Biotechnology, Molecular Medicine and the Future Evolution of Healthcare

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Biotechnology Entrepreneur Lecture Series
25 September 2008

ASU BIODESIGN INSTITUTE
ARIZONA STATE UNIVERSITY

A Few Current Challenges for the US Healthcare System

- $2.3 trillion dollar expenditures (2007): 16% of GDP ($1 in every $7)
- escalating and unsustainable fraction of GDP
- highest per capita expenditure in OECD
- $510 billion cost of chronic disease
- 2 million annual hospital-acquired infections
- 2.5 million hospitalizations due to adverse Rx reactions
- highly variable treatment patterns
- slow diffusion of best practices
- no reserve capacity for disasters, epidemics or pandemics

Healthcare Costs are Unevenly Distributed

- 0.5% patients consume 25% of healthcare budget
- 1% consume 35%
- 5% consume 60%
- 10% consume 70%
- 50% consume 3%
- 75% of cost is for patients with chronic diseases

*Source: Healthcare Reform Now
G. Halvorson,
Chairman and CEO
Kaiser Foundation Health Plan and Hospitals
Wiley, NY 2007 p.2

Market Distortions and Perverse Incentives in Modern Healthcare Delivery

- focus on late-stage detection and intervention
  - high cost
  - low reversibility
- multiple reimbursements for fragmented (siloed) care versus integrated management of patient needs
- illness versus wellness
- inadequate social and economic incentives for wellness

Knowing What Works (or Doesn't)

- Pervasive Inefficiencies and Errors in Healthcare Created by Empirical Care and Lack of Robust Outcomes and Performance Data

Disease Burden/Trends in E7 Nations Mirror G7 Nations

- E7 hypertension
  - 2005 : 639 million
  - 2025 : 1.2 billion
- E7 diabetes
  - 2005 : 140 million
  - 2025 : 228 million
- accelerating impact of chronic diseases in E7
  - urbanization and pulmonary disease
  - deteriorating environmental quality and occupational exposures
  - diabesity, CVD
  - tobacco-use
- chronic diseases account for 80% of E7 mortality but earlier onset than in G7

Global Health: Understanding the Implications of Major Economic and Environmental Dislocations



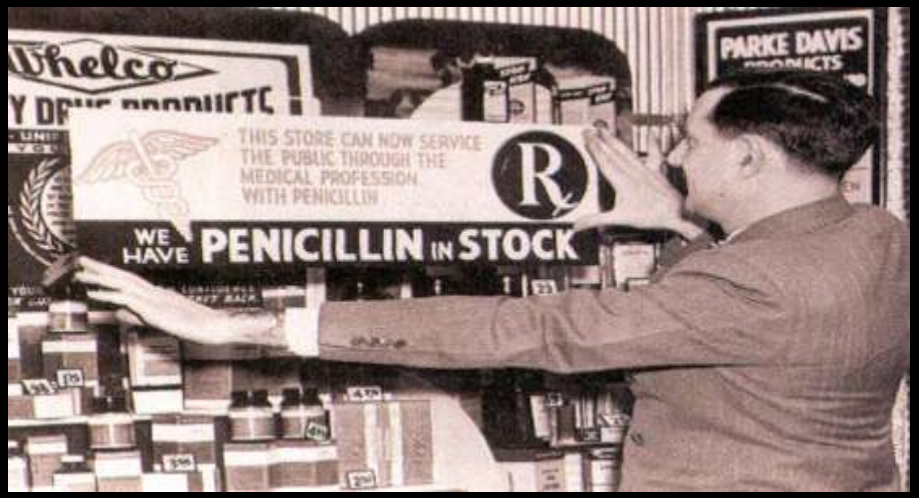


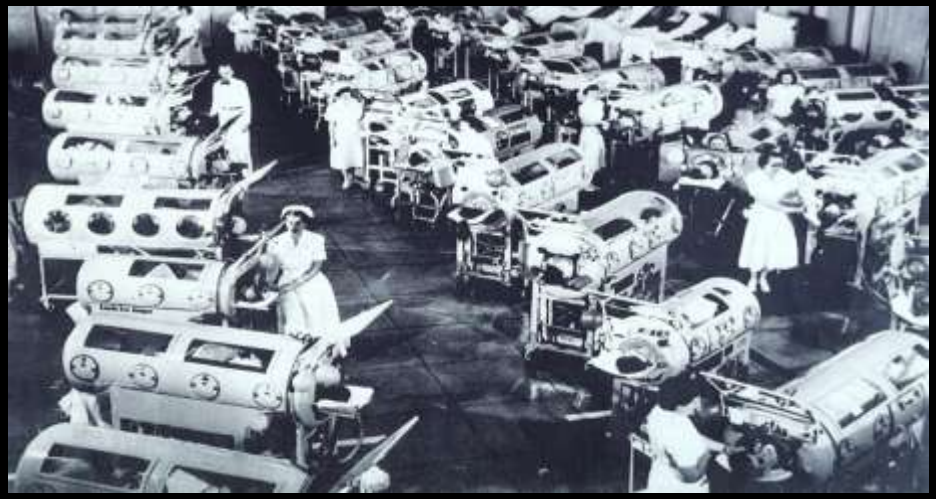






The Urgent Imperative to Control the Growing Global Threat from Infectious Diseases

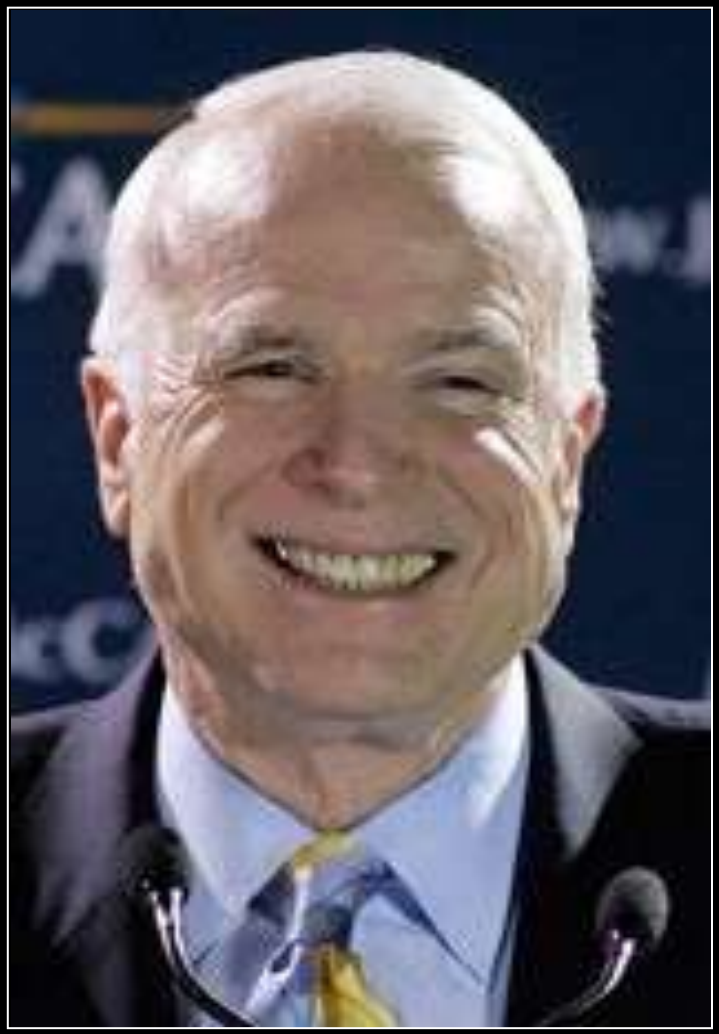




The Strategic Future of Healthcare

Confronting the Imbalance Between Infinite Demand and Finite Resources

The Imperative for the Courage to Address Complexity: Political Populism Versus Stark Realities and Unpalatable Choices



15 June 2008

No Member of Congress Left Behind

Should Politicians Be Required to Take Periodic Intelligence and Mental Status Tests?

Henry I. Miller, M.D.

Henry I. Miller, M.D., a physician and fellow at Stanford University's Hoover Institution, was an official at the NIH and FDA from 1977 to 1994. Phone: (650) 725-0185. E-mail: miller@hoover.stanford.edu.

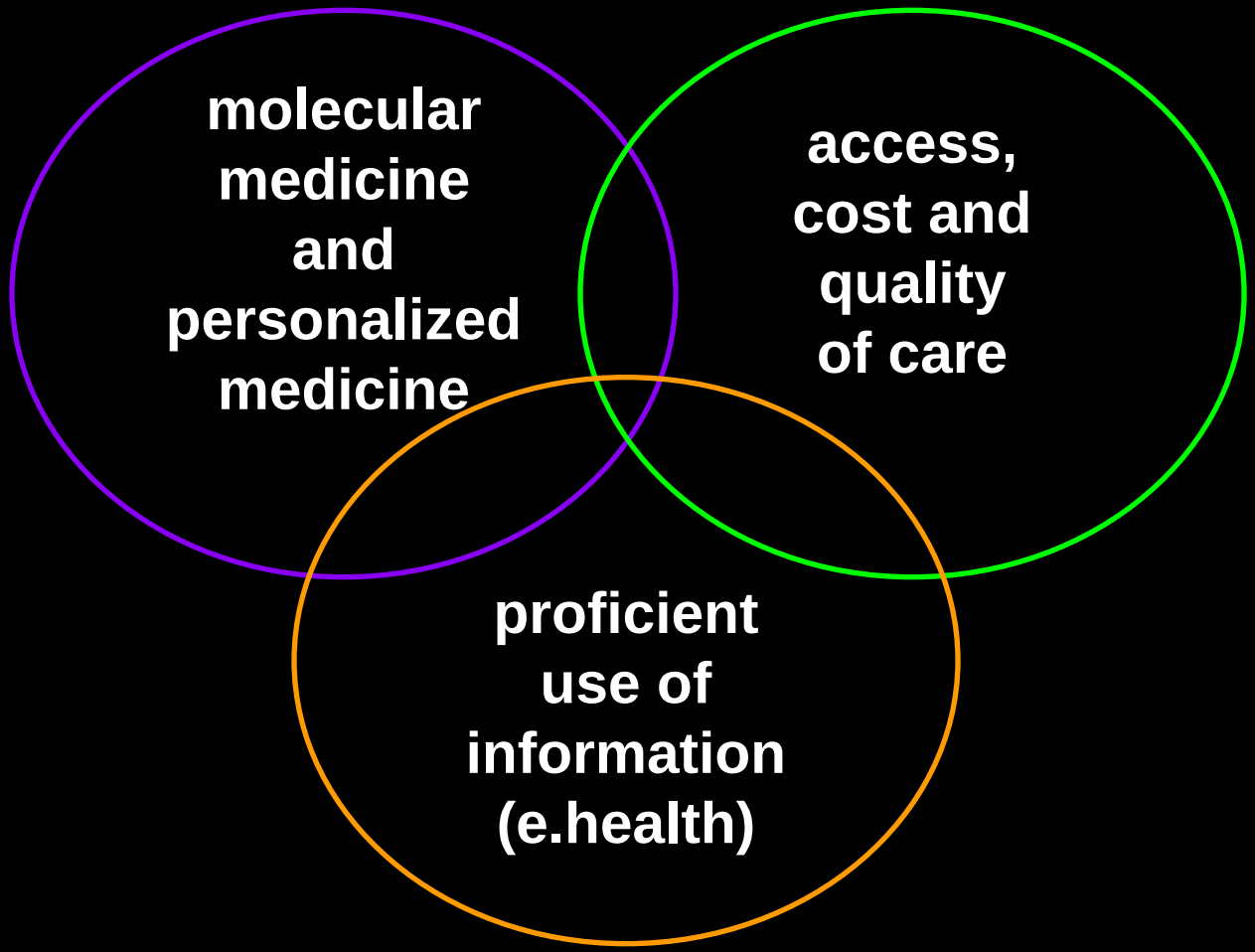
Most Americans are unhappy with the performance of the U.S. Congress, which has granted no favors recently to the pharmaceutical and biotech industries. Both regulation and its congressional oversight are broken with no repair in sight.

Recent polls have found congressional approval ratings in the range of 20–28%, but we continue to elect and re-elect scoundrels, liars, and the intellec-

recited from a prepared statement, he included the stage instructions—such as "Pause for emphasis"—that had been inserted by his speechwriter. And where one line had been inadvertently duplicated, he read it a second time. Carelessness? Stupidity? Senility? Don't voters have a right to know?

