ASU COMPLEX ADAPTIVE SYSTEMS
ARIZONA STATE UNIVERSITY

Molecular Medicine and Digital Medicine: Disruptive Technologies in the Future Evolution of Healthcare

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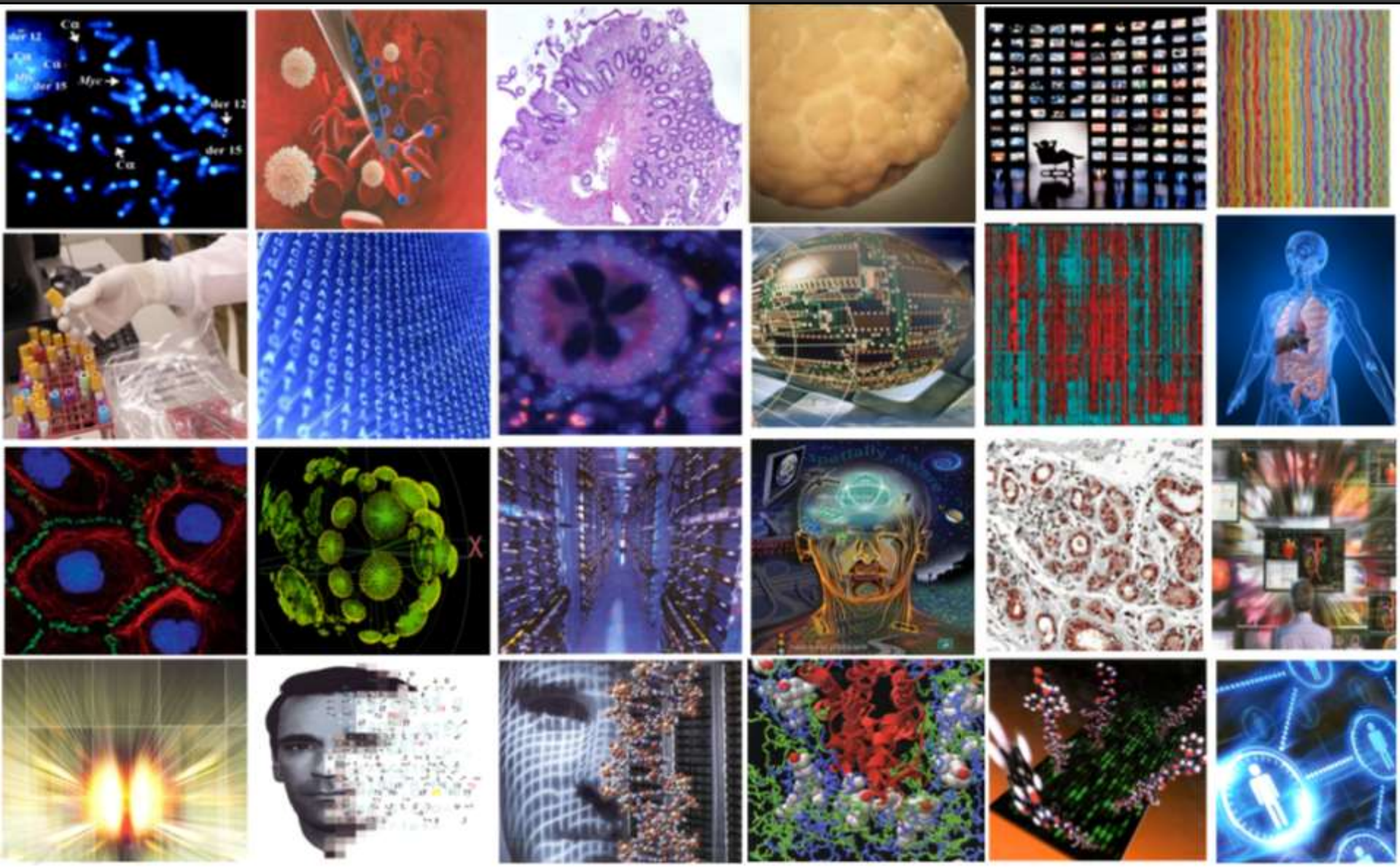
E-health and Telecom in Healthcare IEEE WTS Conference

Ocotillo Golf Resort at Ocotillo, Chandler, AZ.
17 April 2013

Slides available @ http://casi.asu.edu/



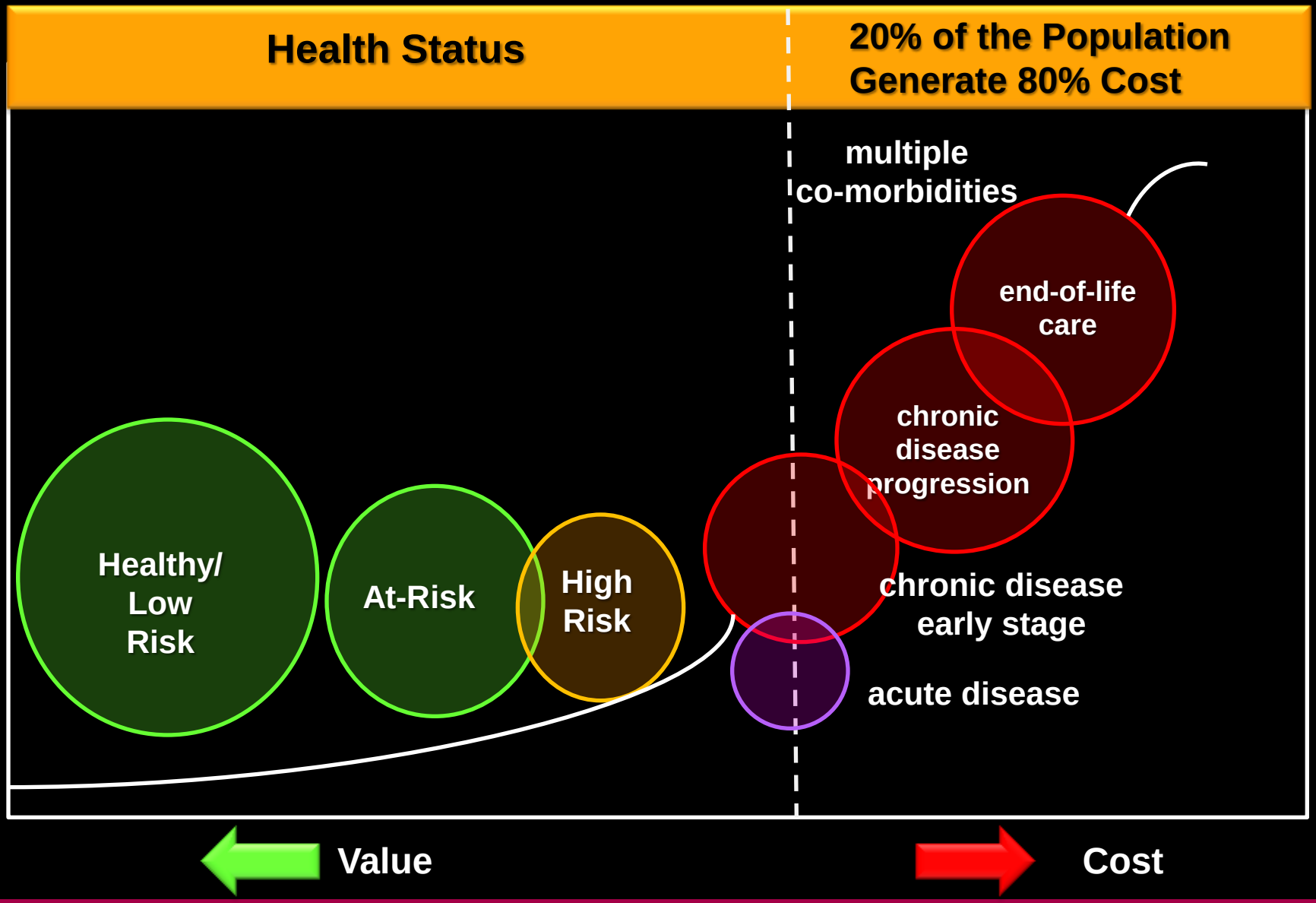
Healthcare: An Expensive Menu Without Prices

Managing the Demands of an Aging Society and Chronic Disease Burden in an Era of Economic Constraint

Shift From a "Do More, Bill More" Healthcare System to Managing Individual Risk for Improved Health Outcomes and Cost Control

Sustainable Health: Societal (Economic) and Individual (Wellness)

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



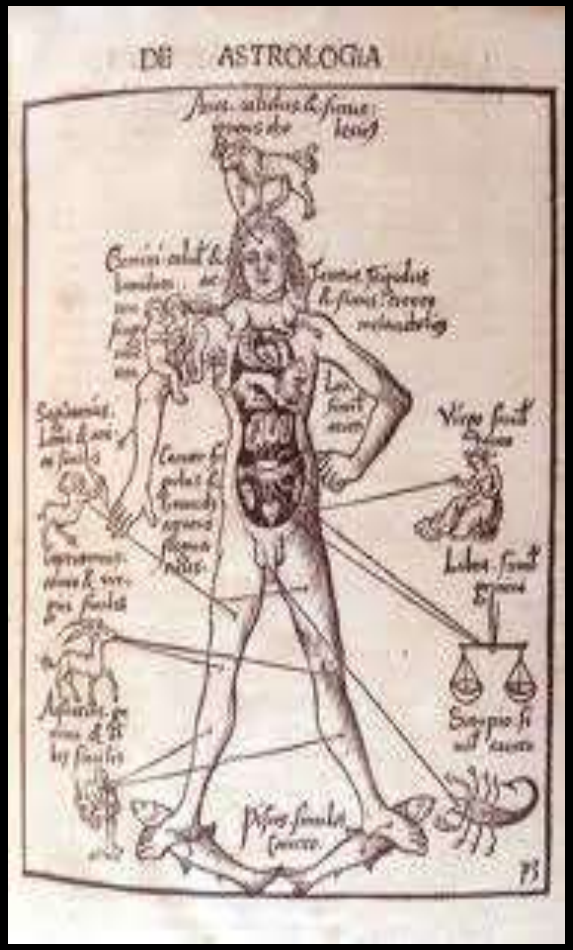
New Value Propositions

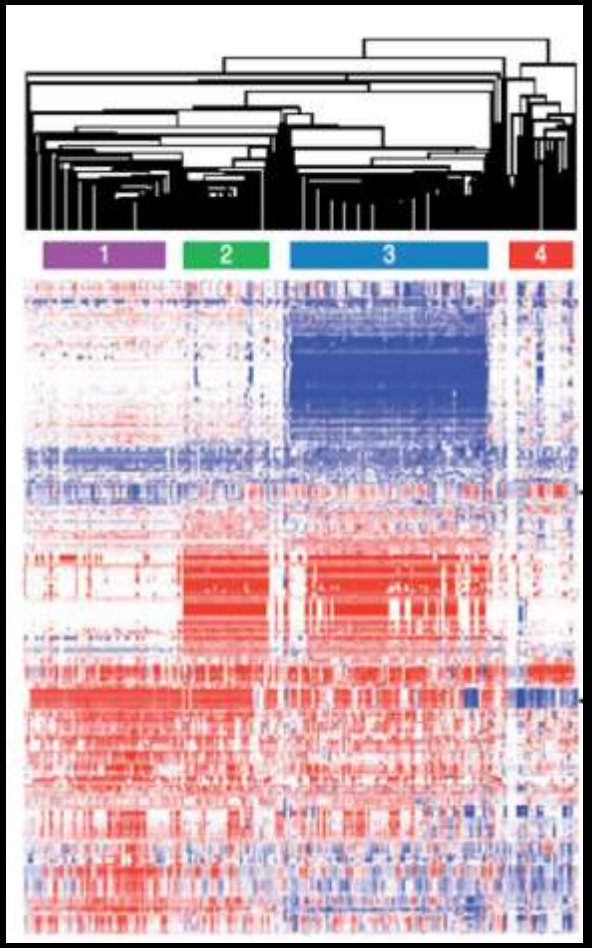
Emergence of a New Health Information Ecosystem
via
Convergence of Molecular Medicine, Digital Networks and Social Media

Shift from Reactive, Incident-Centric Care
to
Proactive Engagement and Continuity of Care
to Mitigate Individual Risk

From “One Size Fits All” Treatment Approaches
to Individual Molecular Profiling and Precision (Personalized) Medicine

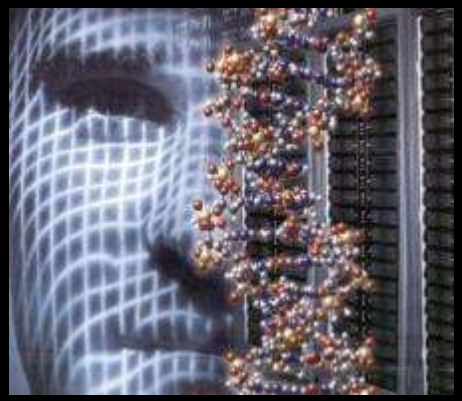
Medical Progress:
From Superstitions to Symptoms to Signatures



