Personalized Medicine: Technology, Law and Policy

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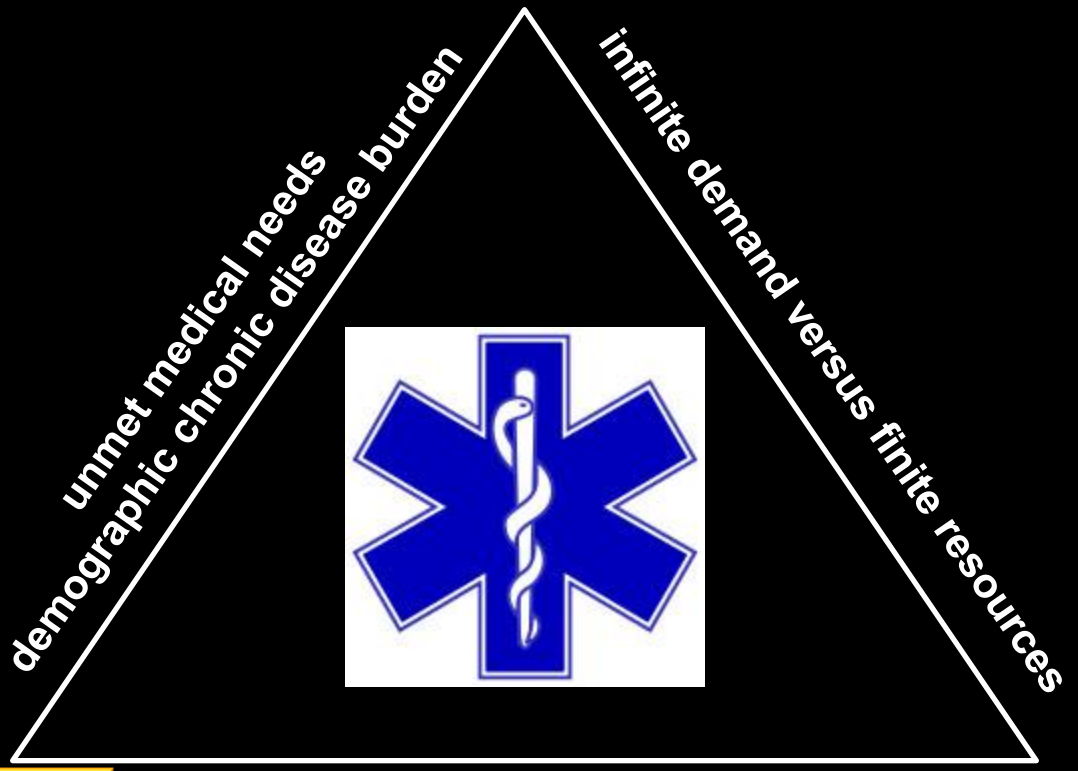
Plenary Session 2: The American Society of Law, Medicine and Ethics
35th Annual Health Law Professors Conference
Tempe, AZ. 8 June 2012

The Healthcare Challenge: Sustaining Innovation and Controlling Cost in an Era of Constraint

Outcomes

clinical, economic, quality-of-life



Innovation and Demonstrating Value

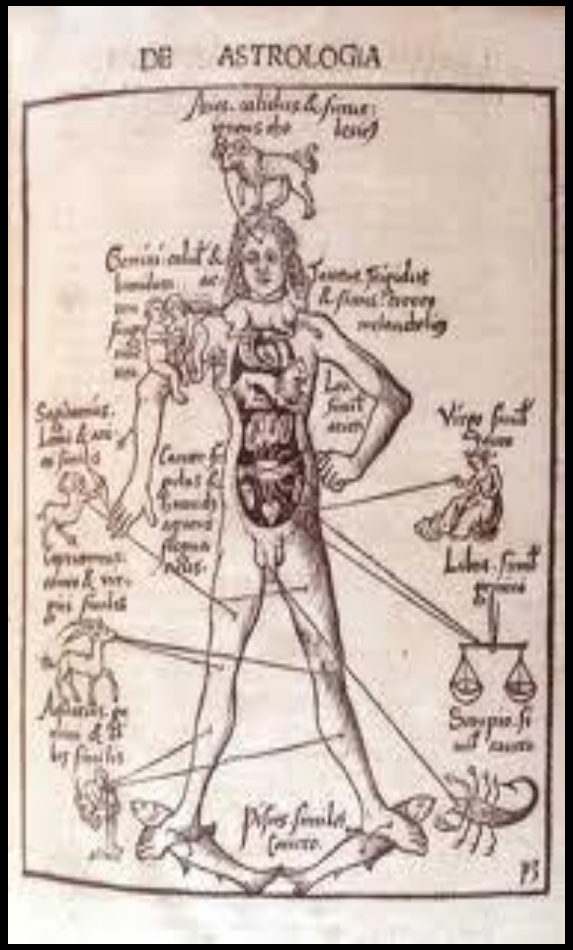
increasing cost of care
and acceleration of new technologies

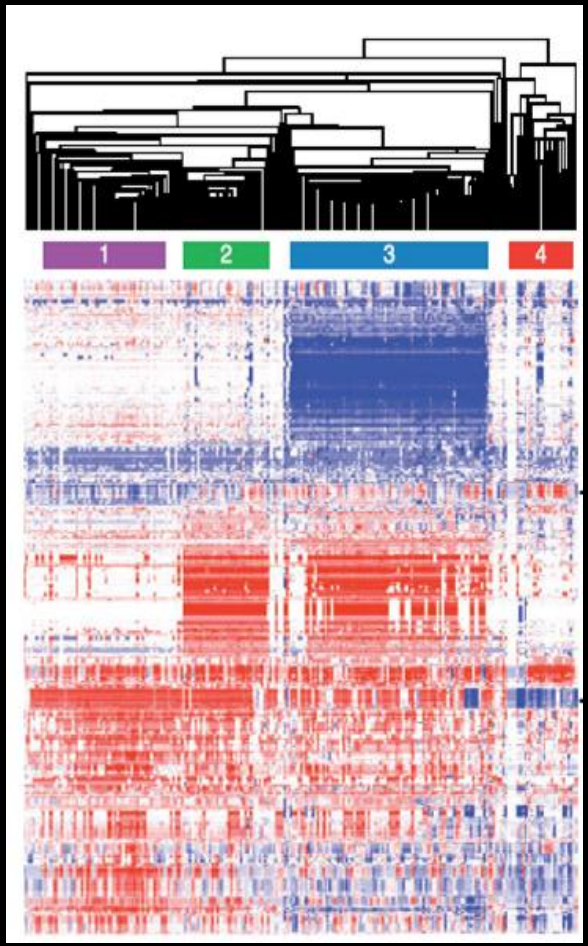
Access to Care

Claims

- personalized medicine is hyperbole
- personalized medicine will be so expensive as to be unaffordable
- personalized medicine is an inevitable outcome of outstanding disease at the level of alterations in molecular information networks and the intellectual foundation for rational care, improved outcomes and cost control

Medical Progress:
From Superstitions to Symptoms to Signatures





Personalized Medicine: Defining Disease and/or Predisposition to Disease as Disruptions in Molecular Information Networks

Molecular Signatures of Health and Disease

- expression/regulation
- modules, pathways, subnetworks and networks

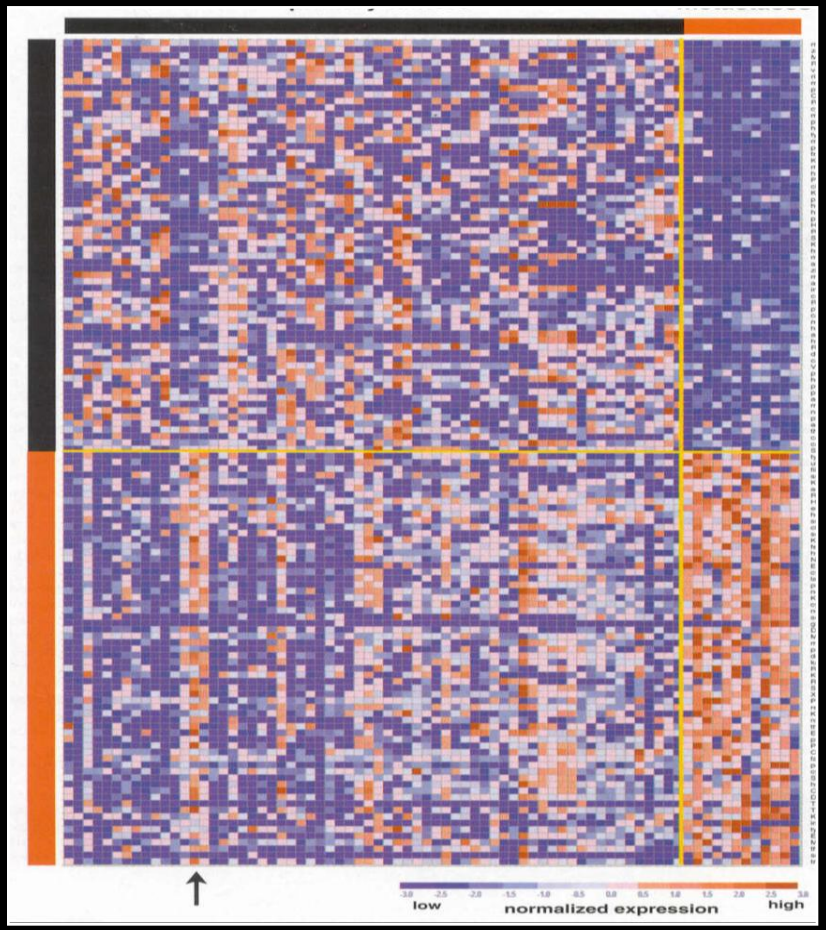
Understanding Biological Systems, Their Regulation and Disease-Associated Perturbations In Terms of Digital Networks

Large Scale Data and Analysis

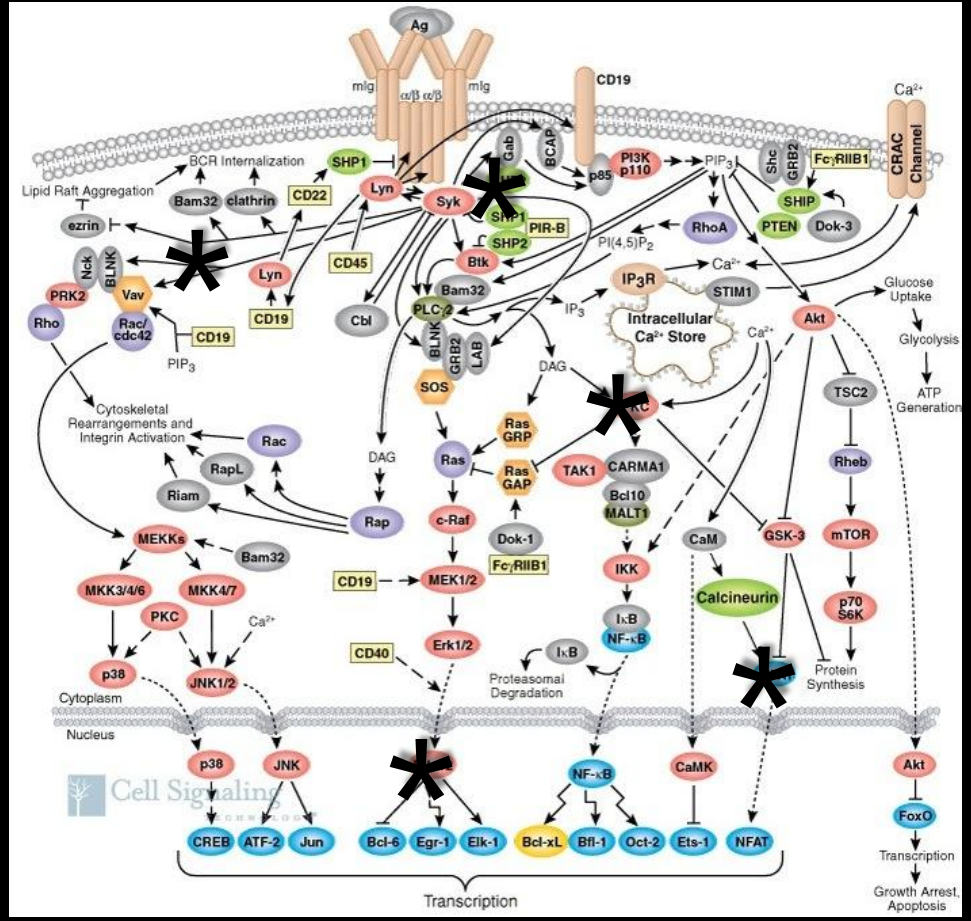
- causality
- rational Dx, Rx
- improved outcomes

