

Research, Regulation, Risk and Reward: The Strategic Environment for Pharmaceutical R&D

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**Keynote address:
Dutch Top Institute Spring Meeting
Utrecht, 23 April 2009**

The Impact of Advances in Technical Knowledge on Human Longevity, Disease Burden and Quality-of-Life

- **public sanitation**
- **clean water**
- **improved nutrition**
- **education**
- **child labor laws**
- **workplace safety**
- **control of toxic waste and
environmental spoilage**

The Impact of Advances in Technical Knowledge on Human Longevity, Disease Burden and Quality-of-Life

Broad Societal Programs

- **public sanitation**
- **clean water**
- **improved nutrition**
- **education**
- **child labor laws**
- **workplace safety**
- **control of toxic waste and environmental spoilage**

Pharmaceutical Innovation

- **control of parasitic and infectious diseases**
- **major reductions in CV, metabolic, musculo-skeletal and mental illness**
- **veterinary medicine and improved productivity and safety of food supply**

Health Matters: Healthcare R&D Occupies a Unique Position in Societal Expectations

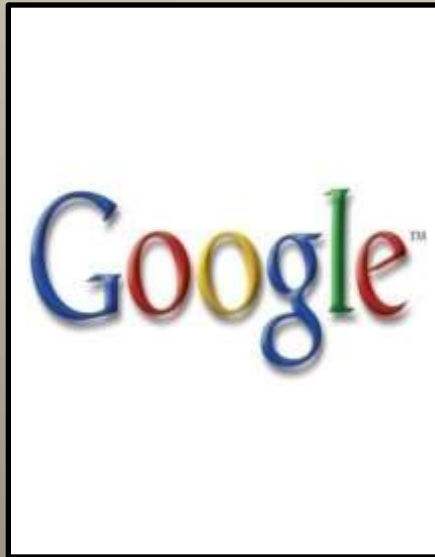
- **public expectancy: the entitlement mentality**
 - **ever faster innovation but at no risk and cost paid by others**
- **political expediency: control of escalating costs**
 - **governments court 'high-tech' corporate R&D investment but set efficacy barriers and pricing policies that hinder innovation/investment**

Health Matters: Healthcare R&D Occupies a Unique Position in Societal Expectations

- **free market forces or a public good?**
 - distrust/rejection of profit-motive
 - media portrayal of corporate ‘greed’ at expense of the ill
- **global equity and distributive justice**
 - the “90:10” challenge
- **negative industry image**
 - profiteers rather than innovators
 - lack of public/political awareness of massive R&D investments and time, cost and complexity of Rx development

COMPLEXITY

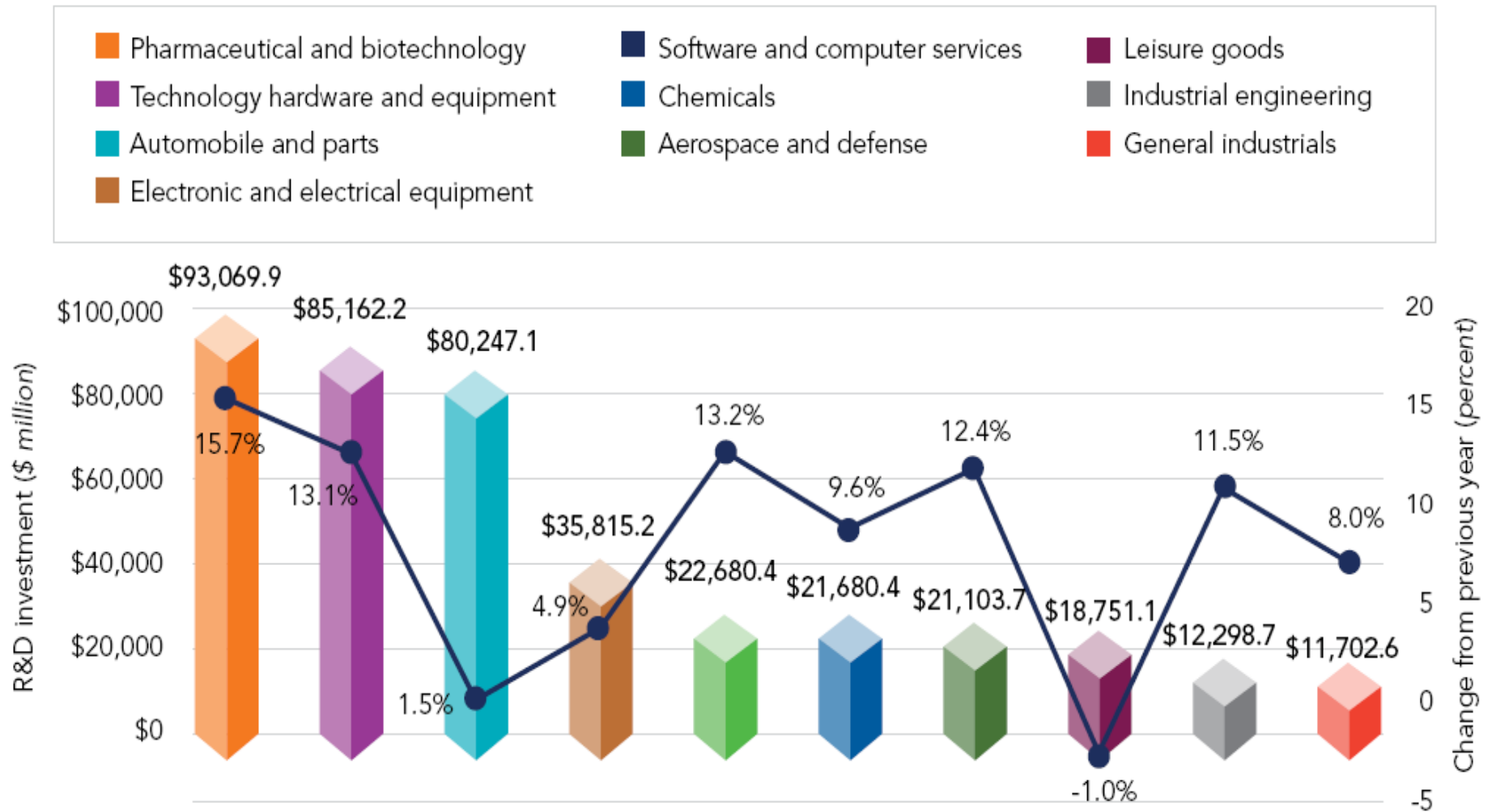
The Mega-Project Industries: Masters of Complexity



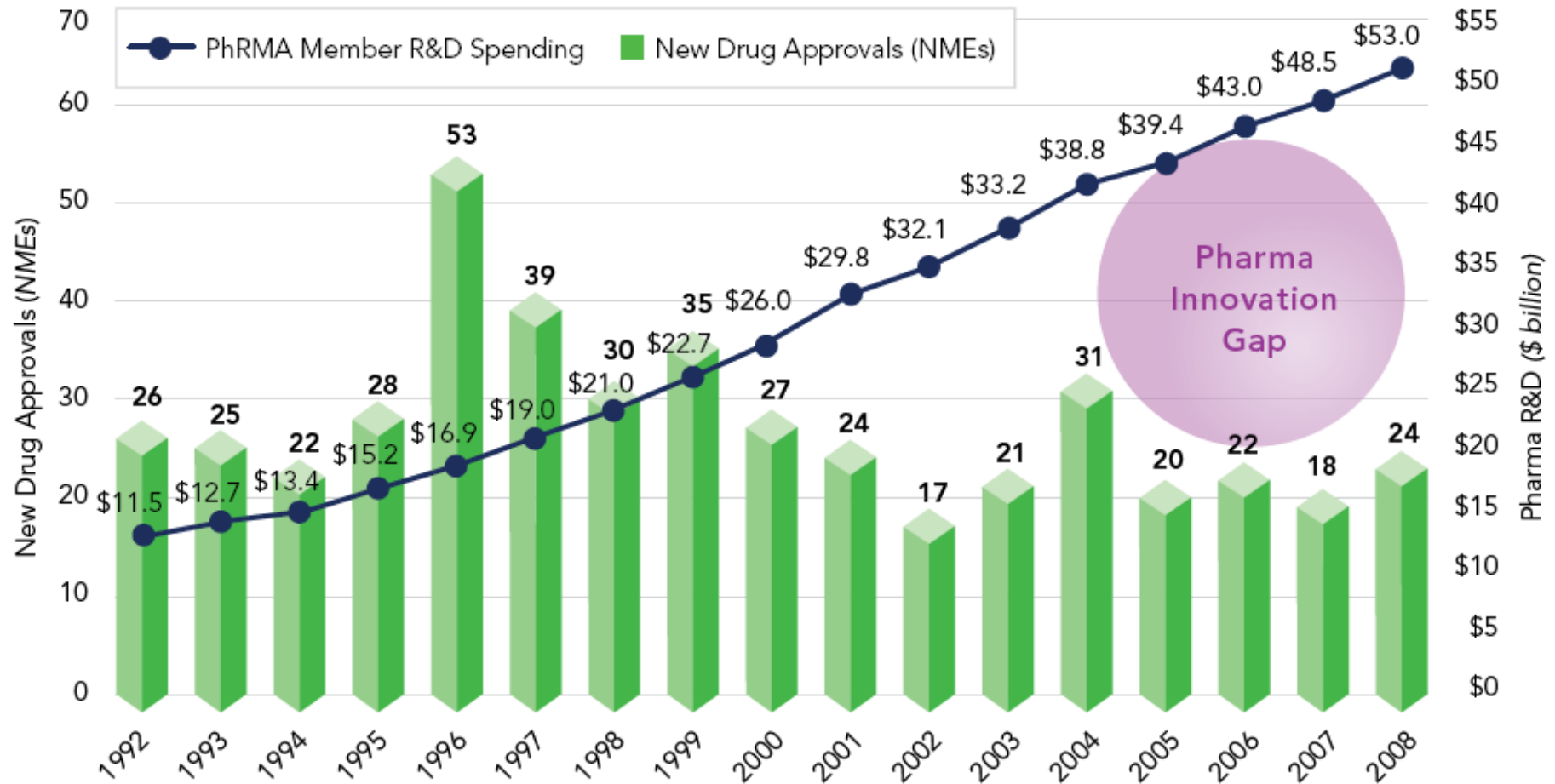
“Mega-Projects”

- **very high R&D investment per project (\$1 billion plus)**
- **extended R&D cycles (10-25 years)**
- **multi-disciplinary integration of diverse specialized skills**
- **multi-national scope**
- **high uncertainty, high risk**
 - **technical failure**
 - **financial risk**
 - **product risk**
- **impact of government and market policies that can change significantly in project lifetime**

R&D Investments by Different Industries



Innovation Gap: R&D Investments Versus New Drug Approvals



*Estimated

Source: Burrill & Company

The Strategic Environment for Healthcare

**COST, CONSERVATISM
AND
RESISTANCE TO CHANGE**

The Strategic Environment for Healthcare

- **escalating costs without major gains in quality**
- **focus on late-stage disease detection/intervention**
 - **high cost**
 - **low reversibility of chronic diseases**
- **demographic trends and additional costs of chronic disease in the aged**
- **fragmented and uncoordinated care**

The Strategic Environment for Healthcare

- **unacceptable levels of misdiagnosis/error**
- **highly variable patterns of clinical care**
- **massive waste and inefficiency by lack of real-time, comprehensive electronic medical records**
- **illness versus wellness**
- **inadequate social and economic incentives for wellness**

U.S. Healthcare Costs are Unevenly Distributed

- **0.5% patients consume 25% of healthcare budget**
- **1% consume 35%**
- **5% consume 60%**
- **10% consume 70%**
- **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



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

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



The Strategic Future of Healthcare

A photograph of a road that splits into two paths, one leading to the left and one leading to the right. The road is paved and has yellow double lines in the center. The background shows a forested hillside under a clear sky. The text 'Economic Unsustainability' is on the left path, 'or' is in the center, and 'Reform and Rational Care' is on the right path.

