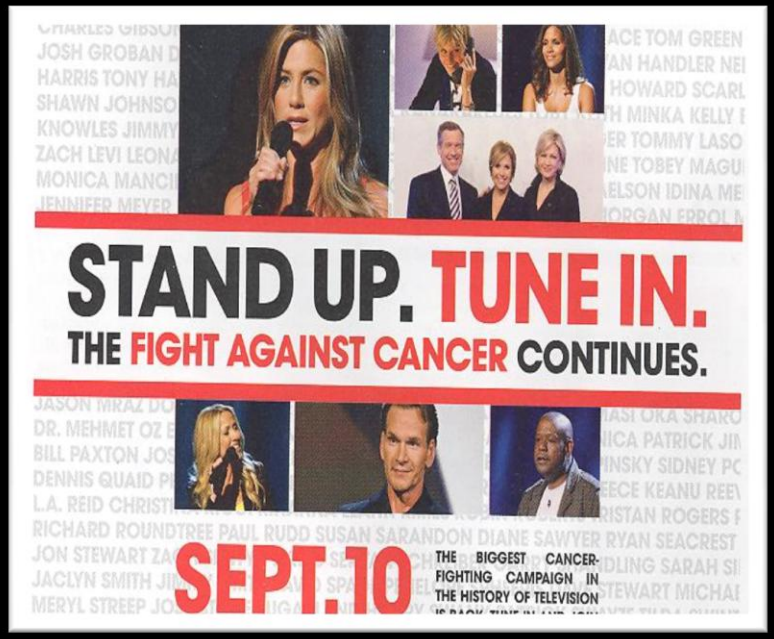
What Are We Willing to Pay for Added Months of Survival in Cancer?

Lifetime cost above standard care	If cancer is on par with other diseases ($150,000 per life year gained), months of added overall survival benefit needed	Treating cancer as worthy of much higher reimbursement ($250,000 per life year gained), months of added overall survival benefit needed
$50,000	4 months	2.4 months
$100,000	8 months	4.8 months
$150,000	12 months	7.2 months
$200,000	16 months	9.6 months
$250,000	20 months	12 months
$300,000	24 months	14.4 months
$350,000	28 months	16.8 months
$400,000	32 months	19.2 months
$450,000	36 months	21.6 months
$500,000	40 months	24 months

Source: Pink Sheet 13 Sept. 2010. Adapted from S. Ramsey FHCRC, ASCO 2010


YOU'RE NOT JUST
STRENGTHENING MUSCLES.
YOU'RE STRENGTHENING
A MOVEMENT.


OBAMA IN POWER: A SECRET HISTORY BY JONATHAN ALTER
DOUBLE ISSUE: MAY 24 & 31, 2010
Newsweek
DESPERATELY SEEKING
CURES
MEDICAL RESEARCH
ISN'T MAKING PROGRESS
RAPIDLY ENOUGH.


STAND UP. TUNE IN.
THE FIGHT AGAINST CANCER CONTINUES.
SEPT.10
THE BIGGEST CANCER-FIGHTING CAMPAIGN IN THE HISTORY OF TELEVISION


National Breast Cancer Coalition
The
Breast
Cancer
Deadline
2020
Breast Cancer Deadline
Why Now?
September 20, 2010
BreastCancerDeadline2020.org

Cancer Therapeutics: Some Perplexing Emerging Questions

- is the multiplicity of pathways dysregulated in metastatic advanced disease an insurmountable technical barrier to design of poly-target (promiscuous) agent/combinations?
  - highest failure rate of new Rx in any therapeutic category (8% success)
- is the only viable strategy for mitigating the clinical, economic and emotional toll of cancer to focus on early diagnosis and removal of pre-metastatic lesions?

Biospecimens, Biomarkers, Biosignatures and Molecular Diagnostics: The Key Value Drivers for Personalized Medicine, Improved Healthcare and Maximizing Wellness

Killing Trees

- ‘publish and vanish’
  - over 120,000 claimed biomarkers or biomarker combinations (biosignatures)
  - less than 100 molecular diagnostics in clinical use or advanced validation
- Google Search (February 2011)
  - companion diagnostics 194,000
  - theranostics 48,762
  - pharmacodiagnostics 25,162
- PubMed (February 2011)
  - 8416 citations
  - 45.4% also categorized ‘cancer’

Disease-Associated Biomarkers and Validation of Novel Molecular Diagnostics

- literature dominated by anecdotal studies
  - academic laboratories
  - small patient cohorts
  - lack of standardization
  - poor replication and confirmatory studies
- very few biomarkers subjected to rigorous validation
  - inadequate stringency in clinical phenotyping
  - case-control studies with sufficient statistical power
- widespread lack of understanding of regulatory requirements in academic research community
  - complexities imposed by multiplex tests
  - new regulatory oversight (IVDMIAs)

Biomarkers and Personalized Medicine: Promises, Pitfalls and Yet Unrealized Potential

"The output (for drug discovery/biomarkers)
has been as close to zero as you can come.
We have achieved nothing substantial
that's the bottom line."

Dr. Tommy Nilsson
McGill Univ.
Nature Biotechnology (2010) 28, 669

"Biomarkers have been the biggest disappointment of the decade, probably because proteomics role in their discovery was overhyped."

Dr. John Yates
Scripps Institute
Nature Biotechnology (2010) 28, 665

Translation of the Major Potential of Molecular Medicine into Routine Clinical Practice

A Complex Multi-Dimensional Challenge

Success Demands a Systems-Based Approach

Biomarkers, Biosignatures and Molecular Profiling of Human Diseases

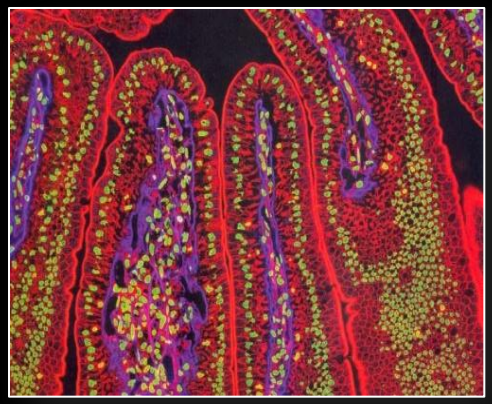
Agnostic

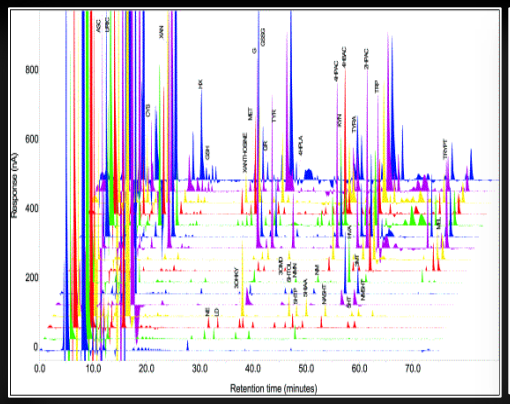
- analytes
- analytical platforms

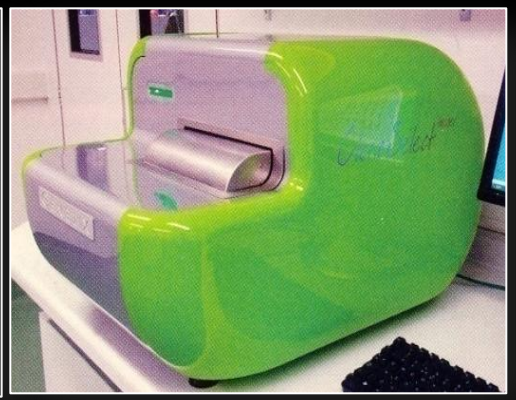
Success Determinants

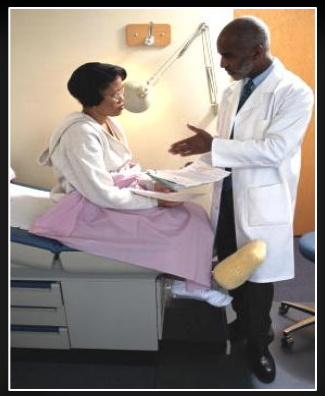
- systems-based strategies
- specimens
- standards/ standardization
- scale/statistics
- silos and sociology
- sustainability

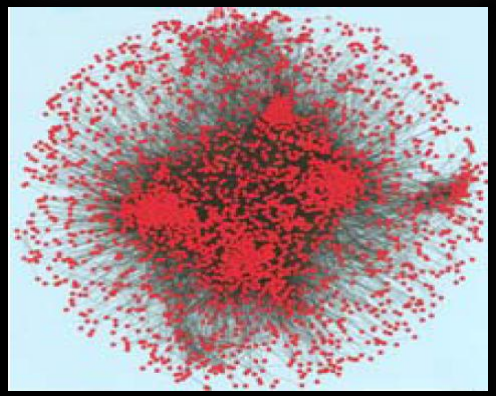
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches