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

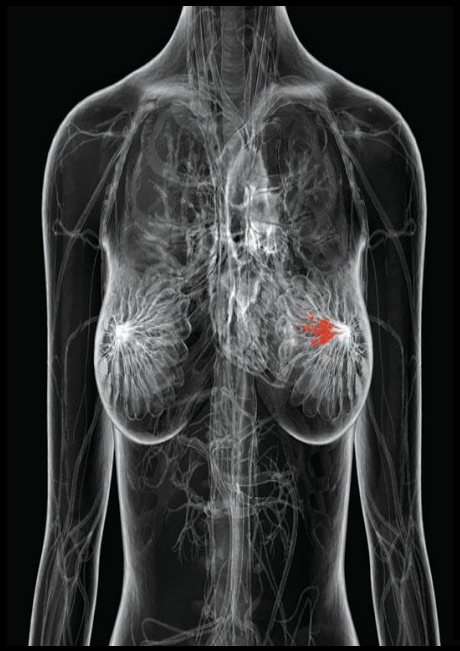
Disease Profiling to Identify Subtypes (+ or - Rx Target)



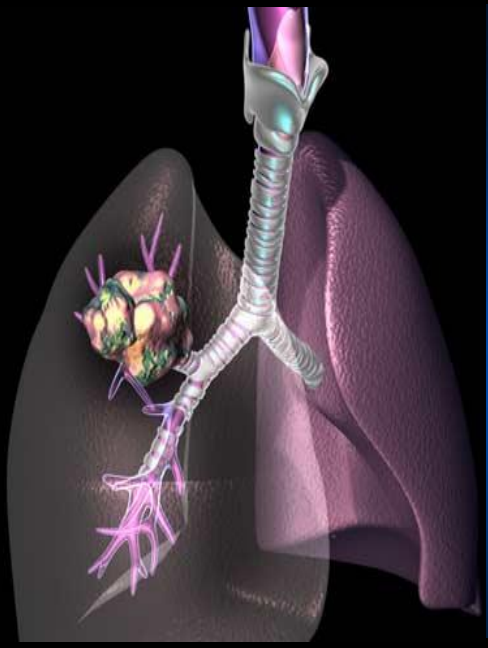
ID Molecular Targets for MDx and/or Rx Action



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

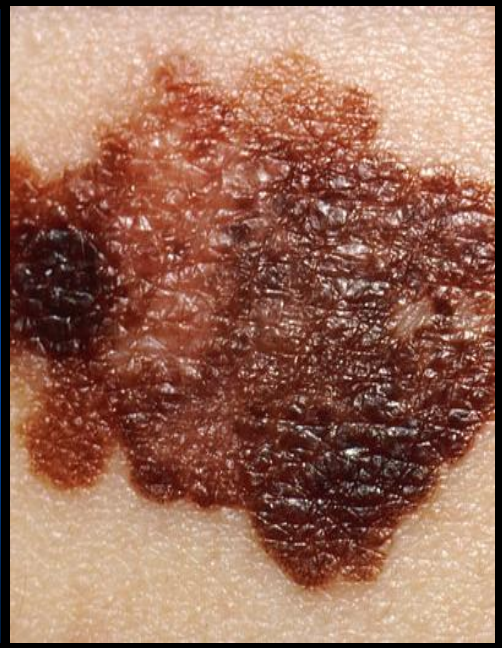


Her-2+
(Herceptin)



EML4-ALK
(Xalkori)

KRAS
(Erbitux)
(Vectibix)



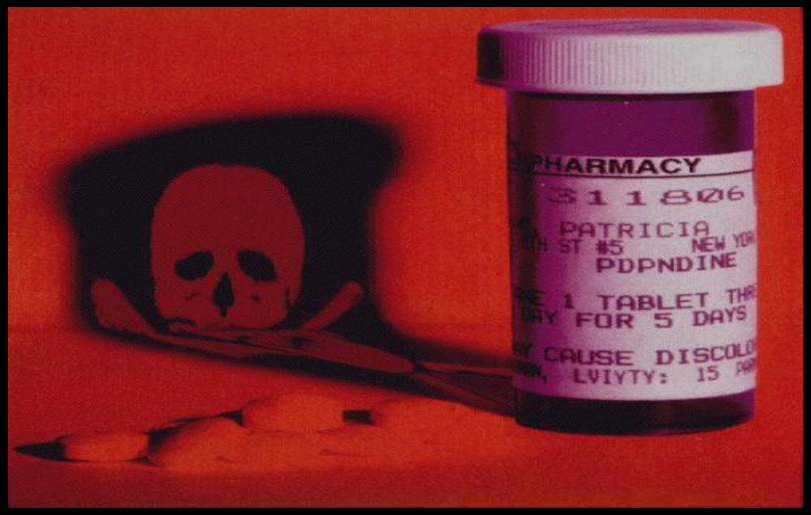
BRAF-V600
(Yervoy)
(Zelboraf)

Molecular Medicine and Rational Therapeutics: Molecular Diagnostics and Targeted Rx

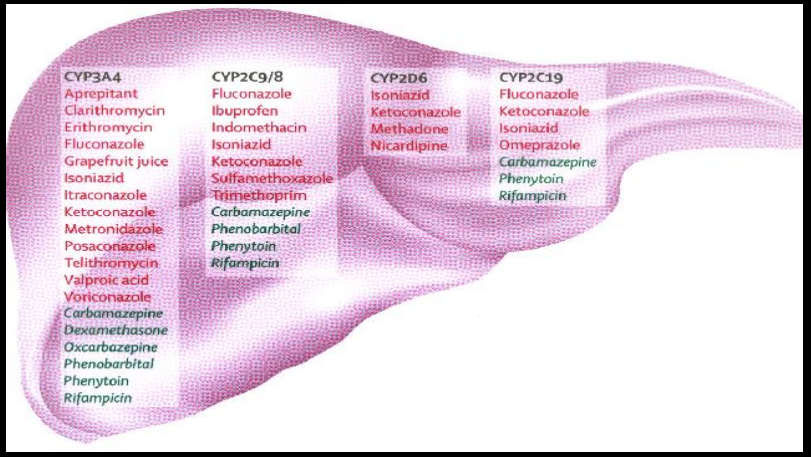
- companion therapeutics selected by precision diagnostics
- opening era in linking disease molecular pathology to rational Rx
- increasing payor, regulatory and public pressures for reliable ID of Rx-responsive patients
- demand for Dx-Rx combinations will intensify
- Dx-Rx combination will become an obligate element of NDA/BLA submission and product labeling
- development of Dx-Rx combinations as intrinsic components of R&D programs for investigational Rx
- need for greater clarity in regulatory and reimbursement policies

Mapping the Genetics of Drug Metabolism: Profiling Patient Risk to Adverse Drug Reactions

Right Rx for the Right Patient



- 1.5 to 3 million annual hospitalizations (US)
- 80 to 140 thousand annual deaths (US)
- est. cost of $30-50 billion



Ethical, Legal and Policy Issues

- inadequate/erratic use of PGx testing
  - professional and payer knowledge gaps
- predictive value of PGx tests may be insufficient for clinical utility
- physician obligations to offer PGx test and obligation to use results
- liabilities
  - physicians, pharmacists, companies, payors
- higher Rx costs for segmented markets and new access barriers?

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

Biomarkers

Experts Claim Errors in Breast Cancer Study Demand Retraction of Practice-Changing Paper

By Paul Goldberg

A group of experts in pharmacogenomics has reopened a scientific question that affects therapy for millions of breast cancer patients worldwide: is it possible to measure how a breast cancer patient metabolizes the drug tamoxifen and tailor the therapy to improve clinical outcomes?

This question first surfaced in 2005, when doctors started to investigate the role of a mutation, called CYP2D6, in the metabolism of tamoxifen. By predicting response or resistance to this inexpensive, widely used drug, doctors were hoping to be able to decide whether a patient would do better on tamoxifen or another therapy—such as aromatase inhibitors.

The ability to make this decision intelligently is of paramount importance to an estimated 150,000 newly diagnosed estrogen receptor-positive breast cancer patients a year in the U.S. alone, many of whom take such drugs for as long as five years.

(Continued to page 2)

The Science Behind the Controversy

Ratain: Data that Killed CYP2D6 Testing Contradict Fundamental Law of Nature

The Cancer Letter asked Mark Ratain, an expert in pharmacogenomics at the University of Chicago, to explain his rationale for challenging a study that suggests that testing for CYP2D6 has no value in clinical practice.

The interview was conducted by Editor and Publisher Paul Goldberg.

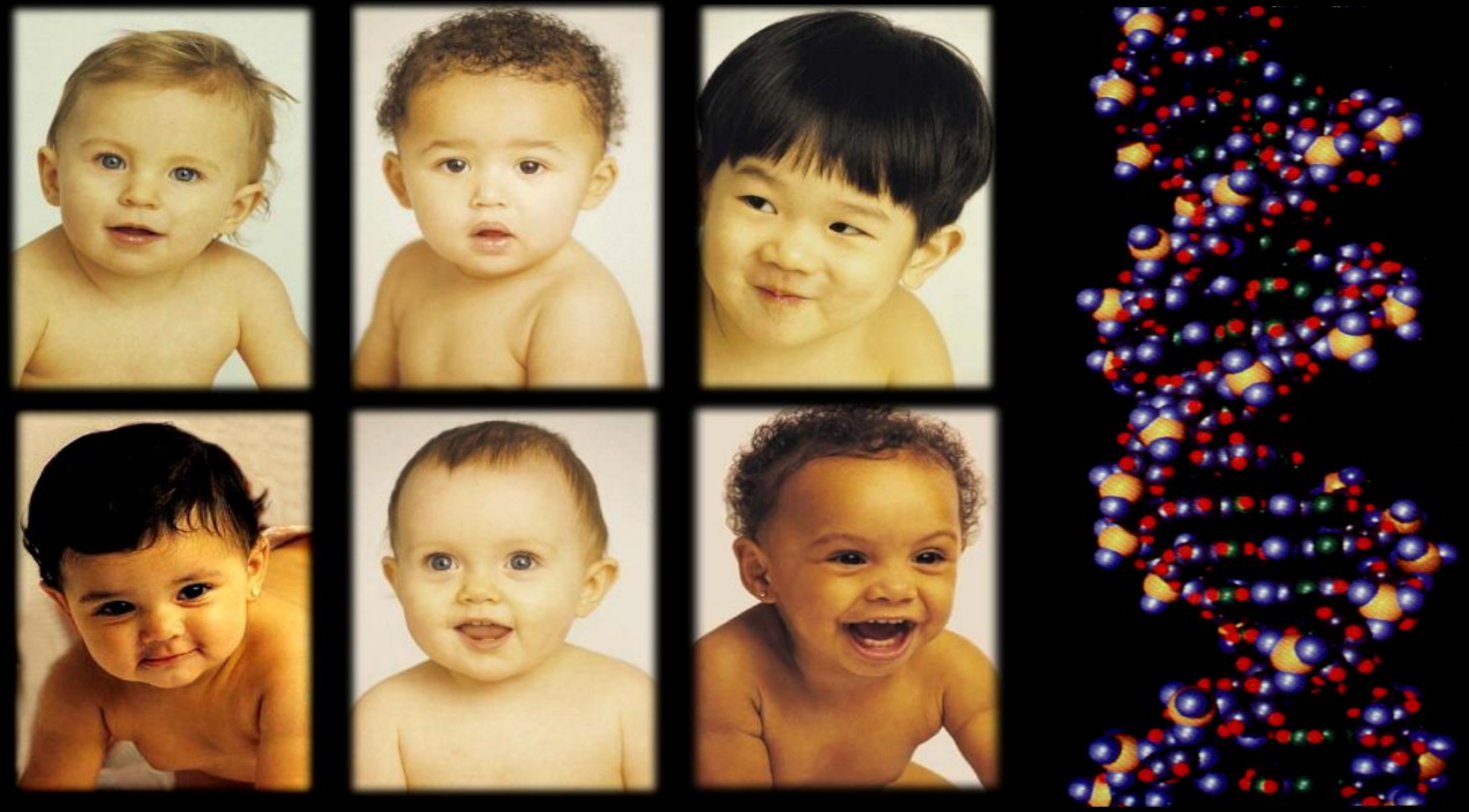
PG: *Why would someone hypothesize that there is a relationship between variation in the CYP2D6 gene and response to tamoxifen*

MR: Tamoxifen is a prodrug, and requires activation by the hepatic P450 system to its antiestrogenic metabolites. The most potent metabolite, endoxifen, is primarily formed by CYP2D6, which is highly polymorphic.