**Economic
Unsustainability**

or

**Reform and
Rational Care**

**Confronting the Imbalance Between Infinite Demand
and Finite Resources**

Reasonable Expectations for Rational Healthcare

- what works
- why it works
- who it works for
- what works best
- when should it be used optimally
- validated evidence
- mechanism of action
- personalized medicine
- comparative effectiveness
- best practice guidelines, standard-of-care and malpractice

VALUE

Defining New Value Propositions for Healthcare Delivery

- **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**

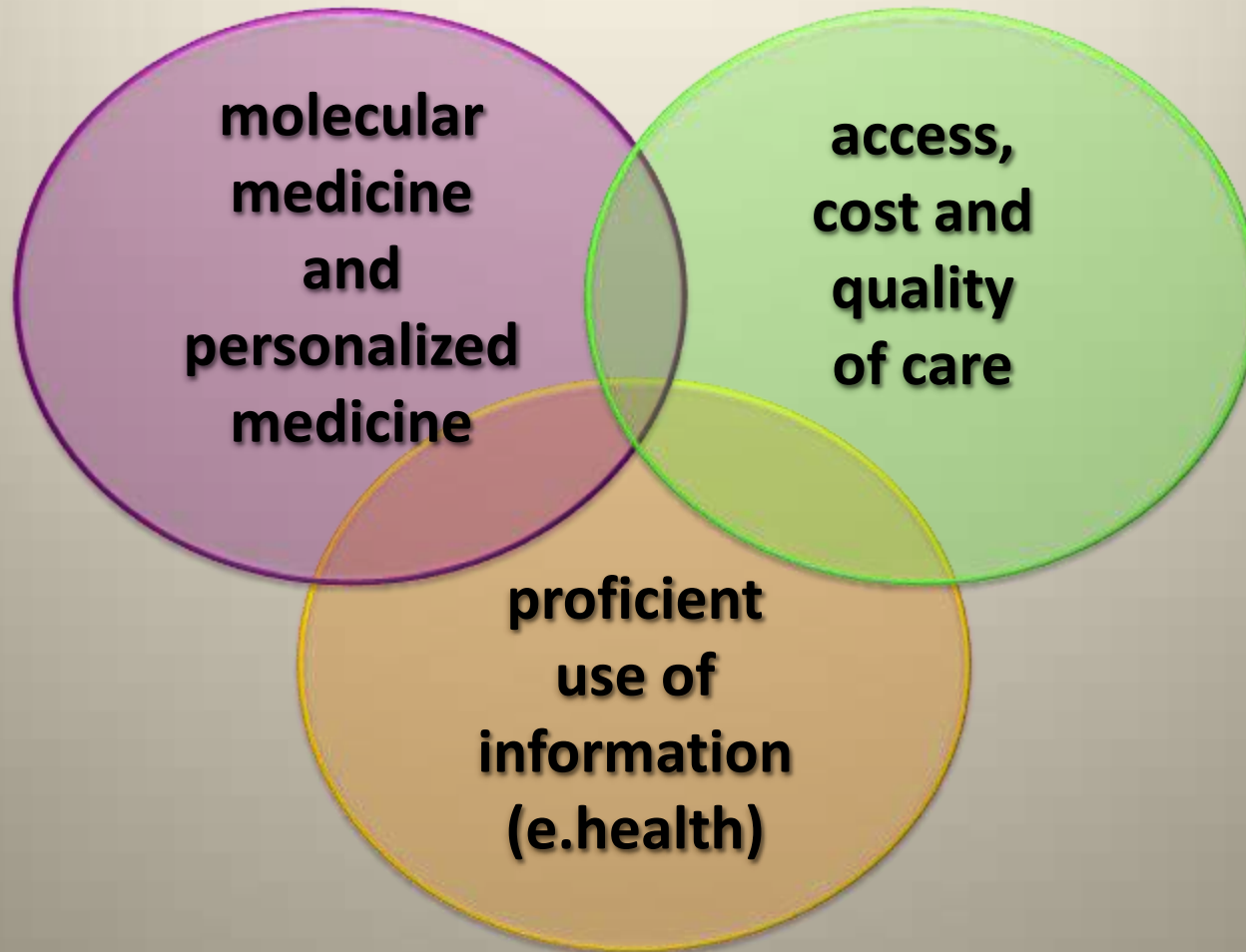
The Future of Healthcare: Personalized Medicine

Urgent Priorities for Improvements in Clinical Practice and Healthcare Delivery

- **from empirical diagnosis (symptoms) to definitive profiling (molecular pathology) of causal disease mechanisms**
 - **personalized medicine and rational therapy**
- **earlier detection of disease (pre-symptomatic) or disease progression**
- **routine monitoring of individual health status**
- **instant access to patient information**
 - **anytime, any place, any patient**

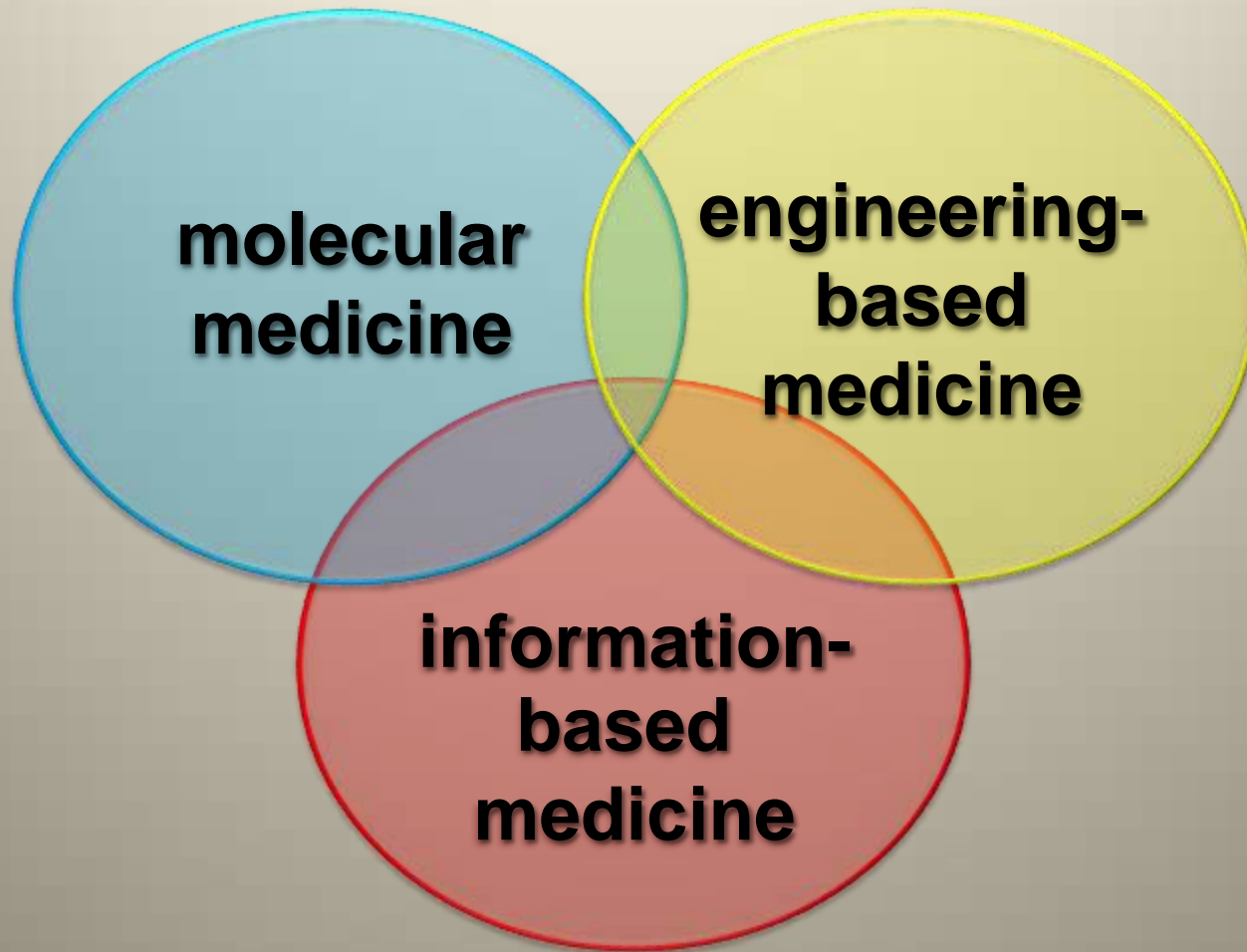
Convergence

The Three Forces Shaping the Evolution of Healthcare

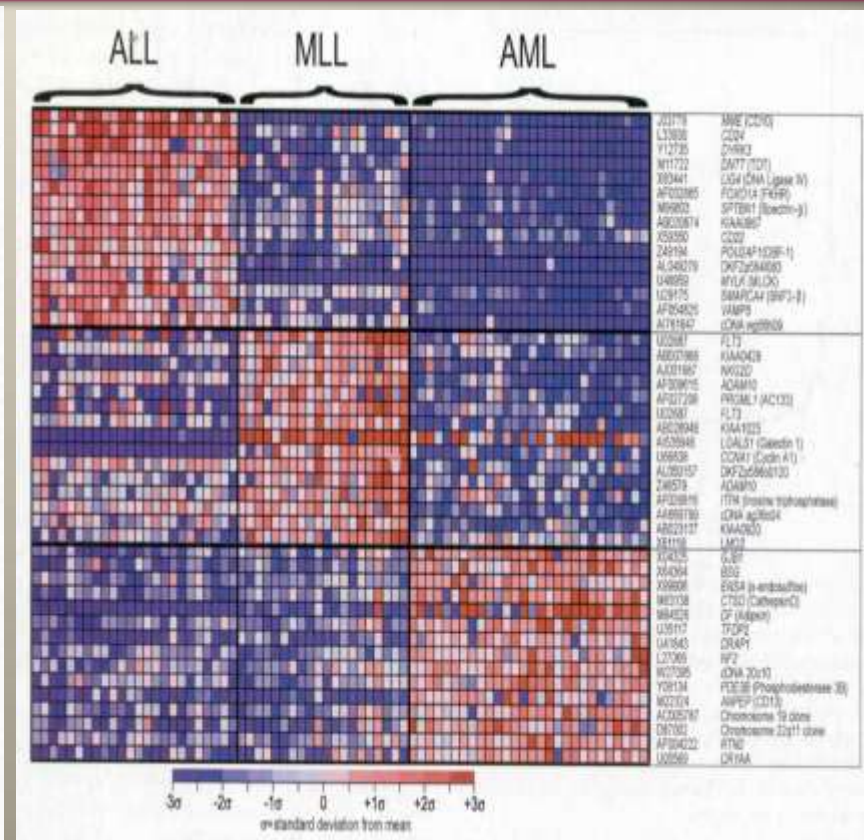
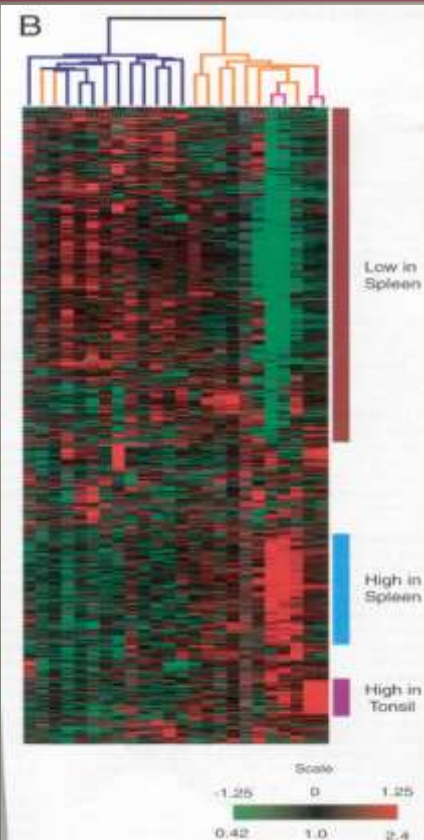


