ASU Complex Adaptive Systems Initiative
Arizona State University

The Evolution of Personalized Medicine: Opportunities and Challenges

Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative
and Professor of Health Innovation, Arizona State University
george.poste@asu.edu
www.casi.asu.edu

Roland W. Frei Lecture
27th Montreux Symposium on LC/MS
Montreux, Switzerland, 10 November 2010

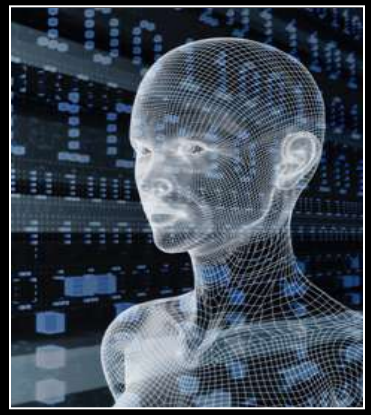
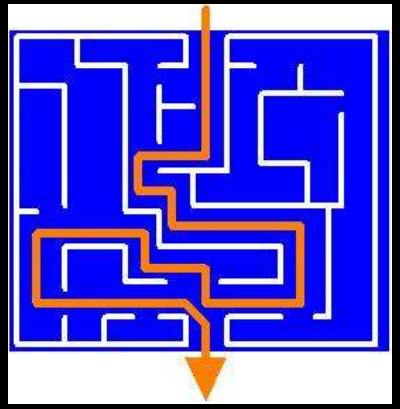
ASU Complex Adaptive Systems Initiative
Arizona State University

Slides available @ www.casi.asu.edu

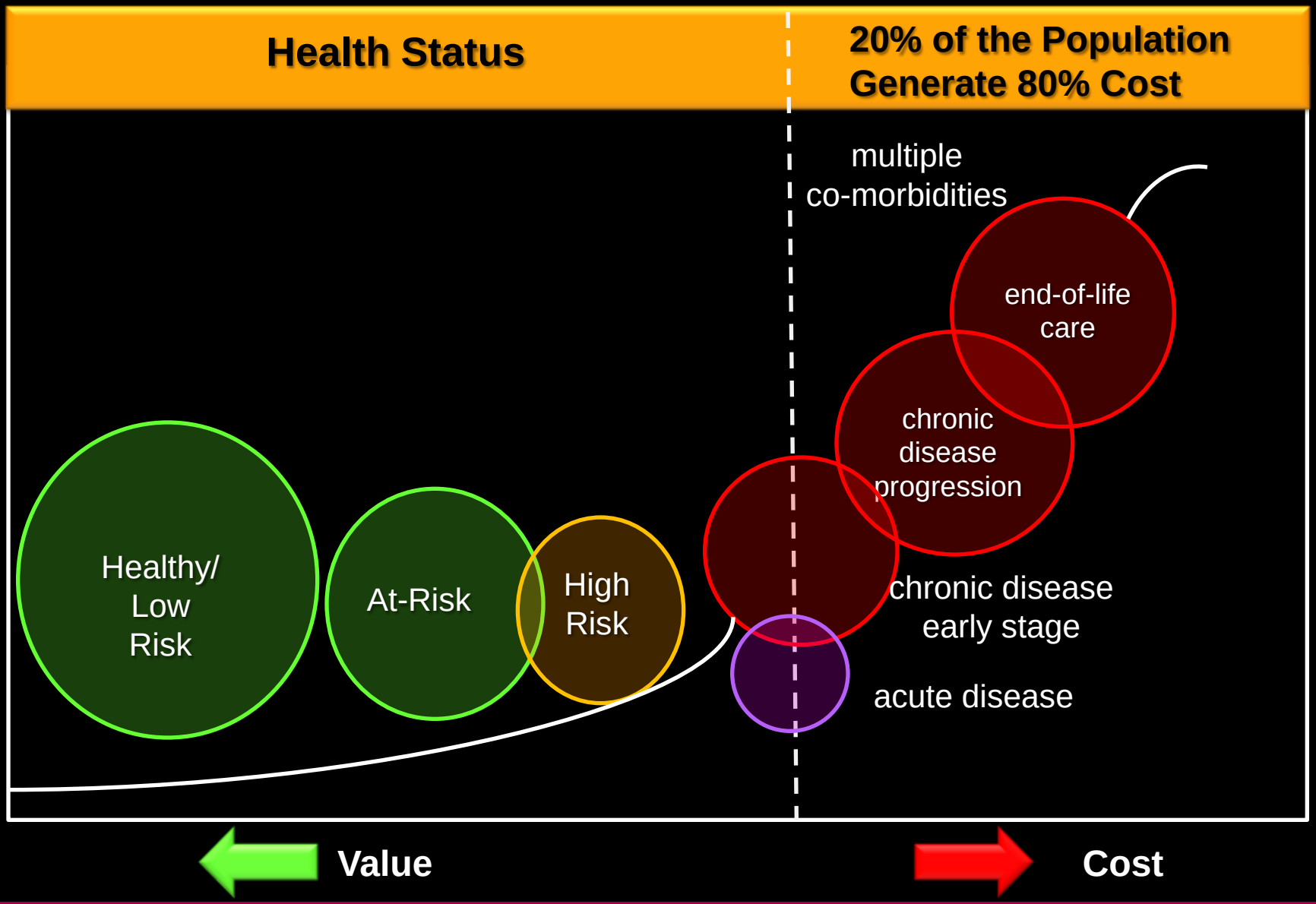
Declared Interests:

- Board of Directors: Monsanto, Exelixis, Caris Life Sciences
- Scientific Advisory Board: Synthetic Genomics, Anacor

Challenges for Healthcare Delivery Systems

Cost	Demographics	Chronic Diseases	Life Style Disease
			
			
Inefficent use of Information	**Fragmented, Compartmentalized Services**	**Protracted Adoption of Best Practices**	**Subsidiarity and Policy Complexity**

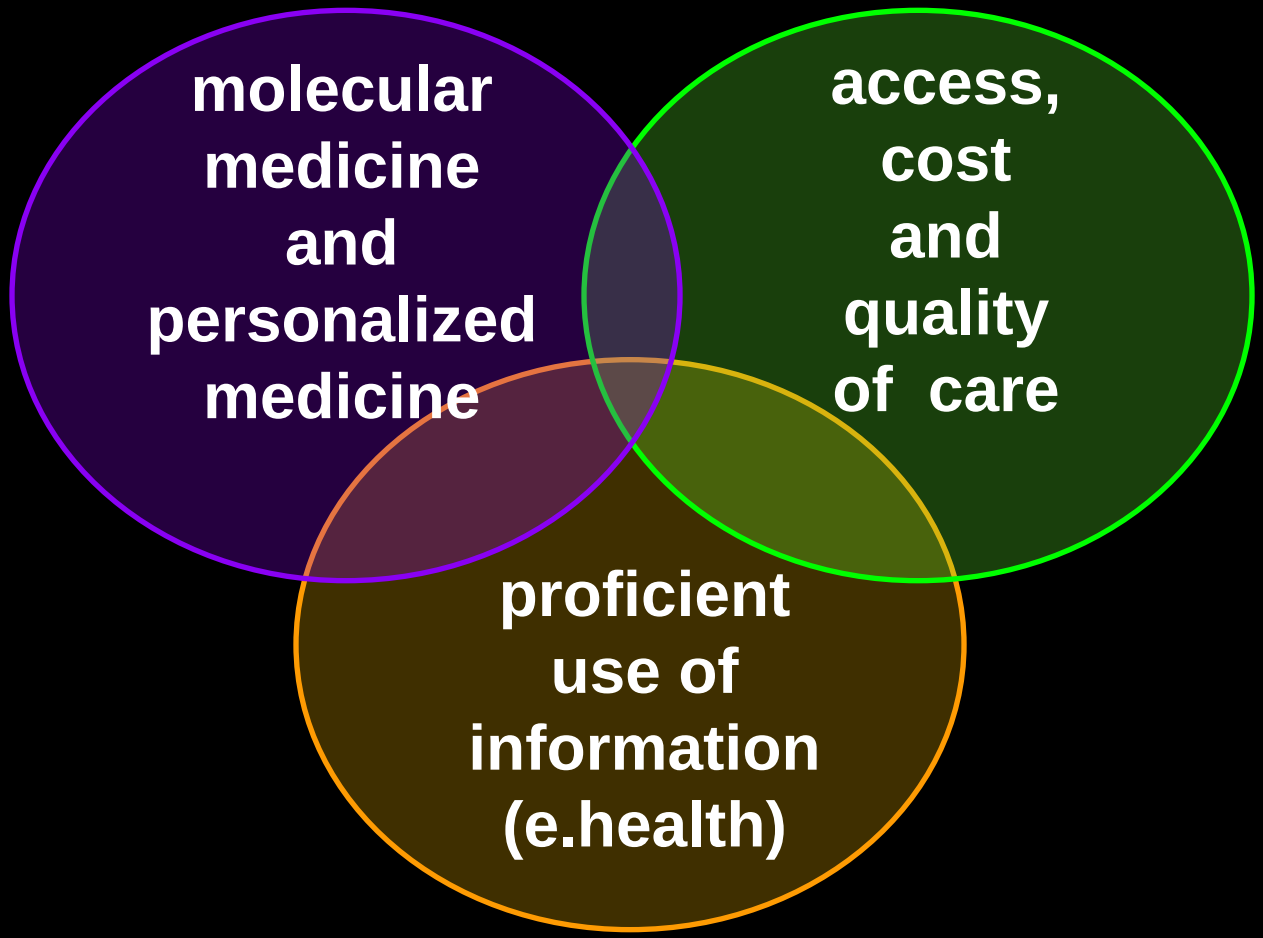
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities



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
  - prospering in an era of increasing constraints
  - managing the limit(s) of society's willingness and ability to pay for innovation

The Three Convergent Forces Shaping the Evolution of Healthcare



VALUE

The Waste and Risk of Empirical Rx: Ignoring The Obvious in Clinical Practice

- diseases are not uniform
- patients are not uniform
- a “one-size fits all” Rx approach cannot continue

