ASU COMPLEX ADAPTIVE SYSTEMS INITIATIVE
ARIZONA STATE UNIVERSITY

Challenges and Opportunities in Molecular Diagnostics as Key Components of Molecular Medicine

Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative
and Del E. Webb Chair in Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

Sandra Day O'Connor Law School Symposium:
Potential Solutions to Regulatory and Reimbursement Barriers for Molecular Diagnostics: Parallel Review and Coverage with Evidence Development
Scottsdale, Arizona 4 April 2012

ASU Complex Adaptive Systems Initiative
Arizona State University

Slides available @ www.casi.asu.edu

Declared Interests:

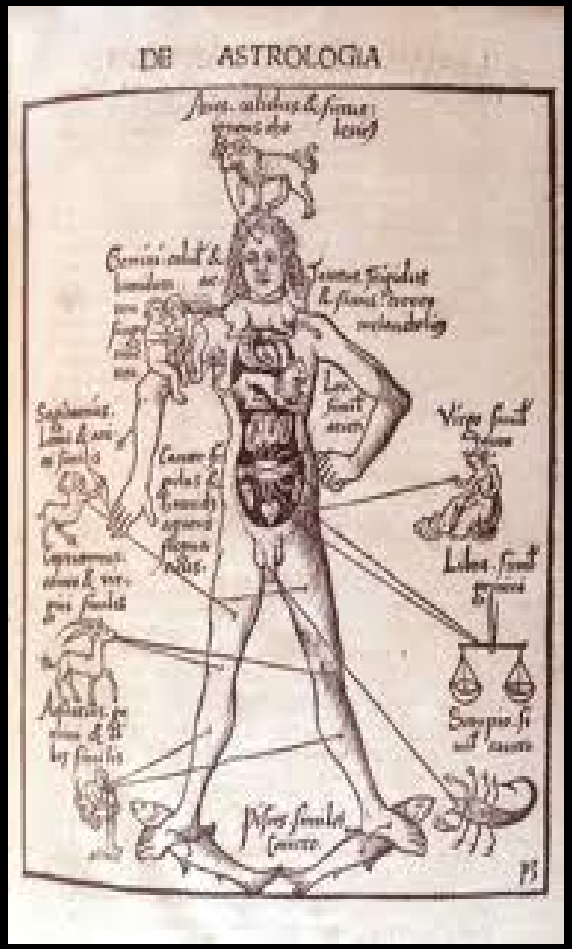
- Board of Directors: Monsanto, Exelixis, Caris Life Sciences
- Scientific Advisory Board: Burrill and Co., Synthetic Genomics, Anacor
- IOM Forum on Global Infectious Diseases
- USG Activities: DoD, DHS

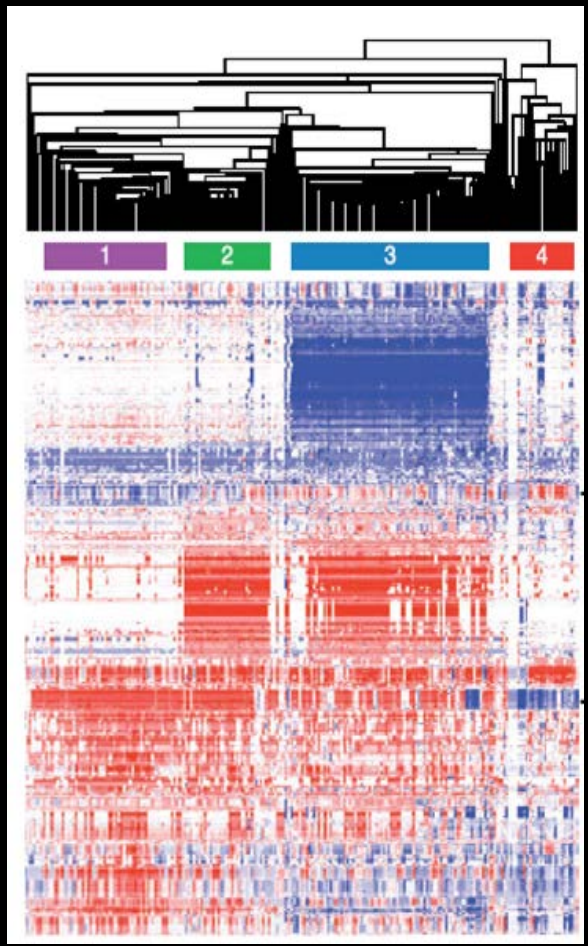
Sustaining Healthcare Innovation
in an Era of Constraint

Biomarkers and Diagnostic Technologies as
Major Value Drivers in Improving Diagnostic Accuracy
Treatment Selection and Controlling Costs

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

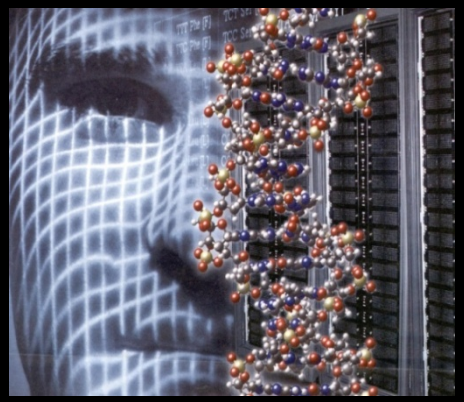
Medical Progress:
From Superstitions to Symptoms to Signatures



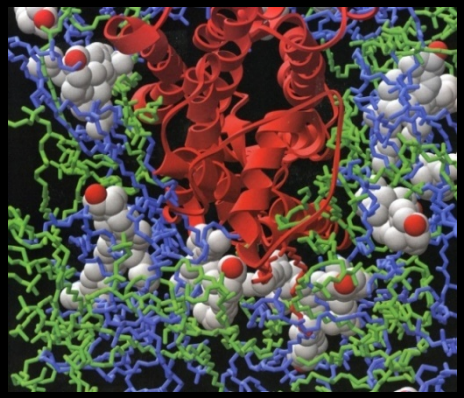


Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

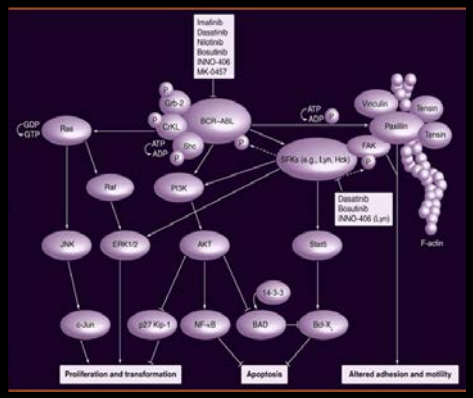
Genomics



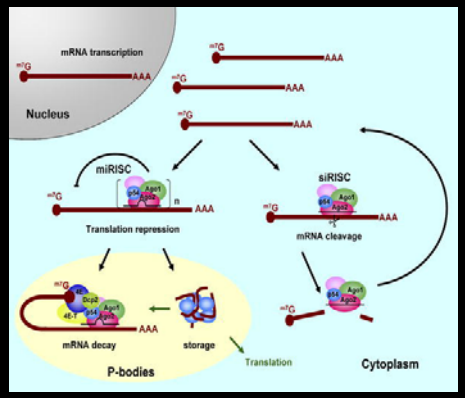
Proteomics

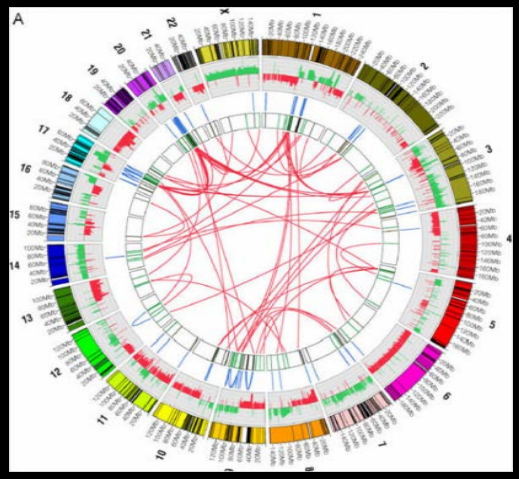


Molecular Pathways and Networks



Network Regulatory Mechanisms



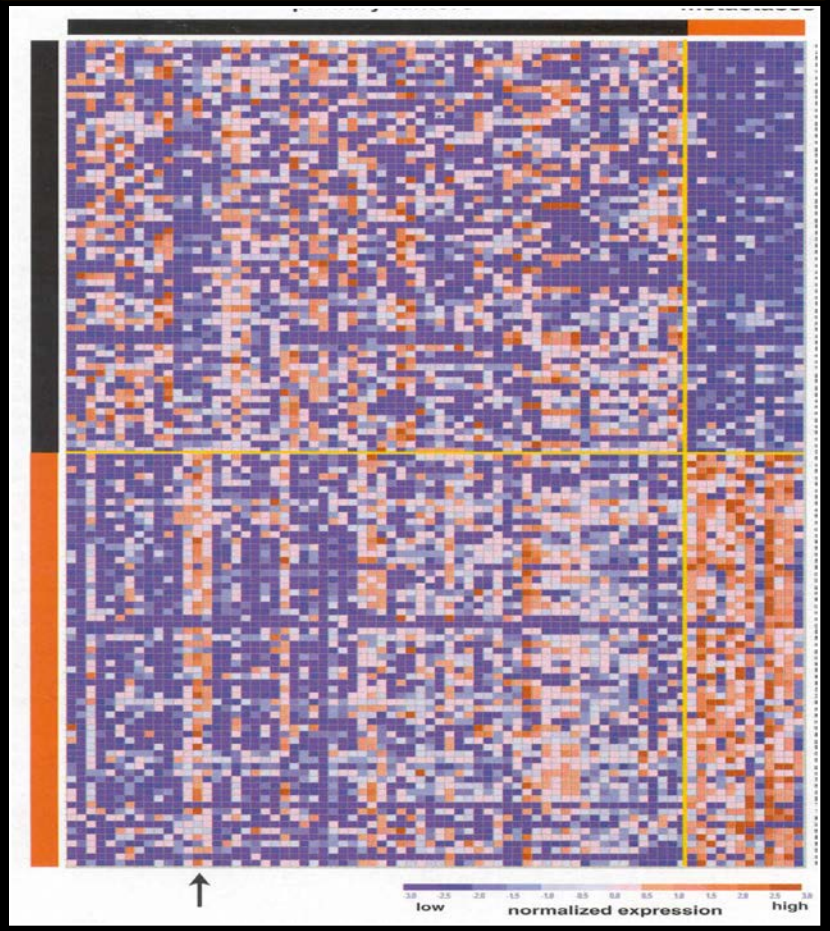


ID of Causal Relationships Between Network Perturbations and Disease

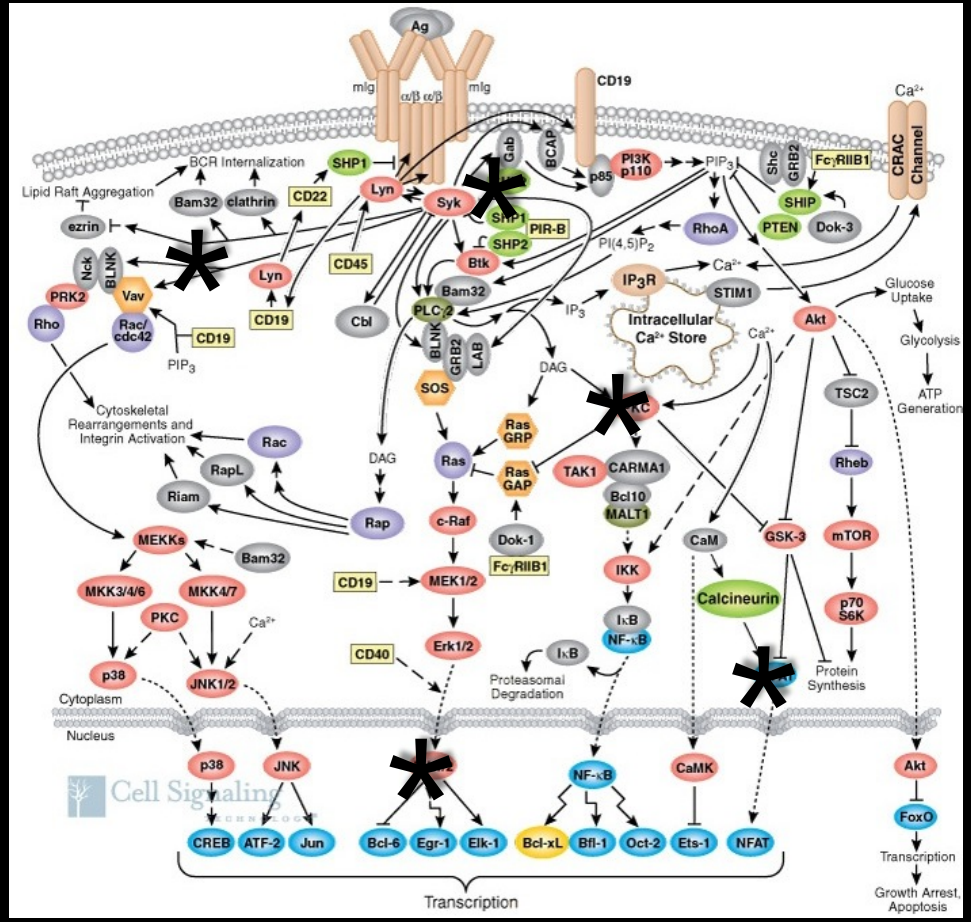
Patient-Specific Signals and Signatures of Disease or Predisposition to Disease

Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

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

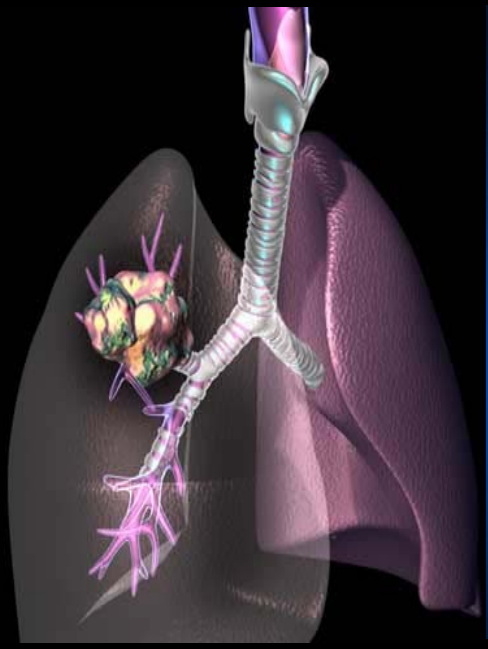


ID Molecular Targets for MDx and/or Rx Action



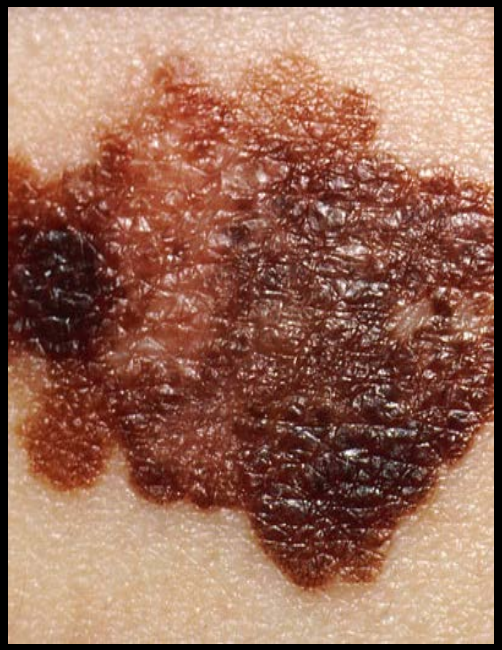
Mapping the Molecular Signatures of Disease, Disease Subtyping and Targeted Therapy: The Right Rx for the Right Disease (Subtype)

Her-2+
(Herceptin)



EML4-ALK
(Xalkori)

KRAS
(Erbitux)
(Vectibix)



BRAF-V600
(Yervoy)
(Zelboraf)

Disease Subtyping and Targeted Therapy: The Right Rx for the Right Disease Subtype

- improved clinical outcomes
- cost-effectiveness in eliminating futile Rx
- reducing high failure rate of investigational drugs in clinical trials by testing only on relevant patients
  - faster and cheaper trials
  - greater regulatory clarity
  - premium pricing for guaranteed outcomes (P4P)

Critical Challenges for Biomedical R&D

- acceleration of discovery phase knowledge without parallel gains in successful clinical translation and commercial ROI
- unacceptable high rates of failure of candidate Rx in clinical trials
- major knowledge gaps for rational discovery strategies to provide solutions for late onset chronic diseases
  - cancer, diabesity and neurodegeneration

Molecular Diagnostics (MDx)

Frost and Sullivan 2011 and Dark Report 16 March 2012

- fastest growing segment of clinical pathology laboratory testing market
  - $4.1 billion vs IVD $48 billion (2010)
  - projected 11% CGR vs <5% IVD
- 600 hospitals and 200 independent labs using MDx assays
- 9 global companies control 75% market share
- 60% MDx revenues from infectious diseases testing
  - HIV, HPV, HBV, HCV, CT/NG
  - C.difficile and MRSA

Evaluation and Validation of Biomarker-Based Diagnostic Tests

- proof of concept (poc) and clinical validation
  - do changes in biomarker expression correlate with disease risk and/or disease development and/or stage of disease and/or predict treatment response?
- analytical validation
  - robust, reproducible assay method
- clinical utility and ‘fit for purpose’
  - validation and regulatory approval for “intended use” setting(s)
  - compatibility with clinical practice/guidelines
- improved outcomes
  - demonstration that biomarker-driven changes in treatment decisions yield clinical/economic benefits

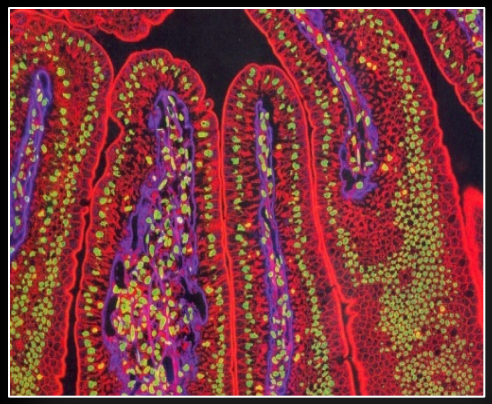
Translation of the Major Potential of Molecular Medicine into Routine Clinical Practice

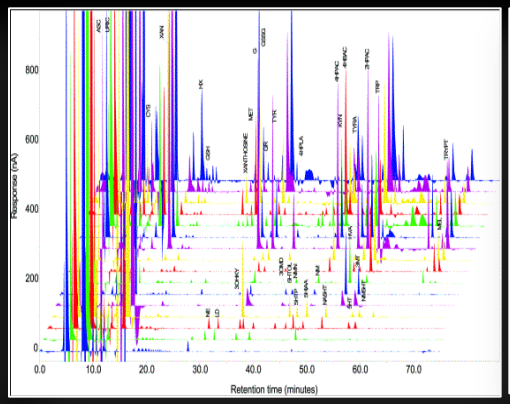
The Poor Productivity of Biomarker R&D is a Legacy of Failure to Address Disease Complexity and the Need for Multidisciplinary Expertise and Rigorous Standards

