

On the Road to Personalized Medicine: Adoption Paths for Molecular Diagnostics and Molecular Imaging

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Caris Diagnostics

**Presentation at “Molecular Summit 2009”:
In Vivo and In Vitro Integration
Philadelphia, 10 February 2009**

The Unattractive Realities of Healthcare Delivery

- excessive incorrect diagnoses
- empirical Rx
- extravagant variability in clinical practice
- cost of medical errors
- cost and risks imposed by lack of comprehensive health information
- slow adoption of best practice and guidelines
- fragmented care
- procedure/intervention-based reimbursement policies
- limited data on outcomes and performance metrics
- profligate waste
- inequities in access to care
- uncontrolled costs
- inadequate incentives for wellness

Fee-for-Service and Runaway Healthcare Costs

- **the invisible hand of Adam Smith is absent from healthcare**
- **terminal illness for governments, business and patients/consumers**
- **supply creates its own demand**
- **caregivers make more money by providing more care**
- **consumers don't select treatment choice**
- **caregivers don't consider cost in treatment decisions**
- **neither consumers nor caregivers evaluate cost or benefit and simply seek “maximum” care**

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**

Demographics Trends and the Clinical and Economic Burdens of Complex, Chronic Conditions/Co-Morbidities



- **23% Medicare beneficiaries have 5 or more conditions**
- **polypharmacy and AEs**
- **poor patient compliance**
- **multiple physician/venue encounters**
- **poor communication/coordination between siloed healthcare services**
- **procedure-based reimbursement versus care continuum and outcomes**

Oops!

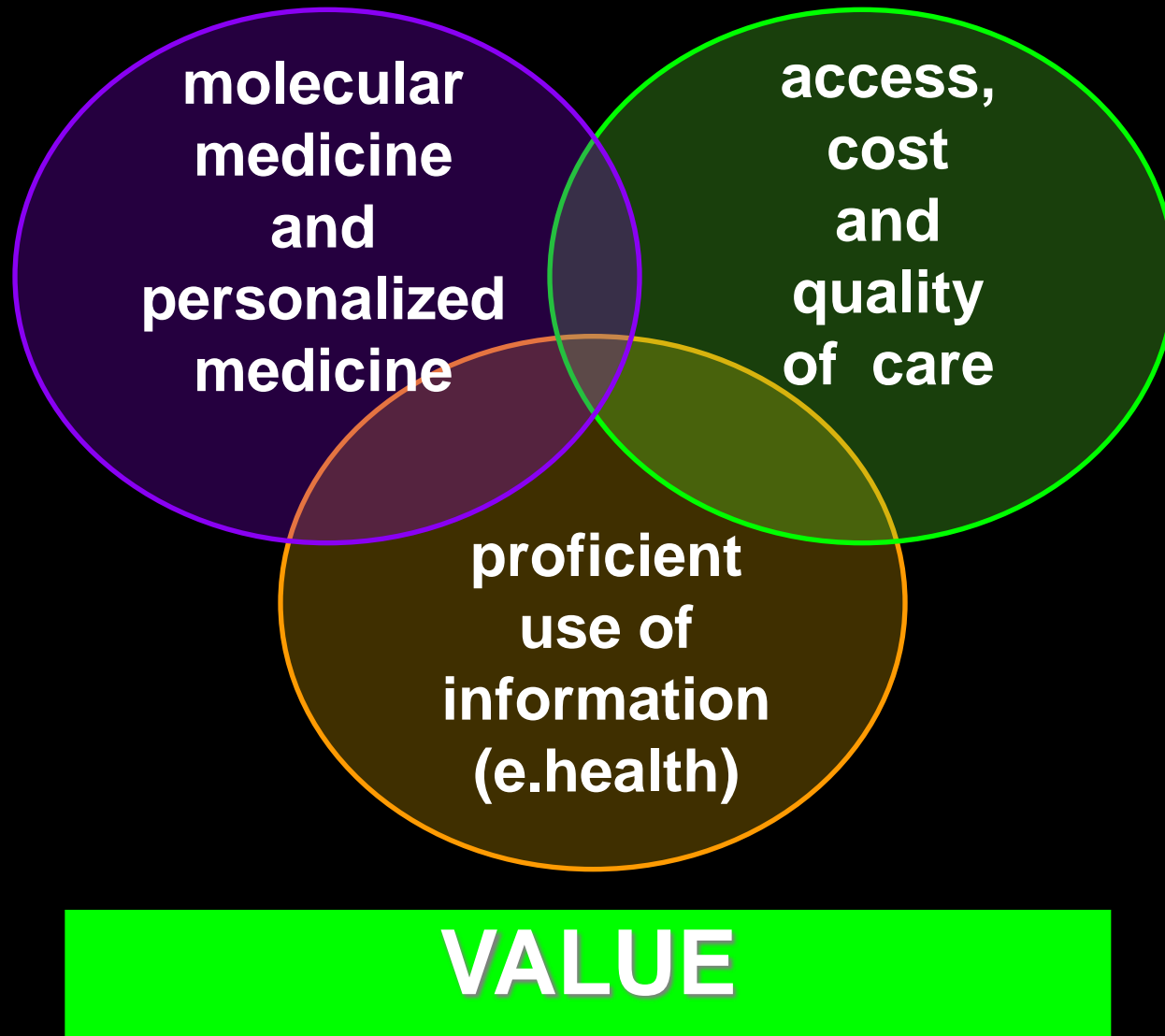


WHAT WE CAN DO
ABOUT THE
HEALTH-CARE CRISIS

SENATOR
TOM DASCHLE

WITH SCOTT S. GREENBERGER
AND JEANNE M. LAMBREW

The Three Forces Shaping the Evolution of Healthcare











The Strategic Environment for Healthcare: New Value Propositions

- **prospering in an environment of increasing constraints**
- **managing the limit(s) of society's willingness and ability to pay for innovation**
- **controlling costs while enhancing quality and outcomes**
- **building new alliances to optimize value-driven outcomes**
 - **integration of Dx, Rx, Ix**
 - **reliable information drives rational decisions**

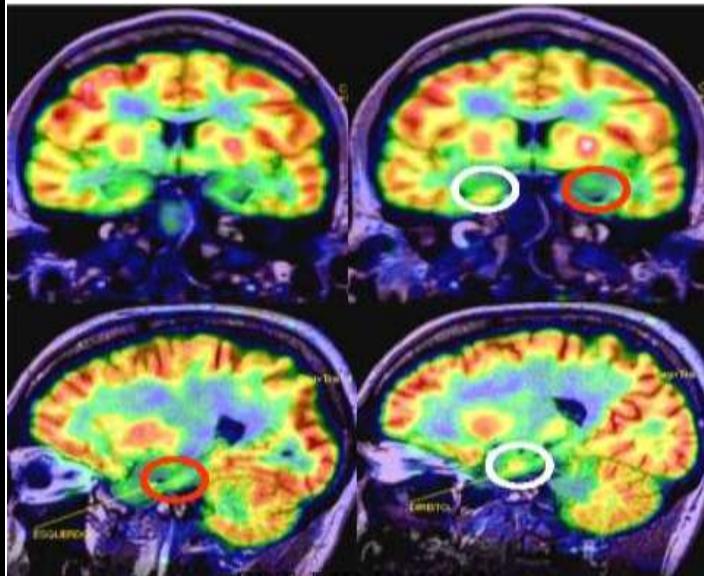
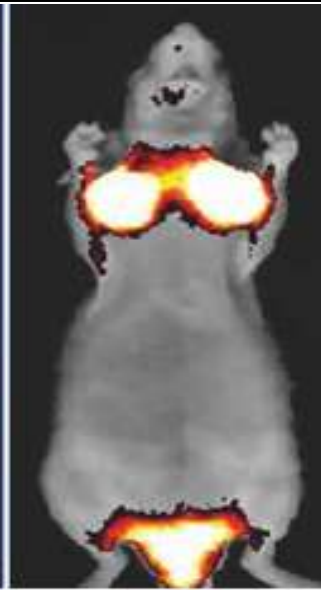
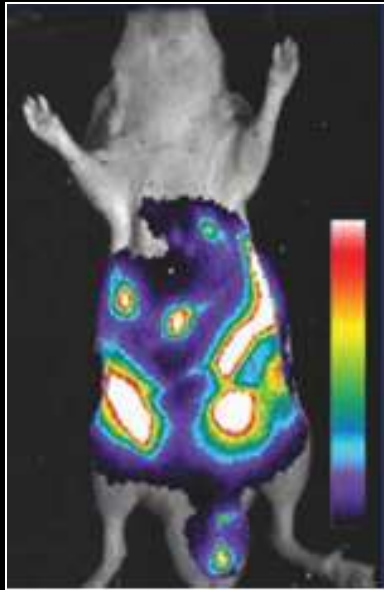
Personalized Medicine: New Value Propositions for Molecular Diagnostics