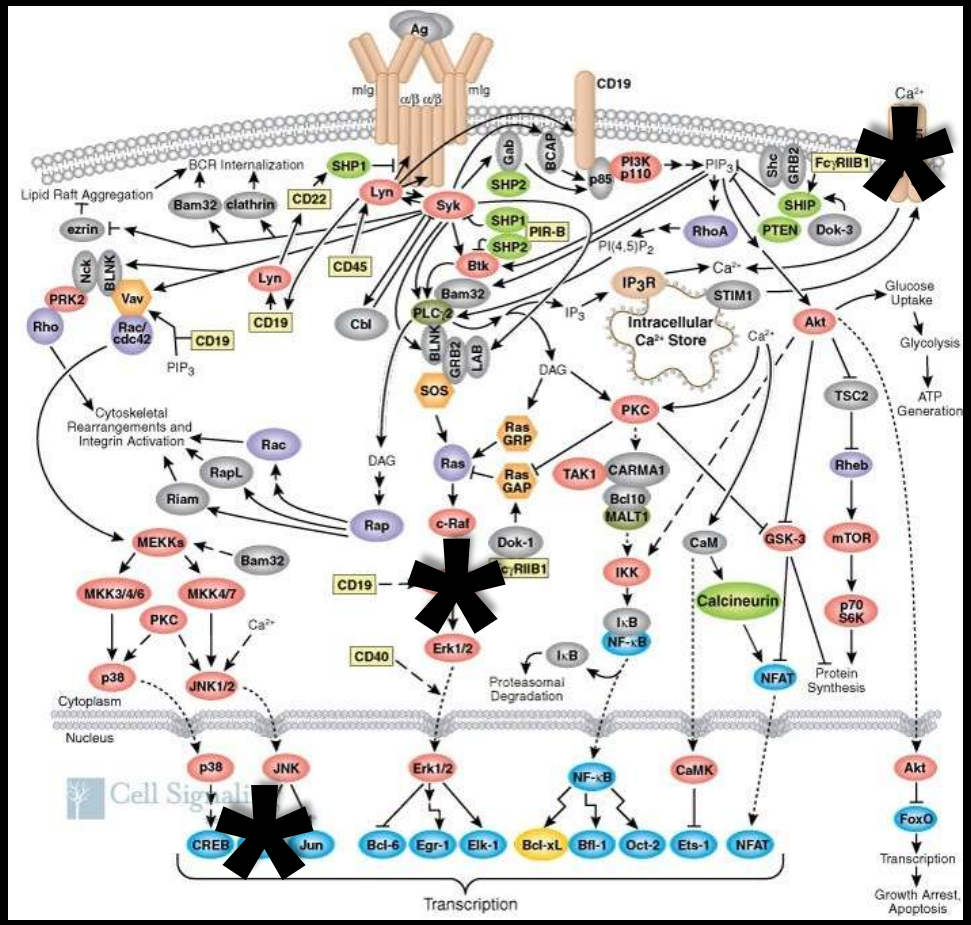
- inefficiency and waste of empirical Rx
- cost of futile therapy
- medical error and adverse events (AEs)

Defining A New Taxonomy for the Diagnosis and Classification of Disease

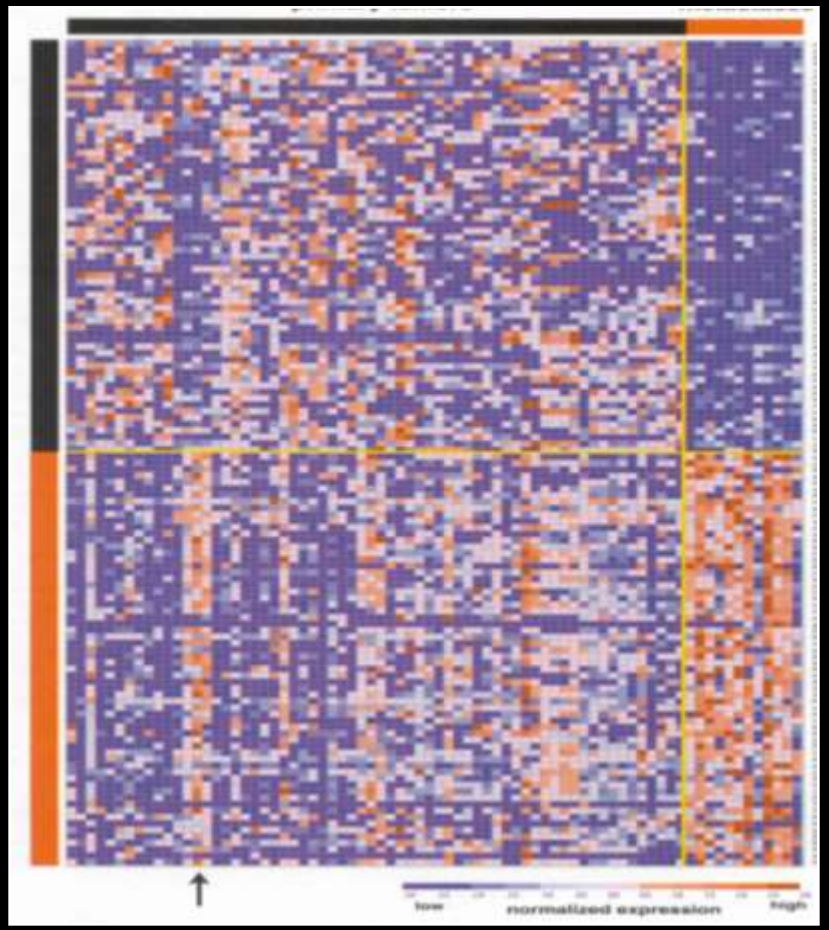
- redefining pathology as the deregulation/dysregulation of specific biological pathways
- disease with similar symptoms can arise in the same cell type via different patterns of pathway dysregulation
  - different points in the same biological pathway
  - multiple points in connected biological pathways
- 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

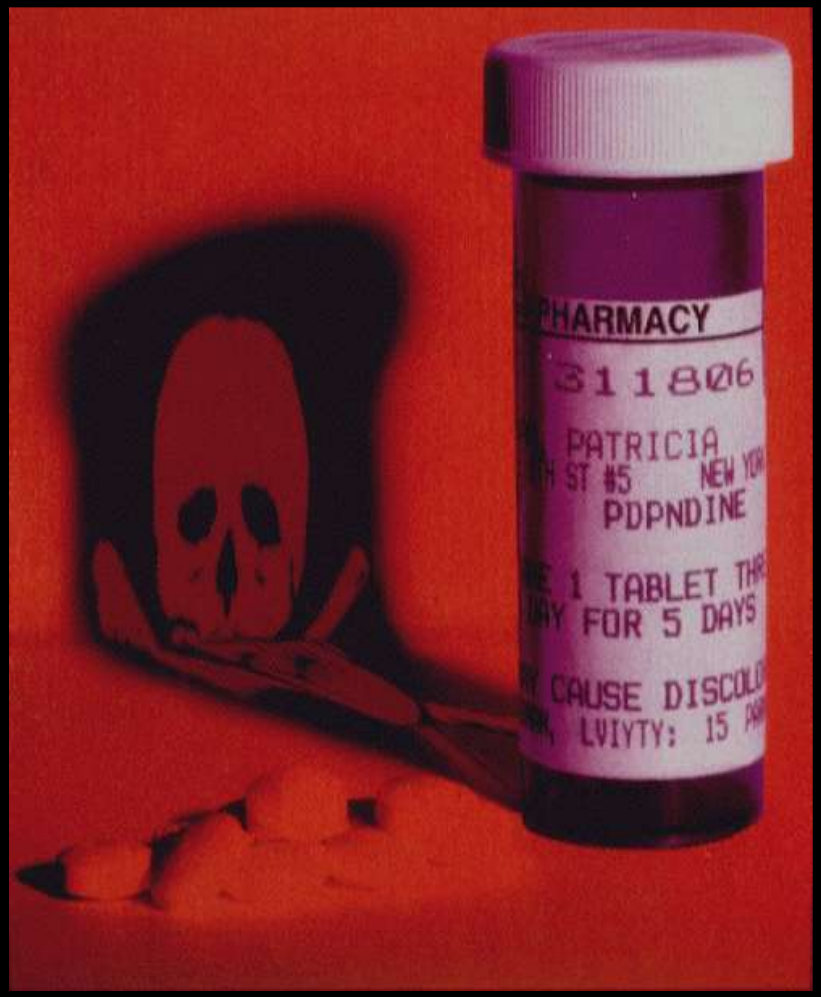
- higher response in patients with K-RAS versus mutant-K-RAS
- estimated $604 million/year savings (ASCO)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

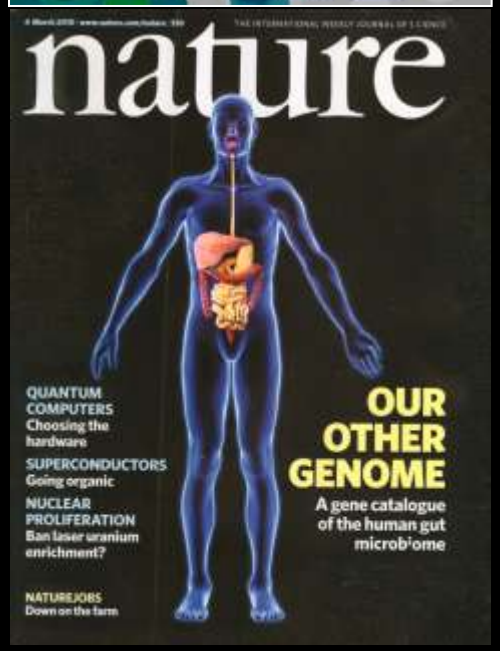
- regulatory endorsement in product labeling