Senator Pete Domenici (R-New Mexico) was sufficiently forthright to reveal last year that he had been diagnosed with frontotemporal lobar degeneration—an inexorably progressive, incurable disease characterized by wasting away of the frontal and

The Three Forces Shaping the Evolution of Healthcare



DEMONSTRATING VALUE

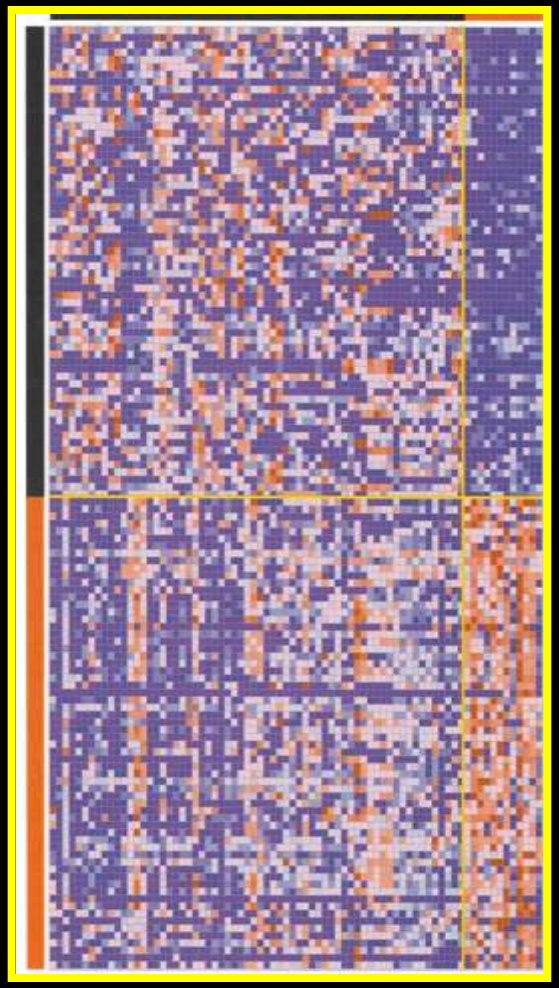
Personalized Medicine

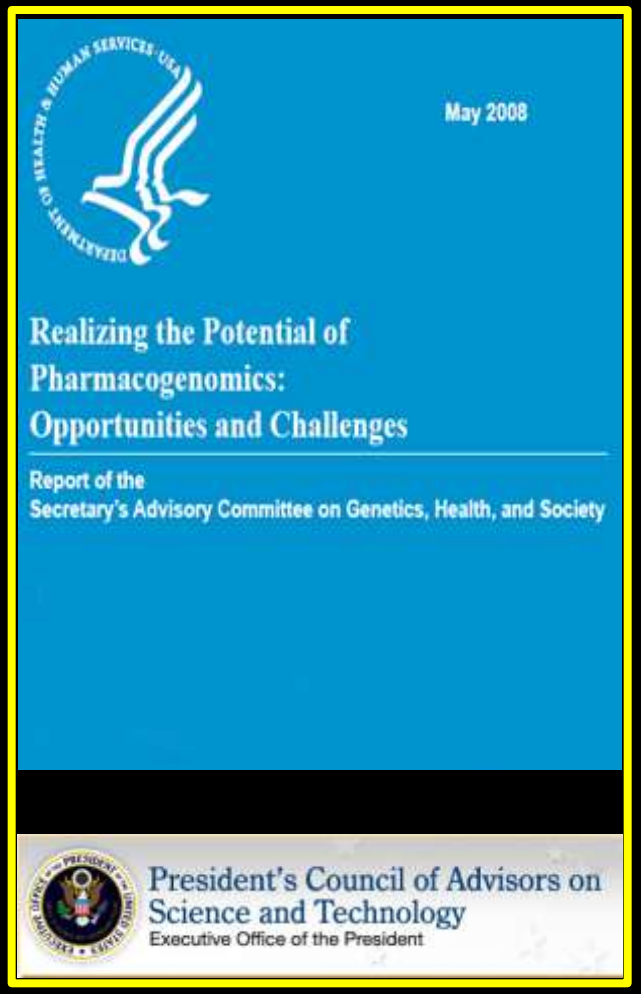
"If it were not for the great variability among individuals, medicine might be a science, not an art"
Sir William Osler (1892)

Osler Reframed

"Because of the great variability among individuals, medicine must finally become a science, not an art"

Personalized medicine: Key Drivers





Science | Policy | Cost and Outcomes

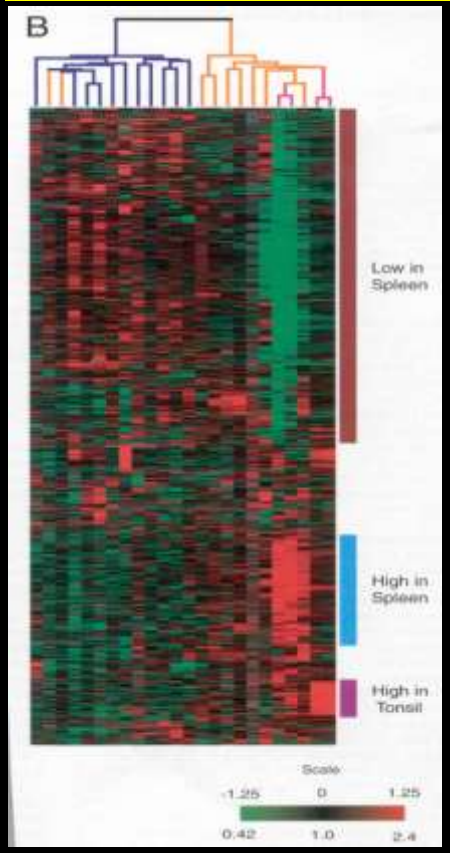
NICE (UK) and Renal Carcinoma Rx (2008)

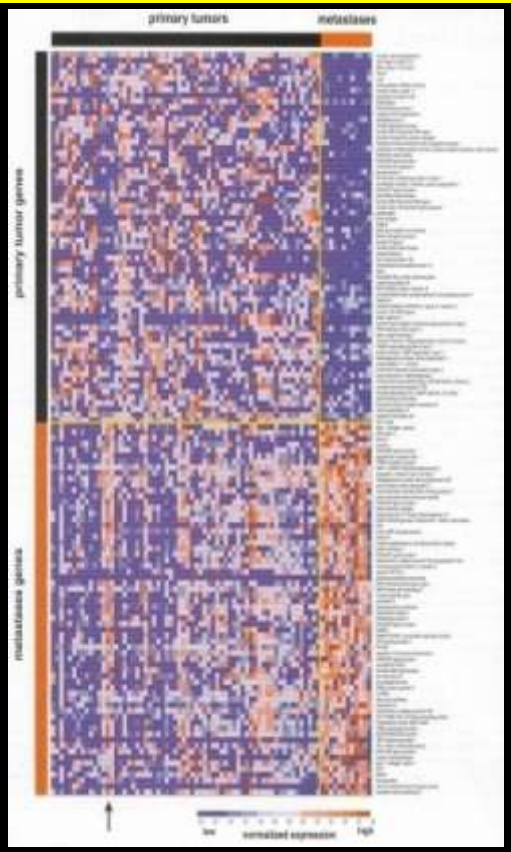
- clinical efficacy but not cost-effective
- QALY threshold of £30,000 or lower
  - bevacizumab £171,301
  - sorafenib tosulate £102,498
  - temsirolimus £94,385
  - sunitinib £71,462

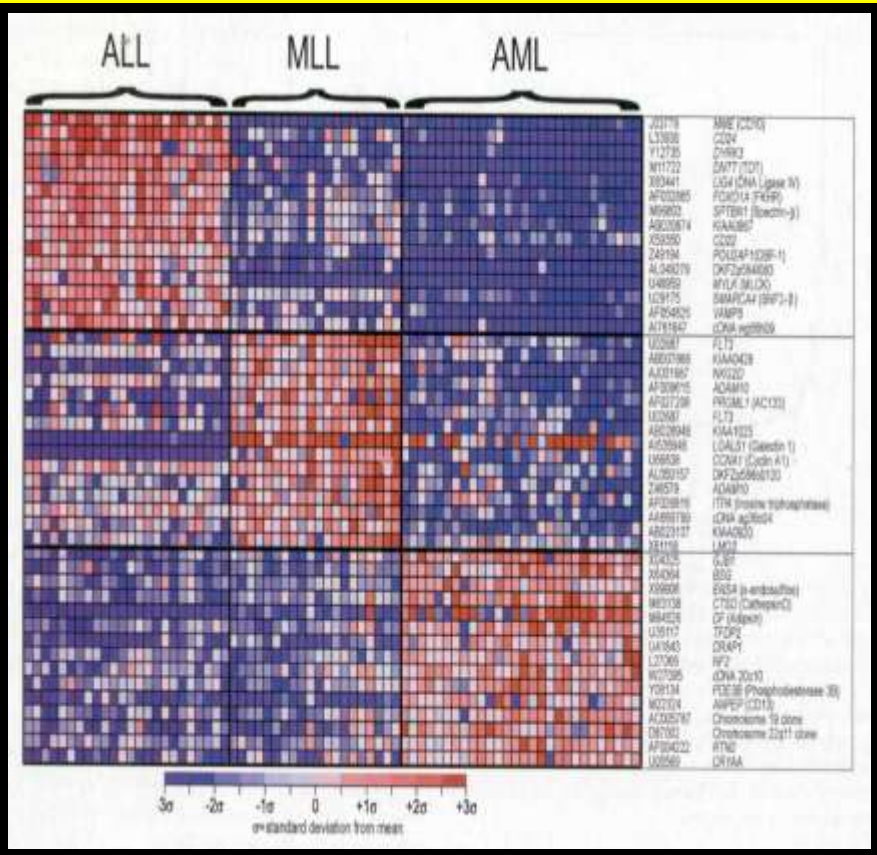
Personalized Medicine: New Value Propositions in Healthcare

- social and economic value of reducing disease burden will rise
  - earlier disease detection and mitigation
  - rational Rx and guaranteed outcomes
  - integrated care management of complex chronic diseases
  - extension of working life
- progressive shift from ‘reactive’ medicine to ‘proactive’ care and ‘integrated’ delivery
  - wellness versus illness
  - predict and prevent versus detect and treat

Molecular Diagnostics and Biomarkers: The Fundamental Technology Platforms For Molecular Medicine and the Future Healthcare Value Chain







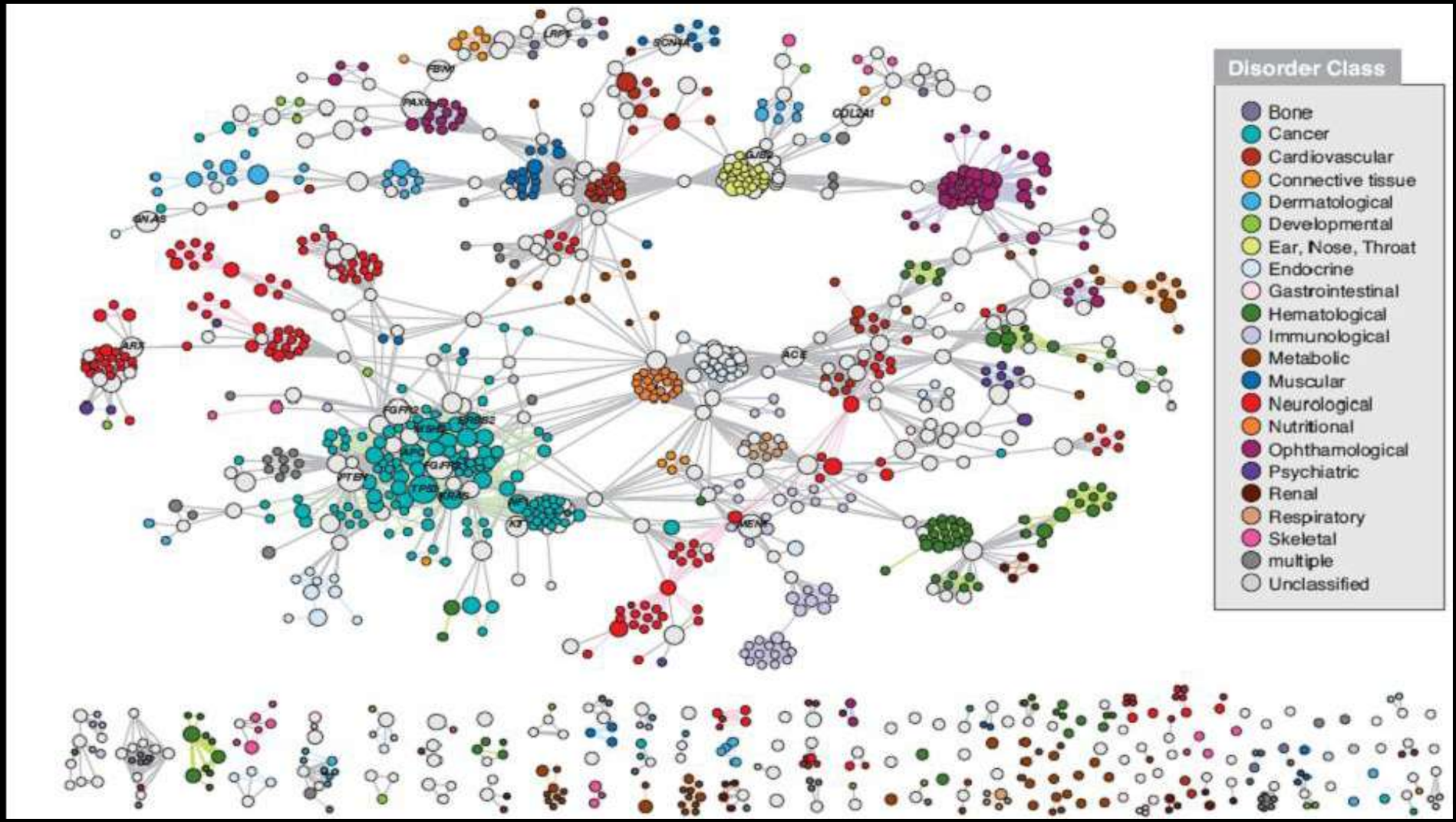
Ignoring The Obvious in Clinical Practice