- **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**
 - **disease patterns in emerging global markets mirror G8 nations**

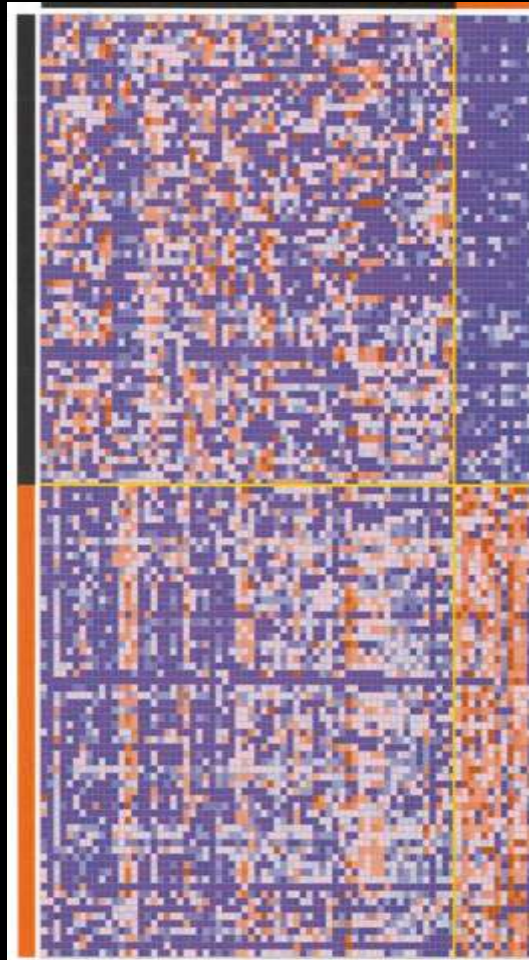
The Central Role of Next-Generation Diagnostic Technologies in Proficient Healthcare Delivery

- precision diagnosis 
- rational Rx selection 
- reduce error 
- increasingly standardized clinical practice 
- remote health status monitoring and patient compliance 
- disease predisposition and risk mitigation 
- increased personal responsibility for risk mitigation and wellness 
- integrated care continuum 

In Vivo Imaging



Personalized medicine: Key Drivers



Science



Policy



Cost and Outcomes

Ignoring The Obvious in Clinical Practice

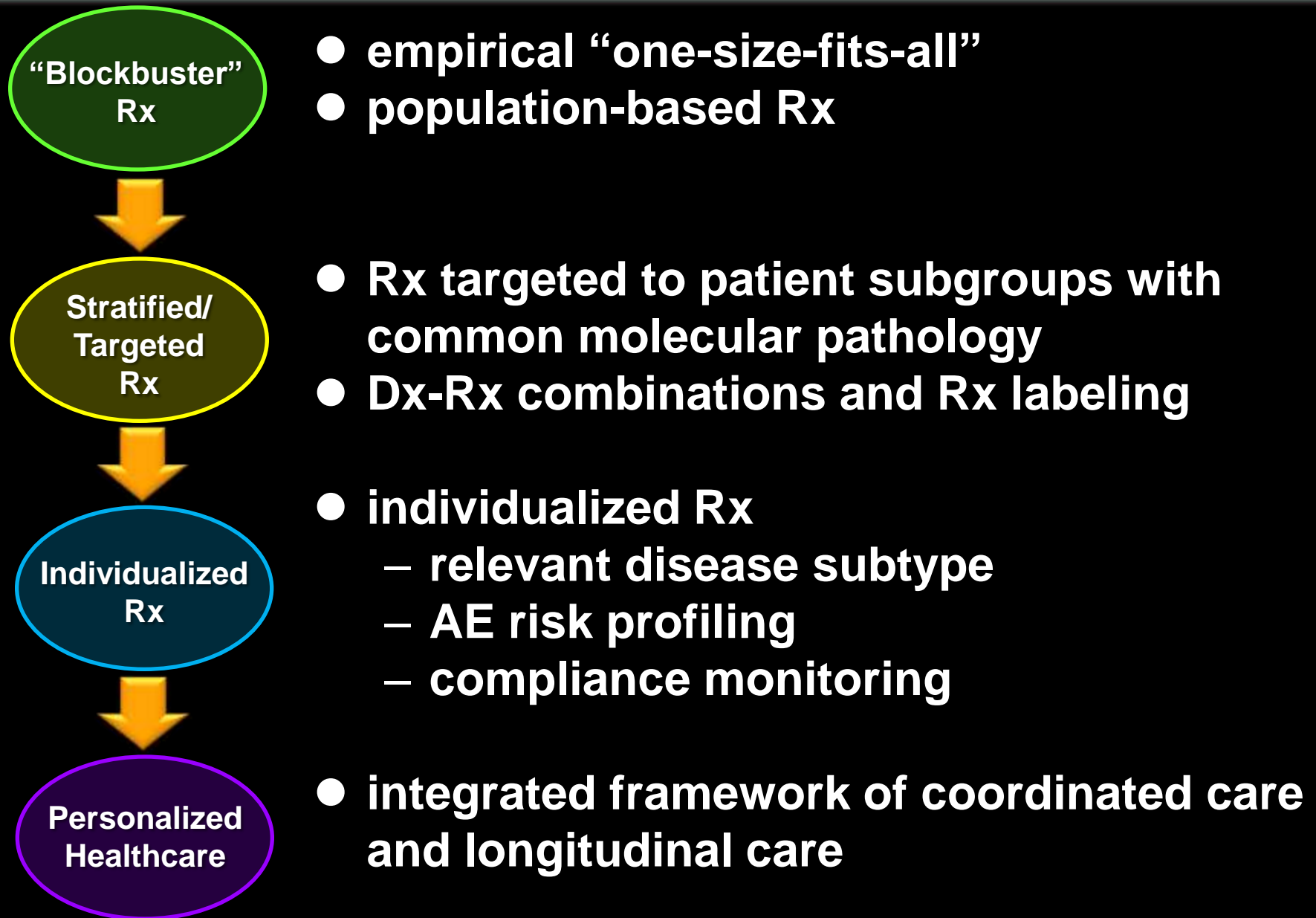


- diseases are not uniform
- patients are not uniform
- a “one-size fits all” Rx approach cannot continue