From Pharmaceuticals to Pharmasuitables: The Right Rx for the Right Patient



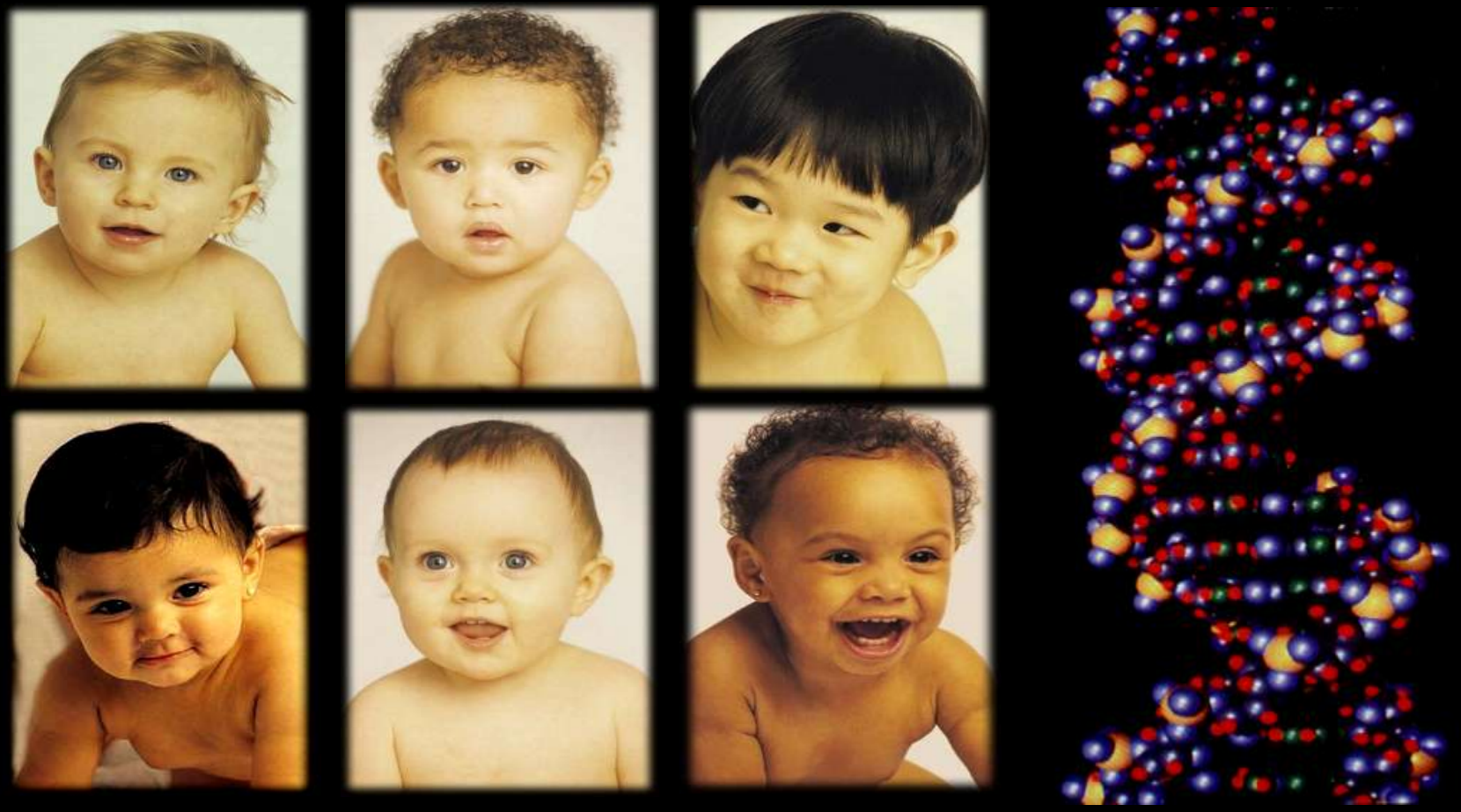
- Rx adverse events (AE) as major source of injury and death
- AEs due to genetic variation in drug transport and metabolism systems
  - fast and slow metabolizers
- AE due to drug interactions
  - action of one Rx in inhibiting metabolic capacity to handle second drug
- AE due to Rx and OTC drugs/supplements
  - latter not tracked

We Are Not Alone:
The Human Microbiome – A Barely Understood Factor in Human Health and Disease



- human body contains 10x more bacterial cells than human cells
- complex meta-system
  - host, microbes, viruses, other organisms, metabolites, xenobiotics
  - is there a core microbiome?
  - how do perturbations affect disease and vice-versa?
  - does the microbiome influence xenobiotic metabolism and the metabolite spectrum?

The Hunt for Gene Loci Associated with Complex Human Diseases



Disease Predisposition Risk Profiling for Common, Multigenic Late-Onset Disorders

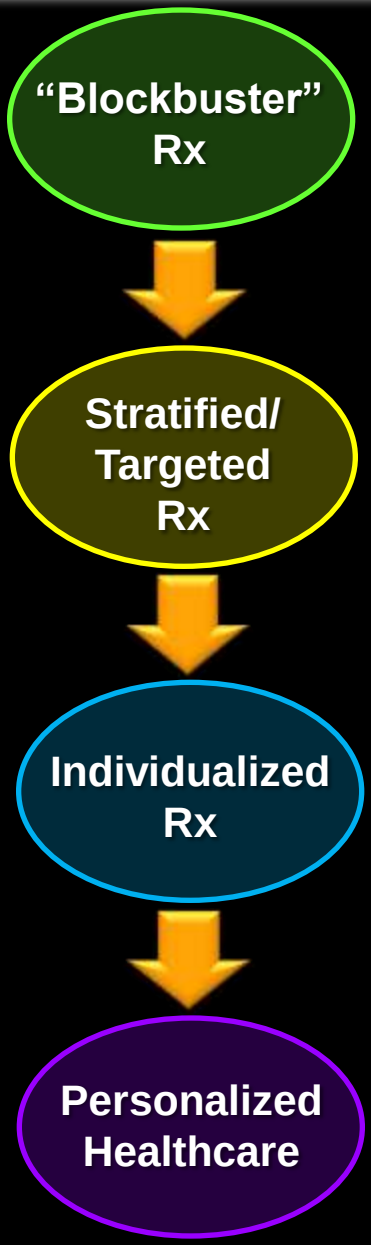
- slower evolution than many predict
- Genome-Wide Association Studies (GWAS)
  - high cost and to date low yield in terms of clinically exploitable markers
  - disease origins from multiple low penetrance alleles versus small set of high penetrance alleles
- substantial ambiguities regarding probabilistic risk of overt disease
  - epistasis
  - epigenetics
  - environmental confounders, including Rx

Disease Predisposition Risk Profiling for Common, Multigenic Late-Onset Disorders

- slower evolution than many predict
- Genome-Wide Association Studies (GWAS)
  - high cost and to date low yield in terms of clinically exploitable markers
  - disease origins from multiple low penetrance alleles versus small, dominant set of high penetrance alleles
- substantial ambiguities regarding **probabilistic risk** of overt disease
  - epistasis
  - epigenetics
  - environmental confounders, including Rx

The premature quest to provide consumer genomic testing (CGx) for future risk of major diseases

The Progressive Evolution of Personalized Healthcare



- empirical "one-size-fits-all"
- population-based Rx

- Rx targeted to patient subgroups with same molecular pathology
- Dx-Rx combinations and Rx labeling

- individualized Rx
  - relevant disease subtype and AE risk profiling
  - identification and mitigation of disease predisposition risk(s)

- integrated framework of coordinated care and longitudinal care

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

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

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, Biosignatures and Molecular Profiling of Human Diseases

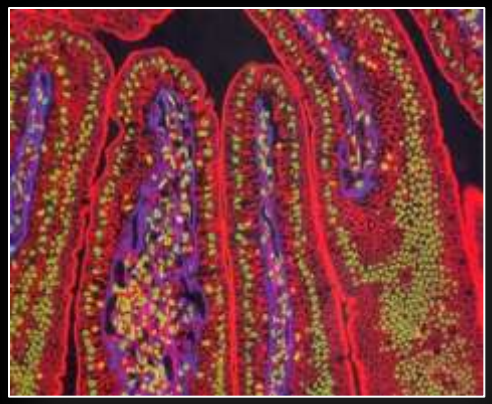
Agnostic

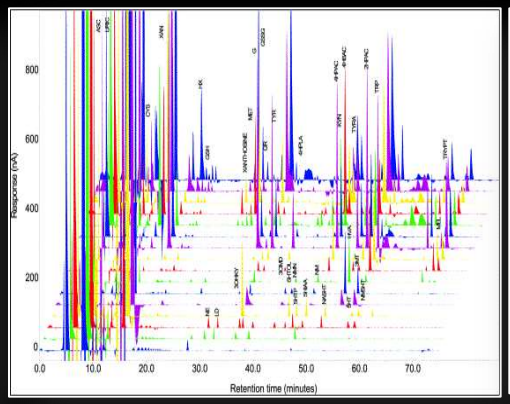
- analytes
- analytical platforms

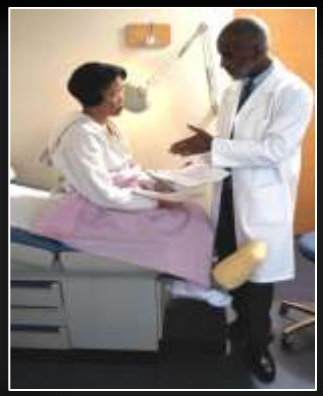
Success Determinants

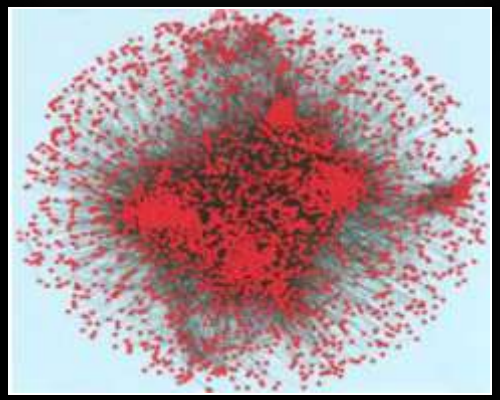
- systems-based strategies
- standards/ standardization
- subjects
- specimens
- scale
- sociology

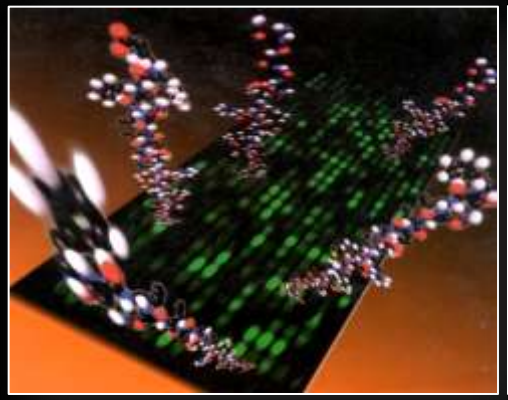
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches

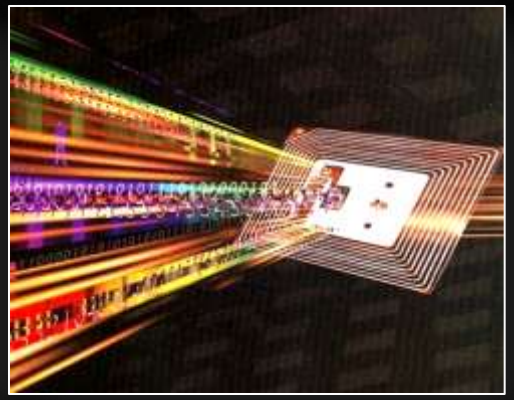












Biospecimens and Molecular Pathway Analysis

Biomarker Validation and Multiplex Assays

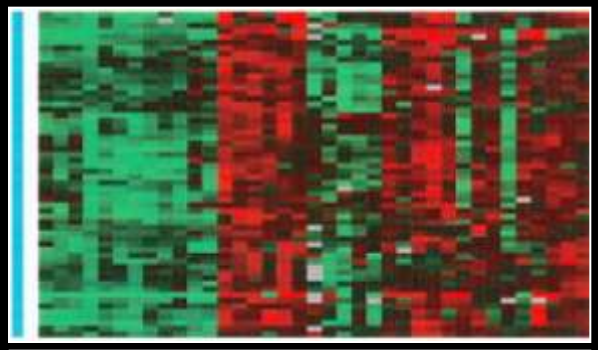
Instrumentation and Informatics

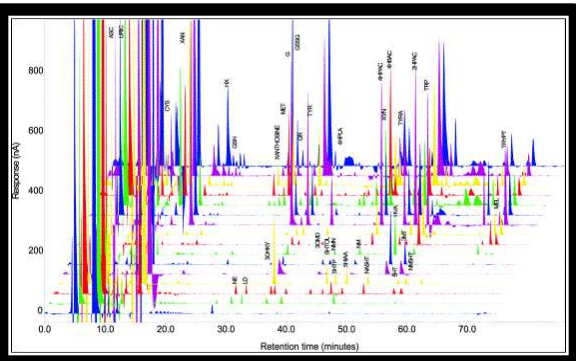
Clinical Impact and Patient Monitoring

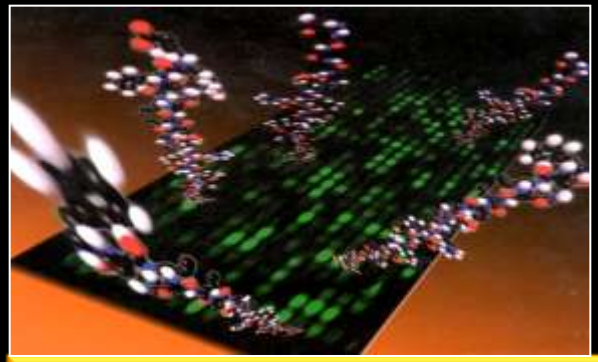
Molecular Diagnostics and Miniaturized Devices: A Key Future Driver in the Healthcare Value Chain