- 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 AEs

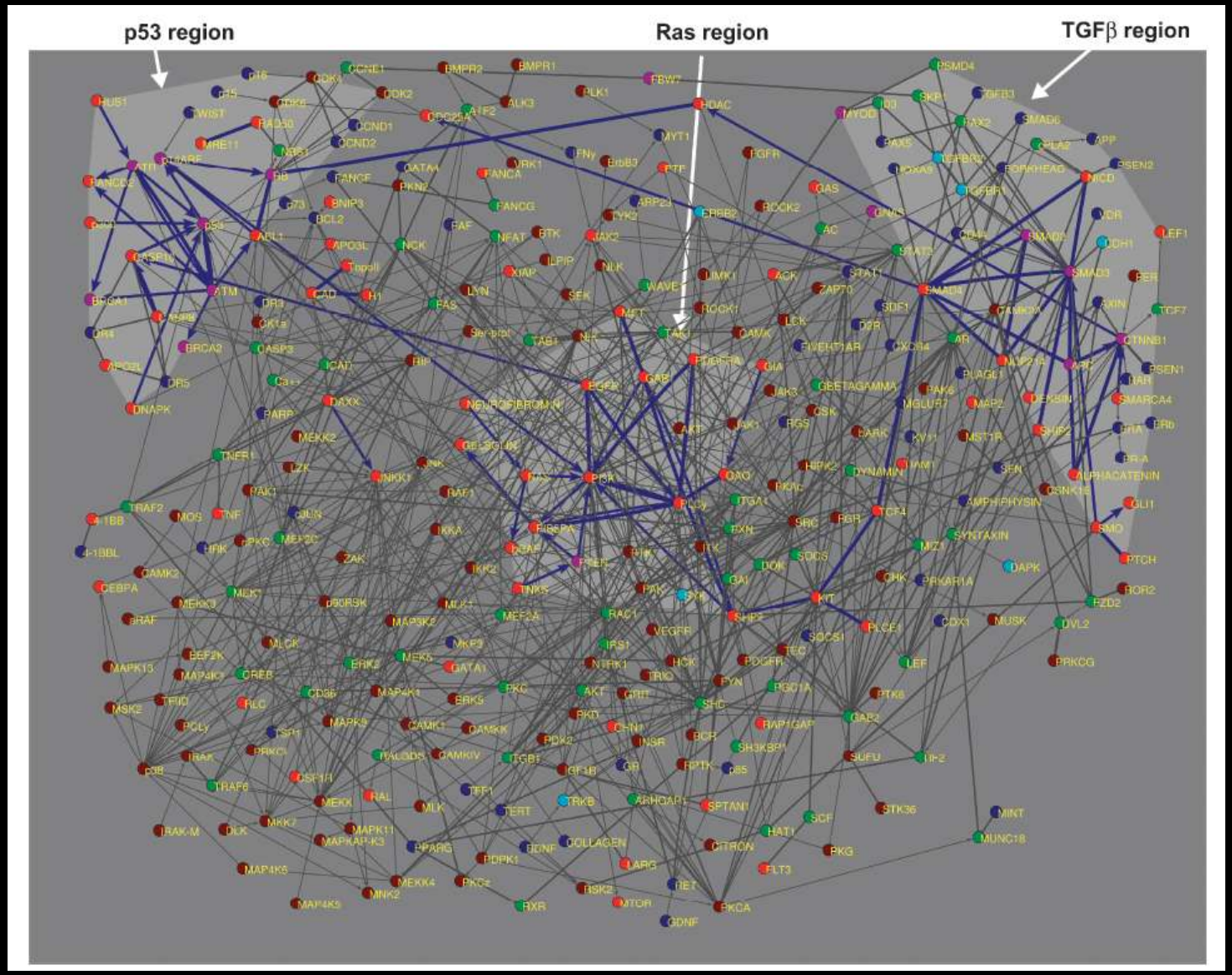
The Disease-Gene Network

K-I Goh et al (2007) PNAS 104, 8685



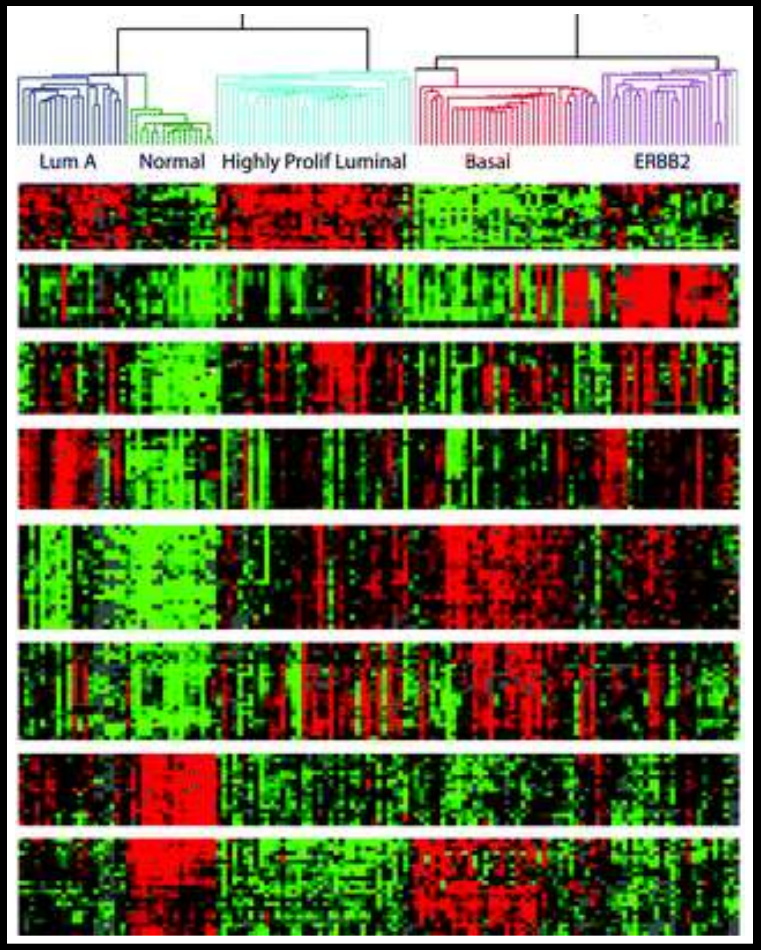
- nodes define specific genes and node size is proportional to # of disorders in which the indicated gene is implicated
- link lines identify genes implicated in the same disorder.

Human Oncogene-Signaling Map



From: Q. Cui et al (2007) Mol. Sys. Biol. 3, 152
326 nodes, 92 links and 12 topological ‘blocks’

Targeted Therapeutics: Identification of Subtypes of Disease with Different Molecular Pathologies

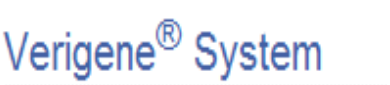


- right Rx for right disease subtype

Dx – Rx combinations

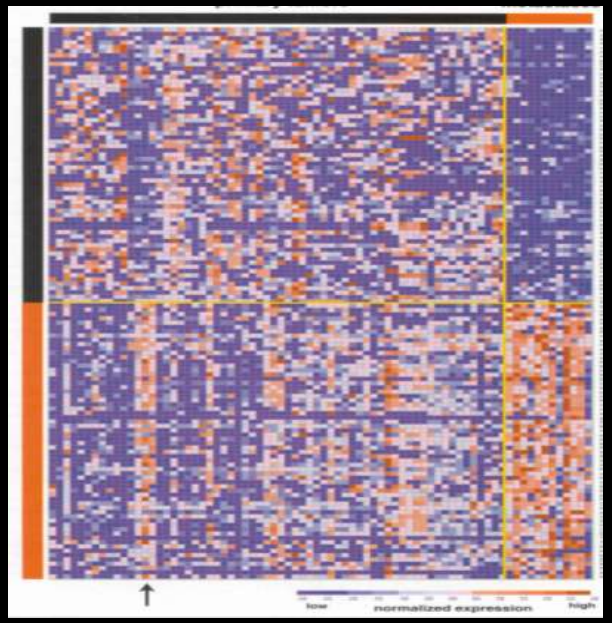
The Emergence of Drug: Diagnostic Combinations

Invader® chemistry



5-Fluorouracil

Molecular Diagnostics, Disease Subtyping and Pharmacogenomics:



- right diagnosis, the first time
- right Rx selection, the first time
- rise of Dx-Rx combination
- Rx approval and labeling only with obligate Dx

- premium pricing for predictable Rx outcomes
- pay-for-performance (P4P)

Johnson & Johnson

VELCADE®
(bortezomib) FOR INJECTION

Adverse Drug Reactions: Pharmacogenomics (2007) 8 (4), 311

- CDC (2006)
  - 6.7% of all US emergency department visits in 2004/05
  - additive burden from drug abuse, suicides and medical errors
- UK NHS (2004)
  - 6.5%
- Germany (2004)
  - 6.2%
- France (2007)
  - 7.1

Adapting to a Safety First World:
RISK Trumps Benefit

VIOXX® (rofecoxib, MSD)

Avandia® rosiglitazone maleate

VYTORIN® (ezetimibe/simvastatin) tablets

Cordarone® AMIODARONUM

+

ZOCOR (SIMVASTATIN)

Byetta® exenatide injection

"Sentinel Initiative"

FDA

"Safety First" Initiative

European Medicines Agency

emea

The New York Times

The Washington Post

abc CBS

NBC

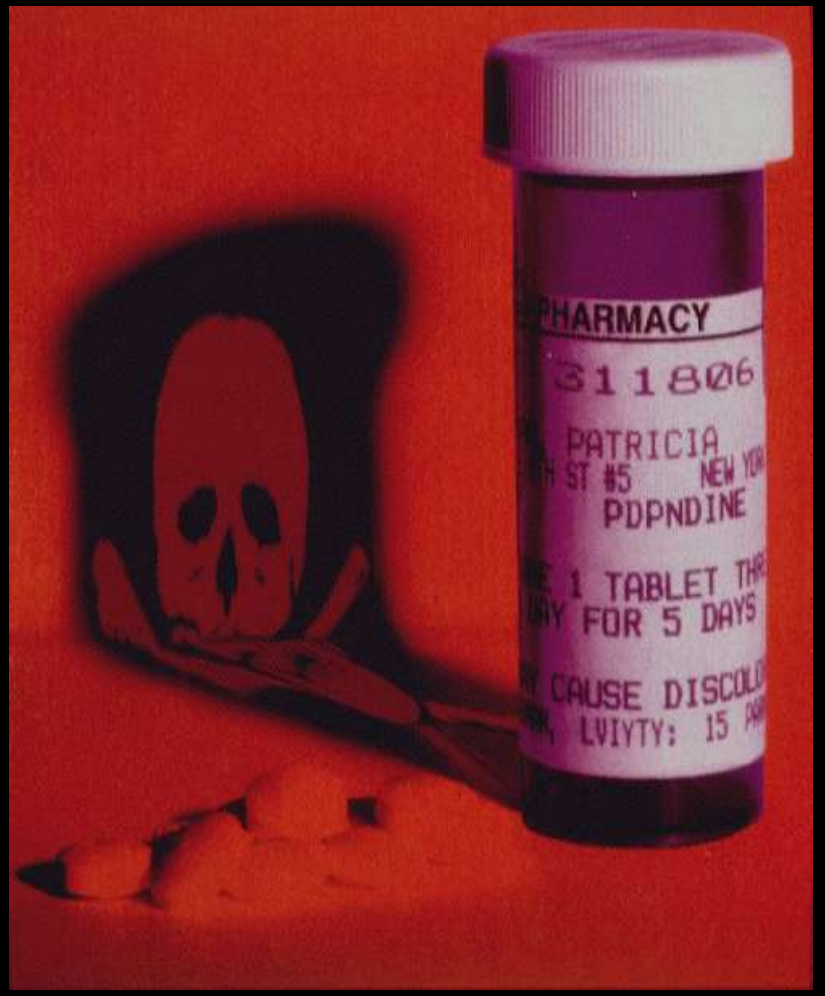
FOX NEWS.com

From Pharmaceuticals to Pharmasuitables

Disease Subtyping:

Right Rx for Right Disease

Individual Variation and AE risk



Right Rx for Right Patient

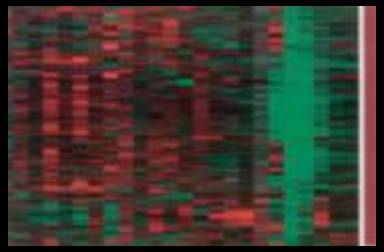
The Evolution of Molecular Medicine and Information-Based Medicine: The Foundation for Rational Care and Personalized Medicine

drug

package insert

Rx 2008

new competencies in molecular medicine and biomedical informatics



molecular diagnostics

real-time information for optimum decision-making

drug

genetic profiling

disease management protocols, patient information

Medicine 2018

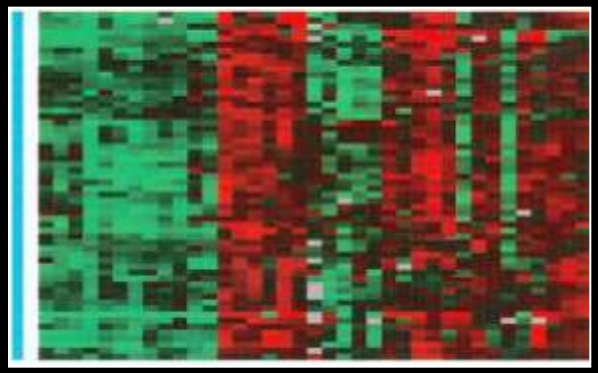
Disease-Associated Biomarkers

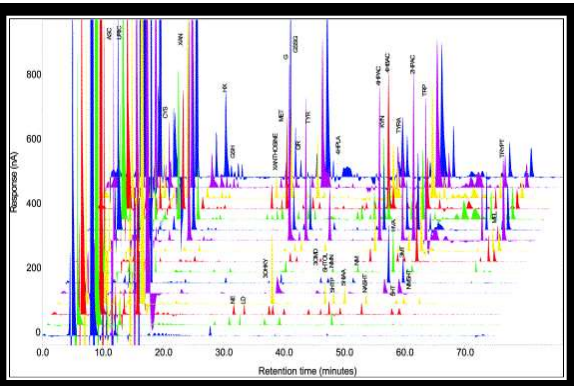
- literature dominated by anecdotal studies
  - academic laboratories
  - small patient cohorts
  - poor replication and confirmatory studies
- lack of standardization
- very few biomarkers subjected to rigorous validation
  - case-control studies with sufficient statistical power
  - inadequate stringency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