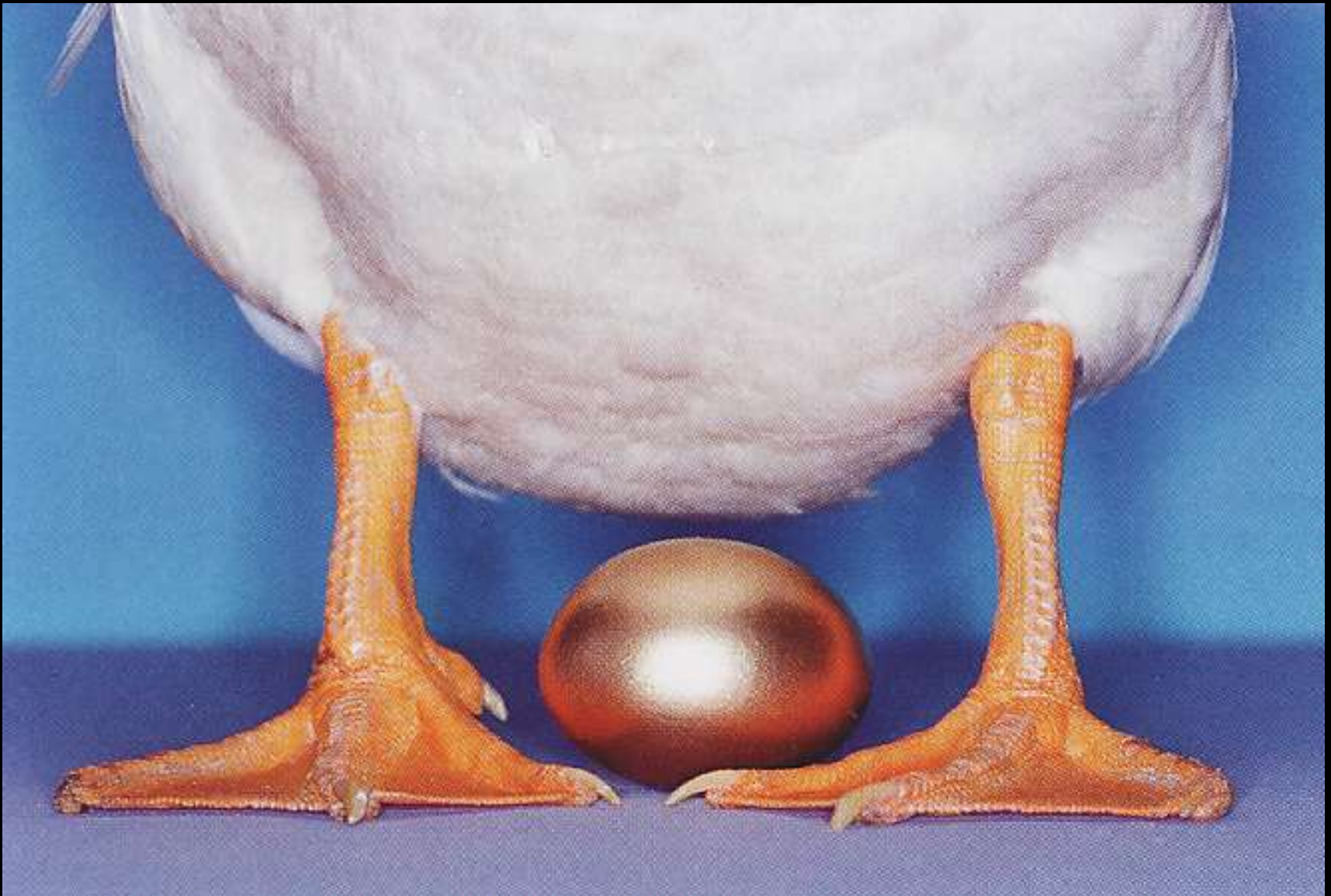


- inefficiency and waste of empirical Rx
- cost of futile therapy
- medical error and AEs

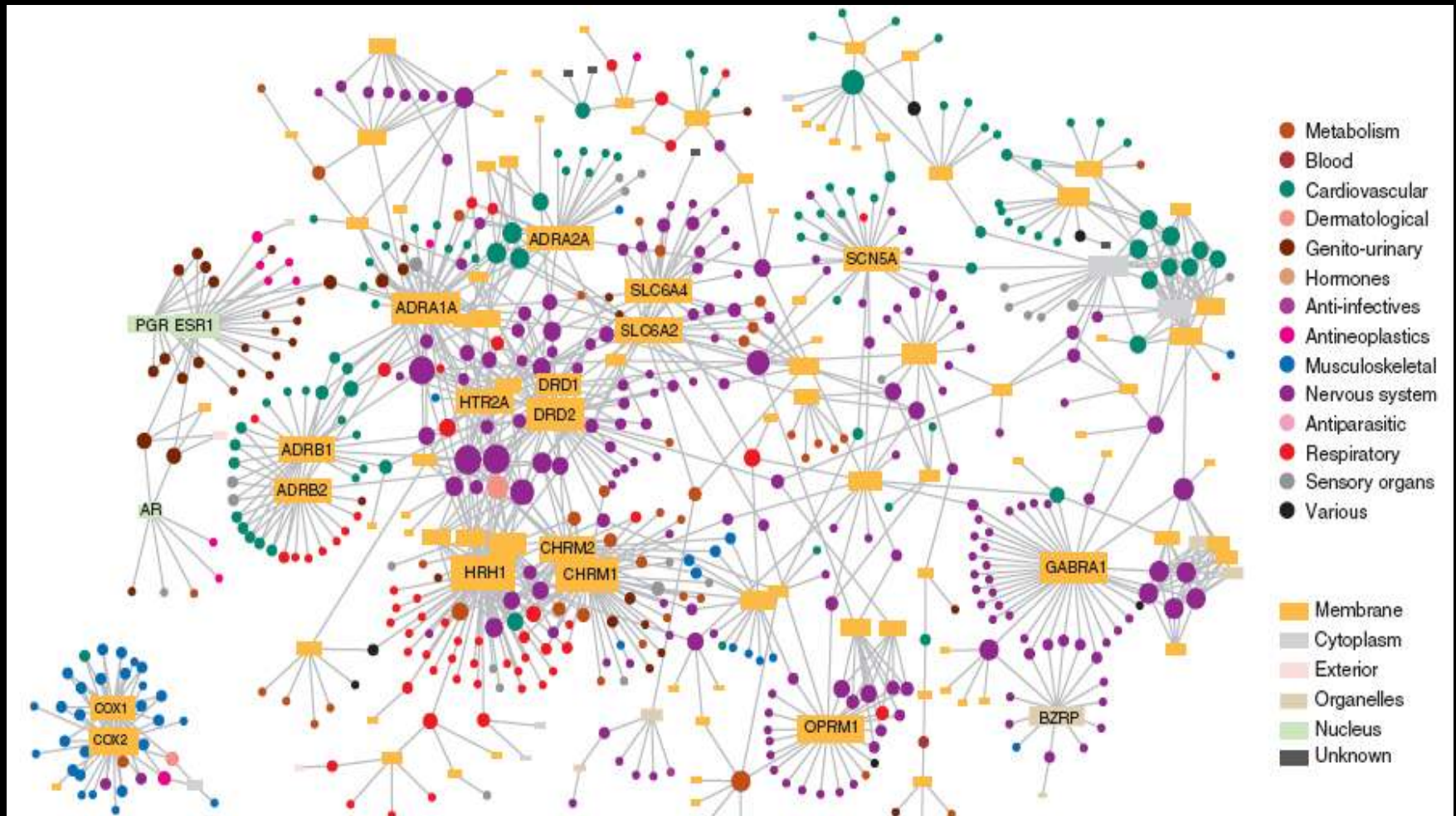
The Evolving Market for (Bio)Pharmaceutical Therapies



The 'Blockbuster Drug' Business Model

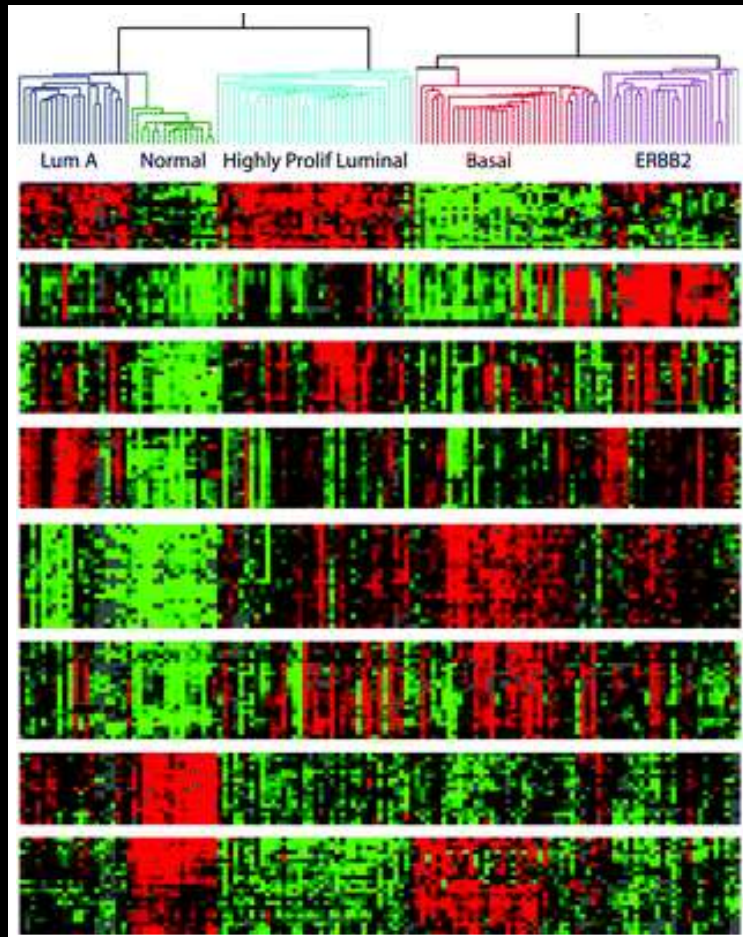


Personalized Medicine: The Initial Era - Targeted Therapeutics



Drug-Target Networks for FDA Approved Rx

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



- right Rx
for right
disease subtype

Dx – Rx
combinations

Molecular Diagnostics, Disease Subtyping and Pharmacogenomics

“Riches in the Niches”



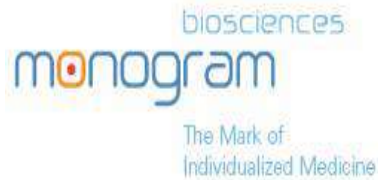
- right diagnosis, the first time
- right Rx selection, the first time
- rise of Dx-Rx combination
- Rx approval and labeling/reimbursement only with obligate Dx?