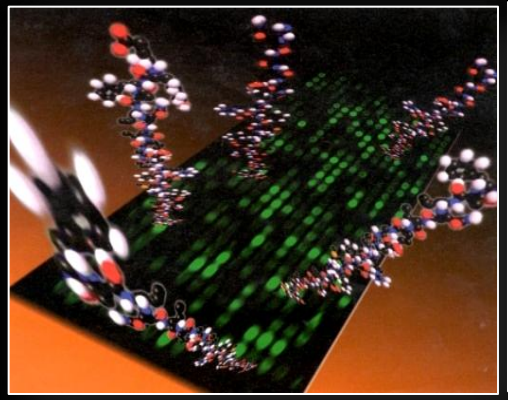


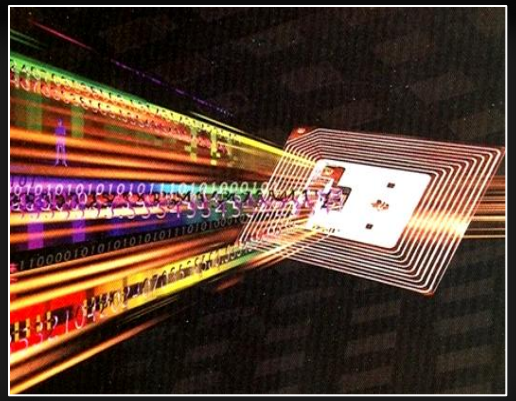












Biospecimens and Molecular Pathway Analysis

Biomarker Validation and Multiplex Assays

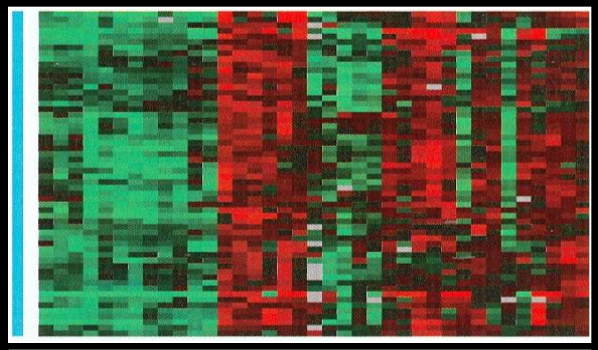
Instrumentation and Informatics

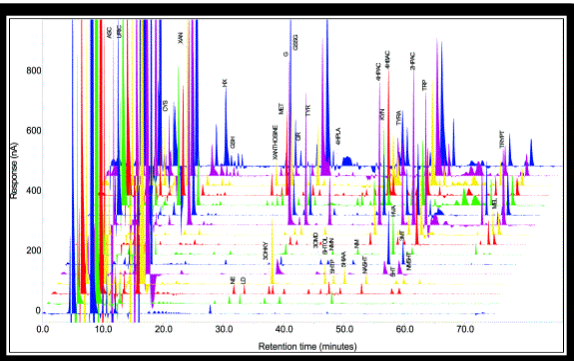
Clinical Impact and Patient Monitoring

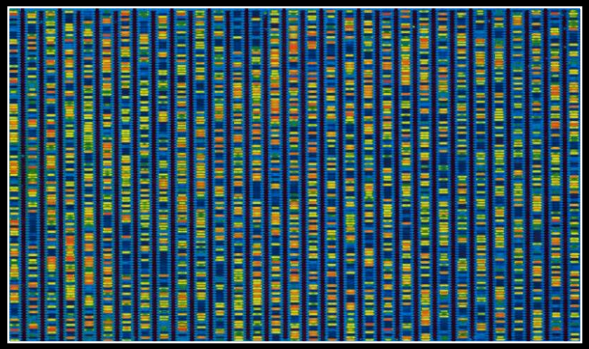
Molecular Diagnostics and Miniaturized Devices: A Key Future Driver in the Healthcare Value Chain

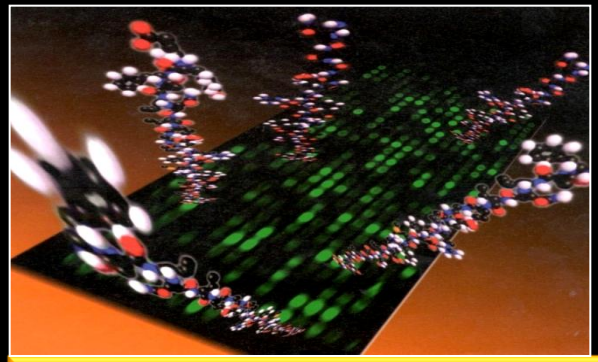
Complex Biosignature Profiling

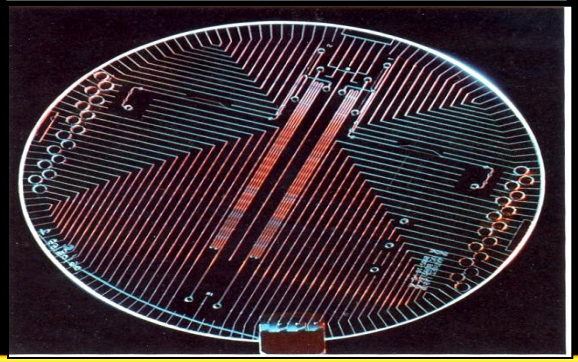
genomics	proteomics	immunosignatures

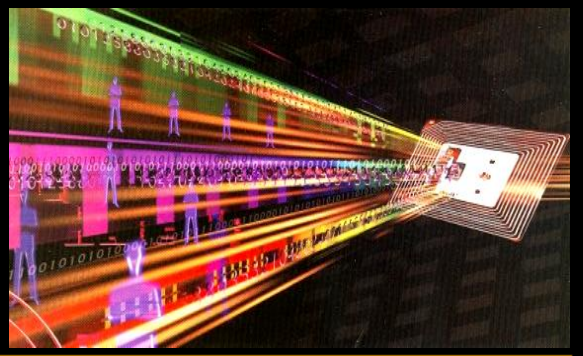








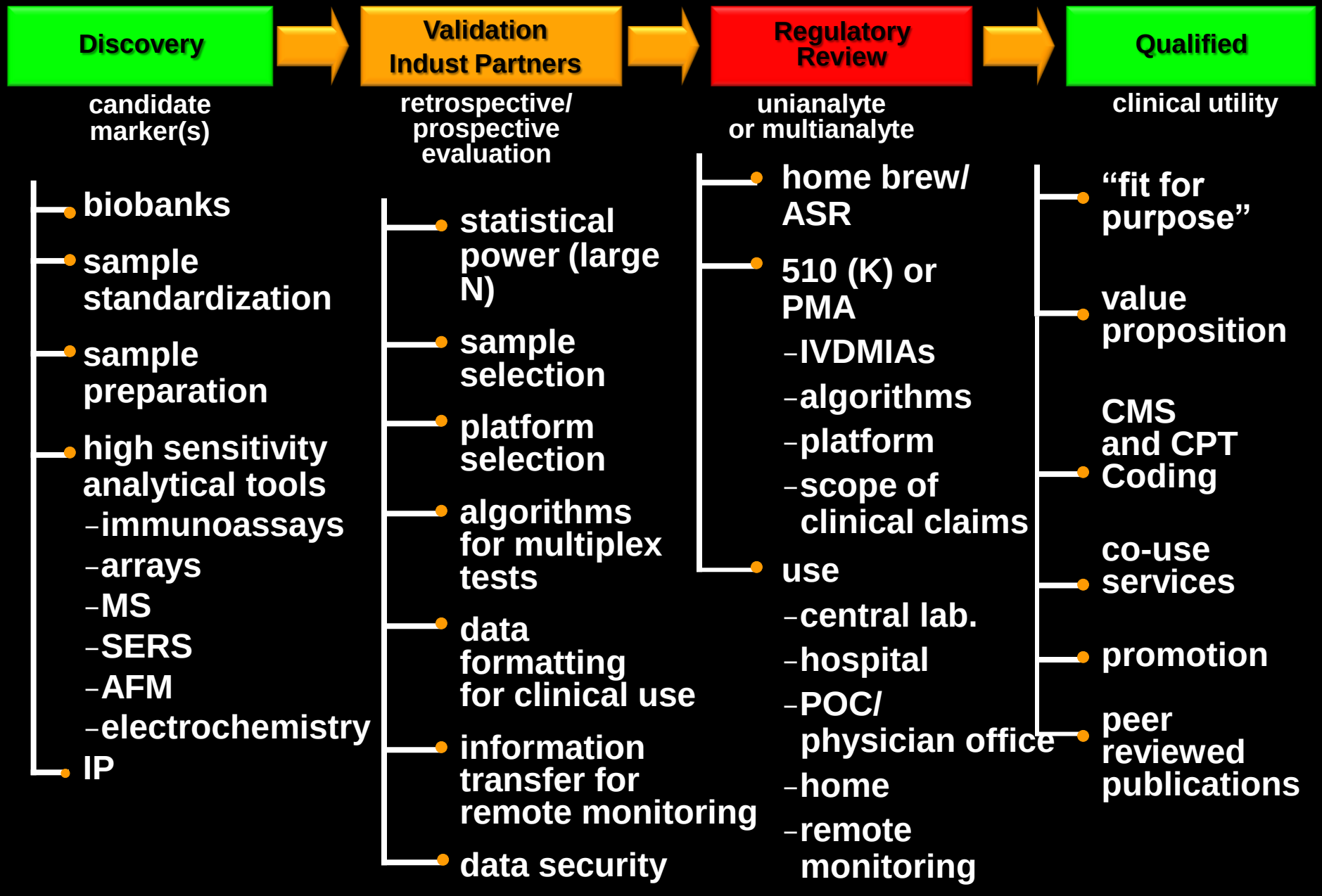




Signature Detection, Deconvolution and Multivariate Analysis

automated, high throughput multiplex assays	novel test formats and devices (POC)	new algorithms for complex signal/deconvolution