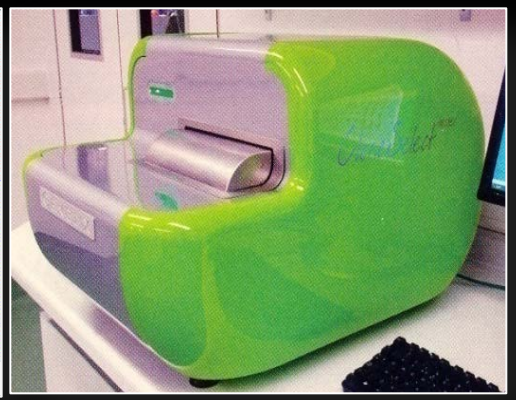
The Complexity of Discovery and Validation of Biomarkers for Clinical Use is Comparable to (Bio)Pharmaceutical R&D

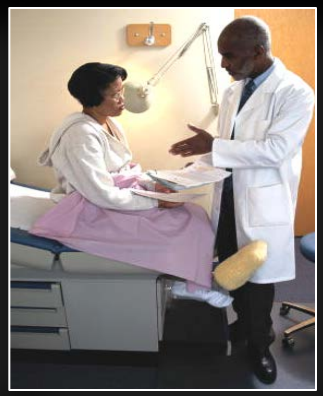
Success Demands a Systems-Based Approach

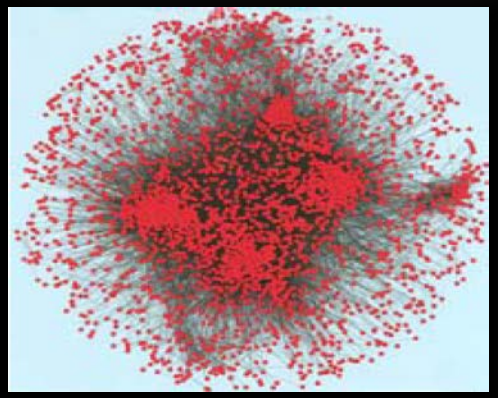
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches

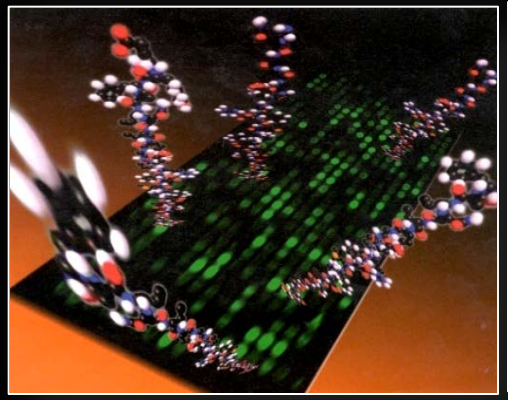


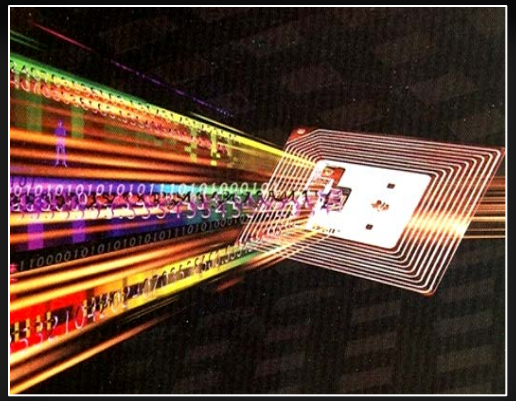












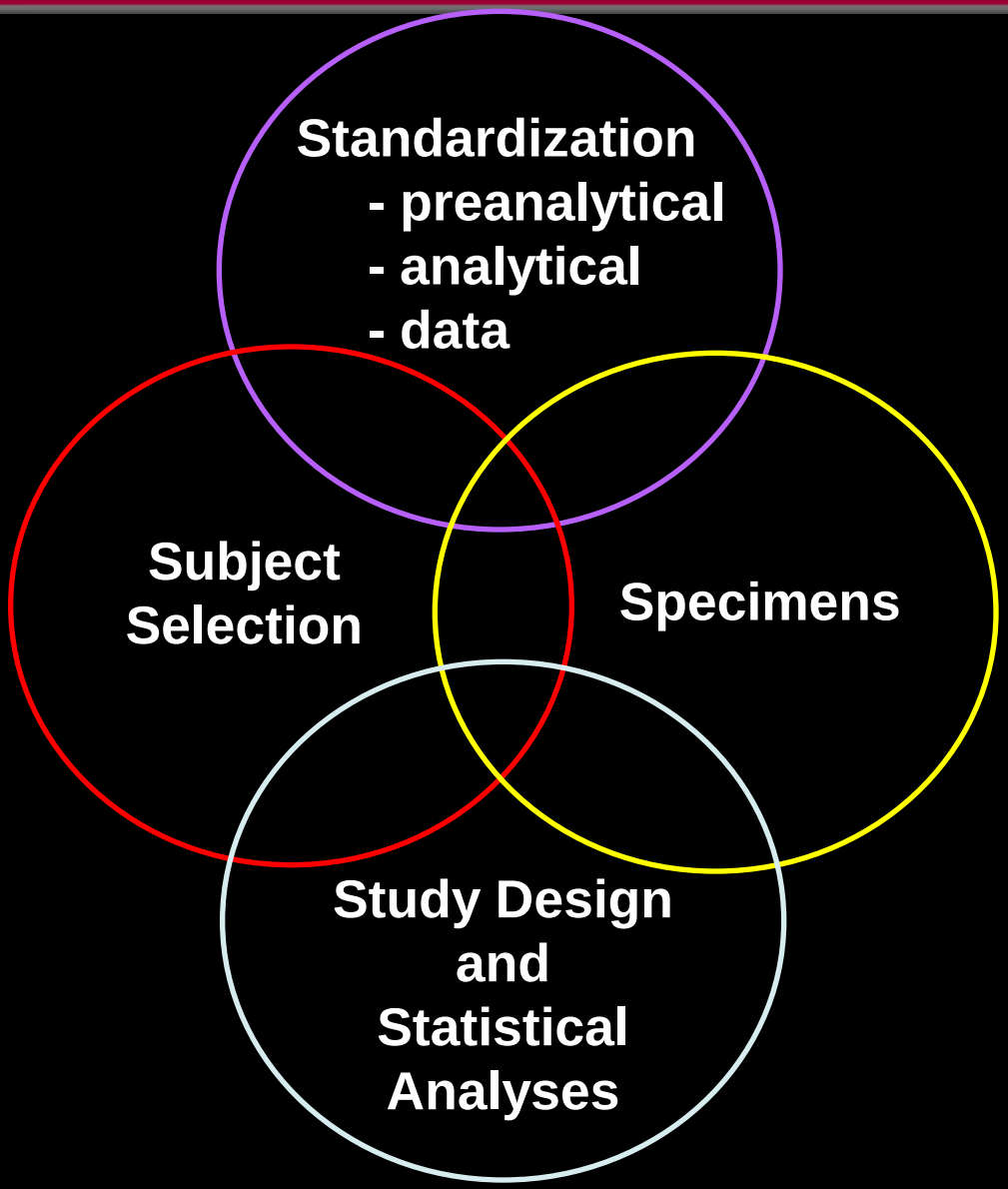
Biospecimens and Molecular Pathway Analysis

Biomarker Validation and Multiplex Assays

Instrumentation and Informatics

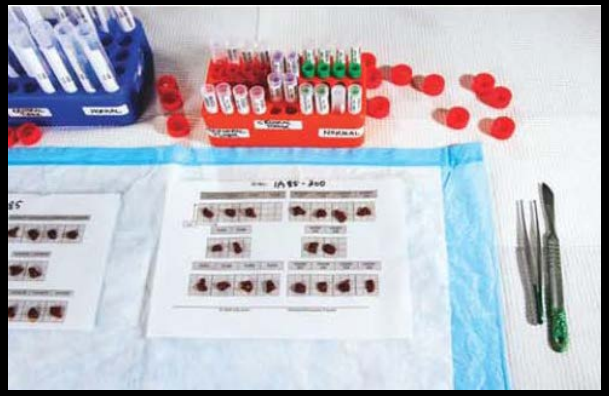
Clinical Impact and Patient Monitoring

The Systems-Based Approach to Biomarker Validation

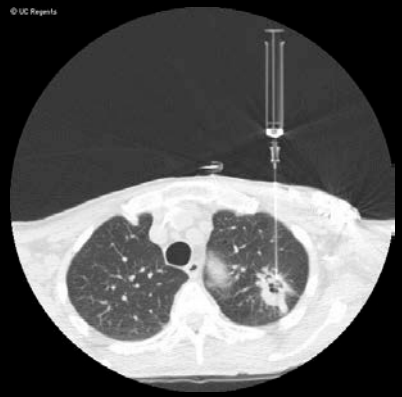


Rigorous Selection of Specimen Donors and Specimen Collection

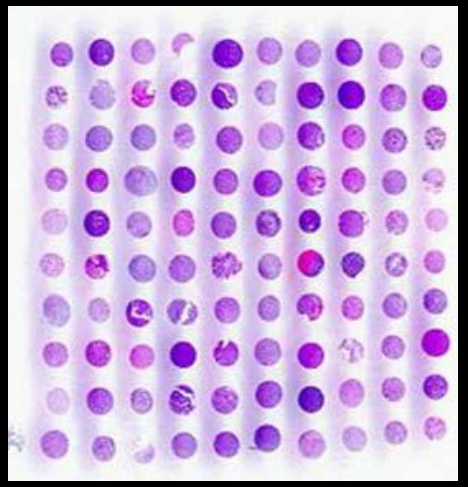
primacy of standardized clinical phenotyping and annotated health records and outcomes for biospecimen collection



poorly standardized tissues and erratic availability



challenge of obtaining fresh tissue



uncertain value of legacy tissue blocks

Access to High Quality Biospecimens, Biobanks and DNA Repositories: A Major Obstacle for Biomarker Discovery

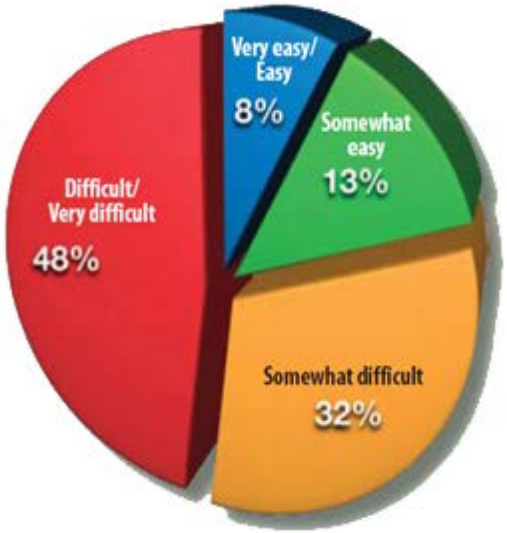
scale
and
standards

or

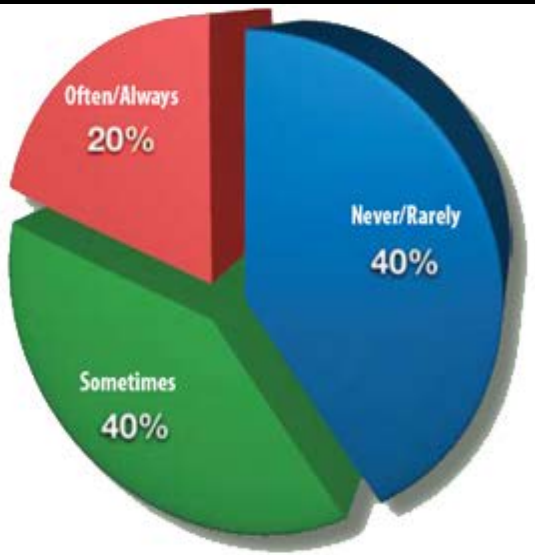
academic
anecdotes

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

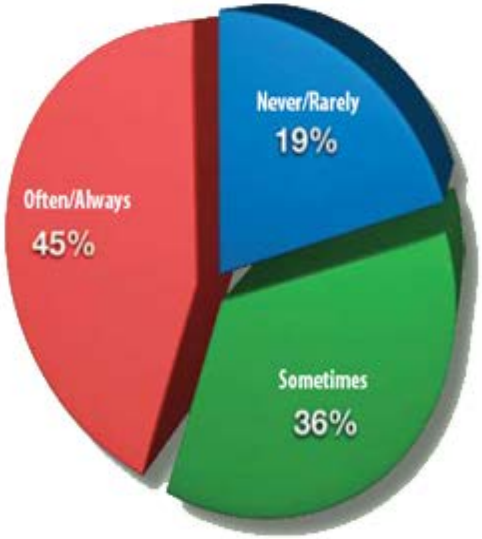
Ease of Acquiring the Quality of Biospecimens



Question Their Data Because of the Quality of Biospecimens



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

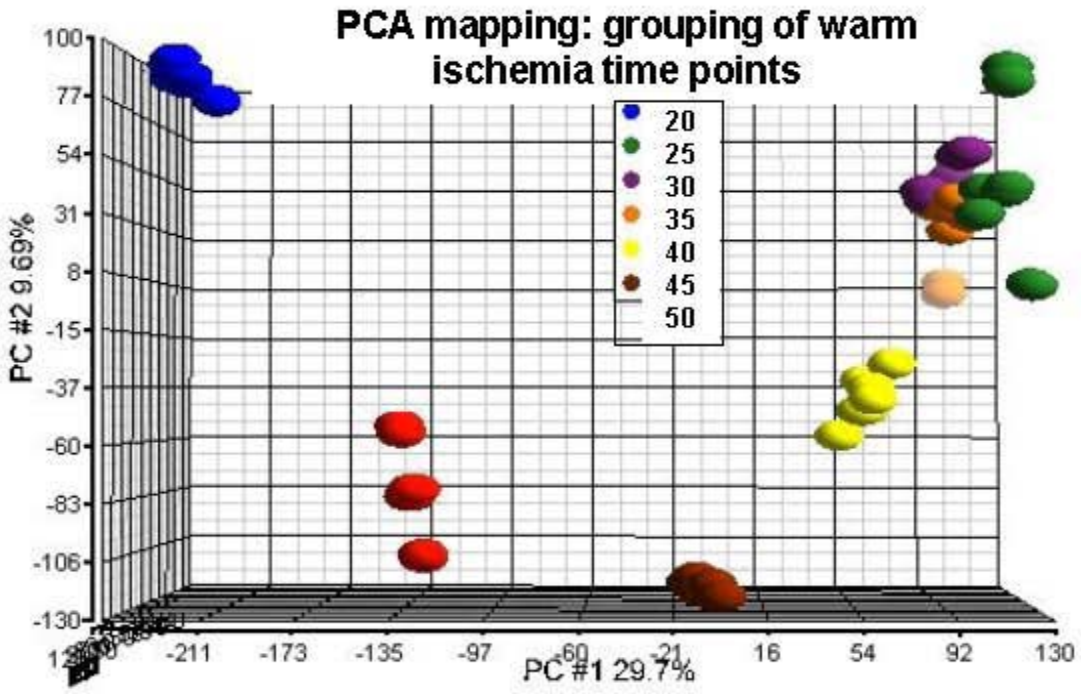


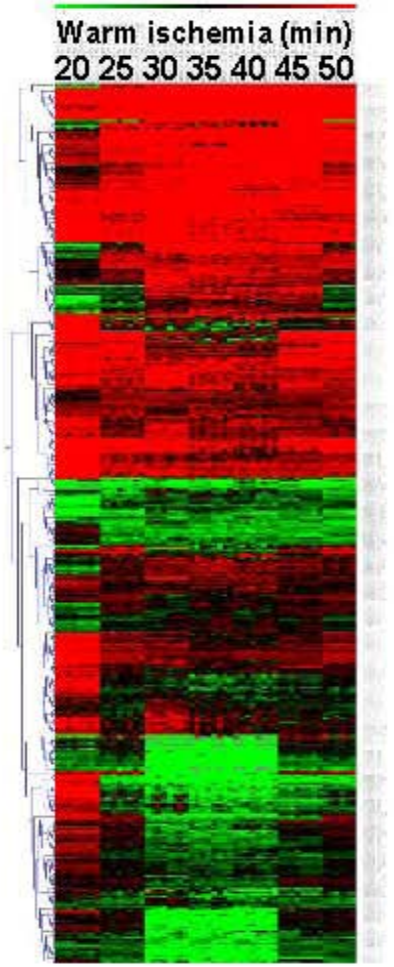
Source: Office of Biorepositories and Biospecimen Research, 2009.
http://biospecimens.cancer.gov/cahub/

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

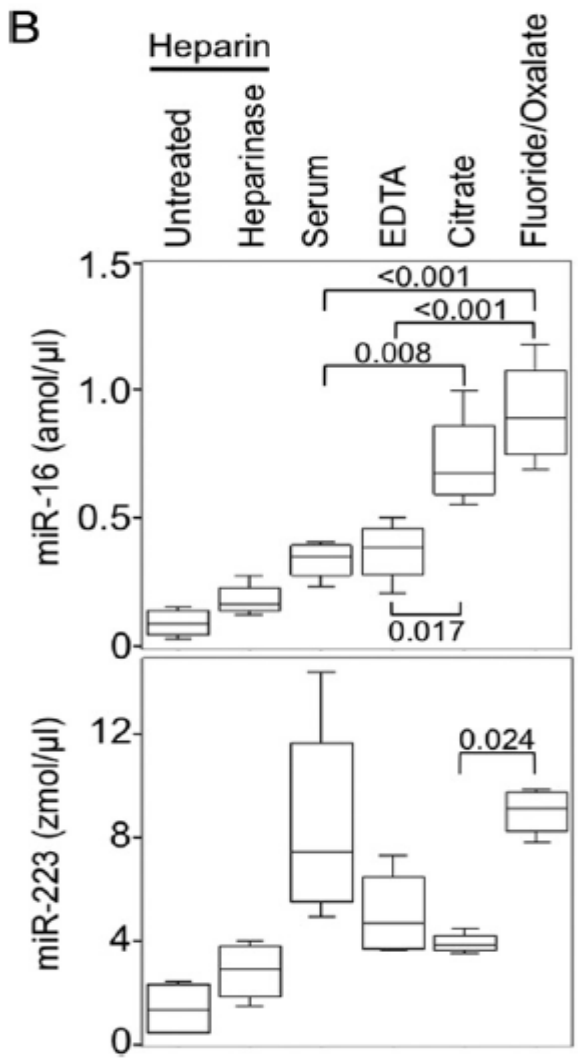
Intrasurgical Ischemia





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

Influence of Blood Collection Method on Detection of miRNAs



From: D. J. Kim et al. (2012) J. Mol. Diag. 14, 71

Pervasive Problems in Biomarker Identification and Validation

The Small 'N' Problem

JAMA (2011) 305, 2200

Comparison of Effect Sizes Associated With Biomarkers Reported in Highly Cited Individual Articles and in Subsequent Meta-analyses

John P. A. Ioannidis, MD, DSc
Orestis A. Panagiotou, MD

Context Many biomarkers are proposed in highly cited studies as determinants of disease risk, prognosis, or response to treatment, but few eventually transform clinical practice.

Objective To examine whether the magnitude of the effect sizes of biomarkers proposed in highly cited studies is accurate or overestimated.

Data Sources We searched ISI Web of Science and MEDLINE until December 2010.

Study Selection We included biomarker studies that had a relative risk presented in their abstract. Eligible articles were those that had received more than 400 citations in the ISI Web of Science and that had been published in any of 24 highly cited biomedical journals. We also searched MEDLINE for subsequent meta-analyses on the same associations (same biomarker and same outcome).

MANY NEW BIOMARKERS ARE continuously proposed[1-3] as potential determinants of disease risk, prognosis, or response to treatment. The plethora of statistically significant associations[4,5] increases expectations for improvements in risk appraisal.[6] However, many markers get evaluated only in 1 or a few stud-

Failure to Work to Industry Standards

Nature Rev. Drug Disc. (2011) 10, 643

Reliability of 'new drug target' claims called into question

Bayer halts nearly two-thirds of its target-validation projects because in-house experimental findings fail to match up with published literature claims, finds a first-of-a-kind analysis on data irreproducibility.

