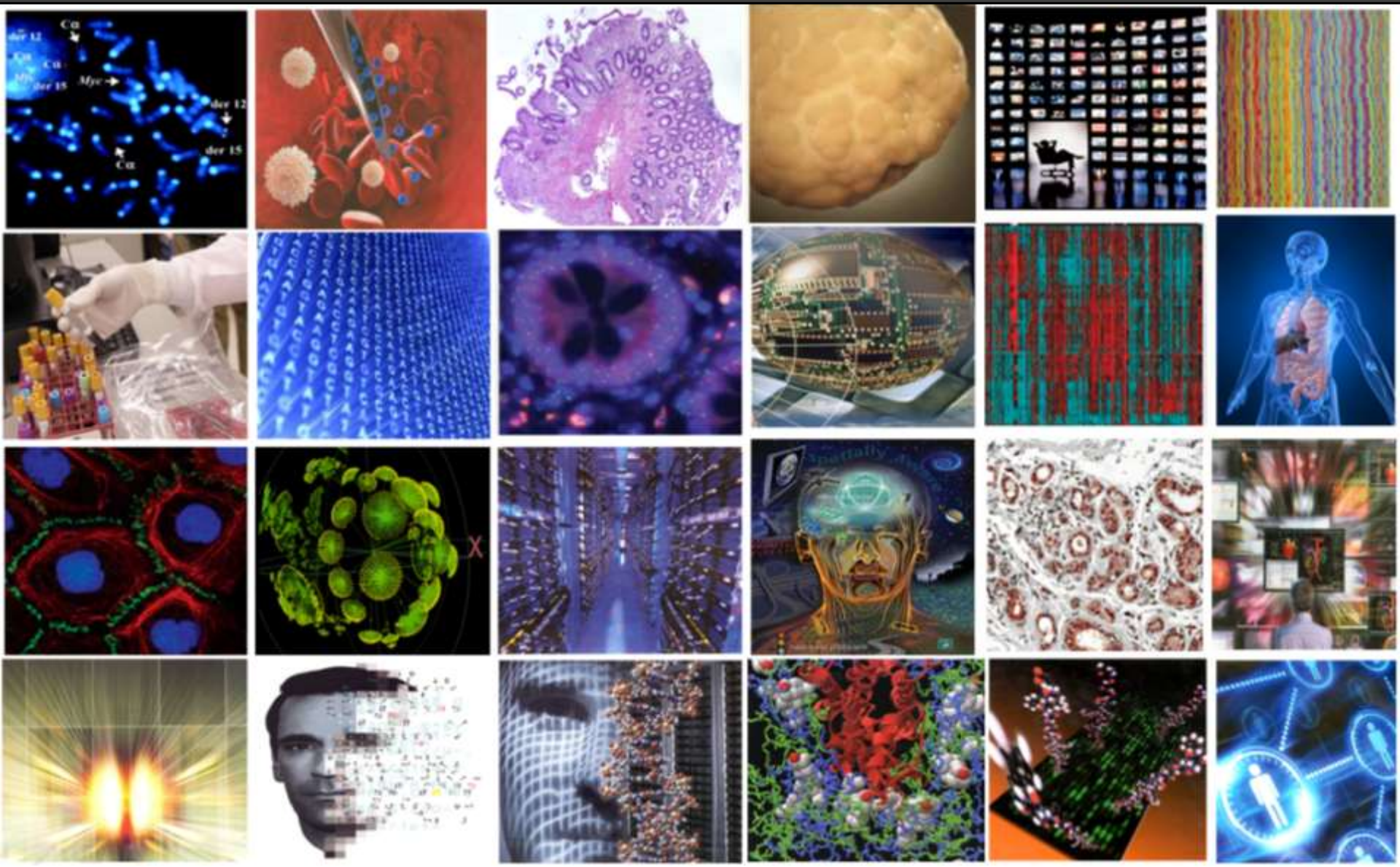
Overview of Regulatory and Reimbursement Challenges for Molecular Diagnostics and Precision (Personalized) Medicine

Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative
and Del E. Webb Chair in Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

ASU Workshop on Molecular Diagnostics:
Reimbursement and Regulation
Arizona State University
3 April 2014

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

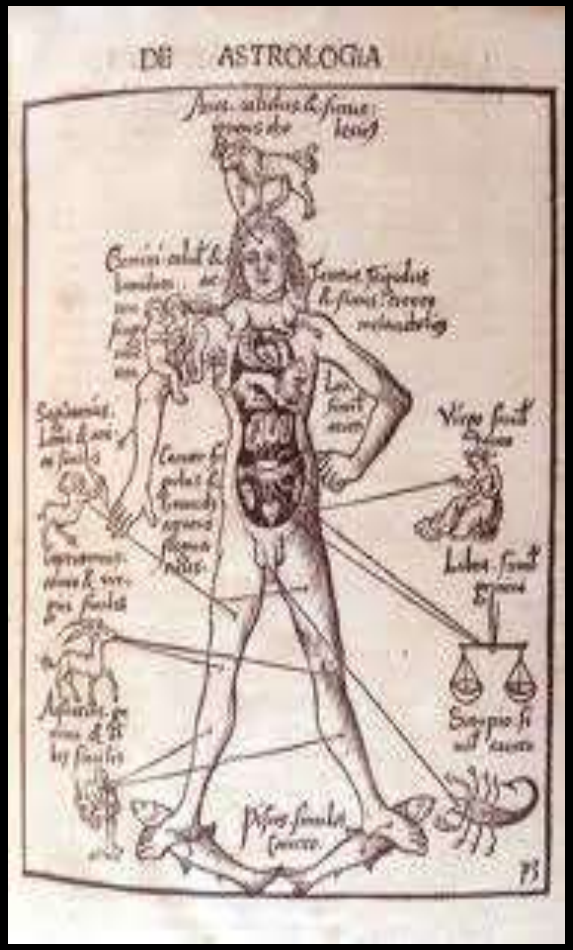
Shift From a “Do More, Bill More” Healthcare System to Managing Individual Risk for Improved Health Outcomes and Cost Control