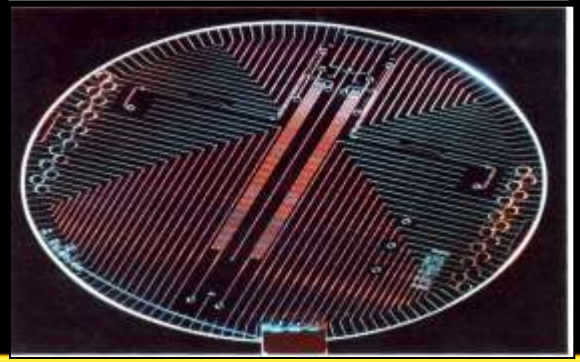
Complex Biosignature Profiling

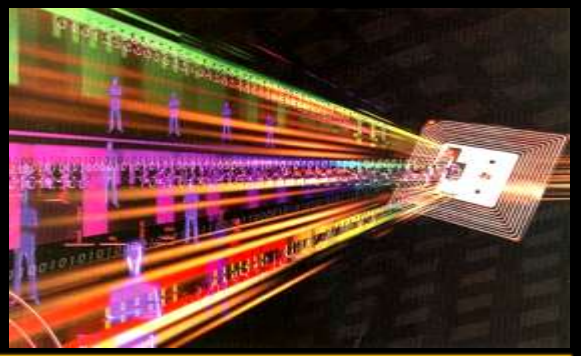
genomics	proteomics	immunosignatures











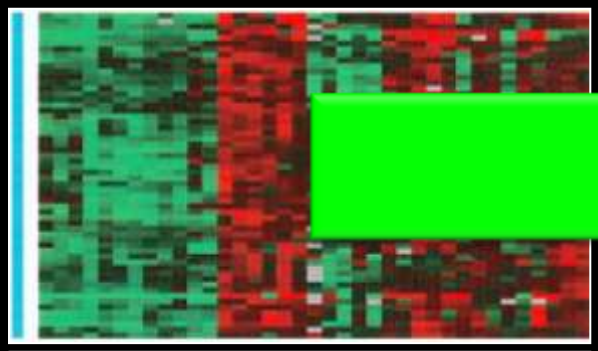
Signature Detection, Deconvolution and Multivariate Analysis

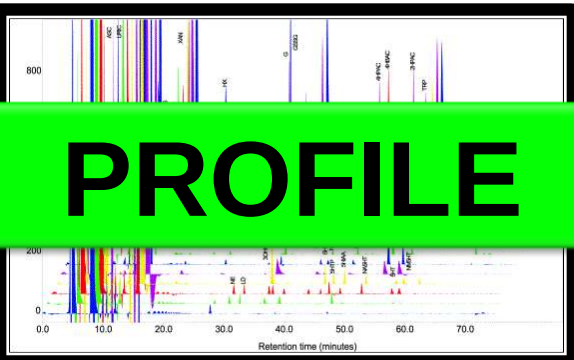
automated, high throughput multiplex assays	novel test formats and devices (POC)	new algorithms for complex signal deconvolution

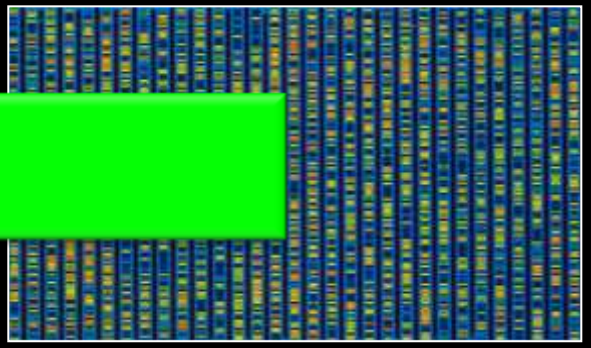
Molecular Diagnostics (MDx)
The Convergence of Molecular Biology, Engineering and Computing

Complex Biosignature Profiling

genomics	proteomics	immunosignatures







PROFILE

SENSE

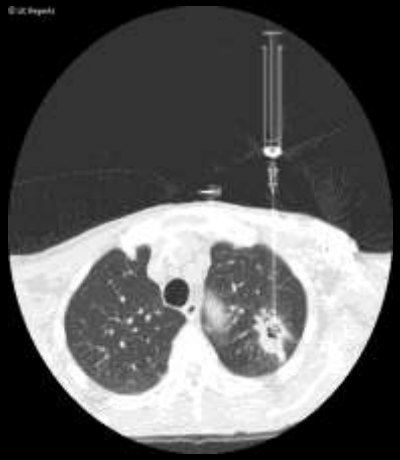
ACT

Signature Detection, Deconvolution and Multivariate Analysis

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

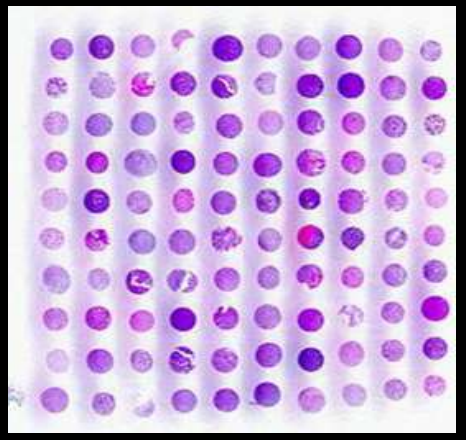
Rigorous Selection of Specimen Donors and Specimen Collection

standardized clinical phenotyping and annotated health records and outcomes



challenge of obtaining fresh tissue

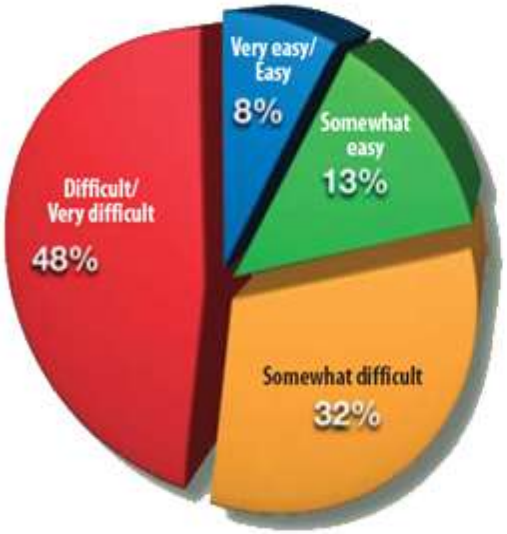
poorly standardized tissues and erratic availability



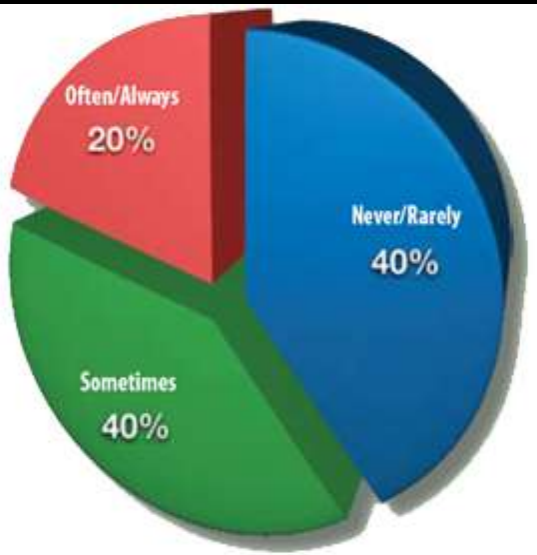
variable value of legacy tissue blocks and consents

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

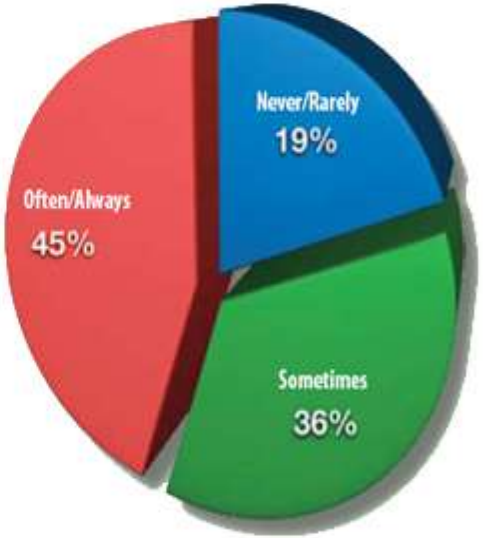
Ease of Acquiring the Quality of Biospecimens



