ASU COMPLEX ADAPTIVE SYSTEMS INITIATIVE
ARIZONA STATE UNIVERSITY

The Evolution of Personalized Medicine: Opportunities and Challenges

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Health Problems and Solutions Seminar Series
ASU Office of Knowledge Enterprise Development
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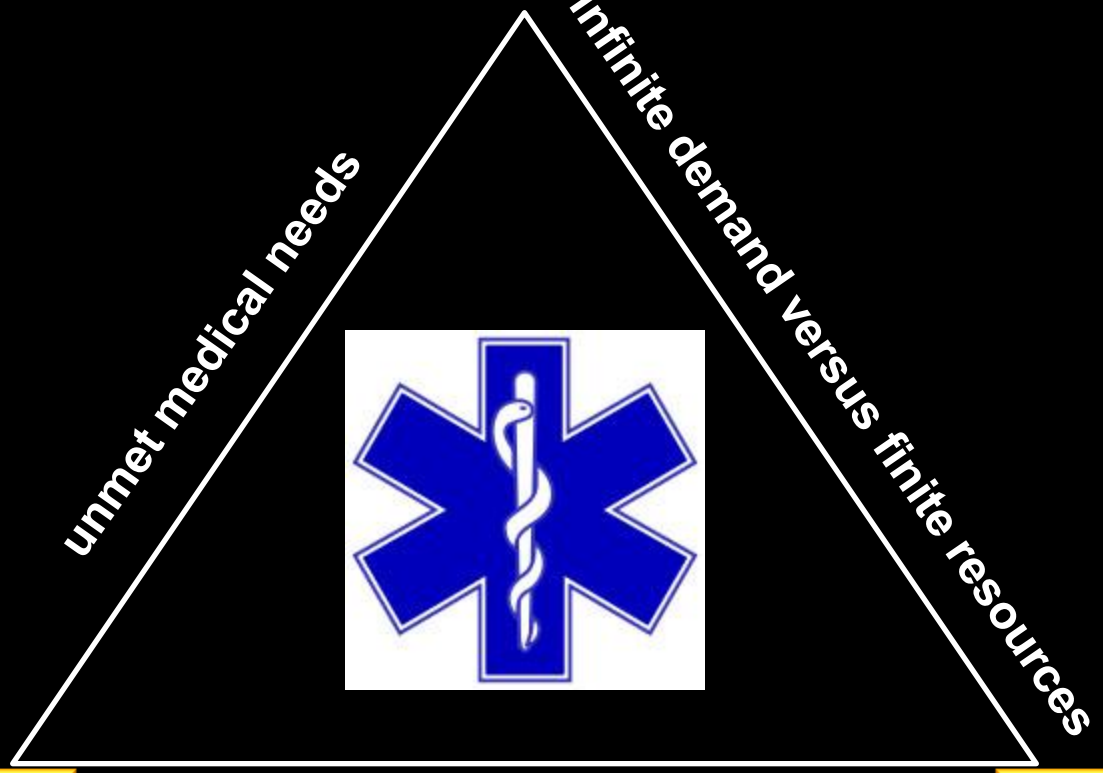
The Healthcare Challenge

Outcomes

clinical, economic, quality-of-life



Innovation and Defining Value

increasing cost of care
and acceleration of new technologies

Access to Care

Economic Distortions and Perversions in the Healthcare "Market"

- "a menu without prices" (A. Garber)
- potential terminal illness for governments, business and patients/consumers
- supply creates its own demand
- caregivers make more money by providing more care and typically ignore cost in treatment options
- patients have entitlement mentality and don't select treatment choice
- payors don't apply comparative effectiveness metrics
- neither consumers nor caregivers evaluate cost or benefit and drift to "maximum" care

Demographics: Ageing, Chronic Diseases and Cost

ageing

- by 2030 number of people over 65 will:
  - increase 140% in developing world
  - increase 51% in developed world
  - outnumber children under 5

chronic disease burden

- by 2020 account for 75% of global deaths

cost

- US cost of chronic disease will increase 2.5X by 2023
- China loss of income due to chronic disease will increase 8X from 2005-2015

US Cancer Prevalence Estimates 2010 and 2020

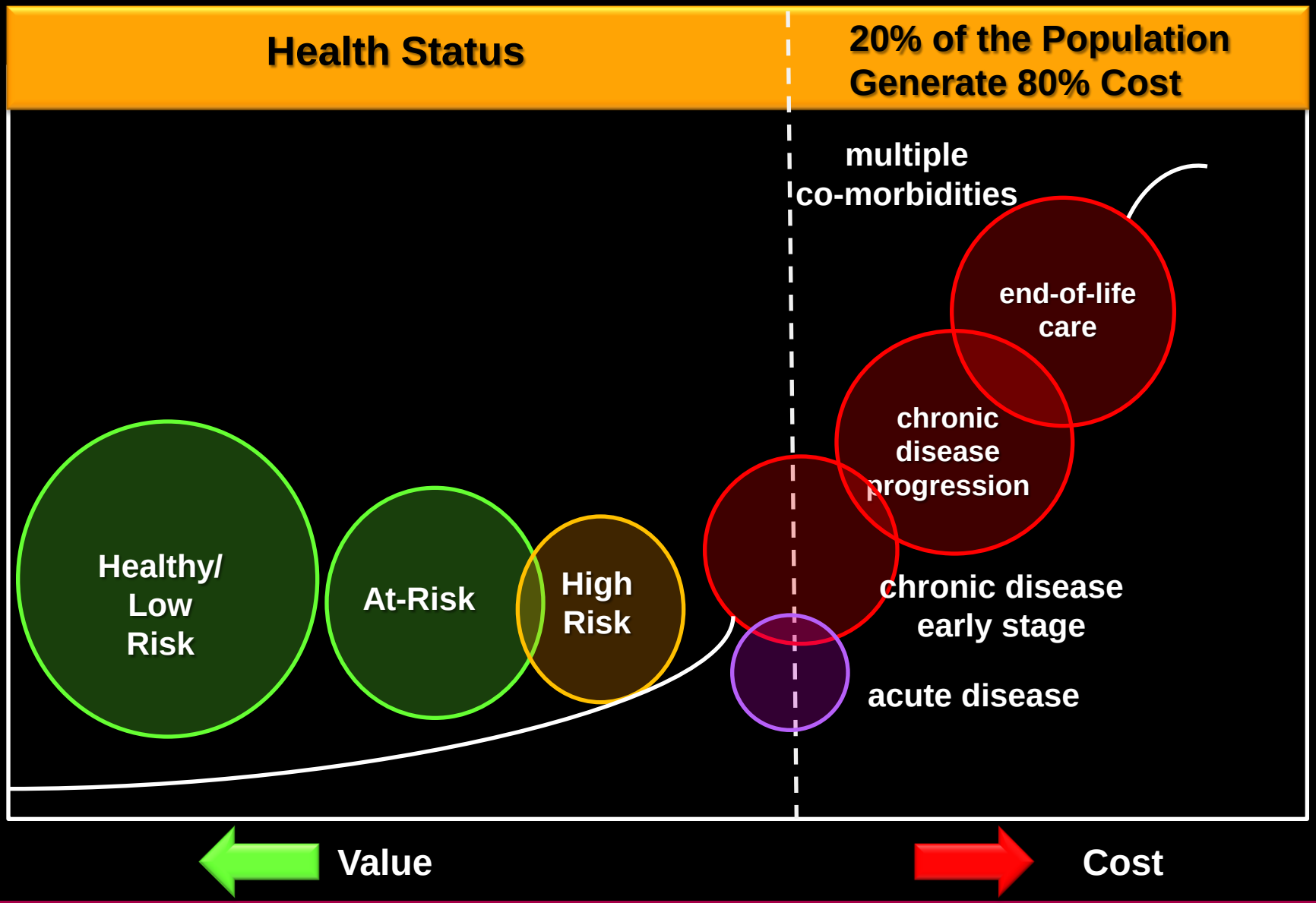
Site	# People (thousands) 2010	2020	% change
Breast	3461	4538	31
Prostate	2311	3265	41
Colorectal	1216	1517	25
Melanoma	1225	1714	40
Lymphoma	639	812	27
Uterus	588	672	15
Bladder	514	629	22
Lung	374	457	22
Kidney	308	426	38
Leukemia	263	240	29
All Sites	13,772	18,071	32

From: A.B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117

Challenges for Sustained Innovation in Biomedical R&D

- inefficient translation of research (valley of dea(r)th)
- macroeconomic uncertainties
  - reduced Federal funding, VC retreat and R&D reductions in bigPharma/biotech
  - budget gap closure actions and industry fees/concessions
  - off shore investment
- complexity of chronic diseases and no immediate prospect of enhancing asset success rate and/or truncation of R&D cycle time
- regulatory uncertainties and increasing hurdles
  - larger trials, zero-risk and REMs
  - inadequate budgets, staffing and science

The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities



Reasonable Expectations for Rational Healthcare

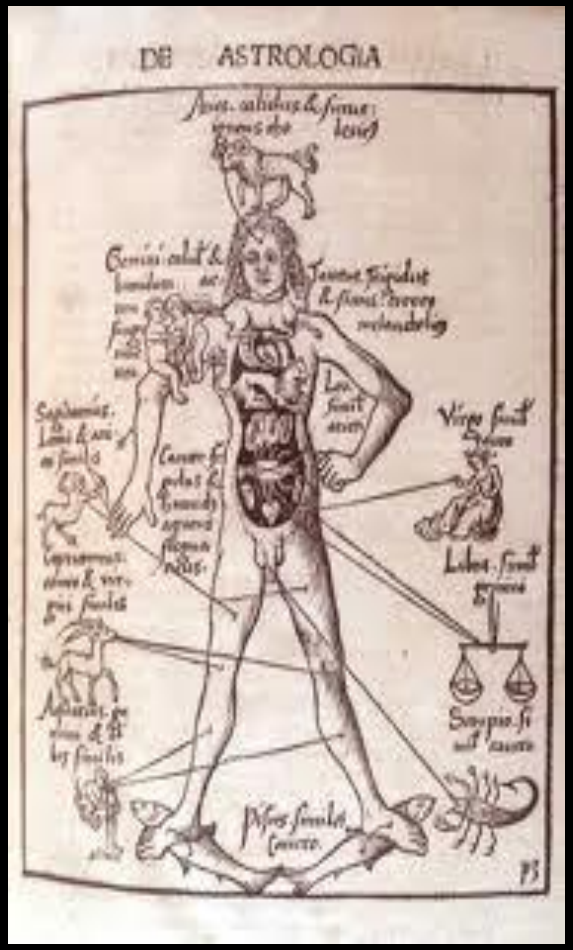
- what works?
- why it works?
- who it works for?
- what works best?
- when should it be used optimally?

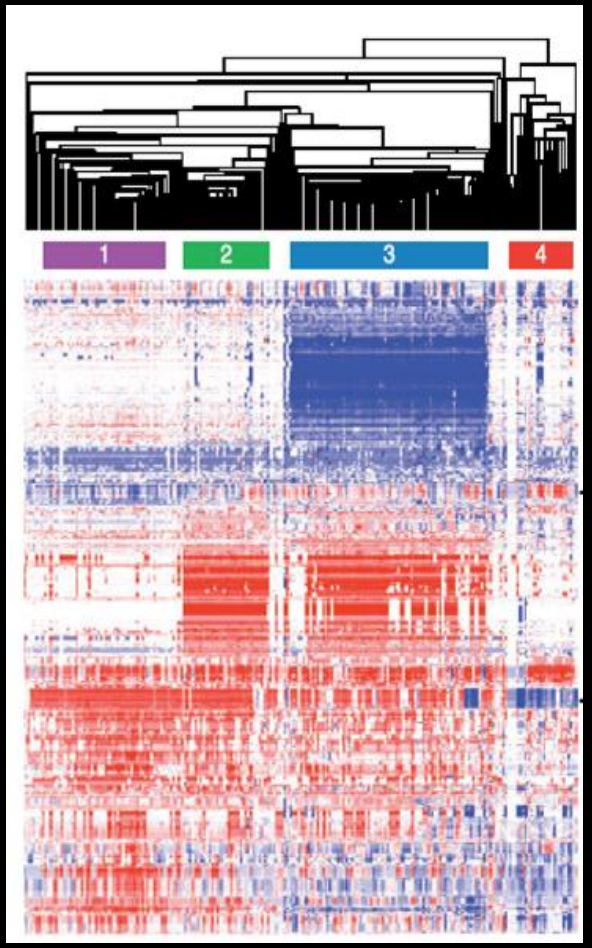
- validated evidence
- mechanism of action
- personalized medicine
- comparative effectiveness
- best practice guidelines and standard-of-care

VALUE

The Innovation Ecosystem for Biomedical R&D and Healthcare Delivery

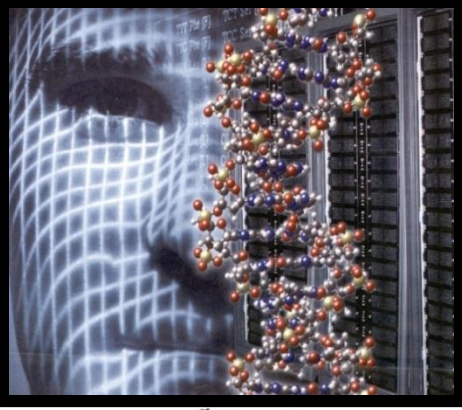
Medical Progress:
From Superstitions to Symptoms to Signatures