Molecular Diagnostics and Targeted Therapeutics

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



The Emergence of Drug: Diagnostic Combinations



Invader® chemistry

THIRD WAVE
TECHNOLOGIES



Verigene® System



5-Fluorouracil



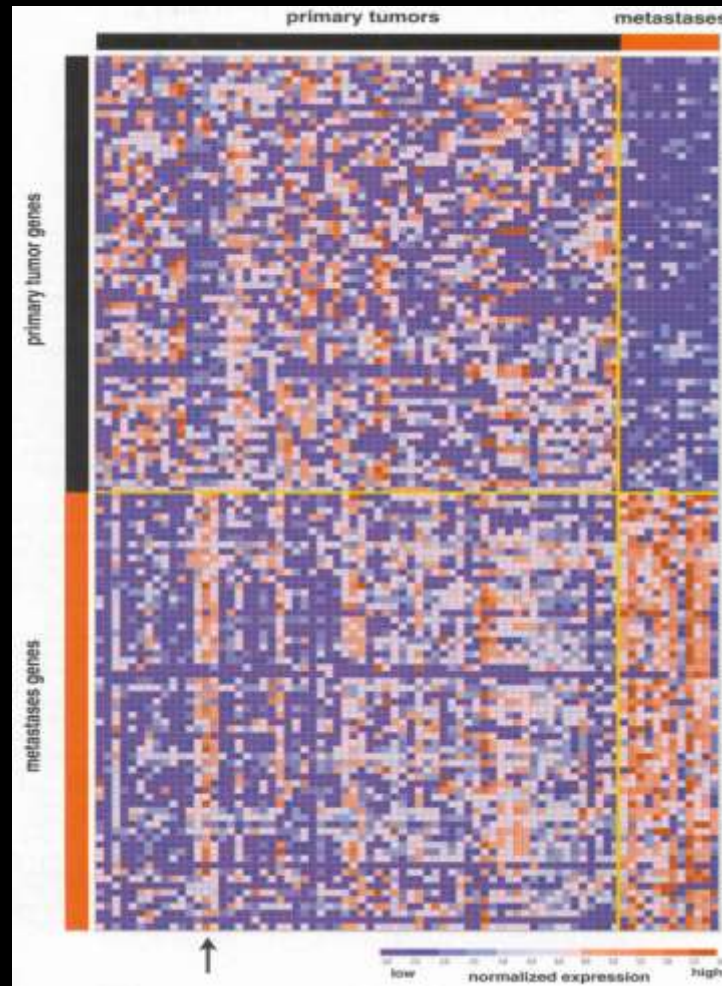
TheraGuide 5-FU®
A test to predict toxicity to 5-FU/capecitabine-based chemotherapy



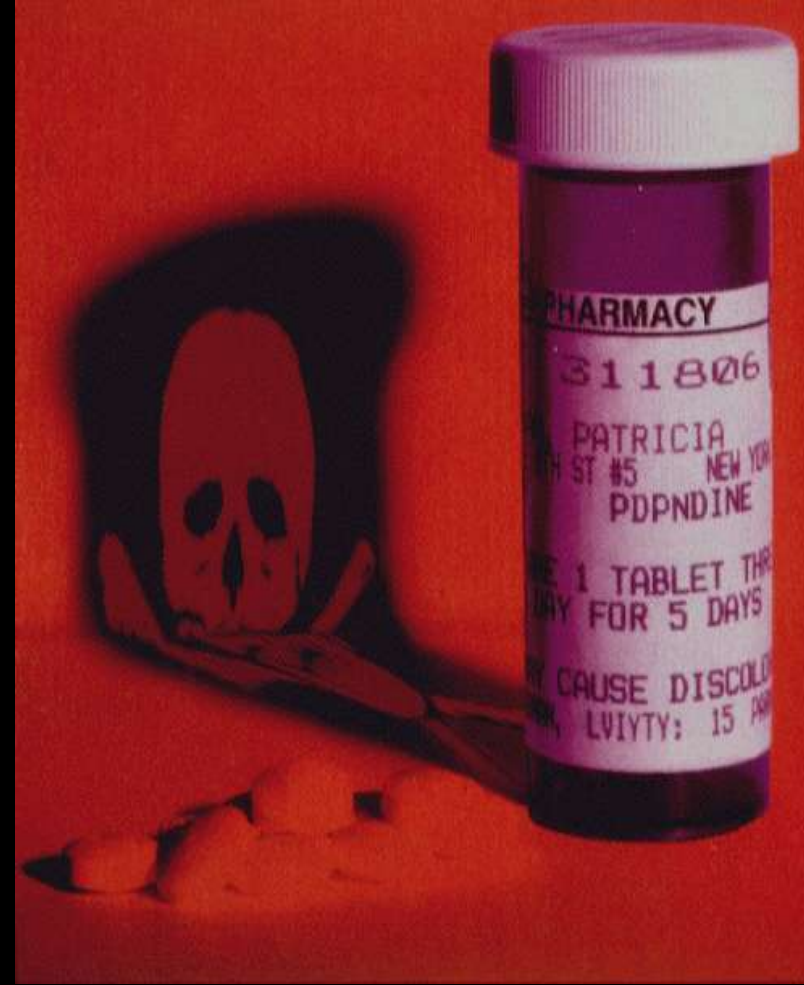
Personalized Medicine: The Initial Era - Targeted Rx

- **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**

Personalized Medicine: From Pharmaceuticals to Pharmasuitables



**Disease Subtyping:
Right Rx for Right Disease**



**Reduction of Adverse
Drug Reactions**

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”



“Safety First” Initiative

European Medicines Agency



The New York Times
The Washington Post





REMS:

Retroactive Risk Evaluation and Mitigation Strategies

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

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

US Regulatory Oversight of Pharmacogenomics and Drug Safety



- August 2008: two year study
- current focus on warfarin and tamoxifen (Mayo/LCA)

“to identify drugs (current/or future)
for which pharmacogenomics may improve
the dosing, effectiveness and safety
..... and data could be used to relabel drugs
or add to drug labels”

Dr. Larry Lesko
FDA Office Clinical Pharmacology
Pink Sheet 8/25/08 p. 12

Identification of Biomarkers for Toxicology and Adverse Events

- **preclinical toxicology**
 - FDA Critical Path Initiative
 - Predictive Safety Testing Consortium (FDA/EMA)
- **genetic polymorphisms and pharmacogenetic liabilities**
 - class I/II metabolic enzymes (slow metabolizers)
 - drug transporters
 - HLAs
 - specific Rx receptors
 - ethnic variation
- **Rx promiscuity and multi-target interactions**
- **genetic predisposition to serious unexpected adverse events**

Adoption of New Technologies in Healthcare

- **not merely innovation in technology**
- **parallel evolution and adoption of new business, financial and organizational models**
- **complexity of harmonizing incentives for diverse constituencies**
- **critical role of public policies in defining market entry barriers**
 - **regulation, reimbursement**
 - **professional standards and sustaining status quo**
 - **administrative procedures**
 - **governance of third party health insurance payments**
- **cost-based, event-/procedure-based incentives versus integrated care/disease management**

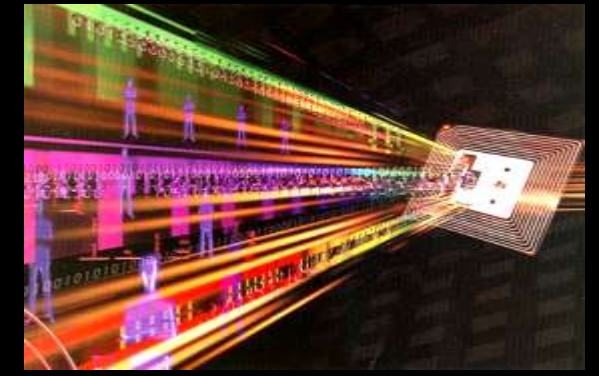
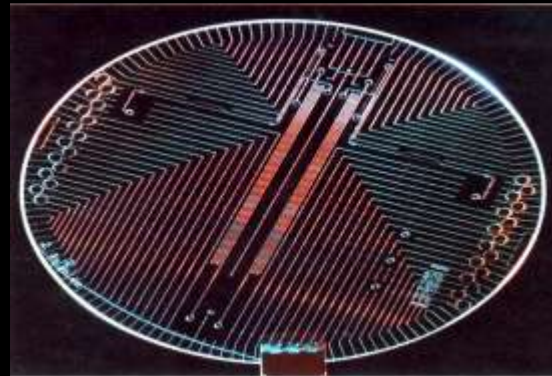
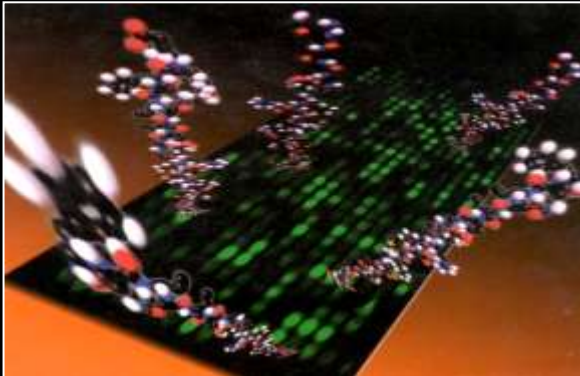
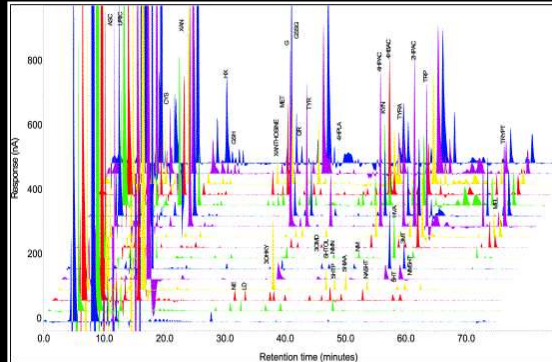
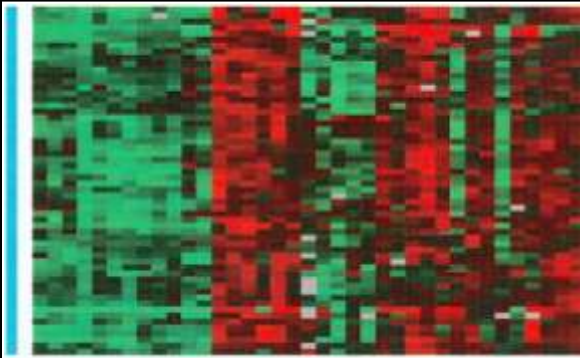
Development of Molecular Diagnostics and Biomarkers for Personalized Medicine: The Need for End-to-End R&D Solutions