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/

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

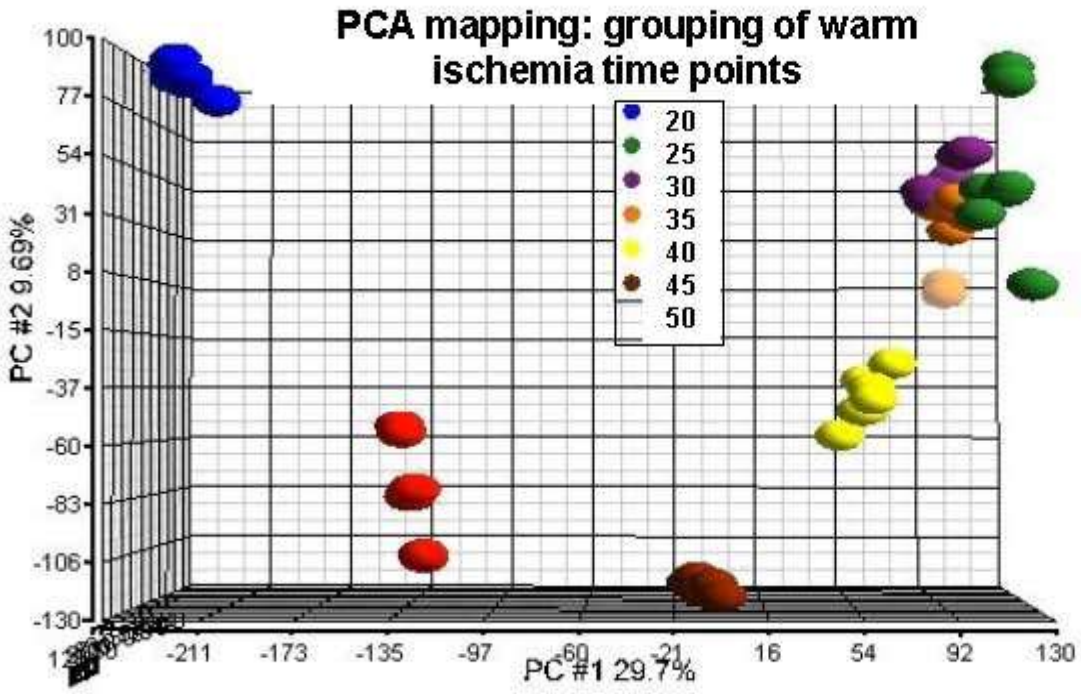
Post-Sampling

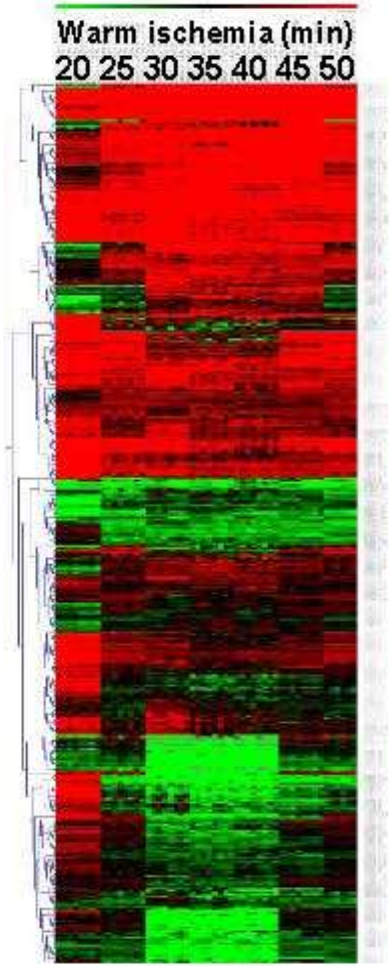
- room temperature
- time at room temperature
- rate of freezing
- fixative type and time in fixative
- collection container(s)
- biomarker extraction methods
- storage conditions
- transport conditions

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

"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 Cancer Institute
'I0M, July 2010'

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

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

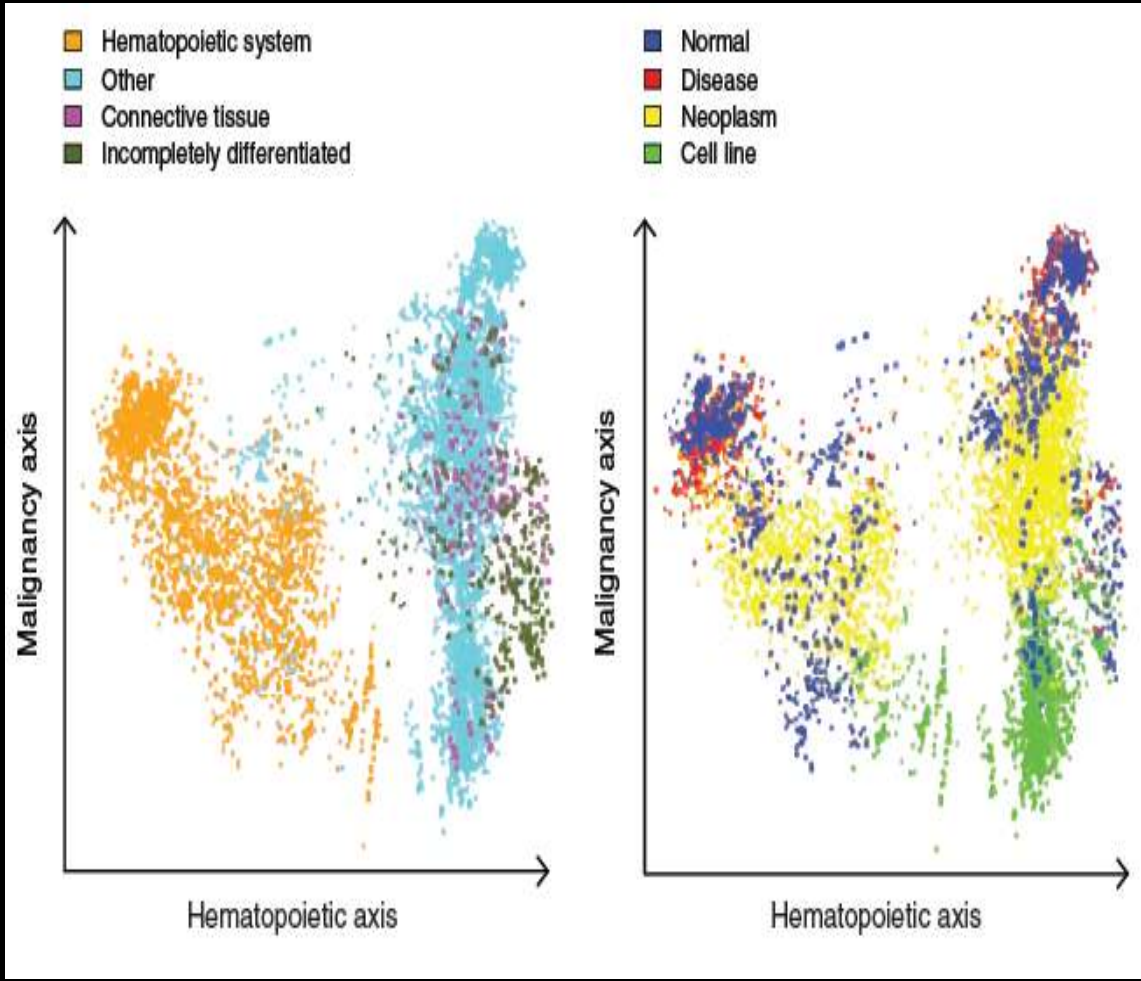
“Medline search reveals that more than 80% of cancer and molecular biologists still use two-dimensional techniques”

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?

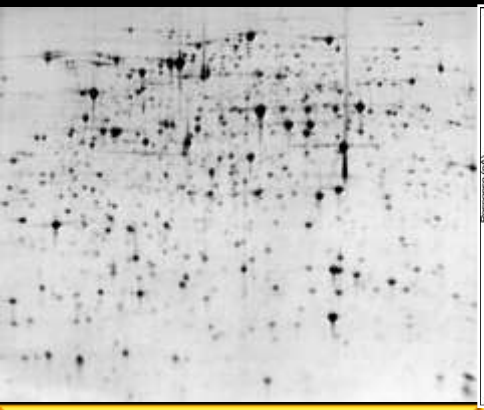
A Global Map of Human Gene Expression
M. Lukk et al. (2010) Nature Biotech. 28, 322



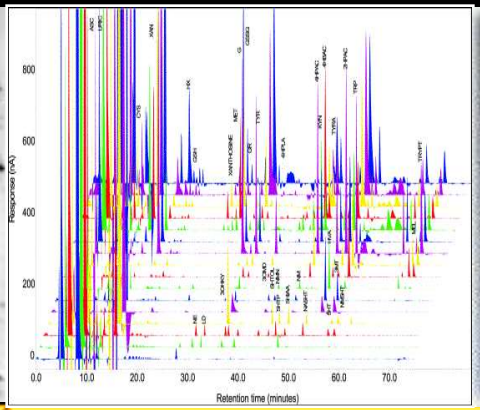
http://www.ebi.ac.uk/gxa/array/U133A

- 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

Challenges for Proteomics Platforms for Applications in Clinical Diagnostics



2-D Gels

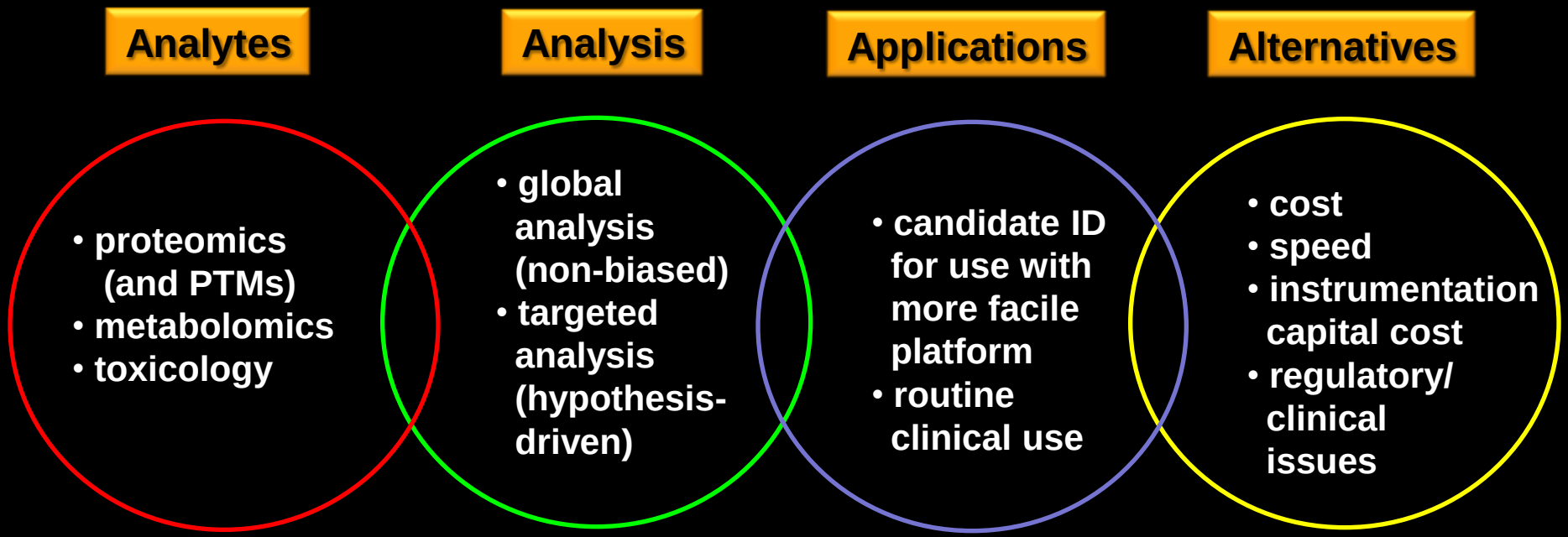


Mass Spec.