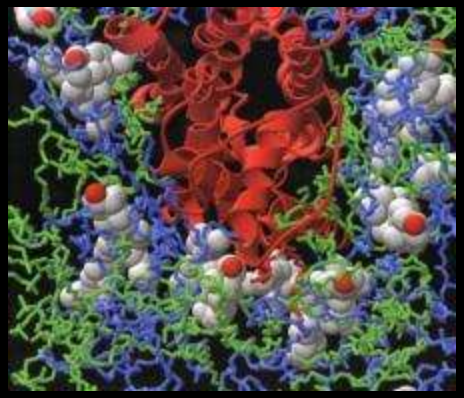


Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

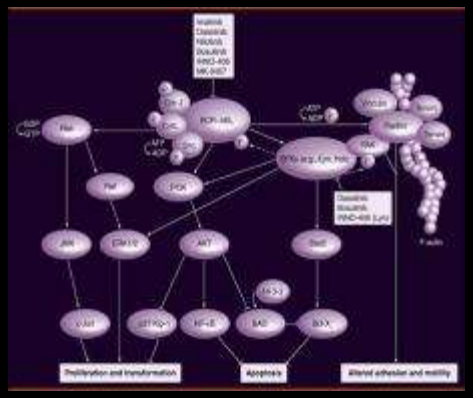
Genomics



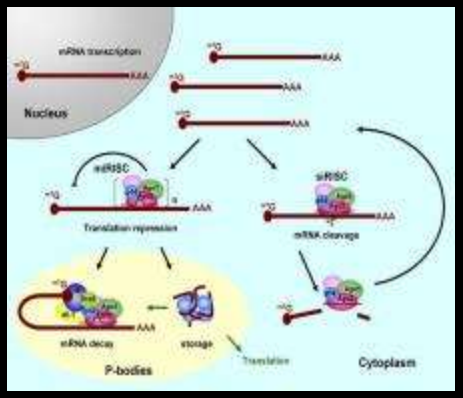
Proteomics

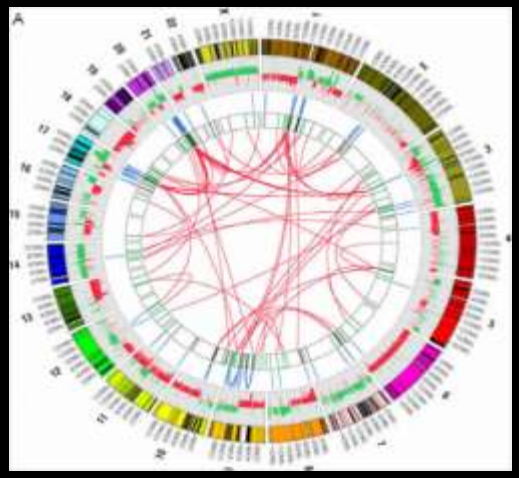


Molecular Pathways and Networks



Network Regulatory Mechanisms

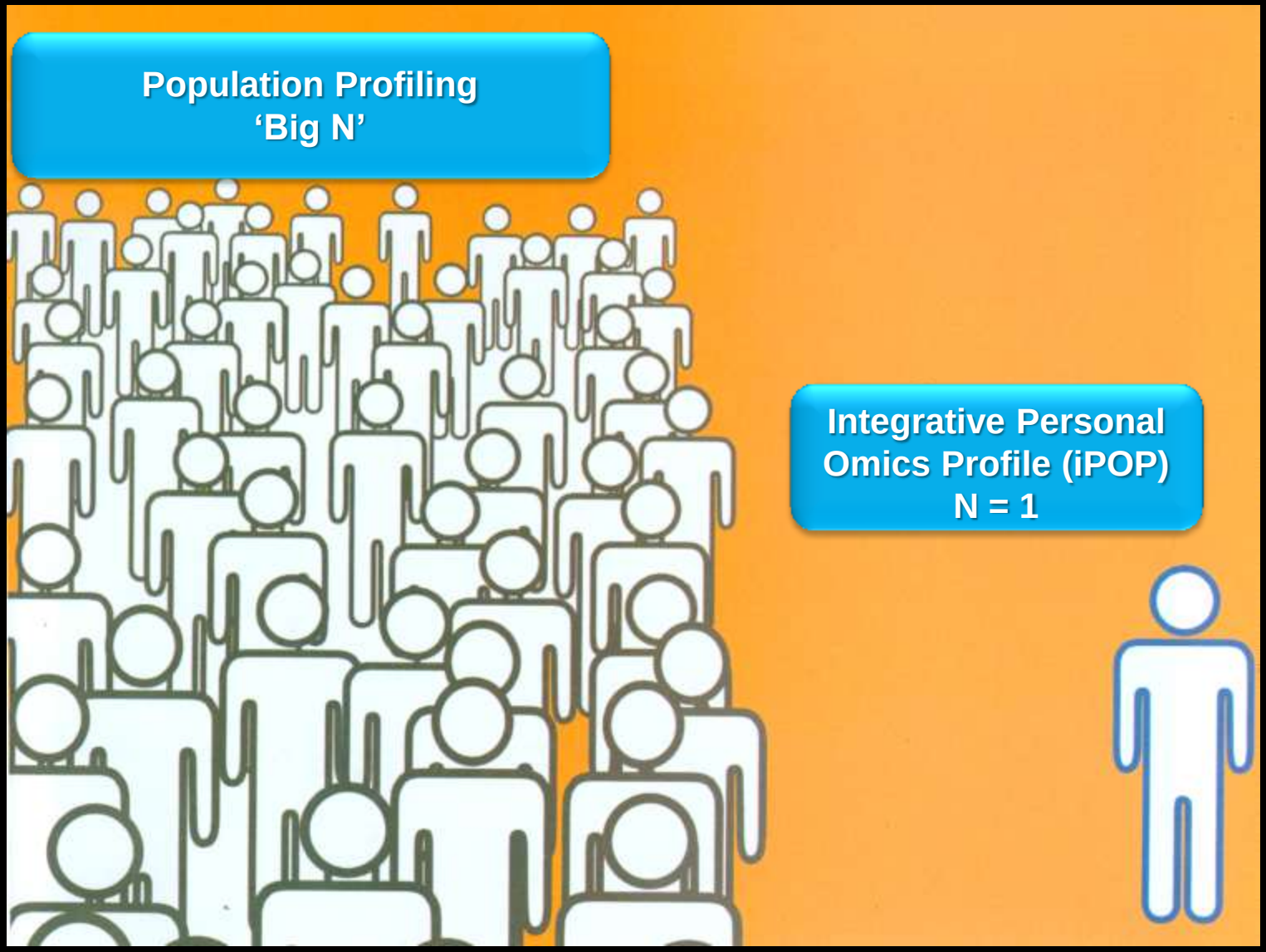




ID of Causal Relationships Between Network Perturbations and Disease

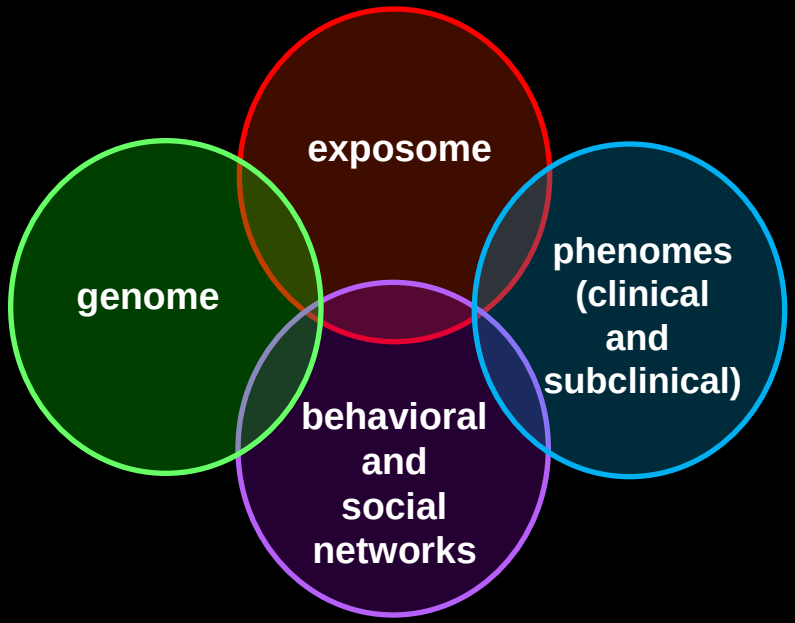
Patient-Specific Signals and Signatures of Disease or Predisposition to Disease

The Integrative Personal Omics Profile (iPOP)



Information-Based Services for Healthcare and Wellness

Precision Profiling of Health Status



Population- and Individual-Datasets

facile integration and analysis of diverse datasets

Actionable Information

risk identification and mitigation

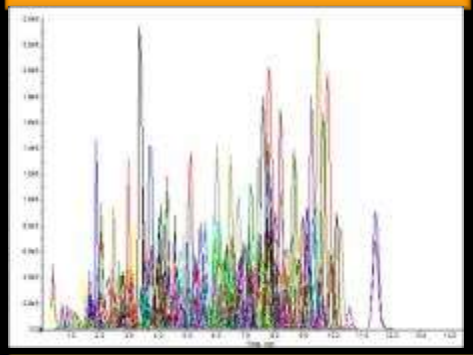
Integrated Care and Wellness

VALUE

The Evolution of Clinical Diagnostic Testing in The Pending 'Omics Era and New Device Technologies

Unianalyte Tests

Multianalyte Tests

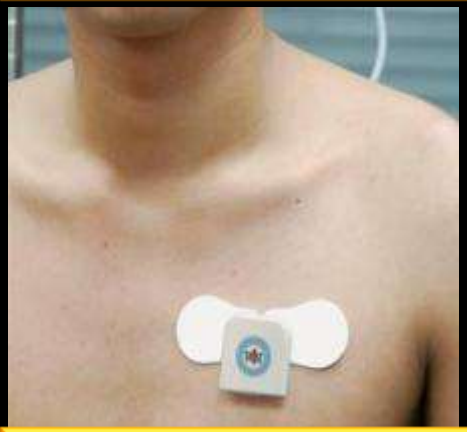


Whole Genome Sequencing

New Regulatory and Reimbursement Policies

Centralized Testing, Large Capital Base Instrumentation

On-Body: In-Body Sensors



Portable and Point of Need Devices

Increasingly Distributed Data Feeds and Real Time Health Monitoring

Will Low Cost Whole Genome Sequencing Change Everything?

Source: Davies, Kevin (2011). The Road to the 1000 Genome. PHT/SLA Spring Meeting

- 1 million genomes x $1,000 = $1 billion
  "It's not even a scary number anymore!"

Lander E. S. (2011) Nature 470, 187-197

The $1000 (or less) Whole Genome Sequence (WGS)

The $? Interpreted WGS

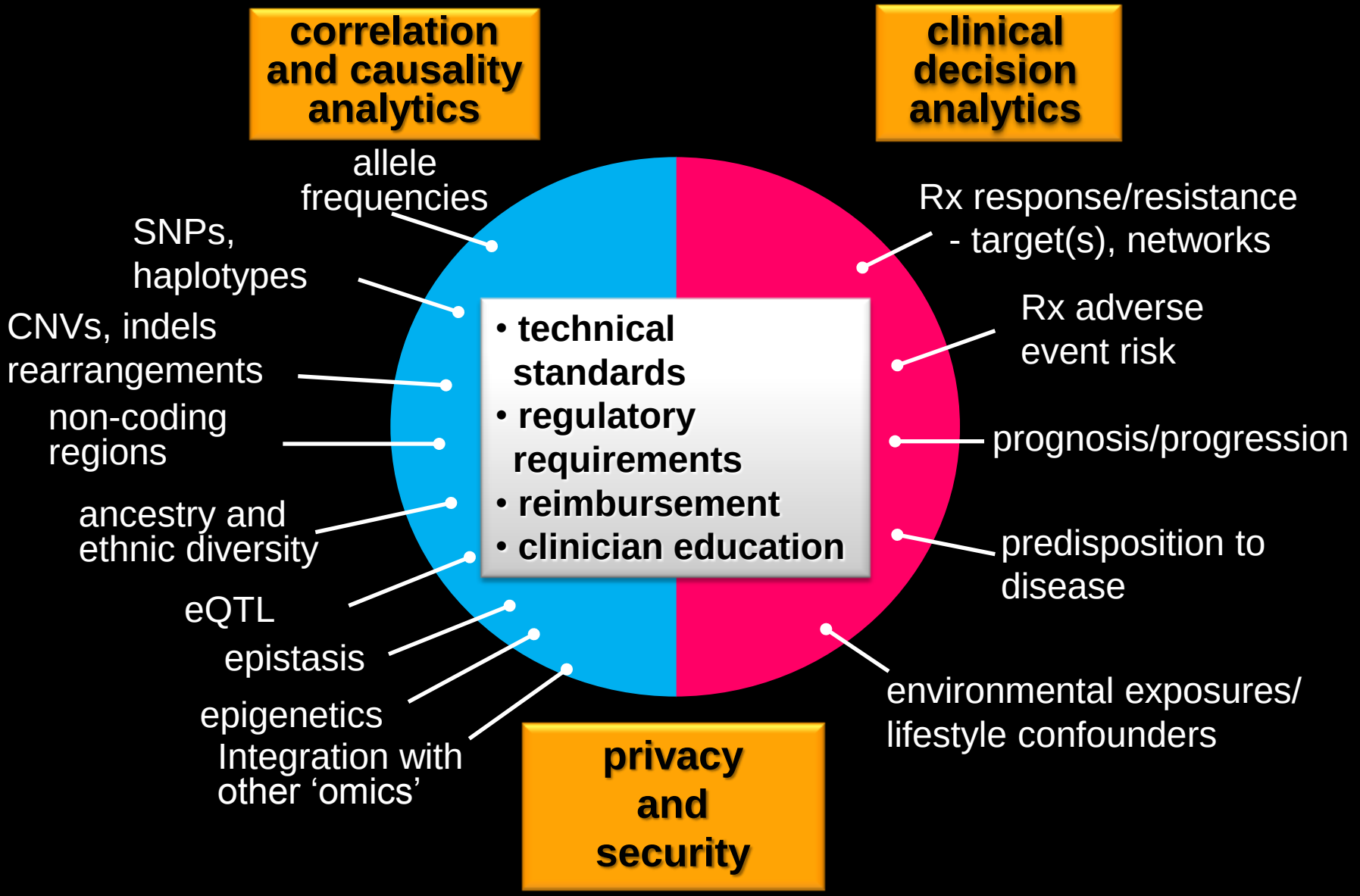
The $? Reimbursed WGS for Clinical Use

Techno-optimism and the Seduction of New Technologies: Omnipresent Hype and Herd Mentalities

From ‘Holes’ to ‘Wholes’ (Heidi Rehm)

- current technical limitations dictate that “hole” exomes/genomes is a more accurate description of status today
- still major challenges in capturing ***complete*** and ***accurate*** WGS

Whole Genome Sequencing and Molecular Medicine



The Scale and Complexity of Human Genome Variation

- individual genomes on average carry:
  - 3.5 -4.0 million SNV, 1000 CNVs (>450bp)
  - 3-4 hundred indels
  - 200-500,000 private SNV
  - 20-400 loss-of-function variants
- estimated up to 60 new inherited mutations/generation
  - gender dependent transmission: maternal 15/paternal 25-45
  - impact of paternal age at fertilization

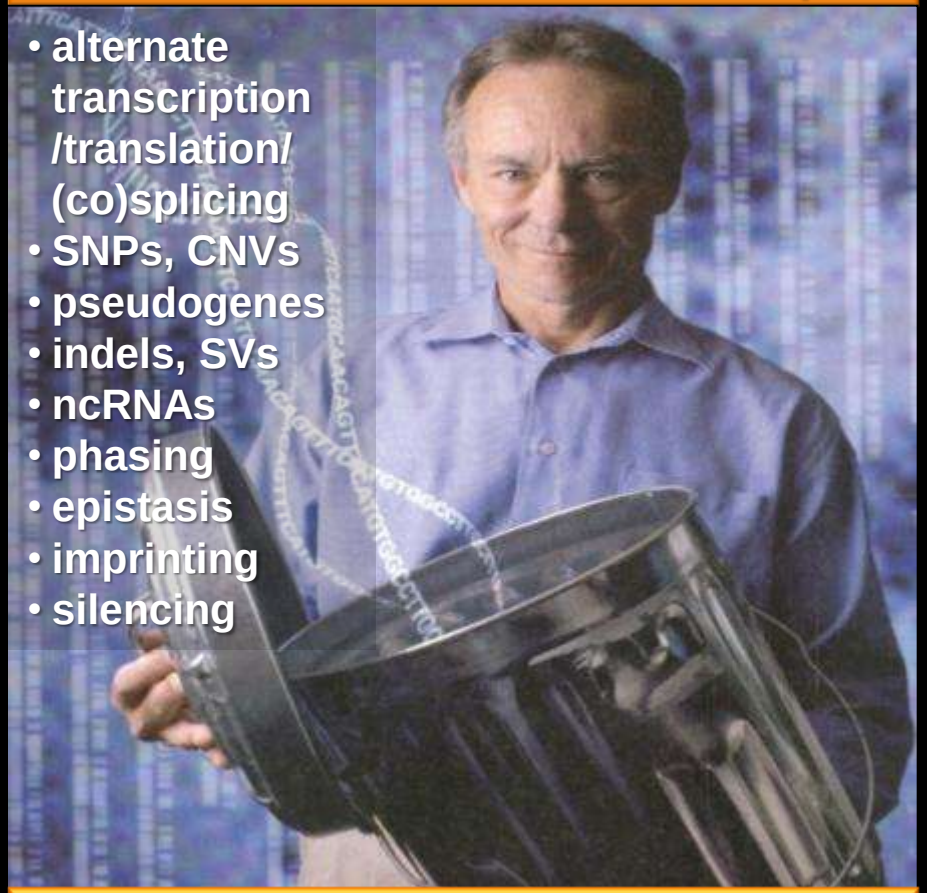
sequencing accuracy of 99.99%
=300,000 misreads per genome

Genes For ….
The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective

The Over-Simplified Perspective That Whole Exome-and Whole Genome-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis

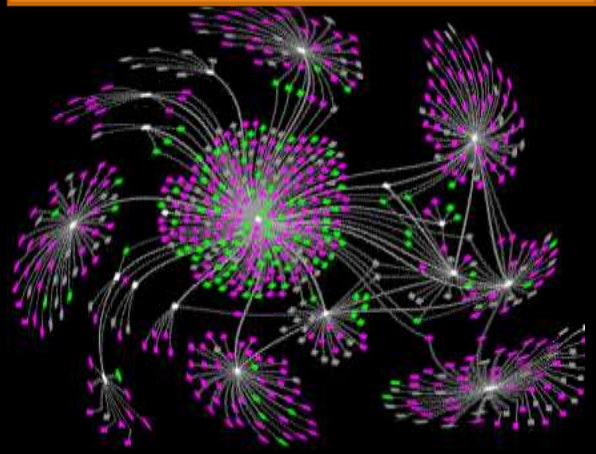
Individual Variation, Genome Complexity and the Challenge of Genotype-Phenotype Predictions

Junk No More: Pervasive Transcription

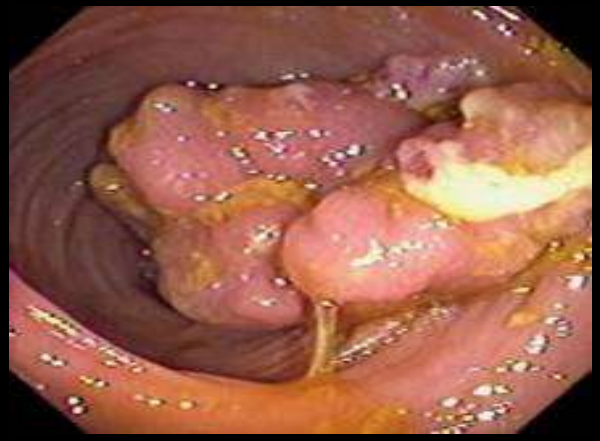


recognition of genome organizational and regulatory complexity

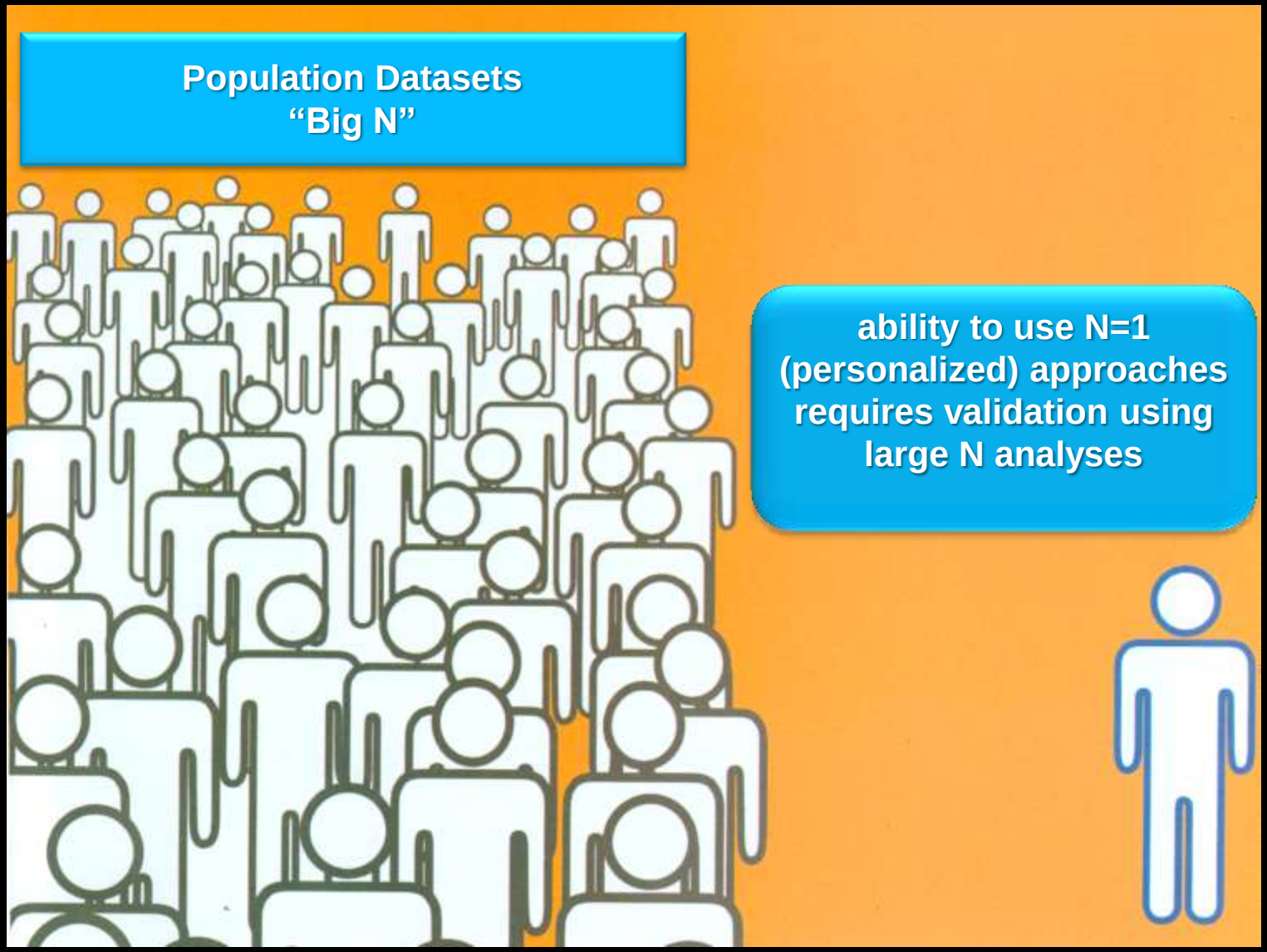
Cell-specific Molecular Interaction Networks