Development of Molecular Diagnostics and Biomarkers for Personalized Medicine: The Need for End-to-End R&D Solutions

Complex Biosignature Profiling

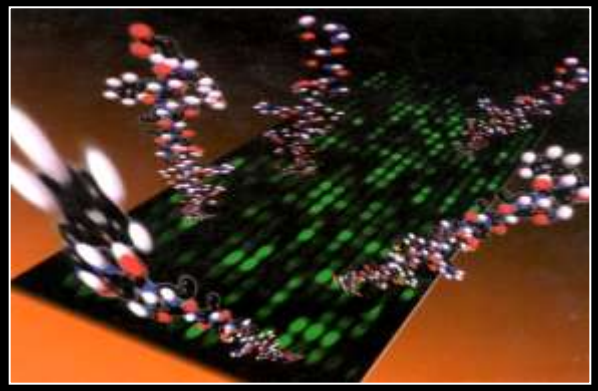
genomics	proteomics	immunosignatures

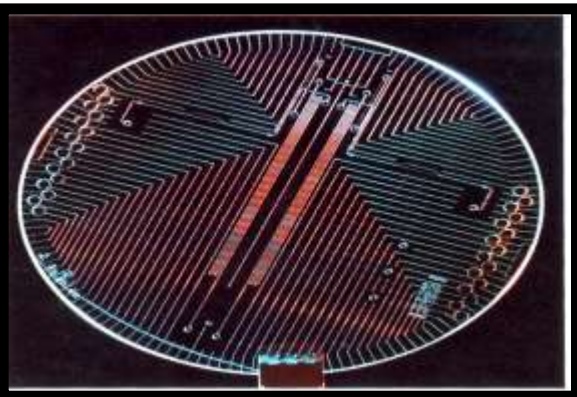


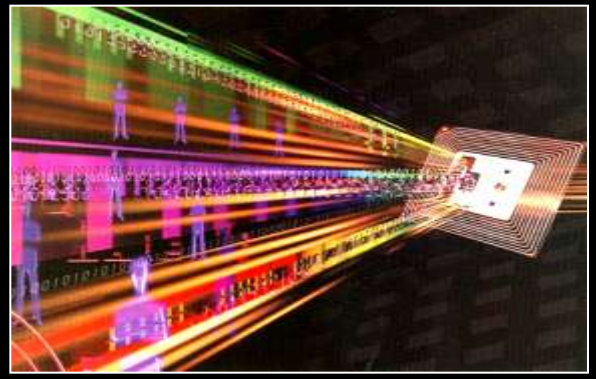


Signature Detection, Deconvolution and Multivariate Analysis

multiplex assays	novel test devices (POC)	new algorithms





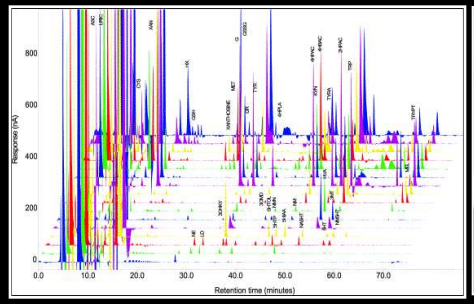


Deriving Value from "-Omics"

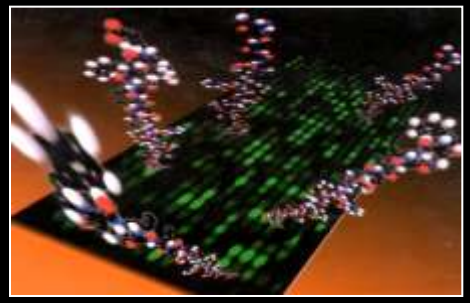
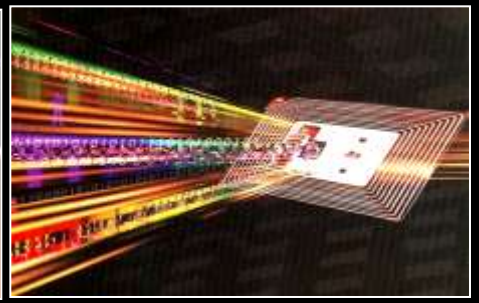
Genomic, Proteomic and Metabolomic Data

- useful only when correlated with additional parameters
  - clinical outcomes
  - clinical utility
  - actionable information
  - demonstrable economic value

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



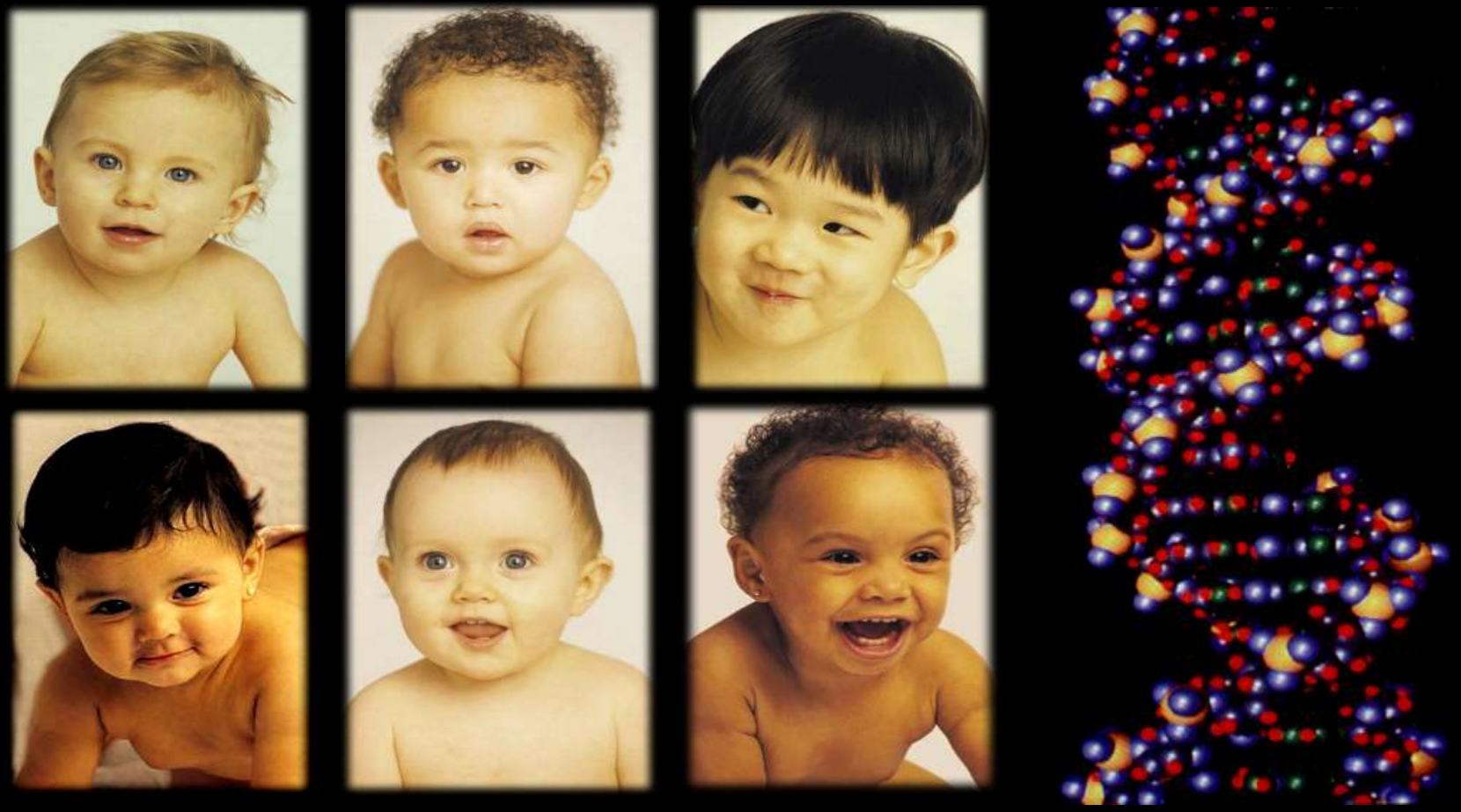

Biospecimens and Molecular Pathway Analysis

Biomarker Validation and Multiplex Assays

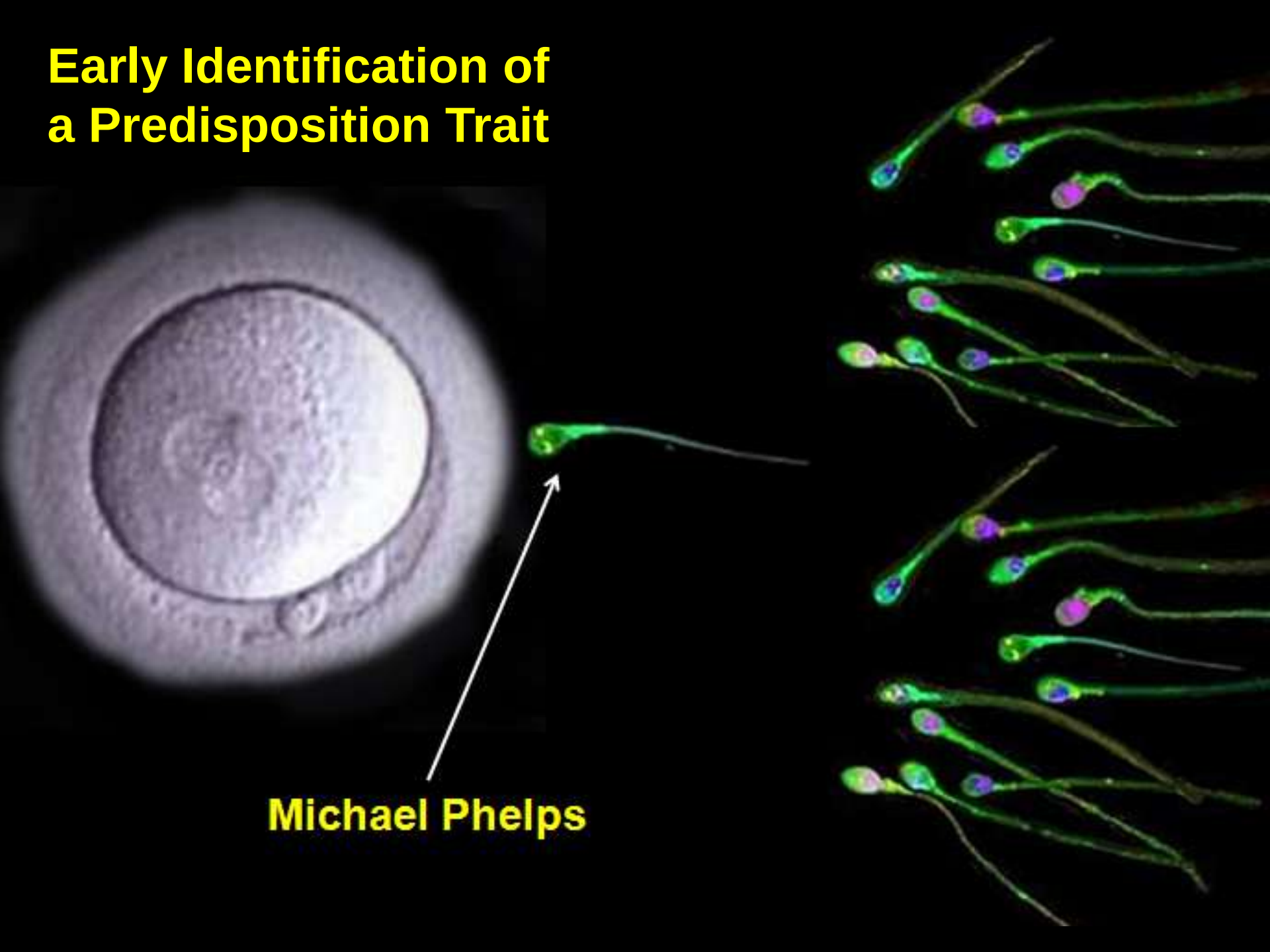
Instrumentation and Informatics

Clinical Impact and Patient Monitoring

Personalized Medicine:
Disease Predisposition Profiling



Early Identification of a Predisposition Trait



nature genetics

Nature Genetics (2008) 40, 955

Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease

Jeffrey C Barrett[*1], Sarah Hansoul[2], Dan L Nicolae[3], Judy H Cho[4], Richard H Duerr[5,6], John D Rioux[7,8], Steven R Brant[9,10], Mark S Silverberg[11], Kent D Taylor[12], M Michael Barmada[6], Alain Bitton[13], Themistocles Dassopoulos[9], Lisa Wu Datta[9], Todd Green[8], Anne M Griffiths[14], Emily O Kistner[15], Michael T Murtha[4], Miguel D Regueiro[5], Jerome I Rotter[12], L Philip Schumm[15], A Hillary Steinhart[11], Stephan R Targan[12], Ramnik J Xavier[16], the NIDDK IBD Genetics Consortium[33], Cécile Libioulle[2], Cynthia Sandor[2], Mark Lathrop[17], Jacques Belaiche[18], Olivier Dewit[19], Ivo Gut[17], Simon Heath[17], Debby Laukens[20], Myriam Mni[2], Paul Rutgeerts[21], André Van Gossum[22], Diana Zelenika[17], Denis Franchimont[22], Jean-Pierre Hugot[23], Martine de Vos[20], Severine Vermeire[21], Edouard Louis[18], the Belgian-French IBD Consortium[33], the Wellcome Trust Case Control Consortium[33,34], Lon R Cardon[1], Carl A Anderson[1], Hazel Drummond[24], Elaine Nimmo[24], Tariq Ahmad[25], Natalie J Prescott[26], Clive M Onnie[26], Sheila A Fisher[26], Jonathan Marchini[27], Jilur Ghori[28], Suzannah Bumpstead[28], Rhian Gwilliam[28], Mark Tremelling[29], Panos Deloukas[28], John Mansfield[30], Derek Jewell[31], Jack Satsangi[24], Christopher G Mathew[26], Miles Parkes[29], Michel Georges[2] & Mark J Daly[8,32]

Several risk factors for Crohn's disease have been identified in recent genome-wide association studies. To advance gene discovery further, we combined data from three studies on Crohn's disease (a total of 3,230 cases and 4,829 controls) and carried out replication in 3,664 independent cases with a mixture of population-based and family-based controls. The results strongly confirm 11 previously reported loci and provide genome-wide significant evidence for 21 additional loci, including the regions containing *STAT3*, *JAK2*, *ICOSLG*, *CDKAL1* and *ITLN1*. The expanded molecular understanding of the basis of this disease offers promise for informed therapeutic development.