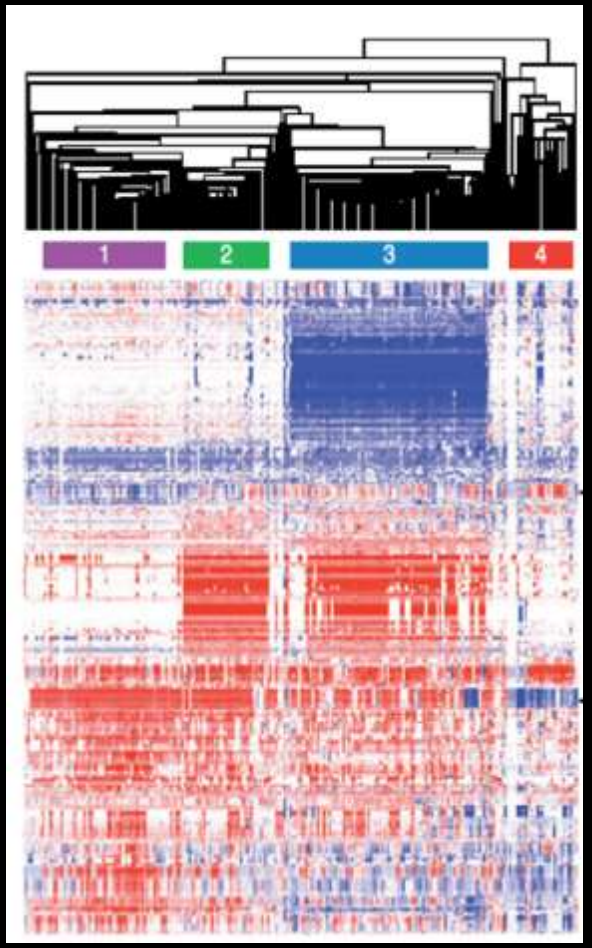
Sustainable Health: Societal (Economic) and Individual (Wellness)

The Future of Healthcare Delivery: Managing Risk

- risk detection (assessment)
- risk mitigation (management)
  - pre-emption
  - earlier detection (MDx, IMx)
  - selection of optimum response (Rx, etc.)
  - behavior (compliance, guidelines)
  - reducing R&D risk and costly clinical trial failures
  - regulatory and reimbursement risk and ROI on increasingly long and costly R&D
- the real ROI: return on actionable information

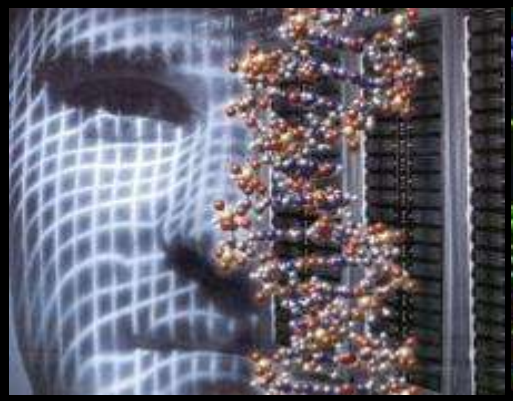
Medical Progress:
From Superstitions to Symptoms to Signatures



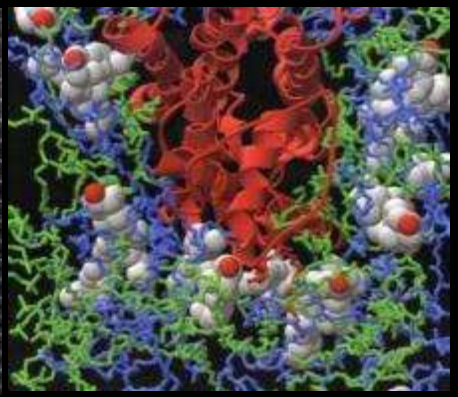


Precision Medicine: Integrated "Omics" Profiling and Mapping Disruption of Molecular Networks in Disease