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 Institutes of Health
‘Institute of Medicine Workshop, July 2010’

Large Scale Profiling of Cancer Patients to Identify Cohorts Expressing Rx Target(s) for Phase II Trials

Target	# Patients Screened	# Eligible Patients	# Centers	# Countries
EML4 ALK^{+}: lung cancer*	1500	82	9	1
HER2^{+}: gastric cancer**	3803	549	122	24

* E.L. Kwak et al. (2010) NEJM 363, 1693

** Y. Bang et al. (2010) Lancet 376, 687

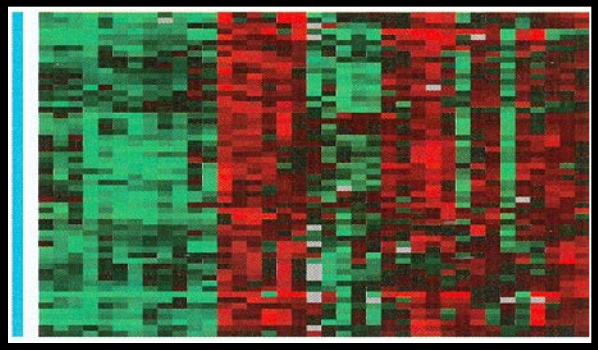
The Importance of Standardized Methods and Data Tracking Systems for Biobanks

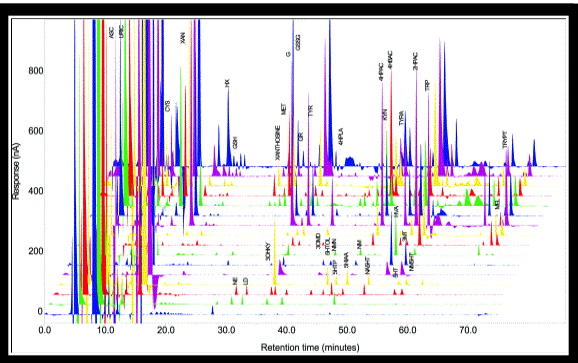
- NCI Office of Biorepositories and Biospecimen
- OECD Research: National Biospecimen Network
- PHOEBE (EU): Promoting Harmonization of Epidemiological Biobanks in Europe
- BBMRI: Biobanking and Biomolecular Resources Research Infrastructure
- P3G: Public Population Project in Genomics
- UK Biobank

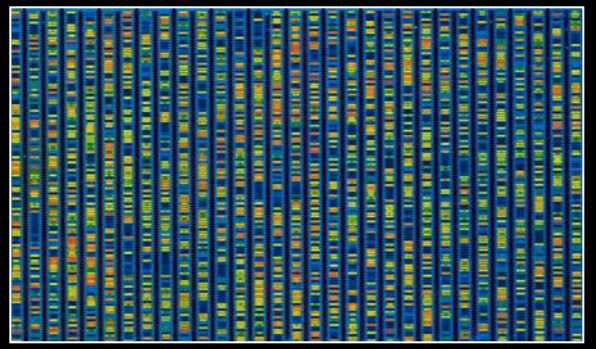
Analytical Platforms for the Elucidation of the Design and Regulation of Complex Biological Networks

Massively Parallel Biosignature Profiling

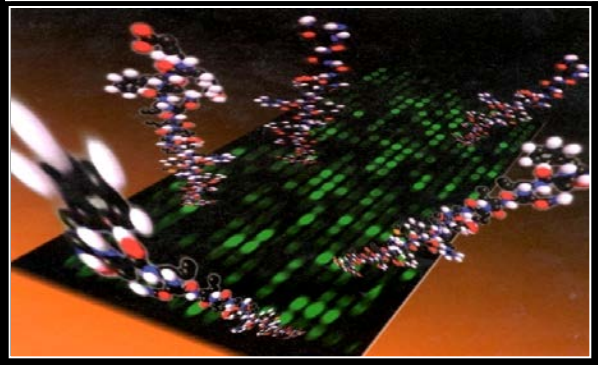
genomics	proteomics	immunosignatures

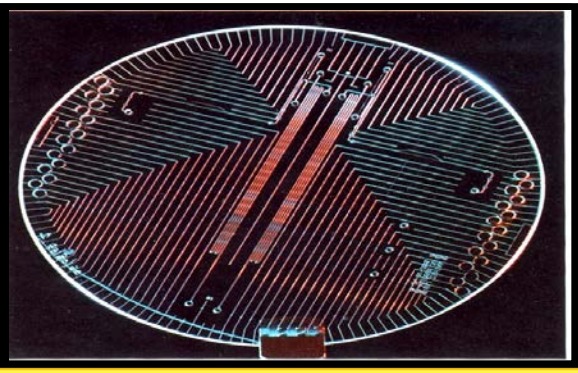


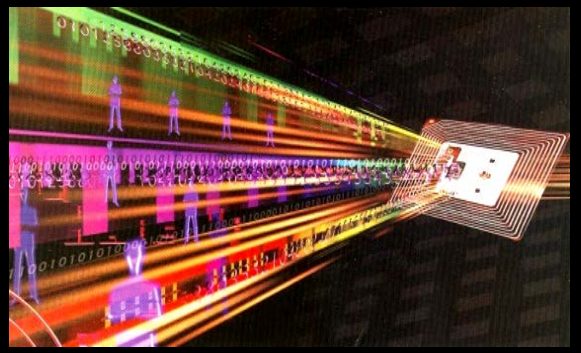




automated, high throughput multiplex assays	novel test formats and devices (POC)	complex signal deconvolution







Large Datasets, Standardization and New Computational Analytics

Identification and Validation of Biomarkers for Disease Risk, Detection, Diagnosis and Staging

- platform agnostic perspective

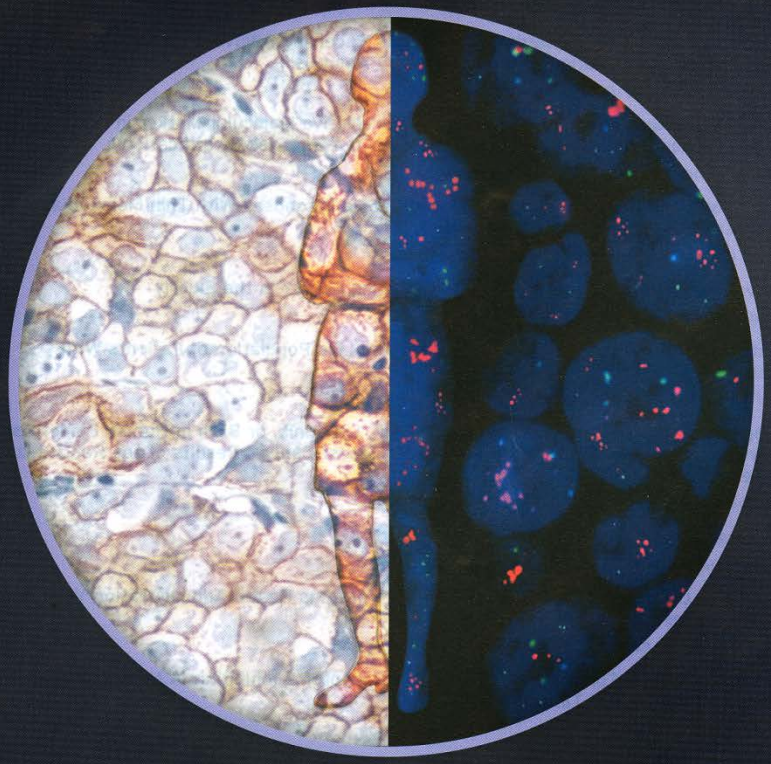
but

- unit cost and compatibility with clinical practice will be highly influential in adoption
  - screening tests versus clinical evaluation
  - convenience and acceptance by physicians and patients
  - value proposition for payors

and

- need to address anticipated barriers to approval/adoption
  - regulatory
  - clinical conservatism/education
  - displacement of existing Dx platforms/installed capital base

When testing for **HER2**



A second test may change her treatment

Because of tumor heterogeneity and assay limitations—
consider a second test

Genentech
A Member of the Roche Group

Duke UNIVERSITY

NATIONAL CANCER INSTITUTE®

THE CANCER LETTER

Vol. 37 No. 1
Jan. 7, 2011

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

IOM Committee Will Probe Duke Scandal Together With Other "Omics" Case Studies

By Paul Goldberg

A committee of the Institute of Medicine will refrain from launching a police-style investigation of the Duke scandal, the group's chairman said.

"We are not an investigative body," said Gilbert Omenn, director of the University of Michigan Center for Computational Medicine and Biology and chairman of the IOM committee. "I think we are heading into a morass, to try to figure out what really happened at Duke and who should bear responsibility and who should be held accountable."

At its first meeting Dec. 20, the 19-member group struggled publicly to interpret its charge and design a plan for deriving science policy lessons

(Continued to page 2)

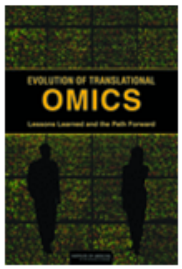
INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

ABOUT THE IOM | REPORTS | ACTIVITIES

Browse History | Reports

Report

Bookmark this Page | Print | E-mail | ShareThis



Evolution of Translational Omics: Lessons Learned and the Path Forward

Released: March 23, 2012
Type: Consensus Report
Topics: Biomedical and Health Research, Health Services, Coverage, and Access
Activity: Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials
Board: Board on Health Care Services

Standards

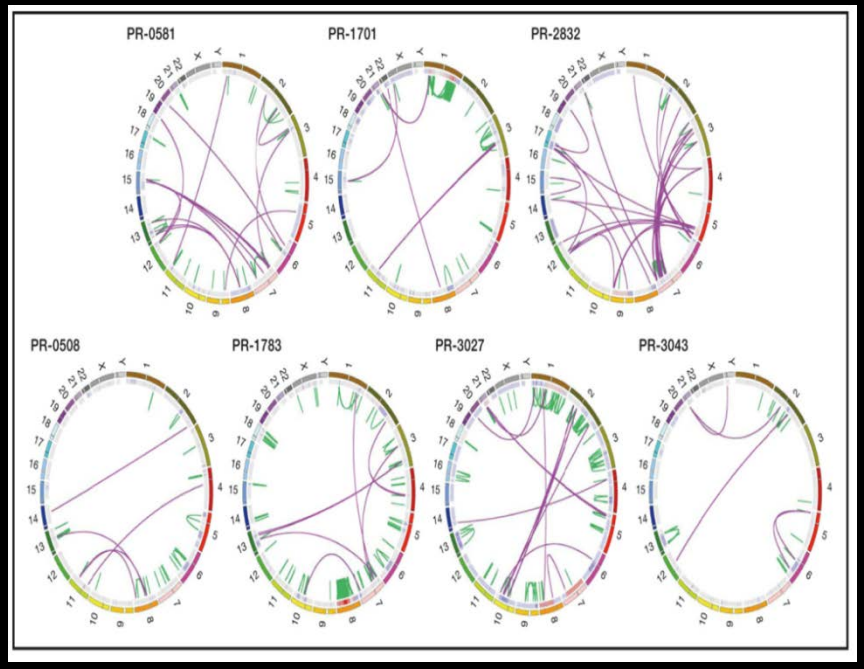
- pervasive end-to-end problem: from sample to answer
  - biospecimen acquisition, handling and storage
  - pre-analytical and analytical methods, data analysis and databanks
  - QC/QA of multiplex assays/equipment
  - trial design(s)
- role of professional societies, publishers and payors in raising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

Will Rapid, Low Cost Genome Sequencing Change Everything?

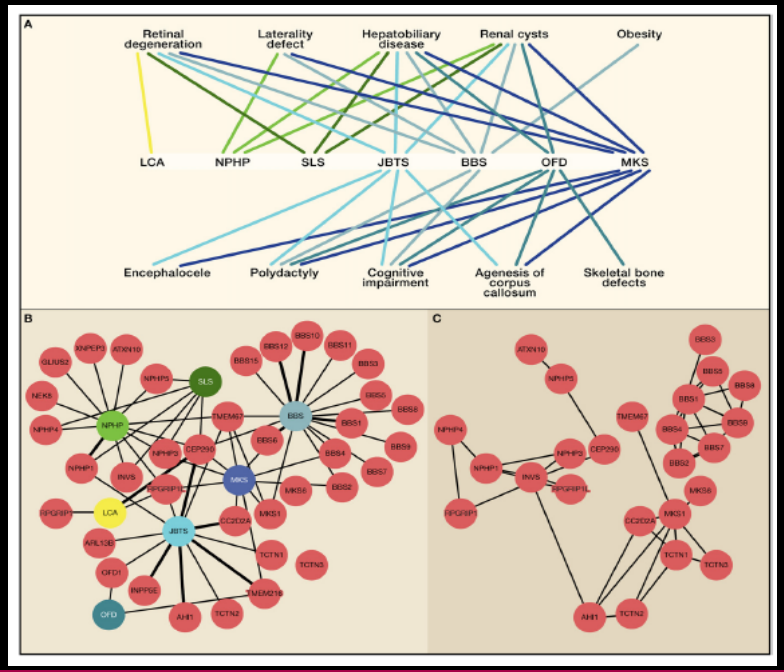
Prepare for the "Tsunami of Genomic Information" ASCO Presidential Address: Dr. George Sledge Chicago, 5 June 2011

- "the day when a patient walks into her oncologists office carrying a memory stick containing personal genomic information could be less than a decade away"
- "when data are that cheap….things will get very, very complicated"

Exome- or Whole Genome Sequencing



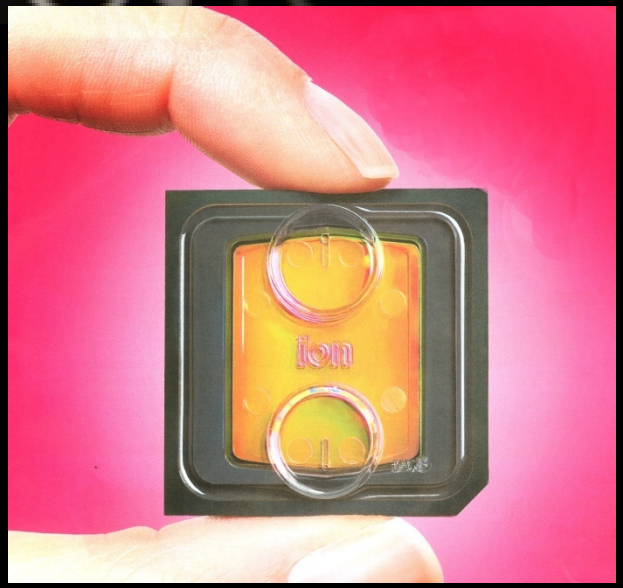
Disease-Associated Perturbations in Pathways and Networks



Next-Next-Generation Sequencing?

- disposable USB pocket-sized sequencer
- $500-1000 unit
- 150 Mbp sequence/hour
- smaller instrument versus pending benchtop GridION 2K machine

Oxford Nanopore
MinION Sequencer



Life Technologies Ion
Proton DNA Sequencer
Cost $149,000
Availability Mid-2012

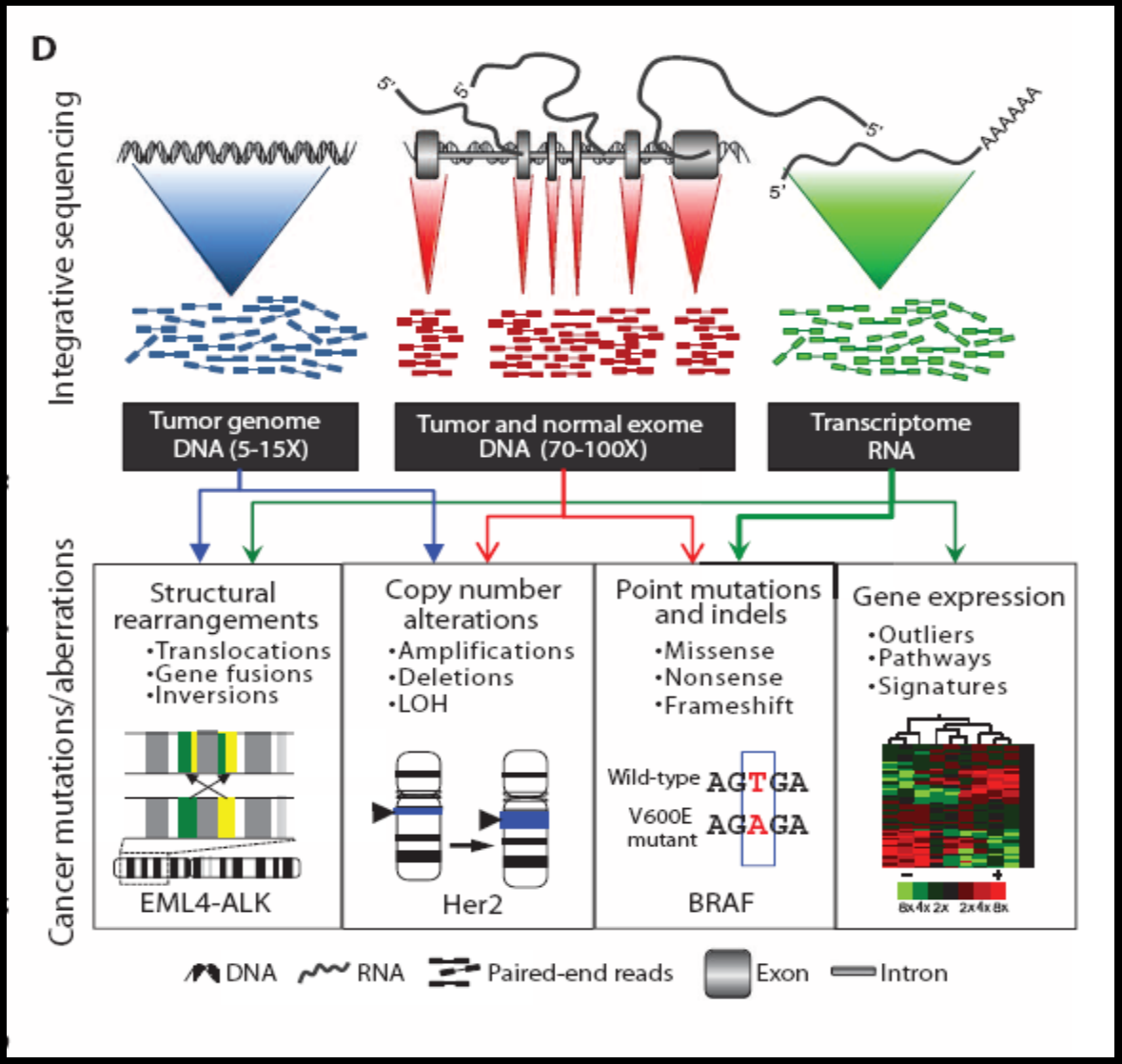
The Cost of Sequencing Versus The Cost of Computational Analysis and Storage

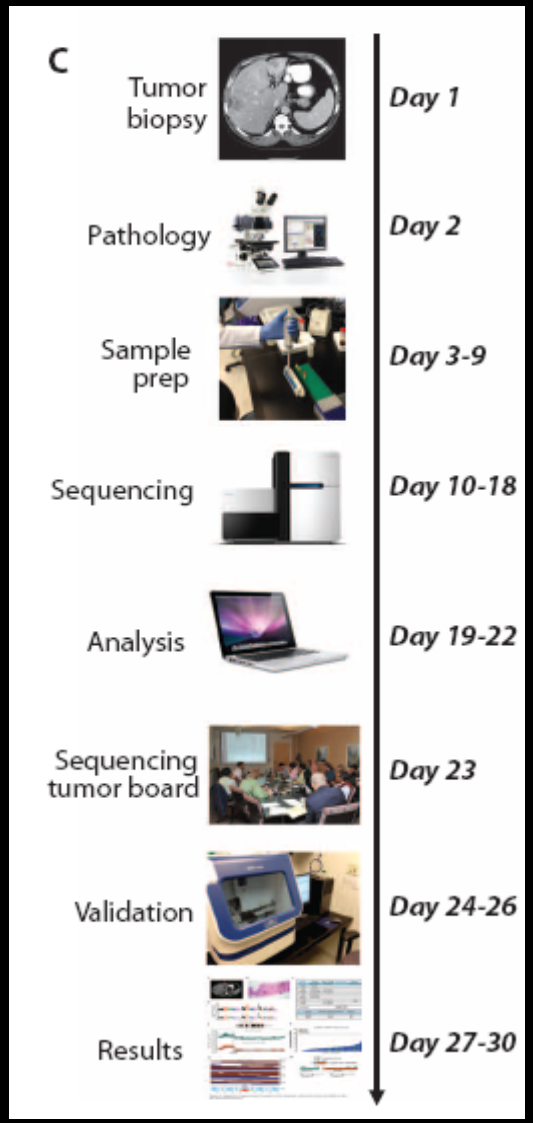
- the $1000 genome,
  - the $? analysis and interpretation cost
  - the $? storage, retrieval and security costs
- turn around time (TAT) and analysis for clinical value cost
- regulatory and reimbursement policies
- obligations/duties to recontact/deidentify research participants/patients regarding Incidental Findings (IFs) and Individual Research Results (IRRs) detected in WES/WGS?