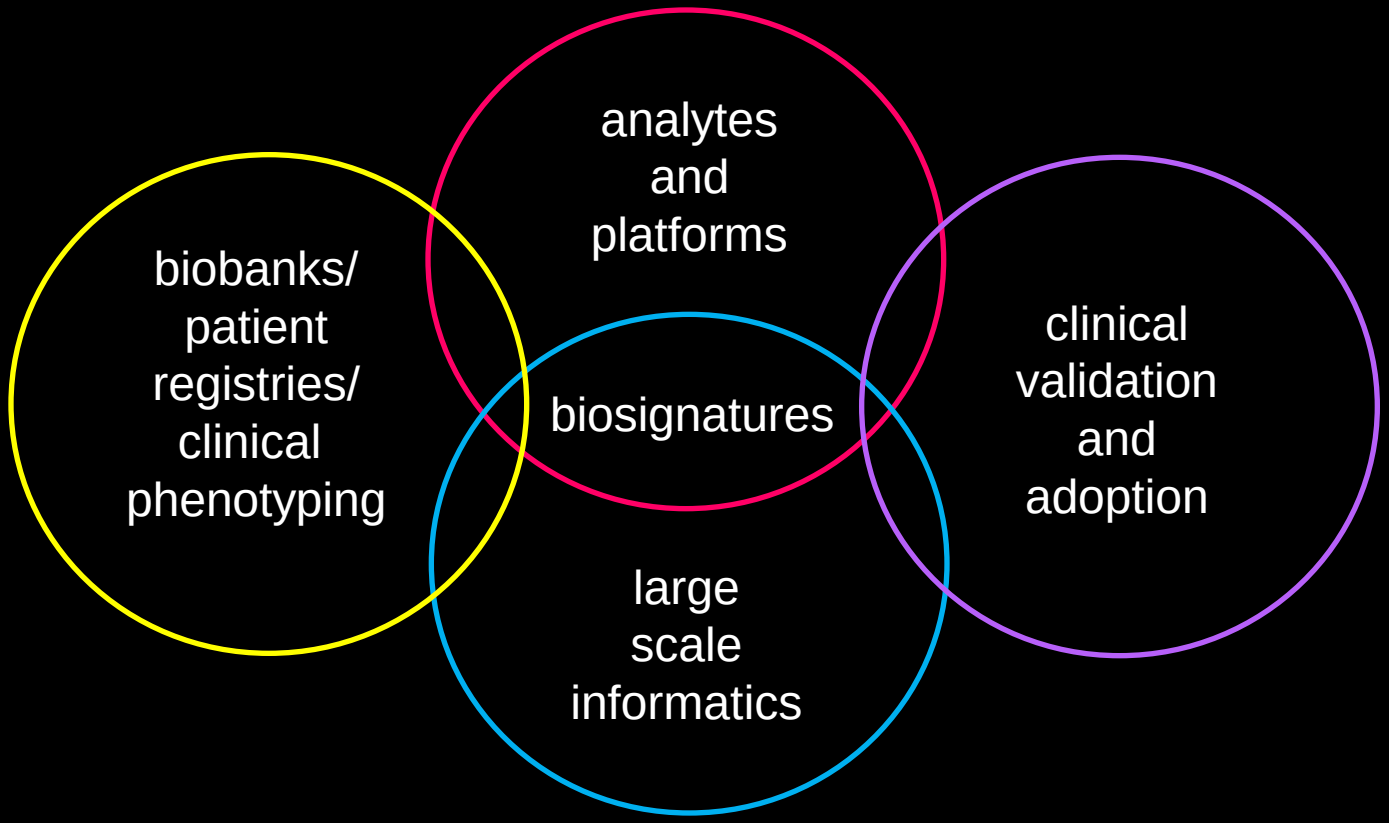
Biomarker R&D
Building An Integrated Framework



Biomarkers and Personalized Medicine: The Imperative for New Research Approaches

Its the Specimens, Stupid!

The Core Components of a Systems-Based Approach to Biomarker Validation and Clinical Utility



Biospecimen Science

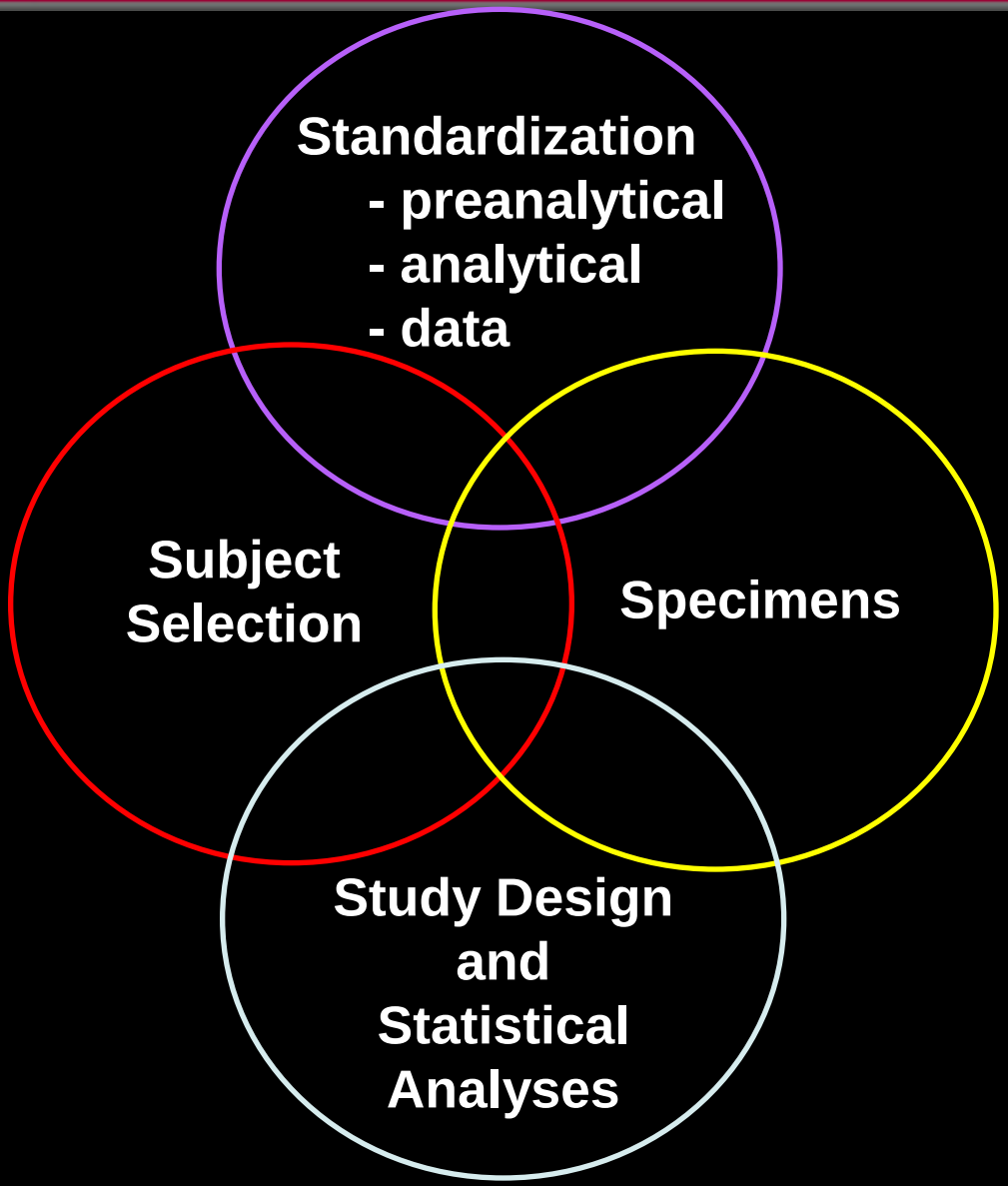
Access to High Quality Biospecimens

- #1 obstacle to ID and validation of novel biomarkers
- unknown or variable quality of legacy biorepositories and limited linkage to clinical records
- historical neglect of national-level leadership/standards for biorepository specimens and management
- poorly developed protocols for systematic classification, coordination or distribution (priorities)

Challenges Associated With Legacy Biobanks

- highly variable storage, curation and clinical annotation
- investigator/institutional ‘terroriality’ (cf. WU case)
- ambiguous and varied informed consent provisions
  - disease specific versus blanket ‘research use’
- limited longitudinal sampling and correlation with clinical outcomes
- relative absence of normal tissue cohorts

The Systems-Based Approach to Biomarker Validation

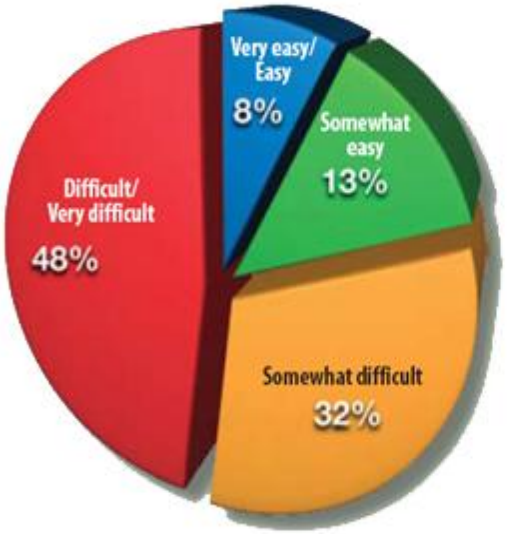


Challenges in Establishing Rigorous Correlations Between Perturbations in Molecular Pathways and Disease