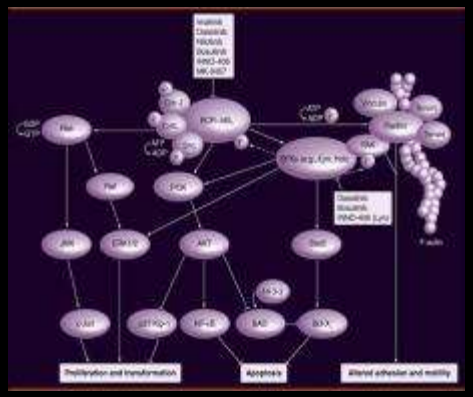
Genomics



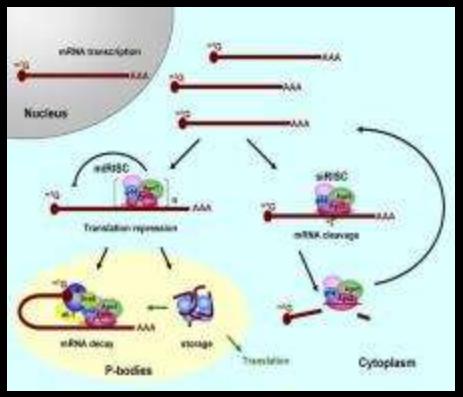
Proteomics

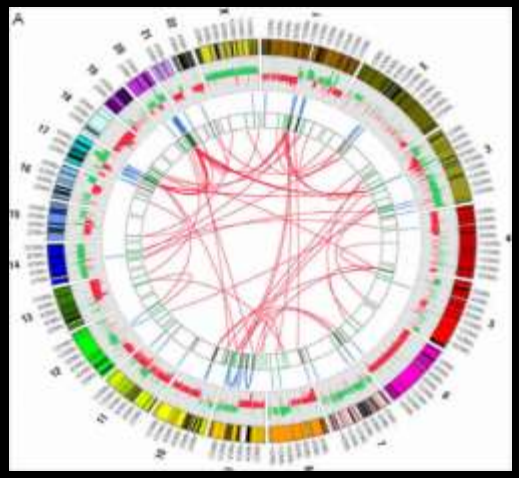


Molecular Pathways and Networks



Network Regulatory Mechanisms





ID of Causal Relationships Between Network Perturbations and Disease

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

The Evolution of Diagnostic Tests

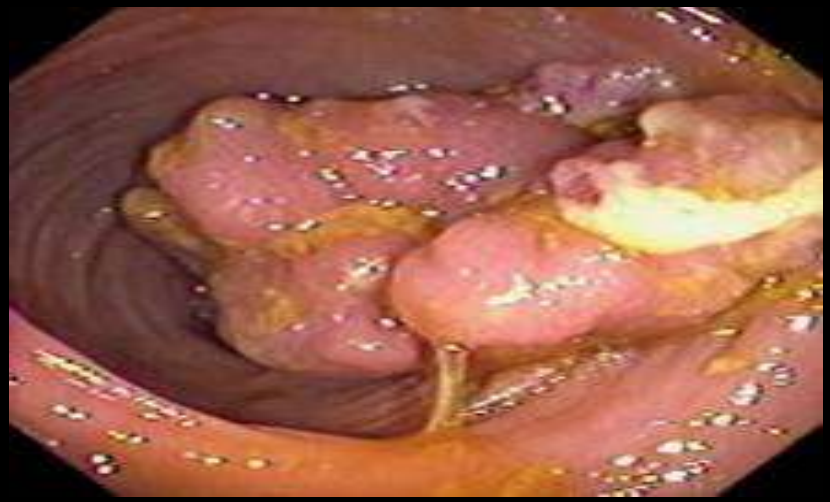
Next-Generation Molecular Diagnostic Profiling
as the Foundation for Rational Rx and Improved Care

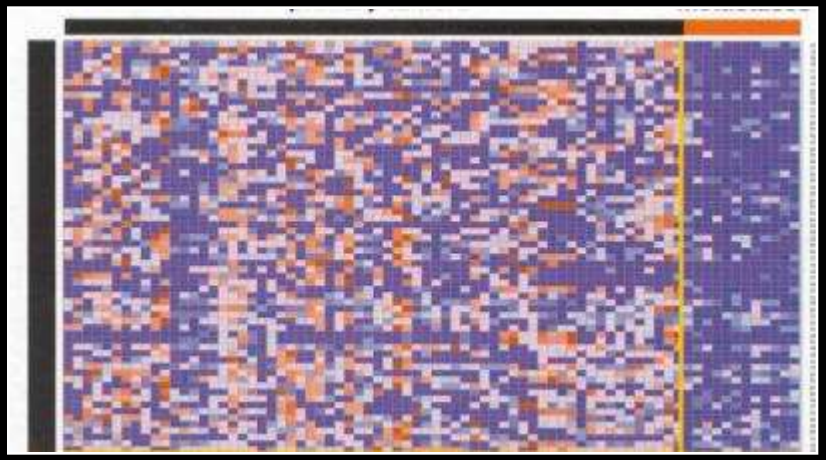
Escalating Technical Complexity of Test Development
and New Regulatory and Reimbursement Policies