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

- slower evolution than many predict
- Genome-Wide Association Studies (GWAS)
  - high cost
  - multiple low penetrance alleles
- substantial ambiguities regarding probabilistic risk of overt diseases
  - epistasis
  - epigenetics
  - environmental confounders
  - source of poor replication of GWAS studies?

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


DNAdirect
Your Genes In Context


Consumer Genetics
Bringing Science Home


CyGene
LABORATORIES


GeneLink


GENECARE
Medical Genetics Center


GENETIC
TECHNOLOGIES, INC.
DNA / FORENSIC / PATERNITY TESTING


genelex


g-Nostics


Graceful Earth
Health Alternatives:Customized Dietary,Nutritional and Herbal Information


HealthCheckUSA


INTERLEUKIN
GENETICS
Empowering


MediChecks.com


23andMe


NEUROMARK


SURACELL
Personal Genetic Health™


The International
TLC-Wellbeing Clinic
Wellbeing through Science, Nutrition and TLC.
Est. 1987. Treating Clients in over 100 Countries.


Navigenics


Knome


ScientificMatch.com
"The Science of Love"

“They (consumer genomics tests) are a premature integration of technology and there is no clinical validation of the information”

Dr. Muin J. Khoury
Director, National Office of Public Health Genomics

The Nations Health
May 2008 p.26

If you build it
will they pay?

Misaligned Reimbursement Incentives: Rewarding Process Versus Results

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

- 9000 billing codes for care procedures, services and units of care
- not a single code for patient improvement
- no billing code for cure of chronic disease

Reimbursement for Diagnostic Tests

- inadequate US Medicare coding and payment mechanisms
  - out moded, out-dated, lacking in transparency, inconsistently applied
- no effort to link reimbursement to value
- inappropriate assignment of existing CPT codes to new tests
- engagement of third party payers who derive economic/clinical value from new Dx
  - Genomic Health Oncotype Dx

Pharmacogenetic Predisposition to Adverse Drug Reactions

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

Courses in Medical Genetics in US and Canadian Medical Schools 2004-2005

Table 1

General Characteristics of Courses in Medical Genetics Taught in U.S. and Canadian Medical Schools, 2004 to 2005

Characteristics	No. (%) respondents
Type of course	
Stand-alone	52/112 (46)
Integrated	60/112 (54)
Course taught with multiple instructors	
Yes	99/112 (88)
No	12/112 (11)
Unspecified	1/112 (1)
Year of curriculum in which course was taught*	
First	86/112 (77)
Second	35/112 (31)
Third	6/112 (5)
Fourth	1/112 (1)
Unspecified	0/112 (0)
Total hours taught in course	
<20	20/112 (18)
20–40	69/112 (62)
41–60	15/112 (13)
>60	5/112 (4)
Unspecified	3/112 (3)
Type of sponsoring unit	
Clinical sciences	55/112 (49)
Basic sciences	32/112 (29)
Multidisciplinary/integrated	19/112 (17)
Other/unspecified	6/112 (5)

* Column total exceeds 100% because some respondents reported teaching medical genetics in more than one year.

From: V. C. Thurston et al. (2007) Acad. Med. 82, 441

Legal pressures and incentives for personalized medicine

Gary E Marchant†, Robert J Milligan & Brian Wilhelmi

†Author for correspondence Sandra Day O'Connor College of Law, PO Box 877906, Tempe, AZ 85287–7906, USA Tel.: +1 480 965 3246;

Legal liability has the potential to be a powerful driver pushing implementation of personalized medicine. Individuals injured by adverse drug effects are increasingly likely to bring lawsuits alleging that they have a polymorphism or biomarker conferring susceptibility to the drug that should have been identified and used to alter their drug treatment. Likely targets of such lawsuits include drug manufacturers, third party payors, physicians and pharmacists, of which physicians are most at risk of substantial liability.

Personalized Medicine (2006) 3 (4) 391-397

Personalized Medicine: A Broader Perspective

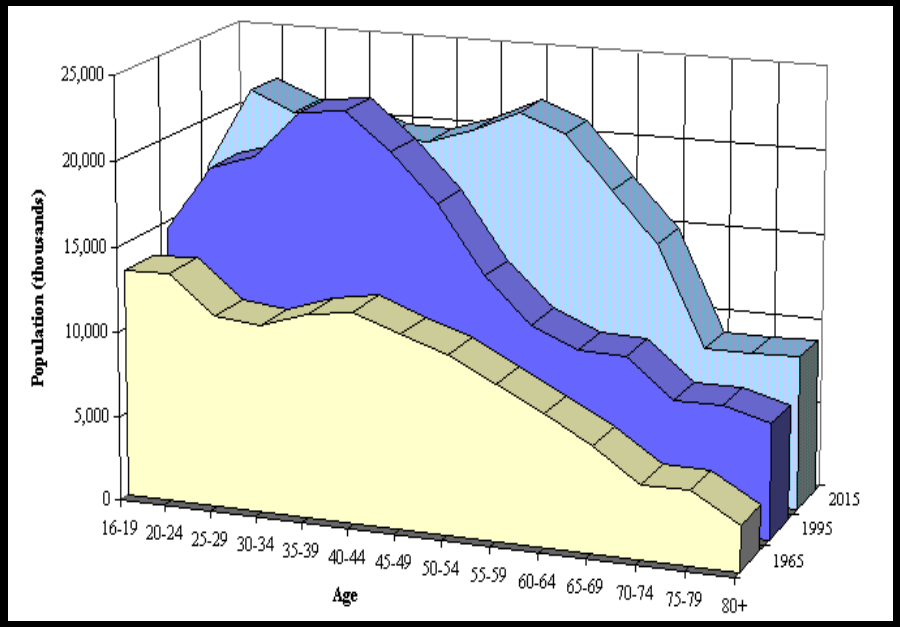
Wellness…….Or Else!

"The public has no idea how big the problem is. The $43 trillion in unfunded Social Security, Medicare and other retirements benefits will drive the government into insolvency by 2040 unless Congress moves quickly."

David M. Walker

Chief, General Accounting Office

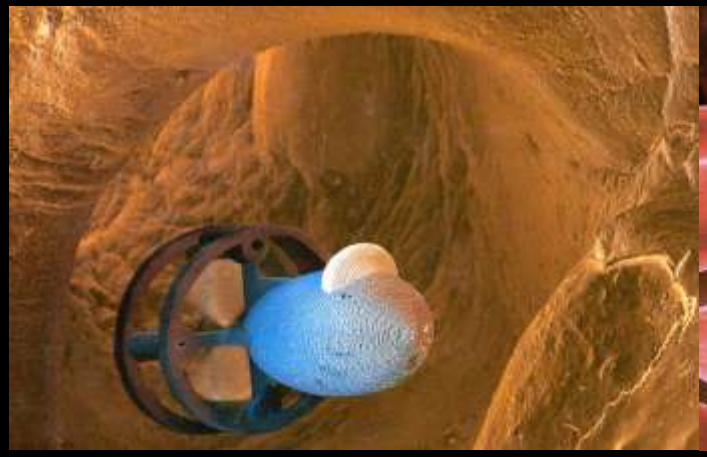
US Government 2007

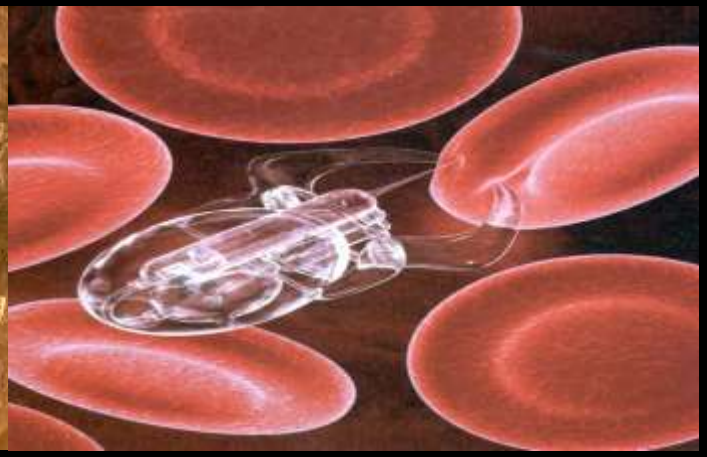


Promotion of Wellness

- increased consumer responsibility for wellness
- remote monitoring of individual health status
- crucial role of healthcare information systems
  - integrated Rx care for complex chronic conditions
  - outcomes and comparative effectiveness
  - earlier detection of disease episodes and risk mitigation
  - wellness versus illness

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





On Body: In Body Sensors and Devices

Healthcare

Objective

- remote monitoring of health status

Applications

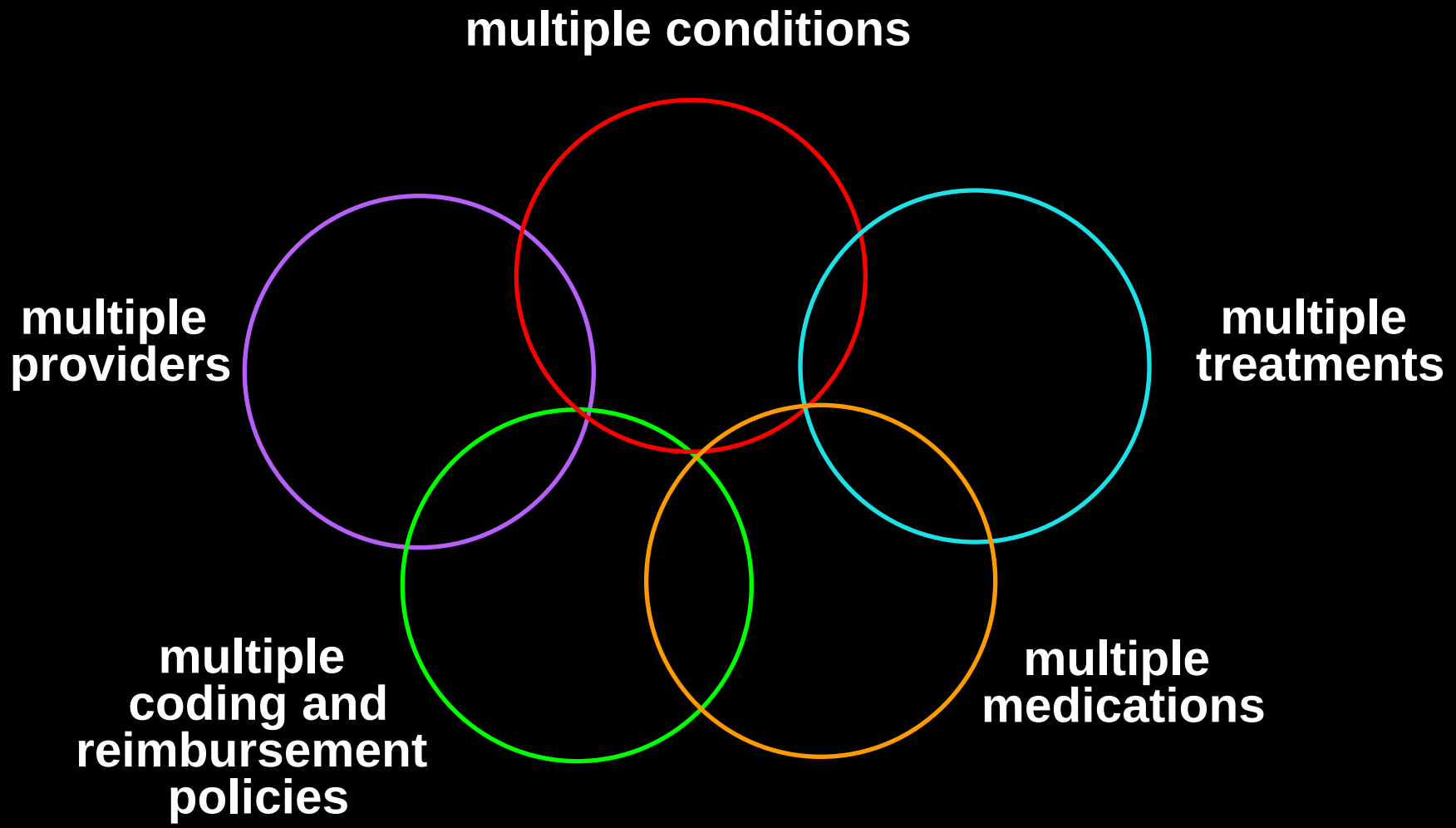
- multi-feature monitoring and broad-band wireless networks
  - ubiquitous sensing
- enhanced autonomy for in-home aged
- proactive alerting and intervention to mitigate health incidents
- monitoring of patient compliance
- coupled linkage to remote Rx dispensing for efficient disease management