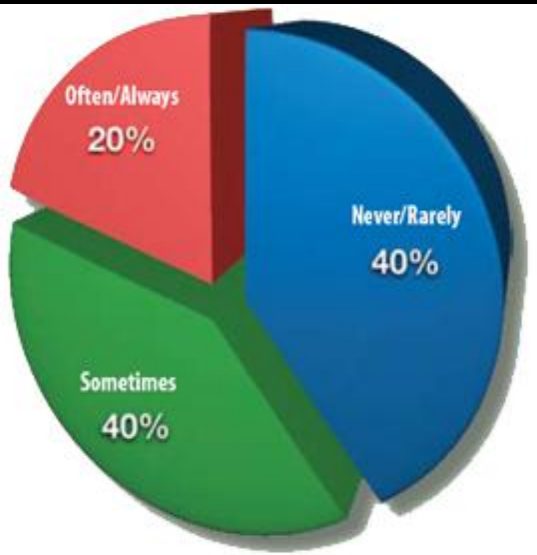
- more stringent criteria for clinical phenotyping
- obtaining the right phenotypes in the right quantity
- obtaining enough investigators with the right training and right resources
- right funding mechanisms to support the right studies

Access to Quality Biospecimens for Medical Research: A Critical 'Choke Point' in Biomedical Research

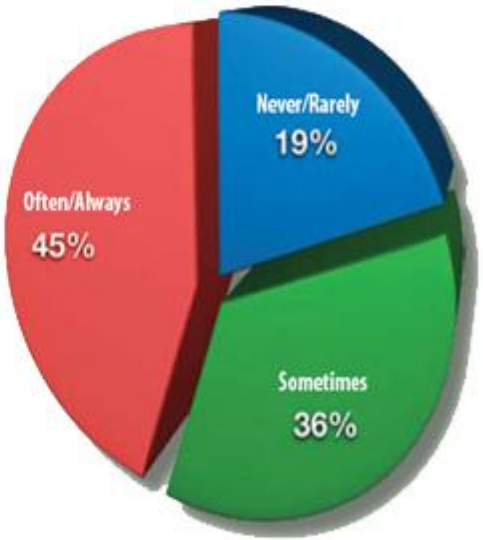
Ease of Acquiring the Quality of Biospecimens



Question Their Data Because of the Quality of Biospecimens



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



Source: Office of Biorepositories and Biospecimen Research, 2009.
http://biospecimens.cancer.gov/cahub/

Challenges in Tissue Procurement

- informed consent
  - specific or broader ‘research use’
  - workflow logistics, time and cost to clinical centers
- IRBs
  - variability, delays, risk averse
  - AMC versus community practices
- disruption to clinical workflows
- sample mishandling
- sample loss
- labeling and documentation errors and unreliable provenance
- dedicated staff
- access policies
- data collection, curation, annotation

Enterprise Grade Biospecimen Collection and Management

- standards, standards, standards!
  - consent and diverse regulatory/legal compliance needs
  - collection, transport, processing, analysis
  - storage and curation
  - chain of custody
  - longitudinal tracking of specimen samples, aliquots
  - integration of clinical and non-clinical sets
  - systems integration LIMS/CTMS, GLP/GCP
  - facile transfer to regulatory dossier/clinical EMR
  - mega-and meta-data capabilities

The Formidable Challenge of Standardization of Pre-Analytical Sources of Variation in Clinical Biospecimens

Pre-Sampling

- pre-existing medical conditions
- Rx
- type and duration of anesthesia
- vessel clamp time and tissue anoxia
- blood pressure variation
- intra-operative blood/fluid shifts

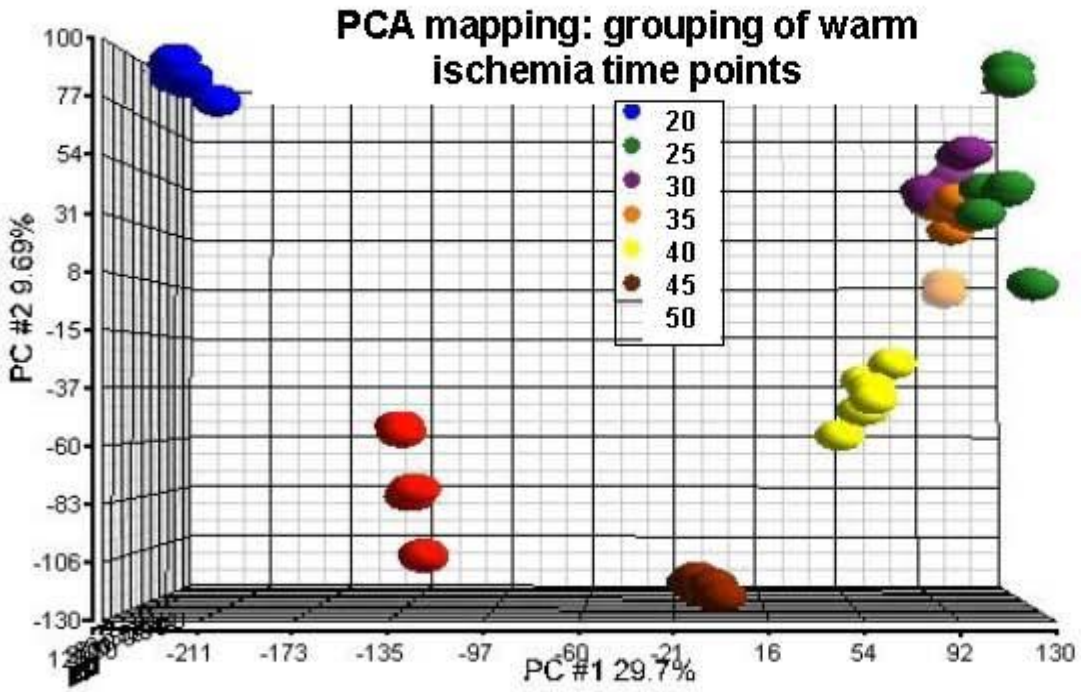
Post-Sampling

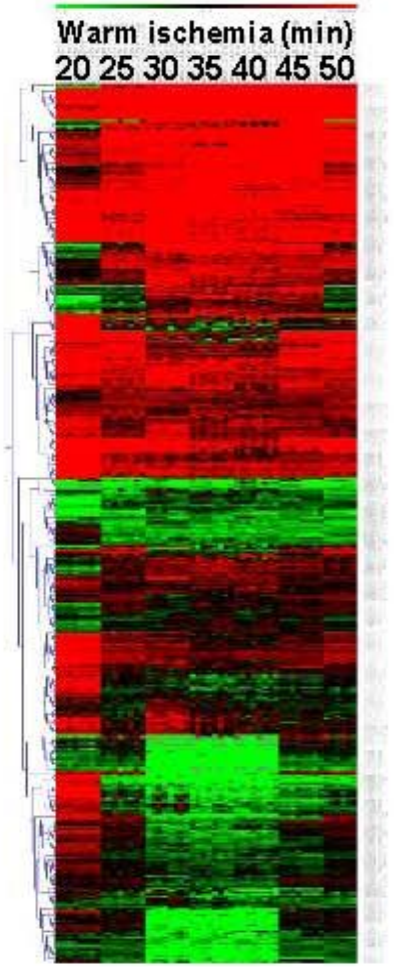
- room temperature
- time at room temperature
- rate of freezing
- fixative type and time in fixative
- collection container(s)
- biomarker extraction methods
- storage conditions
- transport conditions

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

OBBR Office of Biorepositories and Biospecimen Research

Intrasurgical Ischemia





Indivumed-NCI Study: Courtesy of Dr. C. C. Compton

Quotes for Prominent Display in Every Biomarker Research Laboratory

OBBR Office of Biorepositories and Biospecimen Research
NCI Best Practices for Biospecimen Resources

"The technological capacity exists to produce low-quality data from low-quality analytes with unprecedented efficacy."

"We now have the ability to get the wrong answers with unprecedented speed."

Dr. Carolyn C. Compton
Director, Office of Biorepositories and Biospecimen Research
National Institutes of Health
'I0M, July 2010'

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

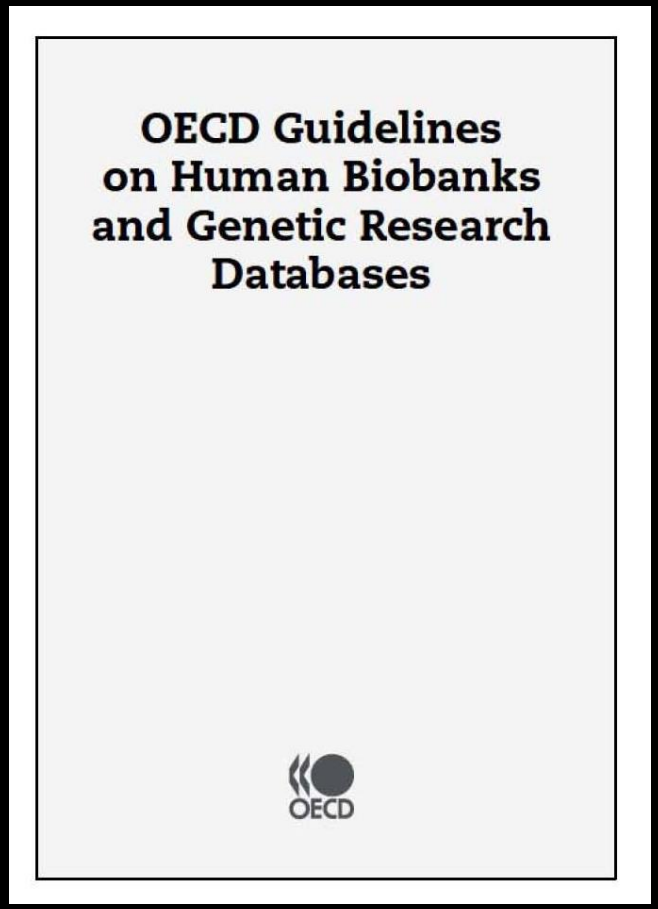
Prepared by:
National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