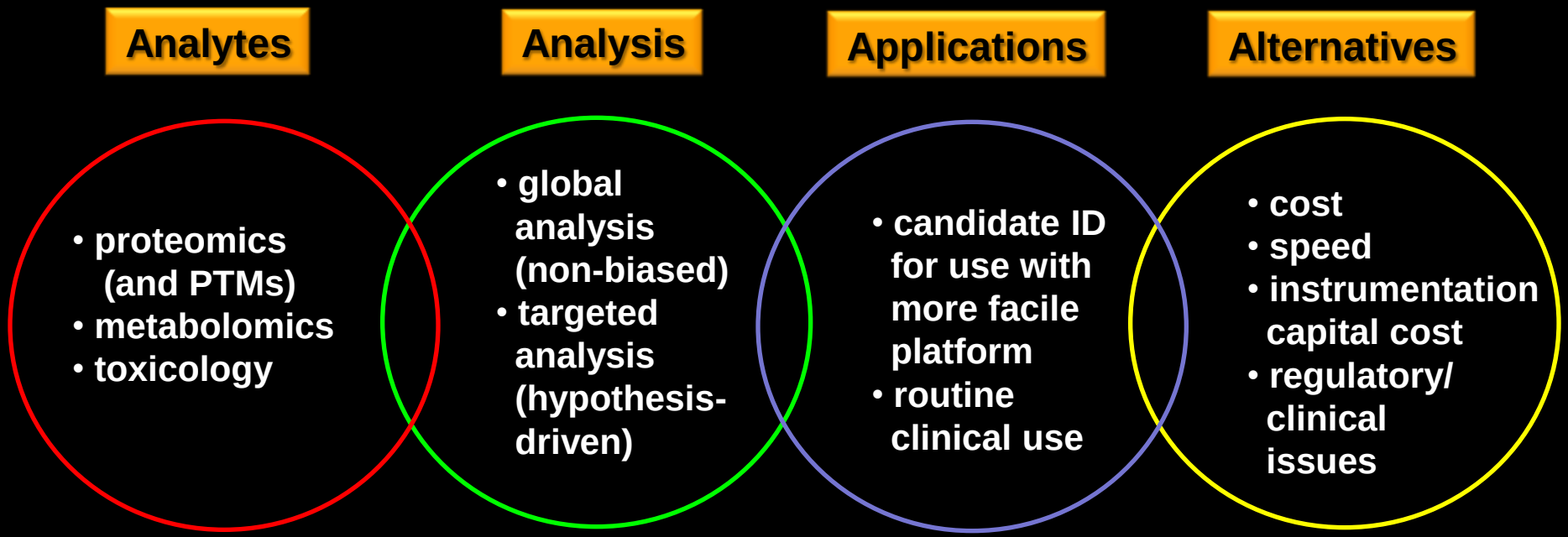
ELISA Assay

Immunosignatures

LC:MS-Based Platforms for Biomarker and Biosignature Profiling



LC:MS-Based 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

Sample Complexity and Dynamic Range in MS-Based Proteome Analysis

- formidable dynamic range of analyte abundance
- detection of low abundance species
- femtomol or attomol 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.

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

Databases and Data Matching for “Shotgun” MS-Based Proteomics

- chaotic legacy of multiple nomenclature identifiers for human proteins
- urgent imperative for standardized ontologies and software search engines
- disparate databases and success rates for automatic mapping across databases rarely reaches 95%
- HUPO Proteomics Standards Initiative proposal
- neXtProt: gene-protein centric proteome annotation scheme
- ProteomeXchange consortium as parallel repository for raw MS data

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

The Open Biomedical Ontologies

Cell Ontology (CL)

Gene Ontology (GO)

Foundational Model of Anatomy

ZFIN

Zebrafish Anatomical Ontology

Chemical Entities of Biological Interest (ChEBI)

Disease Ontology (DO)

Plant Ontology (PO)

Sequence Ontology (SO)

Ontology for Clinical Investigations (OCI)

The Open Biomedical Ontologies

Common Anatomy Reference Ontology

The Open Biomedical Ontologies

Environment Ontology

Ontology for Biomedical Investigations

Phenotypic Quality Ontology (PATO)

Protein Ontology (PRO)

OBO Relation Ontology

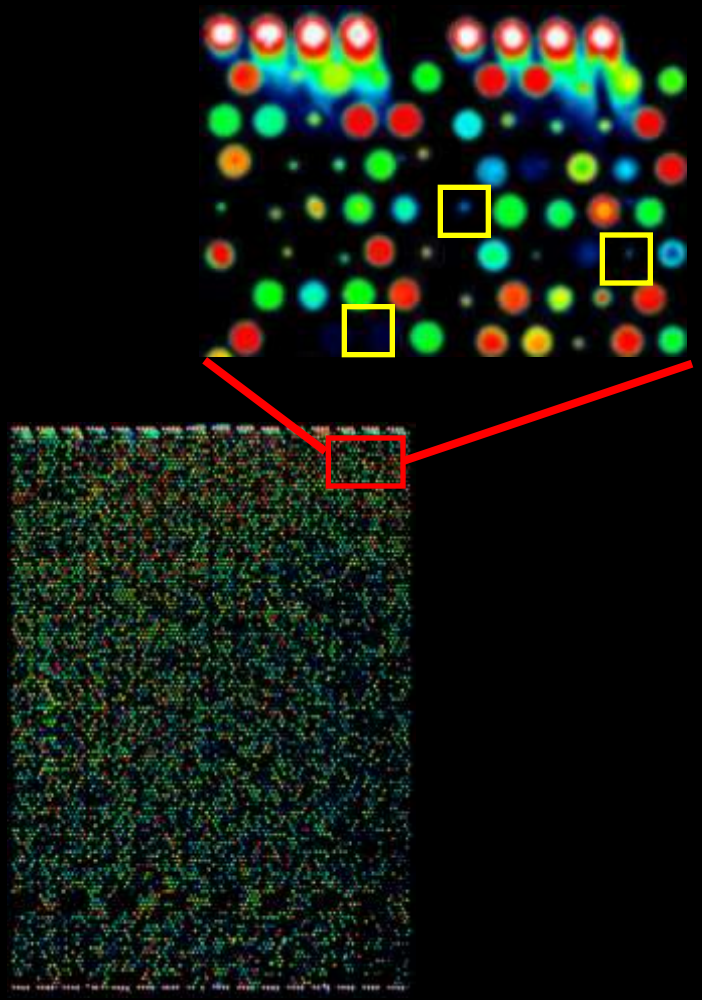
RNA Ontology (RnaO)

BioPAX.org

The Value of Blood-Based Diagnostic Profiling

- minimally invasive
- blood bathes all organs
- organ-specific ‘biosignatures’ detectable in blood
- facile routine tracking of disease progression and Rx responsiveness
- value of highly stable biomarkers for retrospective studies to correlate with clinical outcomes
- Point-of-Care (POC) testing
- repeated testing/longitudinal profiling versus feasibility/cost/trauma of repeated biopsies

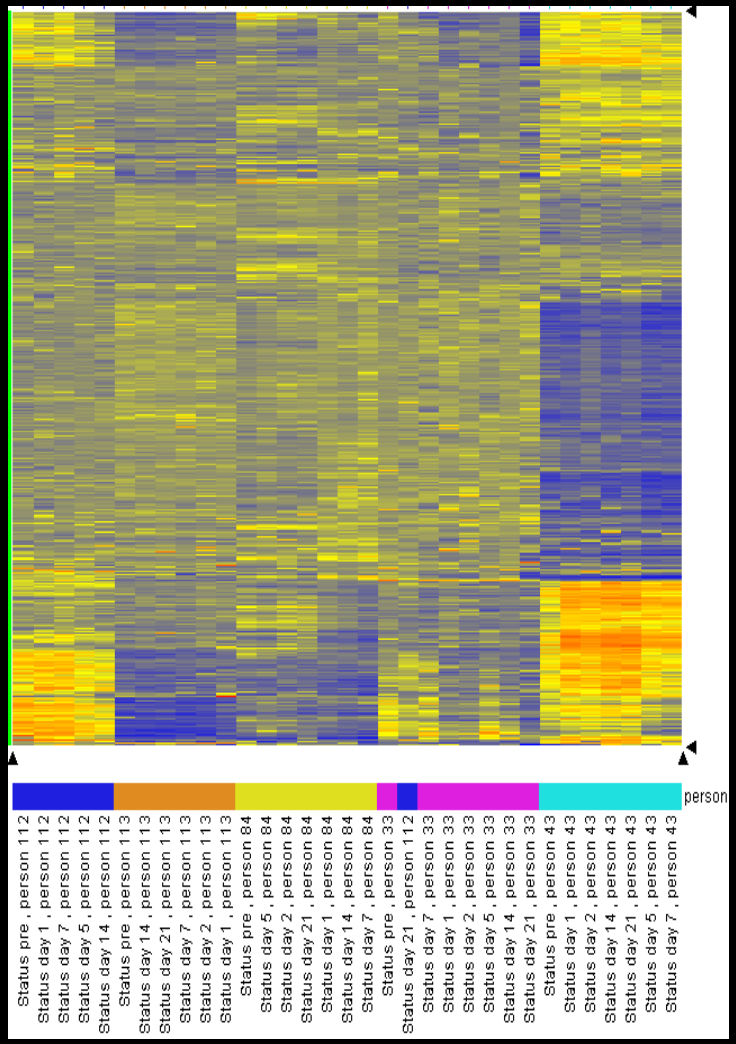
Immunosignatures:



Courtesy Dr. S. Johnston, Biodesign Institute, ASU

- large scale arrays of random peptides (12-20 mers)
- consistent patterns of binding antibodies (polyclonal immunoglobulins and specific monoclonals)
- high throughput dynamic analyses of antibody profile in individual people/animals
  - autoantibodies
  - immune response to infectious diseases and vaccination
  - early pre-symptomatic disease detection

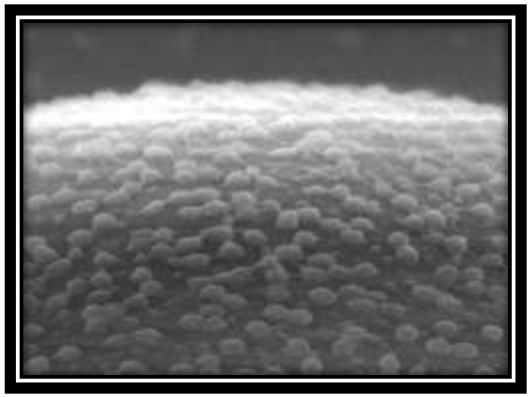
Immunosignatures

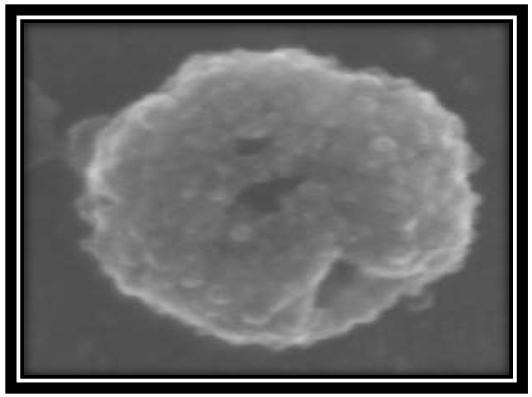


- five healthy individuals sampled across 21 days show consistent pattern
- note that individuals differ from each other
- this difference disappears whenever multiple persons have the same illness (e.g., influenza)