(Continued to page 6)

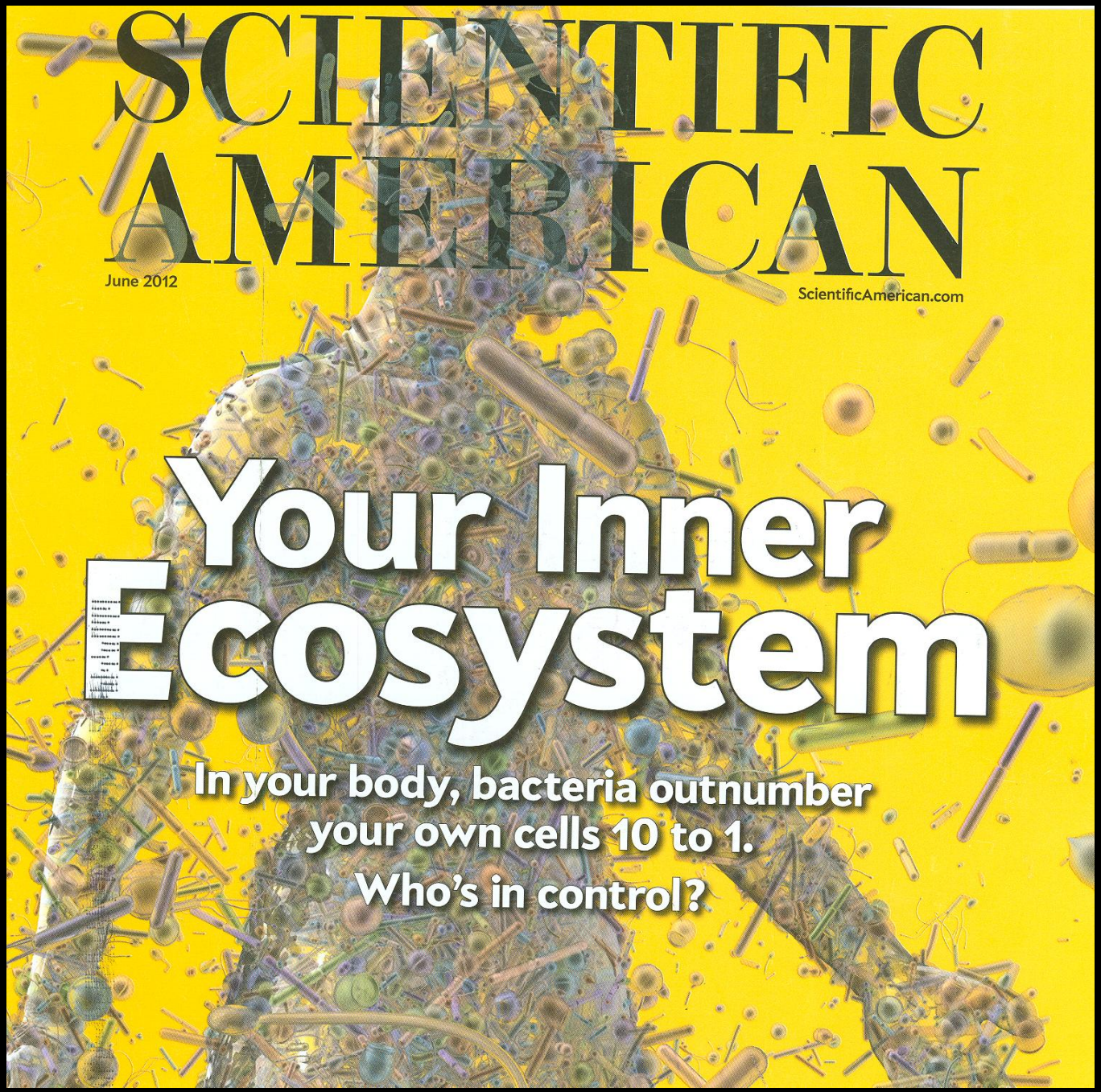
Biomarkers
Standards

Genetic Profiling to Identify Risk of Predisposition to Disease



Profiling Risk of Disease Predisposition

- over-hyped and slow evolution of robust evidence for multigenic diseases
- complex interplay between genes (epistasis) and between genes and environment (epigenetic changes: “the exposome”)
- interactions of multiple low prevalence gene variants each with low penetrance
- probabilistic rather than absolute risk
- major knowledge gaps in both analysis and interpretation
- regulatory oversight (consumer genomics)


SCIENTIFIC AMERICAN
June 2012
ScientificAmerican.com
Your Inner Ecosystem
In your body, bacteria outnumber your own cells 10 to 1. Who's in control?

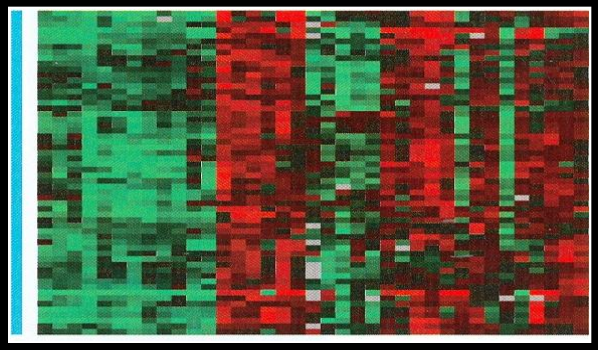
The Principal “’ics” in the Evolution of US Healthcare

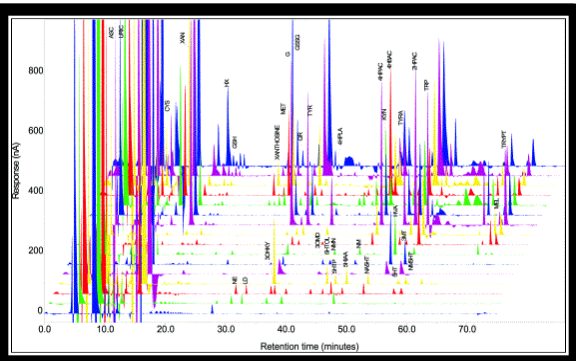
- ‘omics (profiling technologies)
- geriatrics (aging populations and chronic disease burden)
- informatics (data analysis)
- economics (value)
- ethics (societal, law and policy)

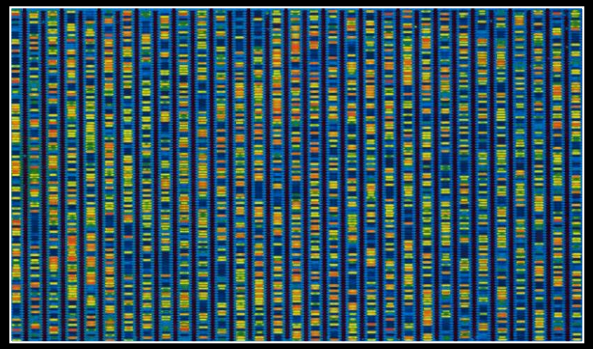
Analytical Platforms for the Elucidation of the Design and Regulation of Complex Biological Networks

Massively Parallel Biosignature Profiling

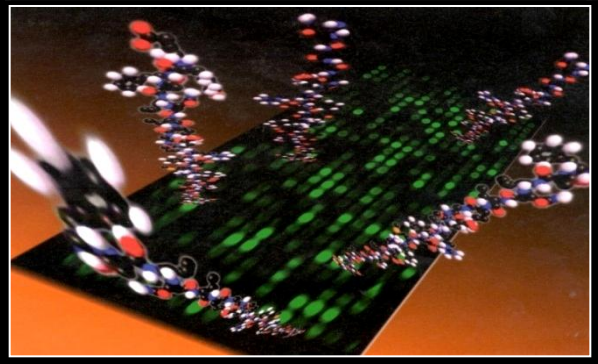
genomics	proteomics	immunosignatures

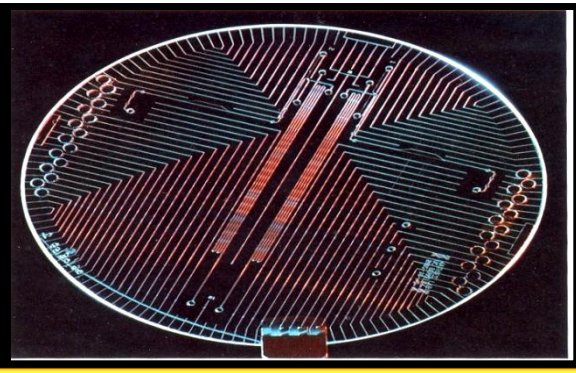


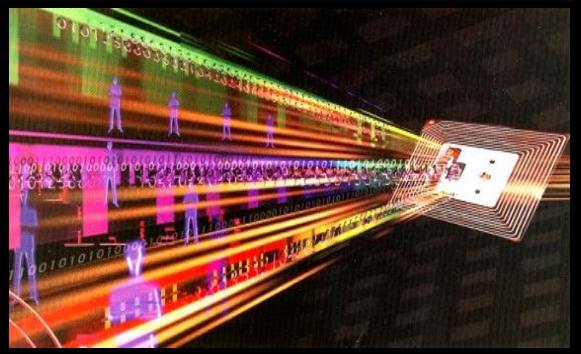




automated, high throughput multiplex assays	novel test formats and devices (POC)	complex signal deconvolution







Large Datasets, Standardization and New Computational Analytics

The Changing Technology Landscape for Diagnostic Tests

- unianalyte (LDTs) → multiplex (‘omics) high complexity tests; whole genome sequencing
- robust analytes → susceptibility to major variation caused by pre-analytical and analytical conditions
- population-based (ubiquitous) analytes → subsets of disease; unique cohorts and individual profiles
- facile interpretation of clinical relevance and actionable decisions → complex interpretation algorithms (obscure to requesting physician); probabilistic risk/outcomes

Lack of Standards and Shoddy Science
Pervasive Problems in Academic Biomedical Research

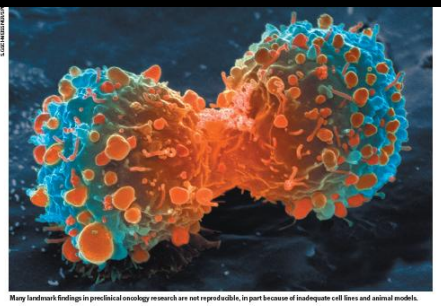
The Small 'N' Problem

JAMA (2011) 305, 2200

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

Slow Adoption of Standards

Nature (2012) 483,531



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

Failure of Academia to Work to Industry Standards

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

Reliability of 'new drug target' claims called into question

Poor Replication and Reproducibility

Statistical Flaws and Bias

Nature (2012) 485, 149

WORLD VIEW *A personal take on events*

Beware the creeping cracks of bias

Evidence is mounting that research is riddled with systematic errors. Left unchecked, this could erode public trust, warns Daniel Sarewitz.