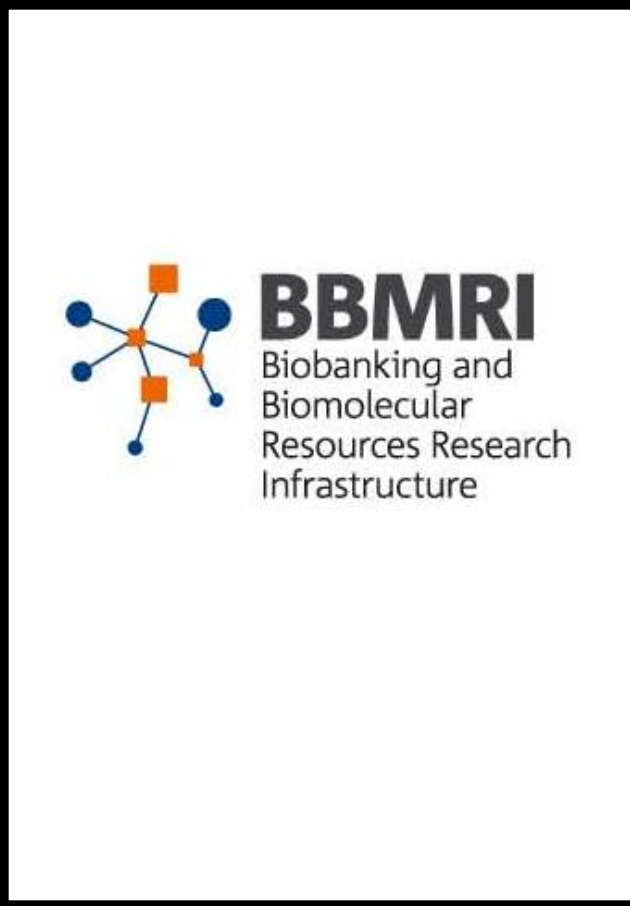
Objectives:

- 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


OECD BEST PRACTICE GUIDELINES FOR
BIOLOGICAL RESOURCE CENTRES
OECD
ORGANISATION FOR ECONOMIC CO-OPERATION
AND DEVELOPMENT


OECD Guidelines
on Human Biobanks
and Genetic Research
Databases
OECD


BBMRI
Biobanking and
Biomolecular
Resources Research
Infrastructure

“The study of cancer cells in two dimensions seems quaint if not archaic”

T. Jacks and R.A. Weinberg (2002) Cell 111, 923

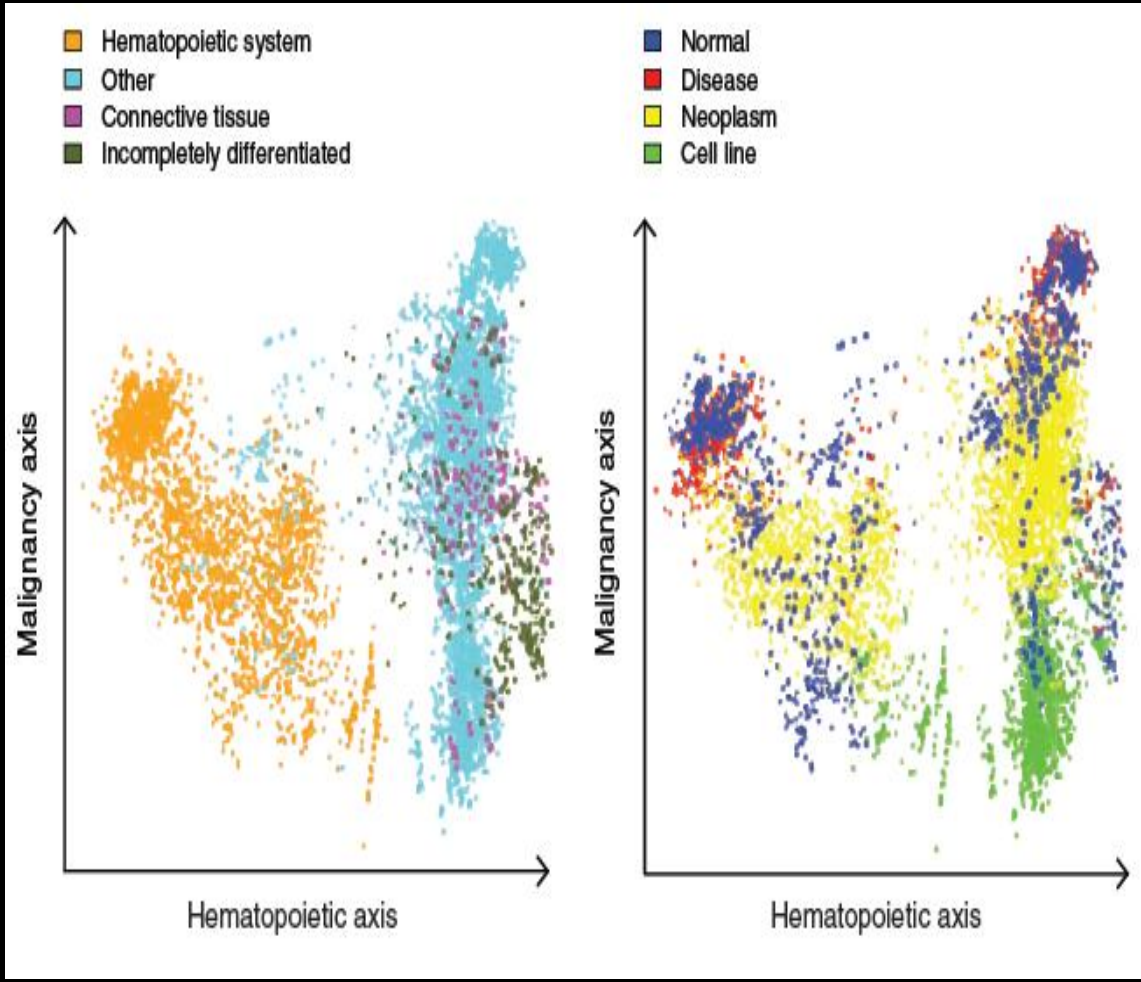
“Medline search reveals that more than 80% of cancer and molecular biologists still use two-dimensional techniques”

D.W. Hutmacher (2010) Nature Materials 9, 90

Challenging Questions

- are the phenotypes and molecular pathways of cell lines and 2D cell cultures so unrepresentative of the situation to render them irrelevant and pose blind avenues for diagnostic/therapeutic discovery?
- can the biology of metastasis be elucidated by analysis of non-metastatic cells?

A Global Map of Human Gene Expression
M. Lukk et al. (2010) Nature Biotech. 28, 322



http://www.ebi.ac.uk/gxa/array/U133A

- 5372 microarray samples
- 206 different laboratories
- 163 different laboratories
- 369 cells, tissues, disease states and cell lines
- solid tissue cell lines cluster together rather than with respective tissues of origin or neoplasms from same lineage
  - 1217 genes upregulated in all cell lines
  - cell cycle, division and mitosis genes