From Cost-Based Pricing to Value (Outcome)-Based Pricing

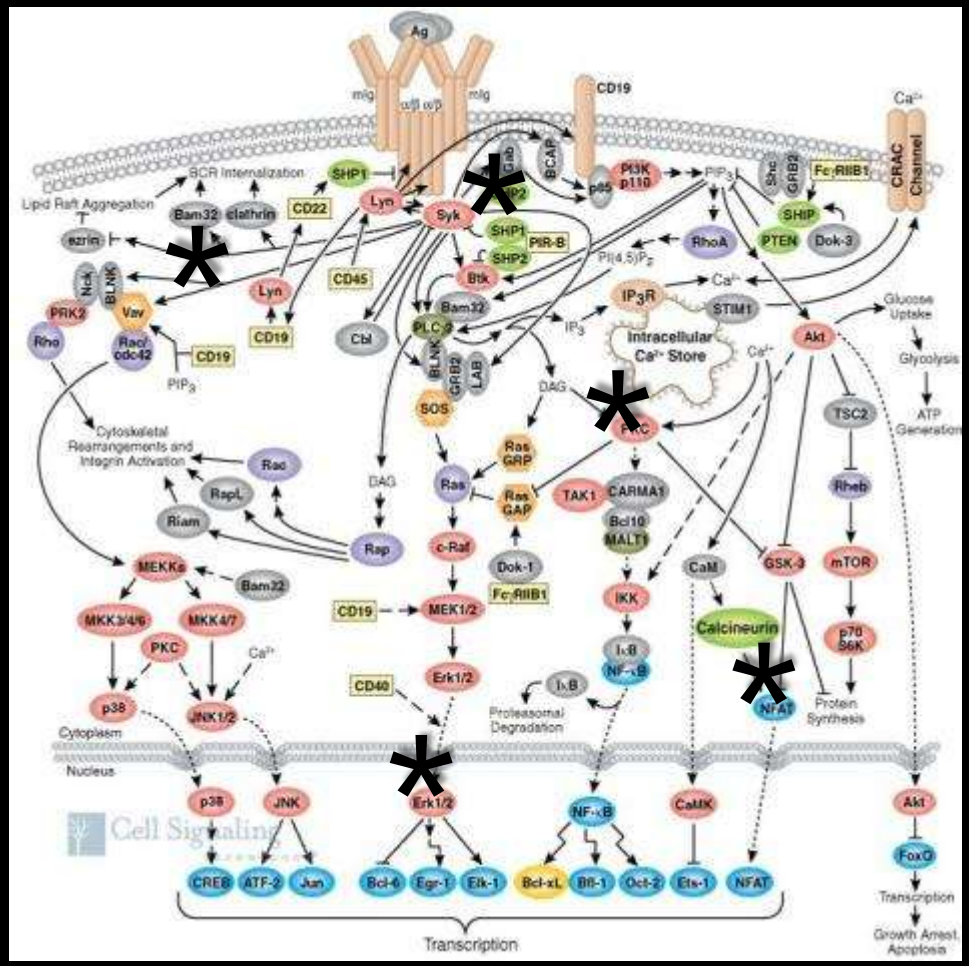
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

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

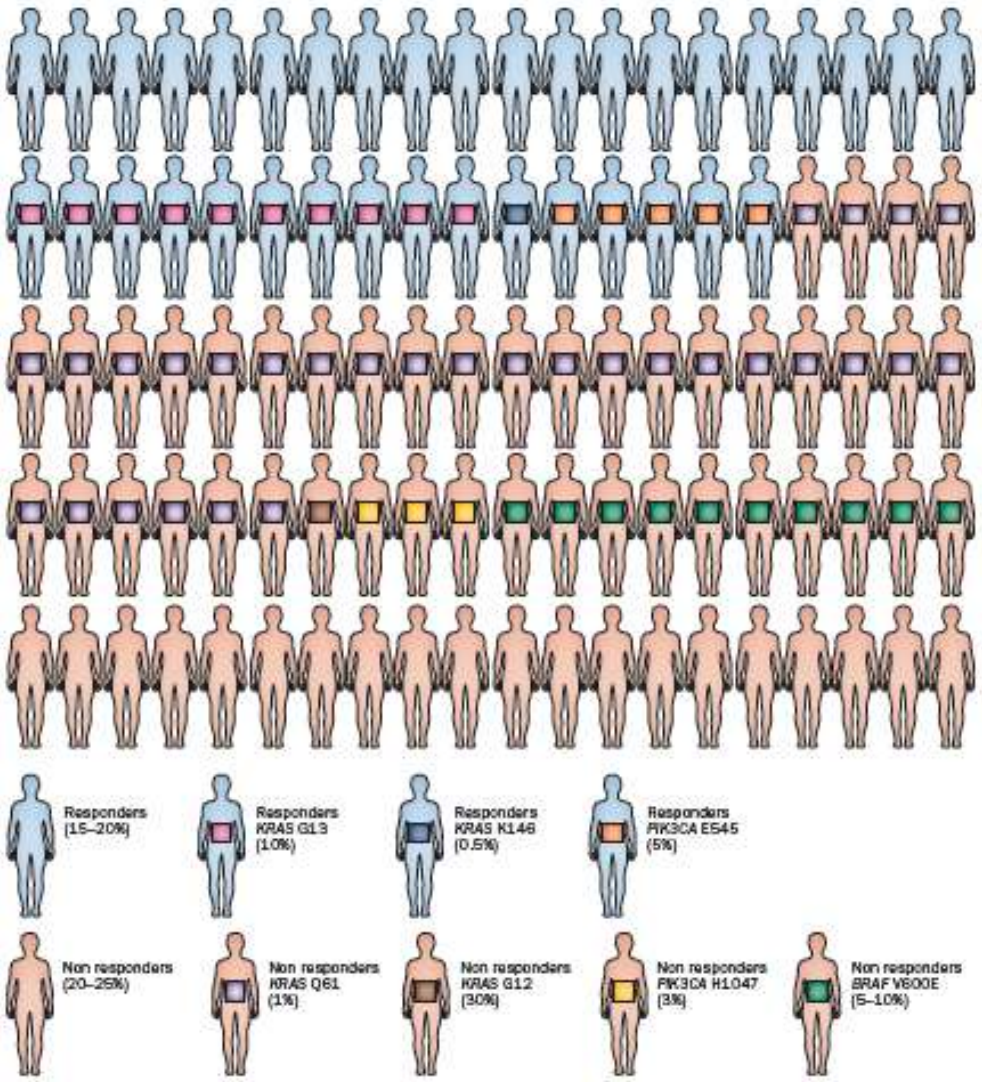




Altered Network Structure and ID of Molecular Targets for MDx and/or Rx Action



Frequencies of Molecular Alterations in CRC and Responsiveness to Cetuximab or Panitumumab