Complex Biosignature Profiling

genomics

proteomics

immun signatures



Signature Detection, Deconvolution and Multivariate Analysis

multiplex assays

novel test
devices (POC)

new algorithms

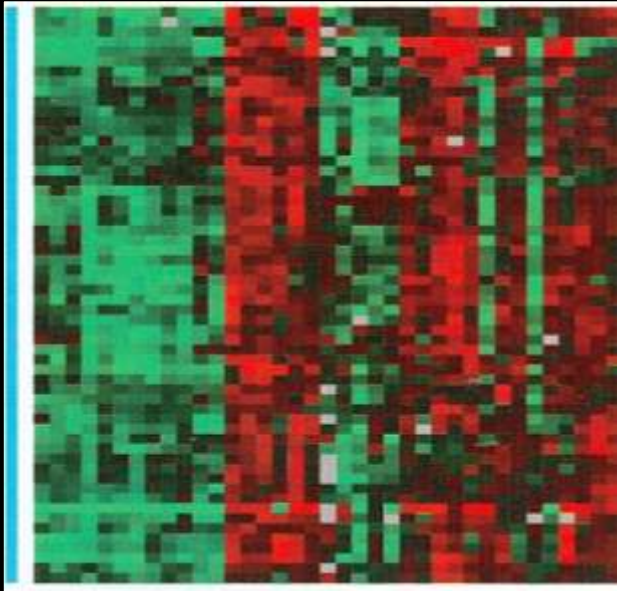
Disease-Associated Biomarkers

- **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**
 - **new regulatory oversight of multiplex tests (IVDMIAAs)**

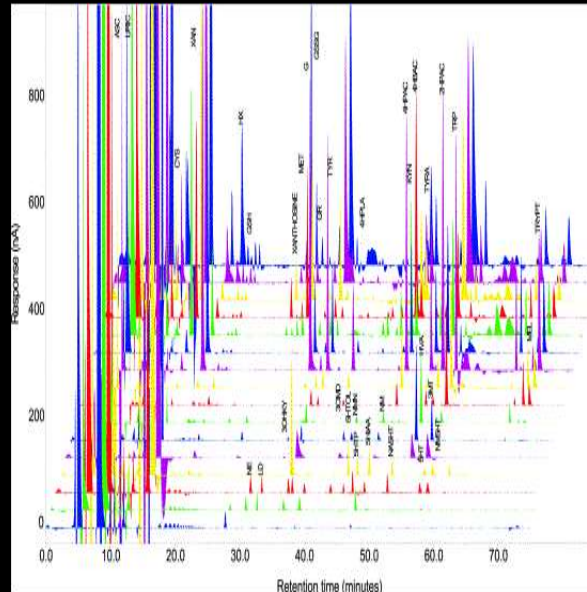
Access to High Quality Biospecimens

- **#1 obstacle to ID and validation of novel biomarkers**
- **inappropriate ‘turf’ battles over legacy specimens**
 - **public versus private funding**
- **unknown or variable quality of legacy biorepositories and limited linkage to clinical records**
- **inadequate national-level leadership/standards for biorepository specimens and management**
- **lack of mechanisms for systematic classification, coordination or distribution (priorities)**

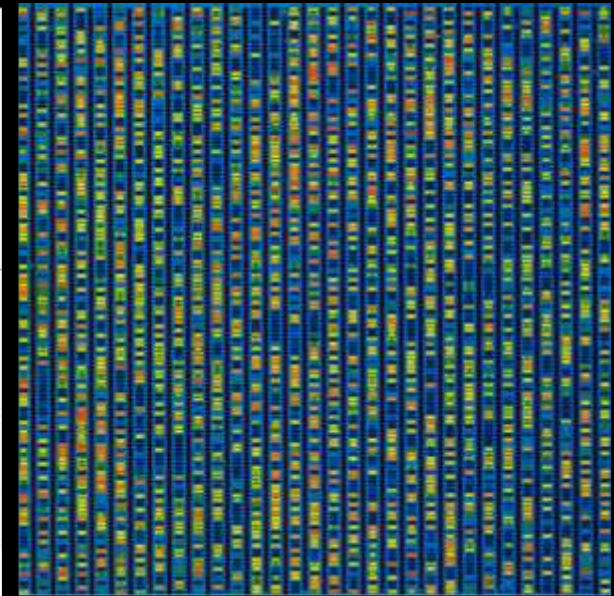
genomics



genomics



proteomics



immunosignatures

Next-Generation Molecular Diagnostics and New Patterns of Regulatory Oversight

In Vitro Diagnostic Multiplex Index Assay (IVDMIAs)

- **patient-specific result (score or index)**
- **analytical/interpretational algorithm non-transparent to end user**
- **result cannot be independently derived or confirmed by another laboratory without access to proprietary information used in the development and derivation of the test**



Companion Molecular Diagnostics for Rx Products

- **lack of inter-agency coherence on policy**
 - **drug and device Divisions**
- **drug standard (CDER) influences Dx review**
 - **reluctance to act to impose labeling change**
- **uncertainty about the level of validation required for predictive assays**
 - **retrospective data**
 - **prospective- retrospective data analysis**
 - **prospective trials**

Citizen Petition to the FDA on Laboratory-Developed Tests (LDTs)



**“request FDA regulatory jurisdiction over all LDTs”
December 2008**

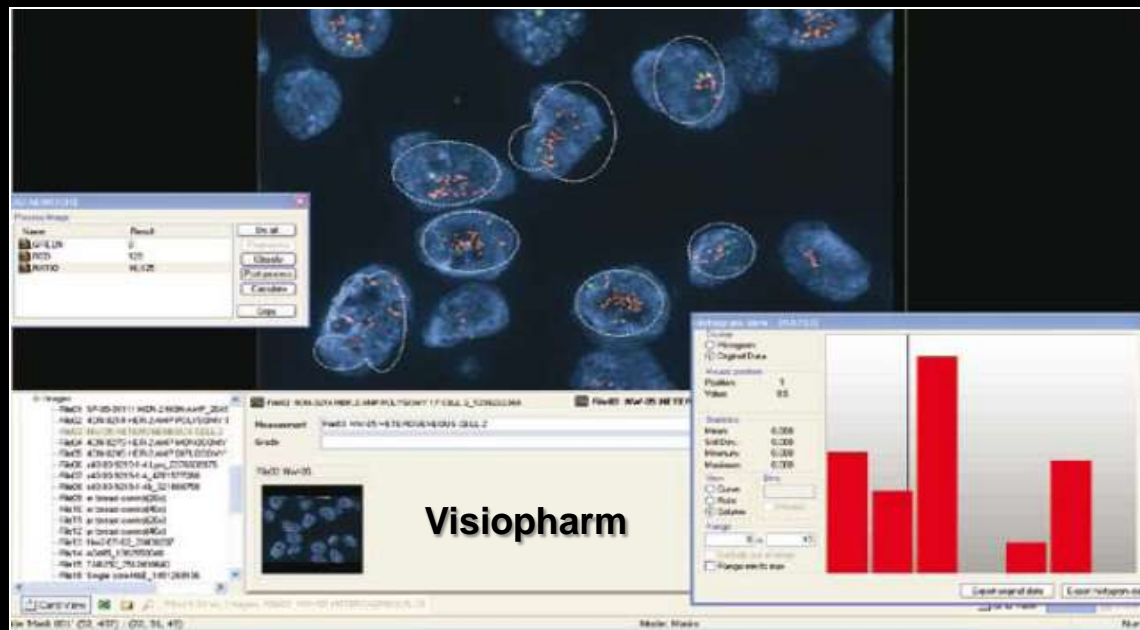


**“Genentech’s proposal poses a chilling effect on
innovation in patient care while stifling the
promise of personalized medicine.”**