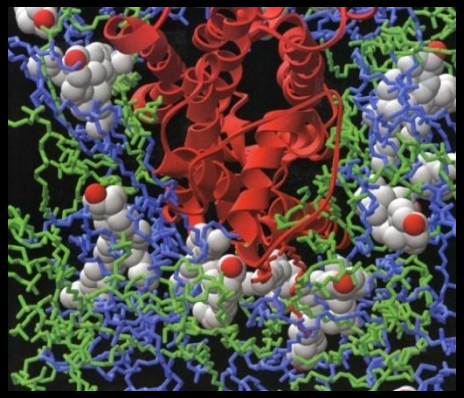


Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

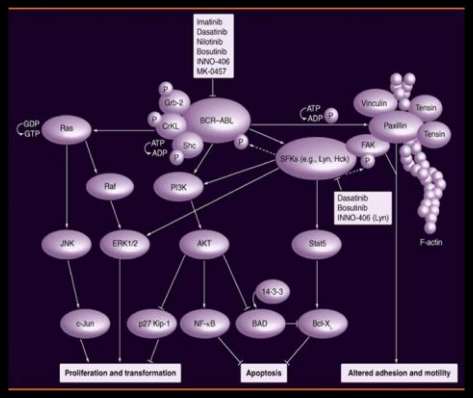
Genomics



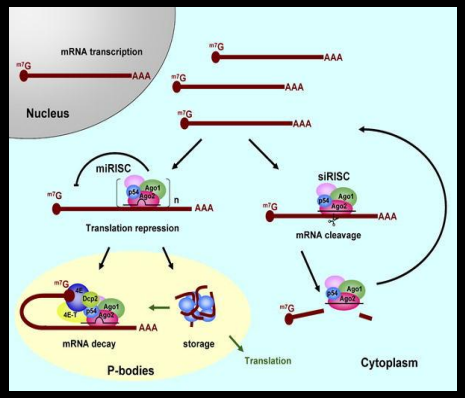
Proteomics

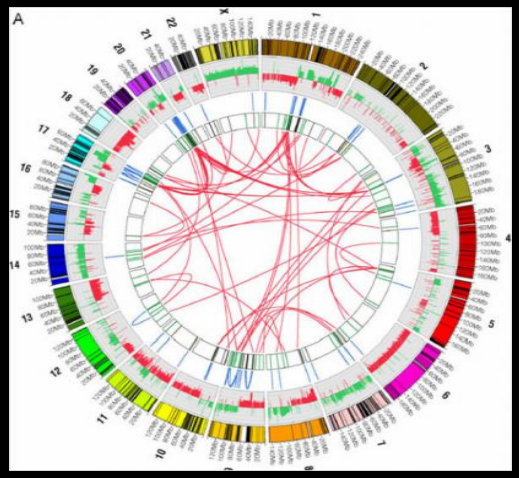


Molecular Pathways and Networks



Network Regulatory Mechanisms



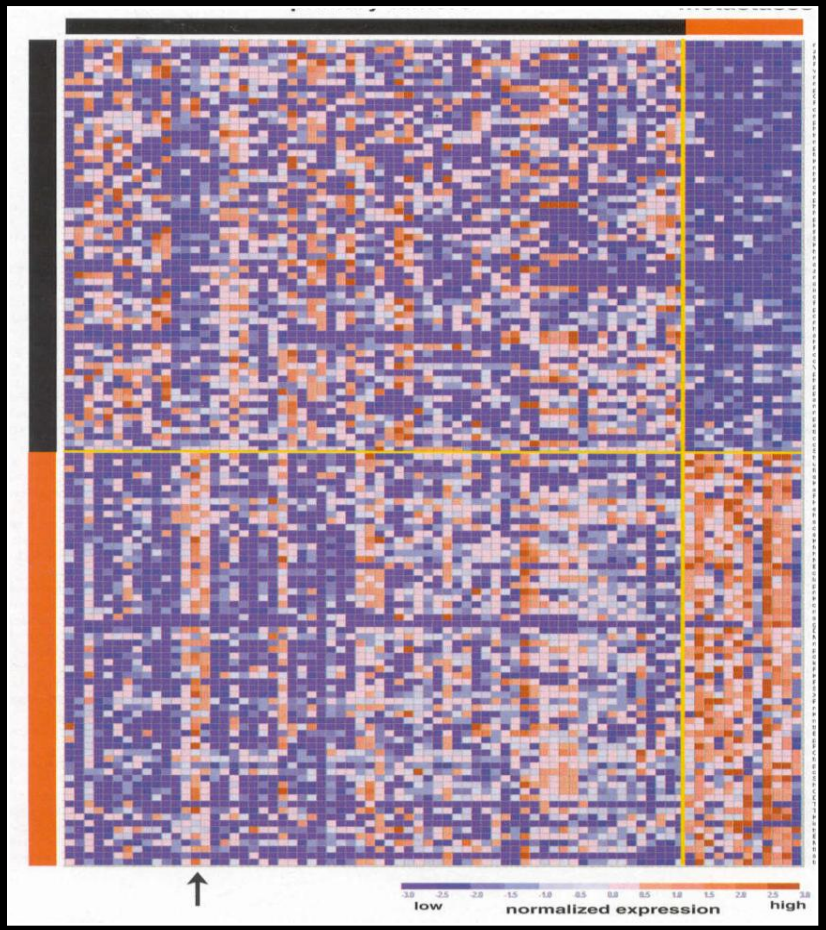


ID of Causal Relationships Between Network Perturbations and Disease

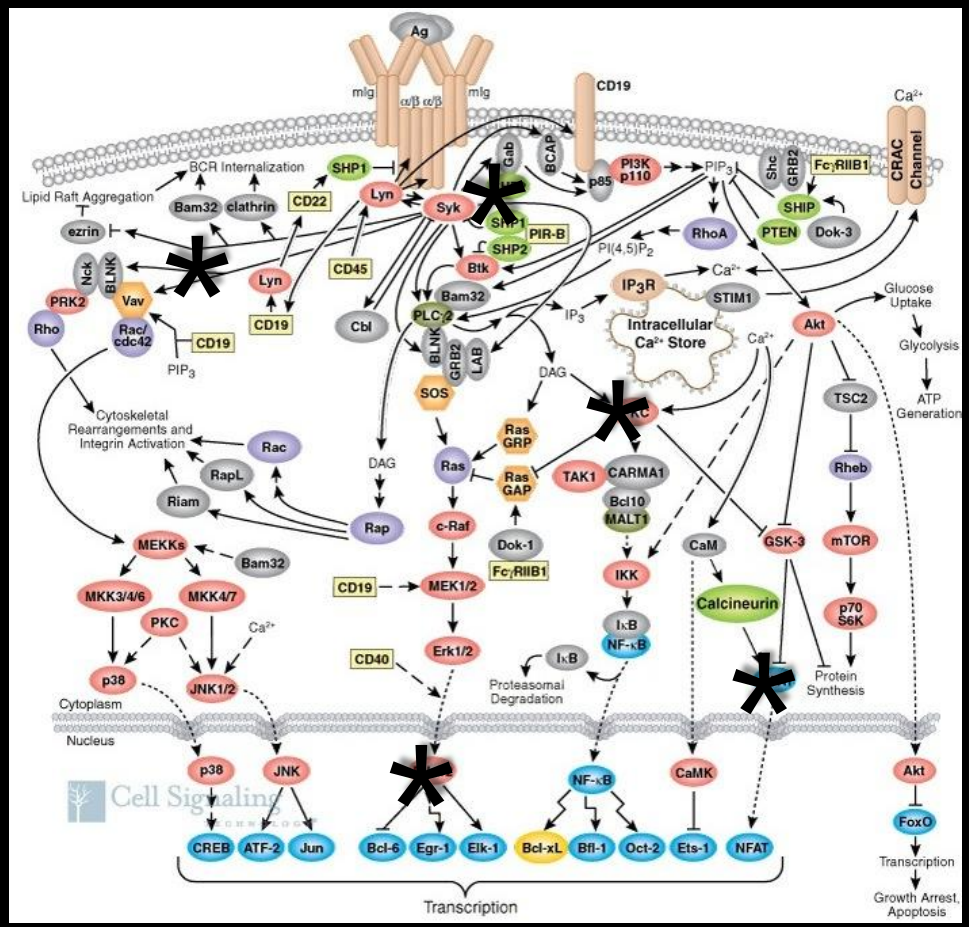
Patient-Specific Signals and Signatures of Disease or Predisposition to Disease

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

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



ID Molecular Targets for MDx and/or Rx Action



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

- improved clinical outcomes
- cost-effectiveness in eliminating futile Rx
- reducing high failure rate of new drugs in R&D clinical trials by testing only on relevant patients
  - faster and cheaper trials
  - improved efficacy, clear regulatory endpoints and faster approval
  - premium pricing for guaranteed outcomes (P4P)

K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy

Vectibix® (panitumumab)

AMGEN

ERBITUX® CETUXIMAB

ImClone Systems Incorporated

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

clinical guidelines

NCCN

ASCO®

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

- regulatory endorsement in product labeling

CMS

BlueCross BlueShield

UnitedHealthcare®
Healing health care. Together.®

- payor adoption

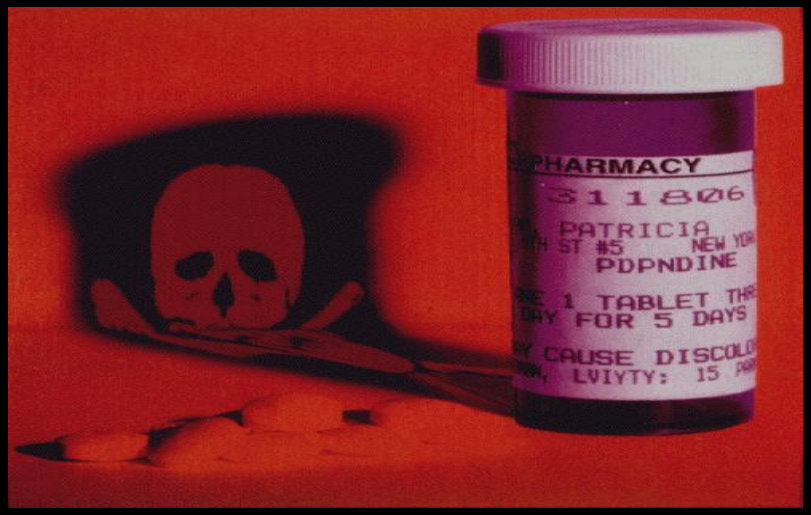
Disease Subtyping and Targeted Therapy: The Right Rx for the Right Disease Subtype

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

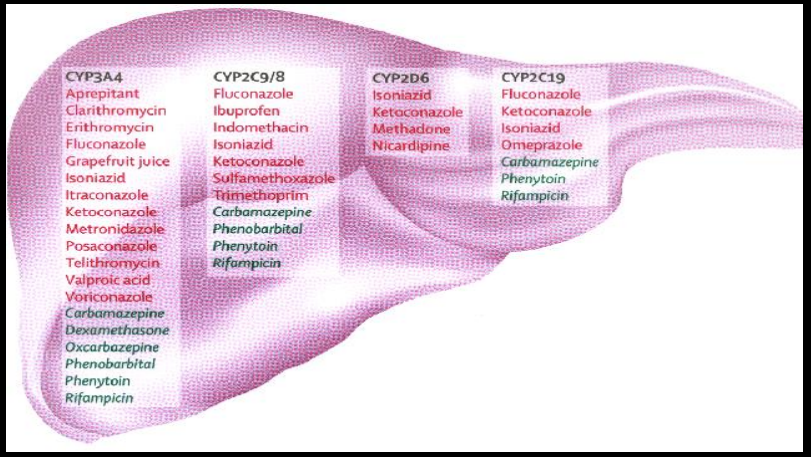
downside implications for ineligible patients with no therapeutic alternative(s)