Inefficient Translation

Nature 5 April 2012

Duke UNIVERSITY

NATIONAL CANCER INSTITUTE®

THE CANCER LETTER

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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

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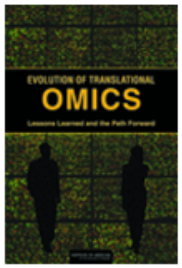


Evolution of Translational Omics: Lessons Learned and the Path Forward

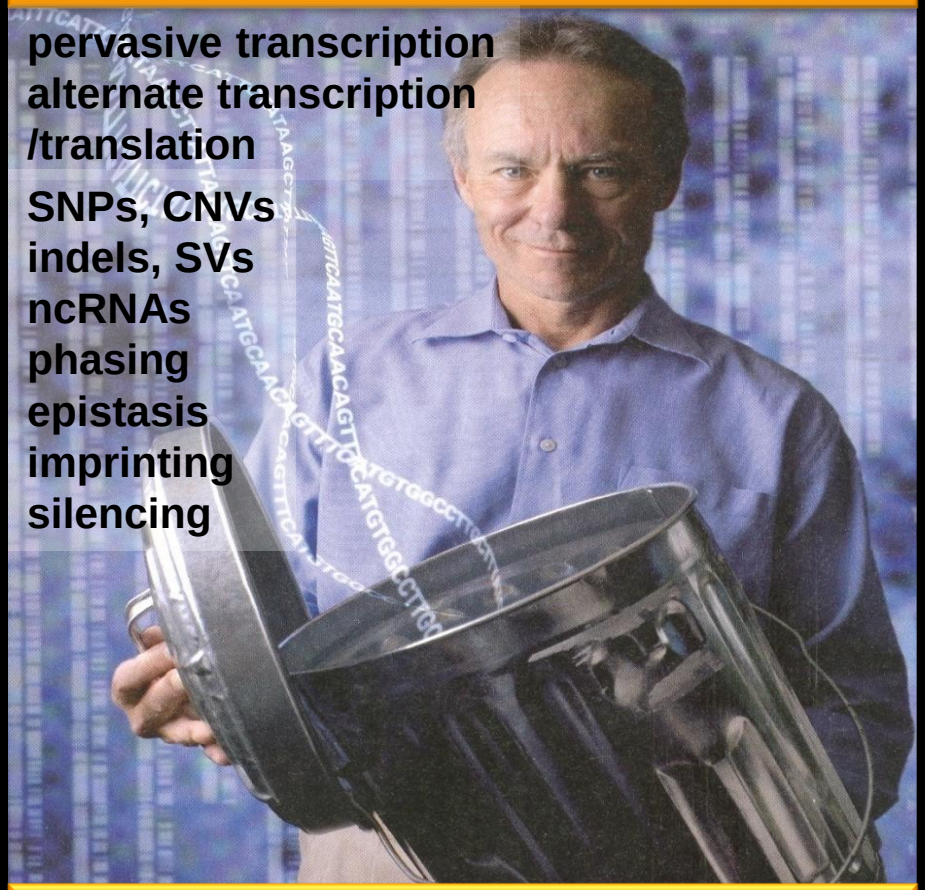
Released: March 23, 2012
Type: Consensus Report
Topics: Biomedical and Health Research, Health Services, Coverage, and Access
Activity: Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials
Board: Board on Health Care Services

Clinical Utility of Knowledge of Individual Genetic Variations

- immediately actionable
- known association/causation of disease but no Rx available
- unknown clinical significance

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

Junk No More!

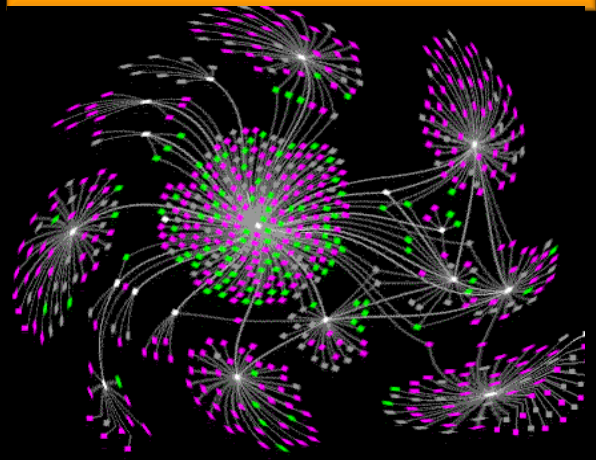


pervasive transcription
alternate transcription /translation

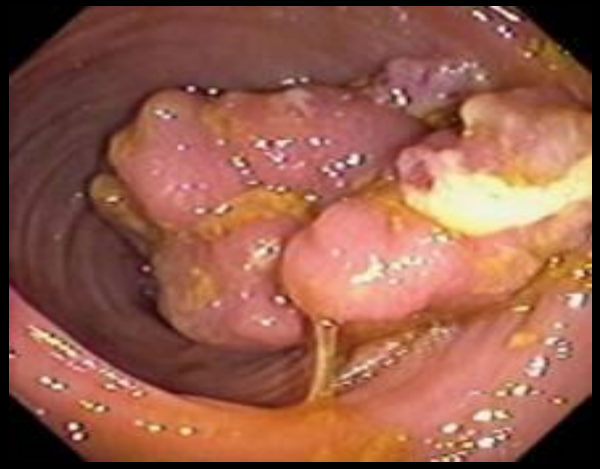
SNPs, CNVs
indels, SVs
ncRNAs
phasing
epistasis
imprinting
silencing

recognition of genome organizational and regulatory complexity

Cell-specific Molecular Interaction Networks

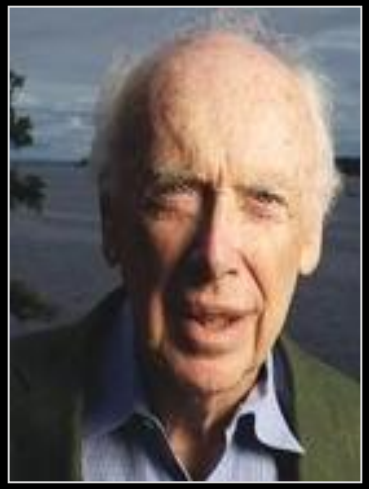
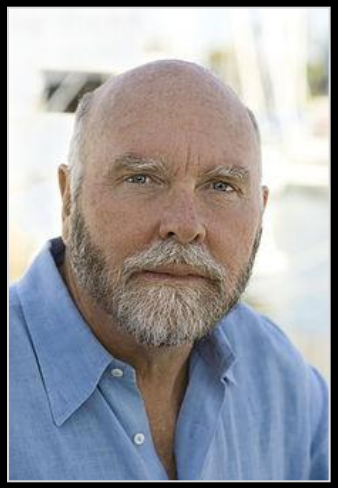
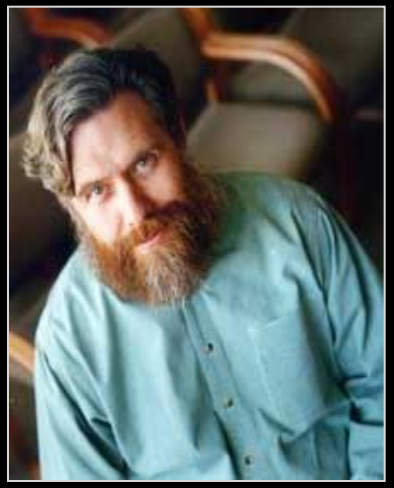


Disease Perturbations



Will Low Cost Whole Genome Sequencing (WGS) Change Everything?

Early Members of the 3 Gigabyte WGS Club

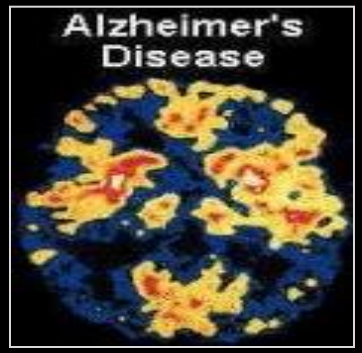




Consumer Genomics: Hype or Personal Freedom?

23andMe

Navigenics

Analysis of Probabilistic Risk(s)



Cost of WGS versus The Cost of Computational Analytics and Dynamic Curation

- the $100-1000 genome
- standards and regulatory validation
- the $? analysis and interpretation cost
- the $? cost of dynamic curation and anticipated extensive updating
- the substantial knowledge gap in linking genotype to phenotype

Regulatory Issues in Genome Sequencing for Clinical Decisions

- accuracy, depth of coverage, validation set, impact of pre-analytic/analytic variables
- CLIA/CAP facilities
- sequencers as Class III devices?
- RUO and IUO materials based on “reason to know” will be used on clinical samples
- source computer code(s) for analytical algorithms
- performance thresholds and QA/QC requirements for error detection (instrumentation + analytics)

“The Incidentalome”

Nature (2012) 483, 373

Incidental benefits

Scientists who screen the genes of volunteers for research should tell participants if they find information relevant to their health.

All research studies on humans can uncover facts relevant to a volunteer's health — at initial screening, during the study itself, or even after the study finishes, when other researchers review the data or conduct their own analyses.

For the most part, researchers have opted not to reveal these potentially important 'incidental findings' to participants. This has been to protect the research process, and to prevent coercing people into studies by unwittingly eliciting the 'therapeutic misconception' — the incorrect assumption on the individual's part that participating in a study will help their own health.

But the emergence of high-throughput genomics, with its ability to catalogue vast amounts of information that may have a bearing on a person's health, has prompted a rethink of this convention.

screw you will probably be able to get a copy of the data they need to do so, and the people who are least likely to get a copy are the people who can do something amazing with it, like researchers," he said. Companies are lining up to market products to consumers on the basis of their genomes. Law-enforcement agencies already use DNA left at crime scenes to find suspects and their relatives, and are funding programmes to create physical profiles of suspects on the basis of their DNA. In other words, people now have incomplete protection for their own DNA, and this lack of privacy is likely to increase in the future.

"No field is likely to be exempt from ethical standards introduced to cover genetic data."

In this free market, how sure can research-

BIOETHICS

DNA donor rights affirmed

NIH committee urges that genome study subjects be told of medically relevant results.

BY ERIKA CHECK HAYDEN

It is a familiar scenario in genetic research: a subject's DNA is collected for one study, deposited in a database or biobank and then analysed by other researchers for separate studies. But what happens when a later study stumbles on something that could be of significance for the donor, such as an allele for familial hypercholesterolaemia — a treatable genetic disorder that causes progressive atherosclerosis — or some other health-related variation? Do researchers conducting secondary studies and biobanks have a duty to share such revelations with the original research subjects?

They do, when possible, according to a detailed consensus statement from a working group funded by the US National Institutes of Health (NIH) in Bethesda, Maryland, and published this week (S. M. Wolf *et al.*

we really believe this is medically valuable and useful data, then we have to act on it," says Leslie Biesecker of the US National Human Genome Research Institute in Bethesda, who contributed to the discussions that led up to the consensus statement but is not a signatory.

S. WILTON/BLOOMBERG VIA GETTY

Genetic testing is increasingly coming up with 'incidental findings'.

recommends that each biobank sets up a committee to oversee the return of results and also that a single central advisory body be created that would foster consistency among biobank research systems. Wolf led a previous NIH working group that in 2008 published recommendations proposing that primary researchers — those responsible for collecting data — should report some incidental findings back to research participants (S. M. Wolf *et al. J. Law Med. Ethics* **36**, 219–248; 2008).