The Adoption of Genome Sequencing in Clinical Diagnostics

- from research odysseys to routine clinical use ("just another lab value!")
- early clinical applications
  - infectious diseases
  - hereditary cancers and individual risk assessment
  - oncology
  - rare diseases of suspected genetic etiology
  - HLA profiling for transplant matching
  - cardiomyopathies
  - X-linked intellectual disability
  - congenital muscular dystrophy
  - mitochondrial disorders

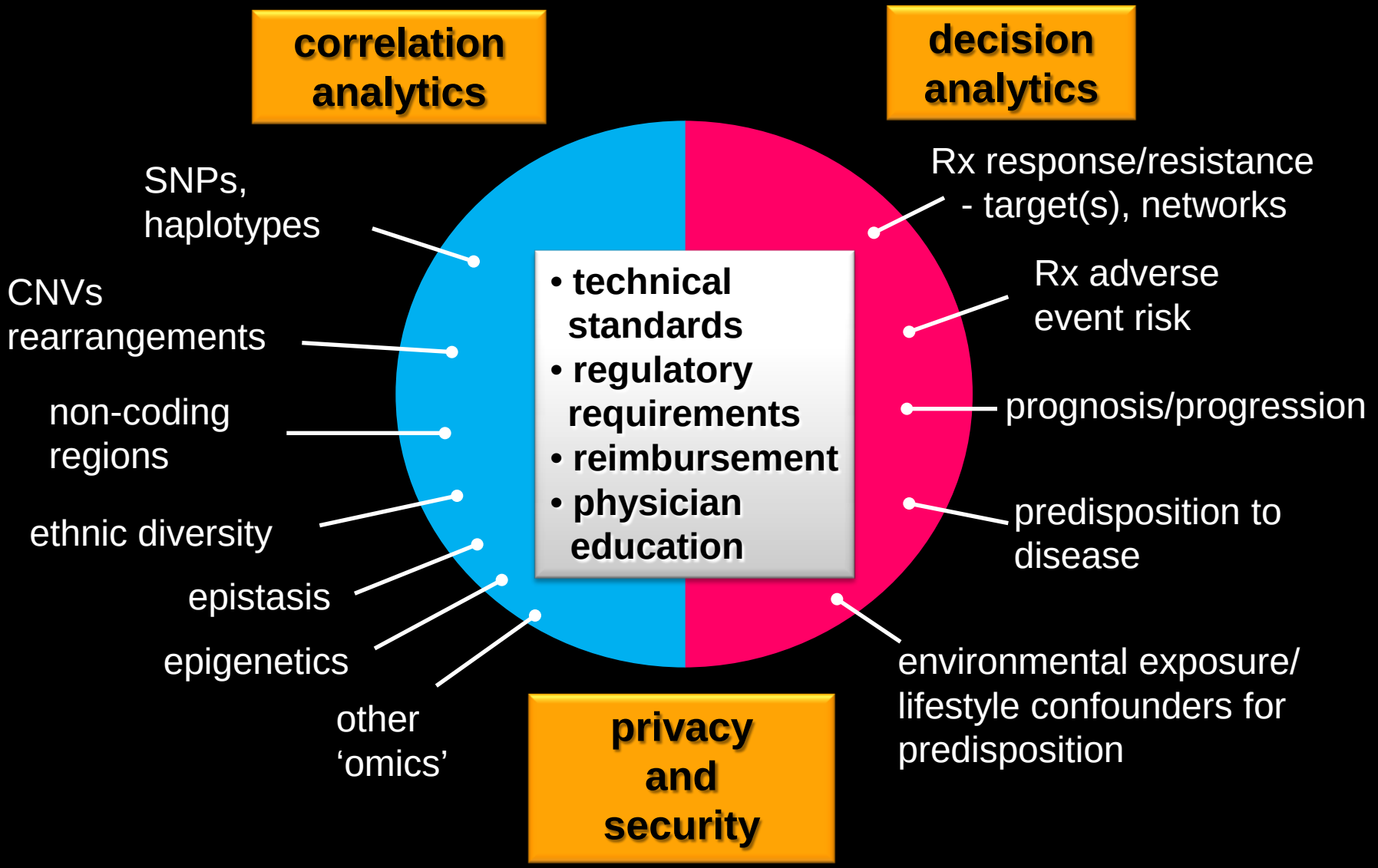
High Throughput WGS for Personalized Oncology





From: S. Roychowdhury (2011) Sci. Trans. Med. 3, 175

Low Cost Whole Genome Sequencing and Molecular Medicine: Dependency on Large Scale (Massive) Data Annotation and Analytics



Review of Validation Issues for Clinical Use of Genome Sequencing 23 June 2011

- minimum sequencing depth for reliable clinical decisions
- appropriate validation sample sets to evaluate platform accuracy
- metrics for quality of sequence assembly and alignment algorithms
- standardization of pre-analytical variables (e.g. preparation of libraries, extraction and quality control of nucleic acids, capture methods, amplification)
- source computer code(s) for analytical algorithms
- sequencers as Class III devices?

The Scale and Complexity of Human Genome Sequencing Data

Accuracy and Comprehensiveness

- need for consensus metrics for these parameters
- population-based studies
  - pooled samples with low depth coverage (<10x)
- personal genomes for clinical diagnostics and care decisions
  - greater accuracy and confidence for base calling
  - regulatory oversight of QA/QC and analytics algorithms
- current technologies
  - 30-40x coverage to ID 92-95% of both alleles
  - 50-100x coverage to ID 99.9% sequence and rare variants
  - final sequence with only 1 error/10^6 bases will still contain 6000 errors

Performance Comparison of WGS Platforms
(H.Y.K. Lam et. al. 2012 Nature Biotechnol. 30, 78)

- sequencing of blood and saliva samples from same individual on Illumina and Complete Genomics Platforms at 76x coverage
- only 88.1% SNVs concordant ≡ 10,000s platform-specific calls in exons and intergenic regions
- need to supplement with exome sequencing to fill gaps in detection of coding variants
- only 26.5% indels concordant
- implications for use of WGS data for clinical decisions/regulatory submissions

Statistical Sampling Powering Needs for Variant ID in Validation Studies: The Proportion of Theoretically Identifiable Variants in Different Population Sample Cohort Sizes (N)

Variant Frequency	N			
	100	200	500	1000
0.001	0.18	0.33	0.63	0.86
0.002	0.33	0.55	0.86	0.98
0.005	0.36	0.86	0.99	1.00
0.01	0.86	0.98	1.00	1.00

Adapted from: L. Bingsham and S.M. Leal (2009) PLoS Genetics 5, e1000481

The Data Storage Challenge: The Price of Sequencing is Falling Faster Than Computer Storage Costs and Availability

- data ‘triage’: store only data deemed relevant and/or with differences to reference set
  - risk of bias/ignorance about value of discarded data elements
- data compression and ‘loss of precision’
  - different compression methods depending on desired end use/reuse needs
- unmapped reads cannot be compressed using current alignment frameworks
  - 10-40% of reads remain unmapped to traditional reference genomes
  - 60-70% for short RNA sequencing reads
- many samples may not be accessible/renewable
  - cancer

Presidential Commission for the Study of Bioethical Issues

Fed. Reg. 27 March 2012
Implications of Large Scale Human Genome Sequencing

- collection, use and governance of exome- and WGS information
  - genetic/genomic databases and biobanks
  - role of health IT
- privacy and access
- balancing of individual and societal interests
- access and use by law enforcement agencies

“The Incidentalome”

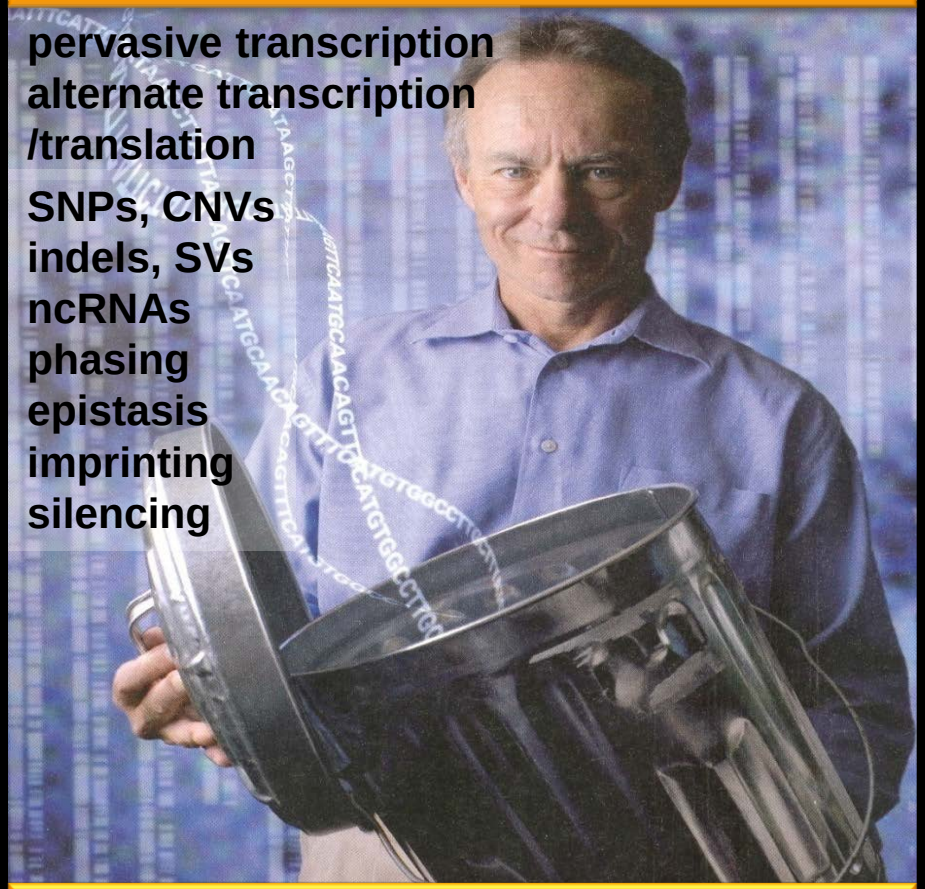
- 2012 NIH proposal for screening exome-and WGS sequence data for findings of potential health or reproductive importance
- obligation to recontact/deidentify individuals in research studies
- criteria for “relevant” and “risk” in returnable findings?
- requirement to reidentify original donor in deidentified samples?
- resources and cost to implement with anticipated rapid growth in datasets?
- why limit to genomic research using biobanks and archived data?
- if research participants are accorded duties why not all patients sequenced as part of clinical care?
- expanded IRB responsibilities and competencies

Genes For…..
The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective

- limits of current knowledge of genome organization and control dynamics
  - relationship to RNA regulome, protein expression and (in)stability of biological pathways
- limited value for robust predisposition profiling (epistasis…….)
- variable utility in different disease categories to inform optimum Rx treatment choice and guide new Rx discovery

Individual Variation, Genome Complexity and the Challenge of Genotype-Phenotype Prediction

Junk No More!

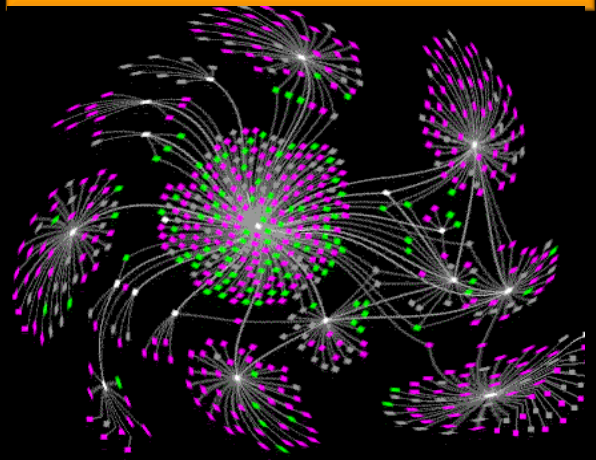


pervasive transcription
alternate transcription /translation

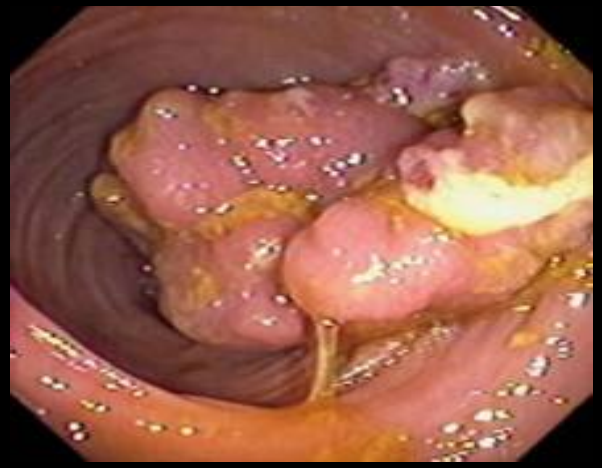
SNPs, CNVs
indels, SVs
ncRNAs
phasing
epistasis
imprinting
silencing

recognition of genome organizational and regulatory complexity

Cell-specific Molecular Interaction Networks

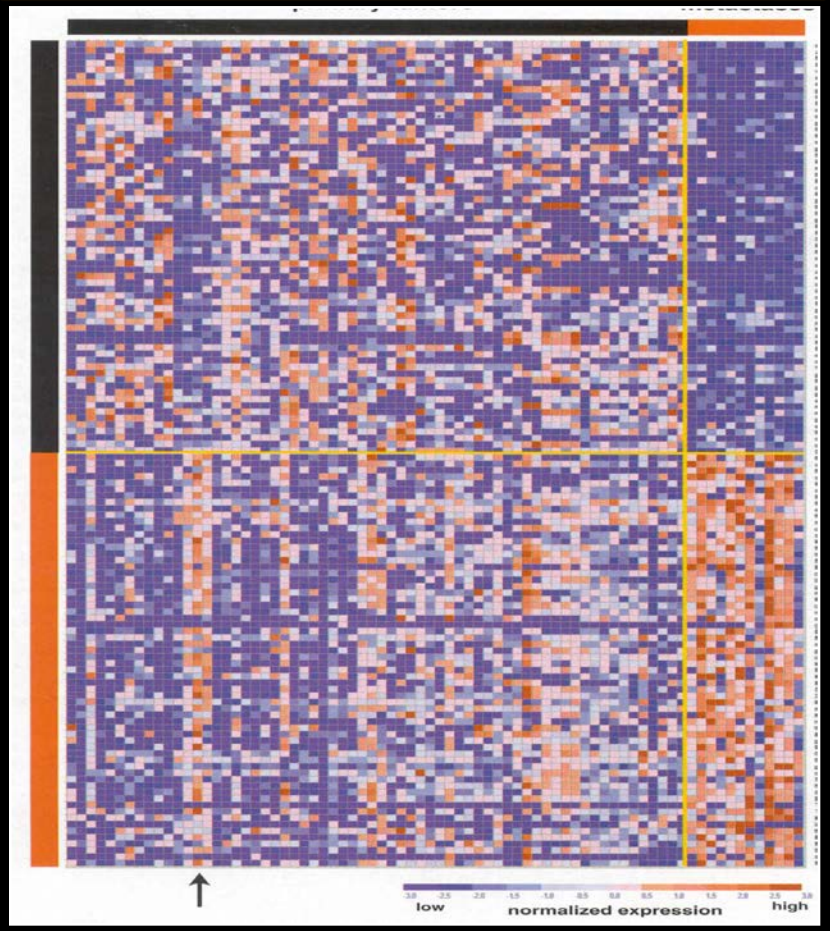


Disease Perturbations

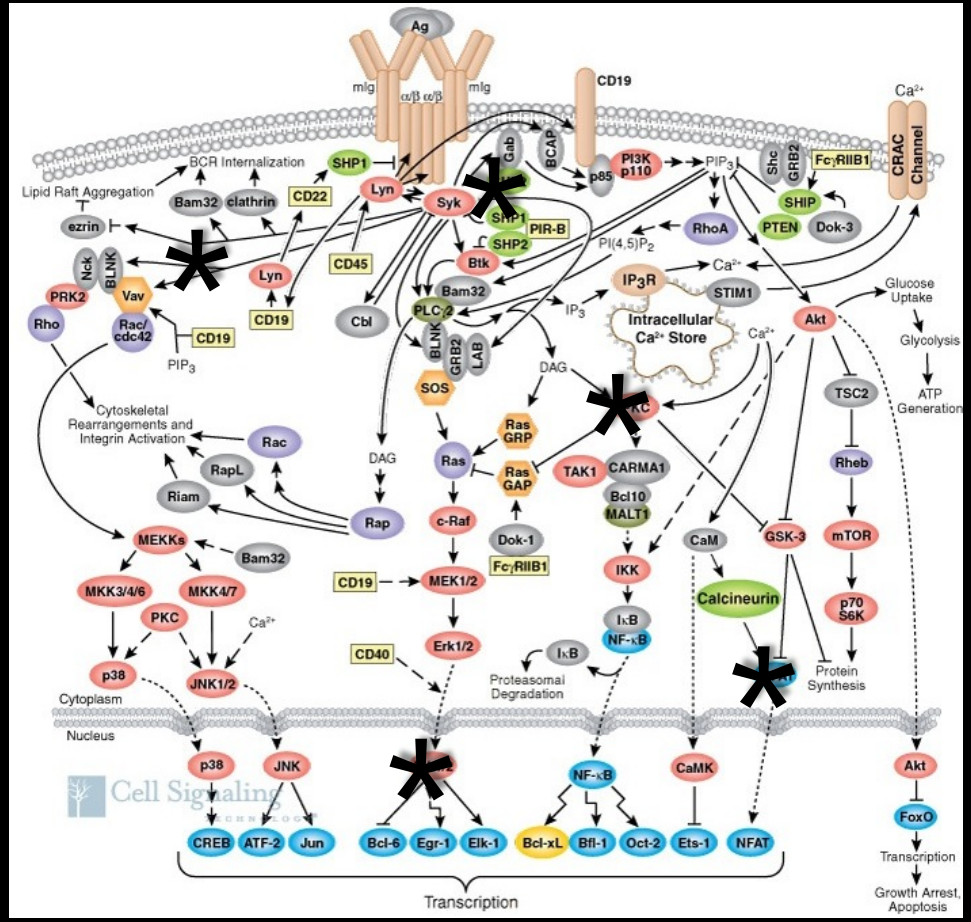


Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

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

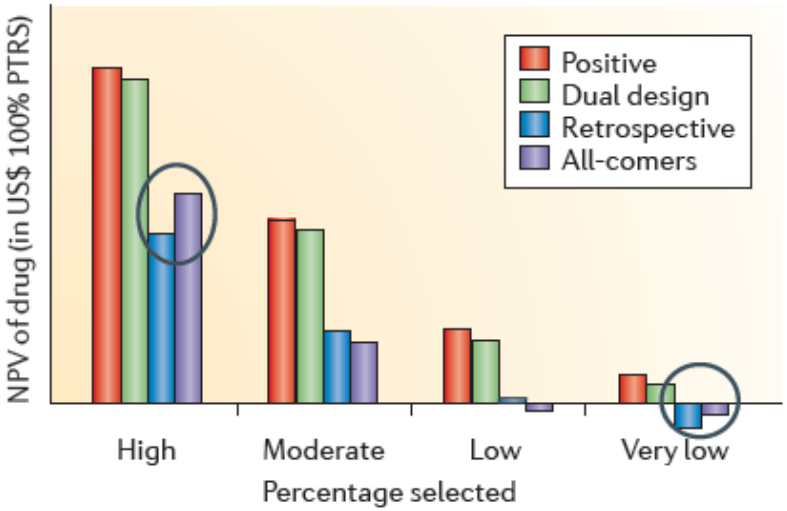


ID Molecular Targets for MDx and/or Rx Action



The Heterogeneity of Biological Pathway Dysregulation in Different Diseases

- frequency of Rx susceptible (Rx^s) and resistant (Rx^r) phenotypes in different diseases and changes with disease progression
- implications for level of inter-patient variation and complexity of MDx profiling requirements