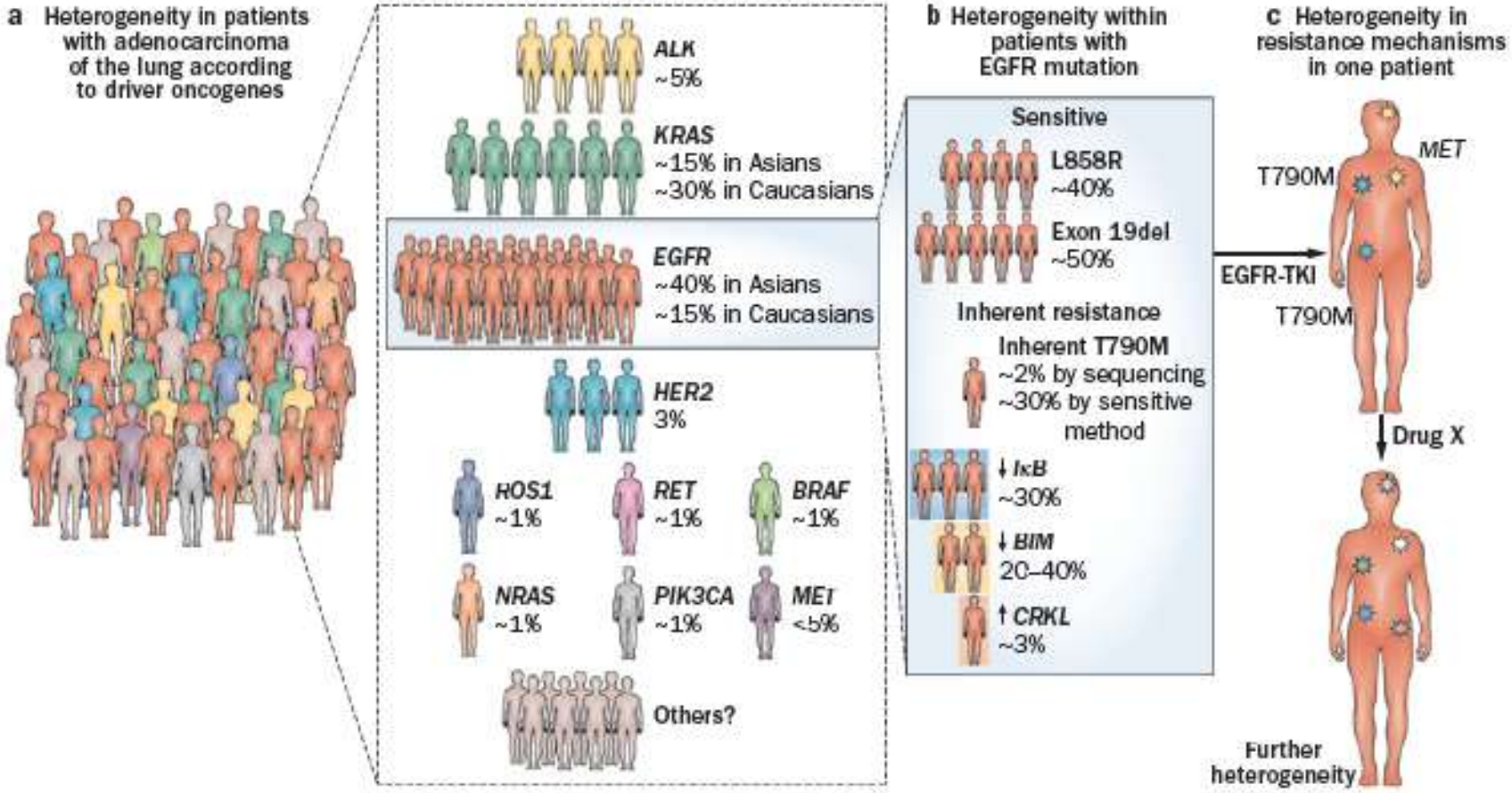


From: M. Martini et al. (2012) Nature Rev. Clin. Oncol.

Precision (Personalized) Medicine

- right Dx for right disease classification (precision)
- right Rx for right disease subtype (efficacy)
- right Rx for right patient (adverse event/AE reduction)
- right behavior to meet treatment guidelines (compliance)
- identification and mitigation of disease risk predisposition (prevention)
- agile regulatory and reimbursement systems to keep pace with technological advances (sophistication and speed)
- dynamic health technology assessment tools (value)

Heterogeneity of Driver Oncogenes in NSCLC



From: T. Mitsudomi et al. (2013) Nat. Rev. Clin. Oncol. 10, 235

Large Scale Profiling of Cancer Patients to Identify Cohorts Expressing Low Frequency 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

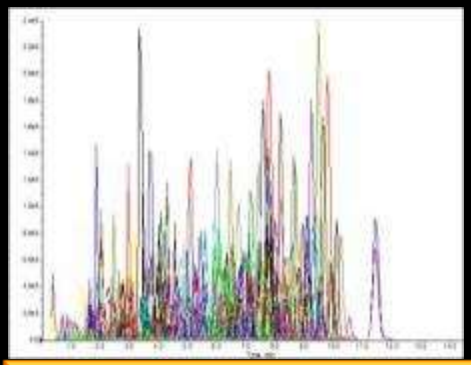
Precision Medicine and
Escalating Technical Complexities