But some researchers warn that keeping track of incidental results and re-identifying participants so that they can be informed could prove costly and pose ethical and legal difficulties. "It's unfortunate that the authors of the consensus statement didn't discuss the cost implications of what they're proposing, because what they have in mind is going to be expensive and difficult, particularly at a time when funding success

“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

Presidential Commission for the Study of Bioethical Issues

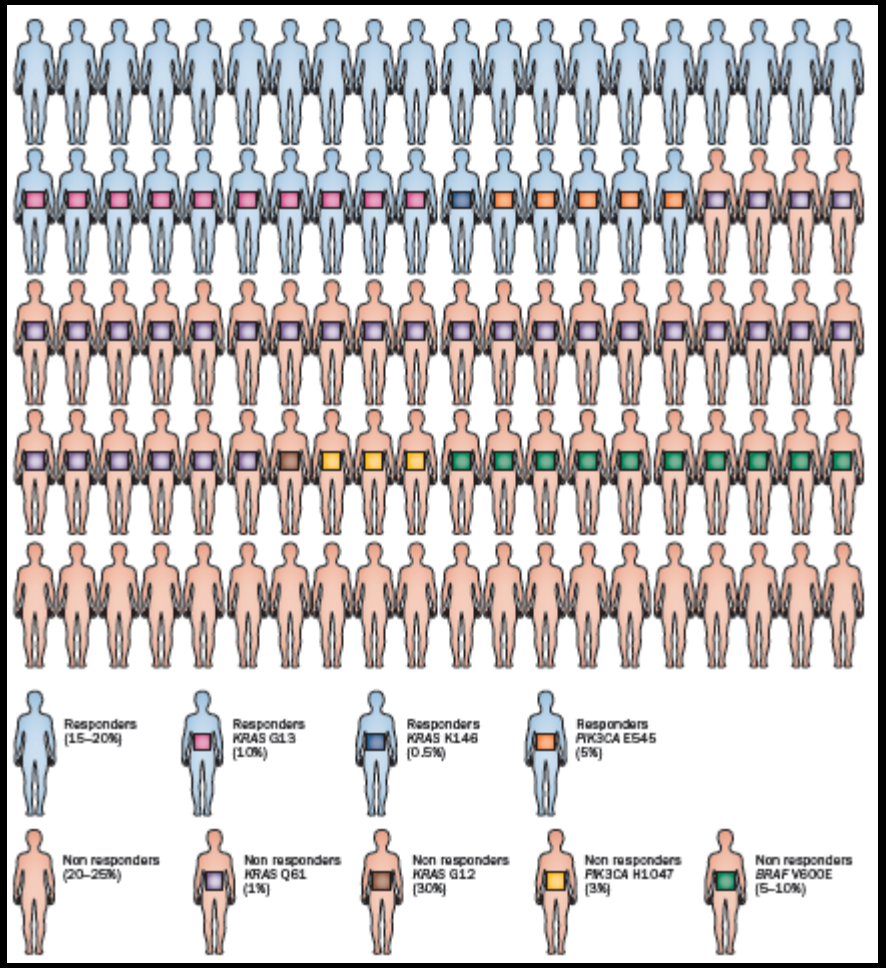
Fed. Reg. 27 March 2012
Implications of Large Scale Human Genome Sequencing

- 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

Individual Genetic Variation, Disease Subtypes and Prospect of New Categories of 'Orphan Diseases'

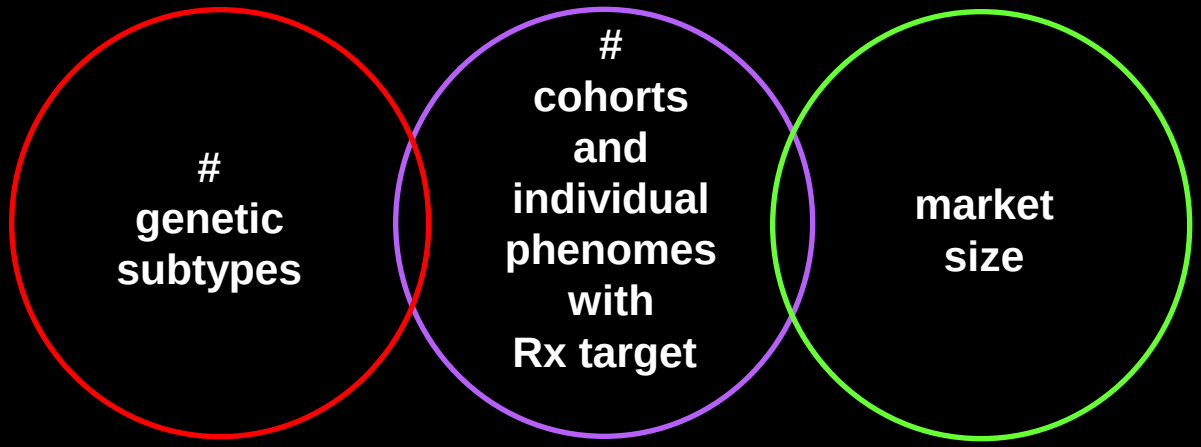
Common Diseases: Are There Any?

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



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

Market Incentives and ROI from R&D Investment in Disease Subtype Profiling (MDx): Targeted Treatment (Rx) Combinations will Depend on Extent of Disease Subtype Segmentation



The Diversity of the Human Variome*

- most human genetic variants are rare (fewer than 5 people in 1000)
- every individual carries between 25 to 30 variants not shared with any one else
- major implications for gene:disease correlations
  - deep sequencing (100 x coverage) of 20,000 or more individuals to link variants/variant combinations to disease phenotypes

*Science (2012) e. 1219240, 1217876
Science (2012) 336, 740; Nature Genetics (2012) 42, 565

Different Numbers (Ns) for Personalized Medicine

Ultimate 'Ns'

- N = 1 = individualized (personalized therapy)
- N = 100 = predictable treatment outcome/avoidance
- N = 0 = avoidance of adverse events

Different Numbers (Ns) for Personalized Medicine

Expensive 'Ns'

- N = 20,000 individuals for deep sequencing (100x) to detect rare variants
- N = 10,000 plus individuals for Genome Wide Association Studies
- N = 2000 = typical size of disease cohort (+ matched control) with statistical power for regulatory validation of target/biomarker for use in N = 1 clinical decisions
- N = ? = size of pooled N = 1 observations to satisfy reimbursement cost:benefit/outcomes/QALY analyses

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

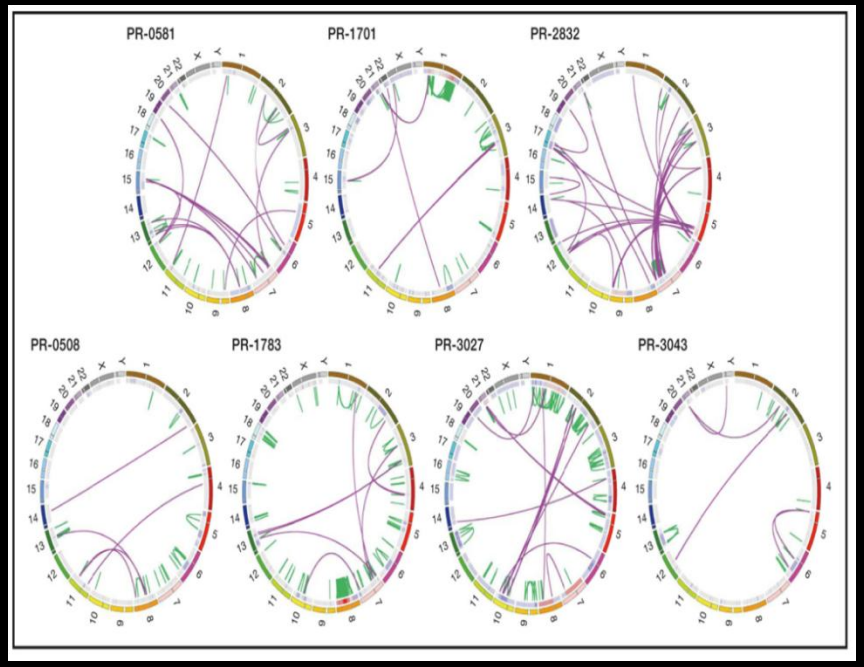
* E.L. Kwak et al. (2010) NEJM 363, 1693

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

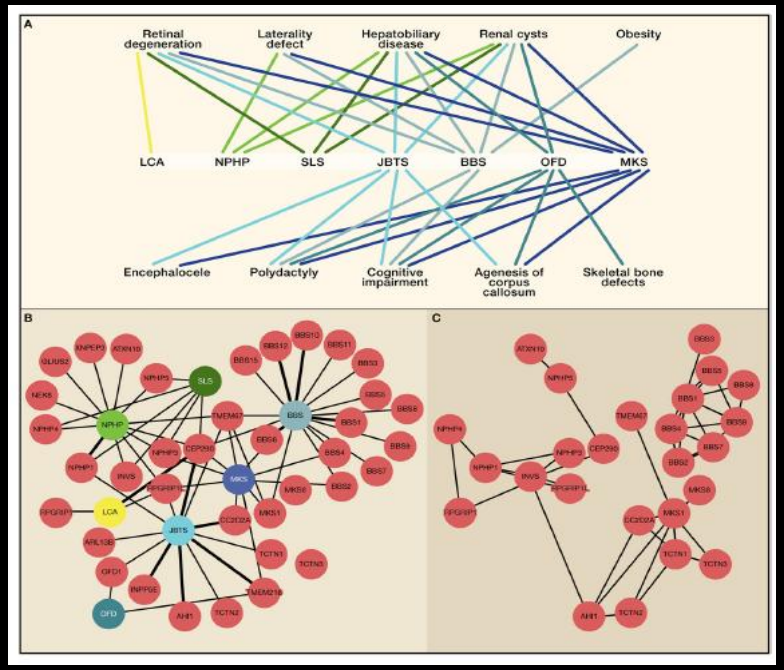
Prepare for the "Tsunami of Genomic Information" ASCO Presidential Address: Dr. George Sledge Chicago, 5 June 2011

- "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"