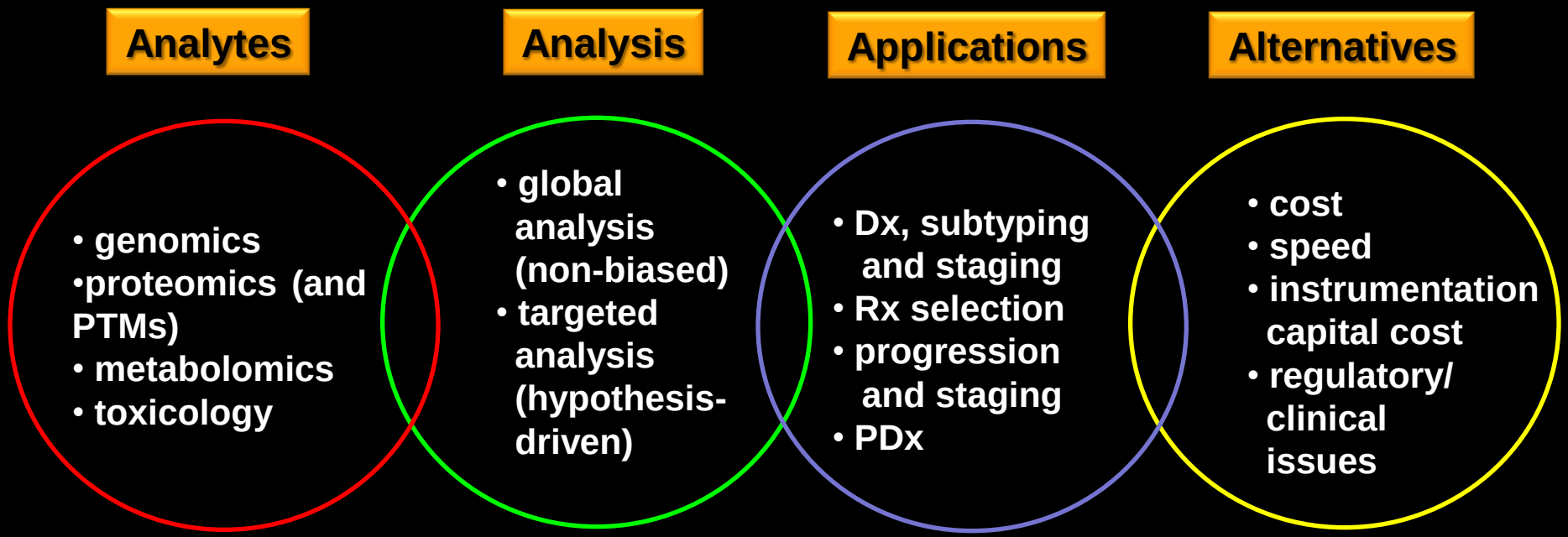
Mixed-Up Cell Lines

- risk of cross-contamination of cell cultures
- 50 years of warnings
  - overgrowth by HeLa cells as ‘early culprit’
- ECV 304
  - “immortalized normal endothelial cells”: over 1000 papers
  - Wilhelm Dirks (1999) revealed as human bladder carcinoma
  - 80 papers in 2008/2009 still referencing as endothelial cells
- contamination of mesenchymal stem cell lines
  - therapeutic implications and regulatory oversight
- obligate requirement for STR profiling
- obligate adoption of validation criterion for publication

Complexity in Biological Systems: The Challenge of Predicting Genotype/Phenotype Relationships

- non-linear relationship between genotype and phenotype
- formidable challenges for biomedical and mathematical sciences
  - individual diversity in genome organization (SNPs, haplotypes, CNVs)
  - gene-gene interactions
  - epigenetics and imprinting
  - non-coding RNA regulatory networks
  - gene-environment interactions
  - gene-Rx interactions

Platforms for Biomarker and Biosignature Profiling



Standardized Methods, Data Reporting and Database Design

GLP/GMP; LIMS/CTMS; Regulatory Dossiers

Instrumentation: Research Use Only or Approval for Clinical Use

Mapping the Dynamic Human Proteome

- daunting complexity of massive combinatorial space
  - 230 different cell types + body fluids
  - pre-and post-translational gene regulation
  - SNPs, copy number variants, mutations
  - 200 PTMs
  - expression, abundance and interactomes
  - localization, trafficking, turnover
  - dynamic range
  - physiological homeostasis
  - dysregulation and disease pathogenesis

Sample Complexity and Dynamic Range in MS-Based Proteome Analysis

- detection of low abundance species
- femtomole or attomole range sensitivity modulated by nature of sample (abundance, dynamic range)
- ion suppression from high abundance proteins/peptides
- 35% estimated human proteins yet to be reliably identified by MS
- under sampling
- time, cost and efficiency of pre-analytical fractionation(s)
- targeted depletion of abundant proteins and/or affinity enrichment of low abundance species

True or False?

"It is time for the debate about the reproducibility of mass spectrometry to end."

Anonymous Editorial:
The Call of the Human Proteome
Nature Methods (2010) Sept. 7 (9) 661

Nature Methods (2010) 7, 681

Mass spectrometry in high-throughput proteomics: ready for the big time

Tommy Nilsson[1,2], Matthias Mann[3], Ruedi Aebersold[4,5], John R Yates III[6], Amos Bairoch[7,8] & John J M Bergeron[1,2]

Mass spectrometry has evolved and matured to a level where it is able to assess the complexity of the human proteome. We discuss some of the expected challenges ahead and promising strategies for success.

Reproducibility: Consistency Using Different Analytical Technologies
T.A. Addona et al. (2009) Nature Biotechnol. 27, 633

- analysis of C-reactive protein (CRP) by 7 labs using MS-CRM and ELISA
  - MS: 0.31 to 1.8 fmol μl^{-1}
  - ELISA: 4 fmol μl^{-1}
  - CRP comparatively abundant but source of discrepancies between platforms unresolved
- even for MS 25% between-lab quantitative variation is too high for clinical laboratory adoption

Common Problems in MS-Based Proteomics

A.W. Bell et al. (2009) Nature Methods 6, 423

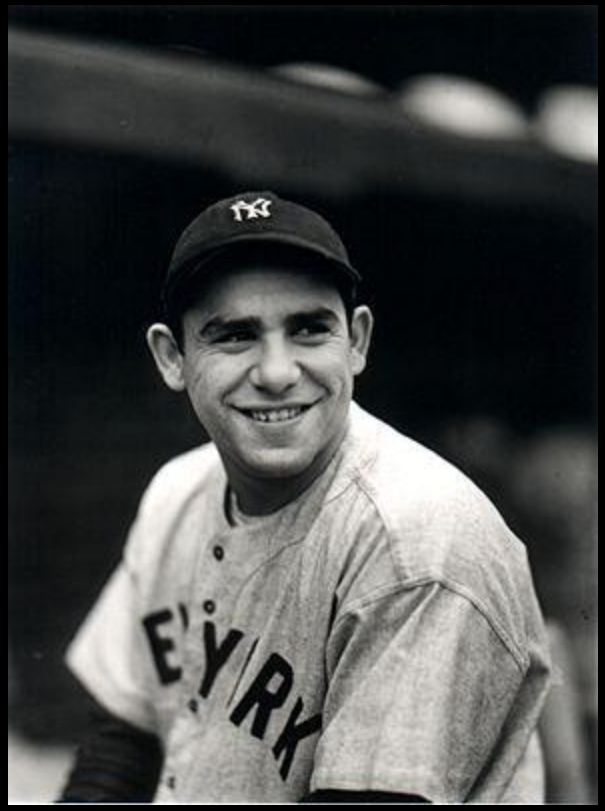
- evaluation of test sample of 20 purified proteins at 5 pmole equimolar abundance
- 7/27 labs with initial correct characterization
- raw data from all sufficient to identify full 20 protein catalog and 22 derivative 1250 Da peptides
- diverse and poorly standardized databases and search engines as principal sources of erroneous reporting
  - variation in curation, annotation, comprehensiveness

- real world challenges: high complexity samples and large preanalytical (collection/storage) sample variation

- education and training to use complex technologies
- publication standards, formats and open-source dbases

Does the Mass Spectrometer Define the Marker? H.G. Gika et. al. (2010) Anal. Chem. 82, 8226-34

- coupling of UPLC sample separation to two different MS instruments
- triple quadrupole linear ion trap MS (QTRAP)
- hybrid quadropole TOF MS (Q-TOF)
  - highest scan rates, high efficiency, resolution, mass accuracy
  - good dynamic range, stability, high sensitivity, MS/MS functionalities
- orthogonal partial least-squares discriminant analysis of number of ions unique to each instrument dataset
  - significant number of unique up-and-down regulated variables in urine from isoniazid-treated rats
- obvious implications for comparison of datasets from different sources
  - different laboratories using different MS even if pre-analytical variables are standardized



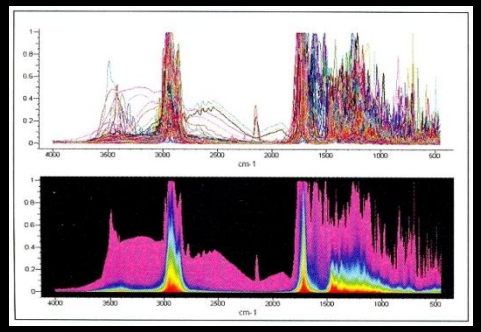
“We may be lost,
but we’re having a good time”

Yogi Berra

Biosignatures and Biomarkers: Chance, Bias and Exclusion of Alternate Explanations

"This field has got too much happy talk.
Biologists spend a lot of time
talking about why it should work
and not enough time figuring out 'does it work'?

Dr. David Ransohoff
UNC, Chapel Hill
Nature Biotechnology (2006) 24, 935



"During the last 30 years
biology has become a discipline
for people who want to do science
without learning mathematics"

M. Cassman et. al.
Barriers to Progress in Systems Biology
Nature (2006) 438, 1079

The Imperative for Rigorous Clinical Sampling Protocols in Biomarker Profiling and Validation of IVD Tests

- statistical powering
- rigorous case-control studies
  - retrospective
  - prospective (piggy back on clinical trials)
- prospectively defined endpoints
  - diagnostic marker(s)
  - Rx responsiveness and resistance markers
  - staging, stratification, progression markers
- regulatory validation of software algorithms for multiplex tests

Validation of Disease Associated Biomarkers

- disease related differences are small compared to biological variability
- many variables behave as QTLs with graded continuum rather than binary normal: disease separation
- the high dimensionality small sample size (HDSS) problem
  - high number of variables (2000-10000) and low sample size (10-100)
  - increased risk of selection of variables due to chance (overfitting)
- standardization and statistical powering of validation studies
  - “the 20:200:2000 rule”
- new regulatory complexities for multiplex ‘signatures’

Payor Perspectives and Reimbursement for Molecular Diagnostics

- #1 will test alter patient management?
  - reduce cost of care
  - improve outcomes
- #2 what additional resources/services/training are affected by test adoption?
- #3 perception of RCT as only 'gold standard'
  - narrow interpretation that discounts value of observational studies
- #4 mindset of 'lab data' as low cost (<1% total cost) despite role in most treatment decisions (>85%)
  - unianalyte versus multiplex tests
  - outdated US reimbursement codes