DEMONSTRATING VALUE

Convergence



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



Ignoring The Obvious in Clinical Practice

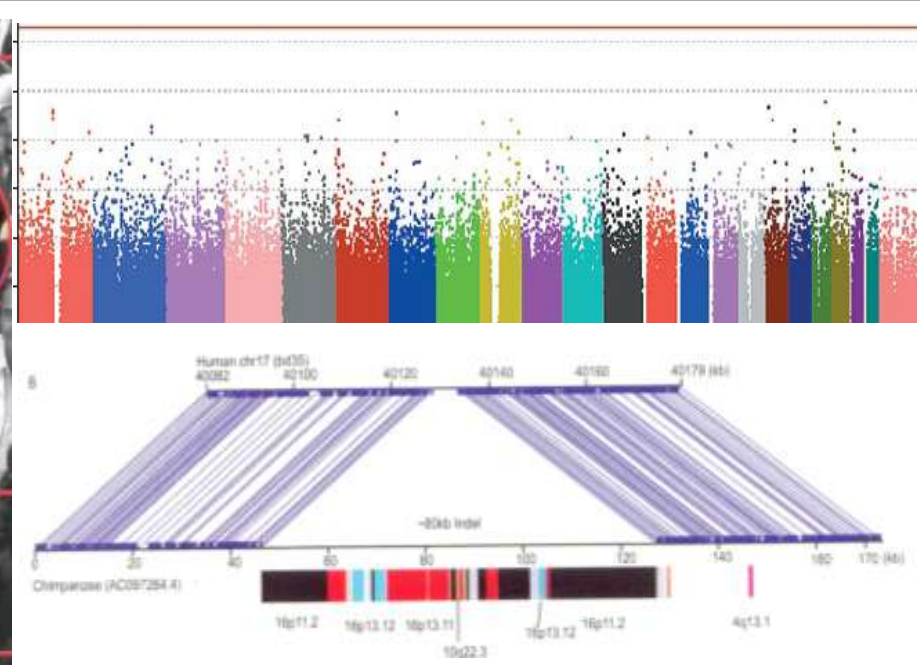


- diseases are not uniform
- patients are not uniform
- a “one-size fits all” Rx approach cannot continue



- inefficiency and waste of empirical Rx
- cost of futile therapy
- medical error and AEs

Personalized Medicine

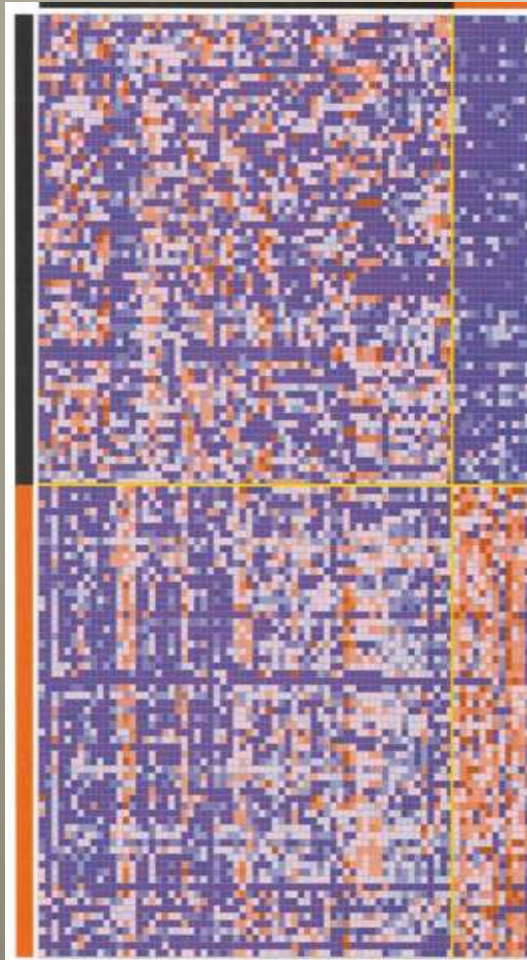


**“If it were not for the great variability among individuals,
medicine might be a science, not an art”
Sir William Osler (1892)**

Osler Reframed

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

Rational Therapeutics and Personalized medicine: Key Drivers



Science

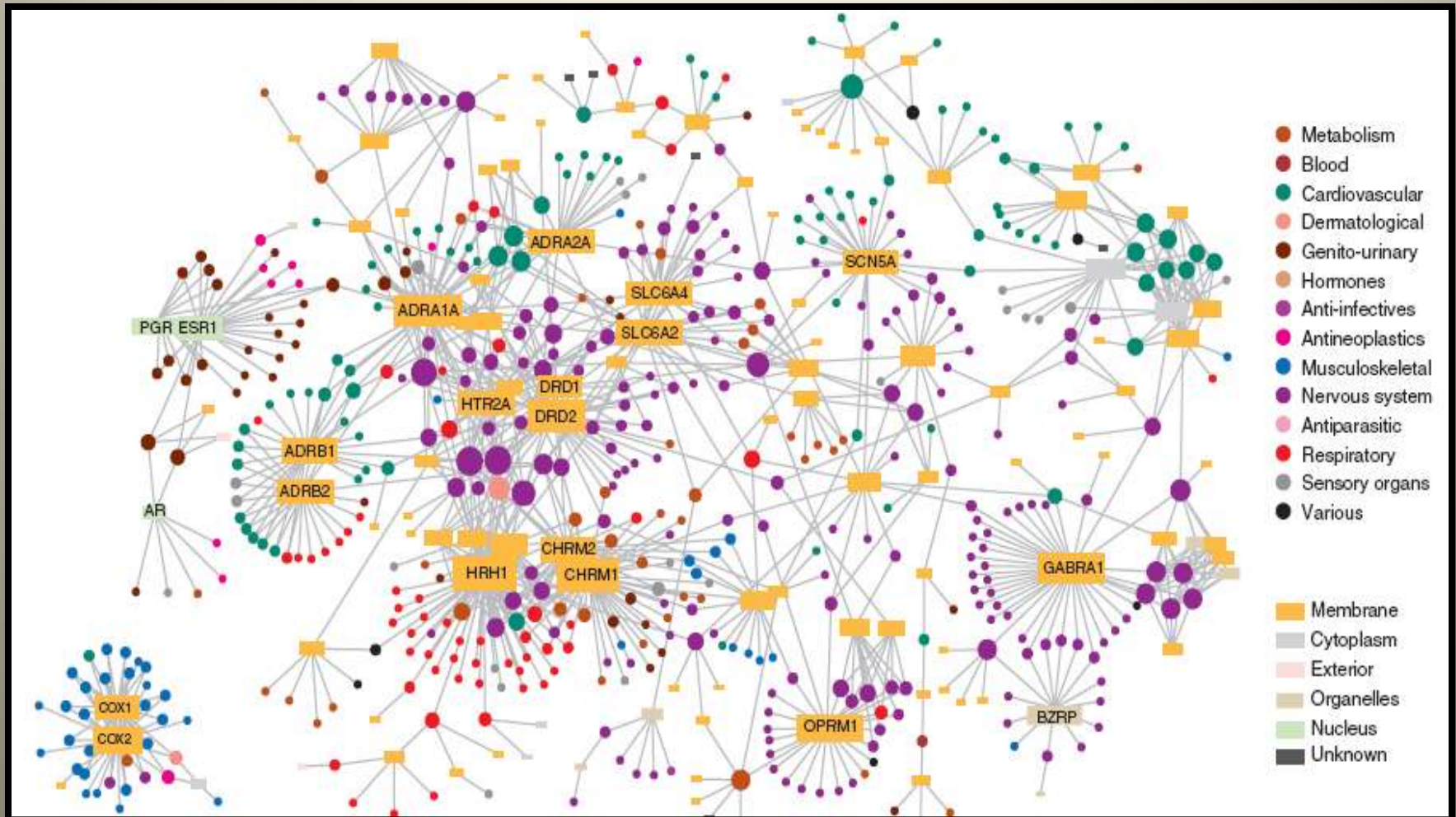


Policy



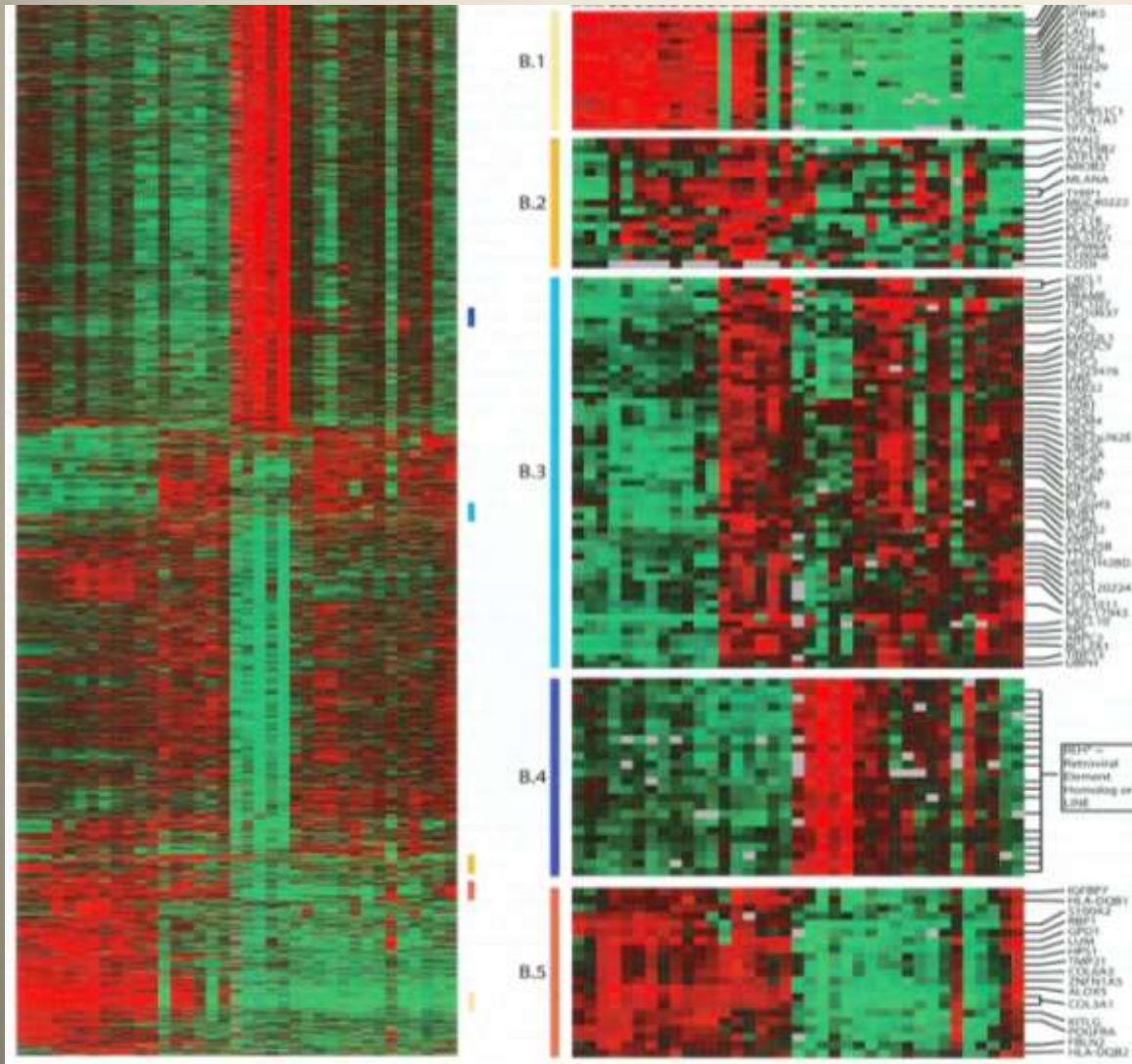
Cost and Outcomes

Personalized Medicine: The Initial Era - Targeted Therapeutics



Drug-Target Networks for FDA Approved Rx

Disease Subtyping: Next-Generation Molecular Diagnostics (MDx) and A New Molecular Taxonomy of Disease