The Costs of Non-Compliance with Rx Regimens

- $177 billion projected cost
- 20 million workdays/year lost (IHPM)
- 40% of nursing home admissions
- projected 45-75% non-compliance (WHO)
- 50-60% depressed patients (IHPM)
- 50% chronic care Rx (WHO)

Managing the Economic and Clinical Impact of Aging Demographics and Complex, Chronic Conditions

Challenges in the Management of Complex Chronic Conditions and Co-Morbidities



Personalized Medicine: Progressive Evolution Based on Increasingly Comprehensive Profiling of Disease Risk and Health Status

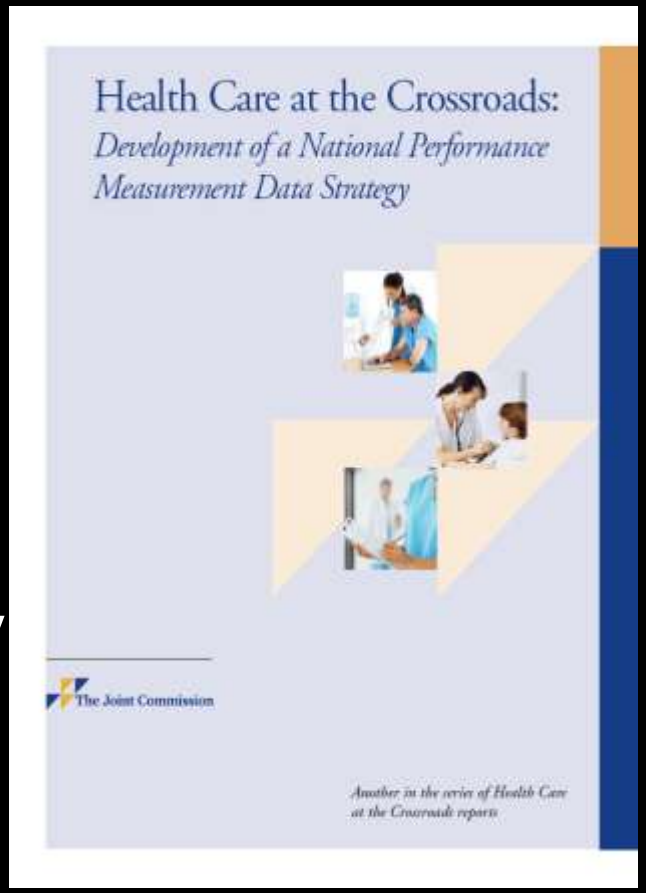
- rational Rx based on profiling of underlying molecular pathology
- MDx and disease subtyping

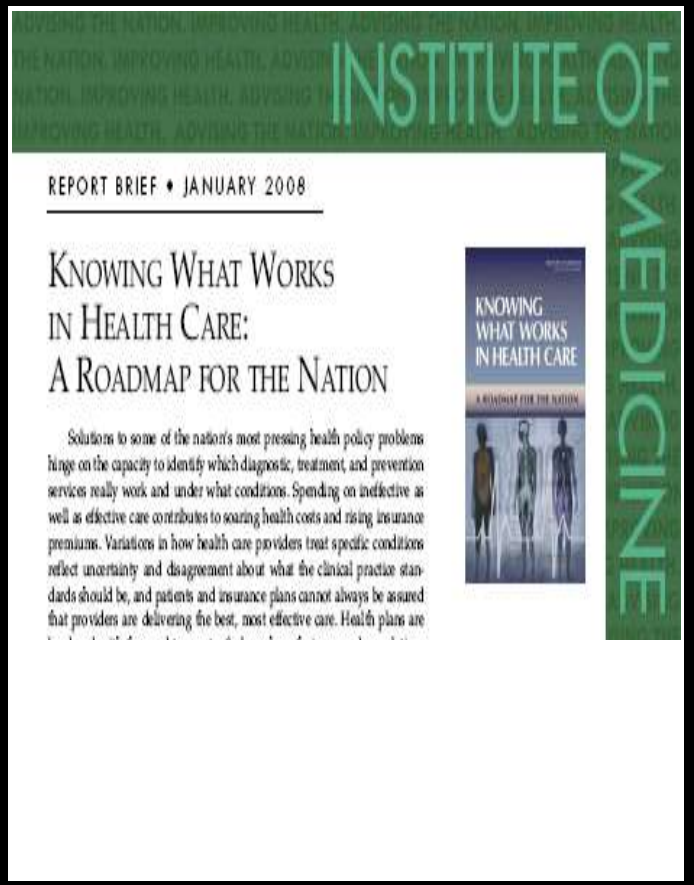
- rational Rx based on comprehensive molecular profiling of individuals
  - disease subtypes and optimum Rx
  - Rx AE risk
  - disease predisposition risk and mitigation

- integrated framework of longitudinal data on individual health status
- real time remote health status monitoring
- transition to disease prediction and preemption

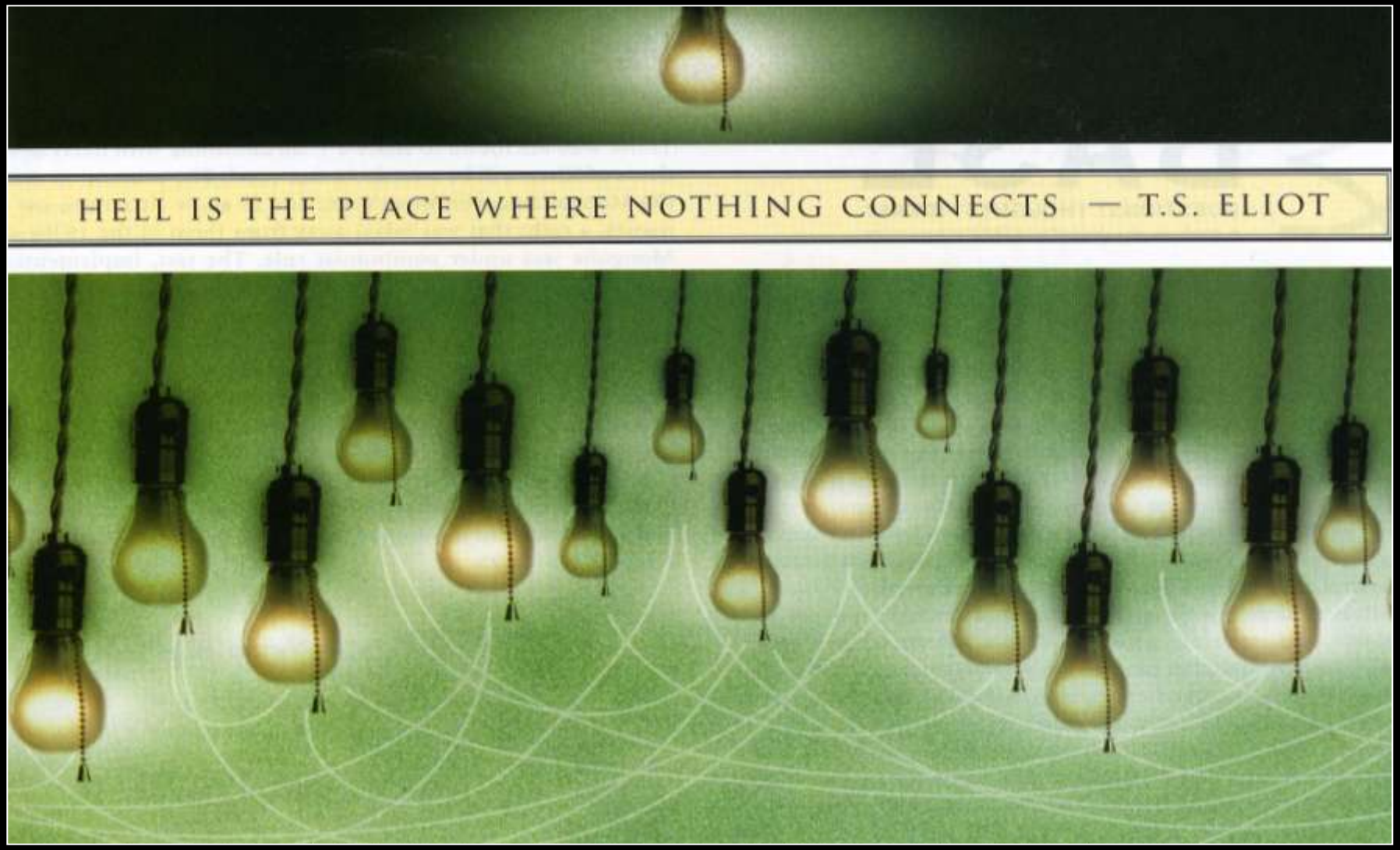
Assessment of New Technology and Outcomes

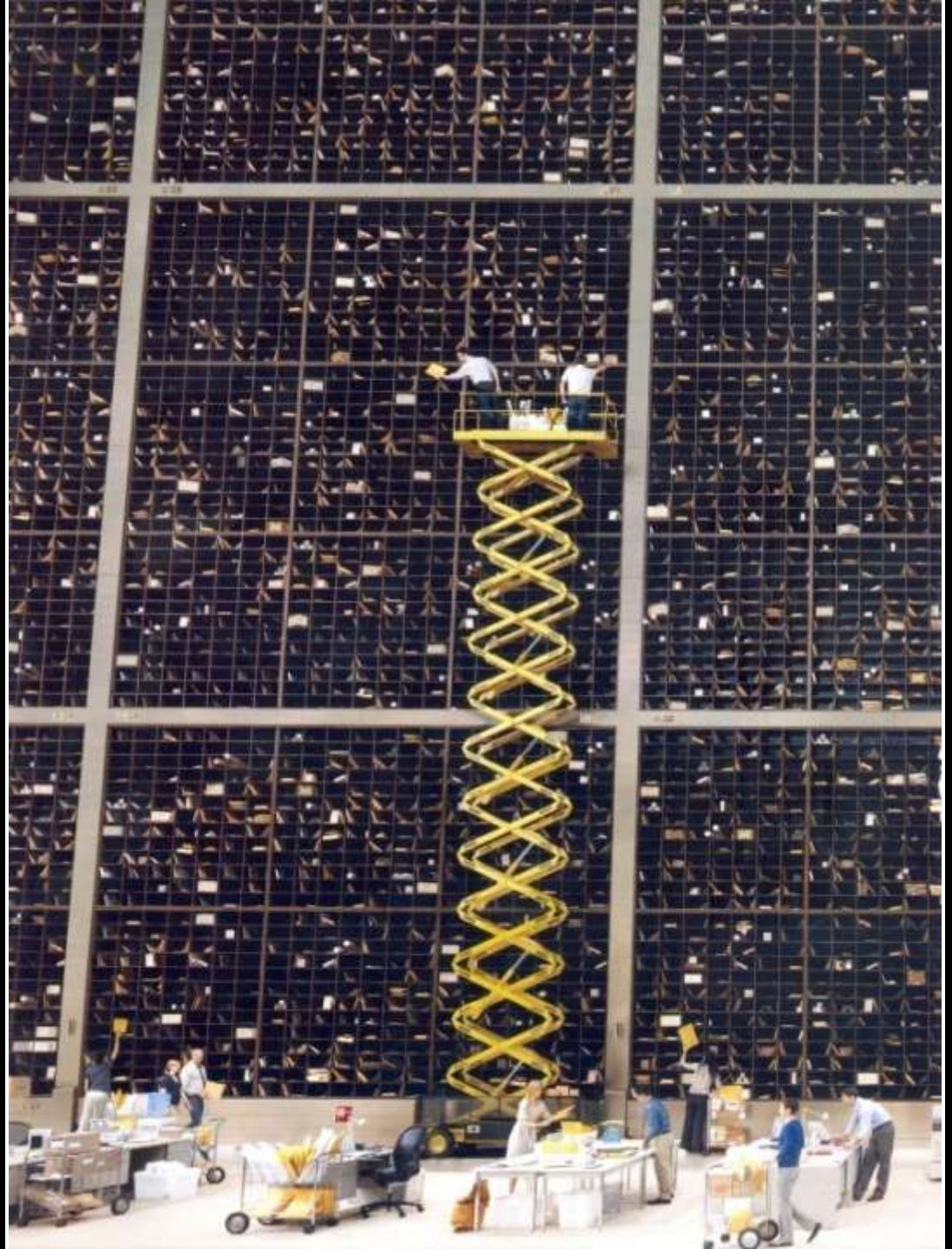
- $2.3 trillion healthcare economy
- $110 billion R&D investment
- $0.9 billion on technology assessment