Input parameters

Percentage selected by companion diagnostic			
94%	64%	25%	6%
Positive predictive value			
41%	33%	39%	64%
Therapeutic response in responders (scale 0–24)			
18	18	18	18
Percentage of all patients who respond			
35%	35%	35%	35%

Calculated parameters

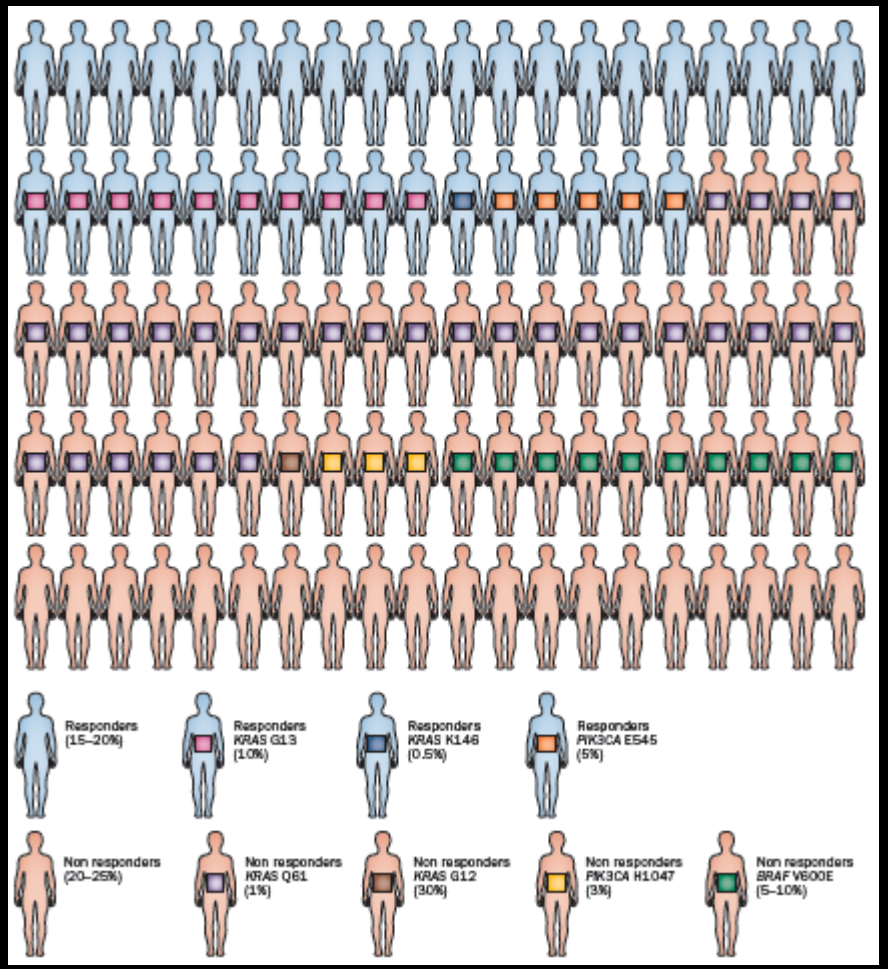
Selected patient therapeutic effect			
7.3	5.8	7.1	11.4
All-comers therapeutic effect			
7.2	4.1	2	1.8
Selected patient market share			
46%	35%	41%	65%
All-comers market share			
44%	24%	12%	11%

Scenario-Modeling of NPV for New Investigational Drug Based on Probability of Technical and Regulatory Success (PTRS) and Biomarker Patient Selection

From: M. R. Trusheim et al. (2011) Nature Rev-Drug Disc 10, 817

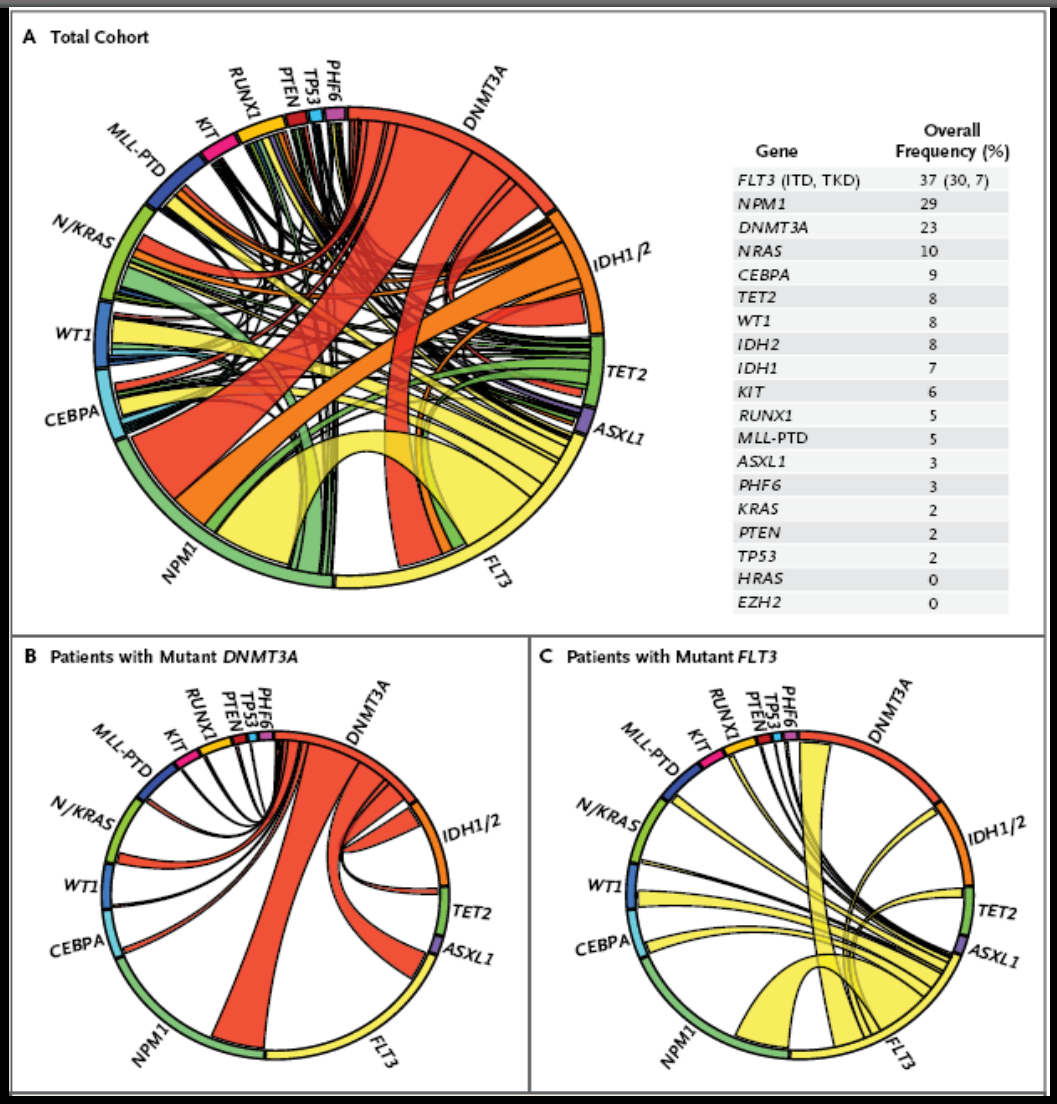
http://www.nature.com/nrd/journal/v10/n11/pdf/nrd3557.pdf

Frequencies of Molecular Alterations in CRC and Responsiveness to Cetuximab or Panitumumab



From: M. Martini et al. (2012) Nature Rev. Clin. Oncol.

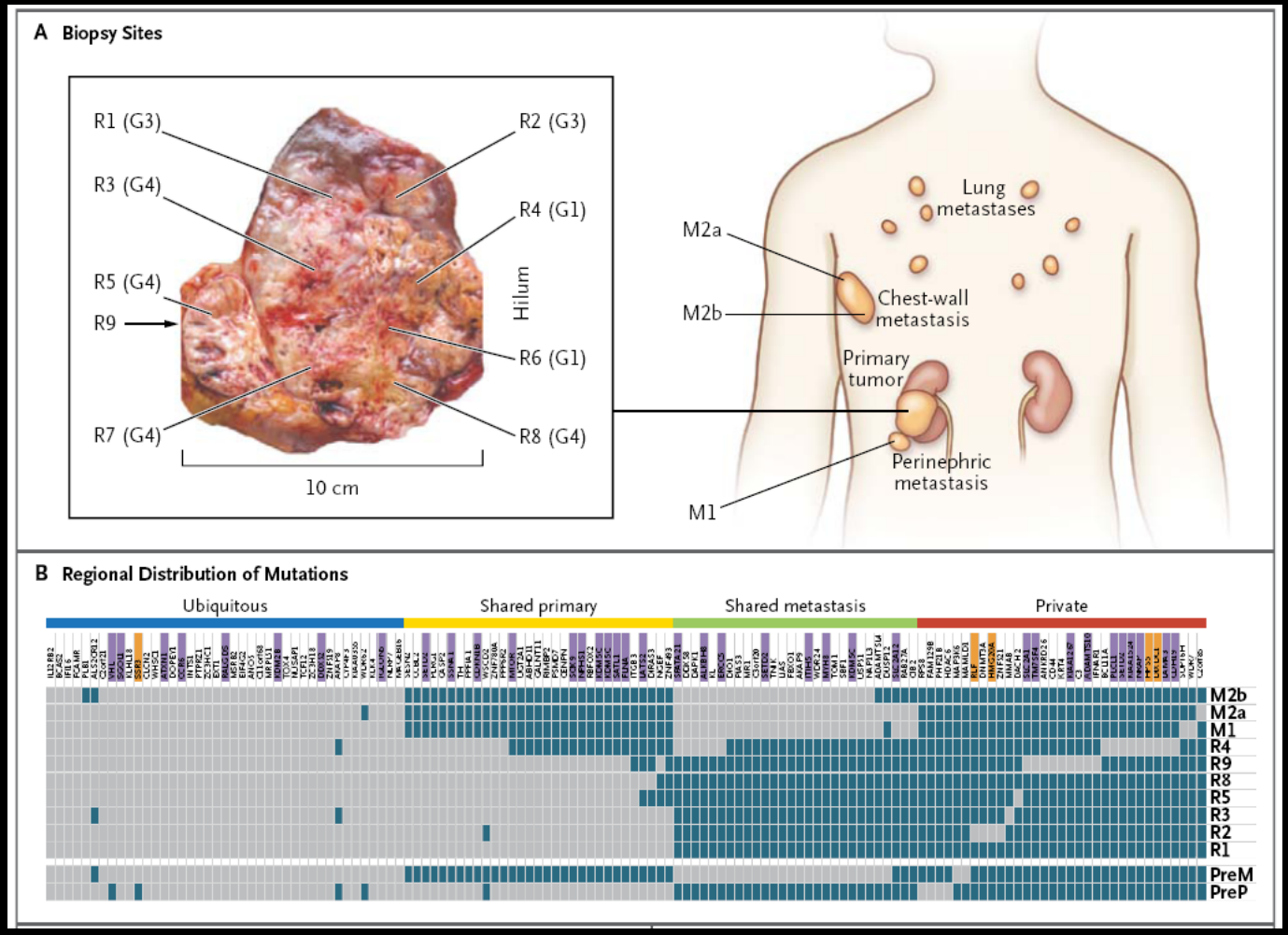
Mutational Complexity of Acute Myeloid Leukemia



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

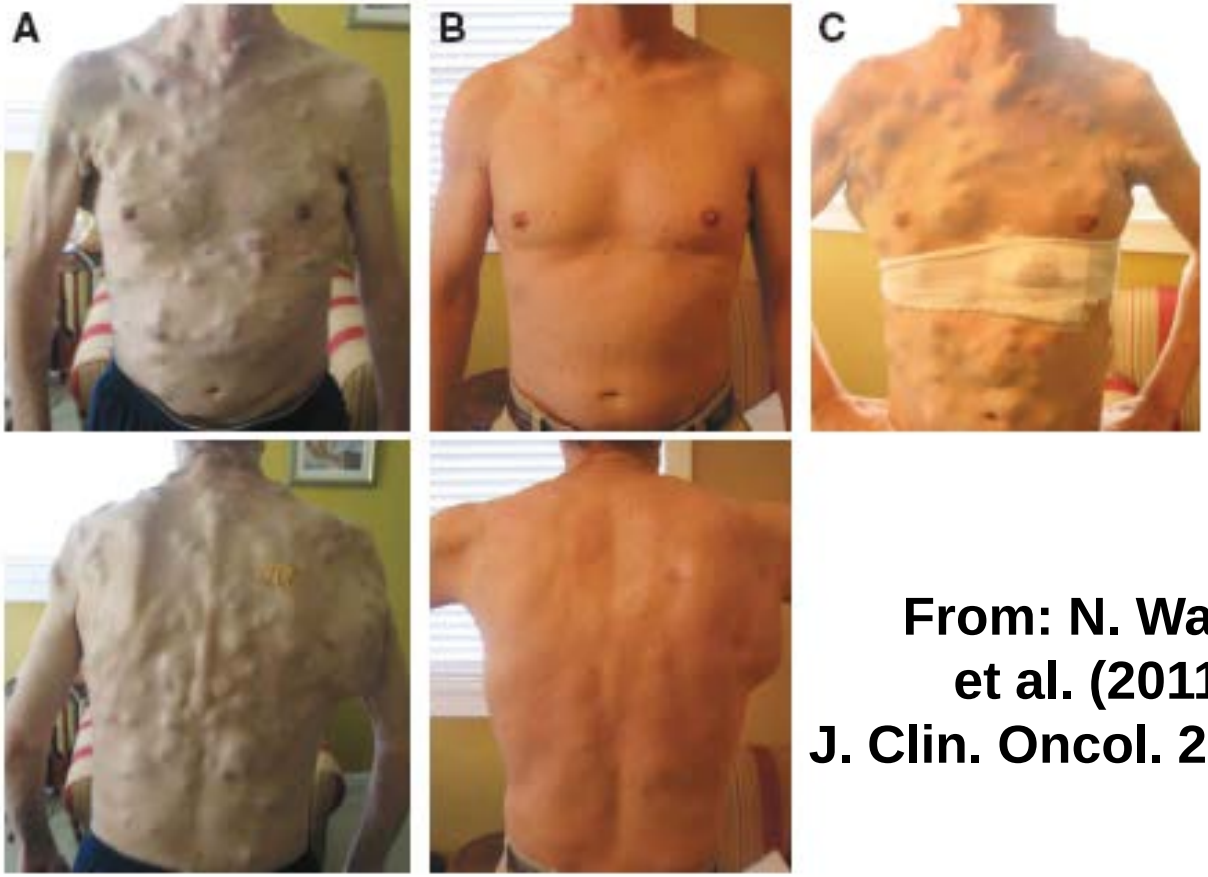
From: J. P. Patel et al. (2012) NEJM 366, 1079

Intratumor Genetic Heterogeneity in Multiple Regions at Primary Clear Cell Tumor and Three Metastases (Perinephric and Chest Wall)



From: M. Gerlinger et al. (2012) NEJM 366, 883

Initial Response (A/B) of BRAF-V600 Positive Metastatic Miliary Melanoma After 15 Weeks Therapy with Vemurafenib (Zelboraf® - Roche) Followed by Rapid Recurrence of Rx-Resistant Lesions with MEKI C1215 Mutant Allele After 23 Weeks Therapy