Courtesy Dr. S. Johnston,
Biodesign Institute, ASU

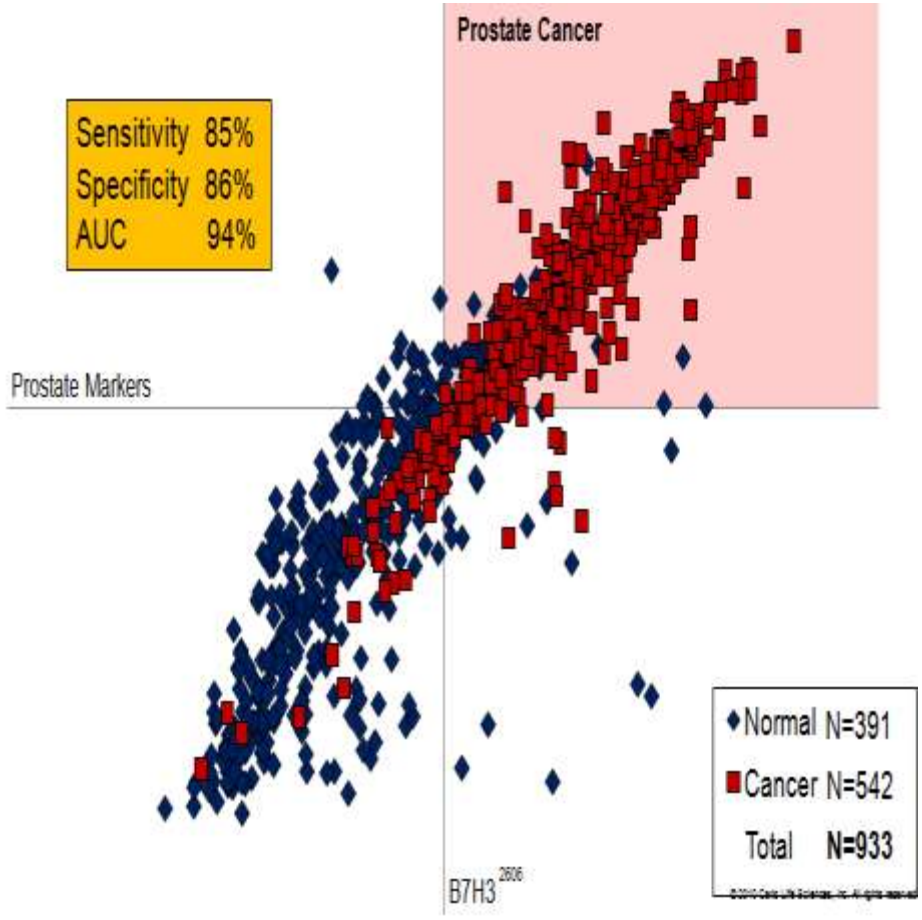
Capture and Biosignature Profiling of Microvesicles

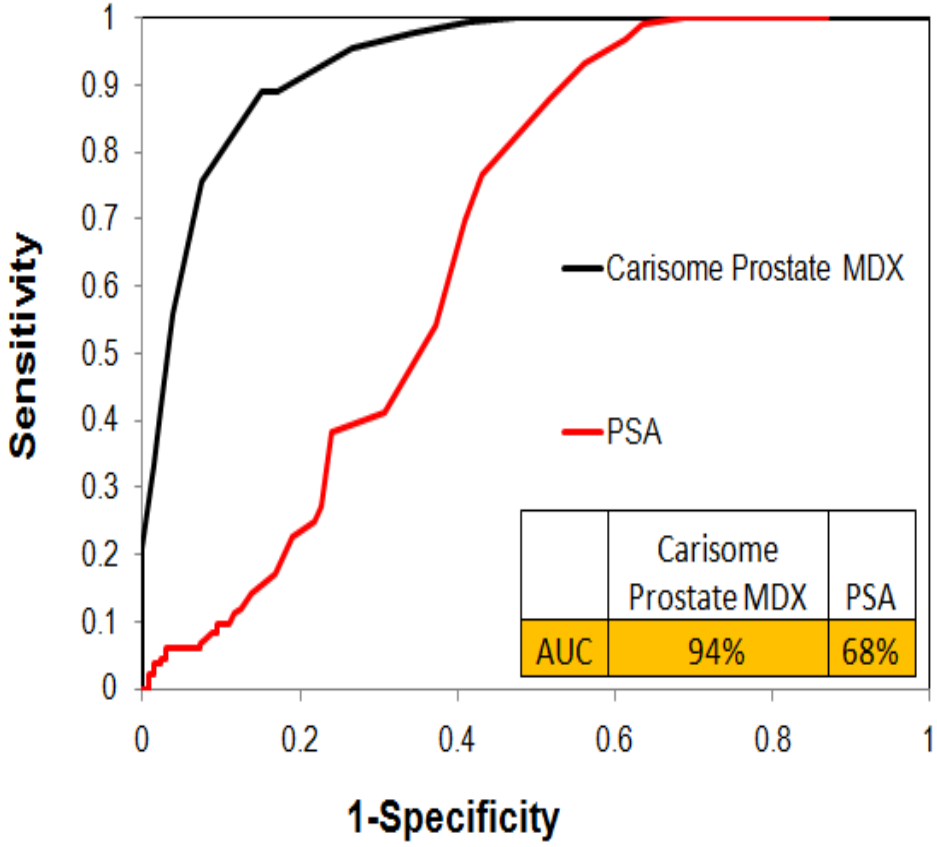




- released by normal and diseased cells
  - 0.03-1.0 micron diameter
- Upto x 4 greater levels in cancer patient plasma smaples
- role in inter-cellular communication
  - immune responses, (stimulation and suppression)
  - epithelial-mesenchymal transition in cancer
- protein markers (membrane)
  - identification of cell of origin
  - novel disease-associated markers
- miRNA and mRNA (intravesicular cargo)
  - novel disease-associated profiles

Carisome™ Prostate MDx 1.0 Diagnostic: A Significant Performance Improvement Over PSA





Microfluidic Paper-Based Analytical Devices (µPADs)

DIAGNOSTICS FOR ALL

Our first project, funded in part by the Bill and Melinda Gates Foundation, is a low cost, point-of-care diagnostic device for measuring liver function – critical for monitoring the adverse side effects of the powerful drugs used to treat HIV/AIDS and TB, and for managing the effects of viral hepatitis.

ABOUT DFA
THE TECHNOLOGY
PROJECTS
NEWS
RESOURCES

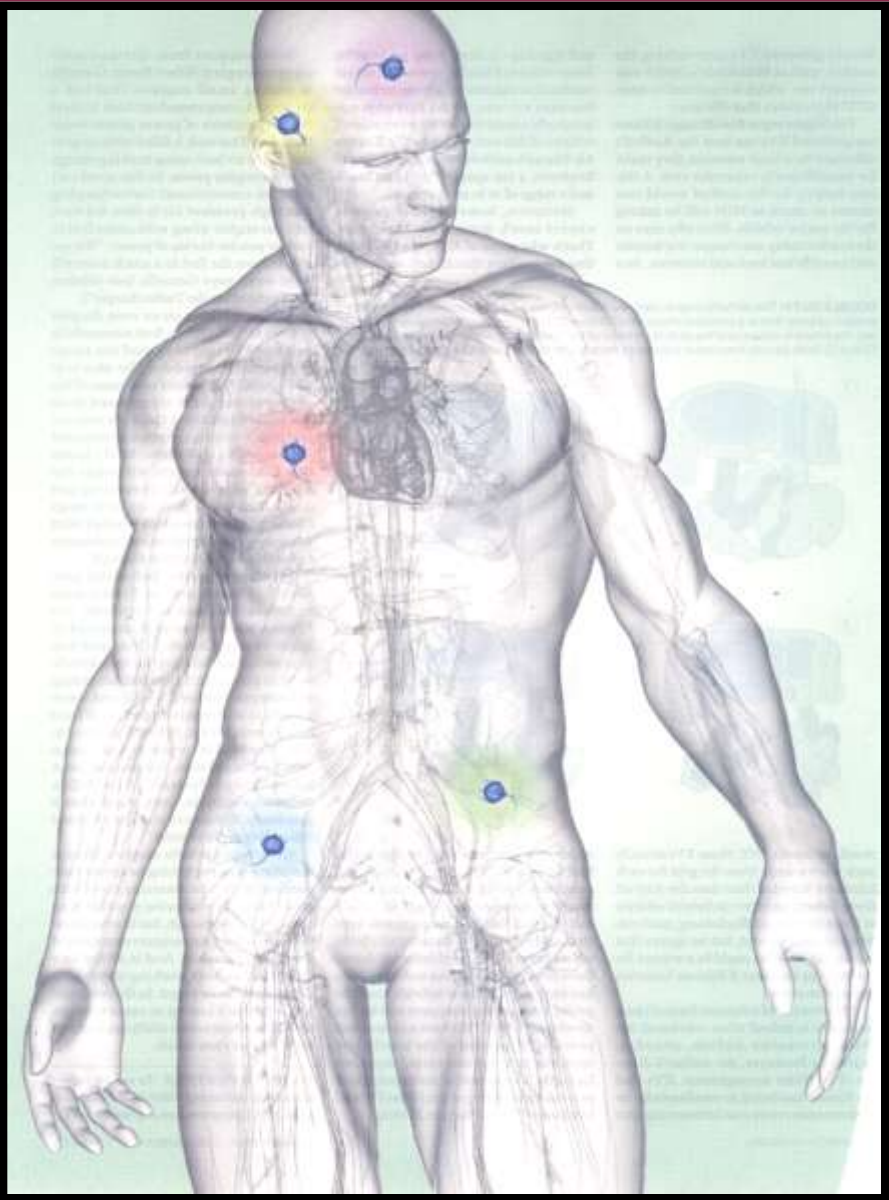
DFA is building on elegantly simple technology developed in the Harvard laboratories of George Whitesides – game-changing technology for delivering medical care in the developing world.