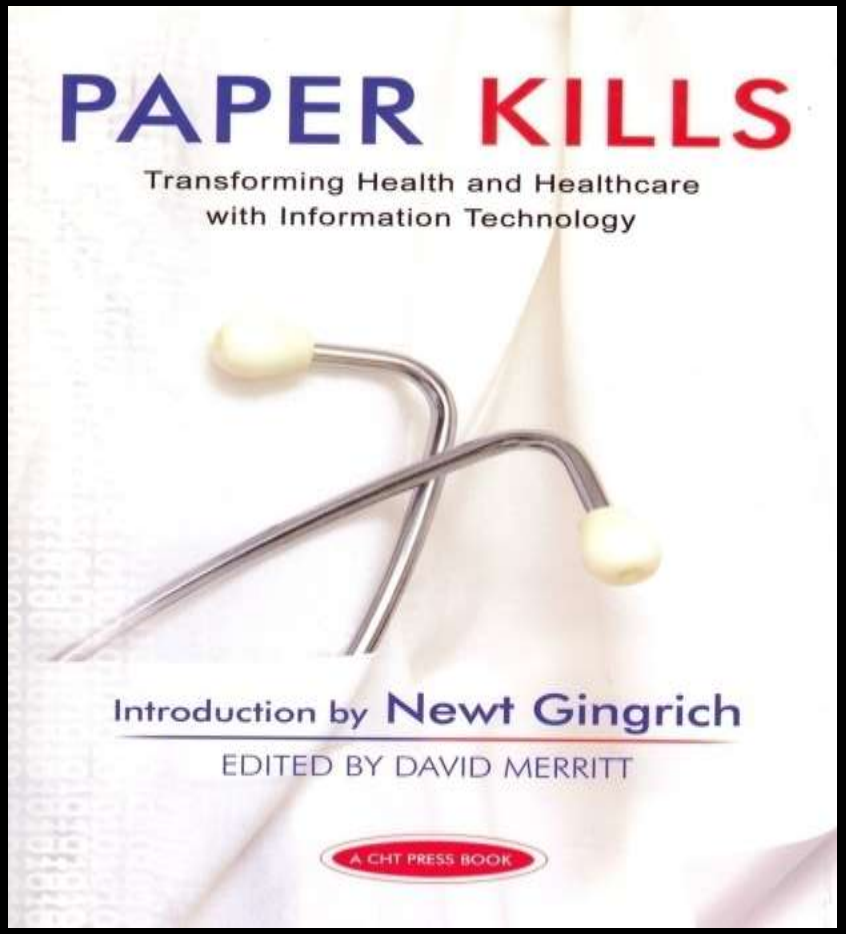


Information-Based Medicine





Paper-Based Medical Records: Fragmented Care, Unacceptable Errors and a Major Hurdle to Performance Analysis



The Unacceptable Cost of Unconnected Healthcare

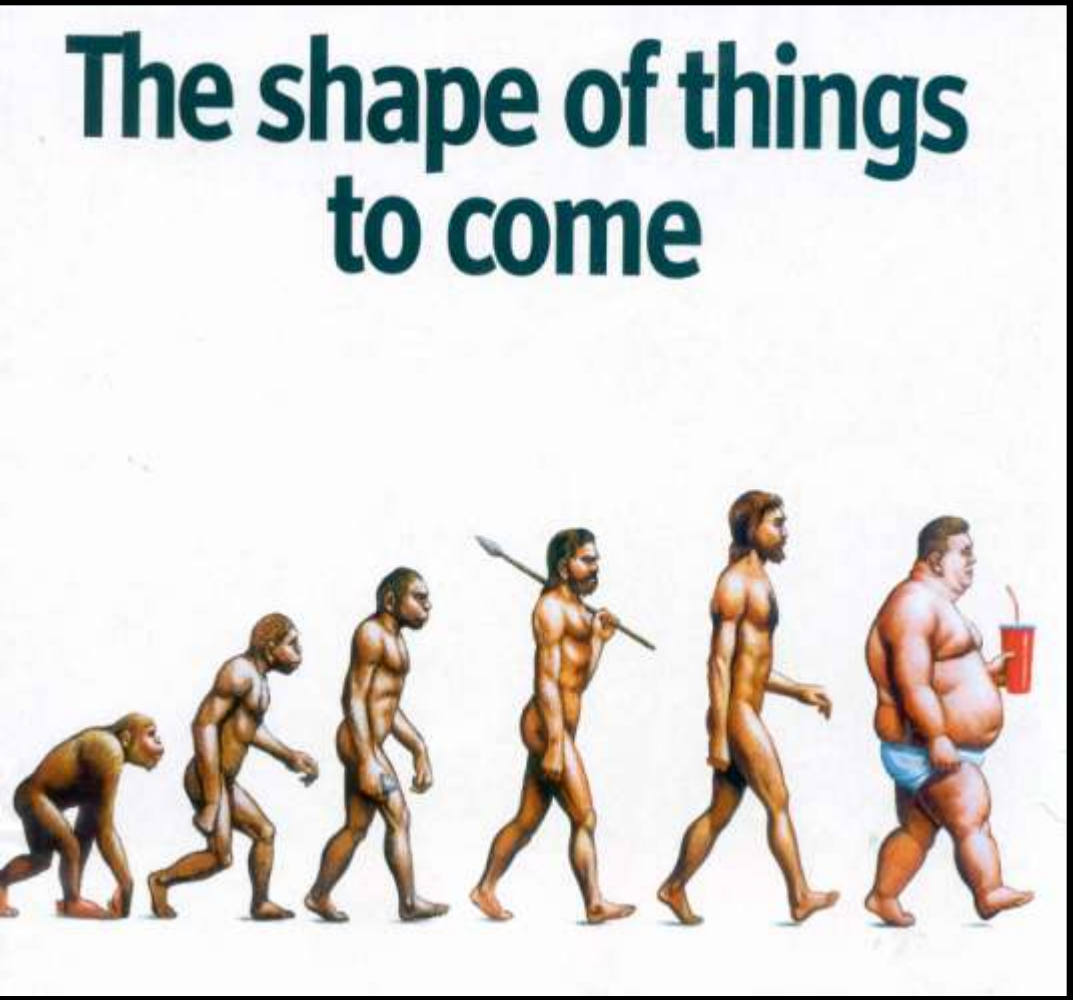
- cultural, fiscal and legal barriers to transformational electronic connectivity achieved by other sectors
- major obstacle to safe and efficient healthcare delivery
  - extravagant waste via excessive duplication of tests/procedures
  - error via lack of crucial data
  - lack of data capture for outcomes analysis and individual physician performance
- failure to capture population-based disease parameters
  - sentinel public health/national security
  - meta-analysis of outcomes
  - drug and device safety and recall

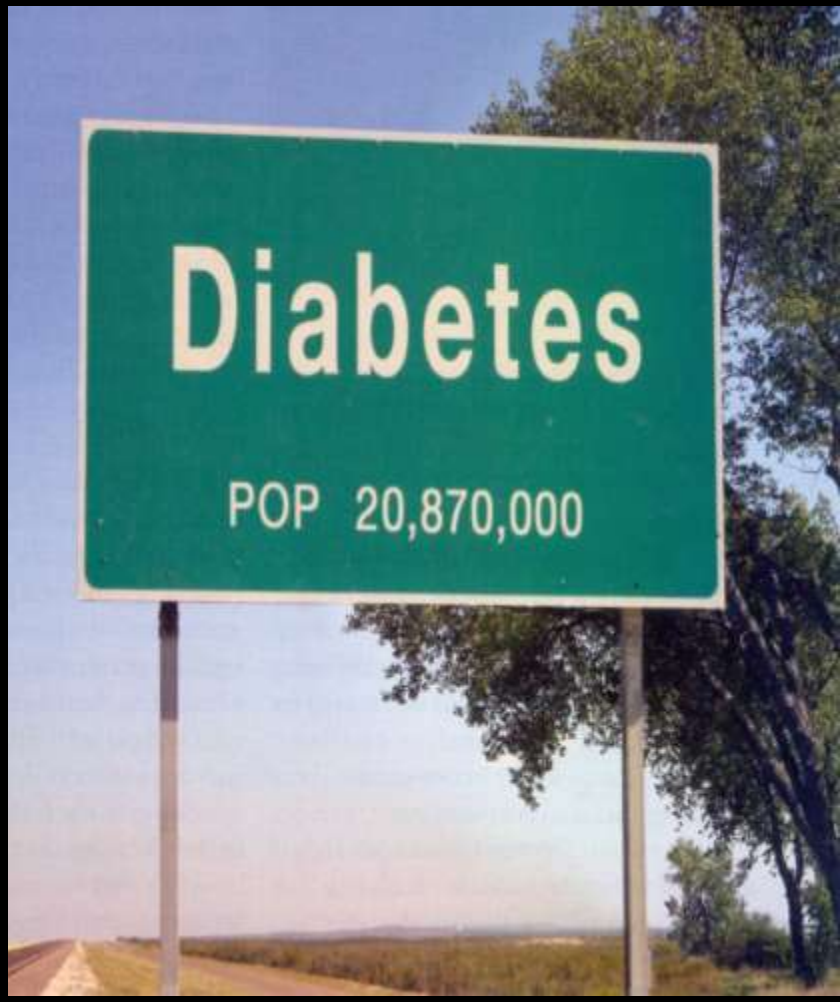
Consumer Directed Healthcare Plans

"Until the person receiving the product is responsible in some fashion for the costs, there will be no incentive to spend responsibly"

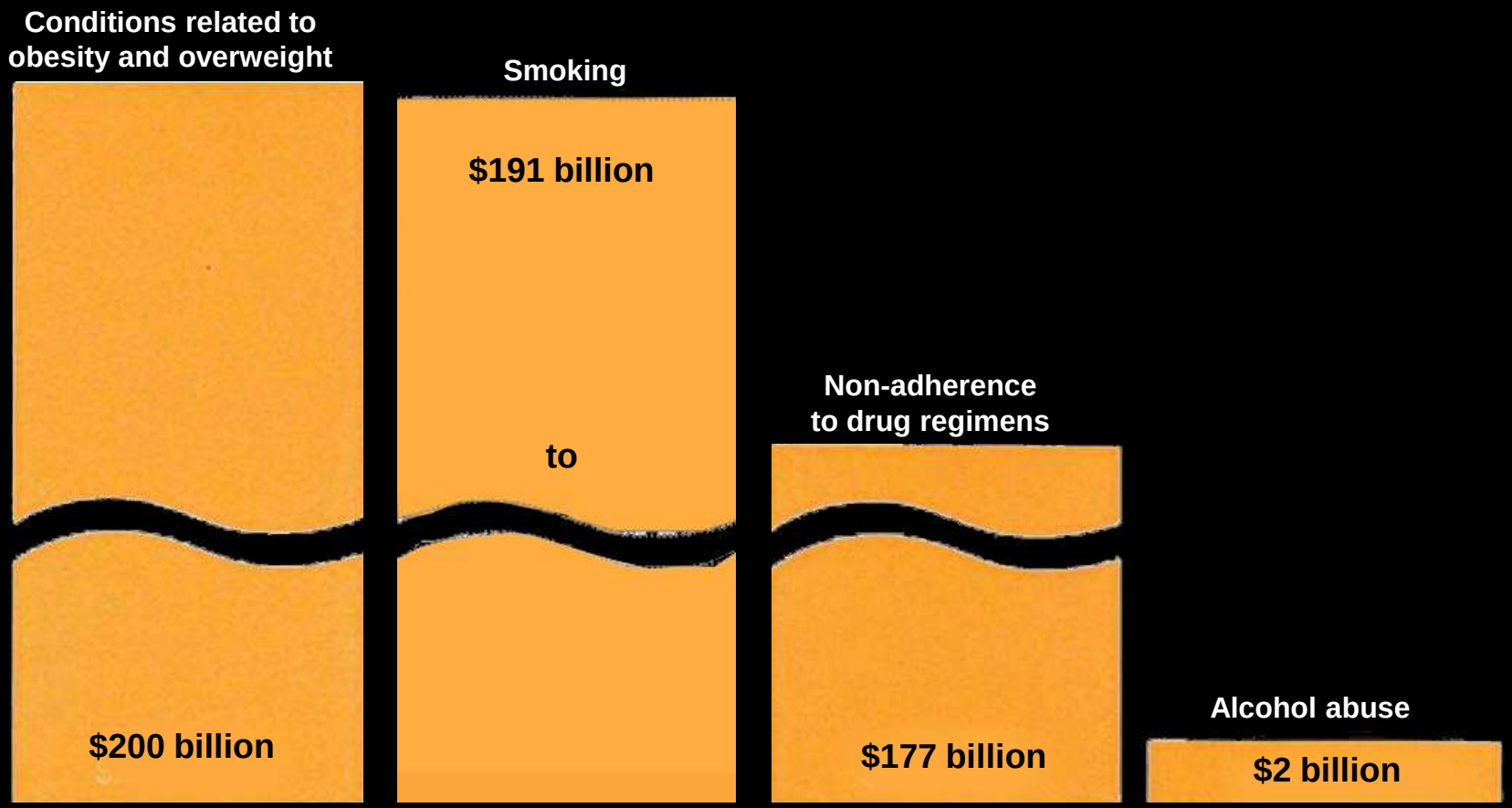
Scott Serota
CEO, BCBS Association of Chicago
Chief Executive Magazine, March 2007 p. 50

After a Short Stay in America, Michelangelo's David Returned to Europe


The shape of things to come


Diabetes
POP 20,870,000

Annual Excess Healthcare Costs Related to Consumer Behavior



Source: RTI International & Center for Disease Control and Prevention (200), Datamonitor (2007), Americas Health Insurance Plans (2007), Commonwealth Fund (2007), Agency for Health Research and Quality (2003), Analysis by PricewaterhouseCoopers' Health Research

Personal Medical Records (PMRs)

Microsoft HealthVault BETA

WebMD Better information. Better health.

revolutionhealth Your home for health and balance

The Official Google Blog
Google Health, a first look

Always WAL★MART

Promoting Wellness

stickK

fitnet

FITNET.ca
CANADA'S NETWORK FOR FITNESS PROVIDERS

Go-getters

Virgin unite

Lifespring History

The Infocosm: Emerging Networks of Global Connectivity

The Information Age: Proliferating Information as a Constant

"It is a shame that the telegraph
has been invented.
Now suddenly anyone can get the news"