Perturbed Networks and Disease



Precision Medicine: Evidentiary Standards for Dissecting the Correlation:Causality Matrix in "Omics" Profiling



Mapping Human Genome Variation and Identification of Causal Variants for Disease

- both causal and protective alleles
- hypotheses
  - small number of common variants with large effects ☒
  - large number of common variants with small effects ☒
  - large number of rare variants with small effects ☑

plus

- role of environmental and epigenetic influences ☑

The Diversity of the Human Variome*

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

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

Implications of Role of Rare/Private Variants in Disease for Identification and Validation Studies

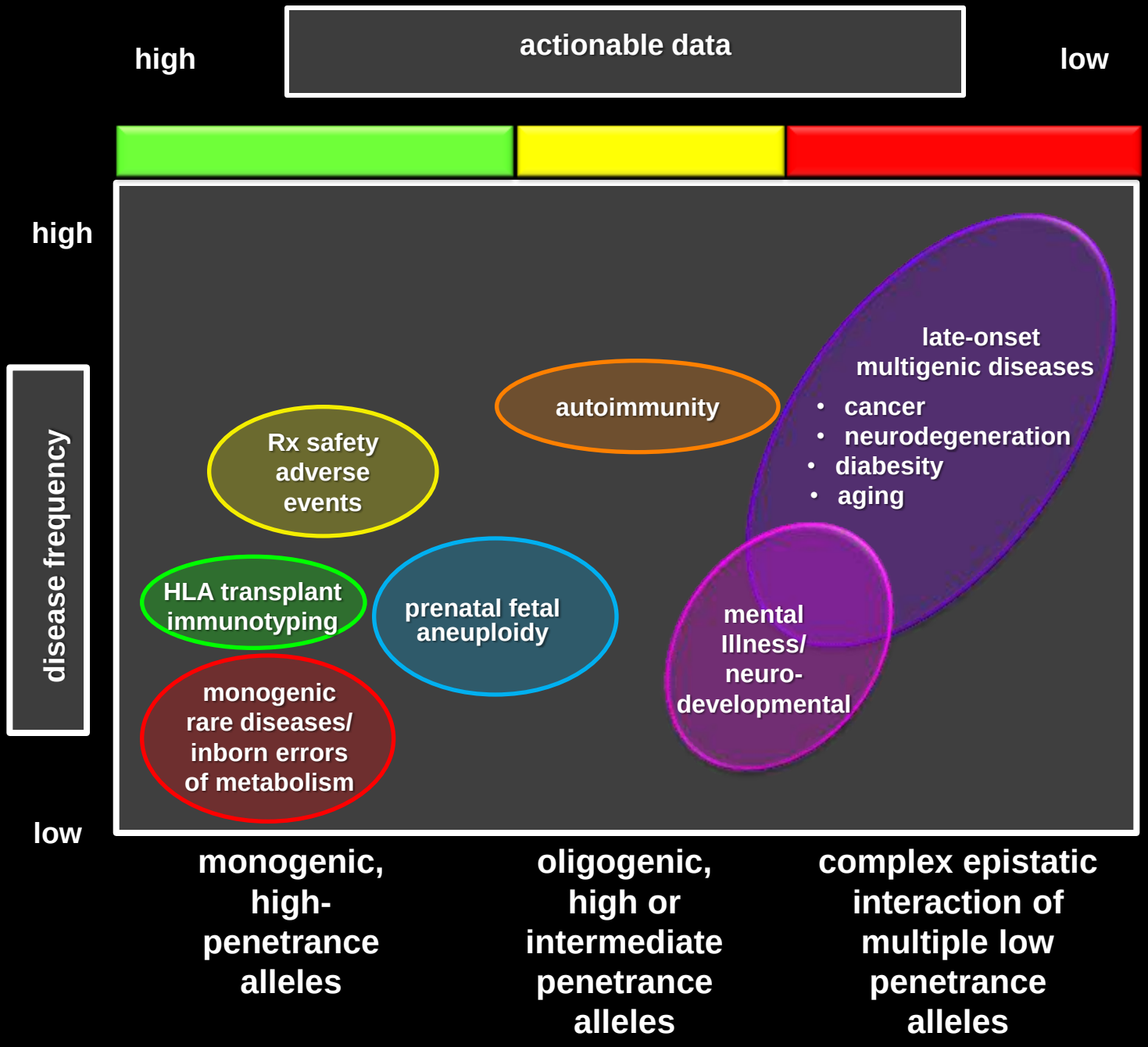
- renewed focus on clan:pedigree cohorts to identify “recent” disease causal variants not yet purged by negative selection
- very large sample sizes (logistics, cost)
- replication of findings across different populations (ethnicity, geographic history) will be limited
- large scale profiling of random cohorts may be less productive

Assessment of the Clinical Significance of Genome Sequence Variation

- availability of ever larger WGS databanks will allow greater precision in linking specific variants to disease risk, disease progression and Rx response
- evidentiary standards and who defines?
- logistics and cost of constant updating of newly identified risk(s) by databanks
- duty to inform individuals of new risk(s)?

American College of Medical Genetics Guidelines on Incidental Findings

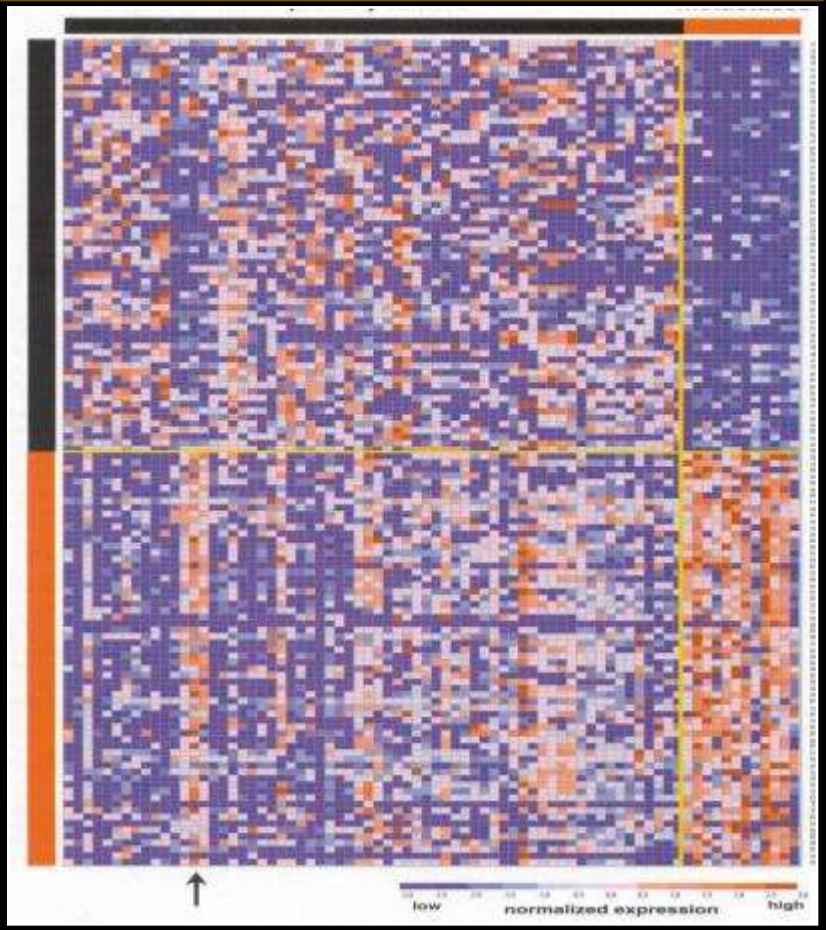
- approved March 2013 AGM
- 56 genes with certain variants for which individuals should be informed, irrespective of individual preference


high
actionable data
low
high
disease frequency
low
Rx safety adverse events
autoimmunity
late-onset multigenic diseases
• cancer
• neurodegeneration
• diabesity
• aging
HLA transplant immunotyping
prenatal fetal aneuploidy
mental Illness/ neuro-developmental
monogenic rare diseases/ inborn errors of metabolism
monogenic, high-penetrance alleles
oligogenic, high or intermediate penetrance alleles
complex epistatic interaction of multiple low penetrance alleles

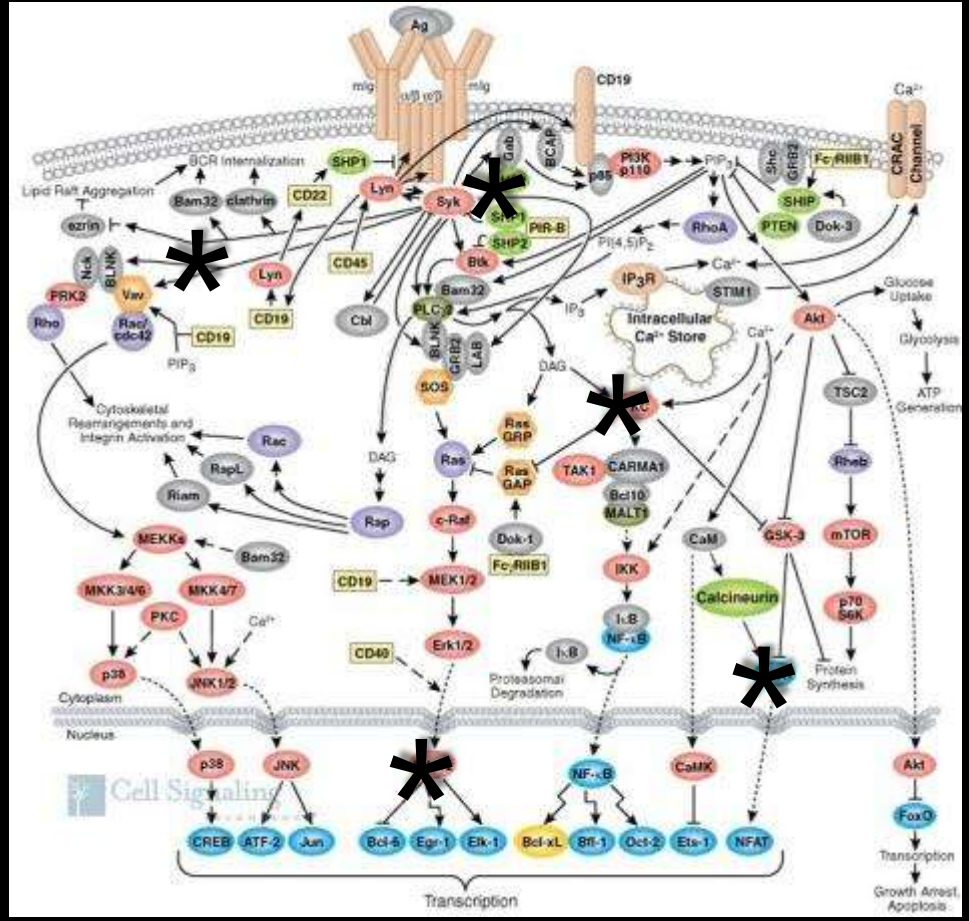
WGS and Claims Outstripping Current Analytical Capabilities
Disease Predisposition Risk Profiling (PDx)

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

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

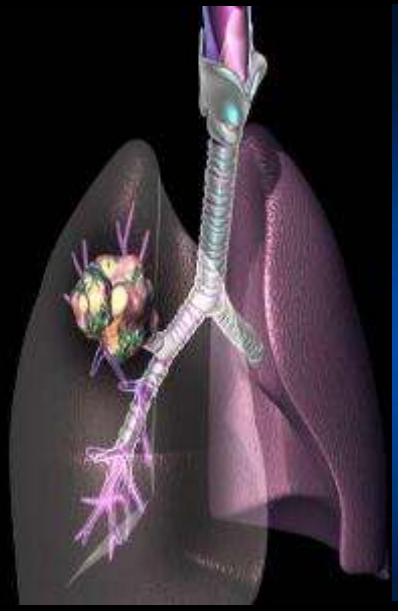


ID Molecular Targets for MDx and/or Rx Action



Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics – the Right Rx for the Right Disease (Subtype)

Her-2+
(Herceptin)
(Perjeta)



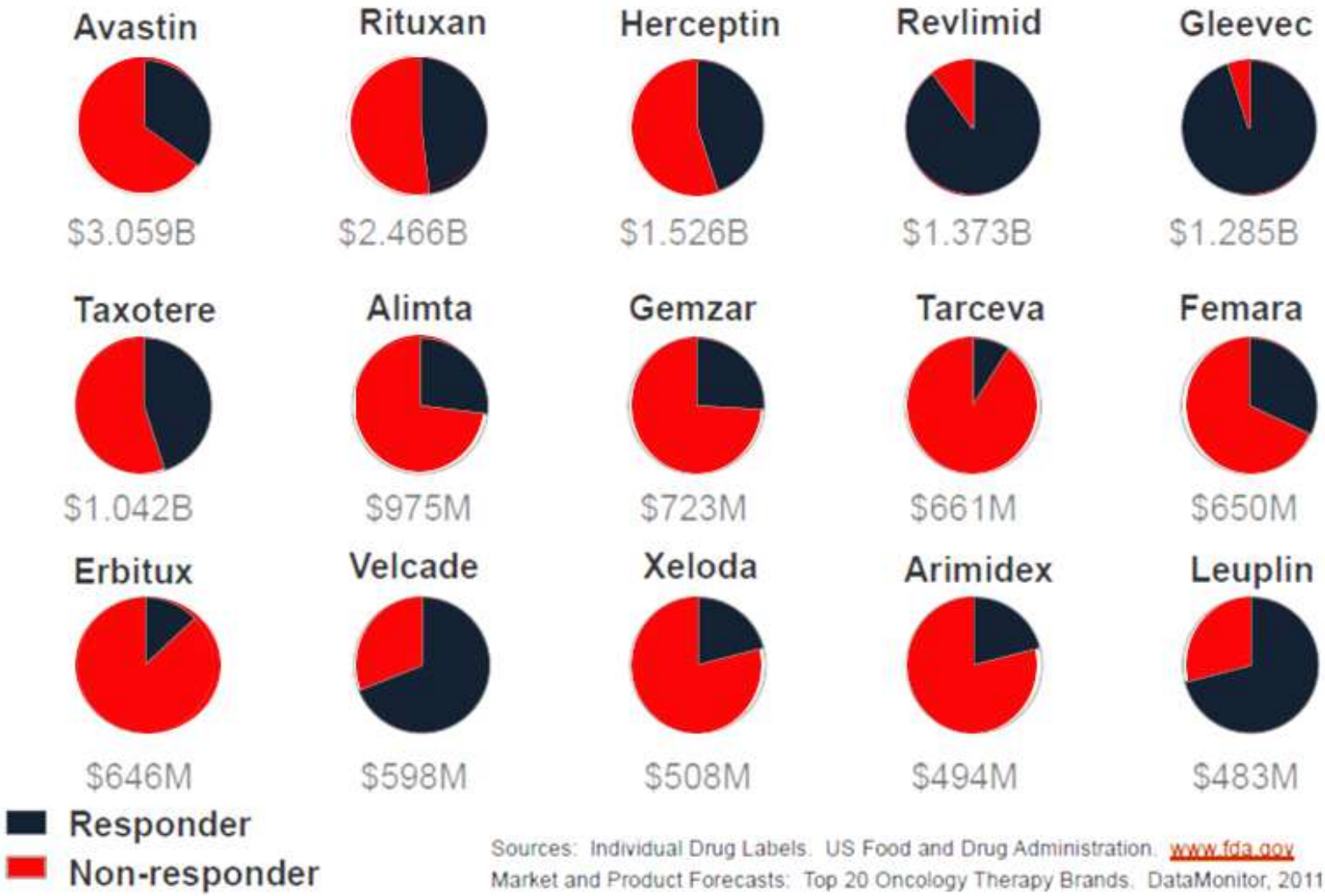
EML4-ALK
(Xalkori)