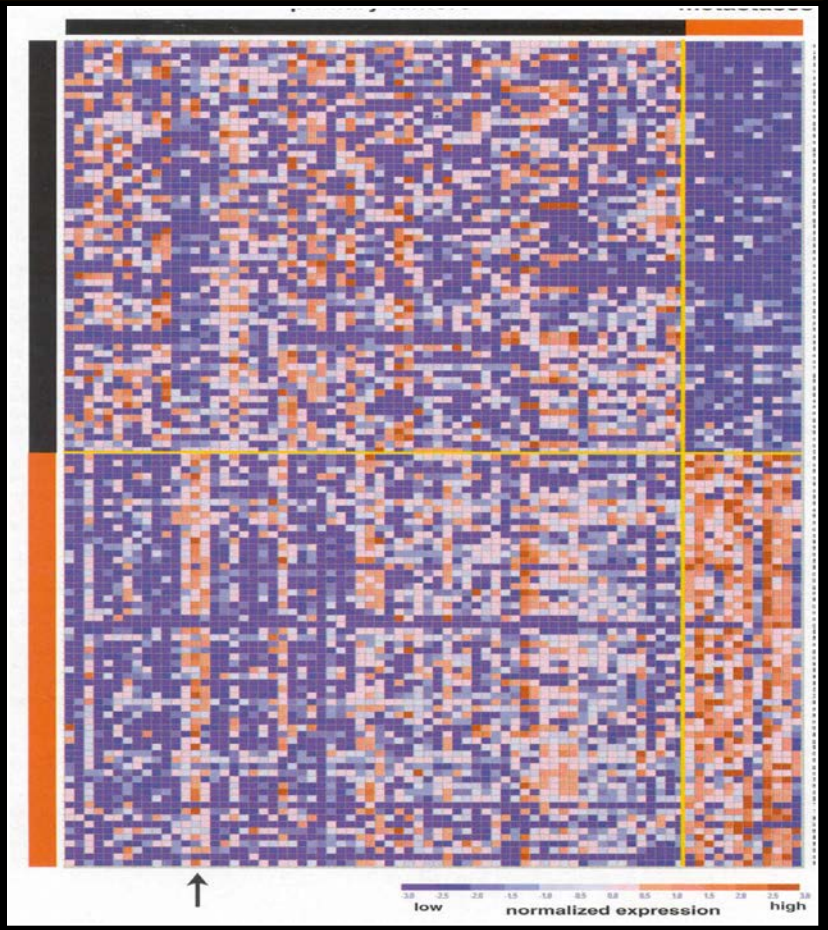


From: N. Wagle et al. (2011) J. Clin. Oncol. 29, 3085

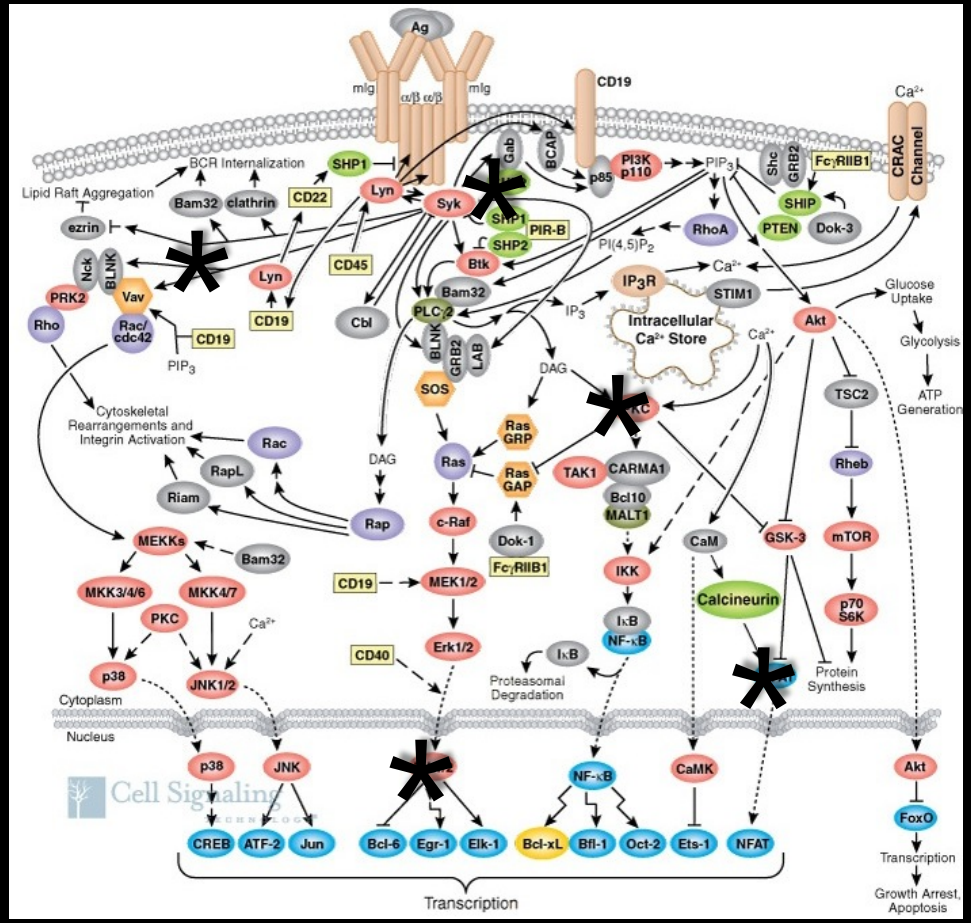
http://jco.ascopubs.org/content/29/22/3085.full.pdf+html

Mapping Dysregulation of Biological Networks in Disease

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



ID Molecular Targets for Rx Action and Blockade of Compensatory "By pass" Pathways



Network Pharmacology

- elucidation of definitive network ‘chokepoints’ as optimum targets
  - subvert adaptive cellular options to use alternate compensatory pathways
- the design challenge for multi-target polypharmacology
  - multi-agent therapy (patient tolerance?)
  - controlled multi-target promiscuity in a single moiety

Mandatory Use of Research Biopsies in Clinical Trials?

Time Point	Purpose
Pre-enrollment/ Pre-treatment	• ID of biomarkers to determine eligibility • patient stratification in enrichment/adaptive clinical trial design
During Treatment Protocol and/or Post-Protocol Termination	• evaluate biomarkers/ biosignature profile and Rx responsiveness • identify mechanisms of acquired resistance to investigational Rx

Tough Questions

Is the scale of pathway dysregulation in progressive late stage multigenic diseases too large to achieve Rx “homeostatic reset”?

Should MDx priorities in cancer, neurodegeneration and diabesity be best directed to earlier disease detection rather than stratification of patients with advanced disease?

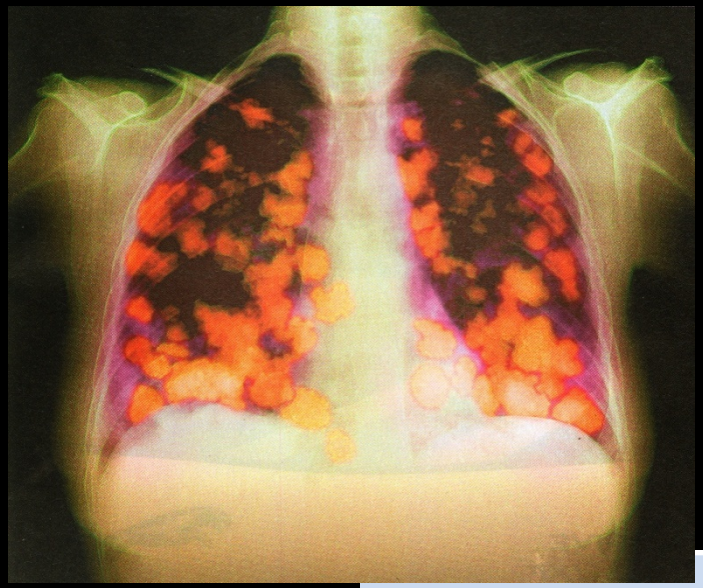
Phase III Studies Comparing Chemotherapy With or Without Bevacizumab as First-Line Therapy for Advanced Epithelial Cancers

Neoplasm	Study	Bevacizumab Effect	
		PFS (months)	OS (months)
Breast	ECOG E2100	+5.9*	+1.5
	AVADO	+0.8*	-1.1
	RIBBON-1	+2.9*	+7.8
Ovarian	GOG 0218	+0.9	-0.6
Lung	ECOG E4599	+1.7*	+2.0
Gastric	AVAGAST	+1.4*	+2.0
Pancreas	CALGB 80303	+0.9	-0.1
CRC	Hurwitz	+4.4*	+4.7*
	Saltz	+1.4	+1.4

*Statistically significant

Adapted from: A. Ocana et al (2011) J. Clin. Oncol. 29, 254

Palliative Care as Evolving Standard of Oncology Care



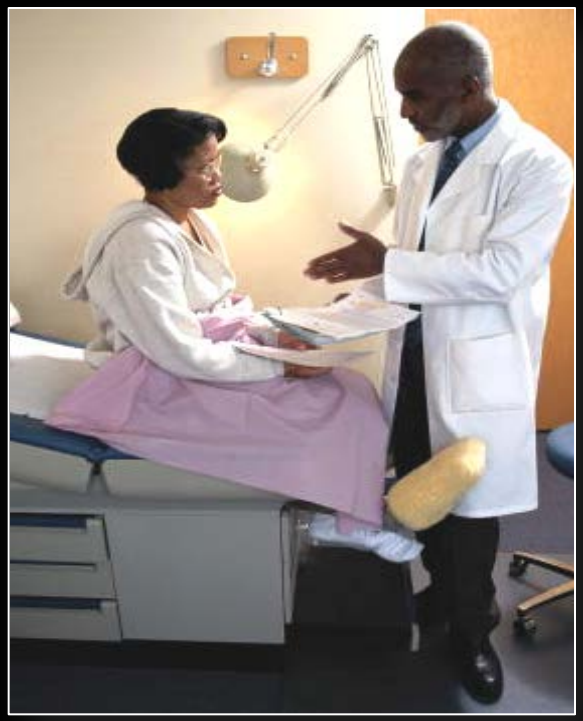
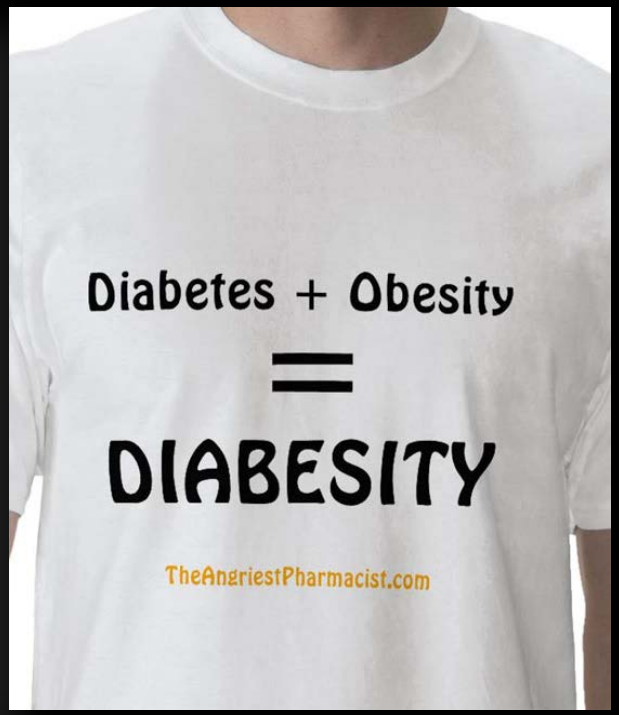
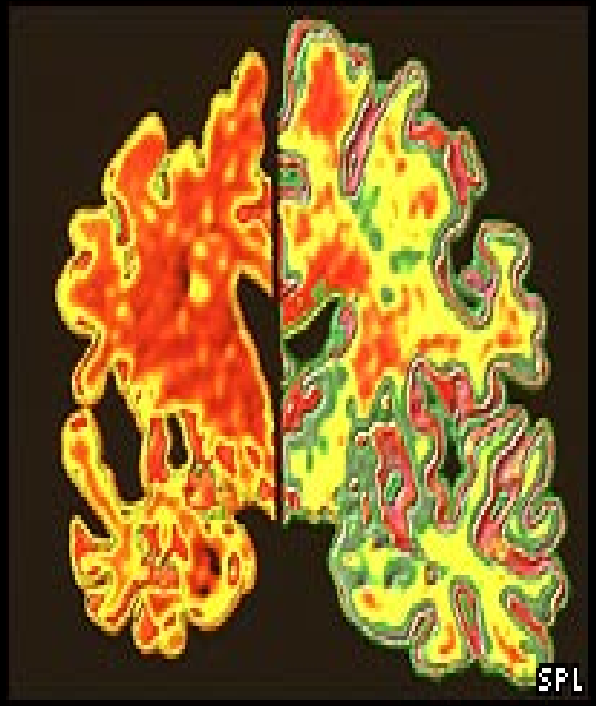
JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Provisional Clinical Opinion: The Integration of Palliative Care into Standard Oncology Care

Thomas J. Smith, Sarah Temin, Erin R. Alesi, Amy P. Abernethy, Tracy A. Balboni, Ethan M. Basch, Betty R. Ferrell, Matt Loscalzo, Diane E. Meier, Judith A. Paice, Jeffrey M. Peppercorn, Mark Somerfield, Ellen Stovall, and Jamie H. Von Roenn

Opportunities and Challenges for MDx for Ever Earlier Detection of Major Diseases

Cancer Detection Before Metastasis	Cardiovascular/ Metabolic Diseases	Neurodegenerative Diseases
		
Early Diagnosis and Curative Surgery	Lifestyle Changes and/or Rx to Limit Risk	The Dilemma of Early Diagnosis Without Rx

Defining The Molecular Taxonomy of Disease

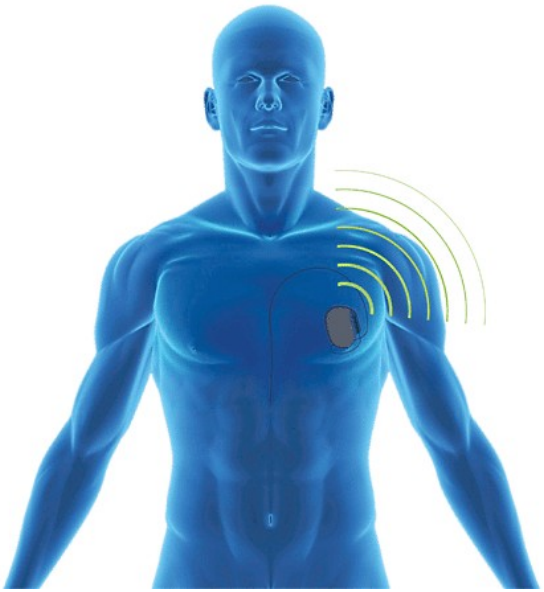
- subtypes of disease
- individual segmentation and unique patient-specific perturbations in biological networks
- increased segmentation and what will constitute an orphan disease?
- ‘the incidentalome’
- longitudinal tracking of health status and early detection of disease

The Invasion of the Body Trackers

Individual Biosignature Profiling Via Sensors and Devices

Remote Health Status Monitoring

m.Health



Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

MICROCHIPS™

Company | Products | Technology | News

Products

MicroCHIPS drug delivery and sensor technology both leverage the ability to microfabricate multiple wells into a microchip, and integrate that into an implantable device that uses these wells to deliver drugs or sense various analytes. Much like existing pacemakers and other implantable devices, the MicroCHIPs device also communicates wirelessly, allowing both control of the device and data transmission.

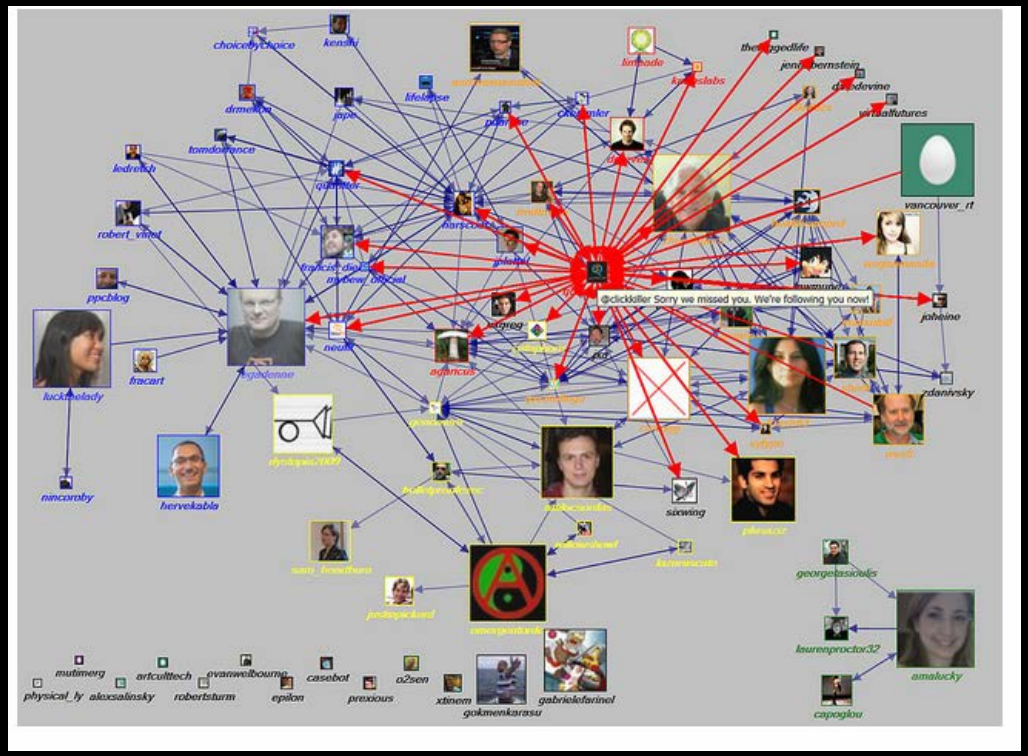
The device is implanted subcutaneously (under the skin) in a simple outpatient procedure using local anesthesia, and a small incision. The device is inserted much like a pacemaker with a couple of sutures to prevent device movement.

 1000 Winter Street, Suite 3350, Waltham, MA 02451 • Phone: 781-522-6798

Bob Langer micro chips and drug delivery

Remote Health Status Monitoring of Biometrics and Biomarkers Using Body Sensors and Devices (m.Health)

- Self-Tracking
- Personal Informatics
- Quantified Self
- Lifelogging
- LifeStream
- The Measured Life

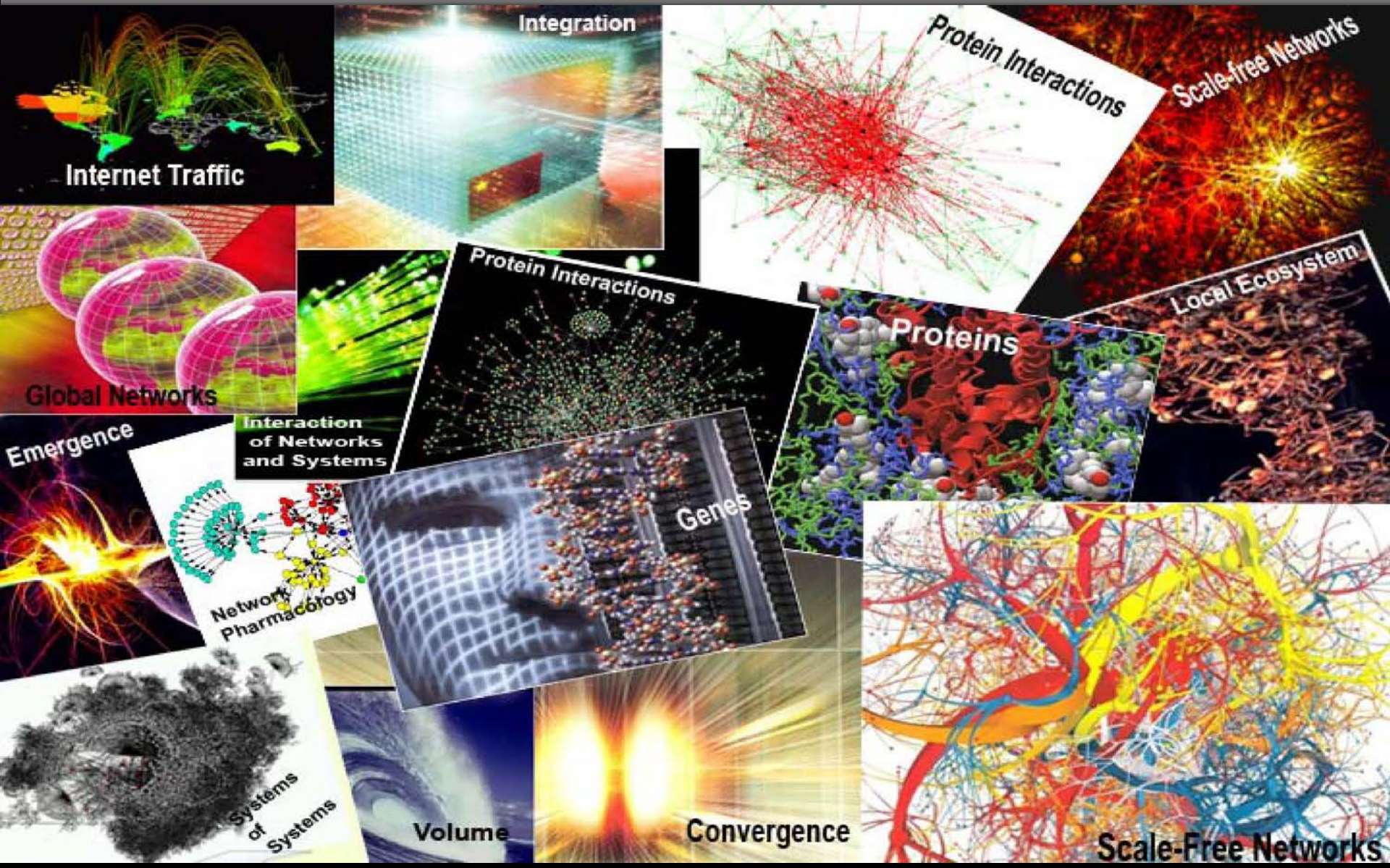


NodeXL maps of tweets about Quantified Self
Posted on January 26, 2011 by Alexandra Carmichael