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

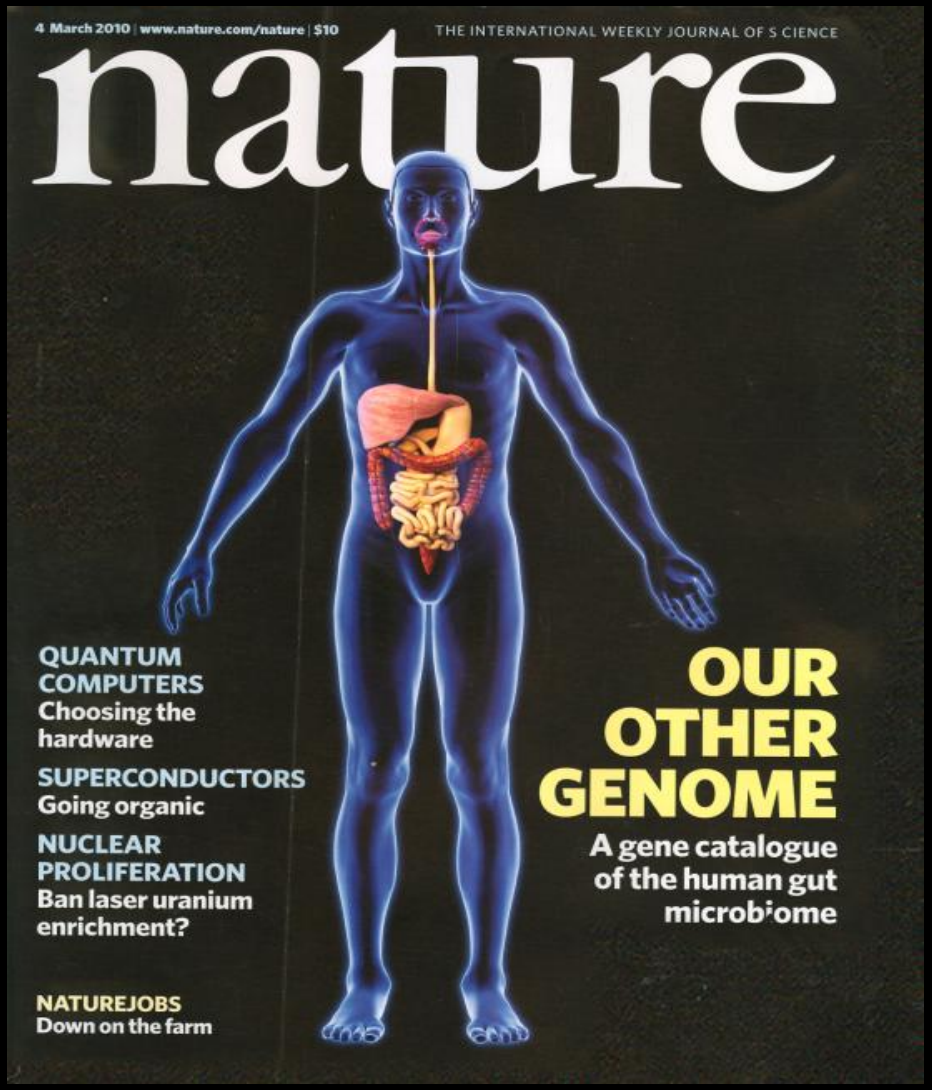
Right Rx for the Right Patient



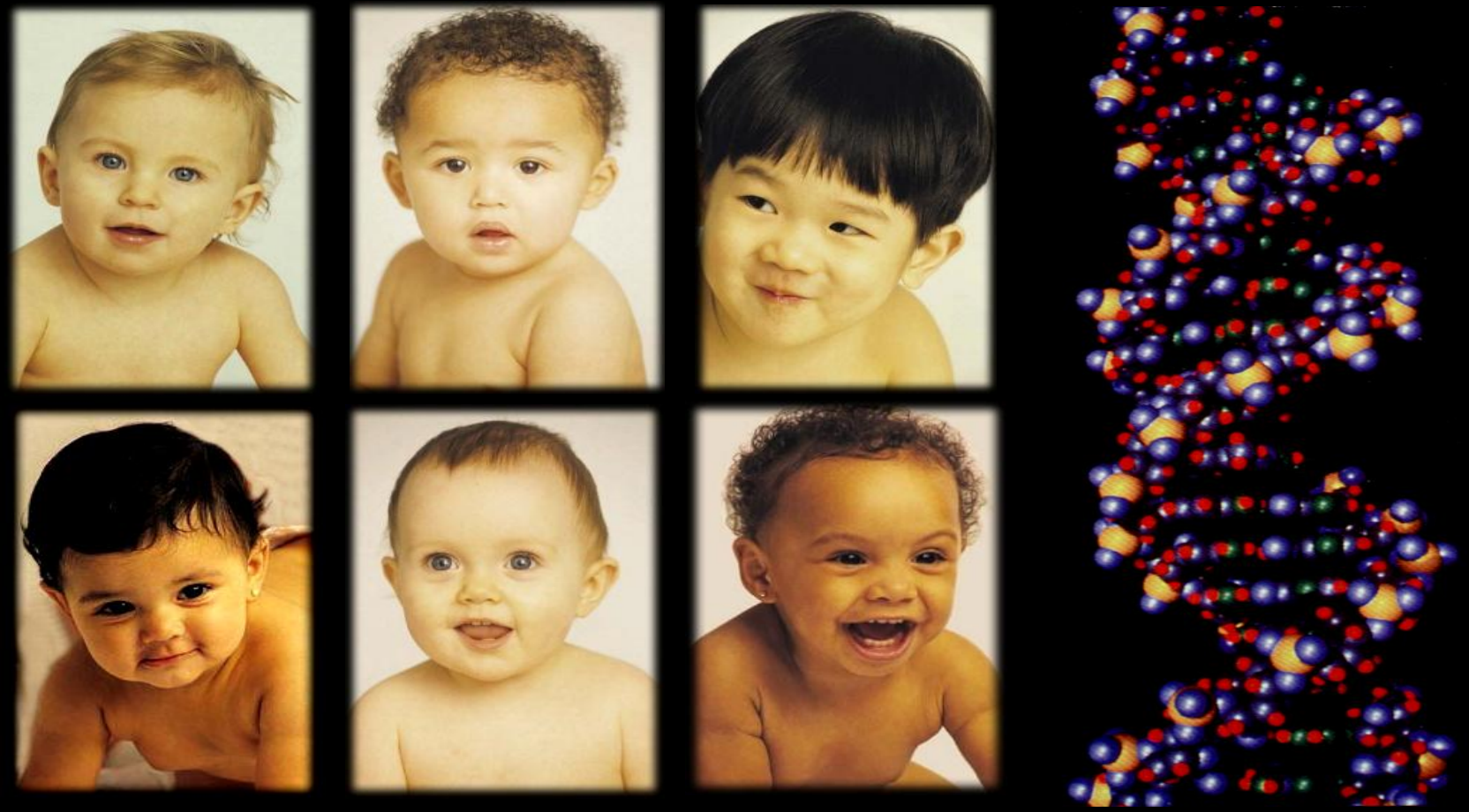
- 1.5 to 3 million annual hospitalizations (US)
- 80 to 140 thousand annual deaths (US)
- est. cost of $30-50 billion



We Are Not Alone: Variation in the Human Microbiome as a Potential Factor in Health and Disease



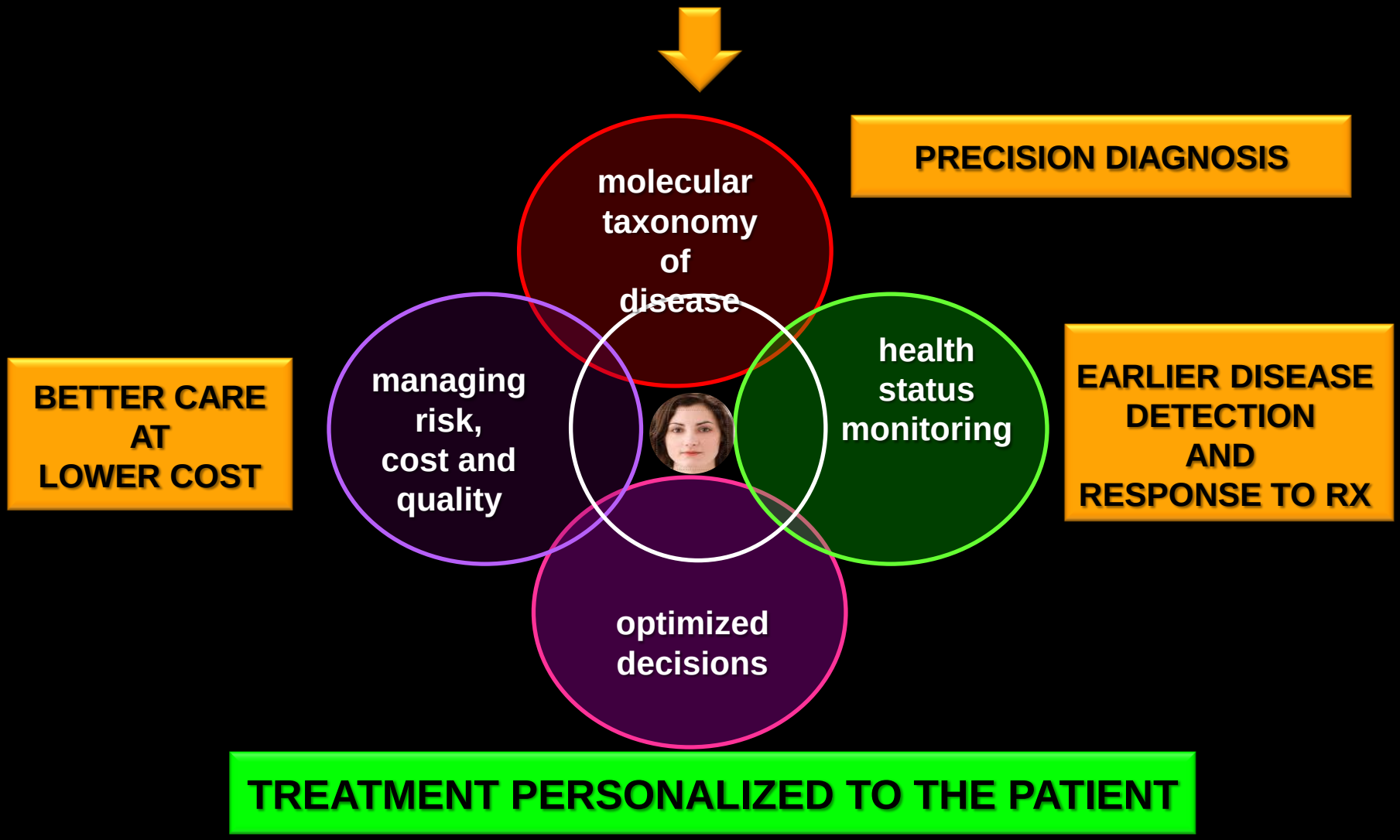
Genetic Profiling to Identify Risk of Predisposition to Disease



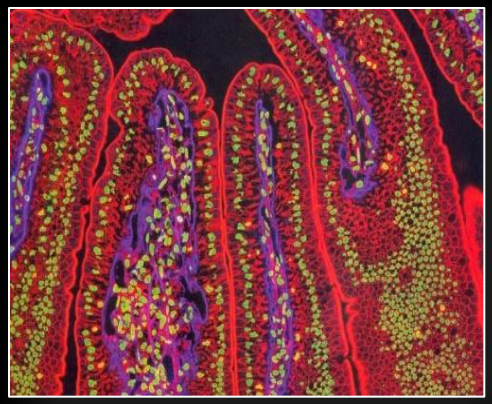
The Rise of Consumer Genomics: Genetic Profiling to Identify Risk of Predisposition to Disease

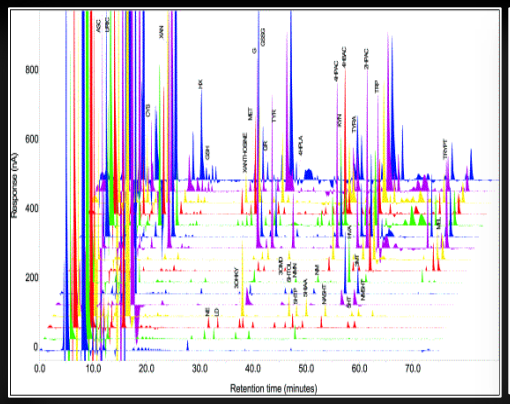
- the much publicized (hyped) $1000 genome
- $1000 genome but big bucks to interpret the results plus myriad ambiguities
  - defining probabilistic risk(s) with greater certainty
  - current unknown rules of gene-gene interactions or lifestyle/environmental factors in increasing or reducing risk(s)
  - ethical issues: privacy, disclosure, discrimination

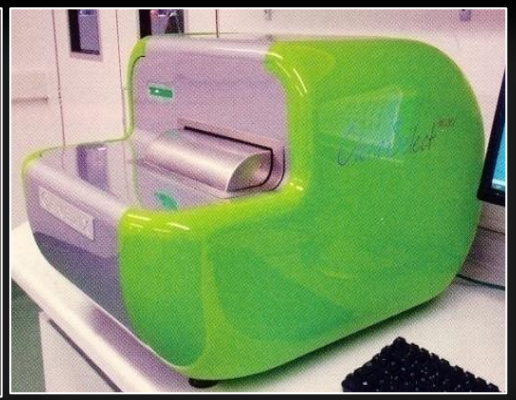
Disruptive Innovation in Healthcare: Redefining the Value Equation in Healthcare