The Need for Agile, Adaptive Regulatory and Reimbursement Policies

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

Unianalyte Tests

Multianalyte Biomarkers

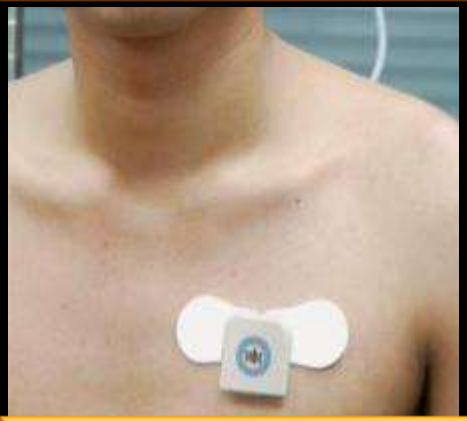


Whole Genome Sequencing

New Regulatory and Reimbursement Policies

Centralized Testing, Large Capital Base Instrumentation

On-Body: In-Body Sensors



Portable, Point of Need Diagnostic Devices

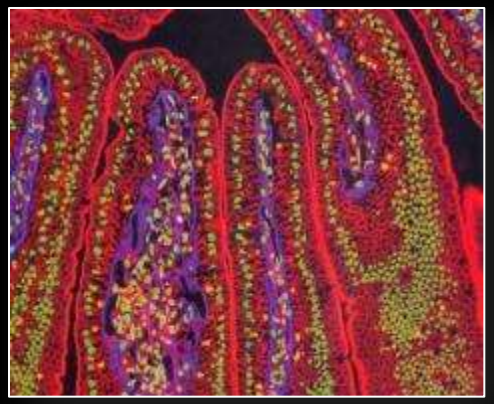
Increasingly Distributed Data Feeds and Real Time Health Monitoring

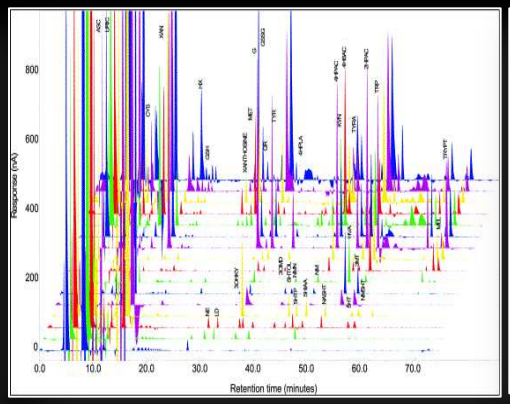
The Evolution of Diagnostic Tests

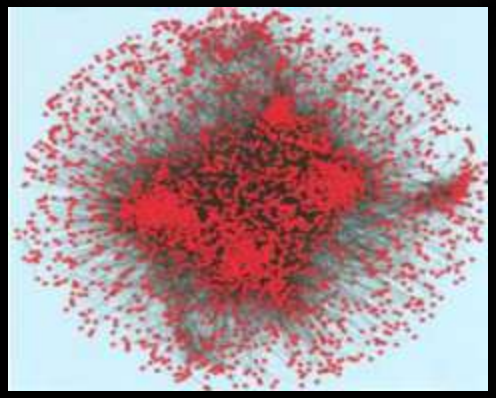
- Laboratory Developed Tests (LDTs) and CLIA oversight
  - analytical validity/competency
  - originated in era of single analyte/simple analyte tests
- 'Omics' technologies
  - multiplex profiling (signatures)
  - high dimensionality problem in analytical validation
  - algorithm based endpoints (IVDMIAs/MAAAs)
  - the looming data deluge from WGS without adequate standards

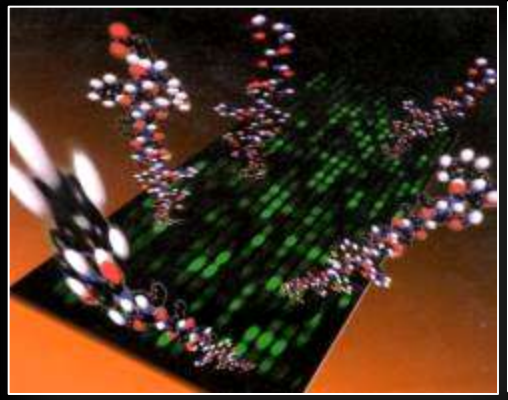
Technology Has Outpaced Regulation and Reimbursement Policies

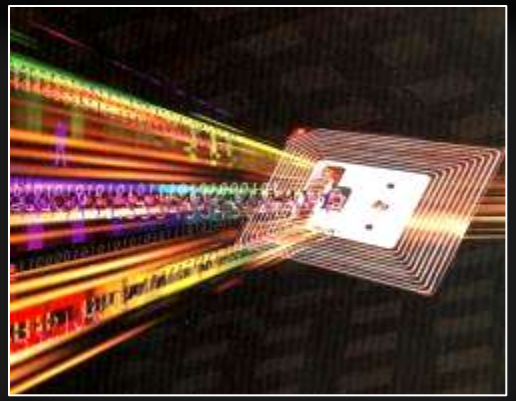
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches











Biospecimens and Analysis of Molecular Pathway/ Network Perturbations

Multiplex Assays and Complex Signal Deconvolution Algorithms

Novel Instrumentation, Automation and Large Scale Informatics

Patient Profiling, Rational Rx and Health Monitoring

Next-Generation “Omics” Diagnostic Tests

- dramatic increase in technical complexity, development time and cost versus traditional LDTs
- requires skillsets, resources and business risk foreign to historical unianalyte test development and industrial investment in diagnostics R&D
- complex probabilistic endpoints versus binary decisions

WILL

- Whole Genome Sequencing (WGS) Change Everything?

WHEN

- Will WGS Become Just Another Laboratory Test Value?

HOW

- Will WGS Affect Patient Care?