Dx Platforms

- massive parallelism
- miniaturization
- automation
- rapid
- POC

RIGHT Rx for RIGHT DISEASE SUBTYPE

B1 skin, B2, melanocytes, B3, melanoma, B4 and 5 metastatic melanoma
From: C. Haqq et al. (2005) 102, 6092

Molecular Diagnostics and Disease Subtyping

“Riches in the Niches”



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

Molecular Diagnostics and Targeted Therapeutics

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



The Emergence of Drug: Diagnostic Combinations

SELZENTRY™
(maraviroc) tablets



trofile™
CO-RECEPTOR TROPISM ASSAY

biosciences
monogram
The Mark of
Individualized Medicine

CAMPTO®
irinotecan



Invader® chemistry

THIRD WAVE
TECHNOLOGIES

COUMADIN®
(Warfarin Sodium Tablets, USP) Crystalline
1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 6 mg 7.5 mg 10 mg



Bristol-Myers Squibb

Verigene® System



Nanosphere

5-Fluorouracil

tablets
Xeloda®
capecitabine



TheraGuide 5-FU®

A test to predict toxicity to 5-FU/capecitabine-based chemotherapy



MYRIAD®

Vectibix™
(panitumumab)

AMGEN

DxS Diagnostic
Innovations

K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy



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



regulatory demand



clinical guidelines



- regulatory inertia



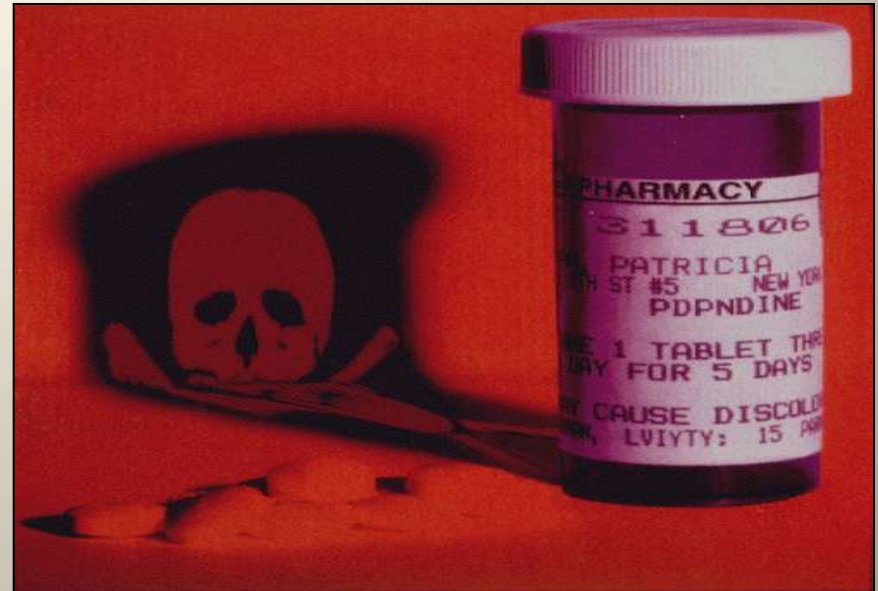
- payor adoption

Personalized Medicine

The Initial Era: Targeted Rx

- **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**

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





REMS:

Risk Evaluation and Mitigation Strategies

Product	Manufacturer
Plenaxis (abarelix) * for prostate cancer	Praecis
Lotronex (alosetron) for irritable bowel syndrome	Prometheus
Letairis (ambrisentan) for pulmonary arterial hypertension	Gilead
Tracleer (bosentan) for pulmonary arterial hypertension	Actelion
Clozaril (clozapine), Fazaclo ODT (clozapine) for schizophrenia	Novartis, Azur and generics
Tikosyn (dofetilide) for atrial fibrillation/atrial flutter	Pfizer
Soliris (exulizumab) for paroxysmal nocturnal hemoglobinuria	Alexion
Ionsys (fentanyl hydrochloride) *, Actiq (fentanyl citrate) for pain	Alza, Cephalon
Accutane (isotretinoin) for acne	Roche and generics
Revlimid (lenalidomide) for myelodysplastic syndromes and multiple myeloma	Celgene
Mifeprex (mifepristone) for pregnancy termination	Danco
Tysabri (natalizumab) for multiple sclerosis and Crohn's disease	Biogen Idec/Elan
ACAM2000 (smallpox vaccine, live)	Acambis
Xyrem (sodium oxybate) for daytime sleepiness and cataplexy	Jazz
Thalomid (thalidomide) for multiple myeloma and leprosy	Celgene
* <i>Plenaxis and Ionsys are currently not marketed in U.S.</i>	

Pink Sheet (2008) 31 March, p. 7



**Alert
7/24/08**

- **update labeling for Abacavir (Ziagen) to require pre-therapy screening for HLA-B*5701 allele to avoid fatal hypersensitivity**

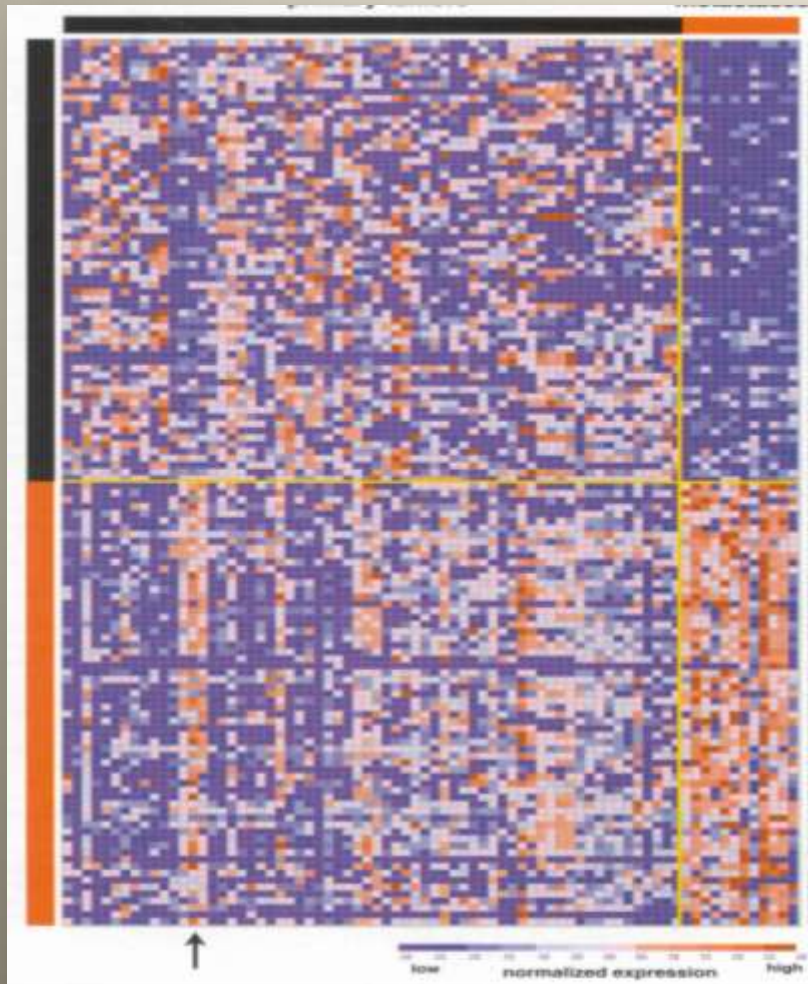


Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

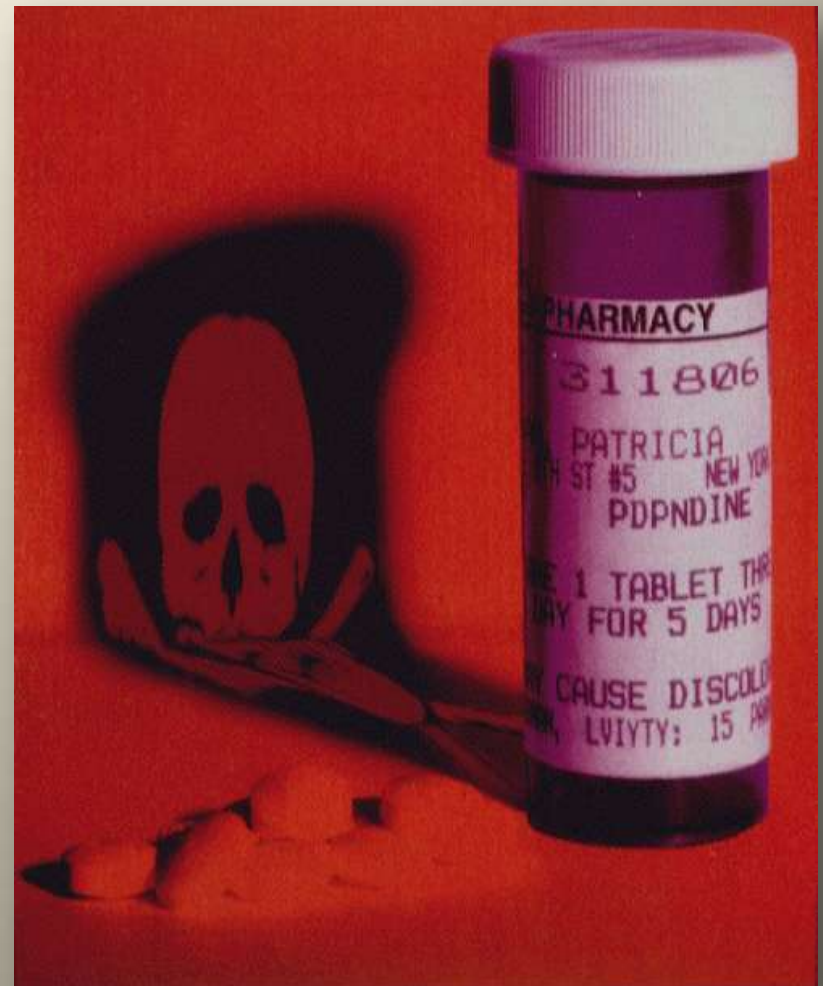
From Pharmaceuticals to Pharmasuitables

Disease Subtyping:



Right Rx for Right Disease

**Individual
Variation and AE risk**



Right Rx for Right Patient

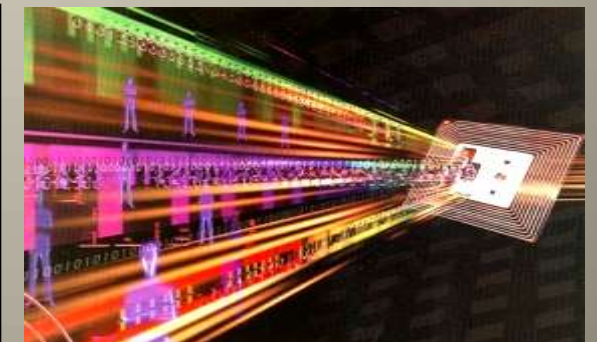
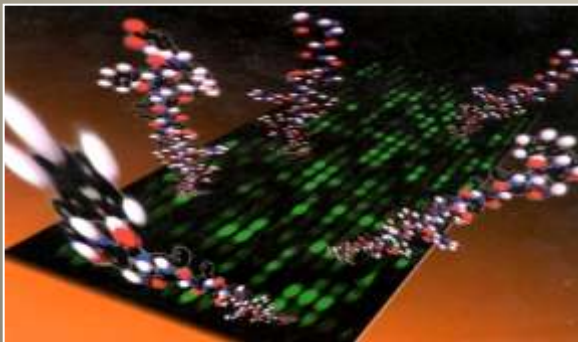
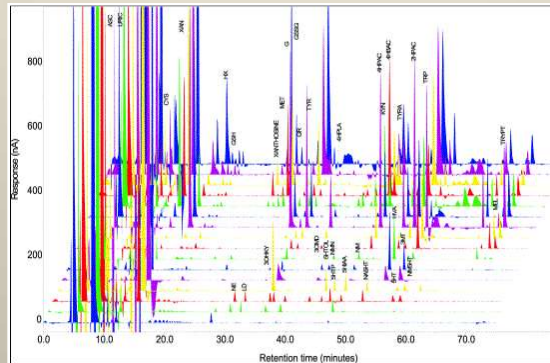
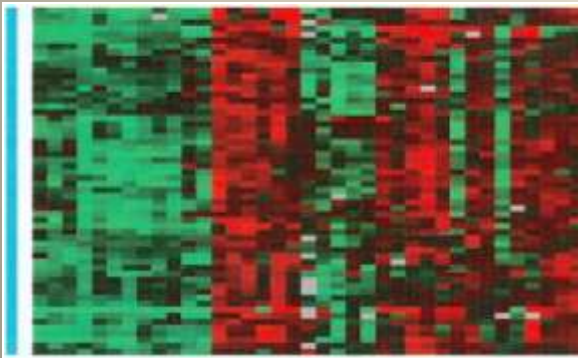
Development of Molecular Diagnostics and Biomarkers for Personalized Medicine: The Need for End-to-End R&D Solutions