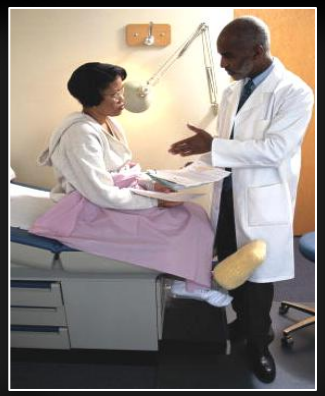


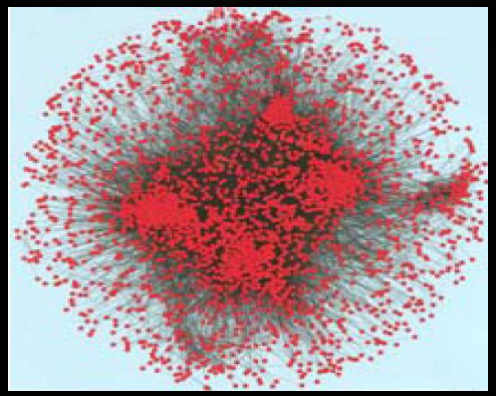
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches

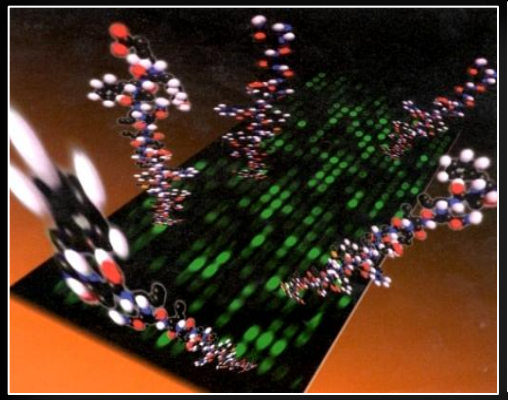


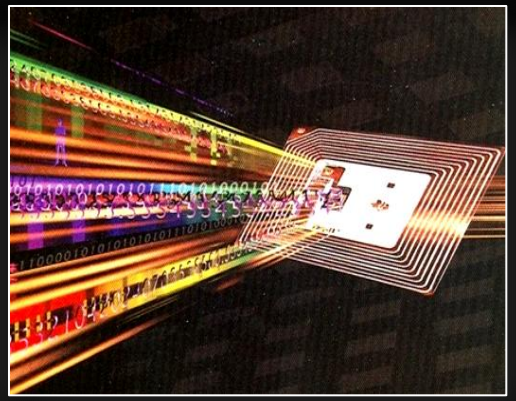












Biospecimens and Molecular Pathway Analysis

Biomarker Validation and Multiplex Assays

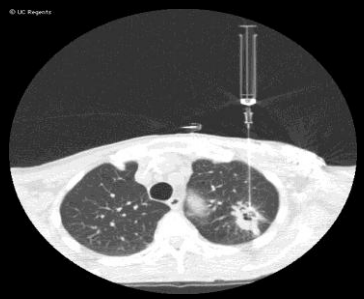
Instrumentation and Informatics

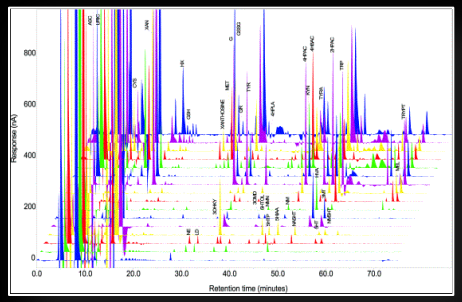
Clinical Impact and Patient Monitoring

The Poor Performance Record of Biomarker Discovery and Validation

- ‘publish and vanish’
  - over 120,000 claimed biomarkers or biomarker combinations (biosignatures)
  - less than 100 molecular diagnostics in clinical use or advanced validation trials
- literature dominated by anecdotal studies
  - academic laboratories
  - lack of standardization: biospecimens to analytical platforms
  - small patient cohorts and insufficient statistical power
  - poor replication and confirmatory studies
- widespread lack of understanding of regulatory requirements in academic research community
  - GLP, GMP, Records, RUO instruments versus Clinical Use
  - technical complexities of multiplex assays
  - new regulatory oversight (IVDMIAs)

Building Large Scale, Standardized Resources for Biomedical Research





- rigorously phenotyped/matched/consented disease and normal specimens
- biobanking: leadership and national policies to create a vital research resource
- standardization of pre-analytical and analytical methods
- standardized data ontologies and formats for large scale datasets/federated databanks

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

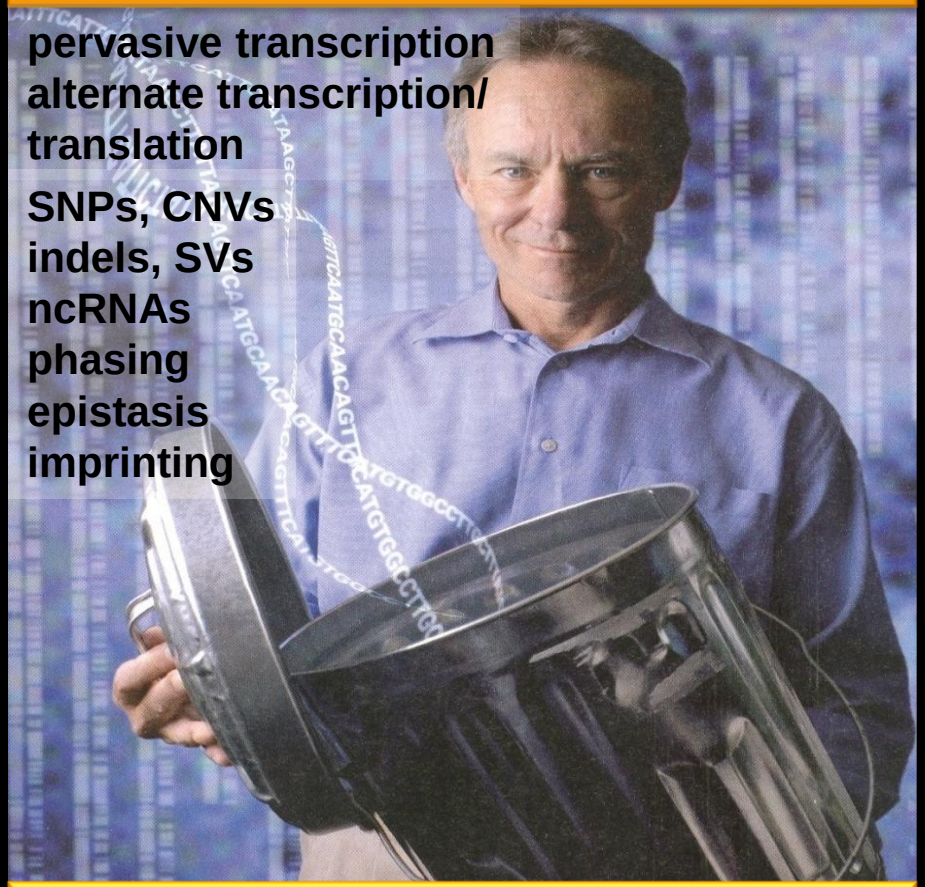
Target	# Patients Screened	# Eligible Patients	# Centers	# Countries
EML4 ALK^{+}: lung cancer*	1500	82	9	1
HER2^{+}: gastric cancer**	3803	549	122	24

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

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

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

Junk No More!

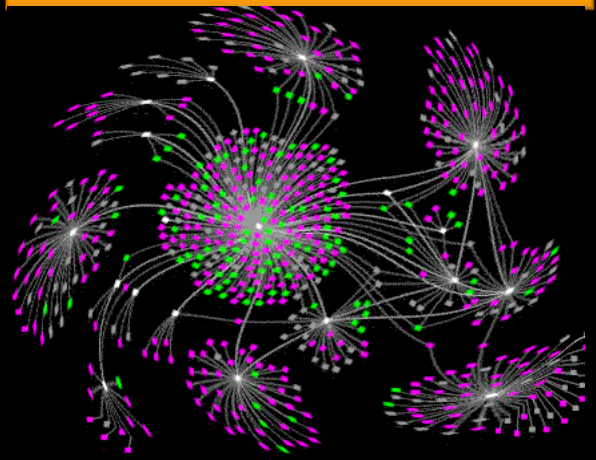


pervasive transcription
alternate transcription/ translation

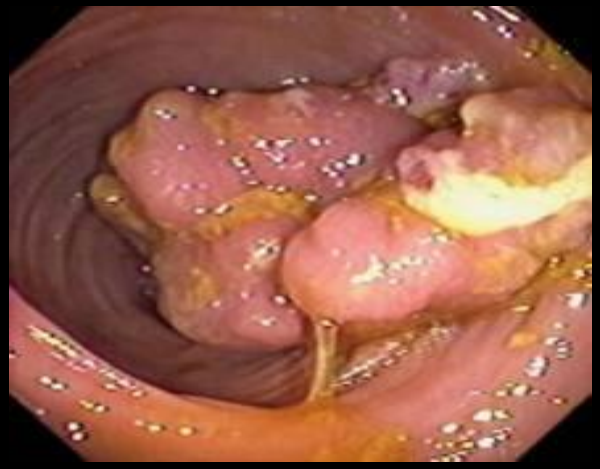
SNPs, CNVs
indels, SVs
ncRNAs
phasing
epistasis
imprinting