KRAS
(Erbitux)
(Vectibix)

BRAF-V600
(Zelboraf)

CFTR-G551
(Kalydeco)

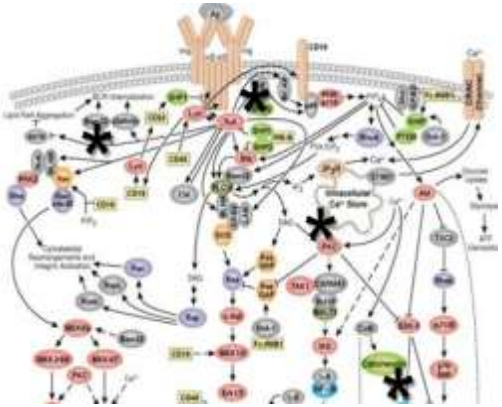
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly

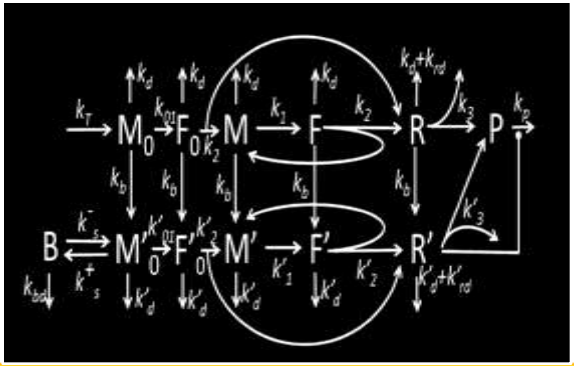


Sources: Individual Drug Labels. US Food and Drug Administration. www.fda.gov
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

Targeted Therapeutics and Cancer

Molecular Subtyping and ID of RX Targets





Modeling of Information Flow in Biological Networks

Initial Rx-Response to Targeted Rx

Rx-Resistance via Redundant Molecular Pathways

B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)

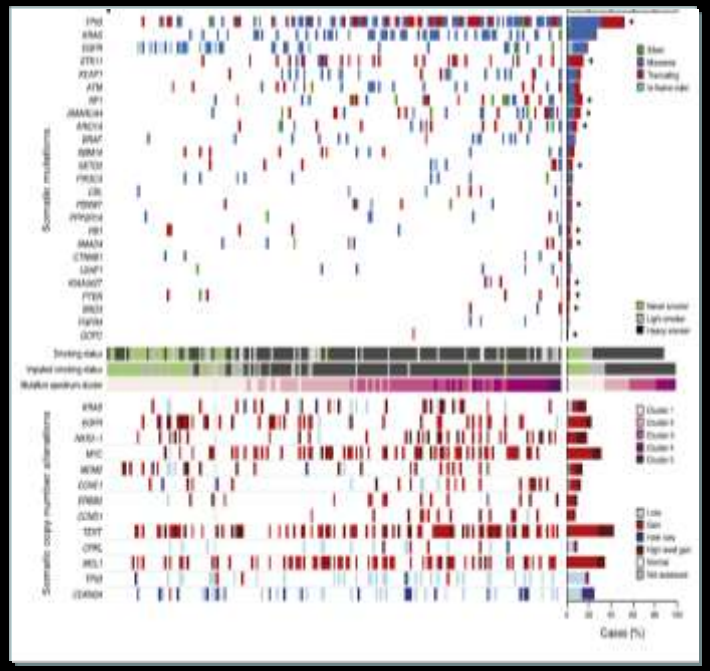
Reducing The Failure Rate of Investigational Drugs in Clinical Trials

- targeted therapies, YES!

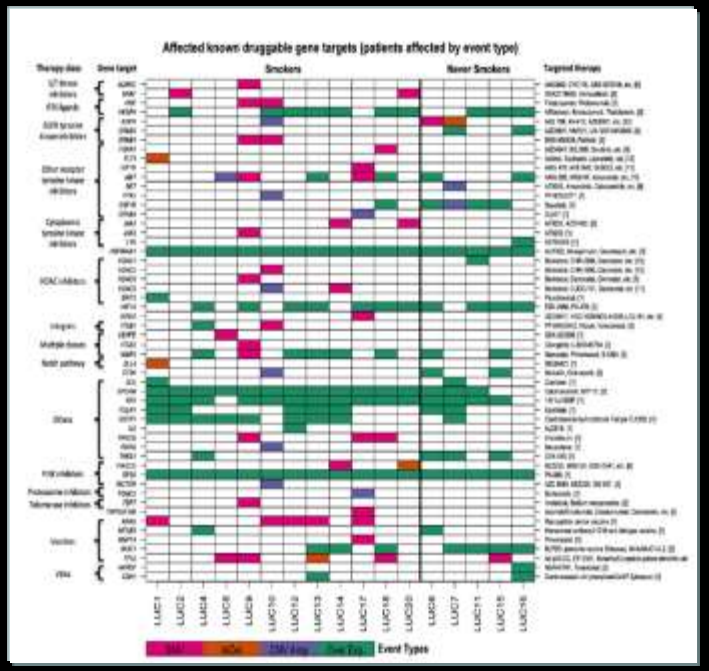
but

- improved success requires targeting network modules, pathways and subnetworks not single molecular targets
- network pharmacology

The Extravagant Landscape of Genomic Alterations in Cancer (Cell 2012, 150, 1107 and 1121)



Mutations in Individual Non-small Cell Lung Cancer



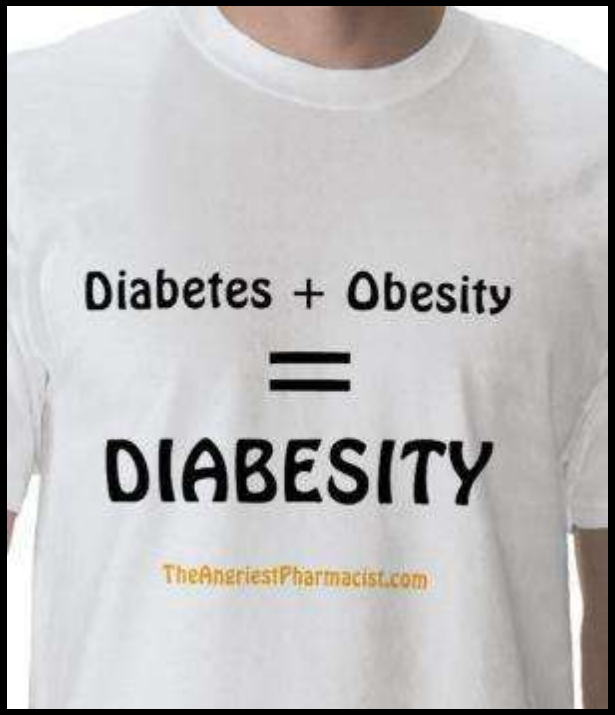
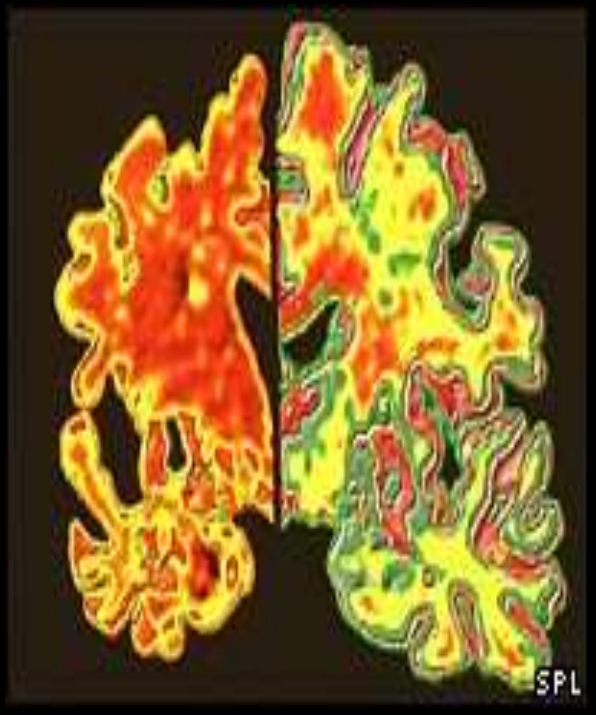
Drug Targets in Individual Non-Small Cell Lung Cancers

- “malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for development of new Rx

Molecular Network Perturbations in Complex Chronic Diseases
A Perplexing Emerging Question

- is the multiplicity of pathways dysregulated in advanced metastatic cancer and the degenerative neuropathies (Alzheimers disease) an insurmountable technical barrier to design of poly-target (promiscuous) agent/combinations?
  - highest failure rates of new Rx in all therapeutic categories

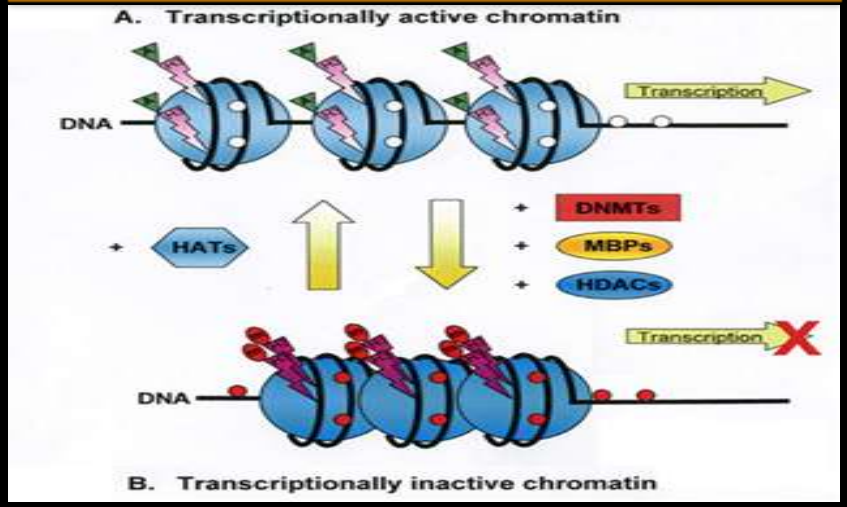
Three Different Scenarios for the Use (Value) of New Diagnostic Technologies for Early Detection of Disease and/or Disease Predisposition

Cancer Detection Before Metastasis	Cardiovascular/ Metabolic Diseases	Neurodegenerative Diseases
		
Early Diagnosis and Curative Surgery	Lifestyle Changes and/or Rx to Limit Risk	The Dilemma of Early Diagnosis Without Rx

The Epigenome

Effect of Maternal Diet/Stress/Rx exposure on Germ Line Genome (+ trans-three-generational?)

Modulation of Gene Expression/Regulation by Environmental Factors, Xenobiotics and Rx (The Exposome)



IHEC
International Human Epigenome Consortium

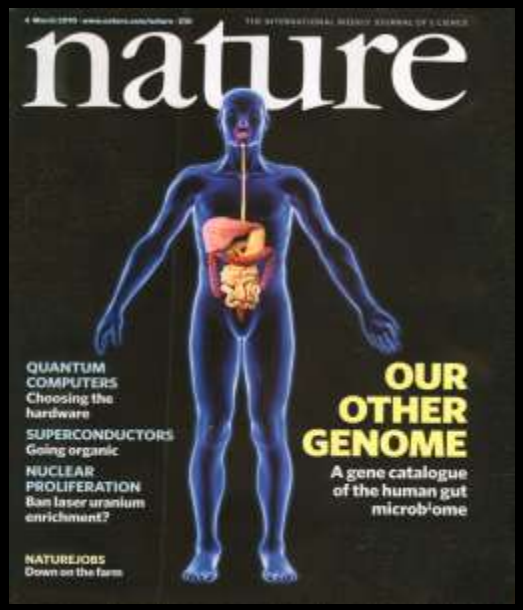
International Human Epigenome Consortium

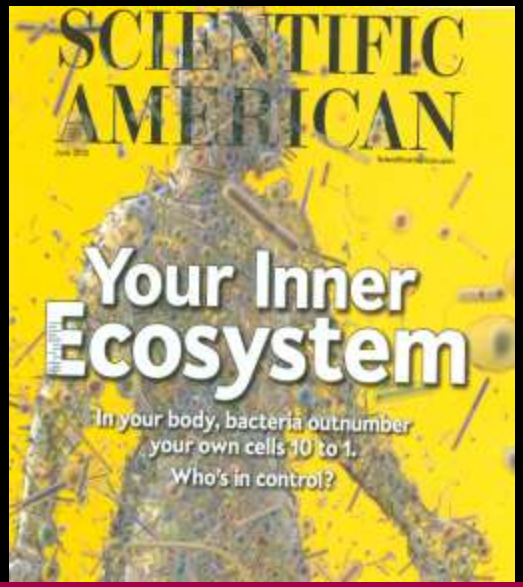
- **1000 reference genomes by 2020**

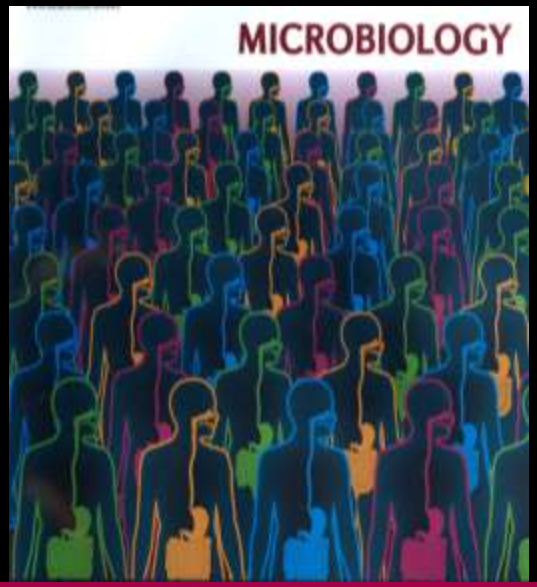
project blueprint

- **launch September 2011 with €30-million**
- **map epigenome in 60 human blood cell classes and neoplastic counterparts**

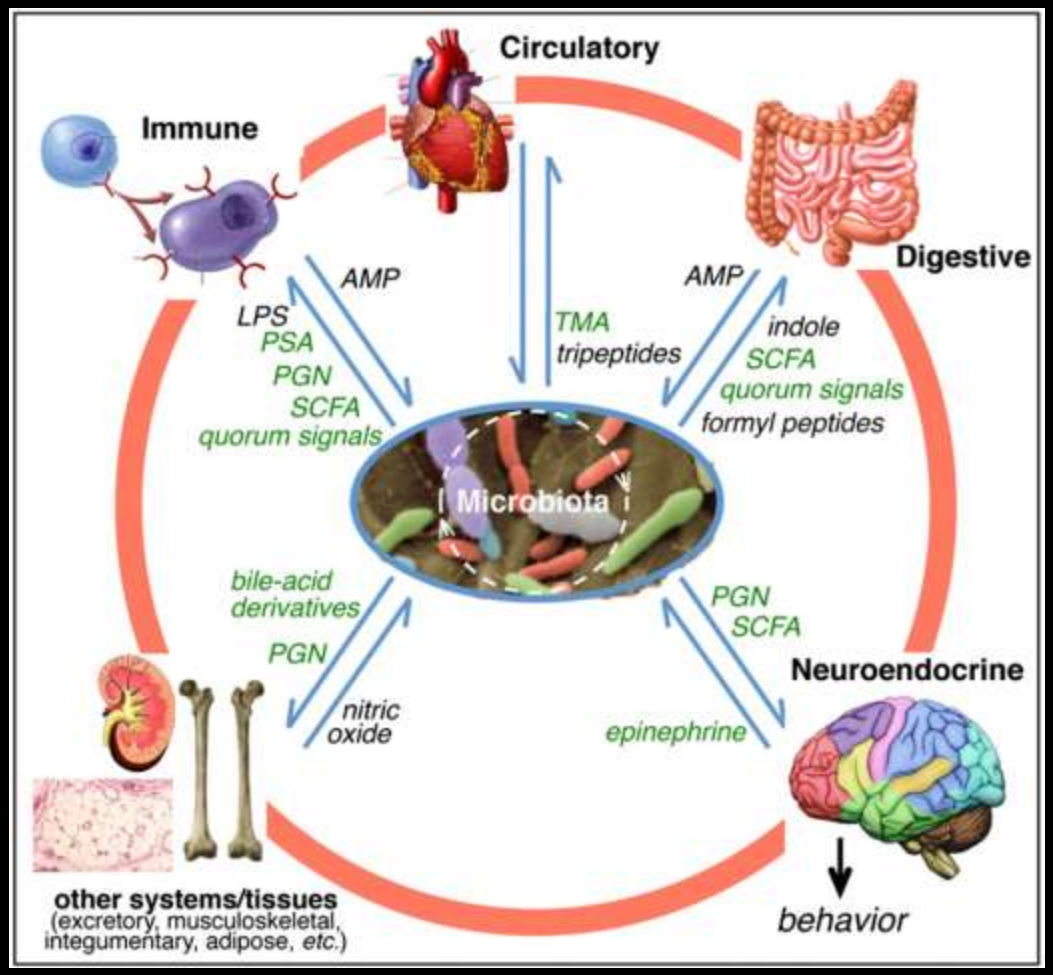
We Are Not Alone: The "Frenemy Within" Variation in the Human Microbiome as a Potential Factor in Health and Disease