January 2009

Automated Image Analysis and Digital Pathology “Virtual Pathology”

- automated high throughput capabilities
- greater efficiency of machine-based image analysis
 - no observer fatigue
 - reduced inter-observer variability
- quantitative market analysis
- crucial importance of standardization



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**
- **understanding payor coverage to ensure appropriate reimbursement**
- **new malpractice risks**

**Payor Value Propositions Do Not Align
with
Clinical Value Propositions**

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**

Annals of Internal Medicine
(2009) 150, 73-83

ARTICLE

Cost-Effectiveness of Using Pharmacogenetic Information in Warfarin Dosing for Patients With Nonvalvular Atrial Fibrillation

Mark H. Eckman, MD, MS; Jonathan Rosand, MD, MSc; Steven M. Greenberg, MD, PhD; and Brian F. Gage, MD, MSc

Background: Variants in genes involved in warfarin metabolism and sensitivity affect individual warfarin requirements and the risk for bleeding. Testing for these variant alleles might allow more personalized dosing of warfarin during the induction phase. In 2007, the U.S. Food and Drug Administration changed the labeling for warfarin (Coumadin, Bristol-Myers Squibb, Princeton, New Jersey), suggesting that clinicians consider genetic testing before initiating therapy.

Objective: To examine the cost-effectiveness of genotype-guided dosing versus standard induction of warfarin therapy for patients with nonvalvular atrial fibrillation.

Results: In the base case, genotype-guided dosing resulted in better outcomes, but at a relatively high cost. Overall, the marginal cost-effectiveness of testing exceeded \$170 000 per QALY. On the basis of current data and cost of testing (about \$400), there is only a 10% chance that genotype-guided dosing is likely to be cost-effective (that is, <\$50 000 per QALY). Sensitivity analyses revealed that for genetic testing to cost less than \$50 000 per QALY, it would have to be restricted to patients at high risk for hemorrhage or meet the following optimistic criteria: prevent greater than 32% of major bleeding events, be available within 24 hours, and cost less than \$200.

KRAS Profiling and Anti-EGFR Monoclonal Antibody Therapy



- greater response in patients with wt-KRAS versus mutant-KRAS



**regulatory
approval**



clinical guidelines



- estimated \$604 million/year savings (ASCO)

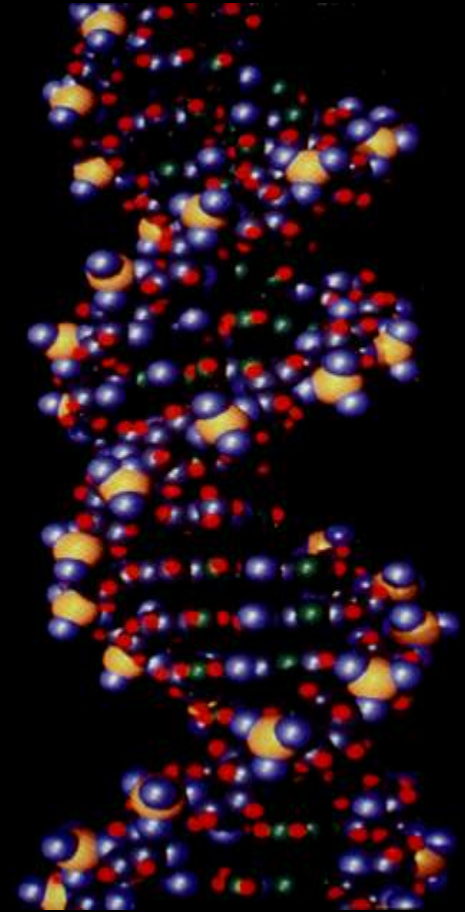


- ODAC meeting 12/08 but formal position not defined

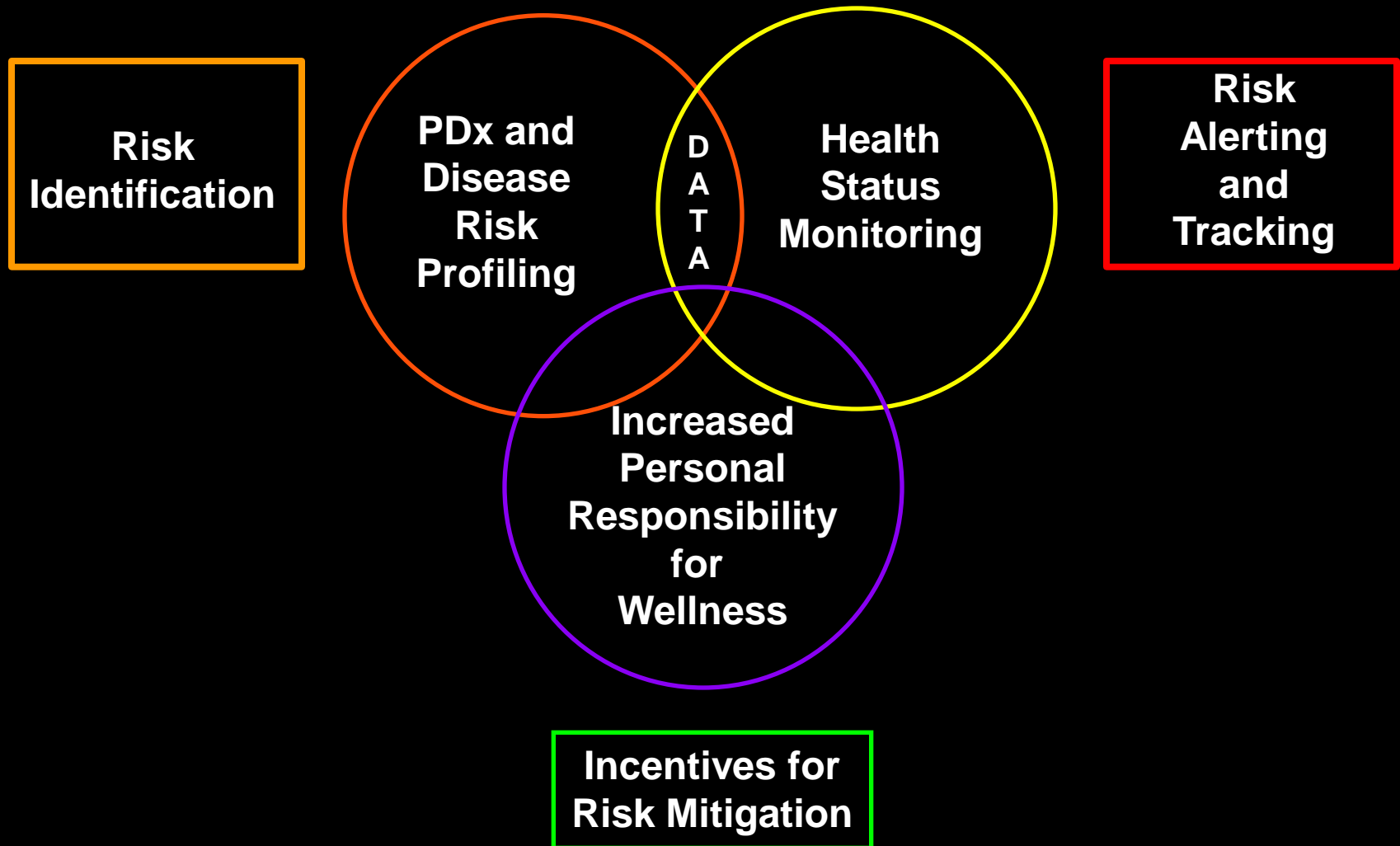
The Perceived Value of Evidence for Coverage Determinations by Order of Significance

- **BCBSA, Hayes, Kaiser Approval**
- **coverage in other plans**
- **inclusion in clinical guidelines of a major Association or College**
 - **discrepancy among guidelines, e.g. mammography**
 - **perceived rigor of the Association or College**
 - **agenda of Association or College**
- **peer review clinical journals**
- **FDA approval**
- **CLIA approval**

Personalized Medicine: Disease Predisposition Profiling



Disease Risk Predisposition Profiling (PDx) and Risk Mitigation



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

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

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

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 - **source of poor replication of GWAS studies?**