recognition of increasing organizational and regulatory complexity

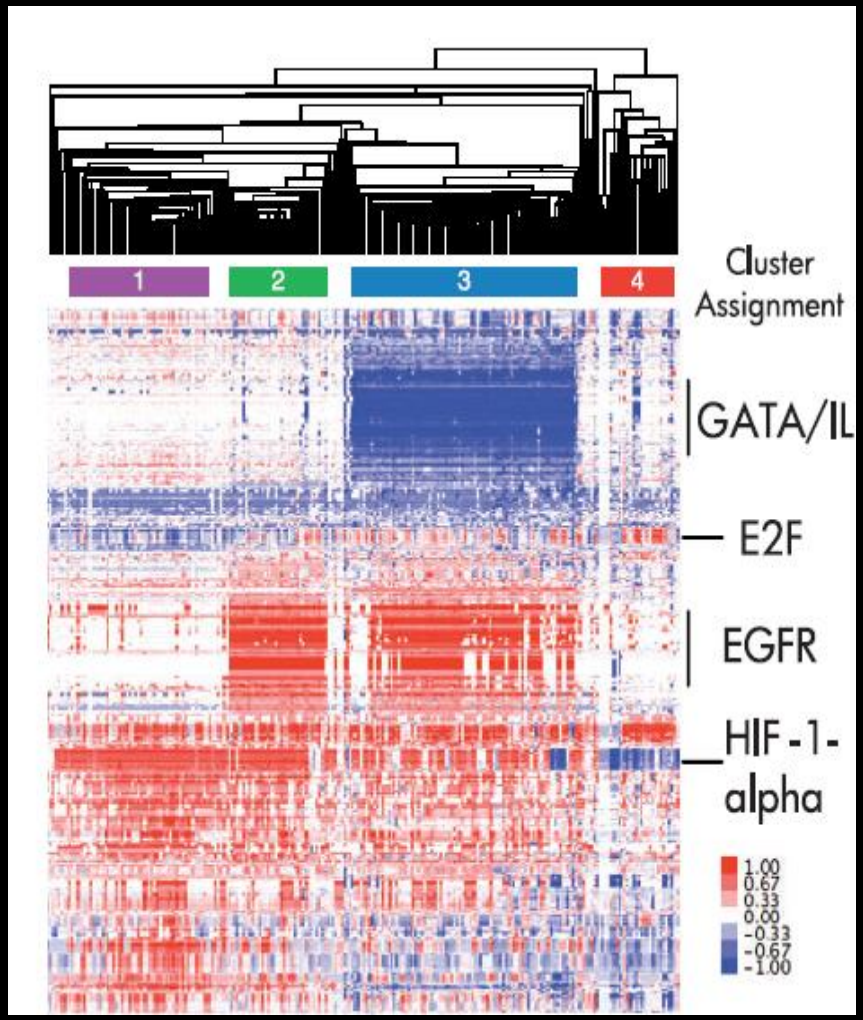
Molecular Interaction Networks



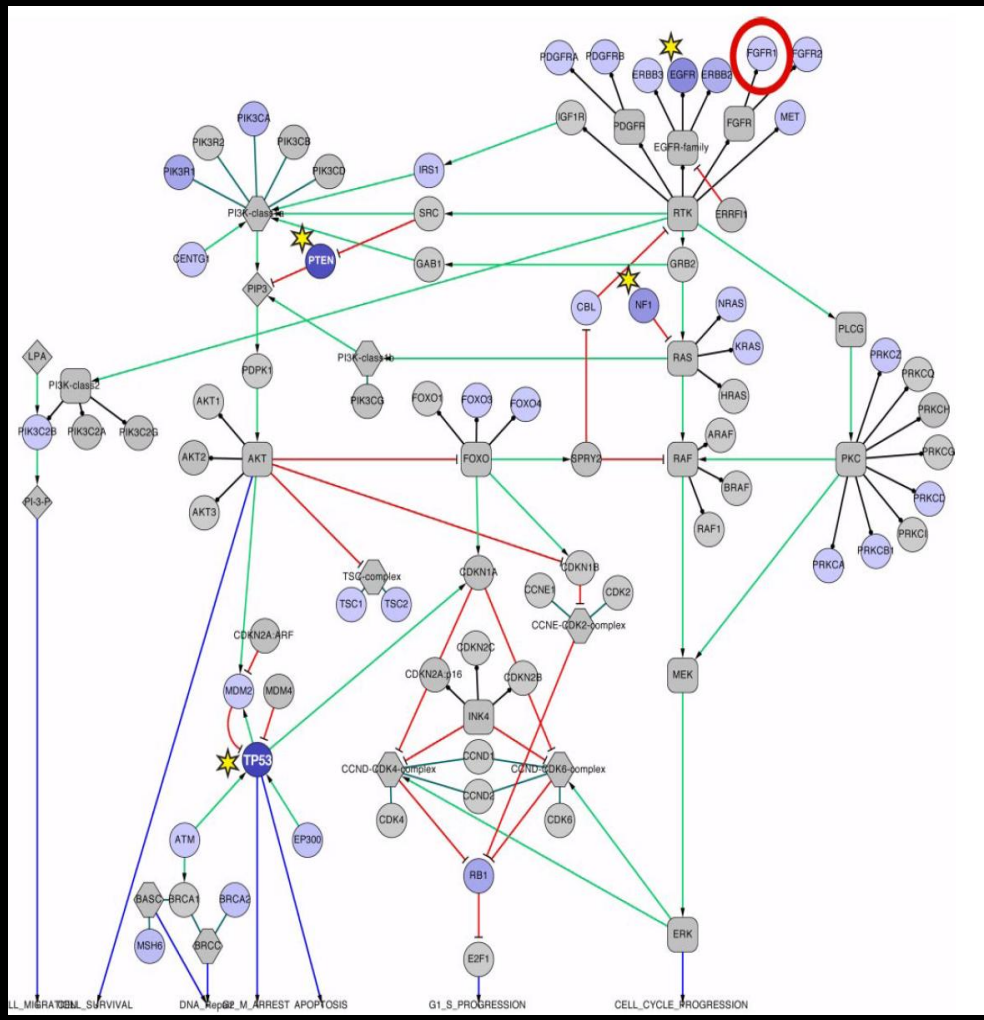
Disease Perturbations



Mapping Modules, Pathways and Subnetworks in Biological Systems: The TCGA Glioblastoma Multiform Dataset and Protein Interaction Networks

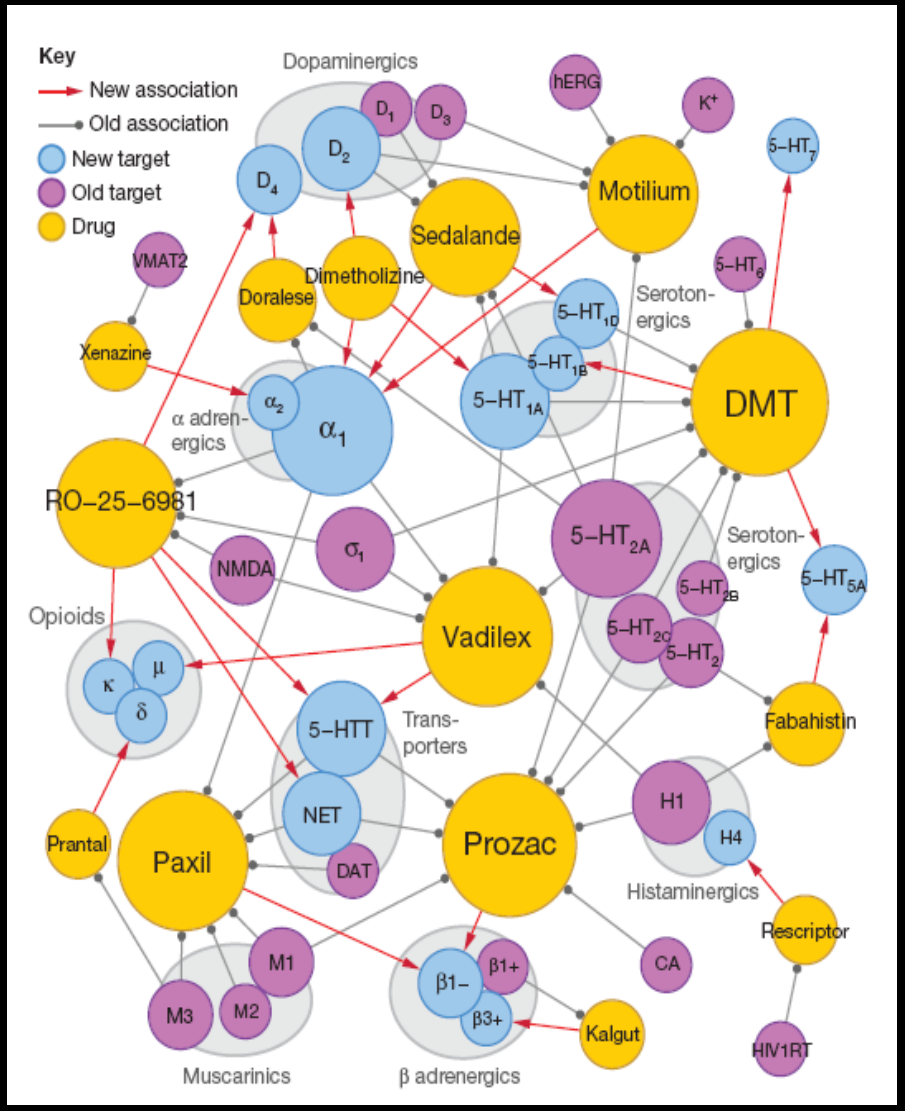


From: C. J. Vaske et al. (2011)
Bioinformatics 26, i237



From: J. H. Morris et al. (2010)
Molec. Cell. Proteomics 9, 1703

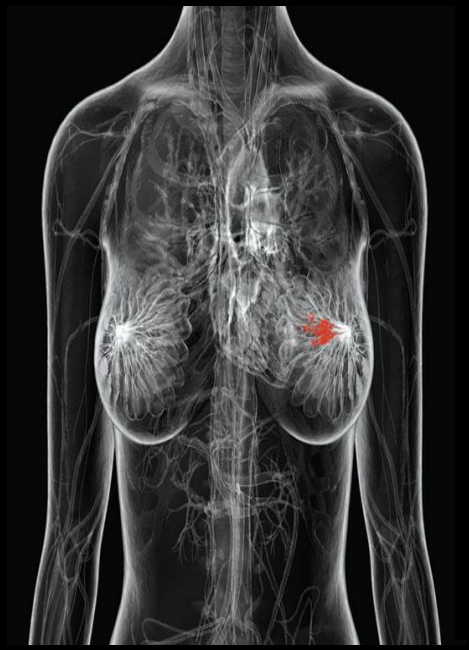
Network Pharmacology



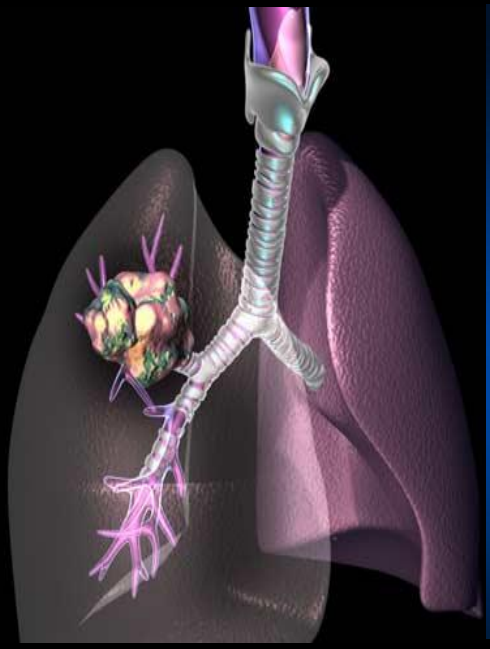
From: M. J. Keiser et al. (2011) Nature 462, 180

- analysis of Rx action in context of network topologies and dynamics
- same drug: interaction with multiple targets
- same target: interaction with multiple drugs
- mapping structural chemotypes to specific pathways and subnetworks for targeted (poly)pharmacology

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

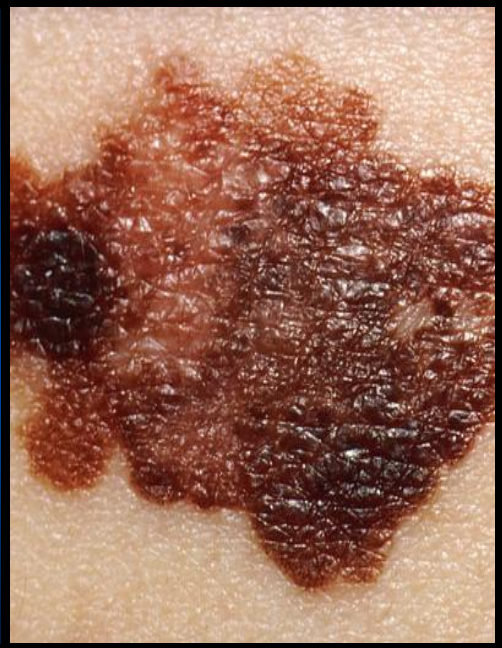


Her-2+
(Herceptin)



EML4-ALK
(Xalkori)

KRAS
(Erbitux)
(Vectibix)



BRAF-V600
(Yervoy)
(Zelboraf)

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

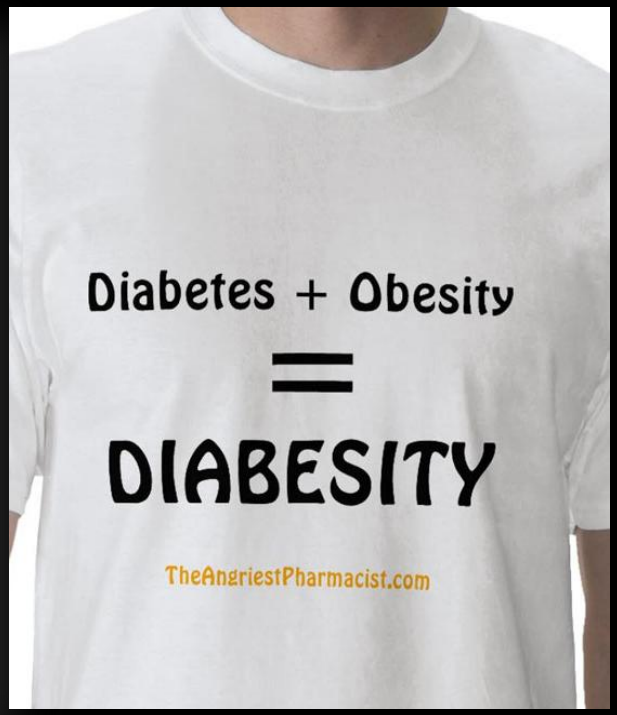
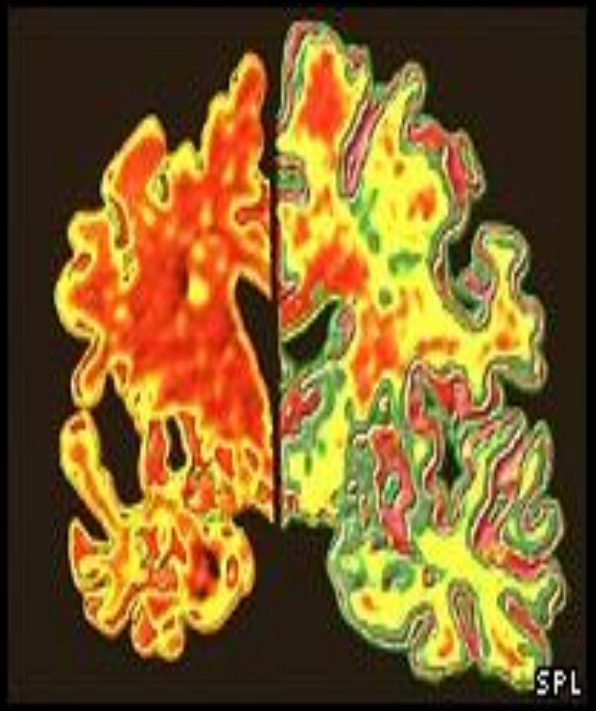
From: N. Wagle et al. (2011) J. Clin. Oncol. 29, 3085

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

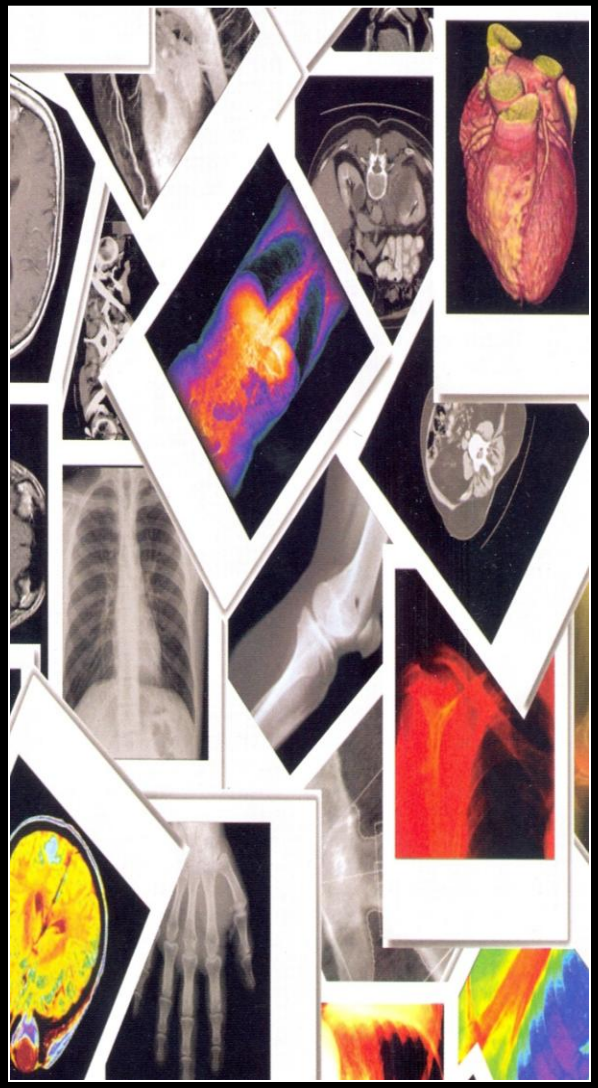
Rethinking Approaches to Rx Discovery for Advanced Chronic Diseases

Is There a Fundamental Imbalance in Investment in Diagnostics Versus Therapeutics?