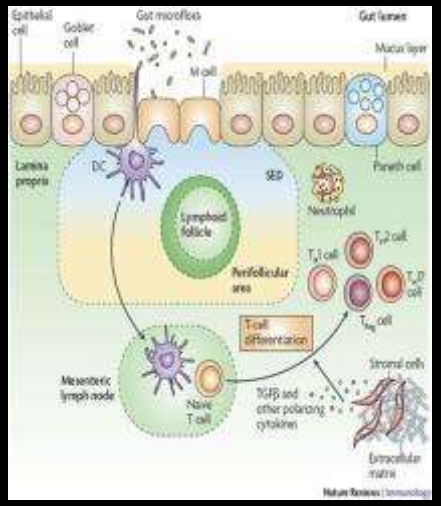
Signaling Between Mammalian Microbiota and Organ Systems

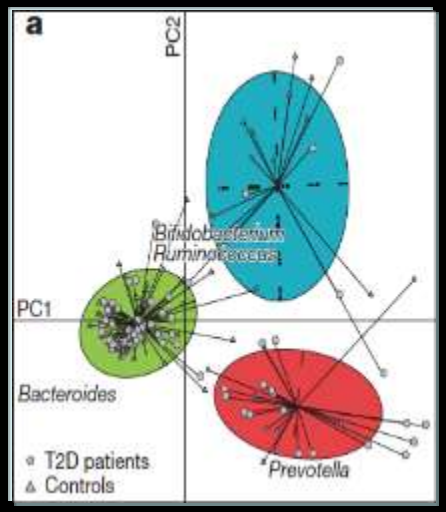


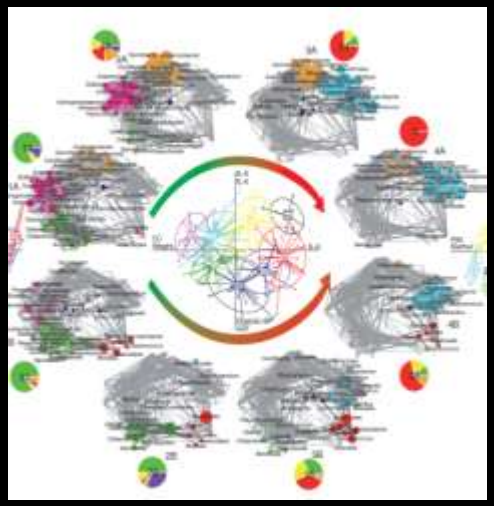
From: M. McFall-Ngai et al. (2013) PNAS 110, 3229

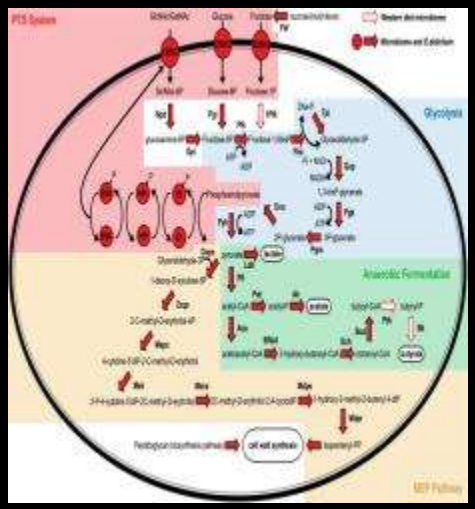
Commensal Microbiomes: The "Frenemy Within" An Additional Dimension to Biomarker Profiling

Metagenome-wide Association Studies (MGWAS)



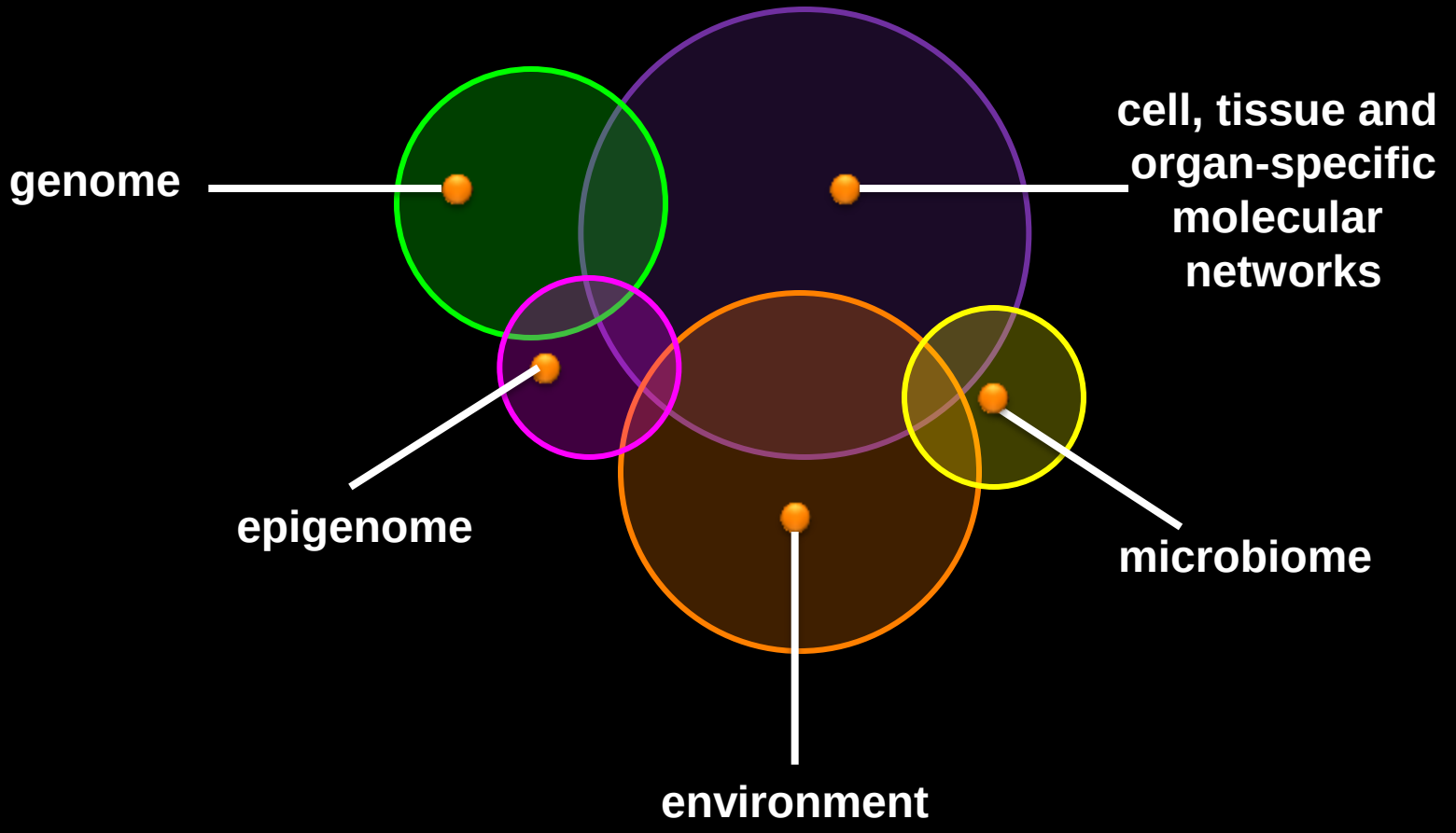




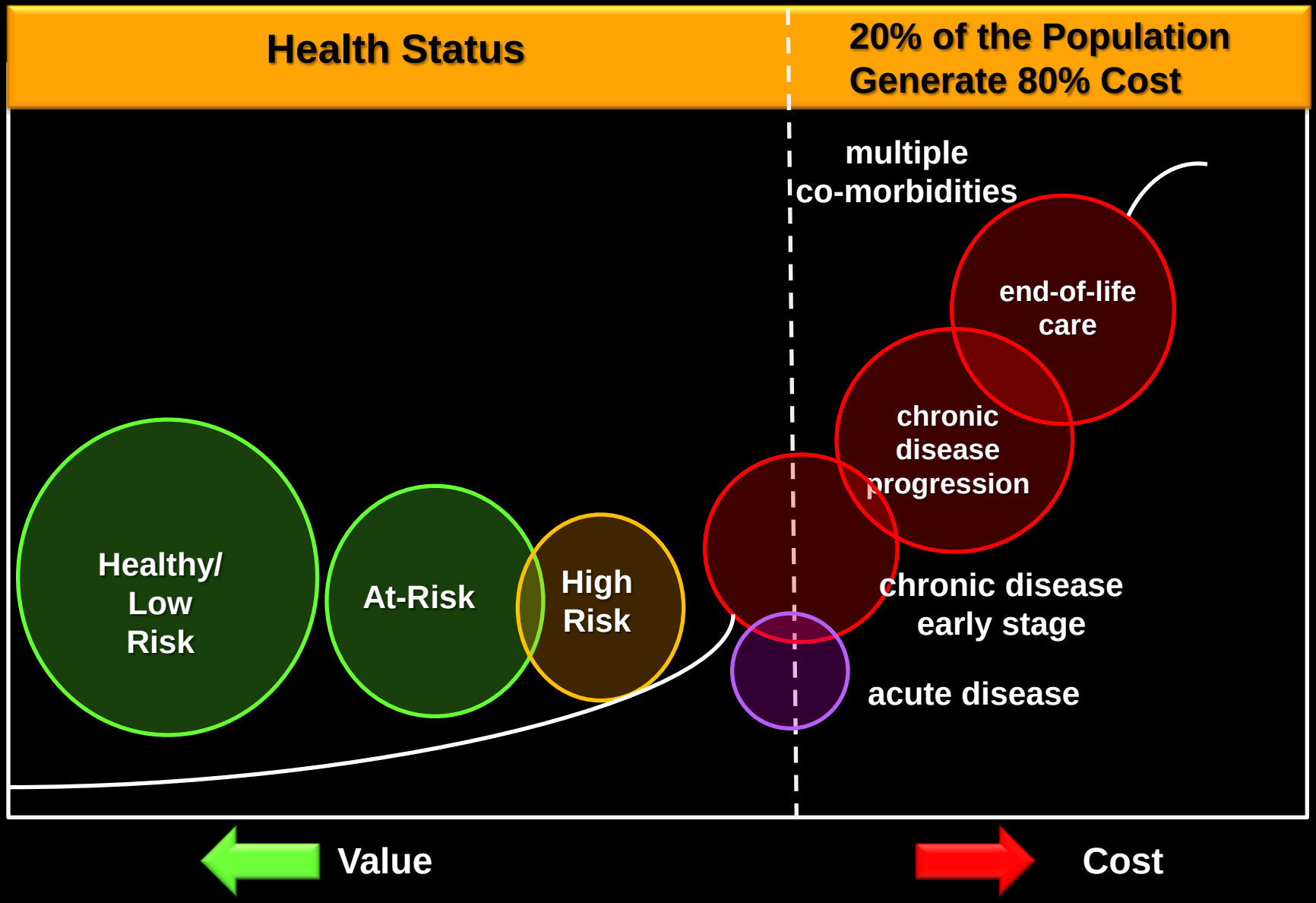


Immune-Mediated GI Diseases	Type 2 Diabetes Profile	Aging Metabolism and Fragility	Metabolic Activation of Carcinogens/ Pollutants

The Complex Interplay Between the Genome, Molecular Networks and Environmental Factors



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

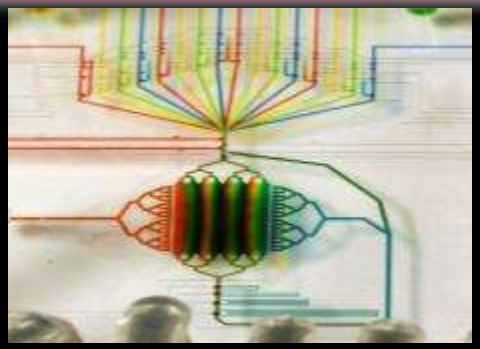


The Wellness Premium

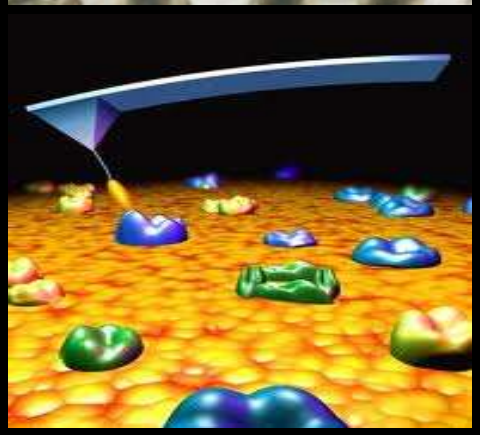
Greater Engagement and Incentivization of Consumers/Patients in Care Decisions and Sustaining Wellness

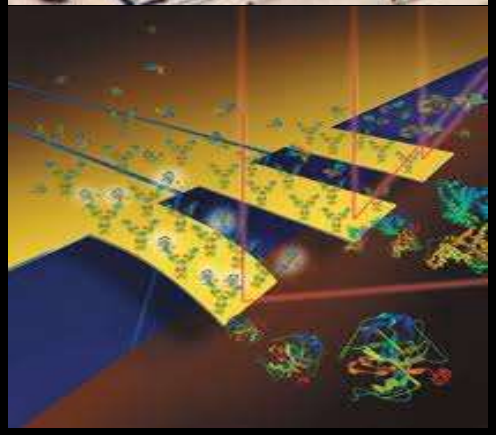
“Patient-Centric Healthcare Without Patient Engagement Is An Illusion”

Miniaturization of Analytical Technologies

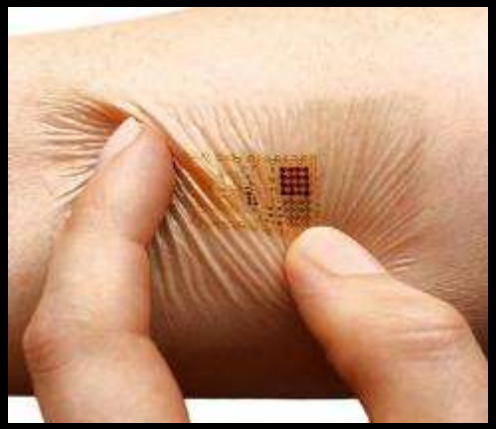


“Lab-on-a-Chip”





“Lab-on-a-Tip”



“Lab-Always On”
and
“Lab-On-Me”

Invasion of the Body Trackers

Individual Biosignature Profiling Via On Body: In Body (OBIB) Sensors and Devices

Remote Health Status Monitoring

M4: Making Medicine More Mobile

m.Health

Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

Evidentiary Standards and Liabilities for Biomedical Apps

Consumer Health Informatics

- on-line help/support services (practice-and patient-specific unrelated to general web information)
- automation of out-of-office care
- decreased office visits
- e-pharmacy
- new tools for improved compliance and coaching
- reduced hospital readmissions
- m.health and remote health status monitoring

Mobile Devices, Wireless Technologies, Big Data and Increasingly Patient-Centric Delivery Channels

- extend reach and continuity in care
- each individual becomes their own control
- better real time patient-specific data and decision-support tools
- new patterns (touch points) of patient engagement with the health system
  - AORTA: Always-On-Real Time Access
  - new delivery channels and services
  - the changing ‘care space’
  - targeted care and ability to monitor larger number of patients

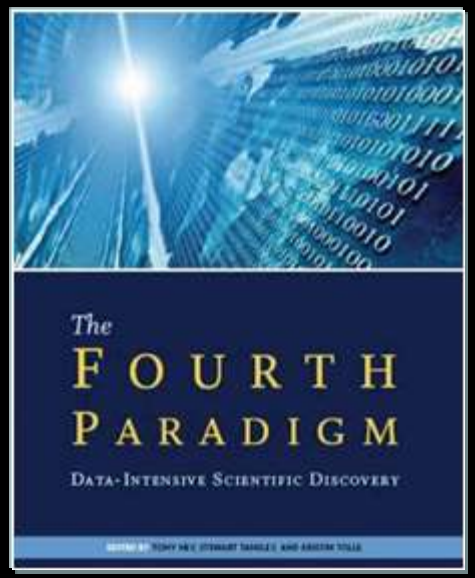
Interactive Participant-Centered Initiatives (PCI)

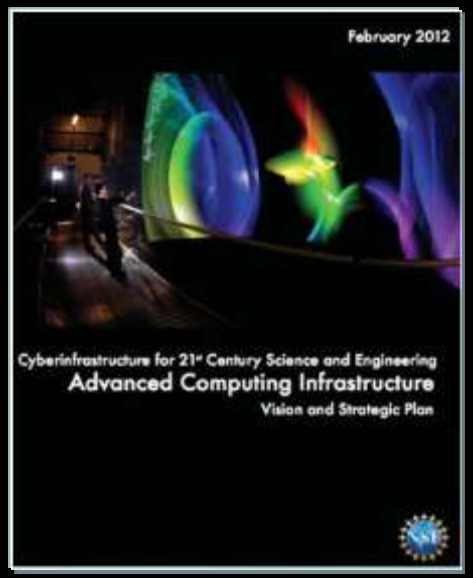
- social media, patient advocacy and consumer/care-giver engagement
- new opportunities to capture, share, mine and integrate data
  - research (deidentified) and clinical care (identified)
- faster recruitment for clinical trials accumulation of large sample sizes for suitable statistical power
- build new repository biobank networks of well curated and standardized samples to support research