"One already has too much to think about
when bathing,
which is not good"

James Rothschild (1852)

Telecommunications and Media Industry Convergence: Implications for Healthcare

The Changing Nature of Social Interaction

Herd Behavior: 1.3 Million Bathers, Coney Island 1951

Herd Behavior: 2008 Social Networks and Virtual Communities

facebook

YouTube

Consumer-Directed Healthcare

- leveraging social-and peer-networks
- increased role of fitness industry and entertainment in healthcare
  - "success via distraction"
- "virtual touch"
  - web-based medical consultation and diagnostic algorithms
  - generational gap in need for physical interaction with physician

Healthcare Information Networks: AORTA: Always On Real Time Access

- end-to-end continuity in use of internet and wireless technologies
- from routine remote monitoring of health status to advanced critical care

- comprehensive connectivity

  plus
- collapsing time

  plus
- global networks

The Growing Internet

Web 1.0

- access to information, products and services
- back-end infrastructure and navigation

Web 2.0

- access to other people (social networks)
- front-end user friendly interface

Web 3.0

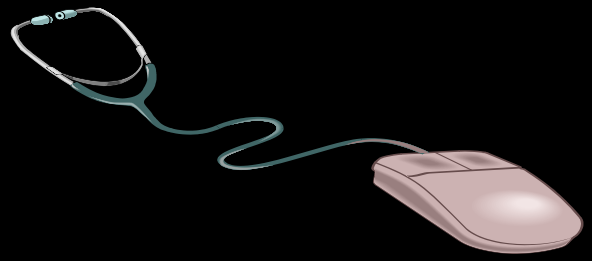
- access to intelligence
- back-end focus on complex intelligence and context
- “the semantic web”
- “a seamless Web of all the data in your life” (Tim Berners-Lee)
- “go where users go”

The Evolution of Molecular Medicine and Information-Based Medicine: The Foundation for Rational Care and Personalized Medicine

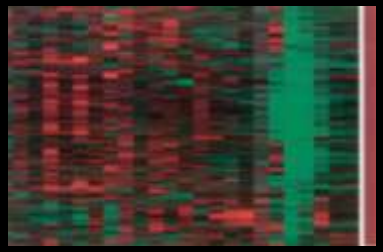
drug

package insert

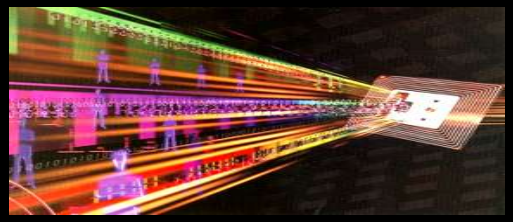
Rx 2008



new competencies in molecular medicine and biomedical informatics



molecular diagnostics



real-time information for optimum decision-making

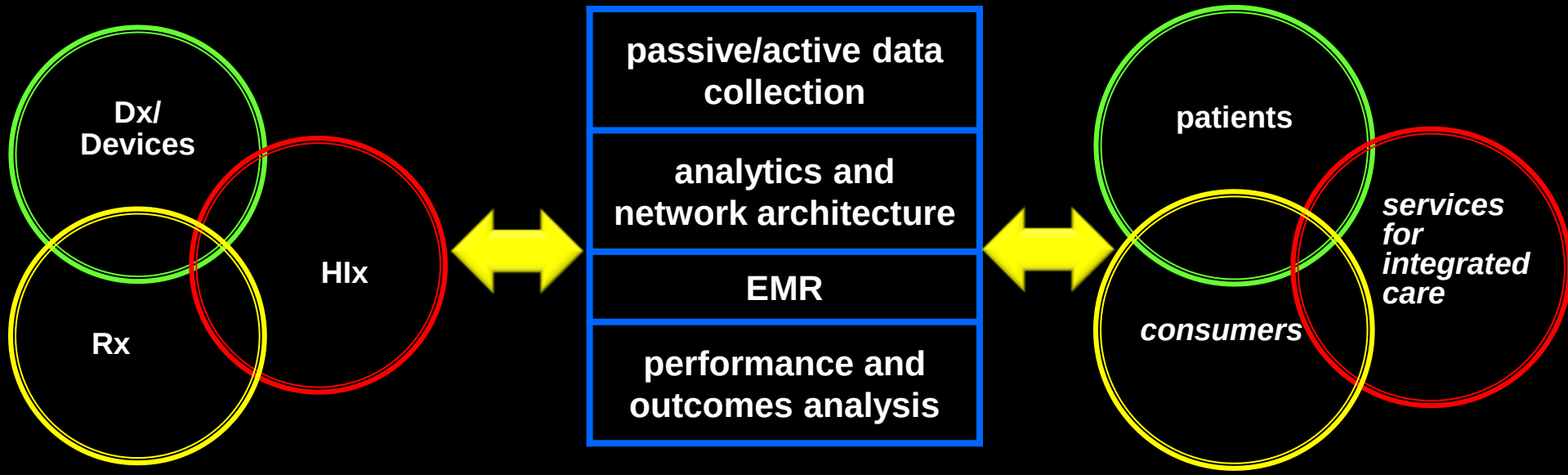
drug

genetic profiling

disease management protocols, patient information

Medicine 2018

A New Healthcare Ecosystem Arising From Technology Convergence



Integrated Technology Platforms

Data Mining and Integration Services

Increasingly Targeted Care and Efficient Use of Finite Resources

Privacy and Information

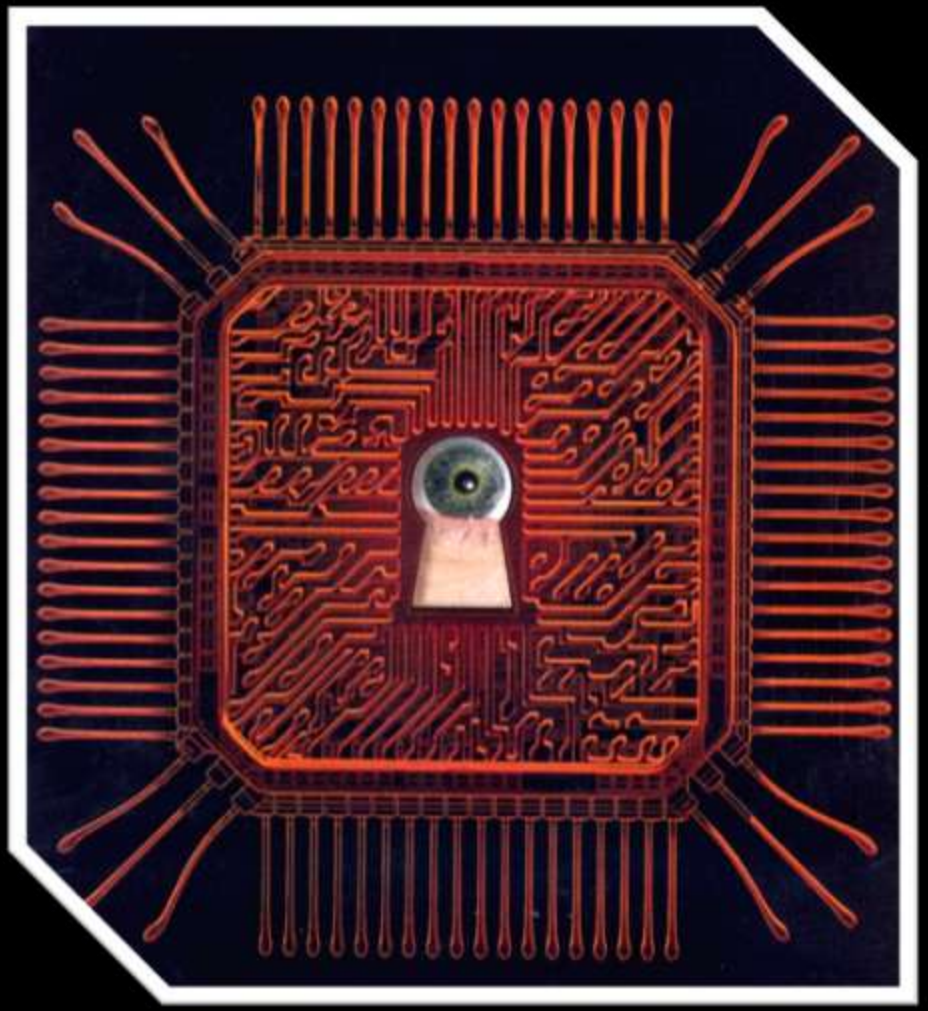
- 2010: 15 Petabits (10^{16}) / $250,000
- Human Genome: 10 Gigabits (10^{11})

For a few million dollars, one could store the complete genome of every American and European

...for several more, could add credit card records, telephone logs, travel history,...


CHASE
blink
PASSPORT
RFID
oyster


SCANNING



The Coming Convergence in Healthcare Delivery

The Coming Convergence in Healthcare Delivery

Technologies

- biotechnology, medicine, engineering, computing

Clinical Practice

- molecular medicine and increasingly customized care
- diagnostic, drug and device combinations
- POC testing and remote monitoring
- reduced error and improved compliance
- improved outcomes

Realigned Incentives

- integrated care for complex chronic diseases
- earlier disease detection and risk reduction
- wellness versus illness
- health status monitoring

The Coming Convergence in Healthcare Delivery

Consumers

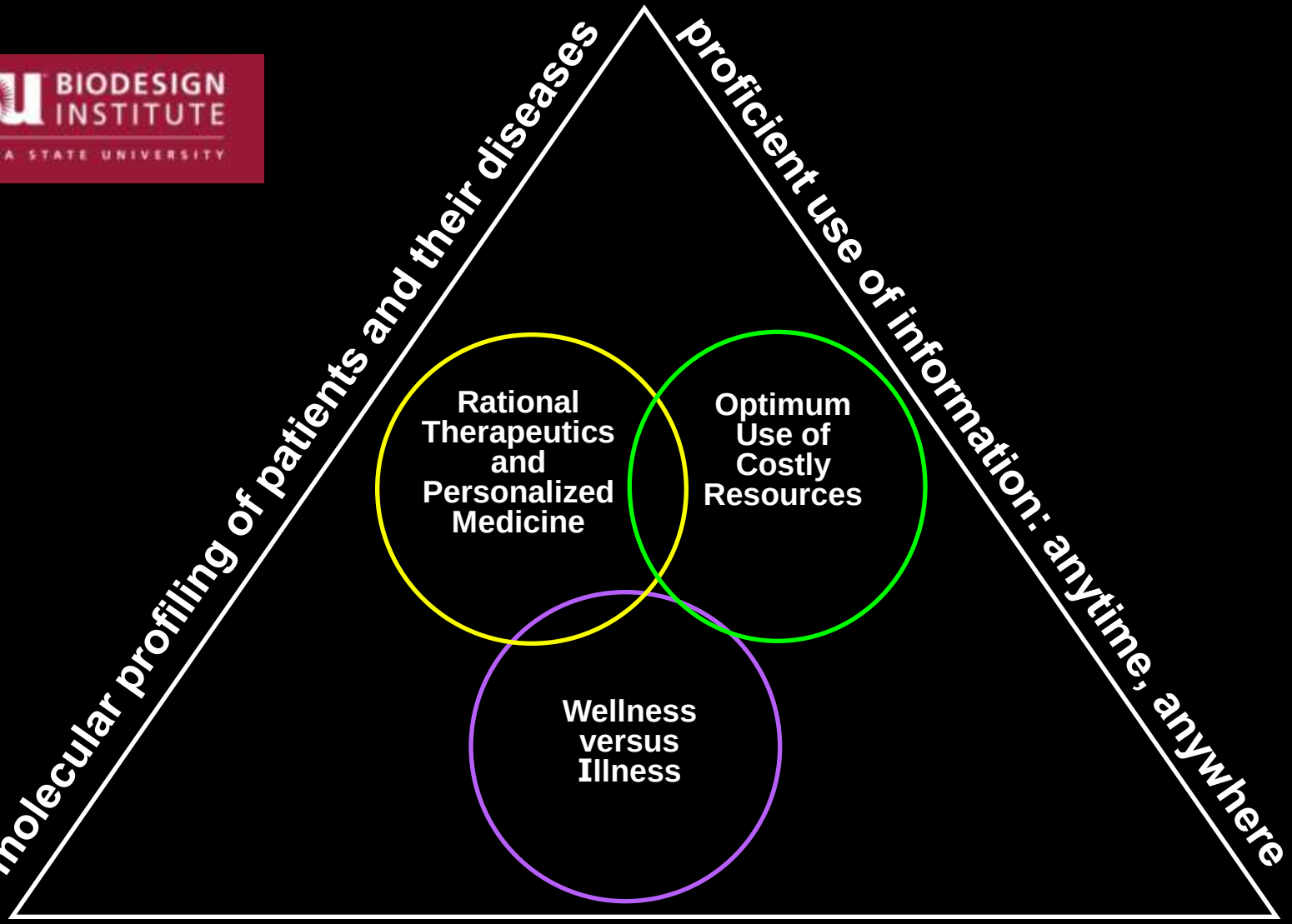
- increased personal responsibility for health
- new incentives for wellness/compliance
- health status monitoring

Connectivity

- integrated care networks for chronic disease
- improved outcomes and effectiveness
- social networks and informed consumers
- new supplier networks of specialized turnkey expertise
- value added ‘content’ services for clinical data mining

Building The Strategic Platforms for Integrated Healthcare Delivery

ASU BIODESIGN INSTITUTE
ARIZONA STATE UNIVERSITY



earlier detection and prevention of disease episodes
coordination of care for complex chronic diseases.