Opportunities and Challenges Posed by 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

How Much New Technology Can We Afford?



Back To The Future
Balancing Public Expectancy with Economic Realities

Cost and Quality of Care

Chronic Disease and Quality-of-Life

Demographics

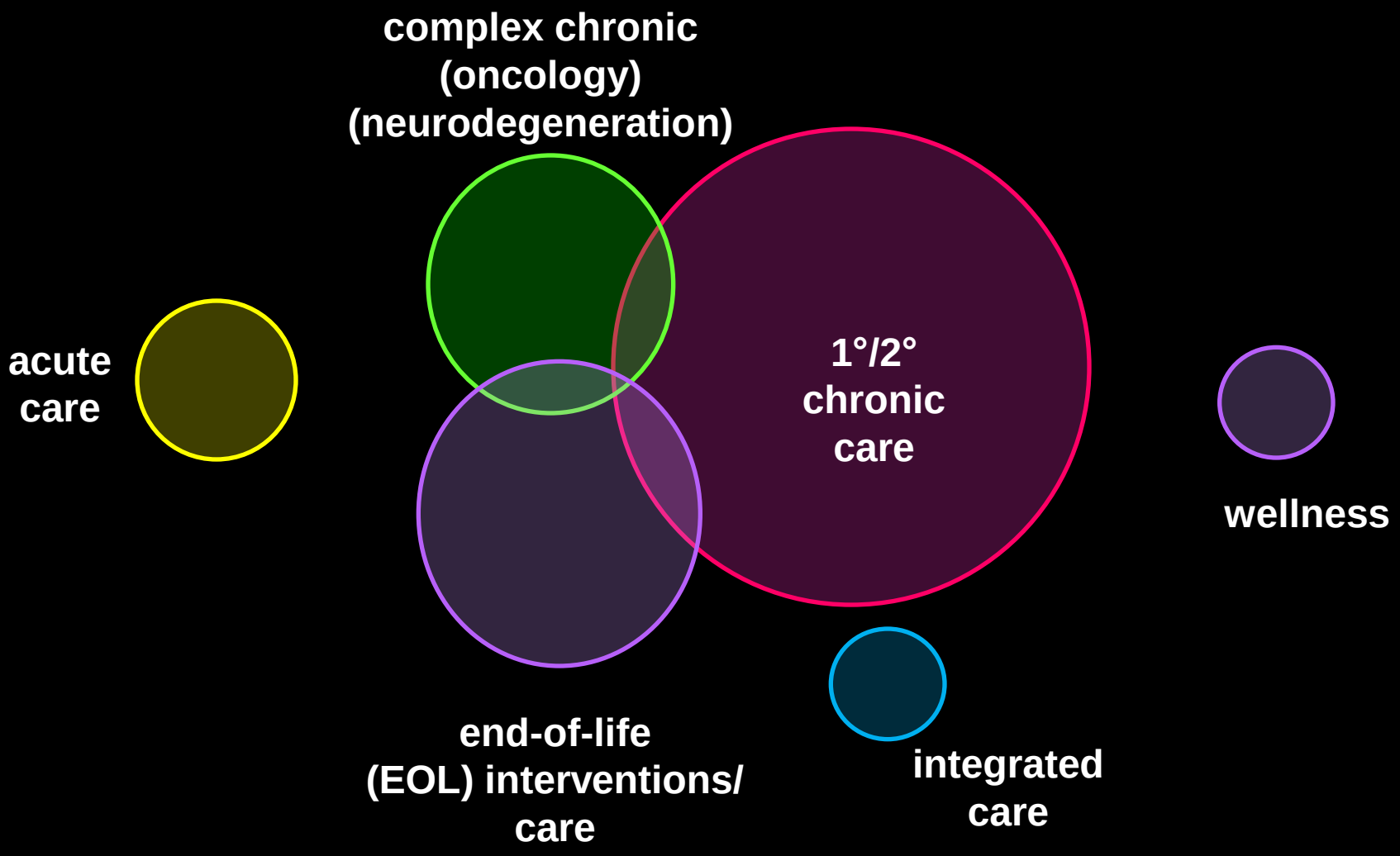
Phase III Studies Comparing Chemotherapy With or Without Bevacizumab as First-Line Therapy for Advanced Epithelial Cancers

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

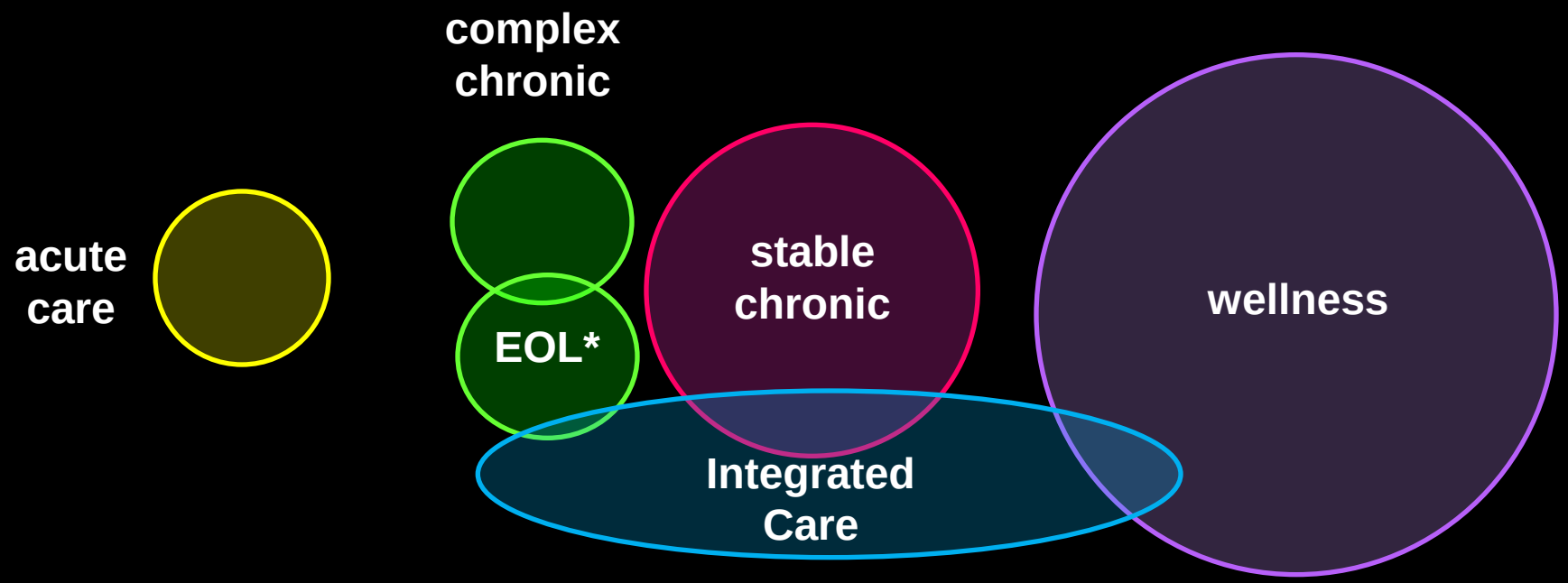
*Statistically significant

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

Categories of Care and Cost: Today



Recalibrating Categories of Care and Cost: Bending the Cost and Quality Curves



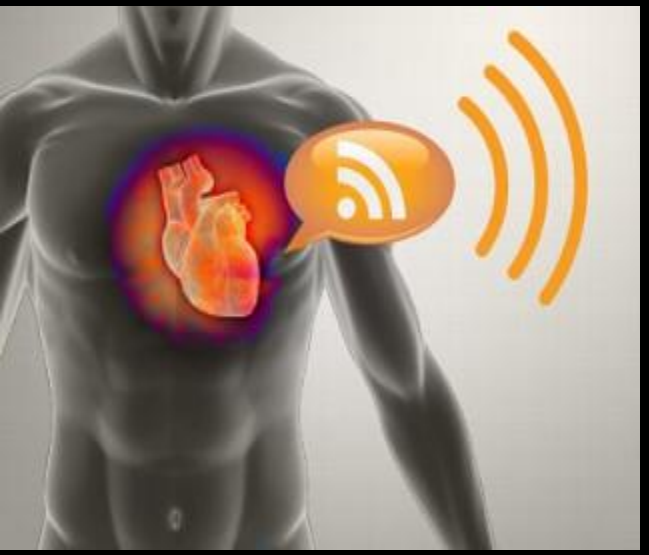
*EOL = end-of-life care

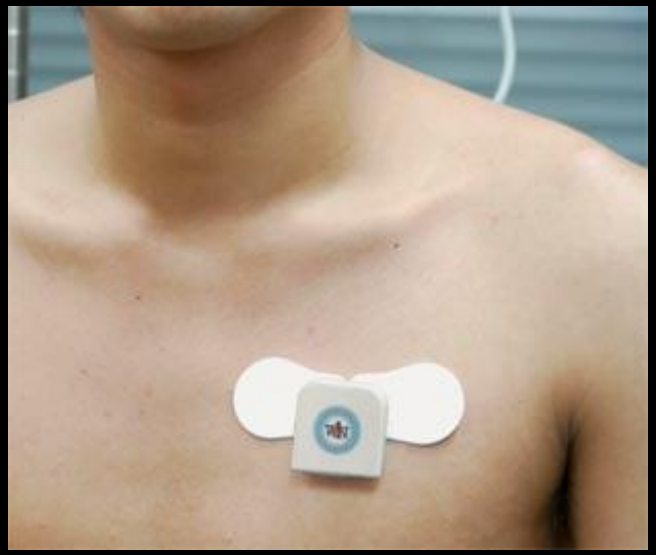
The Rise of m.(mobile)Health and e.Health