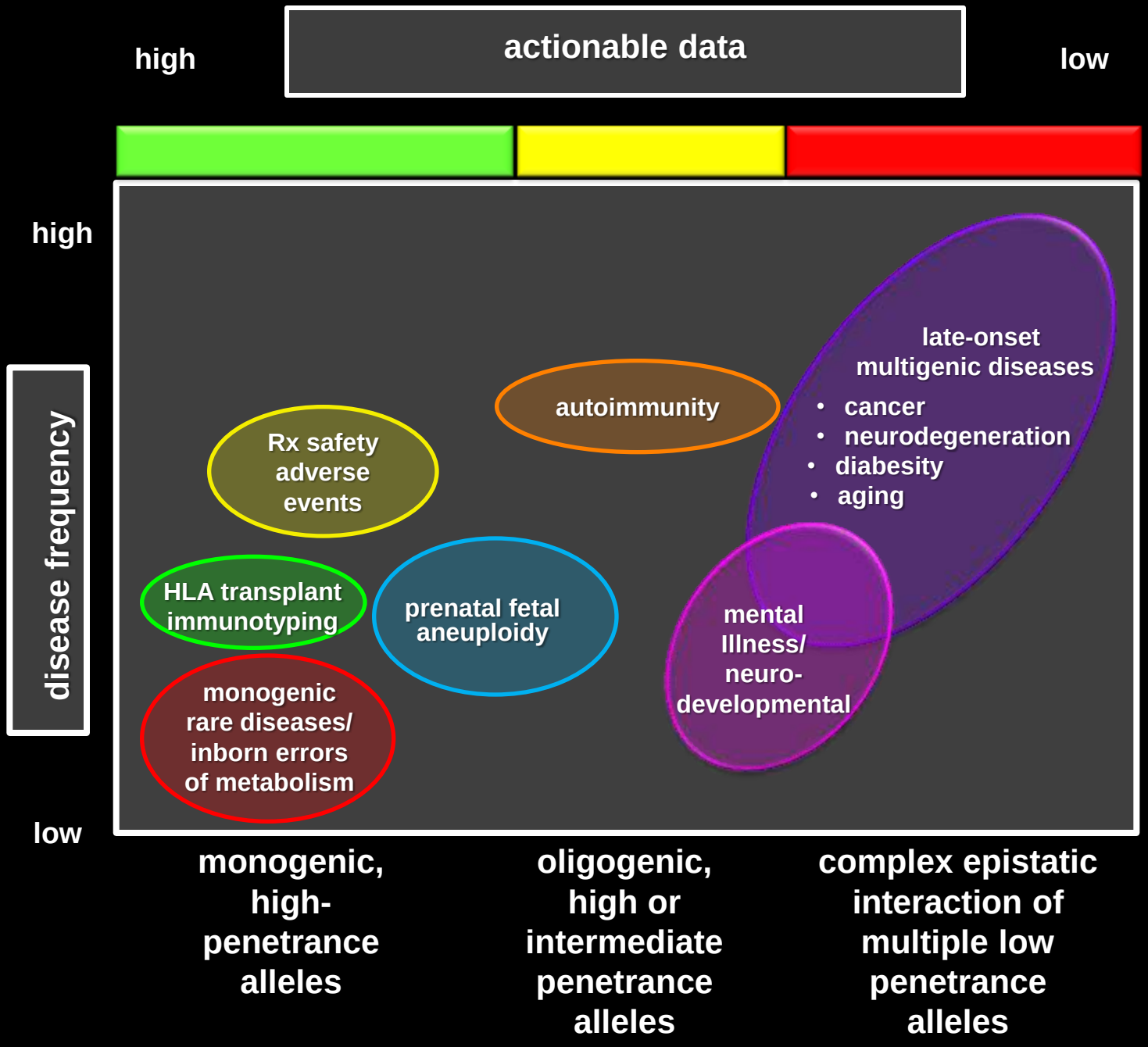
- The $1000 (or less) Whole Genome Sequence (WGS)
- The $? Interpreted WGS
- The $? Reimbursed WGS for Clinical Use
- Techno-optimism and the Seduction of New Technologies: Hype and Herd Mentalities

Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS)

- regulatory issues
  - accuracy, instrumentation, reagents
  - analytical algorithms and evidentiary standards
- reimbursement
  - value (economic and clinical)
- education
  - massive information gap (analysis) and education gap (clinical practice)
- legal and ethical issues

Novel, Actionable Information: The Key Value Driver in Genome Sequencing

- immediately actionable
- known association/causation of disease but no Rx available
- informative (biological plausibility and likely causal but not actionable)
- unknown clinical significance


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

Molecular Medicine: Managing "The Incidentalome"