Complex Biosignature Profiling

genomics

proteomics

immunosignatures



Signature Detection, Deconvolution and Multivariate Analysis

multiplex assays

**novel test
devices (POC)**

new algorithms

**Identification
of
Biosignatures
and
Multiplex
Molecular
Profiling**

**Detection
of
Multiplex
Biosignatures
in
Clinically
Relevant
Formats**

**Actionable
Information**

Profile

Sense

Act

**Life Sciences
and
Mathematical/Statistical
Tools for
Complex Signal
Analysis**

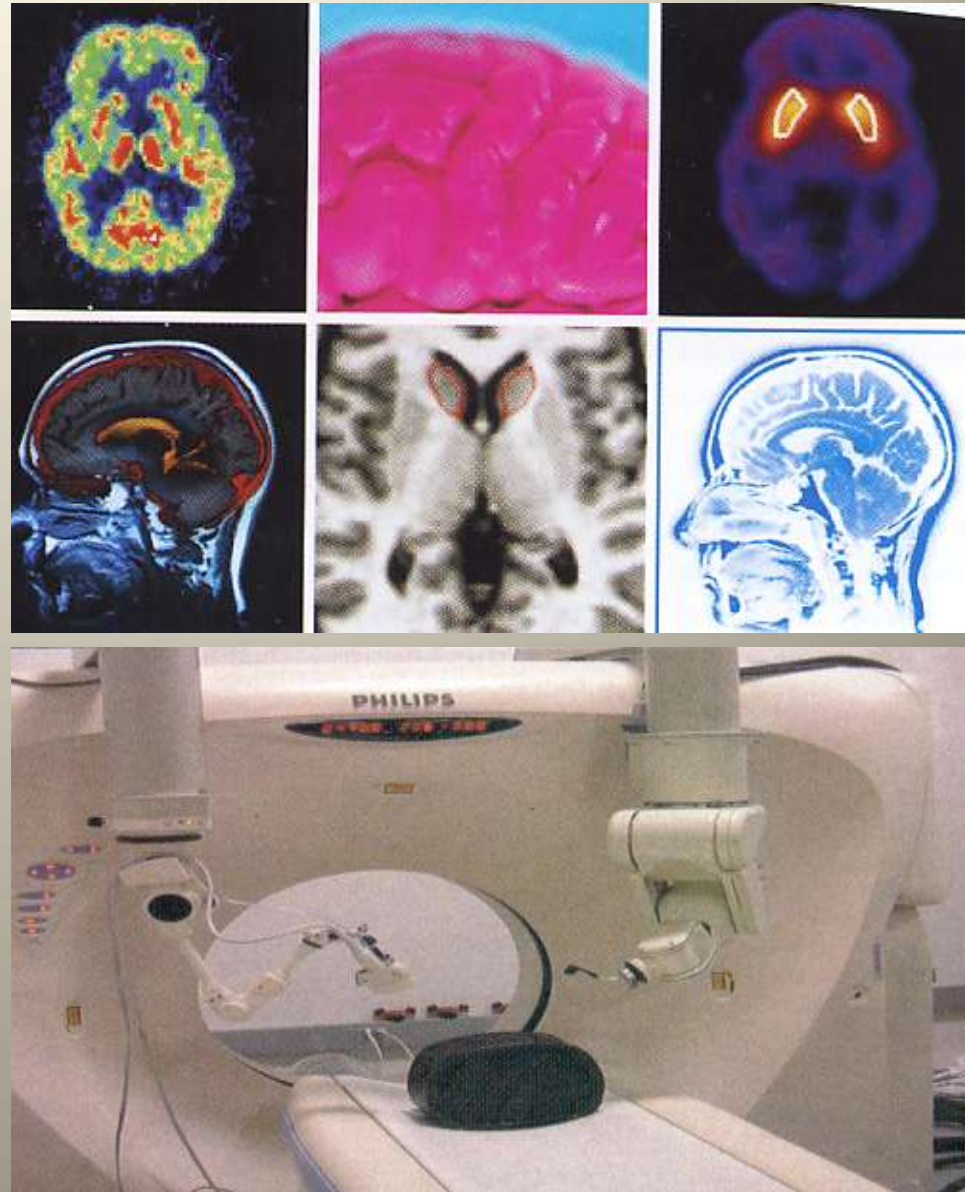
**Miniaturization
Engineering
and
Materials Science**

**Large Scale
Informatics
and
Information
Architectures**

Nanoscale Systems and Targeting Materials to Specific Body Locations

Application

- next-generation body imaging for resolution of specific cell types/metabolic activities (versus current whole organ profiling)
- advanced drug and gene delivery systems for target specific localization and release



Personalized Medicine: Disease Predisposition Profiling



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

- **slower evolution than many predict**
- **cost complexity and poor replication of Genome-Wide Association Studies (GWAS)**
- **substantial ambiguities regarding probabilistic risk of future disease**
 - **combinations of multiple low penetrance alleles**
 - **epistasis**
 - **epigenetics**
 - **environmental confounders**

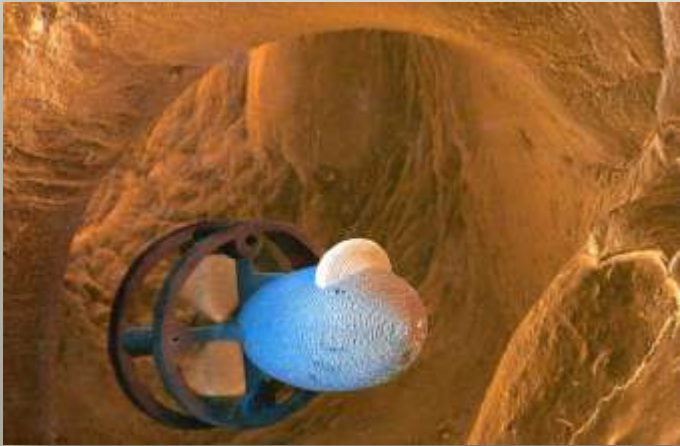
Personalized Medicine: Challenges for Clinicians

- **sustained awareness of relevant conceptual advances and new products/services**
- **timing and training for adoption into routine practice**
- **accurate identification of relevant patients for use of MDx profiling and targeted Rx selection**
- **new malpractice risks**

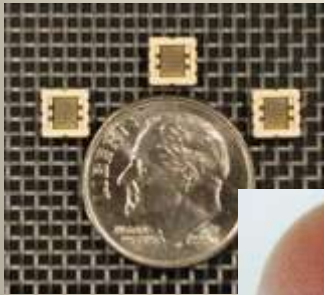
Personalized Medicine: A Broader Definition

**Health Status Monitoring
and the
Promotion of Wellness**

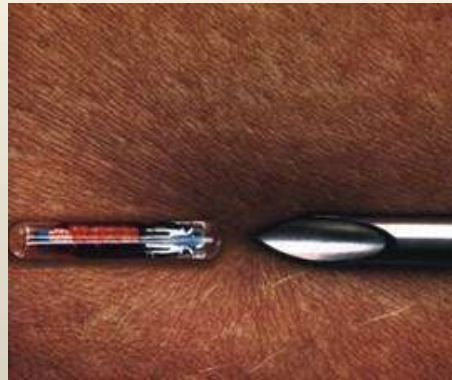
On Body: In Body Sensors/Devices For Real Time and Remote Monitoring of Individual Health Status



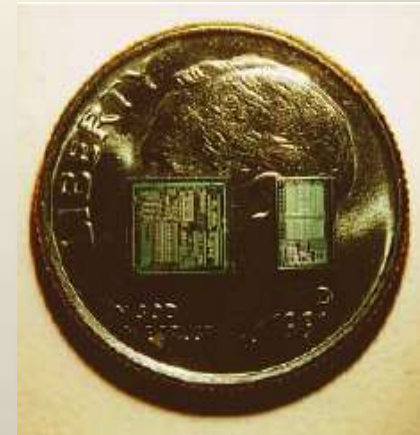
OBIBS and Body Area Networks (BAN's) for Remote Monitoring of Health



Microtags



In-Body Wireless Tags



Sensor on a Chip



**“Savings from broad-band remote monitoring
for all chronically ill patients
are potentially quite remarkable
....as much as 30 percent
of all hospital, out-patient and drug expenses”**

**Robert Litan
Kaufman Foundation December 2005**

**cited in: Advancing Healthcare Through Broadband
Internet Innovation Alliance White Paper 2007**

On Body: In Body Sensors and Devices

Healthcare

Objective

- remote monitoring of health status



Applications

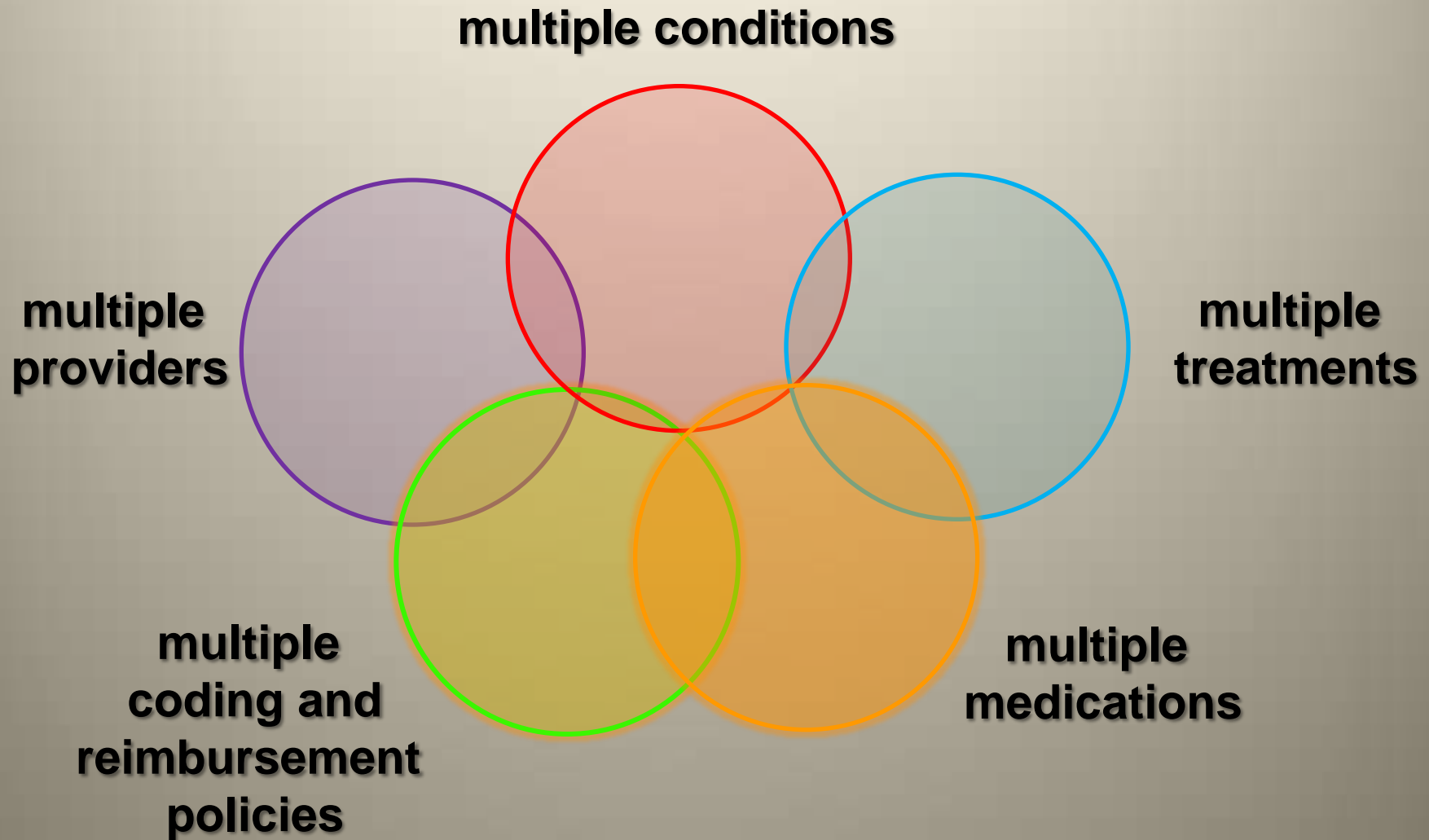
- multi-feature monitoring and broadband wireless networks
 - ubiquitous sensing
- enhanced autonomy for in-home aged
- proactive alerting and intervention to mitigate health incidents
- monitoring of patient compliance
- coupled linkage to remote Rx dispensing for efficient disease management

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)**

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



How Much New Technology Can We Afford?