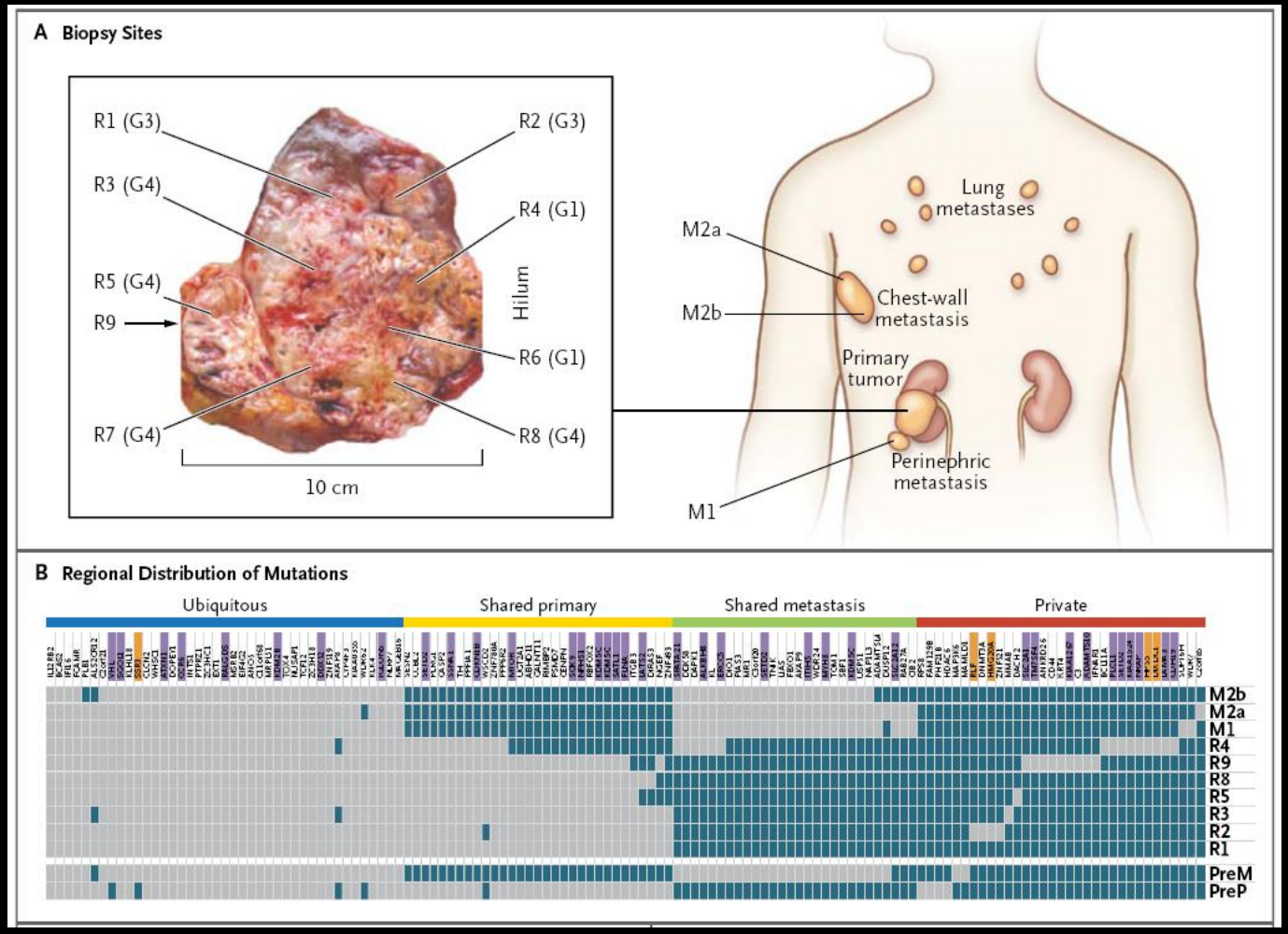
Exome- or Whole Genome Sequencing



Disease-Associated Perturbations in Pathways and Networks



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



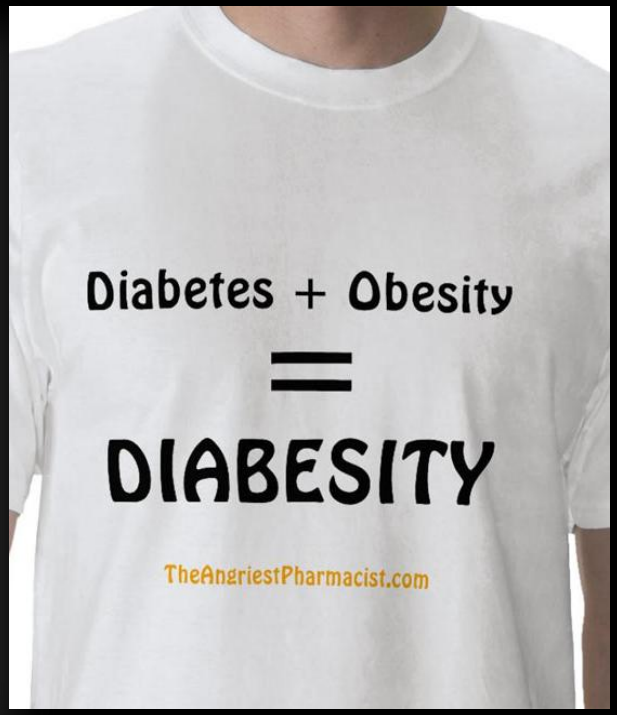
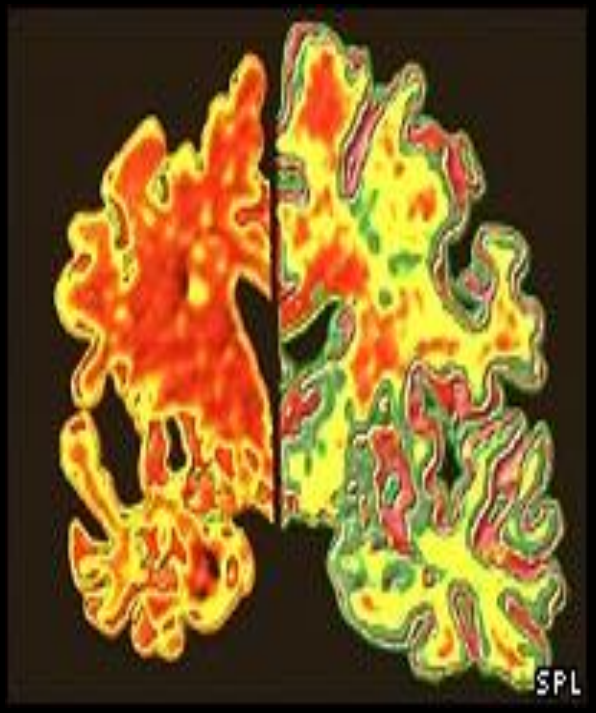
From: M. Gerlinger et al. (2012) NEJM 366, 883

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

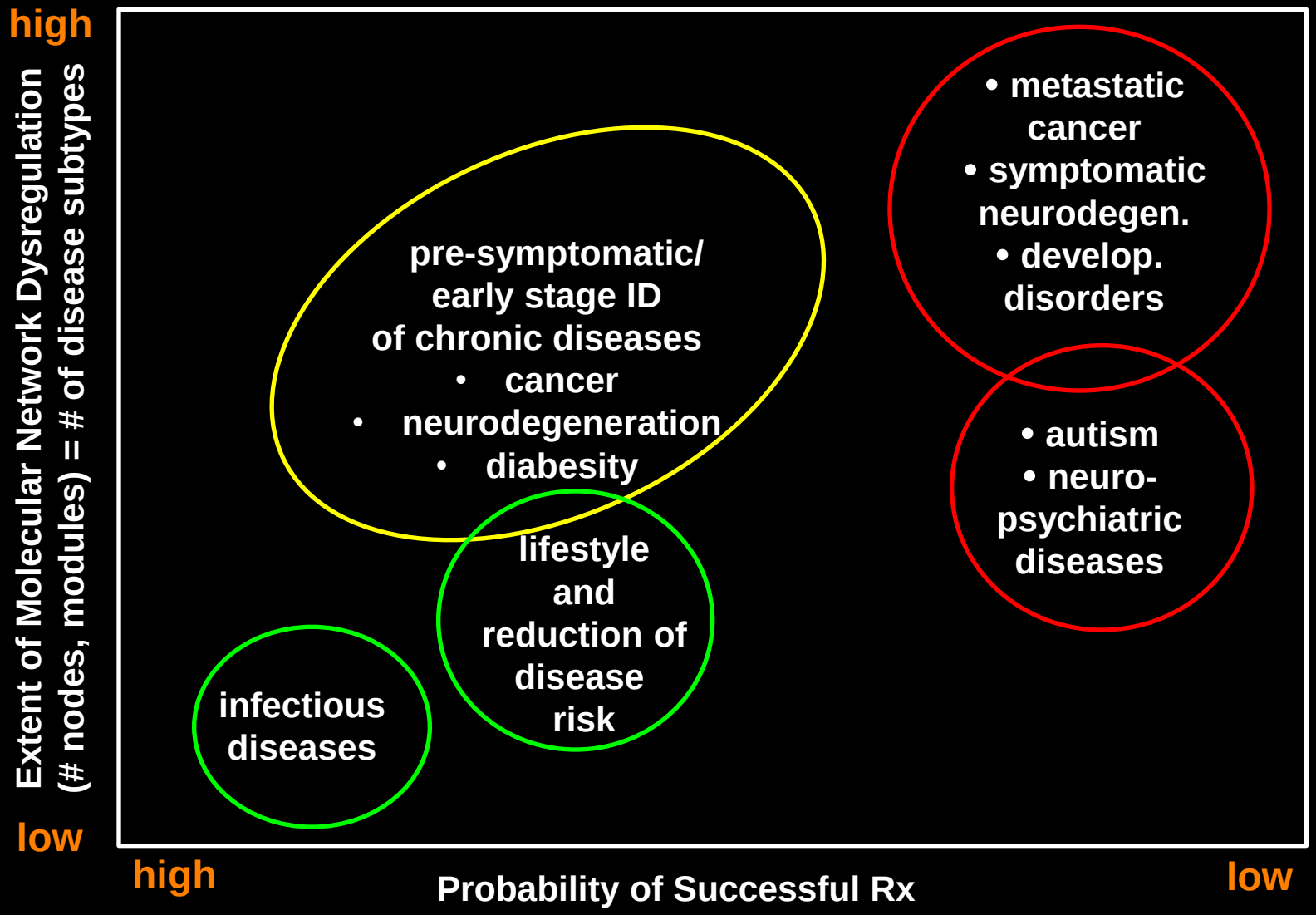
From: N. Wagle et al. (2011) J. Clin. Oncol. 29, 3085

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

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

The Spectrum of Disease-Induced Disruption of Molecular Networks and Prospects for Successful Rx Therapy



Healthcare as a Complex Information Ecosystem

From Fragmented Silos of Reactive Incident-Centric Care to Systems-Based Integrated Frameworks for increasing Proactive Management of Individual Risk

The Wellness Premium

The Convergence of Healthcare, Consumerism and Social Media, and Large Scale Information Networks (Media, Big Data)

Invasion of the Body Trackers: m.Health

Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

Increasing Engagement of Informed Consumers/Patients in Healthcare Decisions: Increased Personal Responsibility for Maintaining Health (Wellness)

Information Resources

- disease specific advocacy groups
- mass media
- web resources and social media
- mobile apps
- healthcare providers/ professionals

Optimizing Wellness and Risk Reduction

- “my profile”
- “my biorepository”
- “my health today”
- early alerts and risk mitigation
- virtual expertise network
- expertise locaters and clinical trial enrollment

Treatment and Side Effect In

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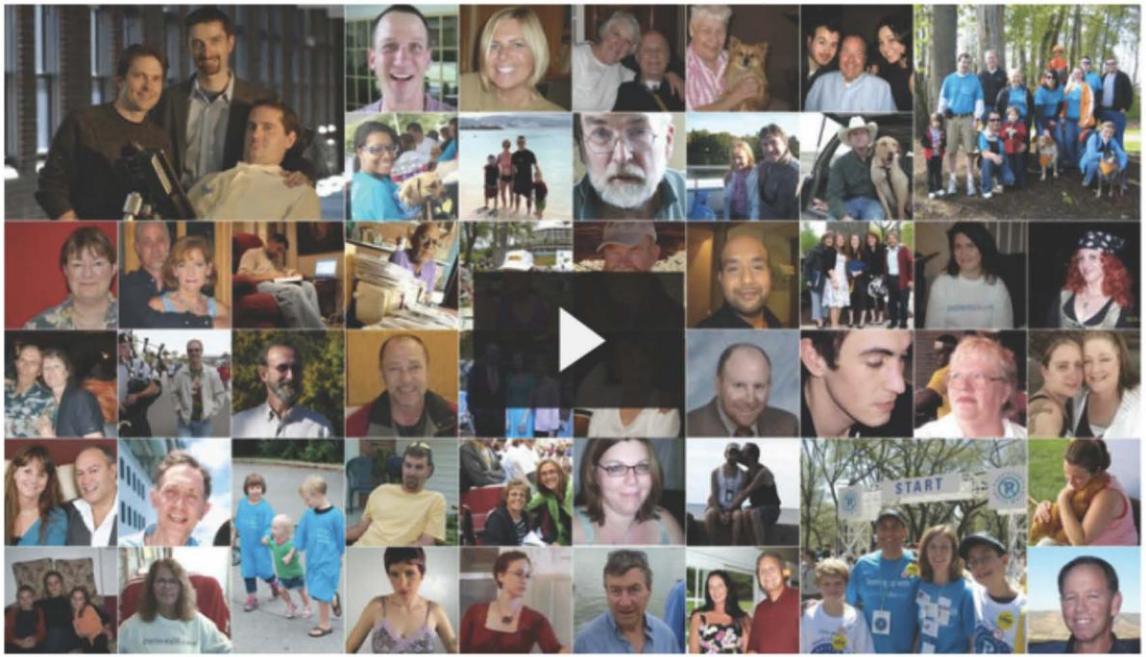

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Putting Patients First. That's the mission of PatientsLikeMe.