SHIFT FROM COST-BASED TO VALUE-BASED REIMBURSEMENT

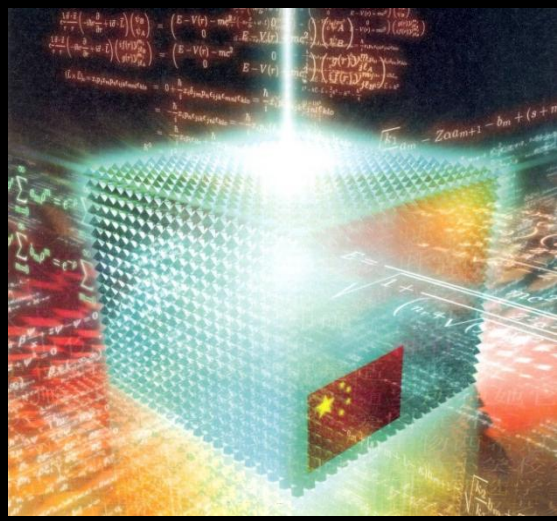
Standards for ‘Omics’ Data, Cross-Domain Integration, Open-Source Data Sharing and Computational Analysis

“Managing Mega-Data”

volume

scale

global networks



multiscale heterogeneity

integration

Data: The Fastest Growing Resource on Earth: Managing the Info-Cosm

- managing the data deluge
- validation of information authenticity
- data integration, federation, distribution
- new analytics for non-linear events and risk management
- data visualization, customization and cognitive optimization
- security
- legal and ethical issues related to ‘duty to disclose’ as definitive marker-disease risk causalities are established

OBO Foundry Ontologies
Nature Biotechnology 25, 1251 - 1255 (2009)

The Open Biomedical Ontologies

Cell Ontology (CL)

the Gene Ontology

Gene Ontology (GO)

Foundational Model of Anatomy

ZFIN

Zebrafish Anatomical Ontology

ChEBI

Chemical Entities of Biological Interest (ChEBI)

Disease Ontology (DO)

Plant Ontology™ PO Consortium

Plant Ontology (PO)

SO The Sequence Ontology Project

Sequence Ontology (SO)

Ontology for Clinical Investigations (OCI)

The Open Biomedical Ontologies

Common Anatomy Reference Ontology

The Open Biomedical Ontologies

Environment Ontology

OBI

Ontology for Biomedical Investigations

Phenotypic Quality Ontology (PATO)

PIR A UniProt CONSORTIUM MEMBER Protein Information Resource

Protein Ontology (PRO)

The Relation Ontology

OBO Relation Ontology

RNA ONTOLOGY CONSORTIUM

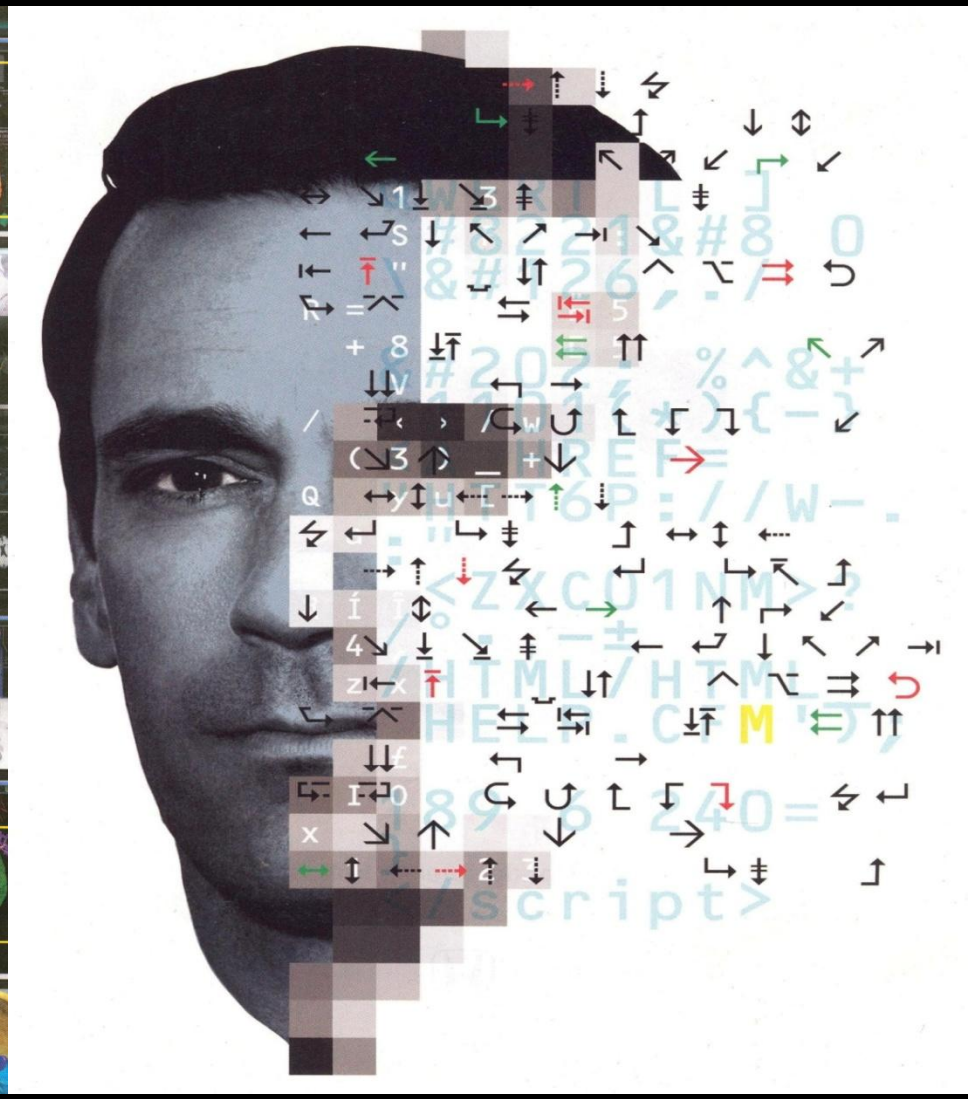
RNA Ontology (RnaO)

Data Exchange Standards

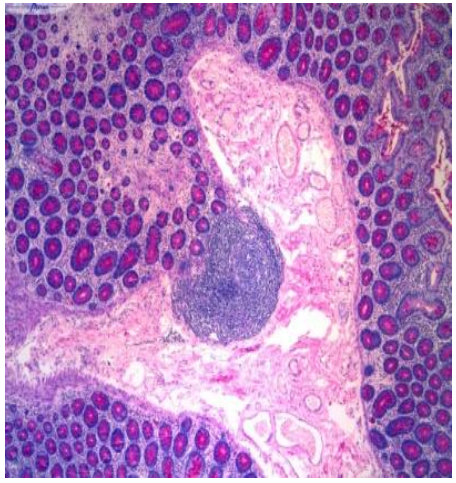
- integrate data from multiple sources
- inter-operability challenge from discovery to clinical practice
- leveraging existing HL7 standards
  - Draft Standards for Trial Use (DSTU)
- engage major data generators to adopt
  - CDISC, ICH
- Digital Imaging and Communications in Medicine (DICOM)
- seamless federation with healthcare system and reimbursement databases
  - CPT, ICD (USA)
- certification of compliance with HITECH EHR Standards (HIMSS, AHIMA)

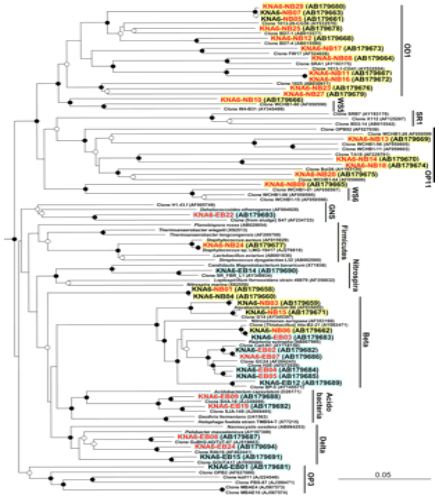
The Race for Low Cost ($<1000) Whole Human Genome Sequencing

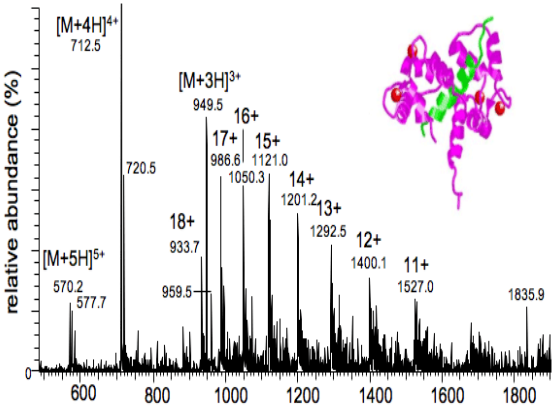
Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency



Pattern-Based Recognition Is An Intrinsic, High Fidelity Element of Human Cognition and Decision Making







Now Comes the Hard Part! Building Large Scale, Standardized Resources for Biomedical Research

- the primacy of high quality biospecimens as the foundation for understanding disease pathogenesis, precision diagnosis and rational Rx
- acquisition of rigorously phenotyped/matched/consented normal and disease samples
- standardization of pre-analytical and analytical methods and data reporting
- curation, ontologies, annotation, analytics for large scale databanks and federations
- new statistical/mathematical/computational approaches to multivariate, non-linear events
- regulatory validation of analytics
- customized data conversion for different decision categories and decision-makers