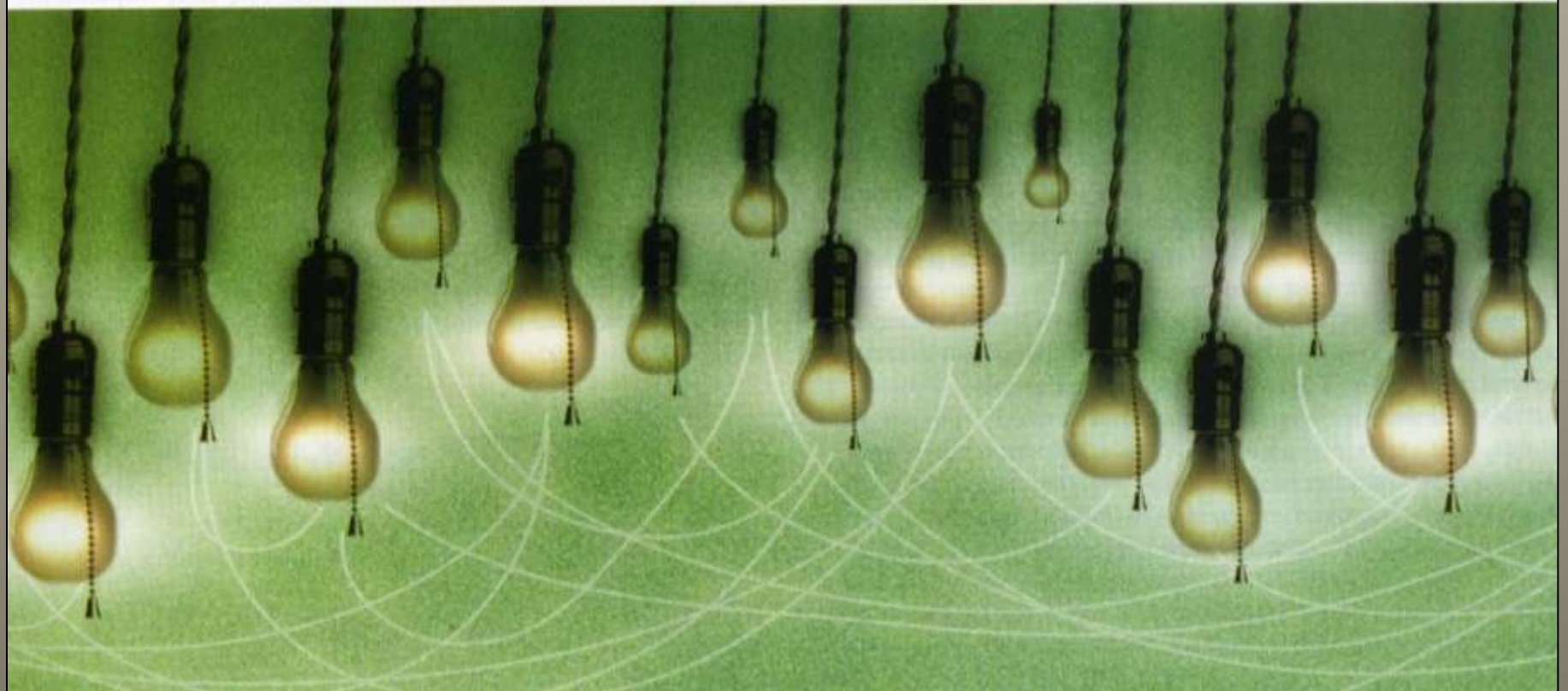
Key Questions

- **what is the role of technology innovation in healthcare?**
- **do current public and private strategies support innovation and disruptive technologies?**
- **how should the ‘value’ of new technologies be assessed?**
- **how should dissemination of new value-added technologies be supported?**

CONNECTIVITY AND INTEGRATED CARE

Information-Based Medicine

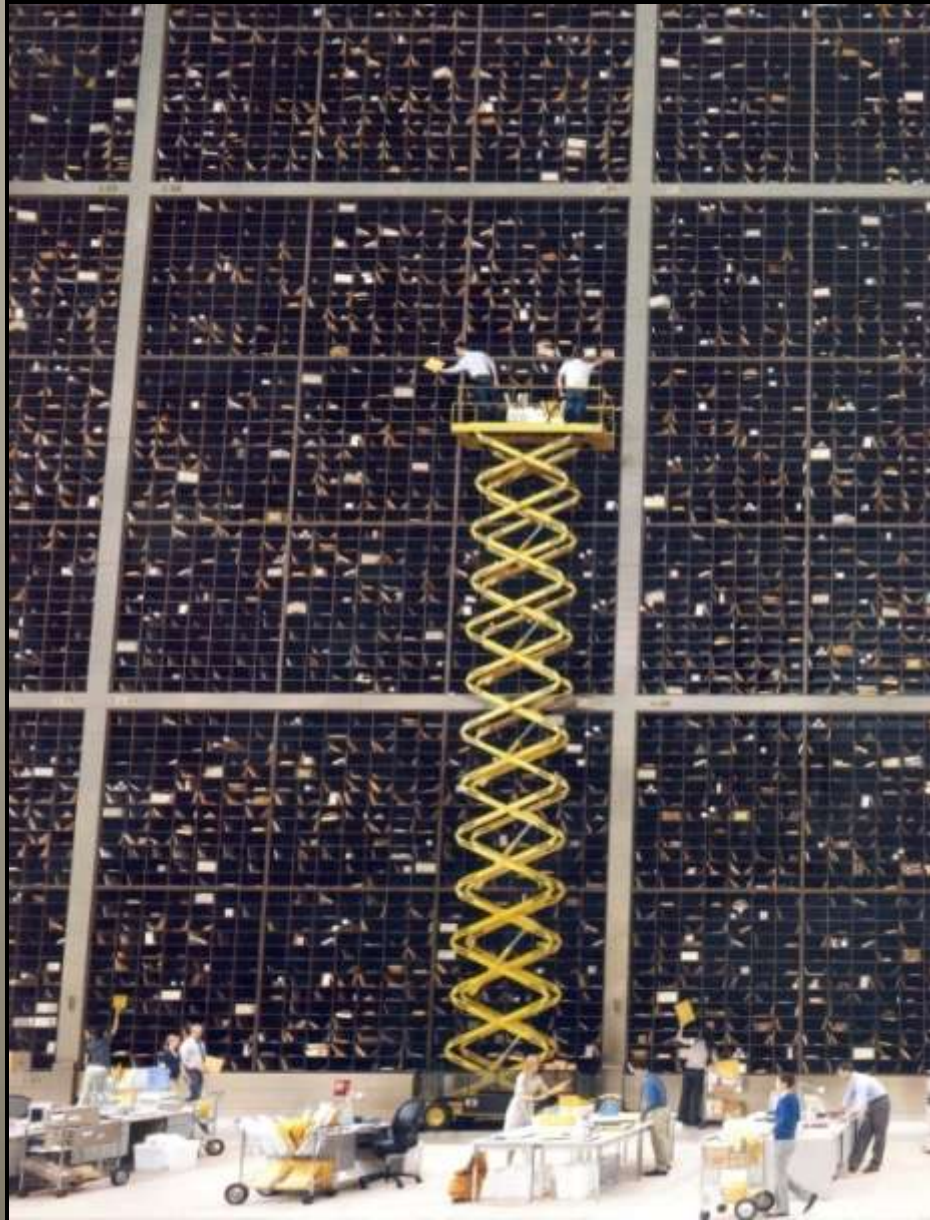
HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT



The Unacceptable Failure to Establish Comprehensive Electronic Medical Records



Paper Kills!



**The Inefficiencies
and Patient Risks
Imposed by
Sustained
Dependency on
Paper Health
Records**

The Unacceptable Cost of Unconnected Healthcare

- **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**

CONSUMERS

Consumer Directed Healthcare Plans

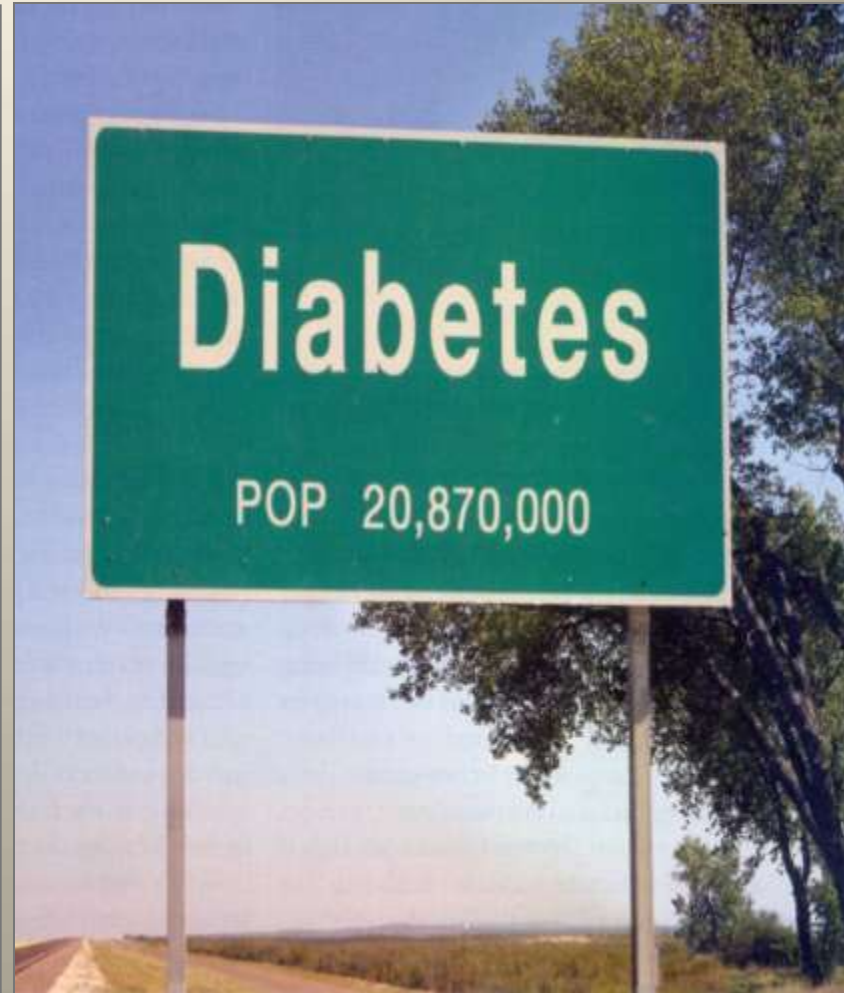
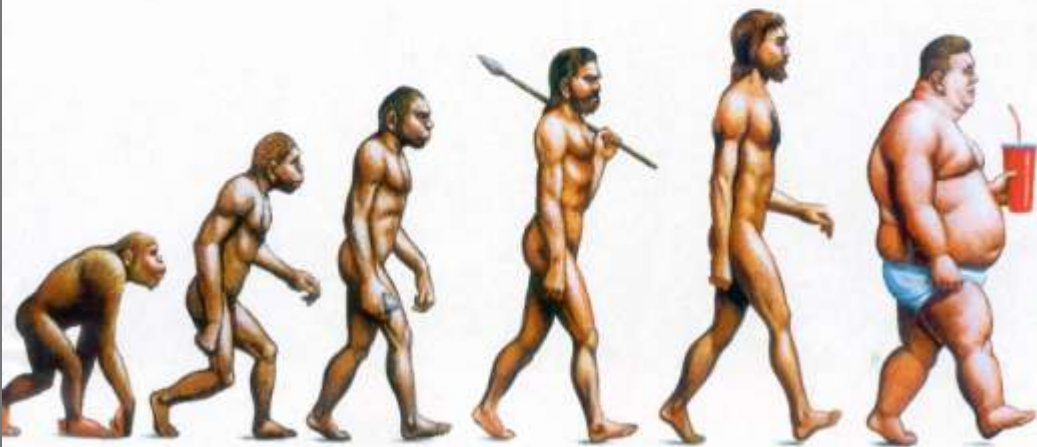
**“Until the person receiving the product is responsible
in some fashion for the costs,
there will be no incentive to spend responsibly”**