Individual Biosignature Profiling Via Sensors and Devices

Remote Health Status Monitoring

Wireless Devices and Remote Monitoring of Health Status and Rx Compliance





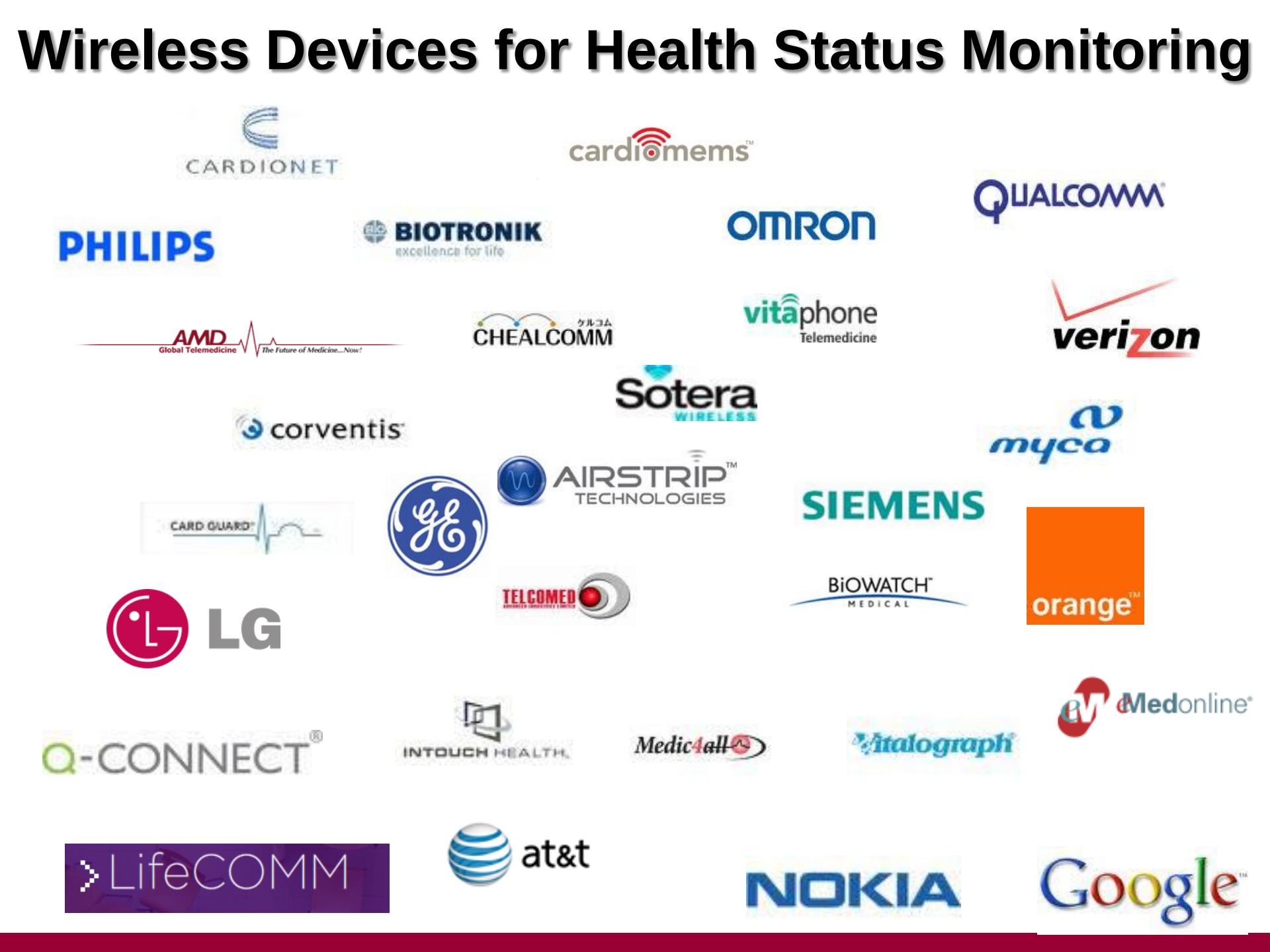
m.Health

Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

Wireless Devices for Health Status Monitoring



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


HealthMap
Global Disease Alert Map
English | Español | Français | Português | Русский | 中文 | بية
NEJM H1N1 Case Reports | About | Twitter | Blog | Donate | Store | Feedba
Map
Satellite
Earth
Terrain
Greenland
Iceland
Россия
Russia
Canada
Mongolia
China
North Atlantic Ocean
Algeria
Libya
Mali
Niger
Chad
Sudan
Brazil
Perú
Bolivia
Chile
Argentina
Angola
Madagascar
South Pacific Ocean
South Atlantic Ocean
Indian Ocean
Australia

The Changing Roles of Consumers (well)/Patients (ill)

past

- passive role and medical paternalism
- reliance on physicians to maintain health records
- reliance on physicians as primary source of trusted medical information
- isolated illness episodes and annual check-up

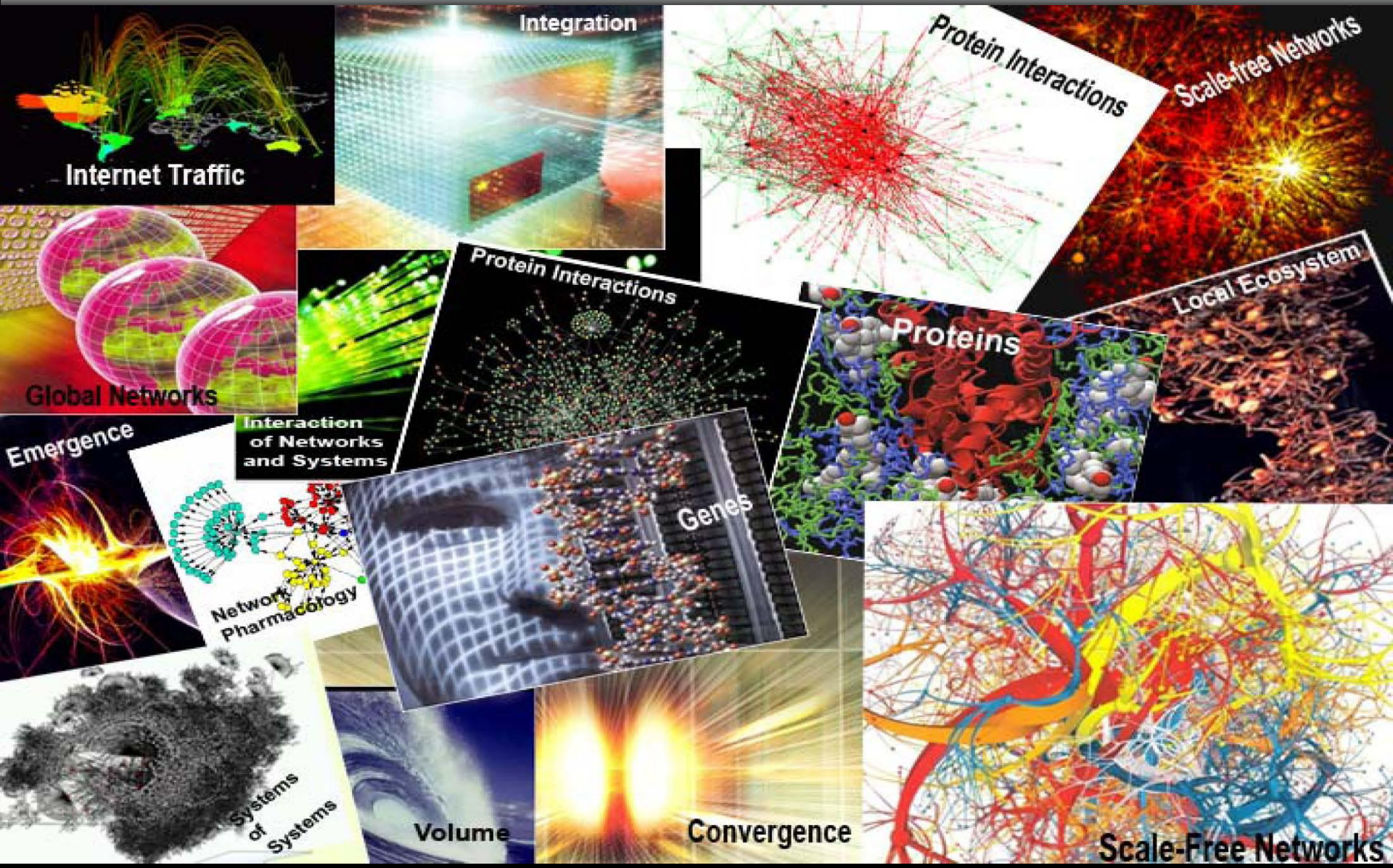
future

- increasingly active managers of personal health
- increasing knowledge of genetic risks, Rx actions
- access to own digital health records
- extensive use of internet, social networks for medical information
- real time, remote monitoring of health and wellness with digital devices

e.Health, m.Health and Patient Empowerment

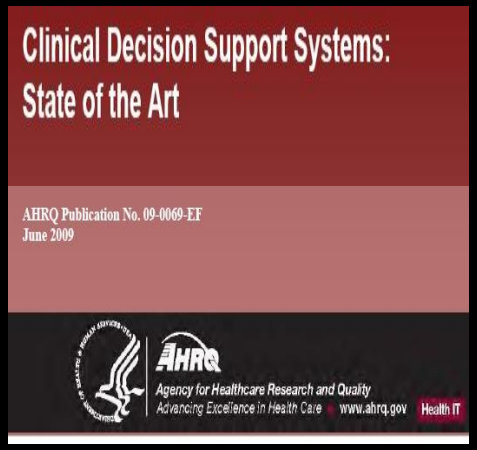
- greater access to information on treatment options
- generation-dependent ease and expectations for shared role in decisions
- new doctor-patient relationships
- new ‘cultural’ skills for healthcare professionals
  - less paternalism
  - patient education
- major gaps in professional familiarity and competencies in molecular medicine

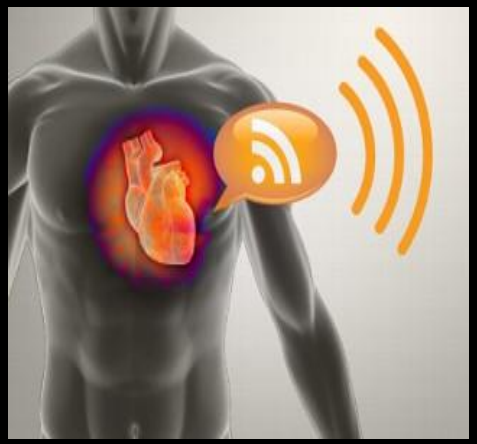
Data: The Fastest Growing Resource on Earth

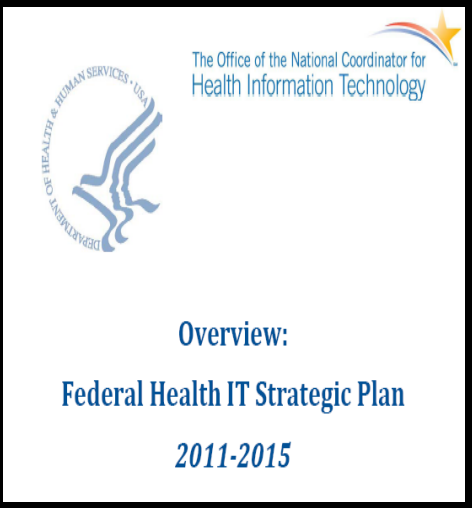


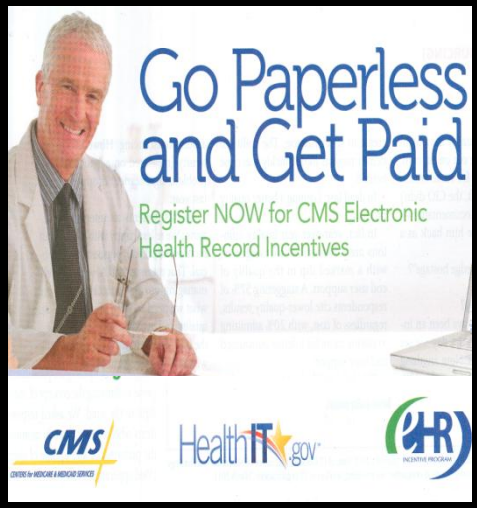
A Learning Healthcare System

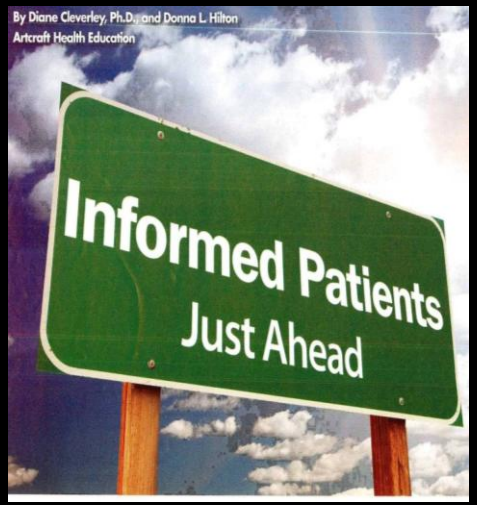
Proliferation of Clinical Computational Systems











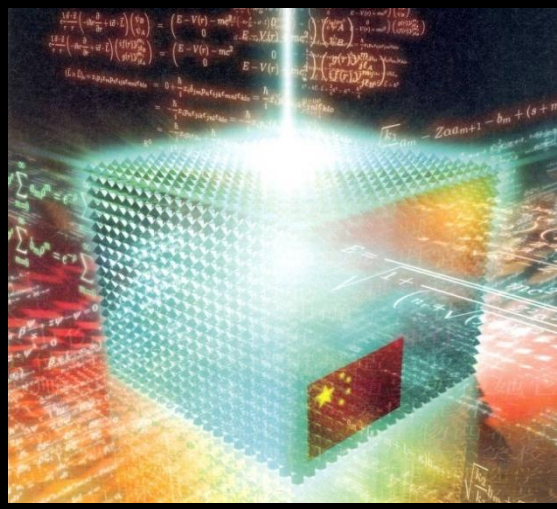
HITECH Mandates	Incentives	EHR and Smart Cards	Informed Consumers/Patients