Mobile Devices, Remote Health Monitoring and Rapid Data Expansion

- expand concept of biobank to include ‘virtual and living repositories’
- individual becomes their own control
  - longitudinal monitoring of individual ‘deltas’ versus comparison with averaged larger cohort
- rich data streams for outcome analysis and epidemiological studies
  - consent, privacy and security
  - compliance monitoring

Data: The Fastest Growing Resource on Earth



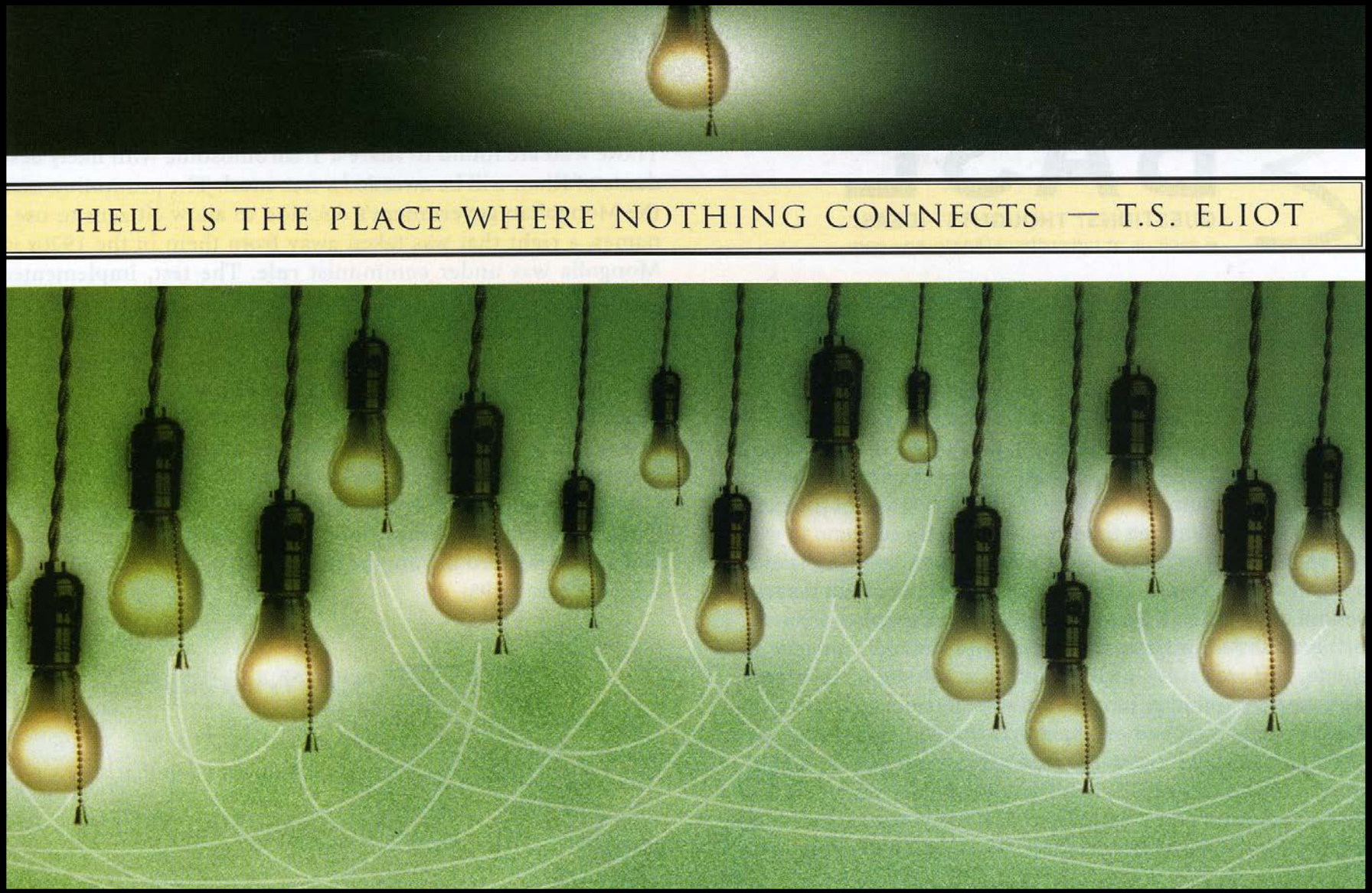
Managing Massive Data

Standards for Data Reporting and Database Design

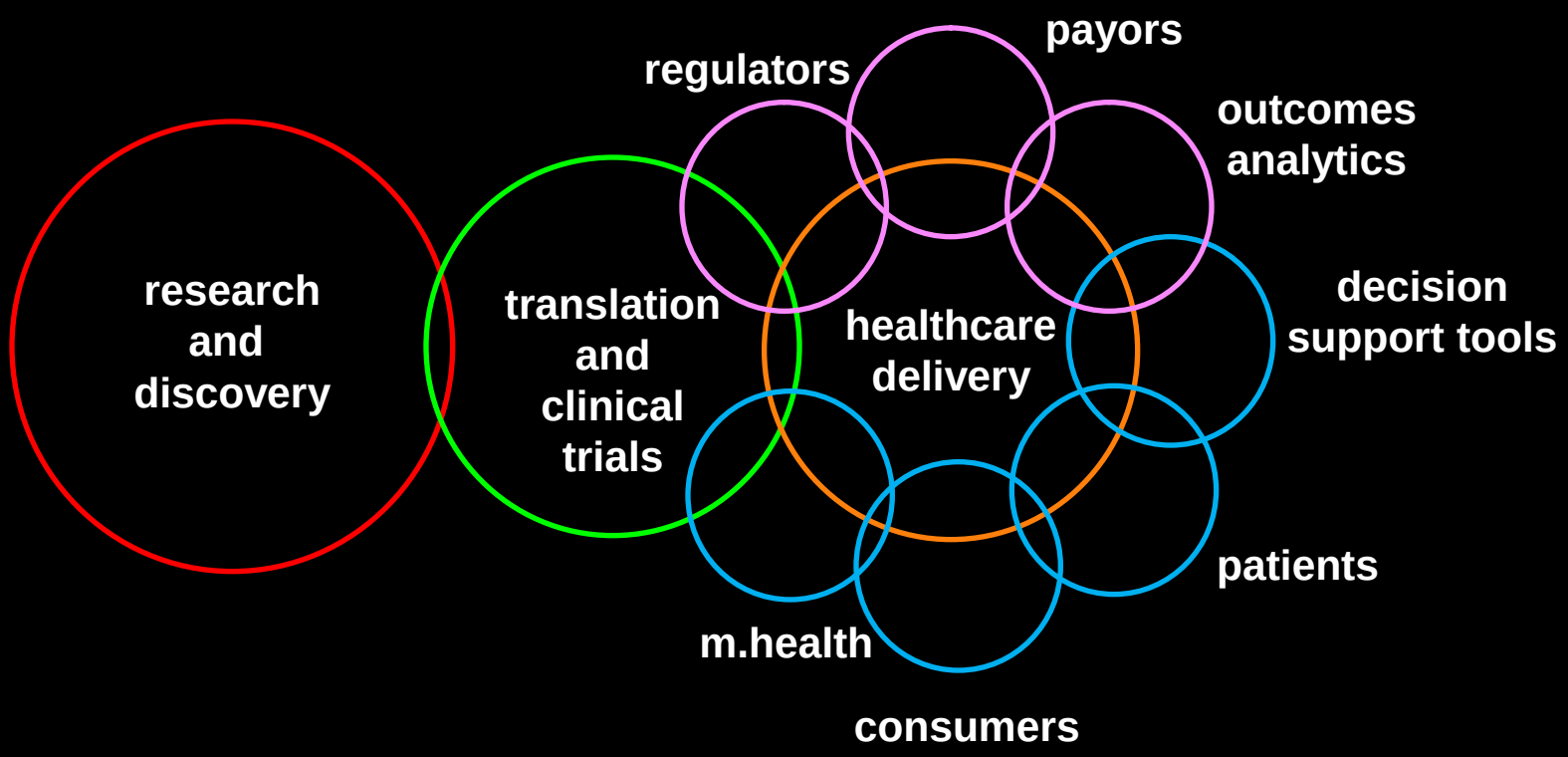
Interoperability of Databases
Across The Continuum from Discovery to Patient Care

New Analytics and High Performance Computing

Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo



The Need for Facile, Seamless Data Exchange Formats for Large Scale Biomedical Data Systems



The Design Challenge for Next Generation HIT Systems

- today EHRs not designed to support secondary use of data to inform research/translational medicine
- lack of harmonized data standards in different disciplines/delivery systems as handicap to data meta-analytics outside of original capture institution
- urgent need for new data integration models
  - current and planned RCTs
  - observational data from primary care provider and patient self-reported data
  - SEER (surveillance, epidemiology and end results) data
  - m.health/sensor net remote data monitoring
  - payer data

Representation of Datasets and Abstractions

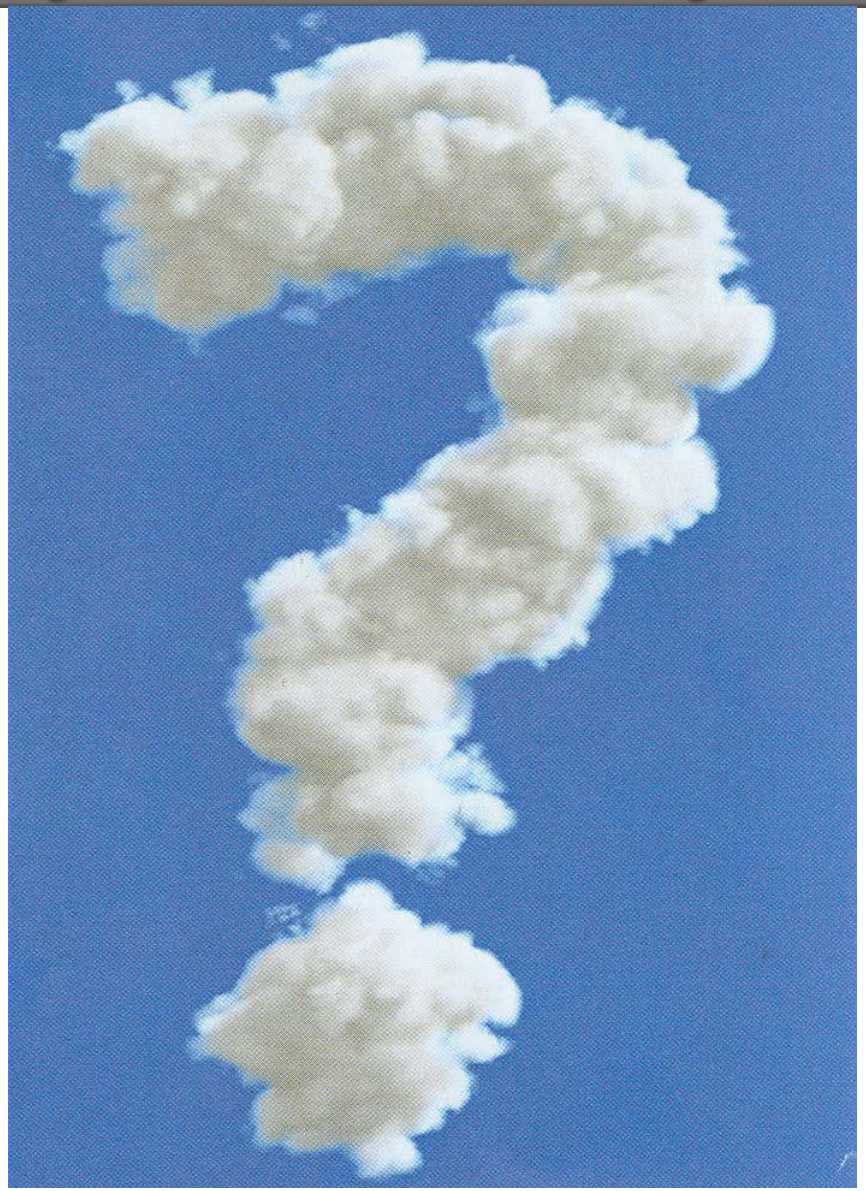
Discovery

- controlled vocabularies and formal ontologies
- minimal information checklists and open source repositories
- algorithms and source code for analytical tools

Translation and Adoption in Routine Care

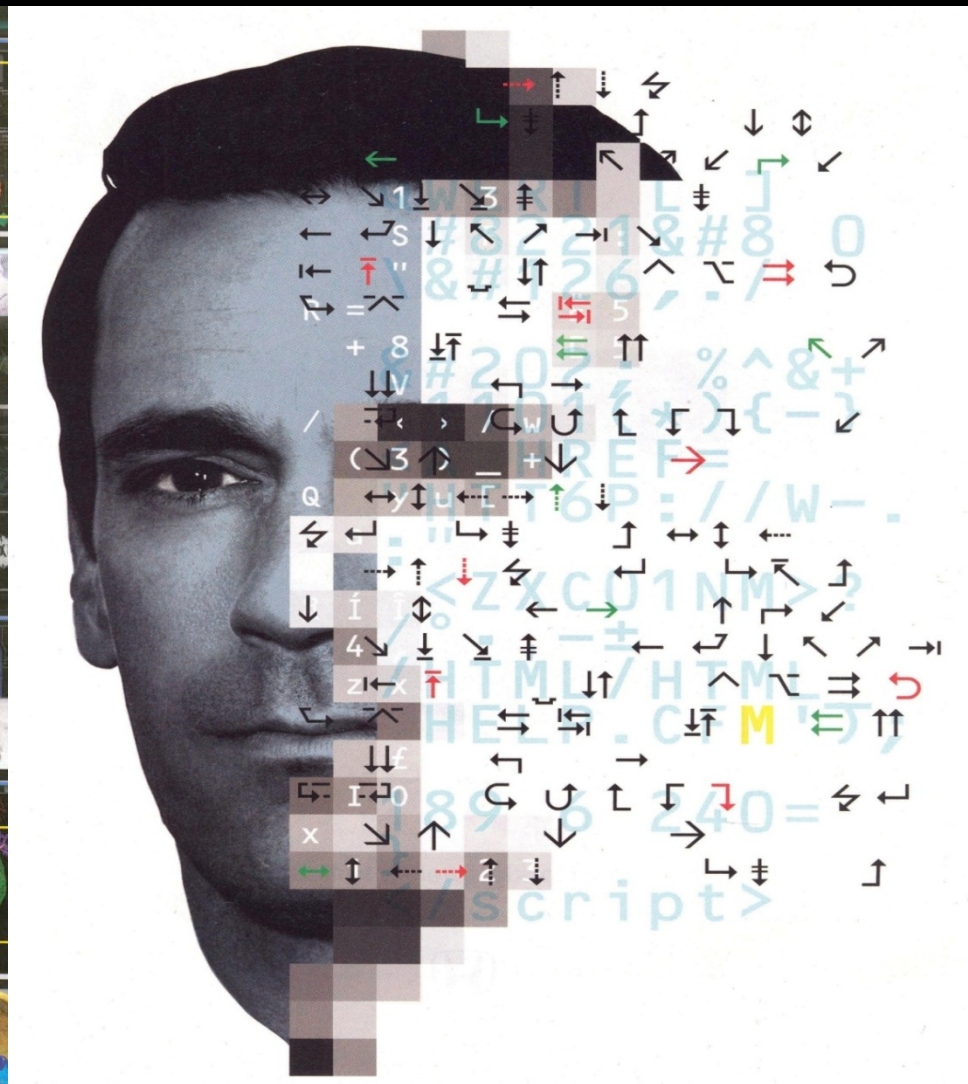
- exchange formats and semantic interoperability
- cross-domain harmonization/integration/migration/sharing
  - community-driven (eg. SMBL.org, BioSharing catalogue), industry-driven (eg. Pistoia Alliance), regulatory-driven (eg. CDISC), clinical (eg. HL7)
  - reimbursement (CPT, ICD) and HITECH EMR/MU
- consent, privacy, confidentiality, security
- meta-data tools
- machine-based natural language processing and decision support algorithms

Healthcare Data in the Cloud: Security, Confidentiality and Access



NewScientist Jobs

Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula



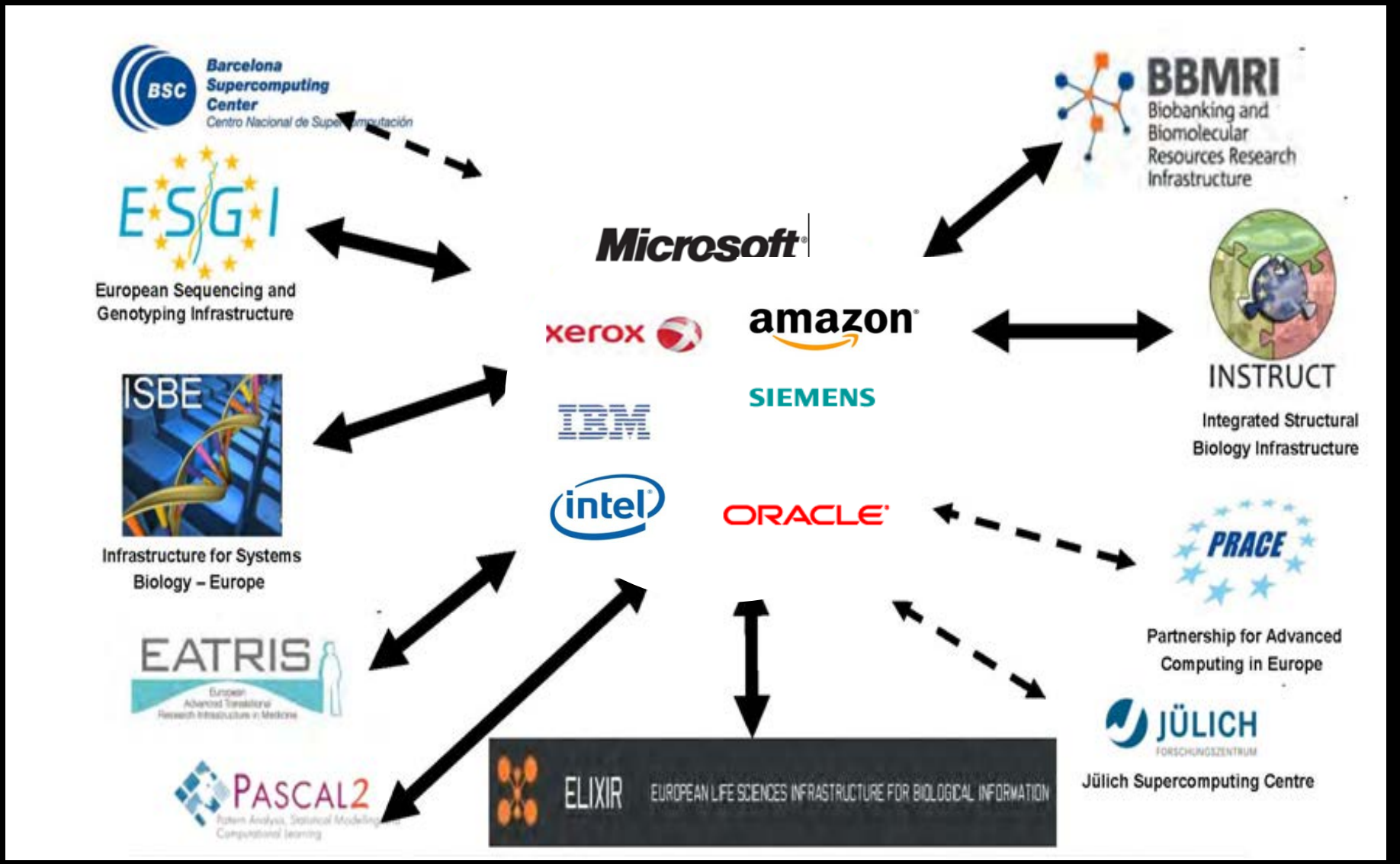
Overcoming Gaps in Physician Knowledge of Molecular Medicine and a Paper-Centric Healthcare System

- 90% of Americans lack confidence in their clinicians ability to understand and use genetic information
  - http://www.cogentresearch.com/news/Press%20Releases/CGAT_2010
- professional cultural vulnerability/reluctance to acknowledge
- refuge in outdated SOC/guidelines that fail to integrate much new molecular profiling data
- protracted deliberations by professional societies/boards
- less than 4% of 8967 ACGME programs relate to genetic expertise (JAMA 2011 306, 1015)
- MD curriculum/CME challenges
- generational gap in IT use/facileness and resistance to computerized decision-support tools

New Partnerships to Advance Clinical and Observational Trials on Biomarkers as a Foundational Element of Molecular Medicine

- public:private partnerships and pre-competitive consortia to establish analytical and data standards
- industry collaboration to validate disease-specific biomarkers in clinical trials
- use of aggregated EMR and observational data to validate biomarkers and CER
- social media and patient advocacy groups as catalysts to accelerate clinical trials and CER

IT Future of Medicine



BATTER-UP:
Biomarkers of Anti-TNF Treatment Efficacy in Rheumatoid Arthritis-Unresponsive Populations

PACeR (www.pacerhealth.org)
The Partnership to Advance Clinical Electronic Research

- use of aggregated EMR data to facilitate clinical research

Proactive Engagement of Patient Communities in Investigational Clinical Trials and Observational Outcomes Studies

- Collate, Annotate, Curate and Host Clinical Trial Data with Genomic Information from the Comparator Arms of Industry- and Foundation-Sponsored Clinical Trials
- Building a Site for Sharing Data and Models to evolve better Disease Maps.