**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

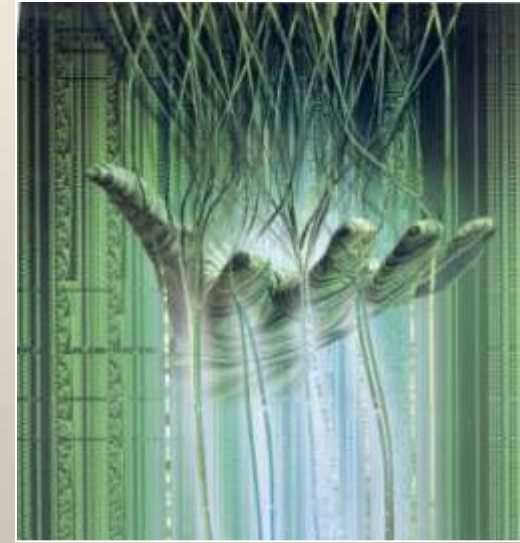


Personalized Medicine: Consumer-Centric Healthcare: A Key Driver

- **cost-shifting to consumers**
- **clinical and economic benefits of coordinated care of complex chronic conditions**
- **lifestyle and disease risk mitigation**
- **new information intermediaries**
- **cost-driven transitions from ‘passive patient’ to ‘engaged consumer’**

Telecommunications and Media Industry Convergence: Implications for Healthcare

The Infocosm: Emerging Networks of Global Connectivity



The Changing Nature of Social Interaction



Herd Behavior: 1951
1.3 Million Bathers,
Coney Island, NY



Herd Behavior: 2008
Social Networks and Virtual
Communities



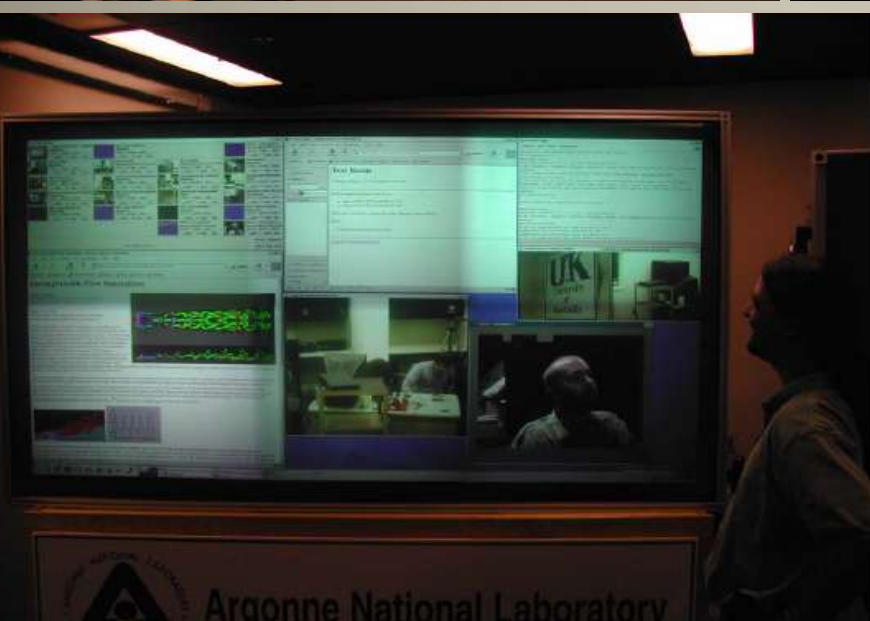
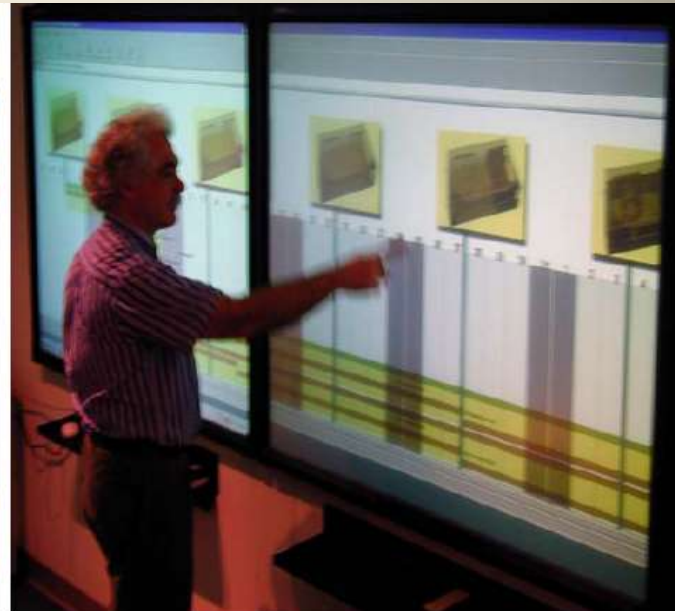
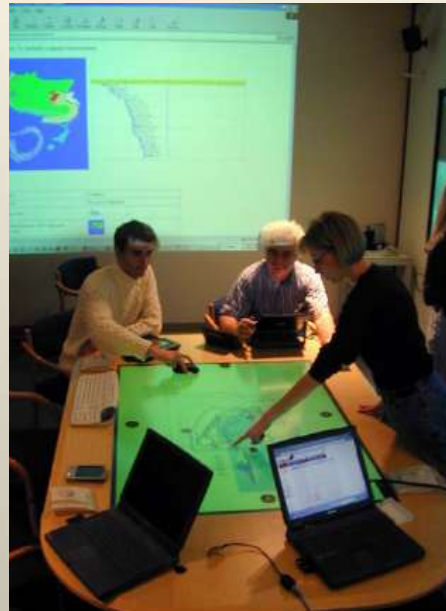
Consumer-Directed Healthcare: The Wellness Premium

- **leveraging social and peer networks**
- **increased role of fitness industry and entertainment in healthcare**
 - **“success via distraction”**
- **“virtual touch”**
 - **web-based consultation and diagnostic algorithms**
 - **emerging generational gap in need for direct physical interaction with physician**
- **evolution of ‘near-patient’ health status profiling**
 - **POC and in-home Dx**
 - **OBIBs**

In-Home Health Connection: Engaging the Elderly



AORTA: Always on Real-Time Access: Interactive, Distributed and Customized Datasets