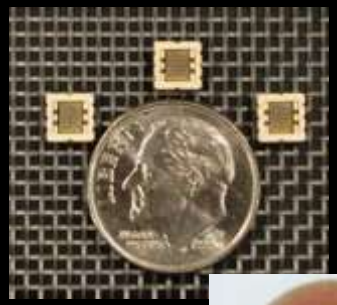
SUPPORT OUR MISSION>

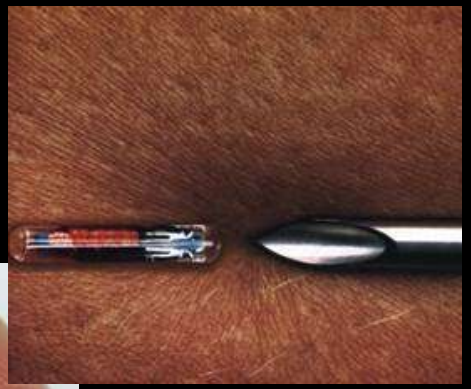
Remote Health Status Monitoring

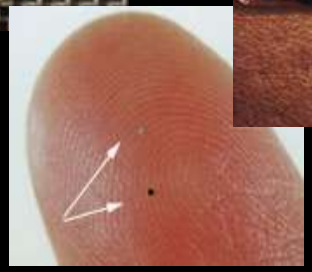
Biosignature Profiling Via Sensors and Devices

On Body: In Body Sensors/Devices: Real Time and Remote Monitoring of Individual Health Status

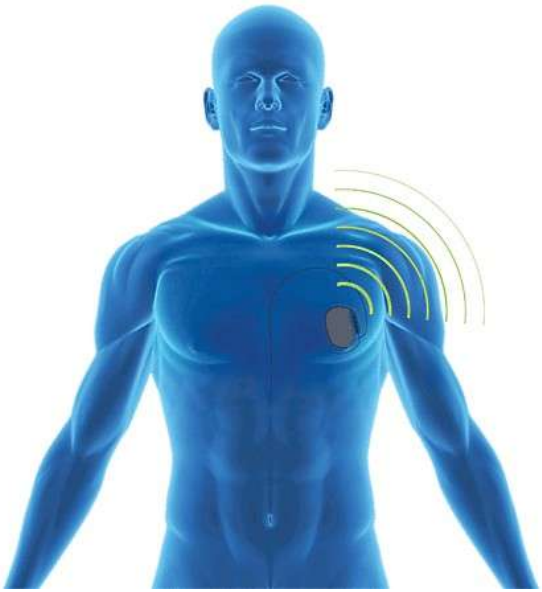








m.Health

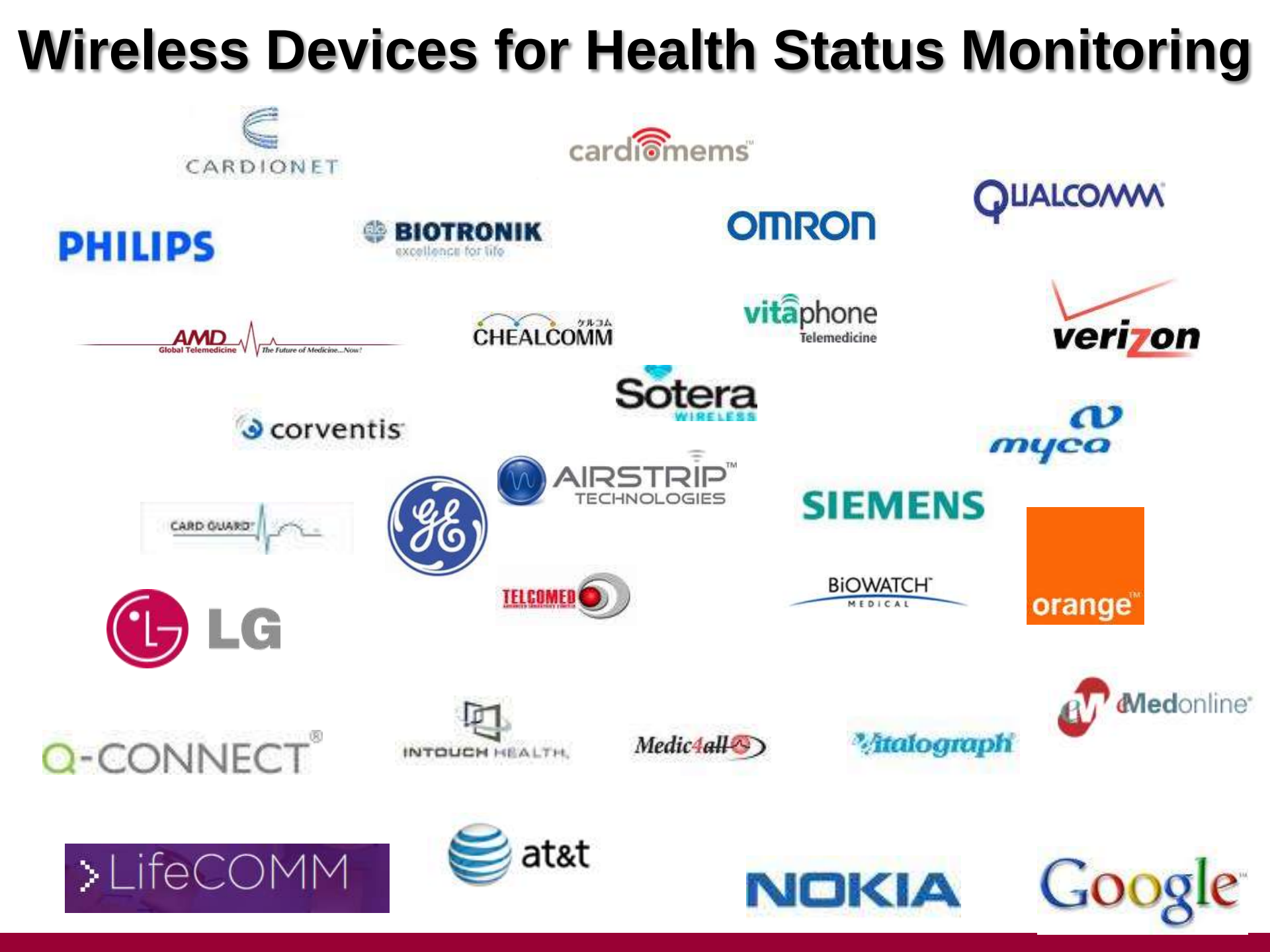


Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

Wireless Devices for Health Status Monitoring



The Real World

- innovation in science and technology alone is necessary but not sufficient
- adoption requires overcoming multiple barriers
  - existing competition/standard of care
  - cultural conservatism
  - reimbursement and other financial obstacles
  - regulatory hurdles
- wide variation in adoption speed by different sectors
  - healthcare (10-30 years)
  - computing (1-2 years)
  - engineering (1-10 years)

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 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

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 mindset of 'lab data' as low cost (<1% total healthcare cost) despite role in most treatment decisions (>85%)
  - transition form unianalyte versus multiplex tests
  - higher regulatory hurdles

SHIFT FROM COST-BASED TO VALUE-BASED REIMBURSEMENT

Genes and Intellectual Property

14 March 2000

SACGHS

5 February 2010 Report

MYRIAD

ACLU

AMERICAN CIVIL LIBERTIES UNION

29 March 2010 SDNY Court Decision

THE UNITED STATES DEPARTMENT of JUSTICE

29 October 2010 Amicus Brief

The High Information Content (Complexity) of Biological Datasets

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’

Regulatory Oversight of Molecular Diagnostics "Specific Intended Use" and "Fit-for-Purpose"

- unianalyte versus multianalyte tests
- profiling existing disease/Rx selection versus claims for probabilistic risks for disease predisposition
- IVDMIAs and validation of algorithms/software
  - "non-transparent derivation that cannot be independently derived or verified by the end user"
- probabilistic versus absolute endpoints
- is the 'kit'/'assay' or the 'information content' the product?

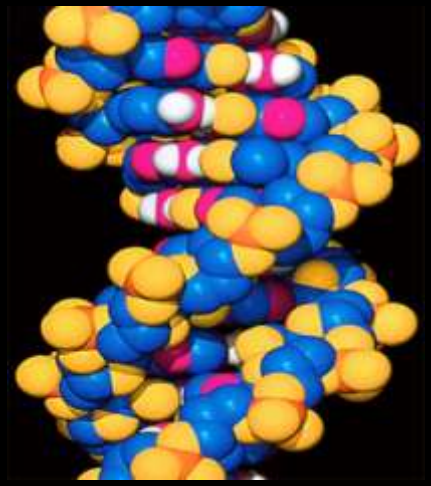
Standards for ‘Omics’ Data: Annotation and Curation Cross-Domain Integration, Open-Source Data Sharing and Managing Massive Data

“Managing Mega-Data”

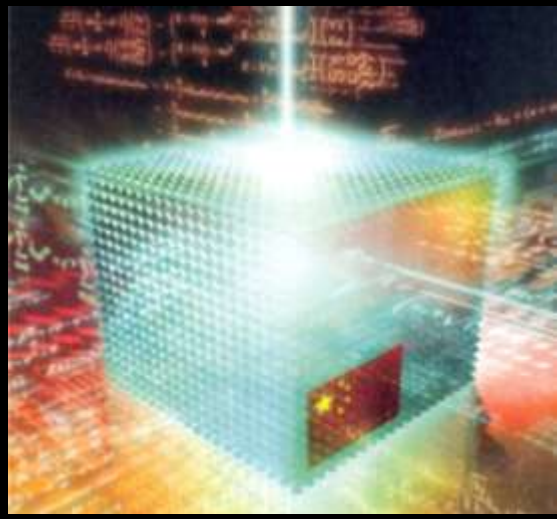
volume

infrastructure

global networks



multiscale heterogeneity



database interoperabilities

Leveraging the Potential of Molecular Medicine

Sustainable Health:
A Complex Multi-Dimensional Challenge

Sustainable Health: Societal and Individual

- current systems for healthcare delivery are economically unsustainable
- earlier disease detection, rational treatment selection and pre-emptive mitigation of disease risk are fundamental to controlling cost, enhancing clinical outcomes and maximizing individual health (wellness)
- biosignature-centric molecular diagnostics provide the intellectual and practical foundations for achieving these objectives
- productive translation of these opportunities requires large scale projects and sophisticated integration of diverse scientific, clinical, industrial and regulatory capabilities

Successful Development of Precision Diagnostic Technologies for Personalized Medicine Requires a Systems-Based Approach

- silos are the enemy
- academia, industry and funding agencies must build new training and research networks for biomarker discovery and validation
- urgent imperative for faster progress in adoption of standards
  - multi-domain: from discovery to health records
  - multiple constituencies
- industry engagement drives adoption of standards
- standards drive industry engagement

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 potential will depend less on technological advances, albeit crucial, than the circumvention of entrenched economic, cultural and institutional interests in sustaining the status quo

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 potential will depend less on technological advances, albeit crucial, than the circumvention of entrenched economic, cultural and institutional interests in sustaining the status quo

DISRUPTIVE INNOVATION DEMANDS BOLDNESS