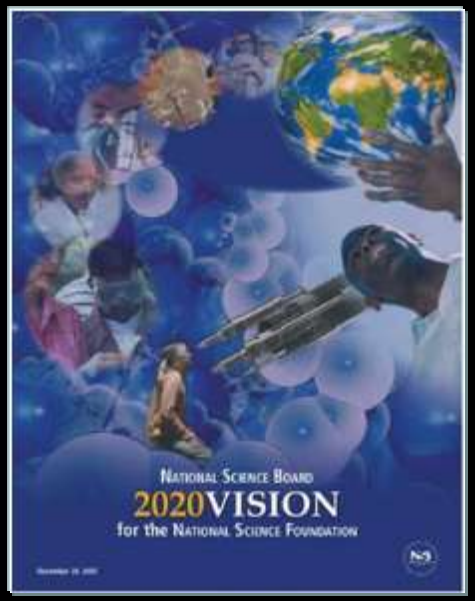
Social Spaces Become Quantifiable

- who knows why people do what they do?
  - the fact is that they do!
- these actions can now be traced and measured with unprecedented precision
- with sufficient data, the numbers reveal increasingly predictable behavior individual risk patterns
- new business opportunities in multiple sectors including healthcare
- new ethical and legal issues regarding privacy and data security

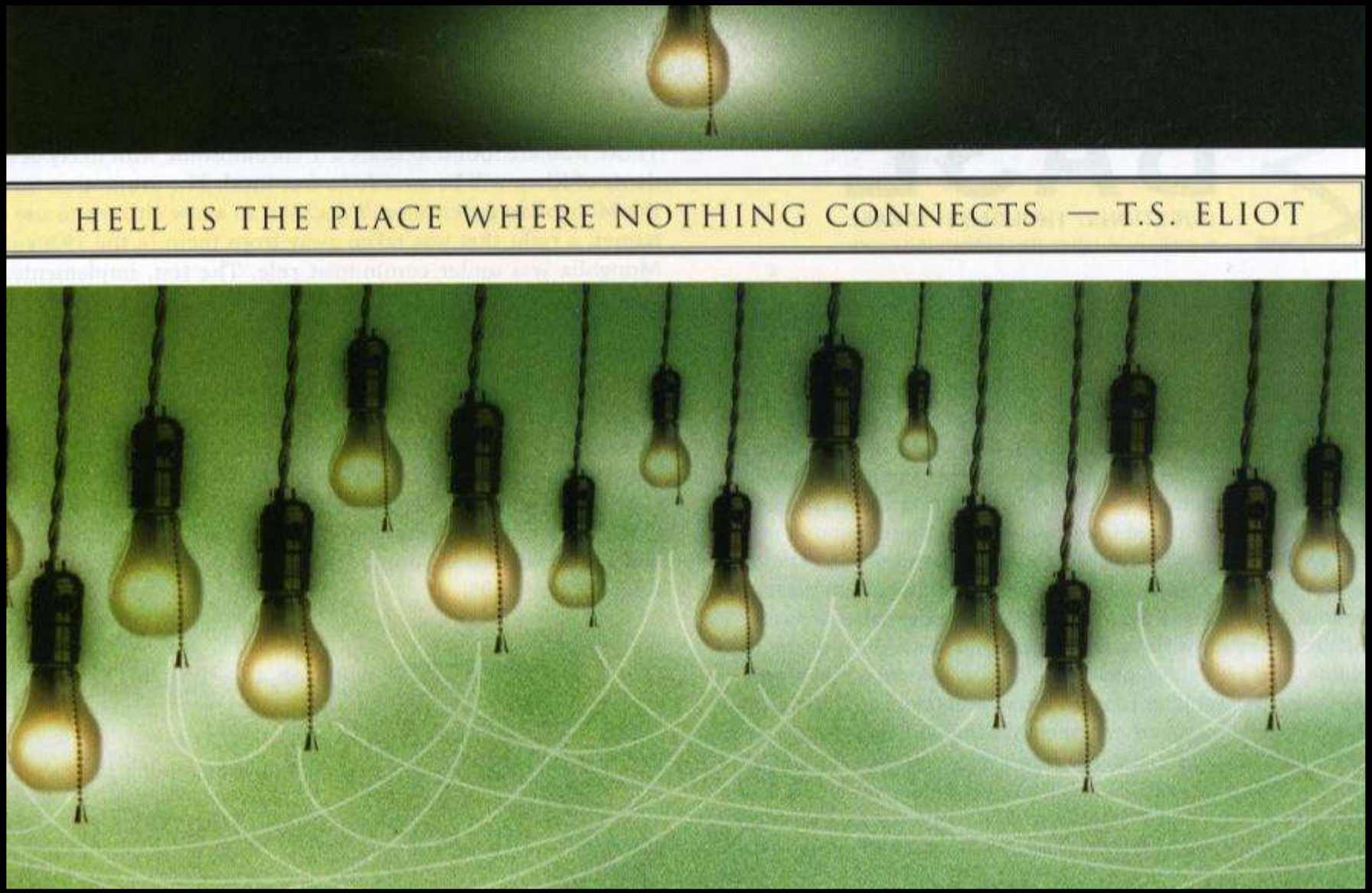
Data-Intensive Computing, Big Data and New Knowledge Networks in Biomedical R&D and Healthcare Delivery



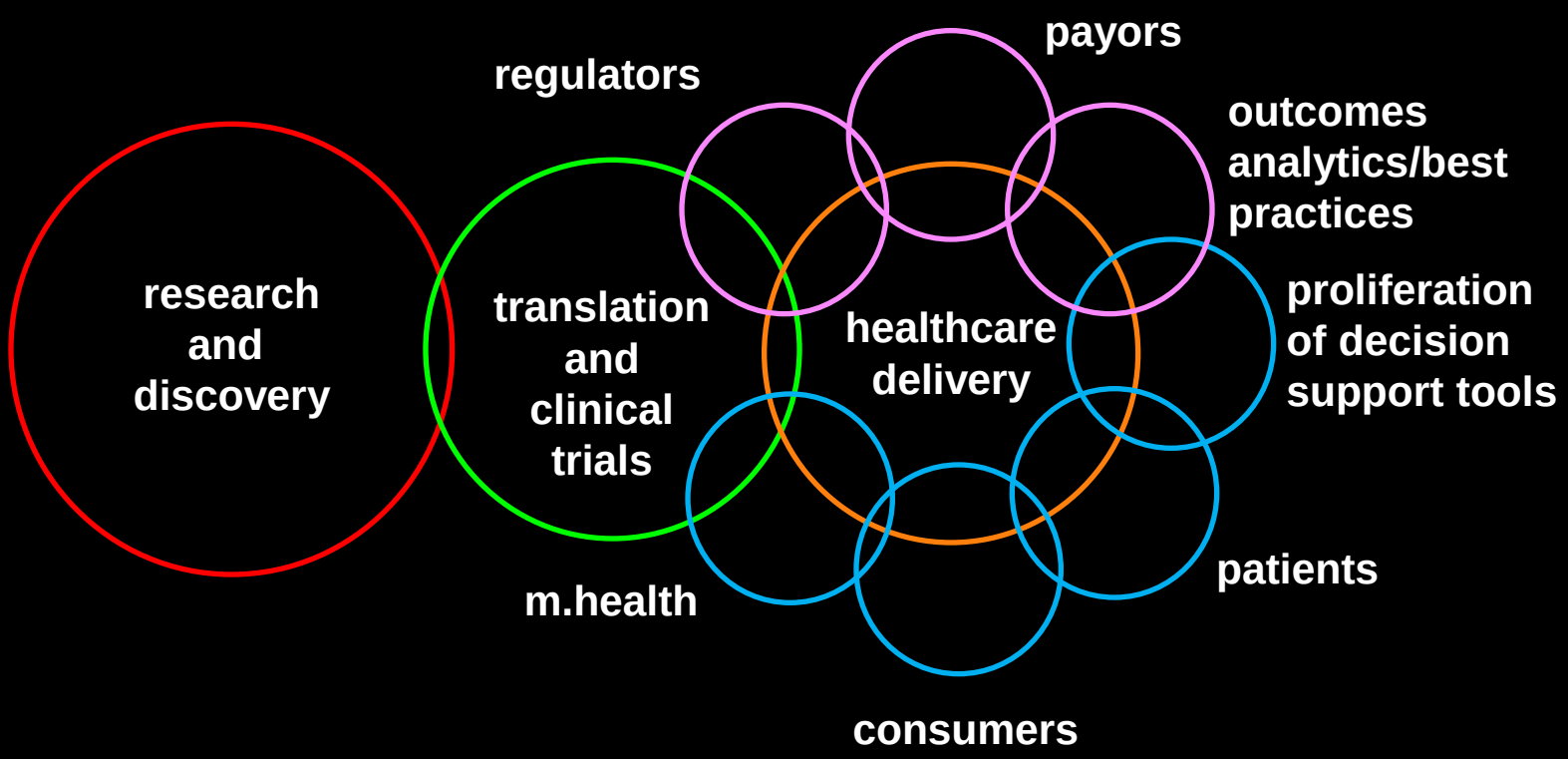




Silos Subvert Solutions



The Design of Facile, Seamless Cross-Domain Data Exchange Formats for Large Scale Biomedical Data



Biomedical R&D and Clinical Medicine: An Unavoidable Transition to Data-and Computation-Intensive Methods

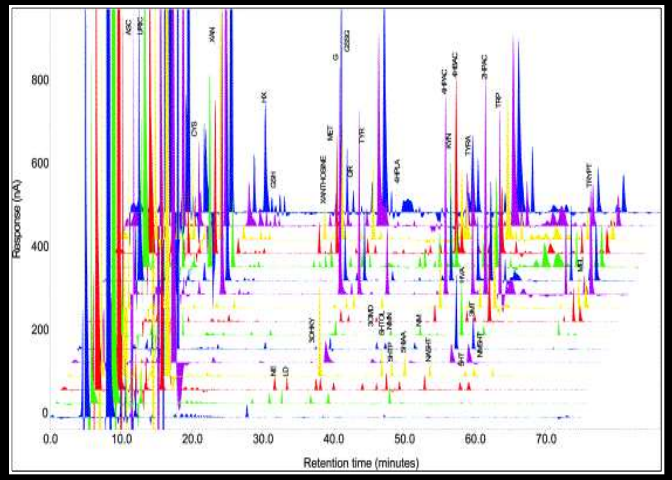
Current Era

- "silos" of research/clinical activities
- opinion-rich, information content-poor
- proliferation of poorly standardized and fragmented data, semantic anarchy and incompatible databases
- unacceptable levels of inaccurate diagnoses, fragmented care provision and flawed clinical decisions
  - highly variable treatment practices and erratic clinical outcomes
- extravagant waste and risk

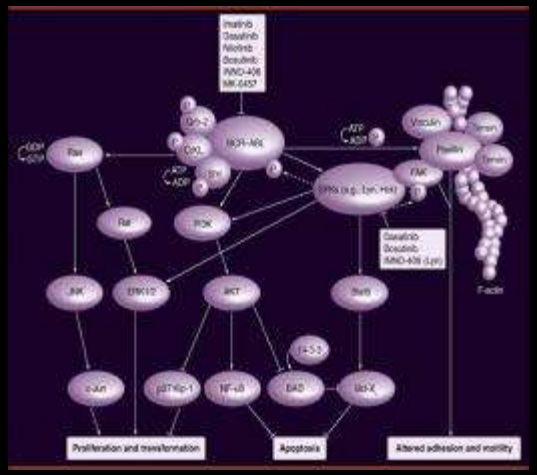
Burgeoning Research Datasets in Biomedical Informatics

Genomics

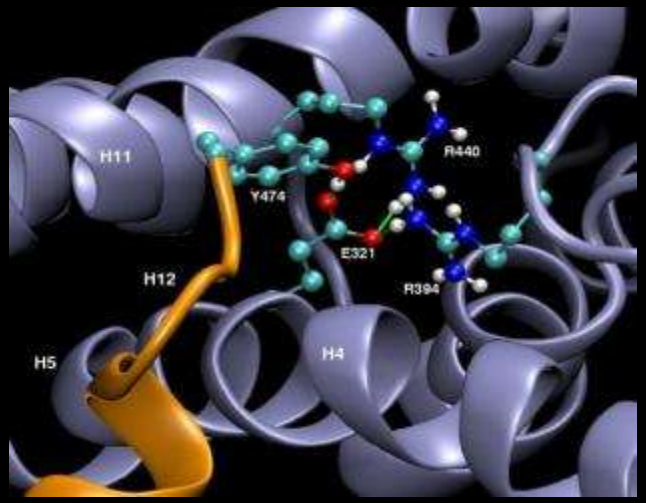
Proteomics



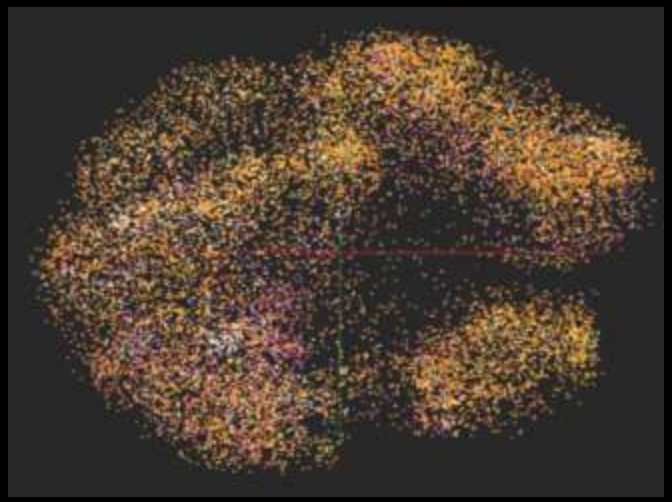
Molecular Pathways



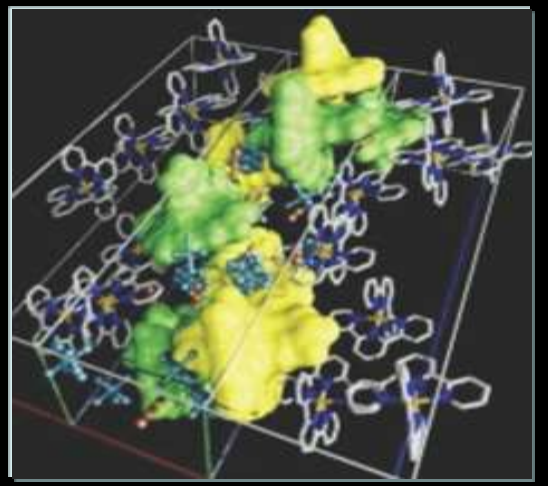
Molecular Interactions



Medicinal Chemistry SAR

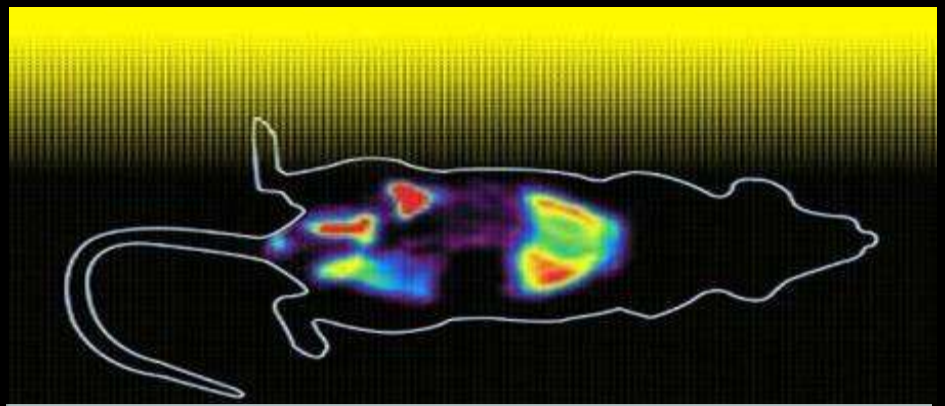


Cell Content Imaging

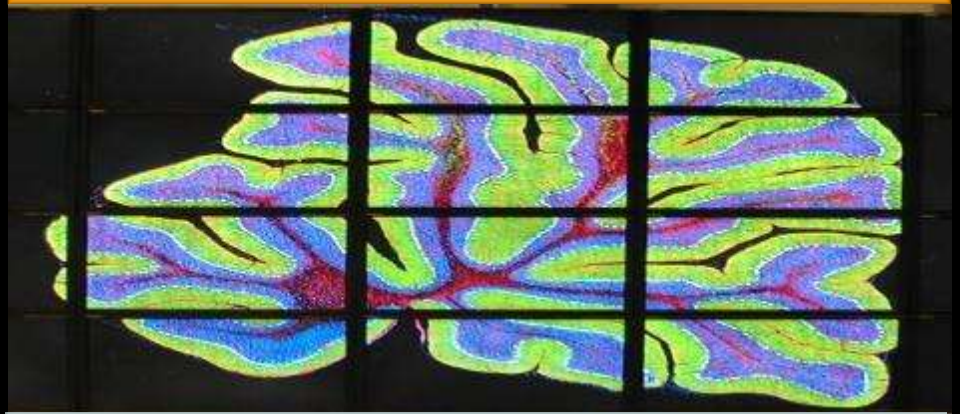


Large Scale Imaging Datasets

Preclinical



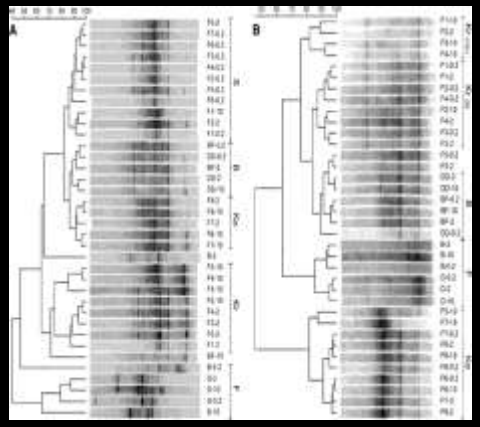
Digital Pathology



Clinical Imaging

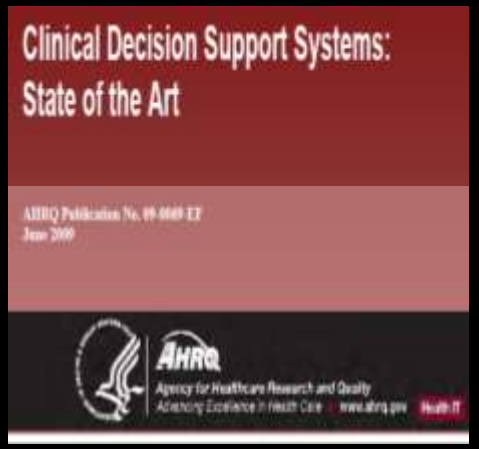
Tele-surgery

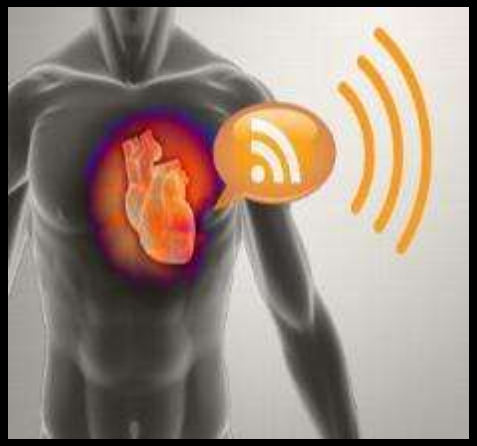
Data-Intensive Biomedical R&D and 'The Data Deluge'