Managing “Mega-Data” in Biomedicine

volume

computational scale

global networks



bench to bedside: multiscale heterogeneity

integration

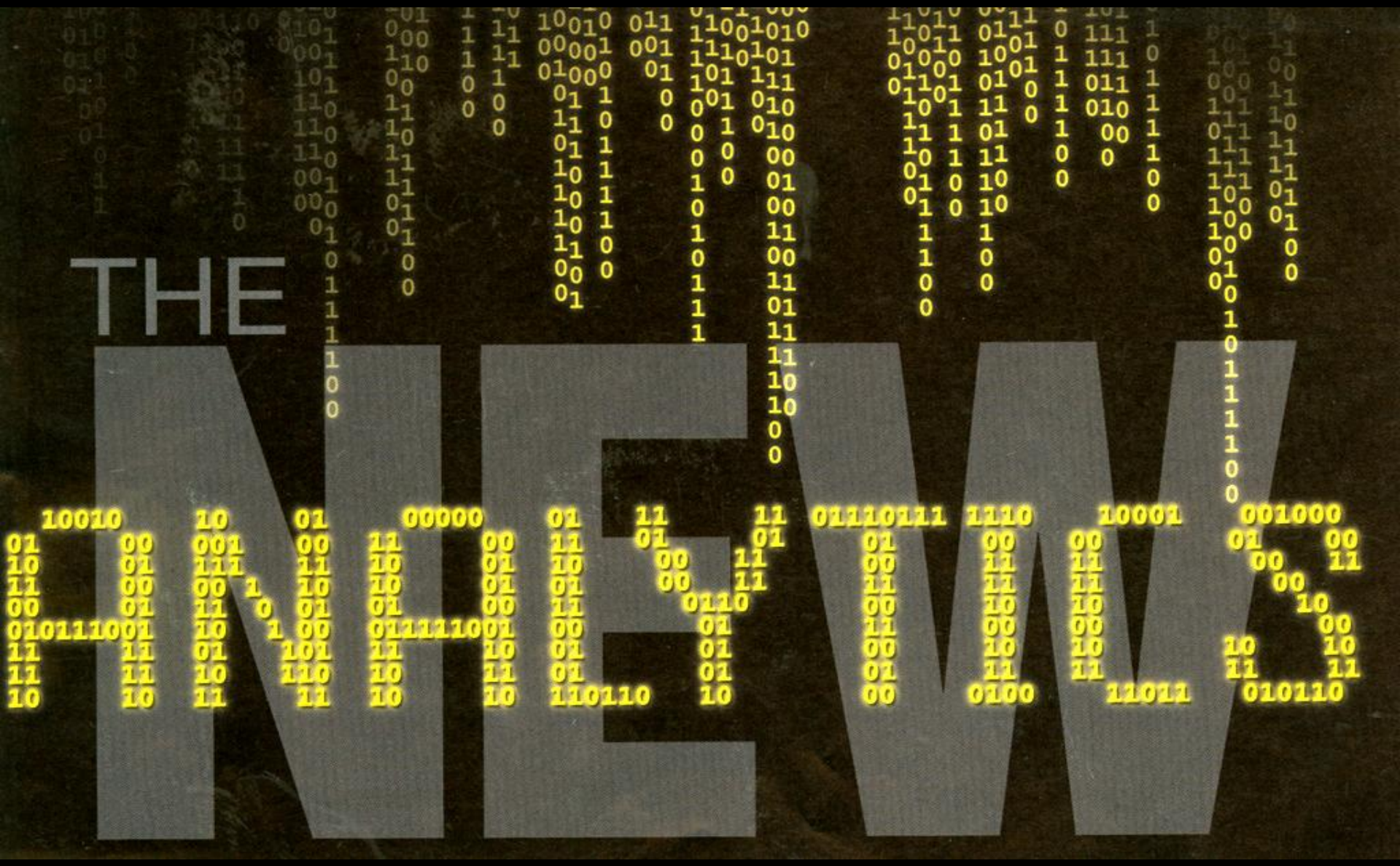
Managing Massive Data

Standards for Data Reporting and Database Design

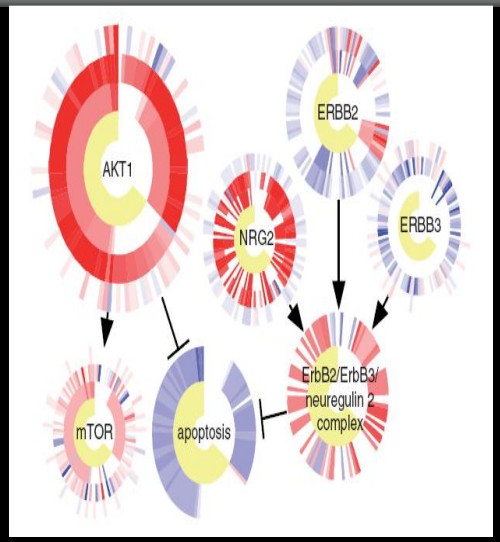
Interoperability of Databases
Across The Continuum from Discovery to Patient Care

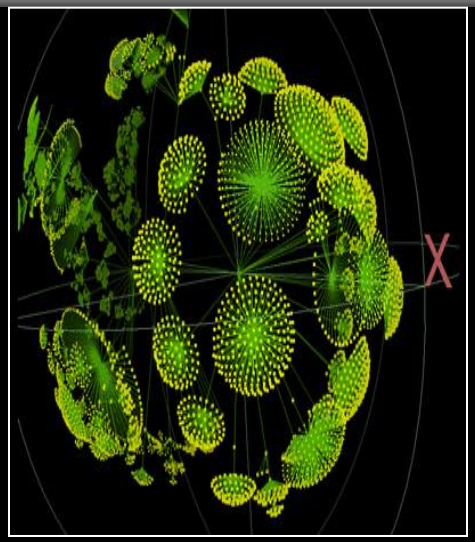
New Analytics and High Performance Computing

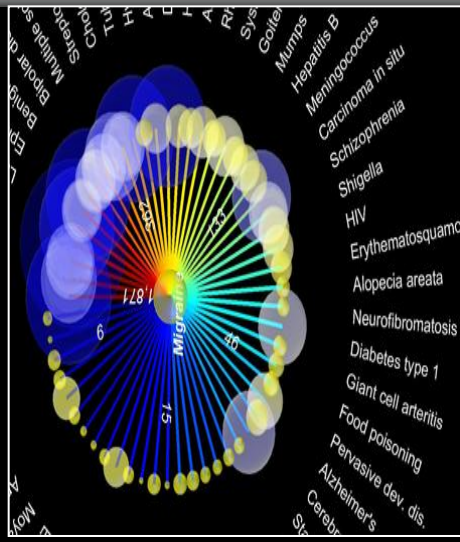
The Only Valuable Data is Validated, Actionable Data

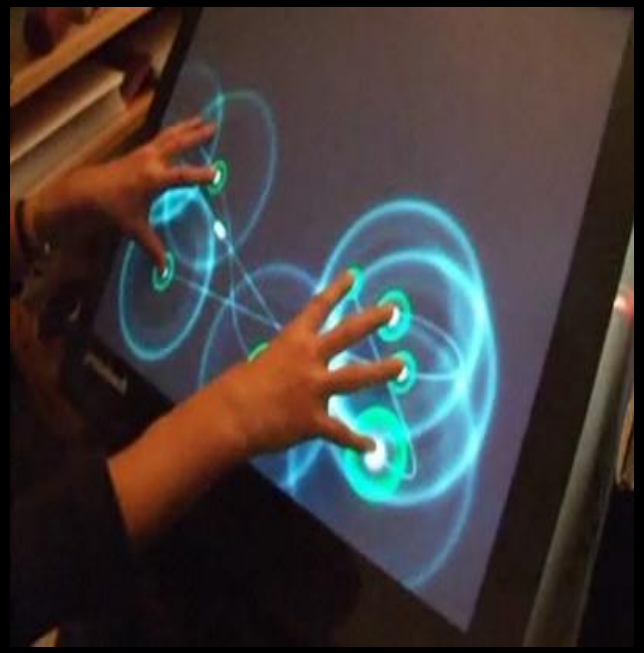


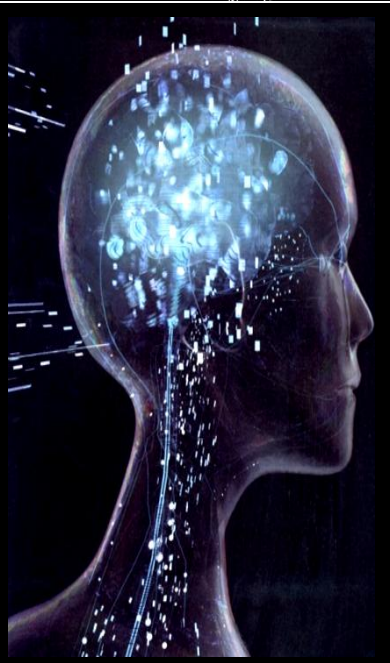
New Visualization Tools, Interactive Interfaces and Rapid Customization Formats



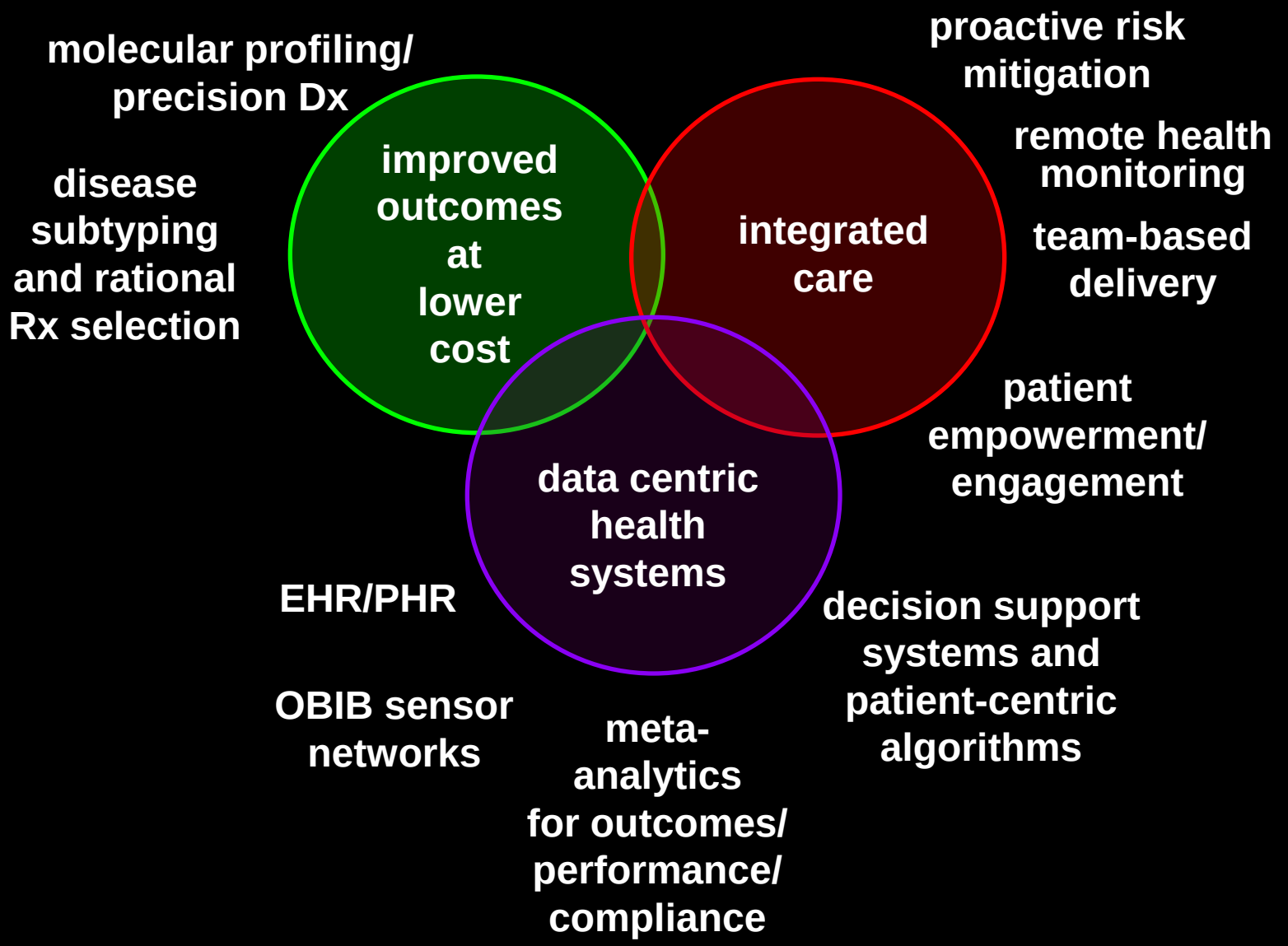








New Value Propositions in Healthcare: Improved Quality and Outcomes at Lower Cost



Building Knowledge Networks to Improve Individual Health and Sustainable Healthcare Delivery

ACKM and superior decisions: improved care, lower cost, better outcomes

on-body, in-body sensors/devices

molecular profiling of patients (personalized medicine) and global disease surveillance (public health)

mapping the dysregulation of biological networks in disease

The Innovation Ecosystem for Biomedical R&D and Healthcare Delivery

- molecular medicine
  - precision Dx and rational Rx
  - regenerative medicine
- engineering-based medicine
  - sensors and remote health status monitoring
- information-based medicine
  - meta-analysis of massive data
  - new decision support algorithms
- networked medicine
  - expertise networks and integrated care
- consumer/patient engagement
  - increased personal responsibility for wellness
- realignment of role of MD in healthcare
  - matching skills to needs
  - education curricula

Disruptive Innovation Demands Boldness!

- the failures of timid incrementalism and the retreat from complexity

- “It’s not because things are difficult that we dare not venture. It’s because we dare not venture that they are difficult.” Seneca