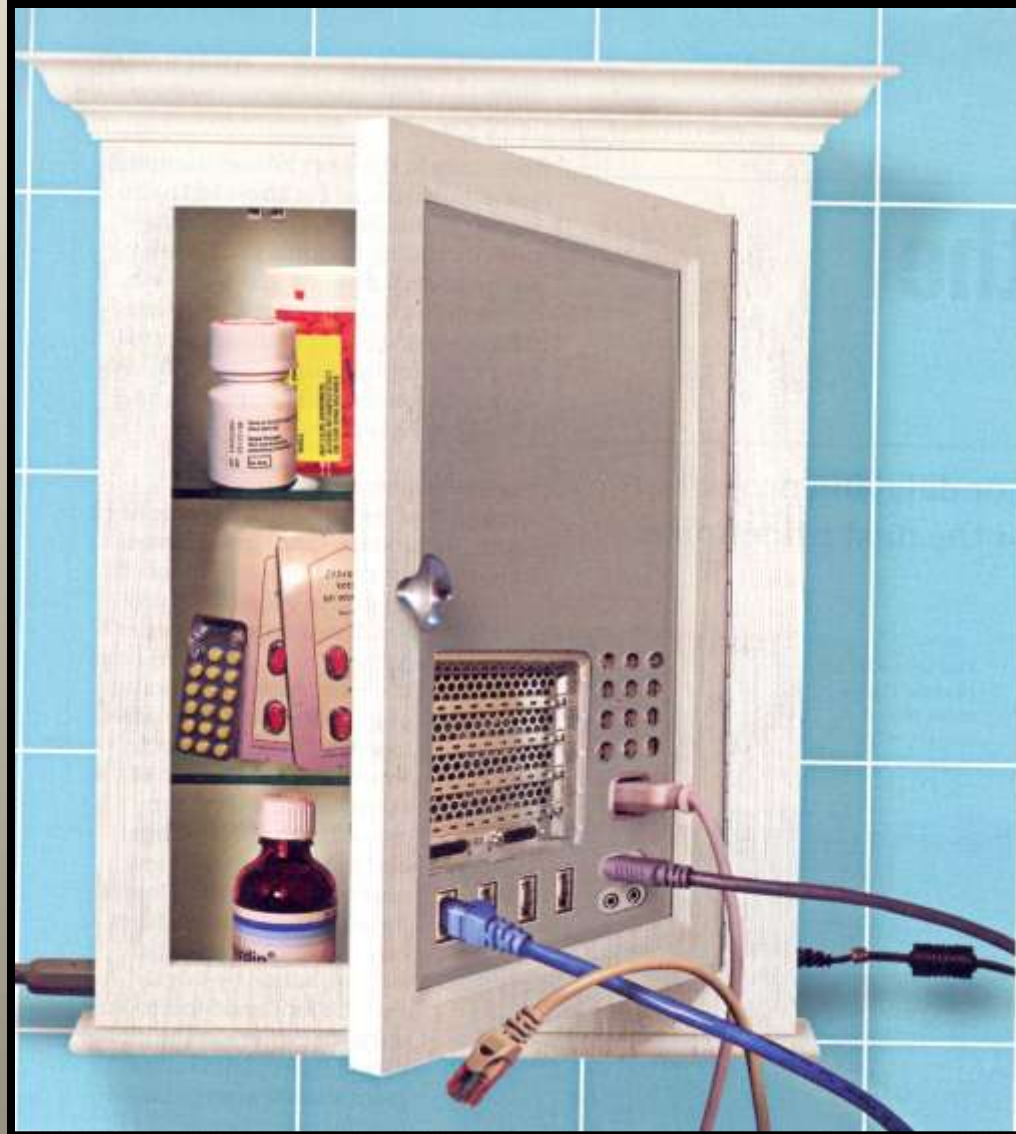


Healthcare Information Networks: AORTA: Always On Real Time Access

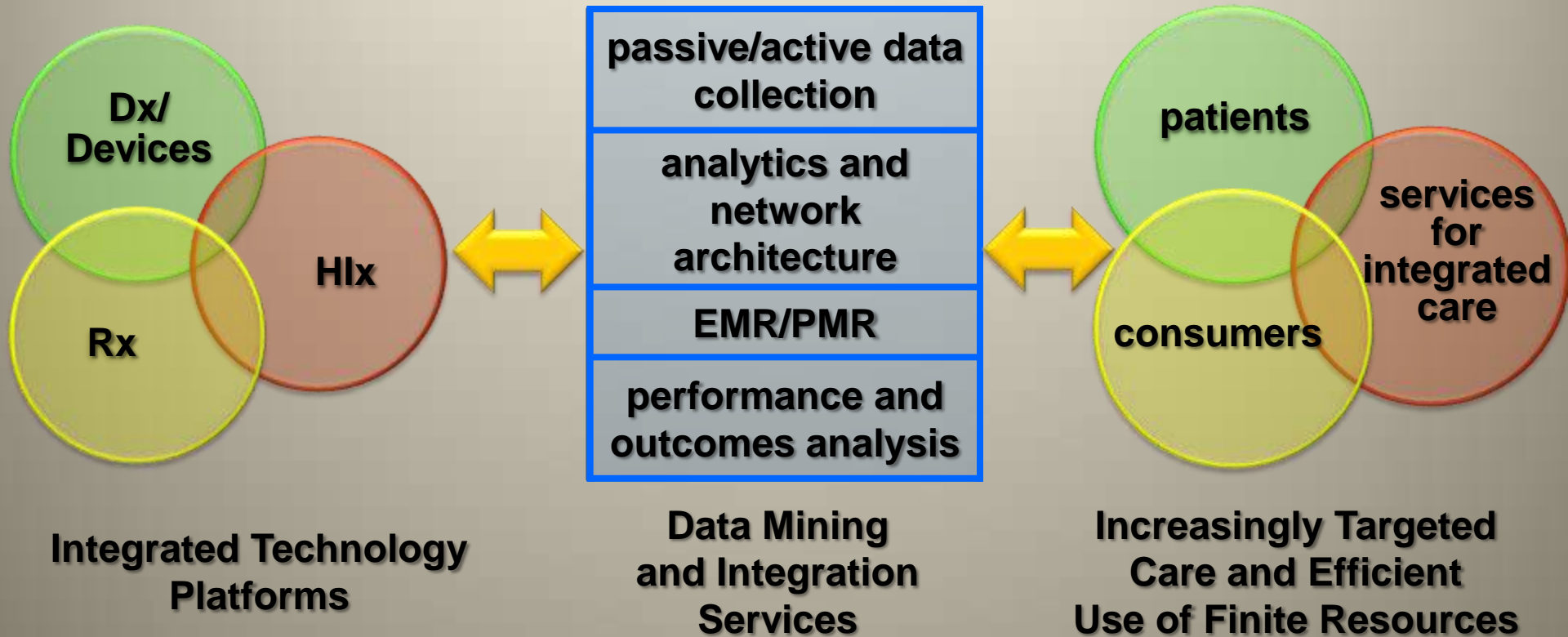
- **end-to-end continuity in use of internet and wireless technologies**
- **from routine remote monitoring of health status to advanced critical care**

- **comprehensive connectivity
plus**
- **collapsing time
plus**
- **global networks**

The Evolution of In-Home POC Diagnostic and Compliance Monitoring Systems



A New Healthcare Ecosystem Arising From Technology and Market Convergence



“Managing Mega-Data”

volume



scale



**Visualization
and Collaboratories**



**Heterogeneity
and Context**

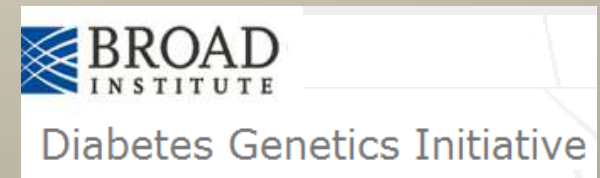
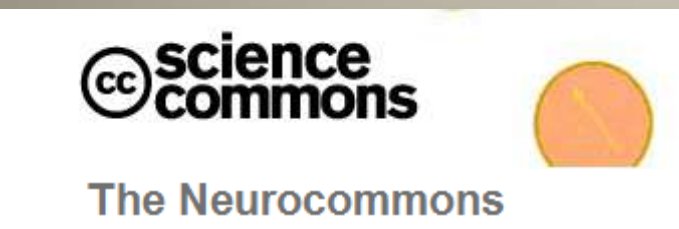


**Cognitive Systems
for Optimum Decisions**

The Rise of Open-Source Networks and Consortia



FDA/Severe Adverse Events (SAE) Consortium



Clinical Semantics Group

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,...



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

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 clinical and economic 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

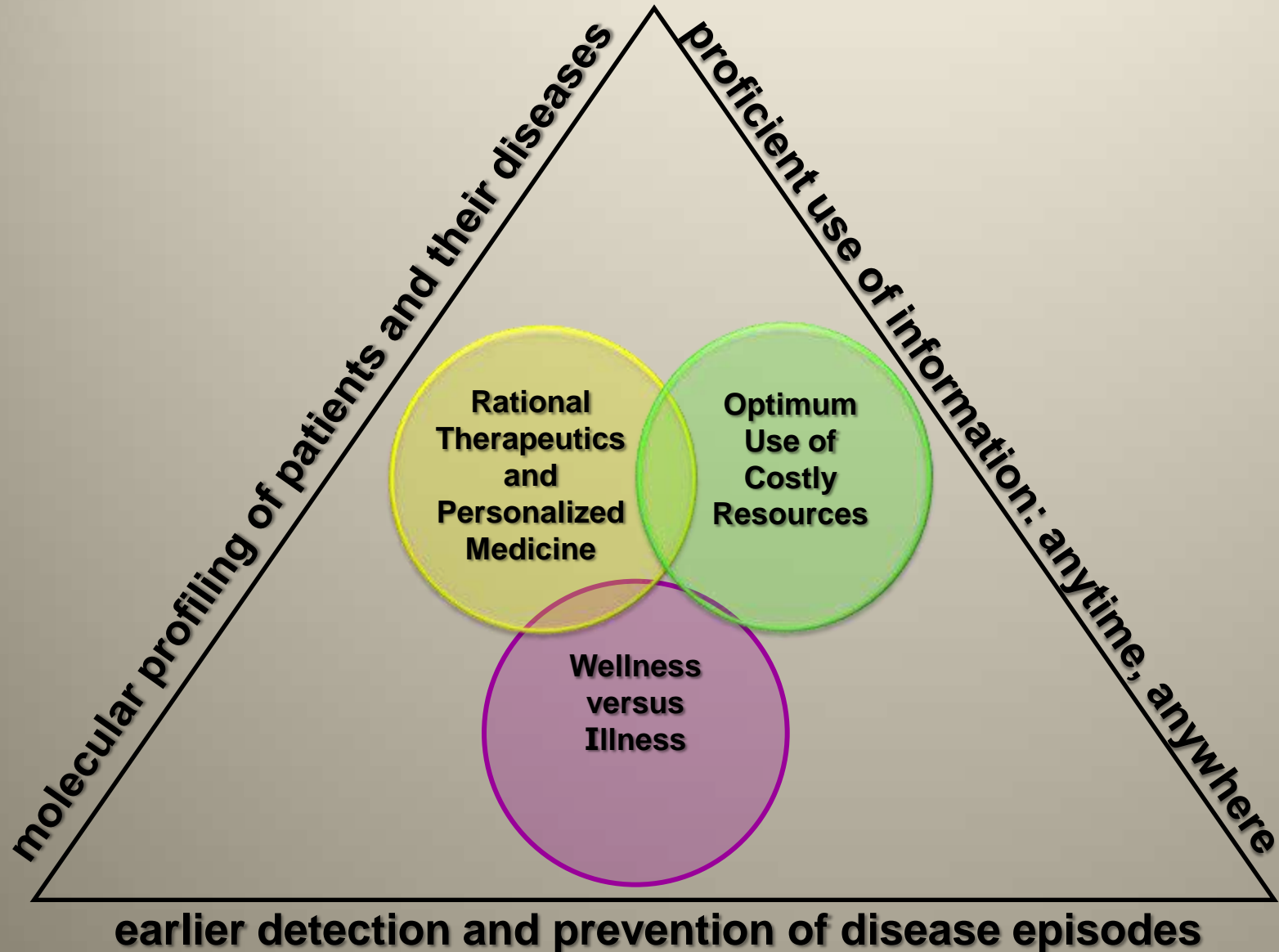
Consumers

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

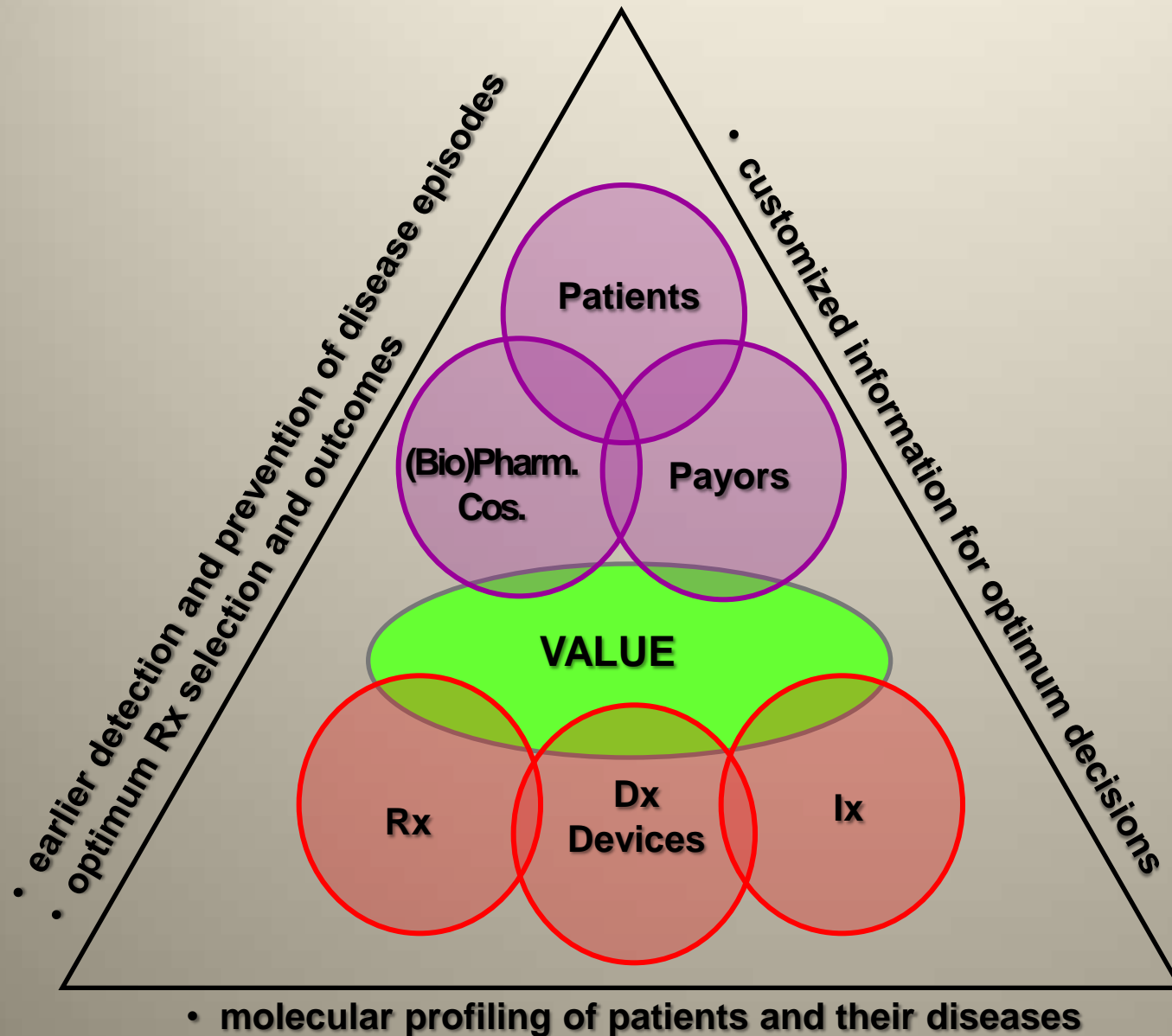
Connectivity

- **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**

The Urgent Imperative for New Drivers of Efficiency and Equity in Healthcare Delivery



Building an Integrated Framework for Personalized Medicine



Aspiration and Engagement with Grand Challenges