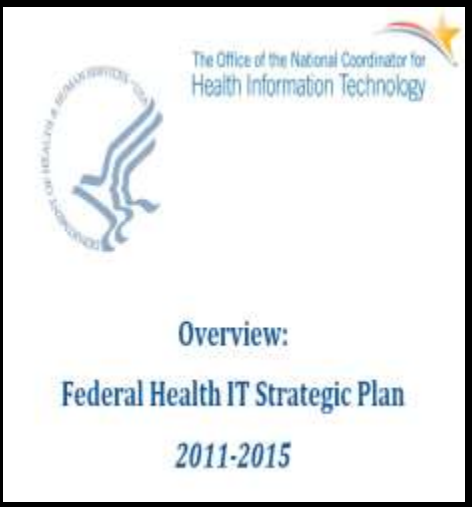
Patient Stratification For Clinical Trials	Pharmacogenomics	m.Health	Monitoring Networks
			
			
Microbial Diagnostics	Biosurveillance and Public Health	Computing Infrastructure	Health IT and EMRs

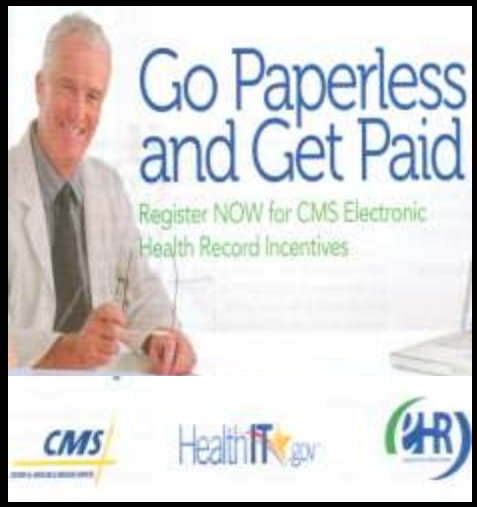
A Learning Healthcare System

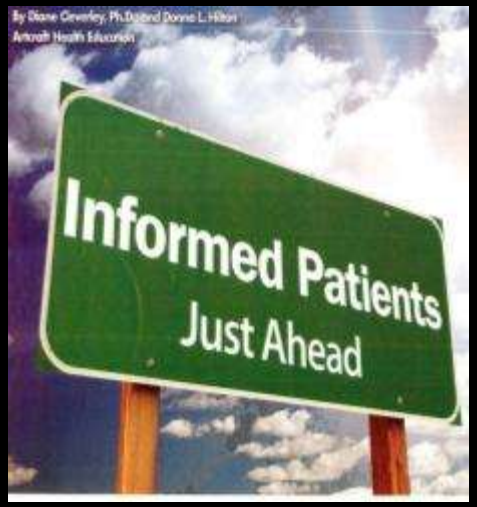
Proliferation of Clinical Computational Systems











HITECH Mandates	Incentives	EHR and Smart Cards	Informed Consumers/Patients

Biomedical R&D and Clinical Medicine: An Unavoidable Yet Essential Transition to Date- and Computation-Intensive Processes

Pending Era

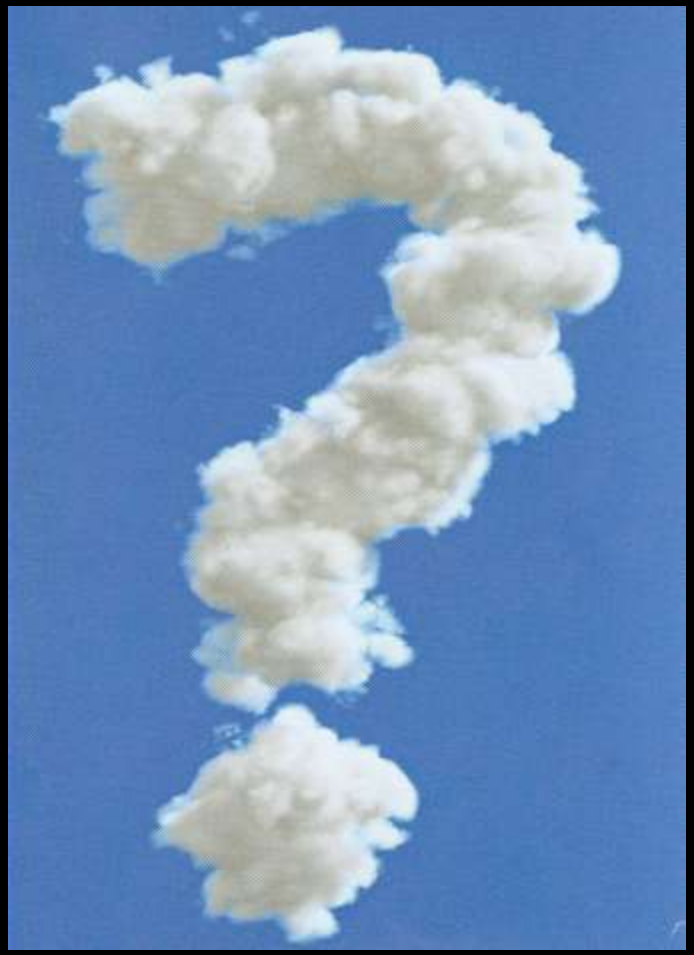
- massive data (big data)
  - V5: volume, velocity, variety, veracity, value
  - automated, massively parallel 'omics' profiling (research and clinical)
- cross-sector convergence and integration
  - biomedicine, engineering, computing, telecommunications, social media
- new machine-based analytics for management of mega-data, customized distribution and decision-support

Design of Facile Exchange Formats for Data Assembly, Curation and Use Across the Continuum from Discovery to Healthcare Delivery

The Design Challenge for Next Generation HIT Systems

- today EHRs not designed to support secondary use of data to inform research/translational medicine
- HITECH funding for health IT promotes largely e-replication of paper records
- lack of harmonized data standards in different disciplines/delivery systems as handicap to data
  meta-analytics outside of original capture institution
- urgent need for new integration models for diverse data

Biomedical Data in the Cloud



NewScientist Jobs

- research data
  (deidentified/anonymized)
  vs.
  clinical trials and healthcare data
  (confidentiality, privacy
  and security)
- informed consent for transfer of personal data to, and use in, cloud-based services?

What Is?
The Evolution of Computation Capabilities for Natural Language Q&A in Large Unstructured Datasets

Jeopardy 16 February 2011

- IBM's Watson
  - 2880 CPUs
  - natural language questions
- prelude to Q&A systems for biomedicine beyond keyword IR searches

WellPoint NUANCE Cleveland Clinic

The Cost, Logistics and Infrastructure for Analysis and Management of Large Population WGS and 'omics' Data and Integration Into Clinical Records

- big data
- big knowledge gaps

- big pipes
- big storage
- big bucks

- big payoffs?

The Omics Data Storage Challenge
(J. Starren et al. 2013 JAMA 309, 1237)

- typical EHR
  - 375 KB/patient
- radiologic picture archiving and communication system (PACS)
  - 104 MB/patient
  - x277 > EHR
- WGS
  - 3-10 million variants/individual
  - 5-10 GB/individual
  - x50 > imaging

Large Scale WGS, Big Data and Cyberinfrastructure:

EECS ELECTRICAL ENGINEERING AND COMPUTER SCIENCES
COLLEGE OF ENGINEERING UC Berkeley

A Million Cancer Genome Warehouse

David Haussler, David A. Patterson, Mark Diekhans, Armando Fox, Michael Jordan, Anthony D. Joseph, Singer Ma, Benedict Paten, Scott Shenker, Taylor Sittler and Ion Stoica

EECS Department
University of California, Berkeley
Technical Report No. UCB/EECS-2012-211
November 20, 2012

http://www.eecs.berkeley.edu/Pubs/TechRpts/2012/EECS-2012-211.pdf

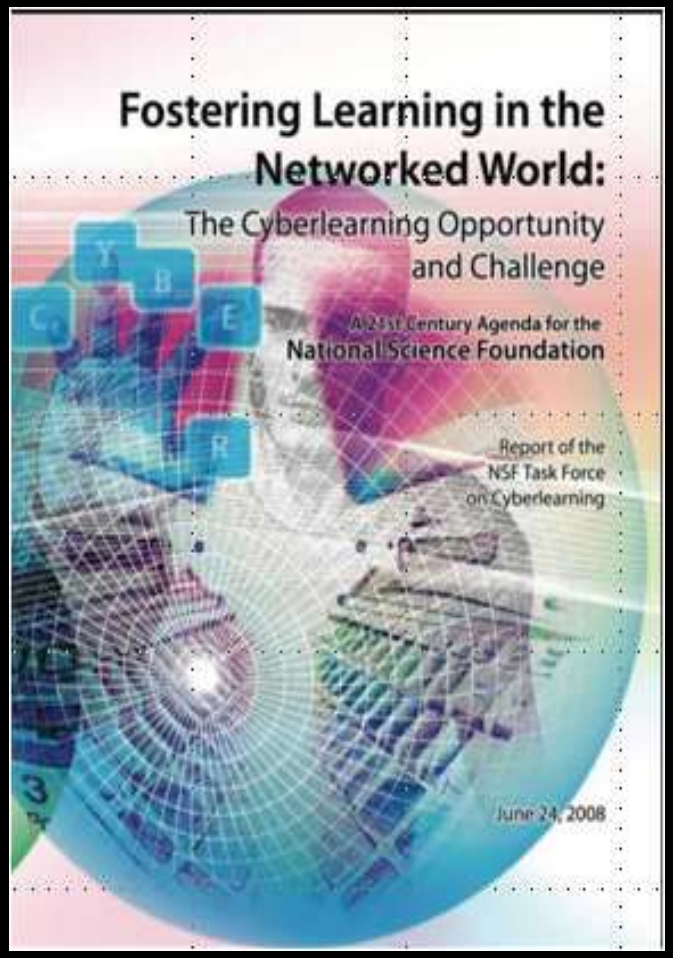
- 1 million cancer patient WGS = 100 petabytes (after compression)
- not feasible to move such datasets
- not feasible to 'add on' to existing databases
- 'digital Darwinism': the prospect of stark separation between data-rich and data-poor enterprises

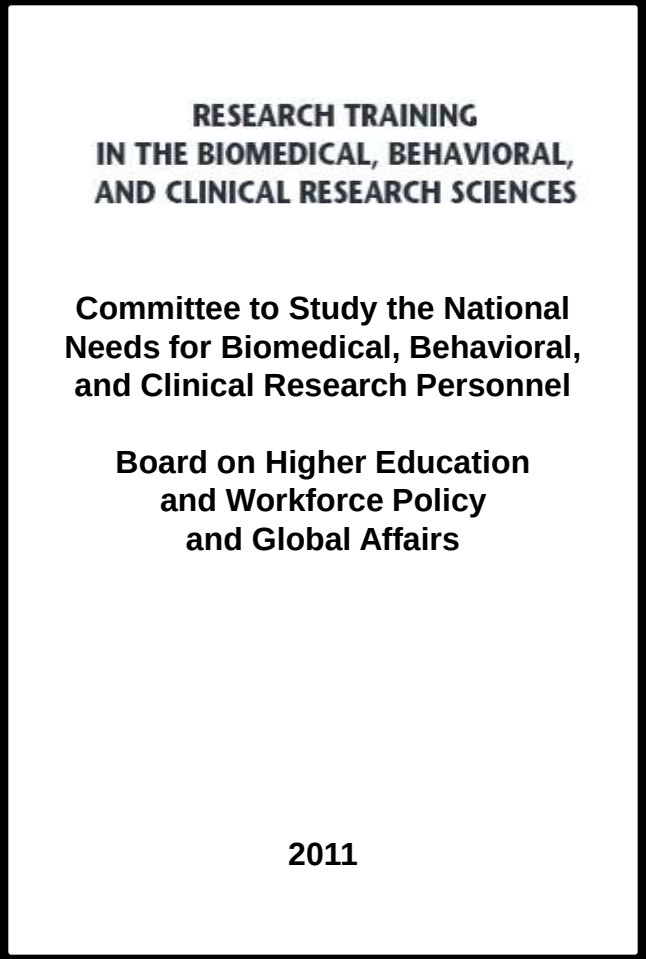
Managing Big Data in Biomedicine is Not a Simple Extrapolation from Current Practices

Radical and Disruptive Changes Await!!!

Current Institutional Structures and Competencies Are Ill-Prepared for Pending Disruptive Change

Education and Training: The Looming Talent Gap





- **by 2018 the US will need 160,000 more individuals with expertise in statistical methods and data analytics**

R.N. Rodriguez
President-Elect, American Statistical Association
Non-Clinical Biostatistics Conference, Boston 19 Oct. 2011

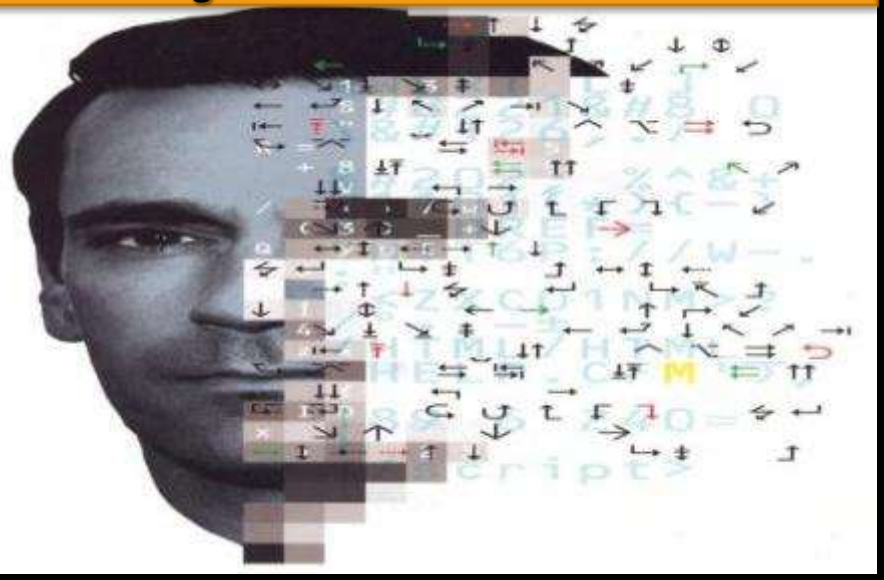
The Pending Era of Cognitive Systems: Overcoming the "Bandwidth" Limits of Human Individuals