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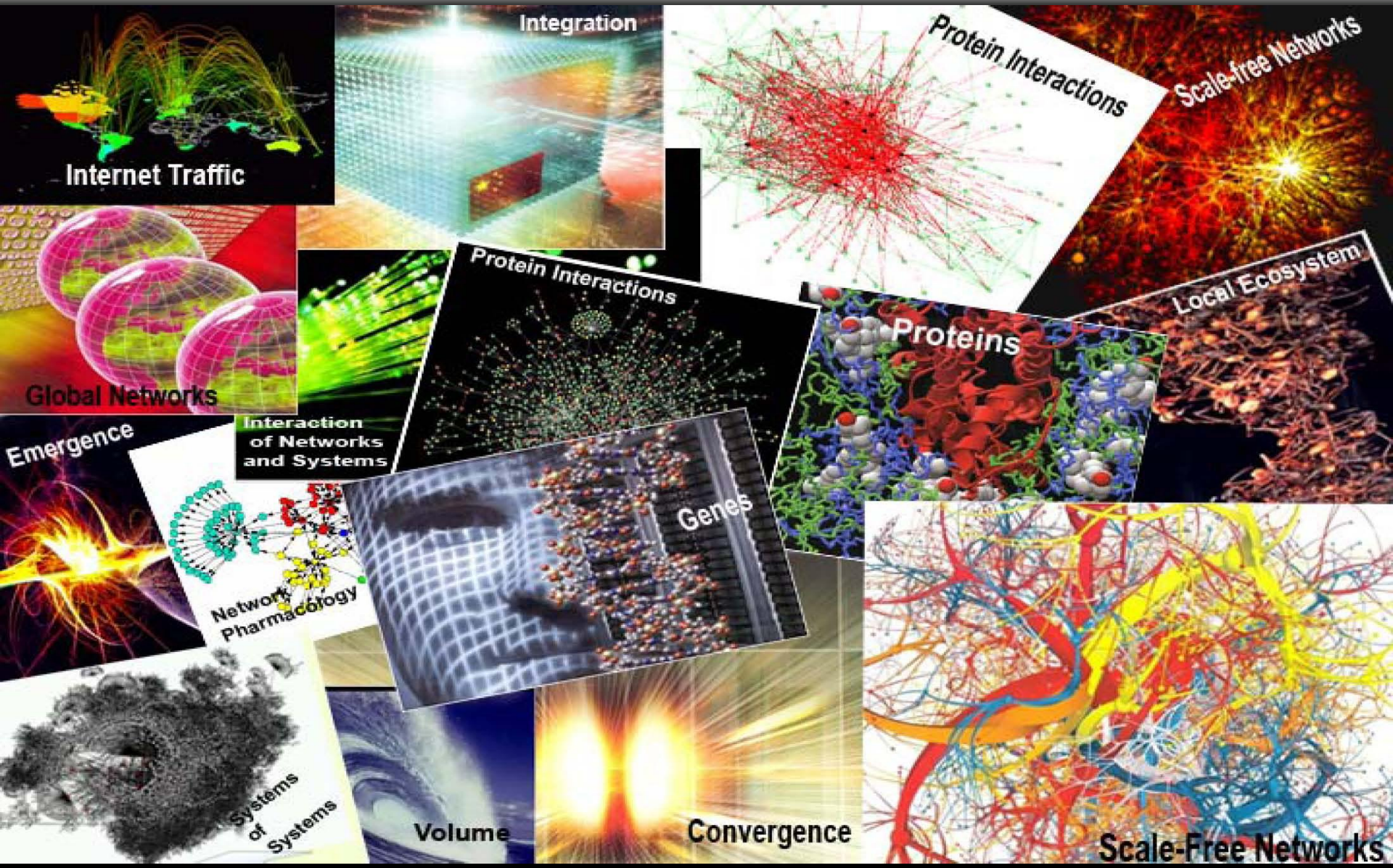
New Patient-and Consumer-Driven Models of Medical Research

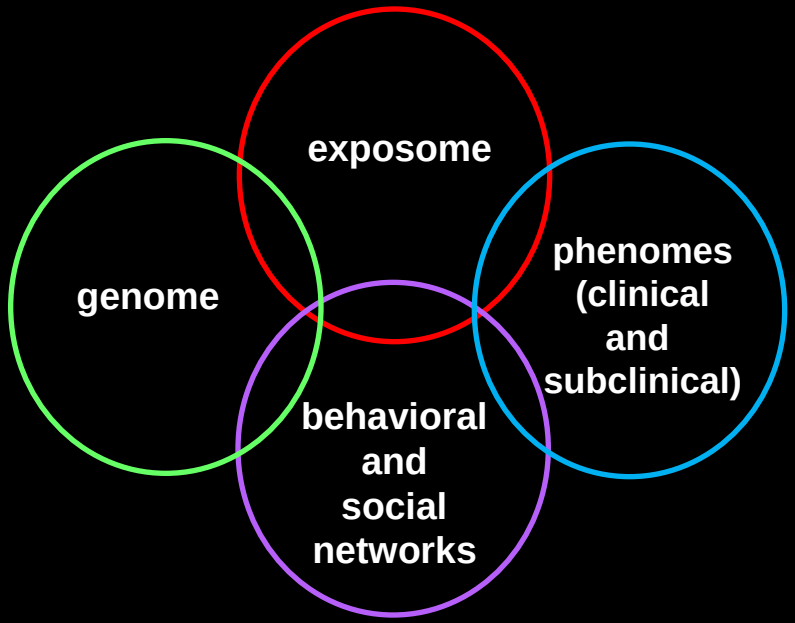
- patient activism and advocacy
  - transcending medical paternalism and/or ignorance of ongoing clinical trials
- consumer genomics
  - premature services or a personal freedom?
- crowdsourced data sharing
  - pooling of user-contributed de-identified data for big-data studies to ID unanticipated correlations
  - genomics, lifestyle, social media
  - Consent to Research Project (Kauffman Fdn.): Portable Legal Consent for Common Genome Research