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

“Celebrity Spit”: Launch of 23andMe Personal Gene Profiling Service



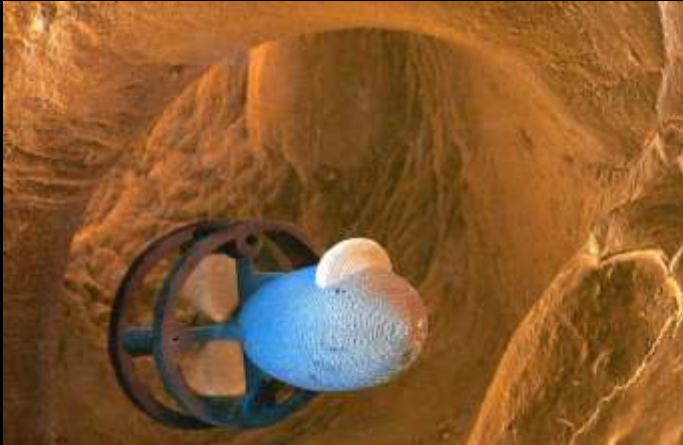
Health Status Monitoring and the Promotion of Wellness

Personalized Medicine: A Broader Perspective

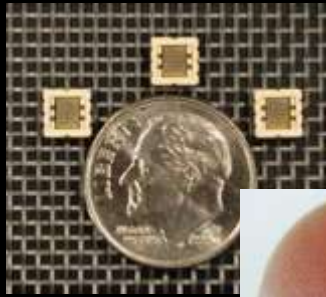
Wellness:

- **economic and societal pressures for 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**

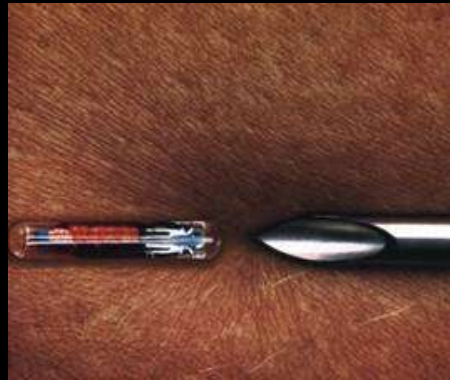
On Body: In Body Sensors/Devices For Real Time and Remote Monitoring of Individual Health Status



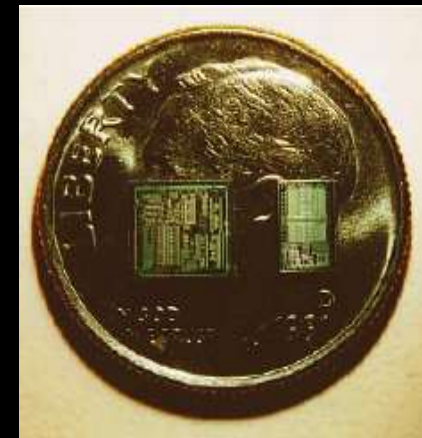
OBIBS and Body Area Networks (BAN's) for Remote Monitoring of Health



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

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)**

“Knowledge and Evidence Doesn’t Translate Easily into New (or Rational) Behaviors”

- **science (impact is too often unknown and abstract)**
- **industry (incremental timidity driven by short-term focus on markets and valuation)**
- **payors (cost control)**
- **physicians and healthcare professionals (status, revenue and recognition)**
- **patients (unaware and uninvolved in healthcare decisions)**
- **politicians (populism and short-term fixes)**

**The Pragmatic Challenge:
Who Pays, Who Benefits and Who Decides?**

Personalized Medicine: Consumer-Centric Healthcare: A Key Driver

- **structural shift in healthcare delivery from encounter-/procedure-driven to incentives for integrated disease management**
- **clinical and economic benefits of coordinated care of complex chronic conditions**
- **cost-shifting to consumers**
- **lifestyle and disease risk mitigation**
- **new information intermediaries**
- **cost-driven transitions from ‘passive patient’ to ‘engaged consumer’**

The Key Element in Future Primary Healthcare Delivery???

Walgreens
As far as you want to go.™

CVS
CAREMARK

WAL★MART®
Save money. Live better.™



The Medical Home Concept for Coordinated Care of Complex Chronic Conditions

Deloitte.

Connected Care

*Technology-enabled
Care at Home*

Produced by the
Deloitte Center
for Health Solutions



Audit • Tax • Consulting • Financial Advisory

State of Technology in Aging Services According to Field Experts and Thought Leaders

By:

Majd Alwan, Ph.D.,

Center for Aging Services Technologies (CAST)

American Association of Homes and Services for the Aging (AAHSA)

and

Jeremy Nobel, M.D., M.P.H.,

Harvard School of Public Health

Report Submitted to: Blue Shield of California Foundation

February 2008

cast 
Center for Aging Services Technologies

The Infocosm: Emerging Networks of Global Connectivity



The Great Network Inflection Point

- multi-billion user internet
- AORTA (always on, real time, access)
- connectivity via low cost, portable, multi-function devices
 - “universal connection devices”
- every piece of information will have geographic and time coordinate
- ubiquitous access plus customized profiling creates a world shaped by individual choices

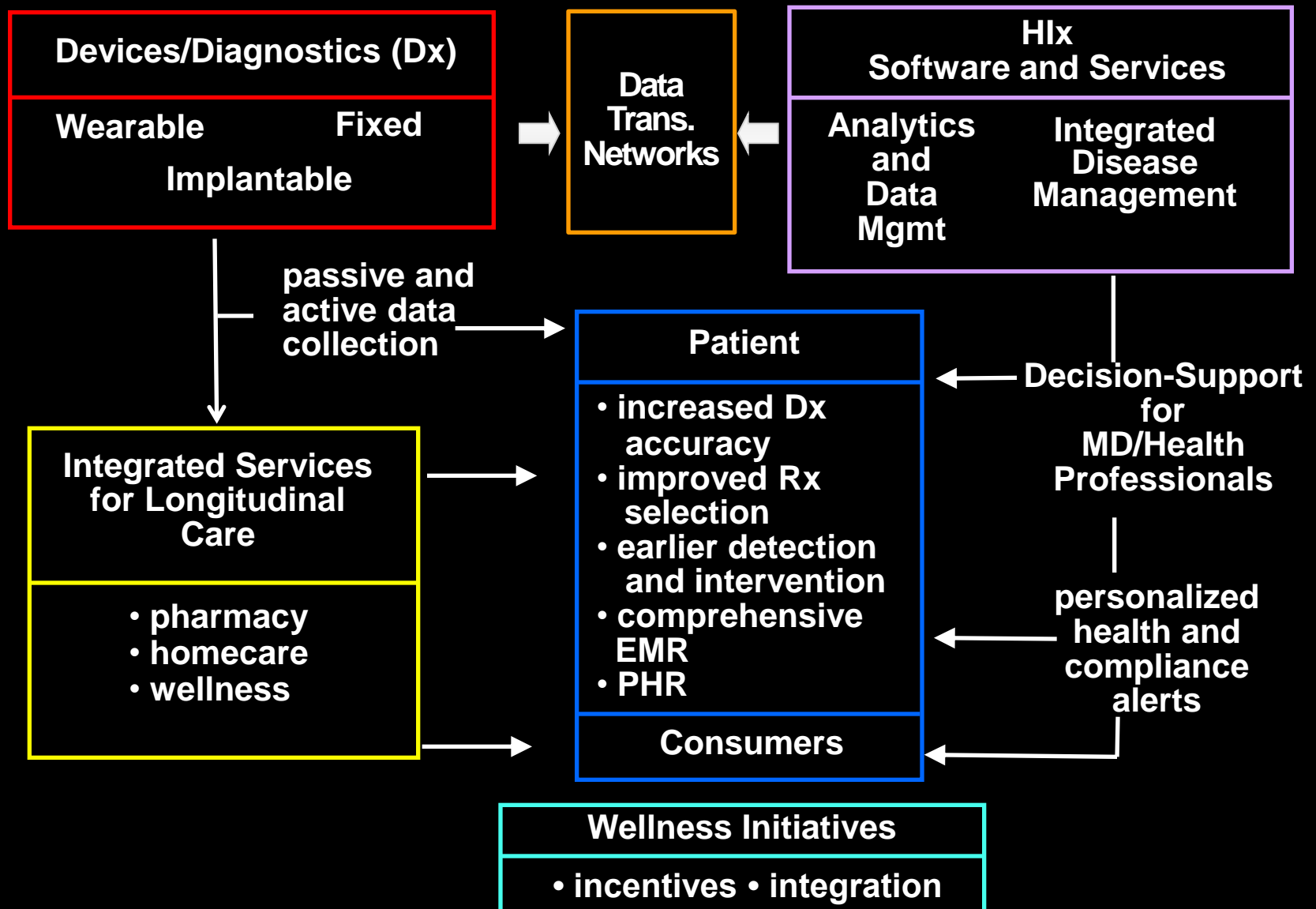
Consumer-Directed Healthcare: The Wellness Premium