Partnering for Cures | A FasterCures Meeting

CYCORE CYber-infrastructure for COmparative Effectiveness REsearch

CW PHS CENTER FOR WIRELESS & POPULATION HEALTH SYSTEMS

PURPOSE

To improve **cancer-related comparative effectiveness research** by better capturing data on physiological, behavioral and psychological status from research participants at home and as the go about their daily lives.

caBIG cancer Biomedical Informatics Grid

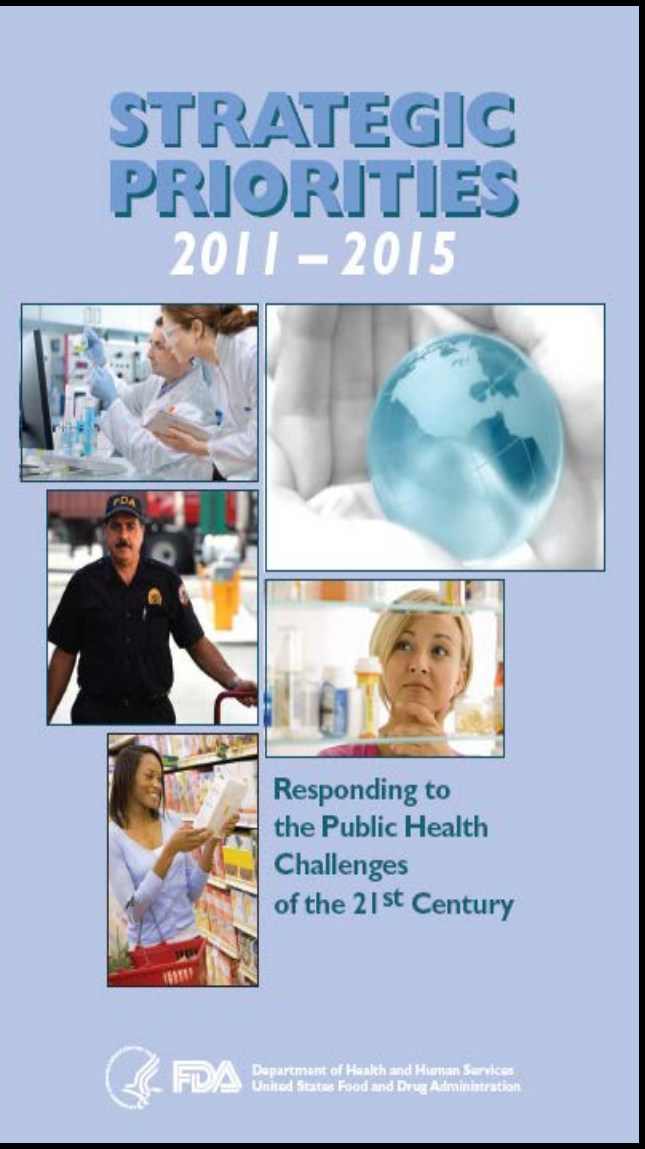
army of women LOVE/AVON Going Beyond a Cure

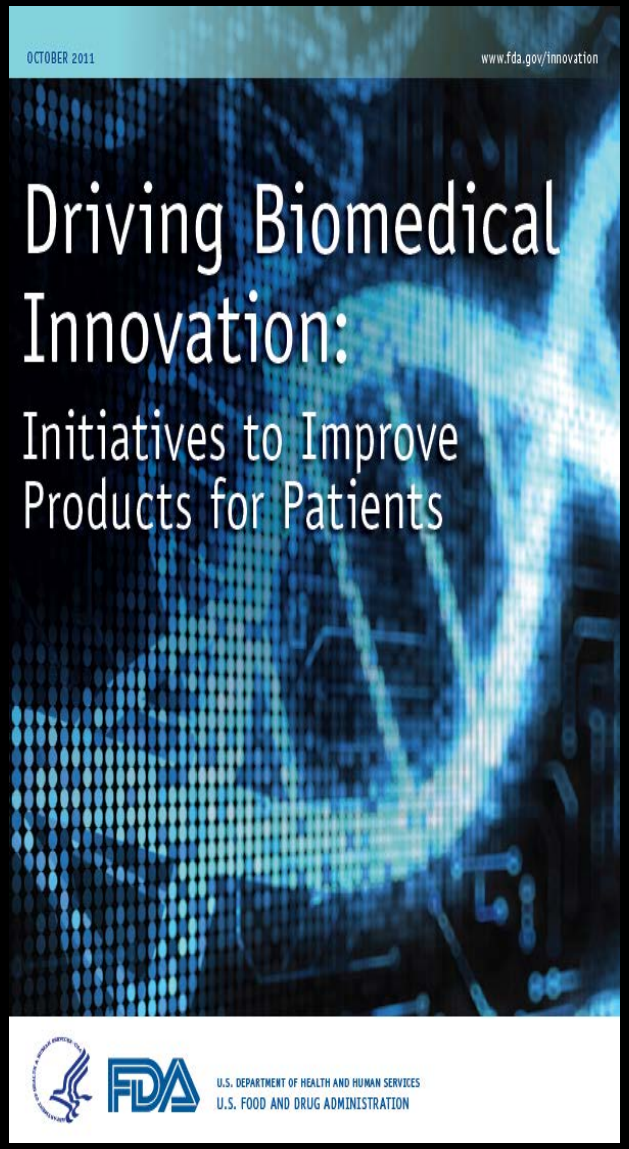
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History

Calit2

CYCORE

Regulatory Science

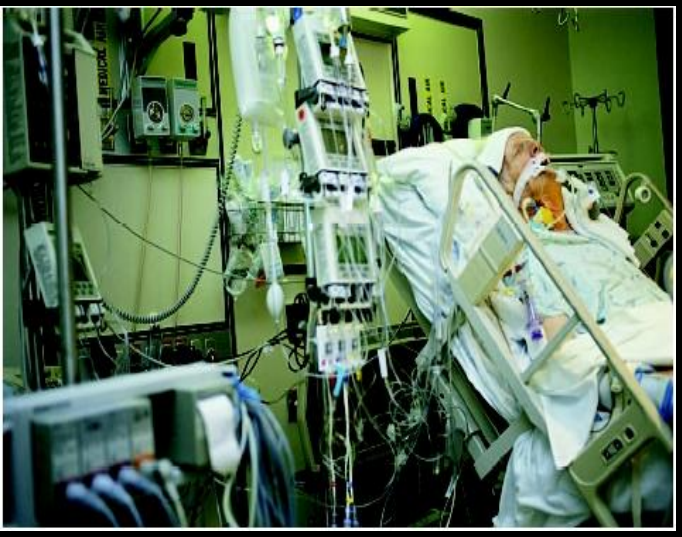


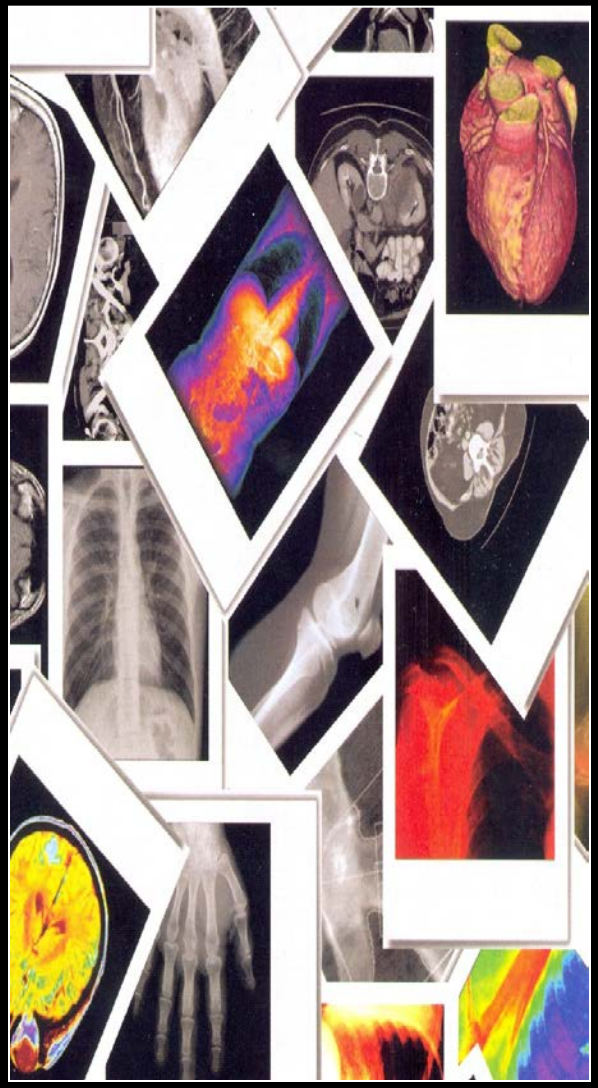


Why LDTs and IVDs May Become MIA

- draft guidelines (1 June 2011)
  - prohibit sale of research use only (RUO)/ Investigational Use Only (IUO) products based on "reason to know" that will be used on clinical samples
- need for greater clarity of guidelines for regulatory approval
  - IVDMIA validation
  - WES and WGS validation
  - MDx: Rx combinations
  - MDx profiling for investigational Rx combinations
  - mandatory biopsy profiling for oncology trials

How Much New Technology Can We Afford?





HEALTH ADVANCES

THE REIMBURSEMENT LANDSCAPE FOR

Novel Diagnostics

- CURRENT LIMITATIONS
- REAL-WORLD IMPACT
- PROPOSED SOLUTIONS

UnitedHealth®
Center for Health Reform & Modernization

Personalized Medicine:
Trends and prospects for the new science of genetic testing and molecular diagnostics

Working Paper 7
March 2012

PMC Personalized Medicine Coalition

Issue Brief

The Adverse Impact of the US Reimbursement System on the Development and Adoption of Personalized Medicine Diagnostics

By David Parker, Ph.D, Boston Healthcare

BOSTON HEALTHCARE

Crossing the Three Chasms:

Complex Molecular Testing and Medicare Regulations

By Bruce Quinn M.D., Ph.D.

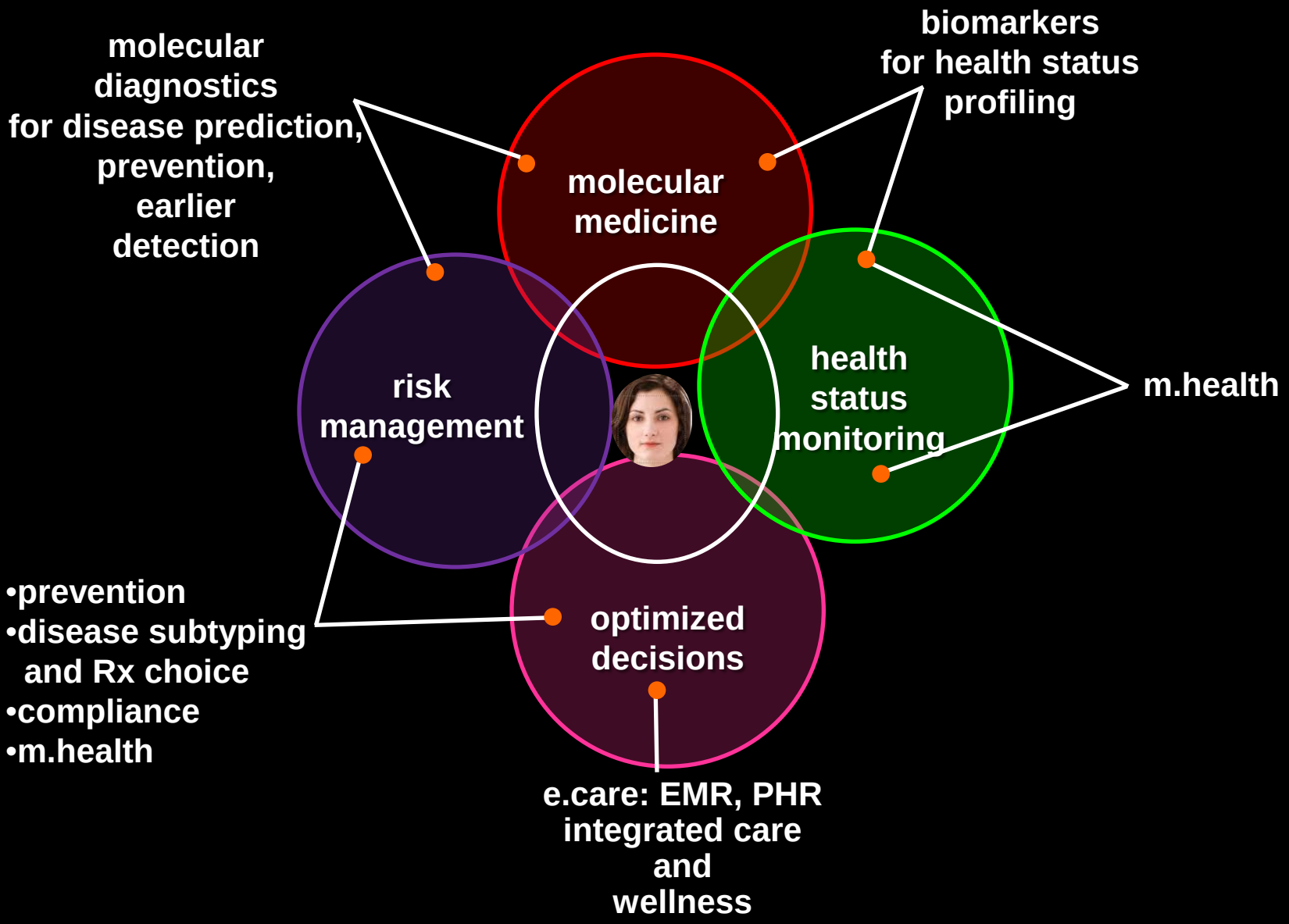
Seaport World Trade Center West
155 Seaport Boulevard
Boston, MA 02210-2600
617 832 1000 *main*
617 832 7000 *fax*

1875 K Street, NW Suite 800
Washington, DC 20006-1238
202 223 1200 *main*
202 785 6687 *fax*

If You Build It, Will They Pay?
If It Isn't Billable, It Won't Happen!

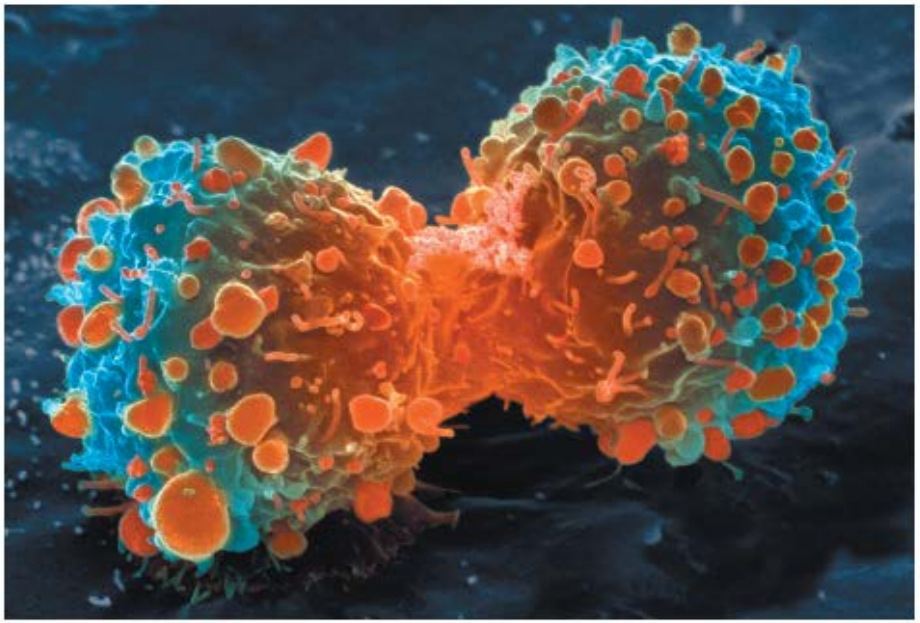
- #1 will test alter patient management?
  - reduce cost of care
  - improve outcomes
- #2 what additional resources/services/training are affected by test adoption?
- #3 perception of RCT as only 'gold standard'
  - narrow interpretation that discounts value of observational studies
- #4 payer demand for regulatory approval to be eligible for reimbursement or CED
- #5 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

The Key Strategic Elements in the Evolution of Molecular Medicine



Nature (2012) 483, 531

COMMENT



Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.

Raise standards for preclinical cancer research

C. Glenn Begley and **Lee M. Ellis** propose how methods, publications and incentives must change if patients are to benefit.

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

- the potential economic and health benefits from biomarkers for molecular diagnostic profiling transcend any other current category of healthcare innovation

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

- realization of this potential will not be straightforward and will require:
  - improved technical standards for biomarker R&D
  - sophisticated integration of complex multidisciplinary expertise (from silos to systems)
  - proactive (inter)national leadership to establish comprehensive resources for biobanks, cyberinfrastructure and HIX data inter-operability
  - new clinical trial designs for Rx/MDx combinations
  - more frequent updating of SOC guidelines to reflect disease subtypes and patient heterogeneity

Biomarkers, Molecular Diagnostics and Molecular Medicine: Regulatory and Reimbursement Reform as Key Success Determinants

- clarity and faster responsiveness of regulatory frameworks to address new MDx technologies
- new reimbursement models for next-generation complex MDx tests that reflect R&D risk, cost and value
- “Crossing the Three Chasms” (B. Quinn)
  - Medicare billing rules
  - coding and reimbursement rules
  - coverage for innovative technologies