Data: The Fastest Growing Resource on Earth



Information-Based Services for Healthcare and Wellness

Precision Profiling of Health Status



Population- and Individual-Datasets

facile integration and analysis of diverse datasets

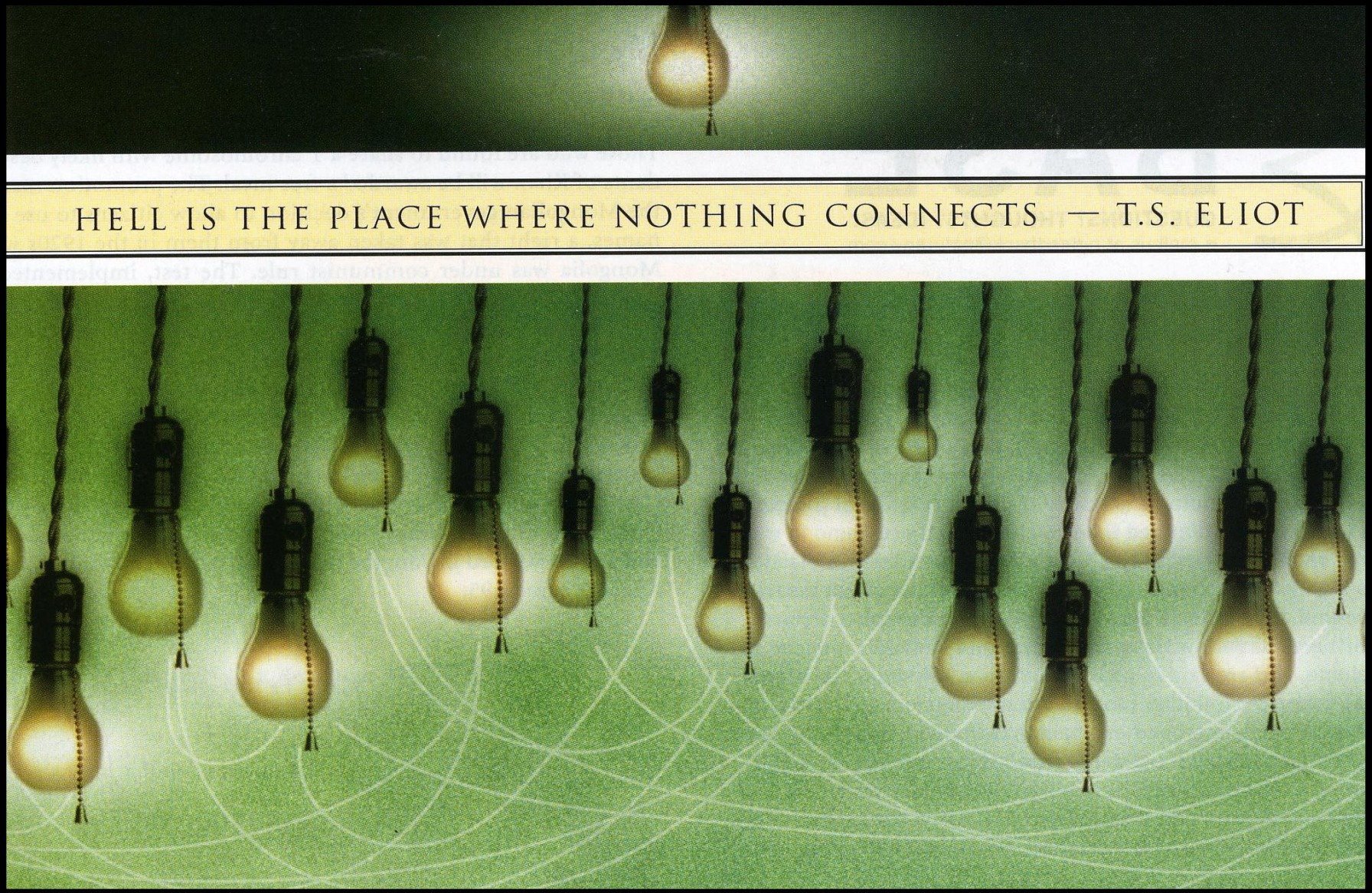
Actionable Information

risk identification and mitigation

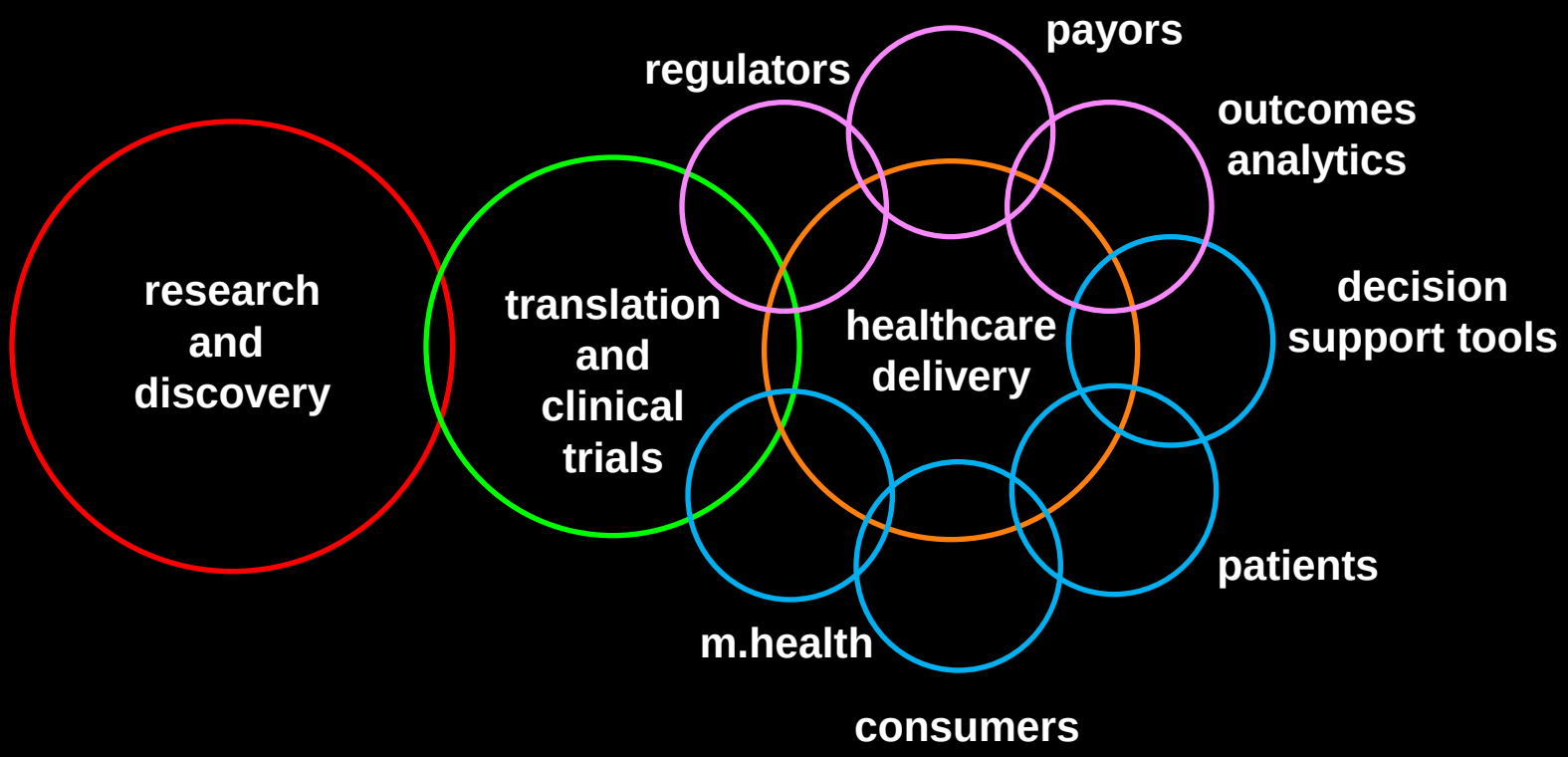
Integrated Care and Wellness

VALUE

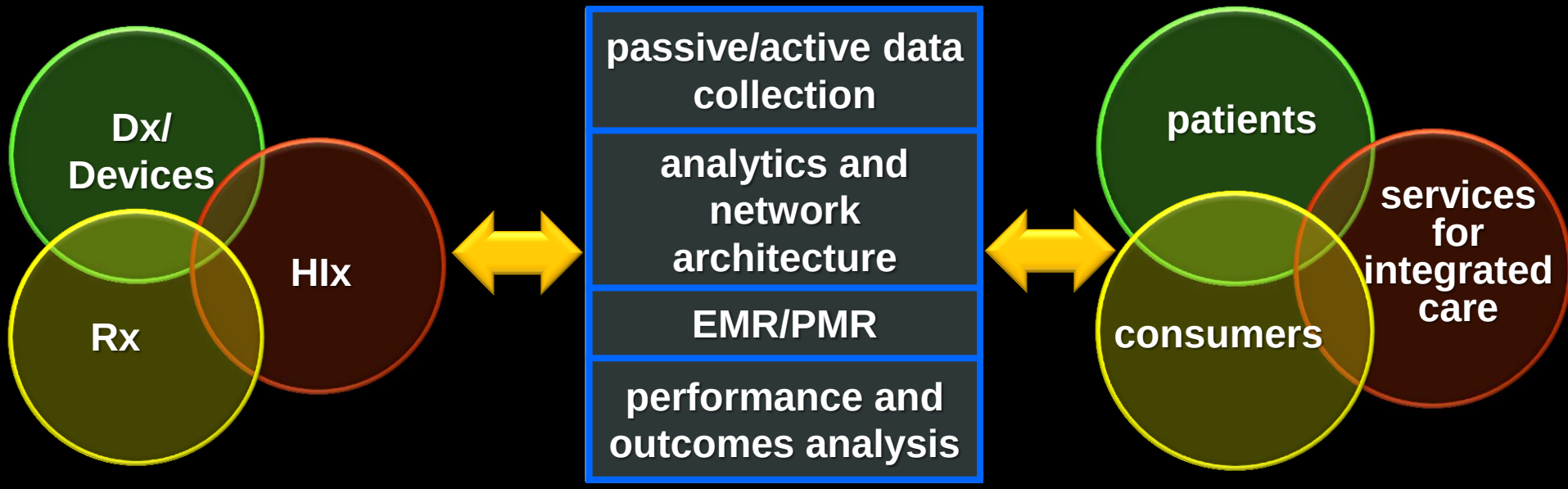
Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo



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



A New Healthcare Ecosystem Arising From Technology and Market Convergence

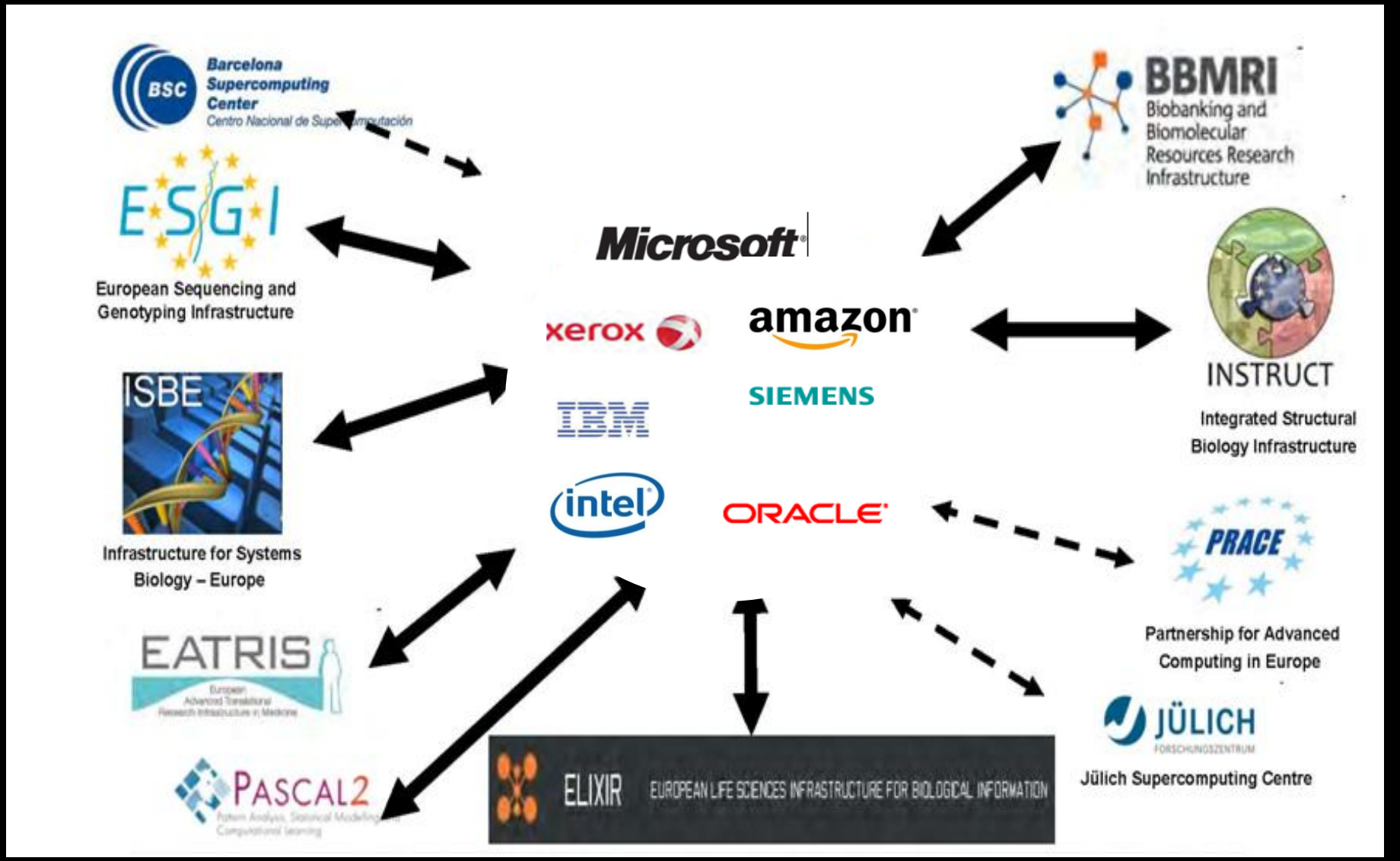


Integrated Technology Platforms

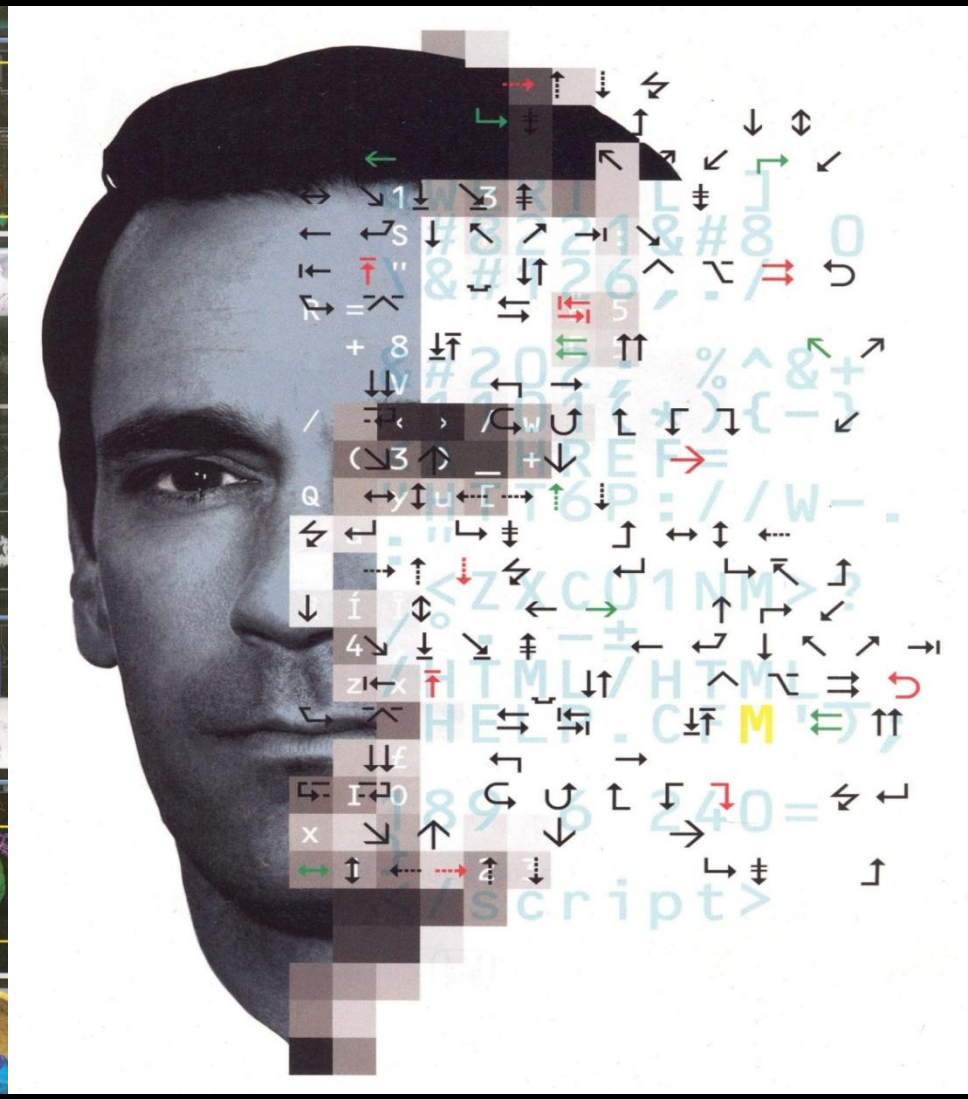
Data Mining and Integration Services

Increasingly Targeted Care and Efficient Use of Finite Resources

IT Future of Medicine



Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency



If You Build It, Will They Pay?
Adoption of Disruptive Innovation

- new technology/service that simplifies a complex/costly problem
- business model that allows market adoption of the simplified solution at low(er) cost
- incentivized supply and demand to networks to reinforce the disruption

"If it isn't billable – it isn't going to happen"

- value-based versus cost-based reimbursement
- new billing codes
- reimbursement for professional analysis of remote monitoring data streams

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.

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202 223 1200 *main*
202 785 6687 *fax*

The Changing Regulatory and Reimbursement Landscapes for Diagnostic Tests

- CLIA → CLIA + 510(k) + PMA?
- validation in small patient cohorts → high dimensionality problem; low penetrance/low prevalence alleles; large scale trials
- low validation cost (<$5m) → escalating cost (>$100M)
- limited IP role → increasing IP importance
  - analytes, algorithms, platforms
  - competitiveness, cost-recovery and ROI
- established regulatory oversight and reimbursement codes for single analytes/ methods → ambiguous regulatory and reimbursement climates and approval criteria for multiplex profiling

SCOTUS Rulings on IP for Diagnostic Tests: Implications for MDx and Personalized Medicine

- Mayo Collaborative Services v Prometheus
  - 6-TG and 6-MMP metabolite profiling
- Association for Molecular Pathology v Myriad Genetics
  - BRCA1 and BRCA2 mutation analysis
  - vacate and remand to Federal Circuit Court
- uncertain IP environment versus escalating cost/regulatory ambiguities for multiplex MDx
- implications for repurposing drugs in which MDx/biomarker will be crucial for cohort ID and/or EA risk detection
- implications for investment in MDx for infectious diseases
  - global surveillance, public health

The Key Strategic Elements in the Evolution of Molecular Medicine