High Quality Biospecimens: The Most Crucial Asset for Advancing Personalized Medicine and Evidence-Based Clinical Decisions

- cost and logistics
- organization of coordinated programs
- international scope
- consortia and public-private partnerships
- regulatory harmonization
- intellectual property
- financing and sustainability
- role of public and private sectors

Biospecimen Economics and the Sustainability of Biobanking

- full costing needed to implement rigorous SOPs/QA/QC largely unknown
- the ‘3F’ challenge: financing freezer farms
- the ‘3P’ challenge: public: private partnerships
- the ‘3S’ challenge: standards, stewardship, sustainability
- new models for market pricing for quality biospecimens

Biospecimen Economics and the Sustainability of Biobanking

- new enterprise models and market analytics
- data richness and differential pricing?
  - normal versus common diseases
  - rare versus common diseases
  - minimum data versus outcomes data
  - customized data
  - proprietary data exclusion versus mandated data deposition
- roles of public and private sectors

Biobanks and Biomarker Discovery and Validation

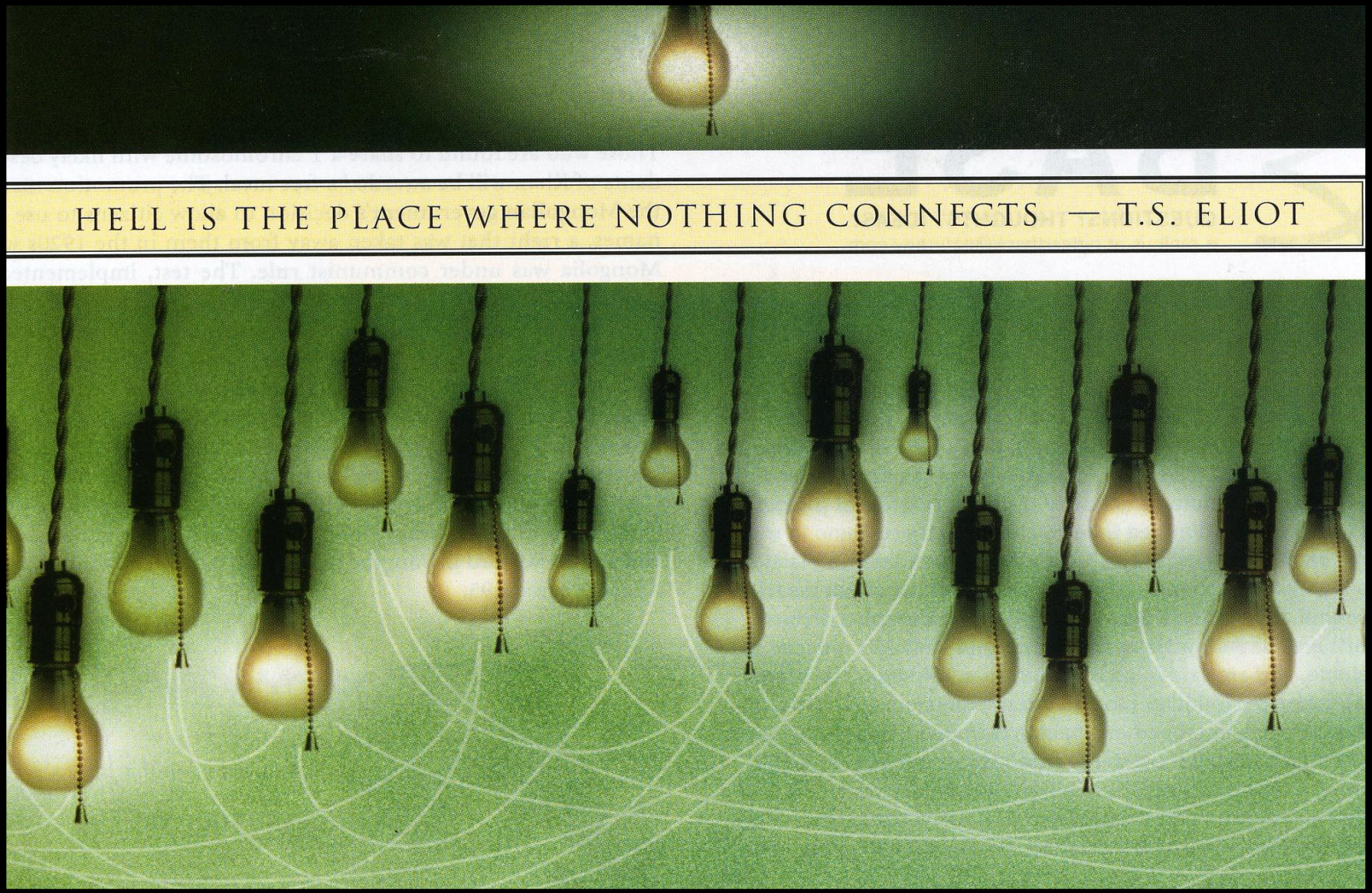
"Biobanking is a gift and
a partnership between patients
and medical science"

Dr. David Kerr,
Professor of Clinical Pharmacology
and Cancer Therapeutics, University of Oxford

"Patients must be assured that
their tissue gifts will be dedicated
to advancement of medical science."

Dr. Fortunato Ciardiello
Professor of Oncology,
Seconda Universita di Napoli

Silos Subvert Solutions



From Silos to Systems-Based Strategies

- extravagant waste of uncoordinated, fragmented research
- fragmentation reinforced by anachronistic government funding policies
- insufficient interdisciplinary leverage of convergent technologies (academia and industry)
- inadequate standards for molecular profiling data
- systemic deficits in electronic connectivity in healthcare as major obstacle in integration of molecular profiling with disease patterns and treatment outcomes
- inadequate market incentives for integration of Dx, Rx and Ix products/services and healthcare delivery

Adapting to the Scale and Logistical Complexity of Translational Medicine

- single investigator awards and incremental (at best) progress → high risk, high reward projects with prospect of radical, disruptive innovation
- single discipline focus → obligate assembly of diverse expertise for multi-dimensional engagement
- funding agencies ill-prepared to review inter-/cross-disciplinary research → new study sections with broader expertise, including industrial experience
- ‘islands’ of individual datasets with minimal standardization, diverse ontologies and poor inter-operability → large scale, standardized, inter-operable open-source databases with professional annotation, curation and analytics

Forging the Complex Interactions Required to Build a Productive Translational Medical Research Capacity

Academia

- cross-disciplinary education and training
  - mathematical and computational biology
  - complex systems design and optimization
  - status of translational medicine as legitimate research domain
- reform of the medical curriculum
- incentives and career structure

Coordination of the Complex Interactions Required to Build a Productive Translational Medical Research Capacity

Government

- reform current CTSA awards for obligate assembly of full expertise spectrum and obligate industry participation
- promulgation of standards and centralized orchestration of resources (national/international)
  - biorepositories and biospecimens
  - ‘omics’ analytics reference standards
  - informatics platforms (BIX, HIX)
  - ID/recruitment of, relevant case:control patient cohorts
- proactive design of regulatory frameworks to address new technologies
  - complex multivariate assays
  - remote health monitoring
  - review process for combination products
  - new CER tools/metrics

Forging the Complex Interactions Required to Build a Productive Translational Medical Research Capacity

Industry: Products and Services

- greater recognition of value and participation in pre-competitive, open-source networks/consortia
  - drive standards
  - defray risk
  - broaden partnerships
- more proactive role in shaping new trans-disciplinary education/training/employment opportunities
  - translational medicine
  - large scale dbase analytics
  - new analytics/models for non-linear dynamics in complex systems
  - health economics outcomes/systems modeling

Publication Standards

- full disclosure as prerequisite for replication and evidence-based meta-analytics
- increasing omission of key ‘methodological data’ as handicap to meta-analytics
- burgeoning ‘supplemental sections’ to papers but myriad critical omissions persist
- pervasive end-to-end problem: from sample to answer
  - biospecimen acquisition, handling
  - pre-analytical and analytical methods, data analysis and databanks
  - QC/QA of multiplex assays/equipment
  - trial design(s)
- role of professional societies, publishers and payors in raising the evidentiary bar?
  - CONSORT, REMARK, STARD, STROBE, MIAME loc.cit

Forging the Complex Interactions Required to Build a Productive Translational Medical Research Capacity

Culture

- courage
  - to declare that major change is needed versus safe refuge of status quo
- heavy lifting
  - engagement will impose great demands without immediate short-term benefit(s) to individuals/institutions
- integrity
  - hope, hype, overselling and hubris
  - with patients (current and future)
  - with next generation of researchers (competency and competitiveness)
  - with investors (public and private sectors)

Sustainable Health: Societal and Individual
The Complex Path to Proficient, Personalized Healthcare

- the potential economic and health benefits from biosignature diagnostic profiling transcend any other current category of healthcare innovation
- realization of this objective will require radical changes in the organization and funding of biomedical research
- three parameters: specimens, scale and standards are fundamental to achieving tangible progress in comprehending disease pathogenesis, improved diagnosis and rational Rx selection

Sustainable Health: Societal and Individual
The Complex Path to Proficient, Personalized Healthcare

- realization of this potential will depend not only on technological advances but equally on circumvention of entrenched cultural, institutional and economic interests in sustaining the status quo
- moving from silos to systems

DISRUPTIVE INNOVATION DEMANDS BOLDNESS