- **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**

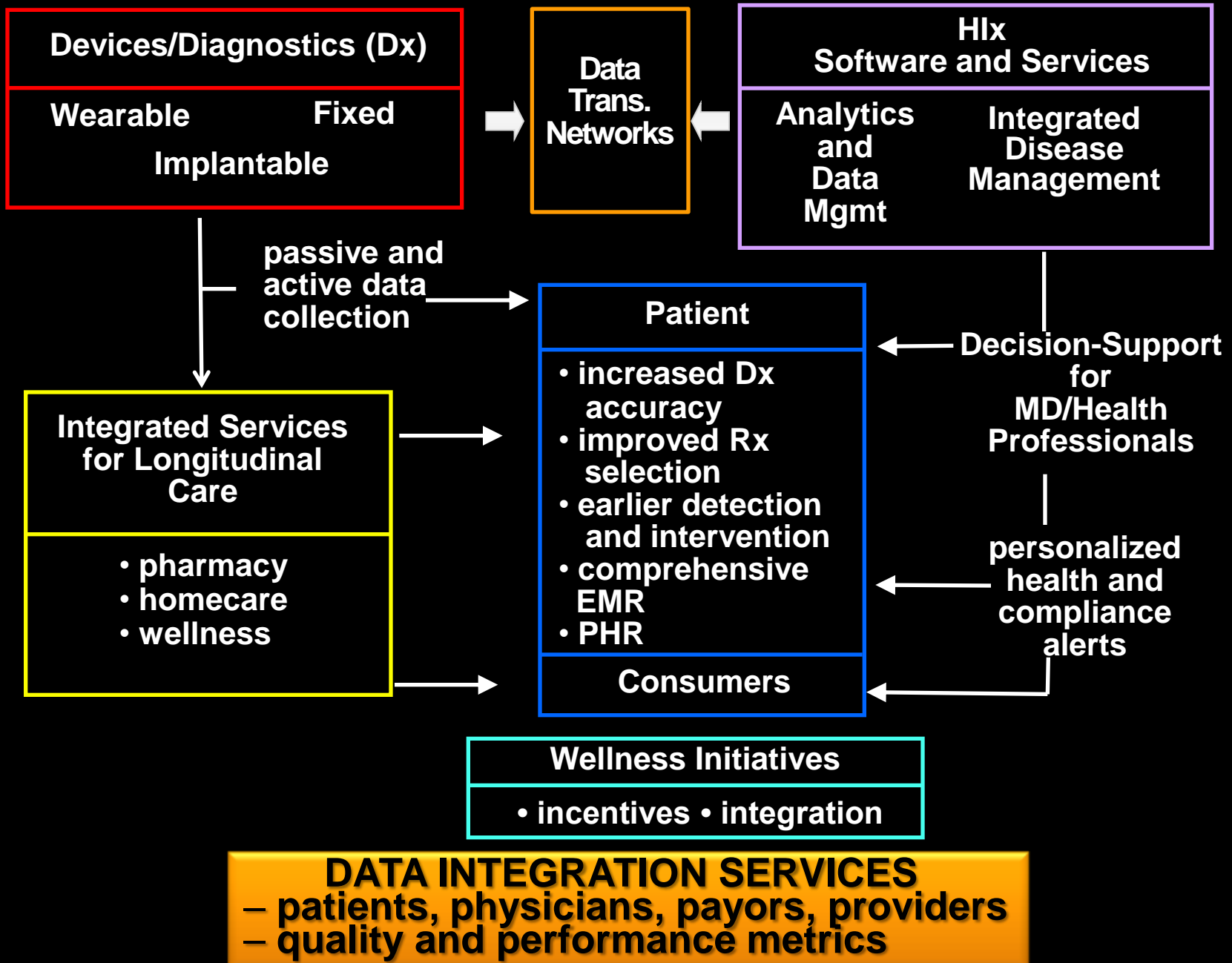
In-Home Health Connection: Engaging the Elderly



A New Healthcare Ecosystem Arising From Technology Convergence



A New Healthcare Ecosystem Arising From Technology Convergence



**“If we want to get universal health IT in the near term,
I do not see an alternative to the “stick”,
even if combined with carrots”.**

**Peter Orszag
Director, Congressional Budget Office
Medical Device Daily
25 July 2008, p.2**

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



**Targeted
Care**

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

**Individualized
Care**

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

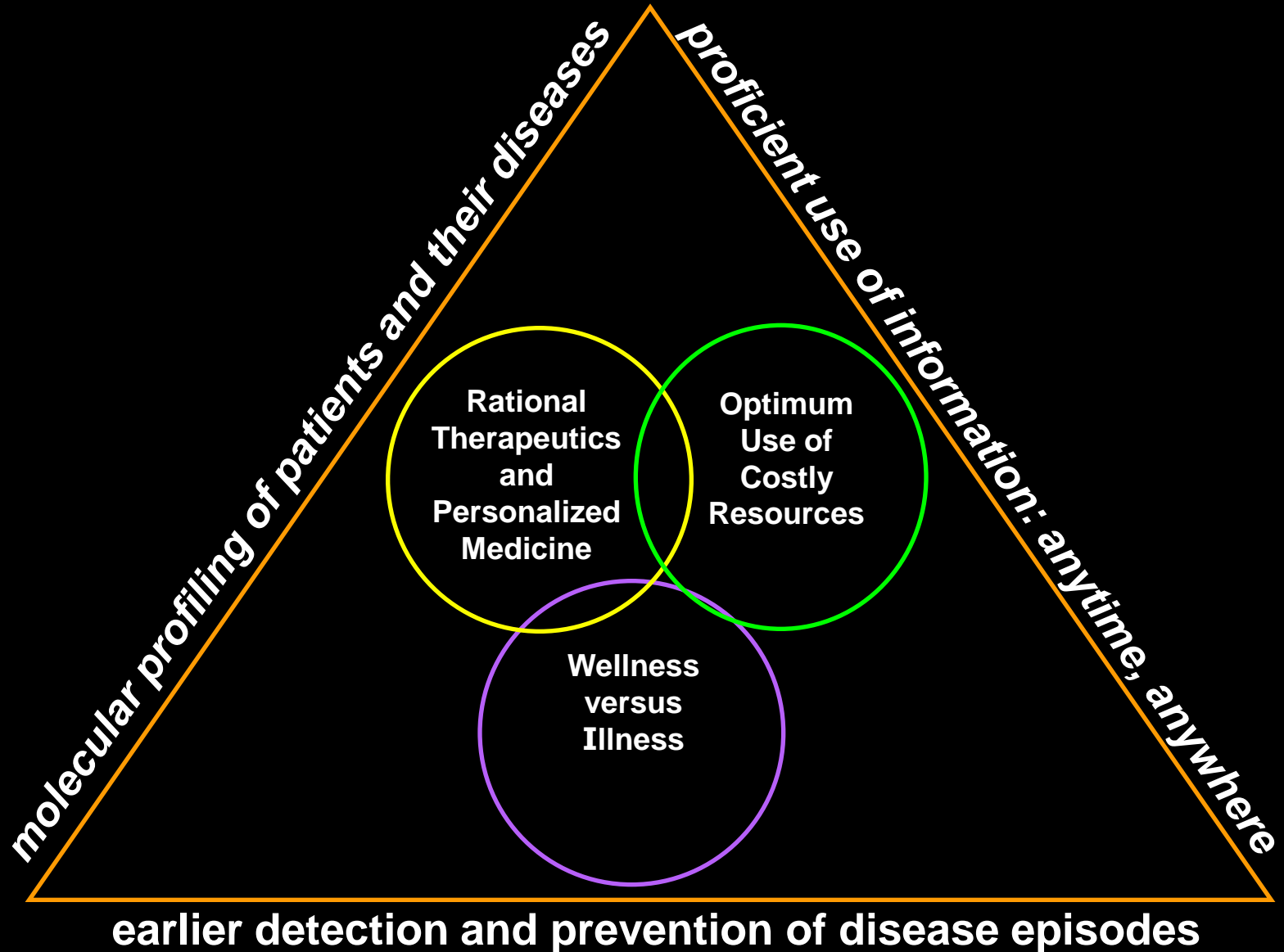
**Personalized
Care**

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

Adoption of New Technologies in Healthcare

- **not merely innovation in technology**
- **parallel evolution and adoption of new business, financial and organizational models**
- **complexity of harmonizing incentives for diverse constituencies**
- **critical role of public policies in defining market entry barriers**
 - **regulation, reimbursement**
 - **professional standards and sustaining status quo**
 - **administrative procedures**
 - **governance of third party health insurance payments**
- **cost-based, event-/procedure-based incentives versus integrated care/disease management**

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



Building an Integrated Framework for Personalized Medicine