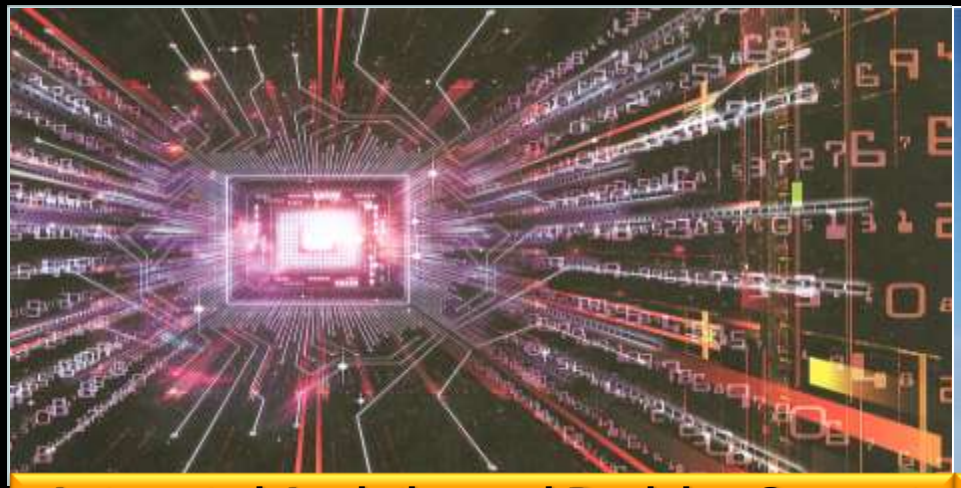
- limits to our expertise
- limits to our multi-dimensionality
- limits to our sensory systems
- limits to our experiences and perceptions
- limits to our objective decision-making

Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula

Data Deluge

Cognitive Bandwidth Limits





Automated Analytics and Decision Support

Facile Formats for Actionable Decisions

21st Century Knowledge Networks versus 20th Century Organizations

The Need for New Conceptual, Methodological and Organizational Frameworks for Data-Intensive Biomedical R&D and Healthcare Delivery

- burgeoning datasets and dimensionality of hypotheses spaces transcend human cognitive capabilities
- tractable solutions to urgent clinical and economic challenges will depend increasingly on mastery of massive data and complexity
- successful development of requisite data-intensive systems and computational sophistication will require new cross-domain capabilities and design of new knowledge networks
- current institutional structures and research funding policies are ill-prepared to undertake this critical transition

Big Science: Multi-Disciplinary, Multi-Institutional Science

- biomedicine lags other fields of science and technology
  - engineering, materials science, computing, physics, astronomy, ecology, climate modeling
- big science antithetical to traditional organizational structures and career rewards in academic life sciences
- slow adaptation of public funding agencies to shift from individual-investigator to team-based science and enforce standards demanded by translational research
- ‘3M’ projects: multi-investigator, multi-institution, multi-million

BioIT World 2011 - by **Sorena Nadaf, M.S. M.MI**
Director - Translational Informatics, CIO

Changing Minds and Changing Cultures: The Barriers of Entrenched Behaviors and Current Reward Structures

- re-engineering a complex ecosystem approaching 20% of GDP
- perverse incentives
  - academic research: silos, inefficient translation and lack of accountability
  - clinical: “do more, bill more”; “one-size-fits-all”
  - industry: short termism and timid incrementalism
- current institutions and their financial revenue base cannot be expected “to vote themselves off the island” absent new incentives/disruptions

- rethink
- recalibrate
- design

What is required?

What is sustainable?

The Changing ‘Care Space’ in Healthcare Delivery

- from fixed, tethered, compartmentalized, provider-centric facilities

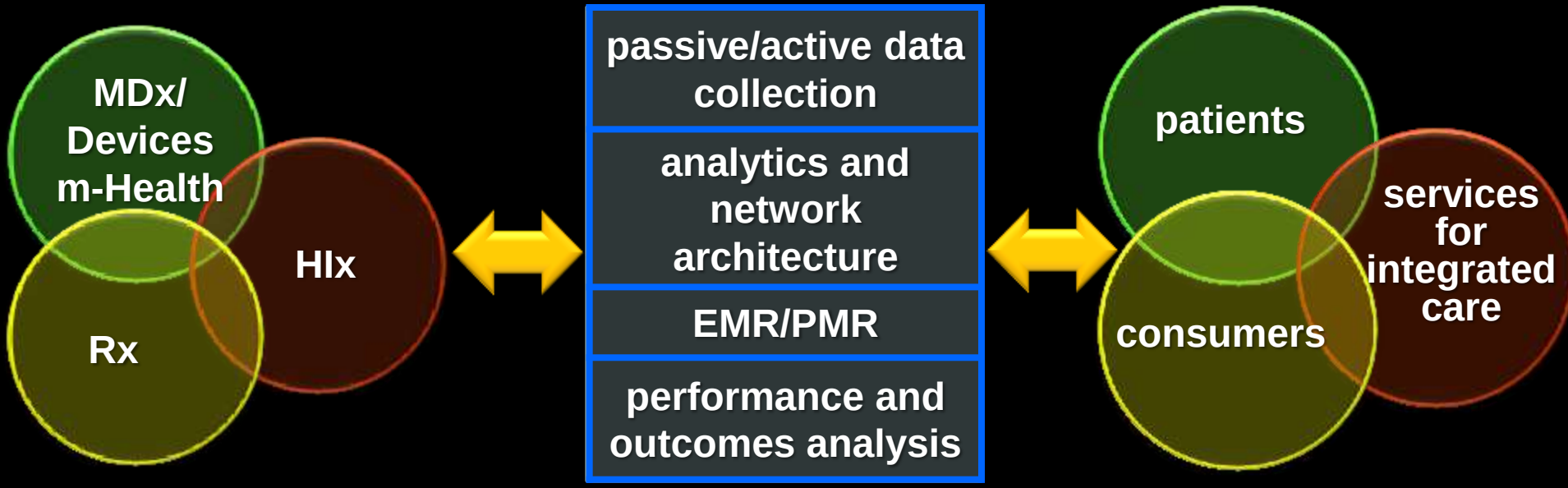
to

- distributed- and virtual-architectures connecting multiple providers, home, work and the internet
- from reactive, incident-centric, poorly coordinated and sequential referrals and inefficient post-incident monitoring

to

- pervasive, persistent monitoring of health status for pre-emptive risk mitigation and improved compliance/personal stewardship of health

A New Healthcare Ecosystem Arising From Technology and Market Convergence

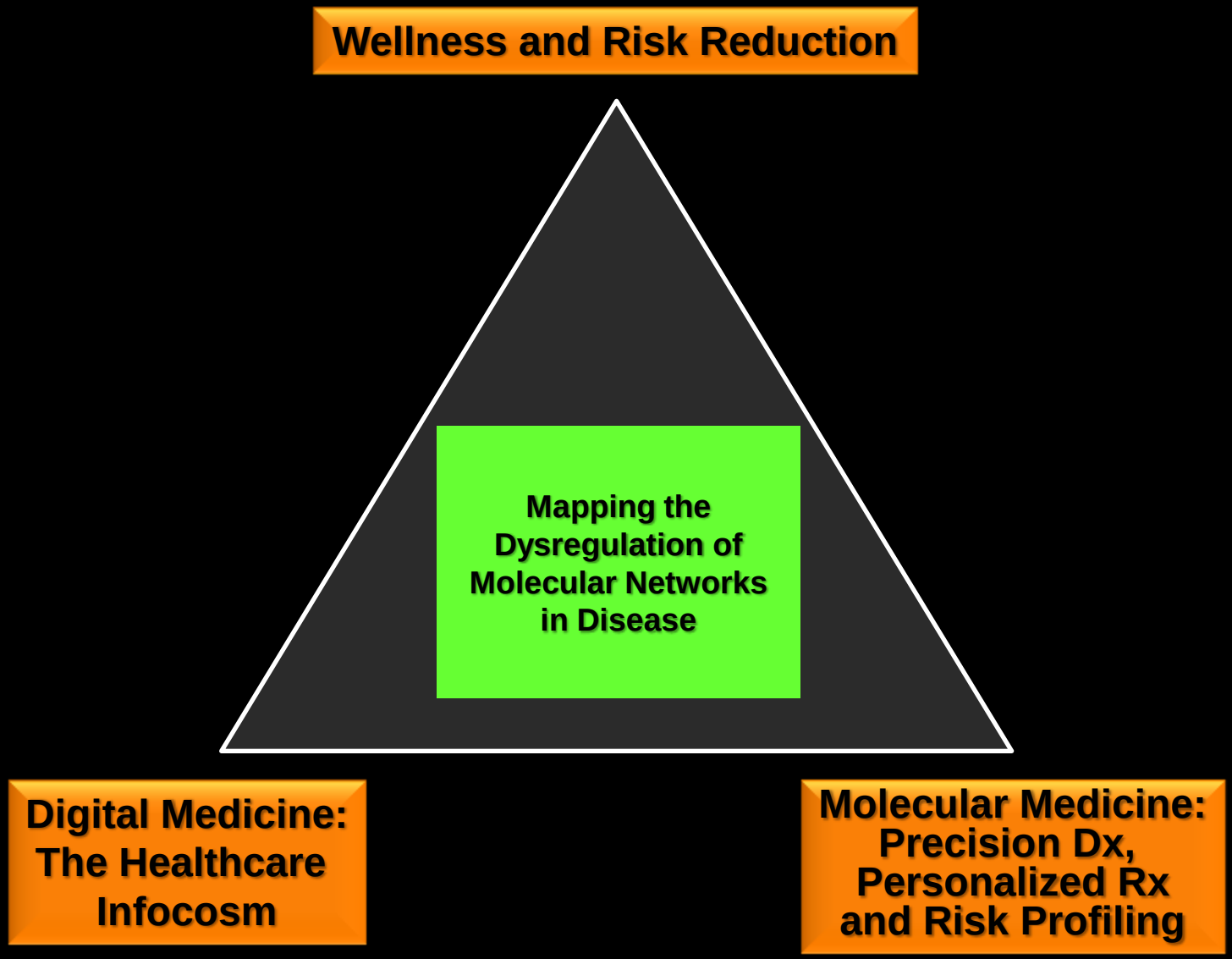


Integrated Technology Platforms for Comprehensive Profiling and Remote, Real Time Monitoring

Data Mining and Integration Services

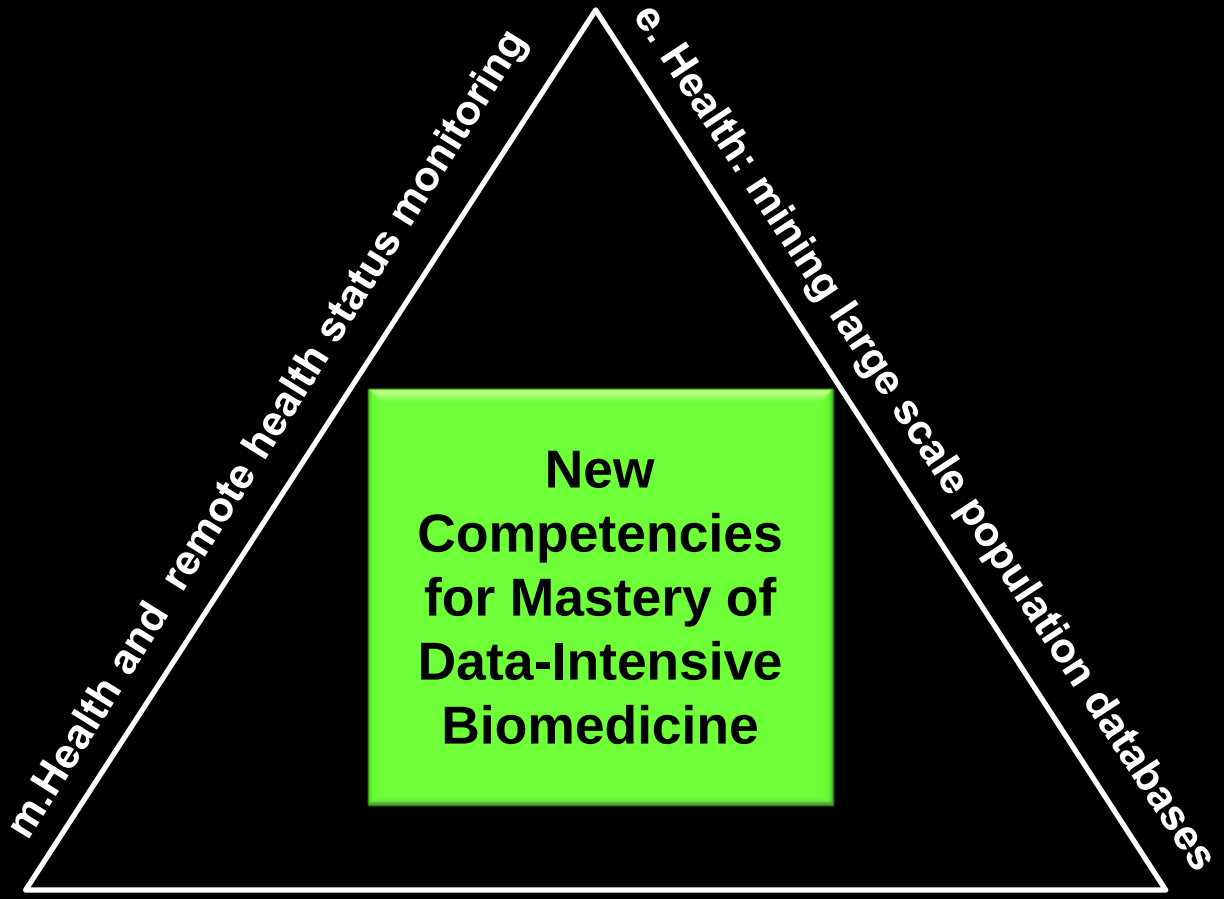
Increasingly Targeted Care and Efficient Use of Finite Resources

Charting a New Ecology for Healthcare



Building Knowledge Networks to Improve Individual Health and Sustainable Healthcare Delivery

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

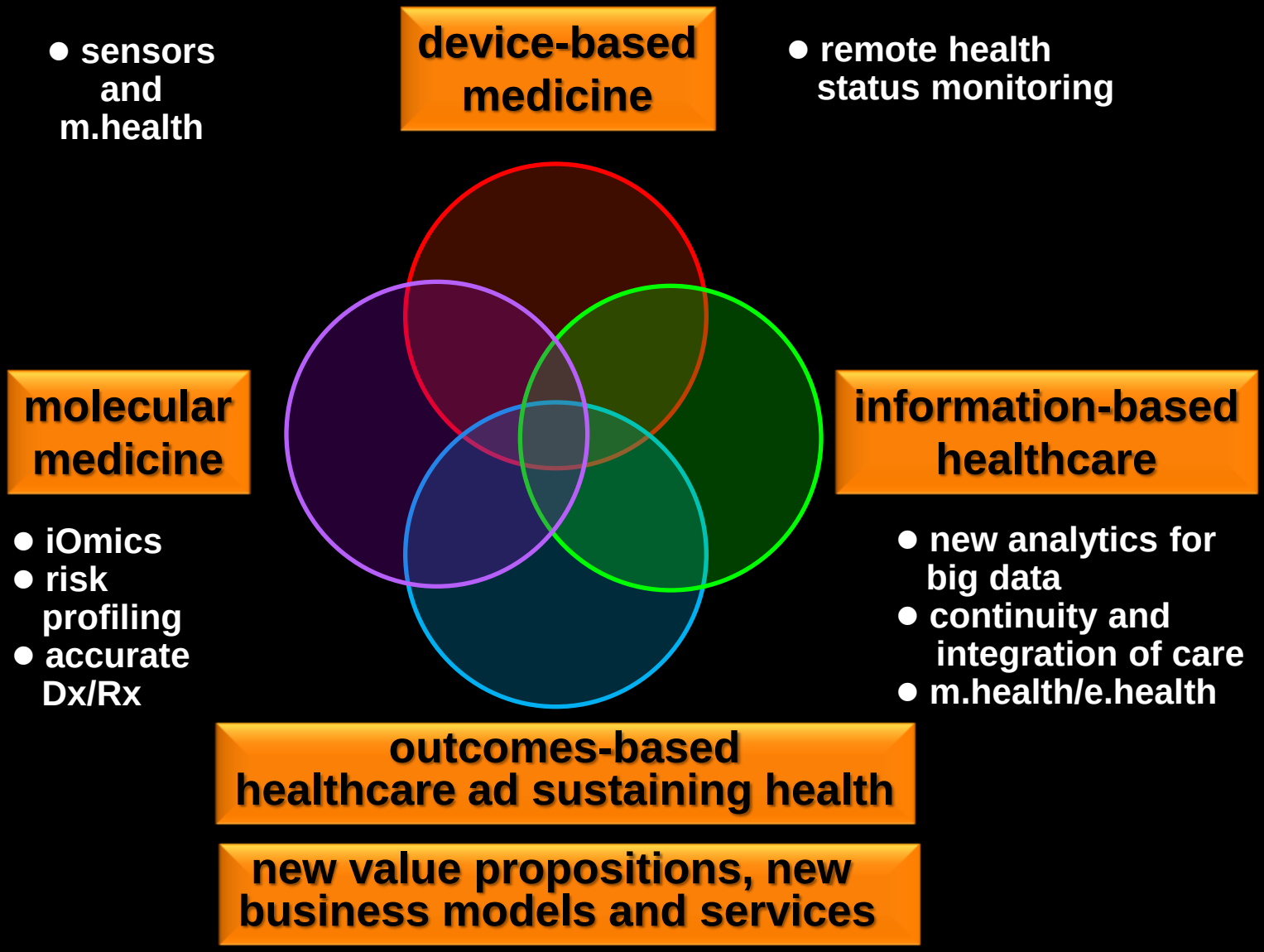


on-body, in-body sensors/devices

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

mapping the dysregulation of biological networks in disease

The Principal Forces Shaping Biomedical R&D and Healthcare Delivery



Slides Available: http://casi.asu.edu/