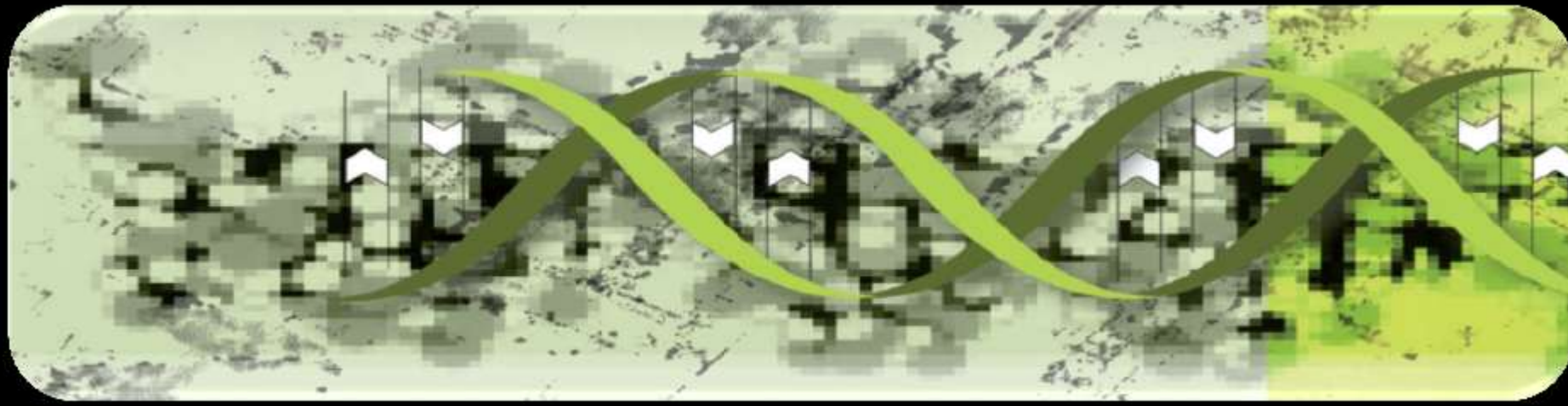
- identification of incidental disease risk factors during research and/or clinical omics profiling for a different purpose
- evidentiary standards and decision thresholds for follow-up/recontact research participants
- duties/obligations to recontact/reprofile based on new knowledge?
- consented vs. non-consented follow-up
- obligations to inform extended biological pedigree of serious risk(s)
- declining guarantees for anonymity, privacy and confidentiality

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

“FDA is concerned about the public health consequences of inaccurate results from the (Personal Genome Service) device; the main purpose of compliance with FDA’s regulatory requirements is to ensure that the tests work.”

Alberto Gutierrez
Director of the FDA’s Office of In Vitro Diagnostics and Radiological Health,
in a letter to 23andMe CEO Ann Wojcicki
telling her company that the company must stop marketing its genomic testing kits or face FDA sanctions
November 22, 2013

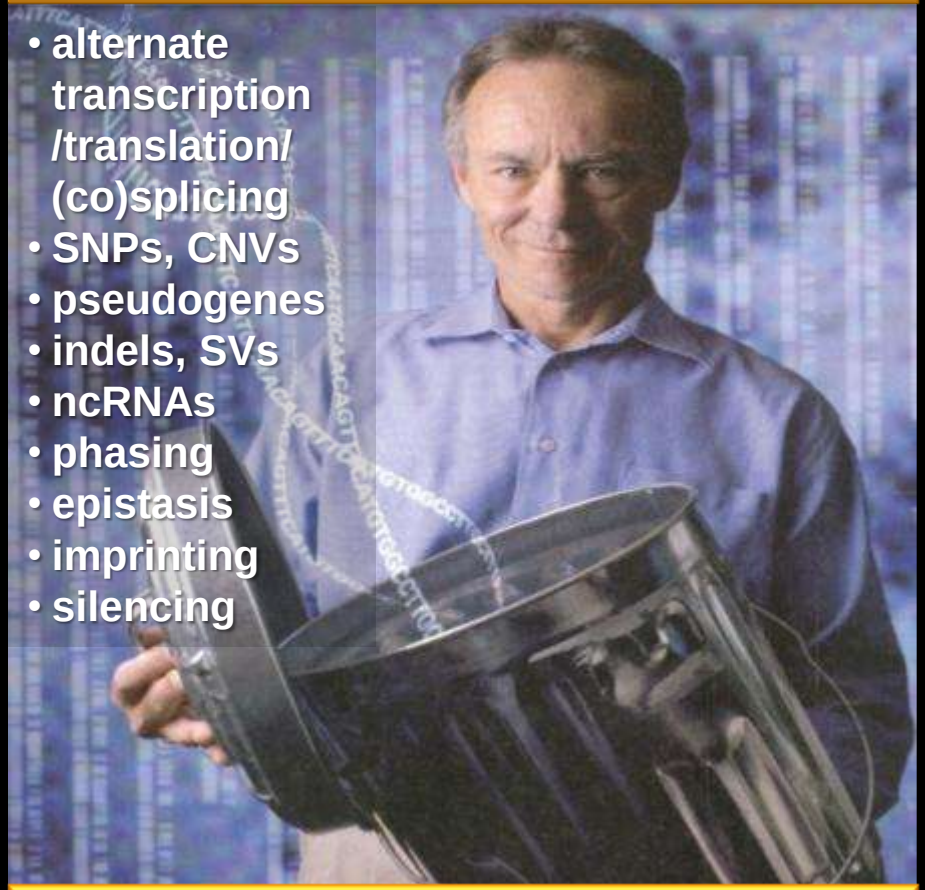
Genes For ….
The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective



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

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

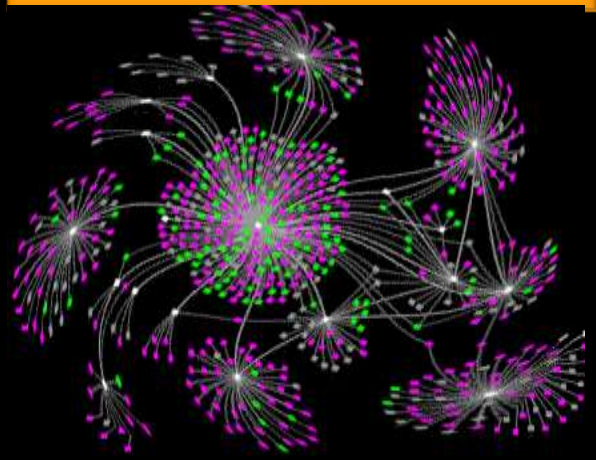
Junk No More: Pervasive Transcription



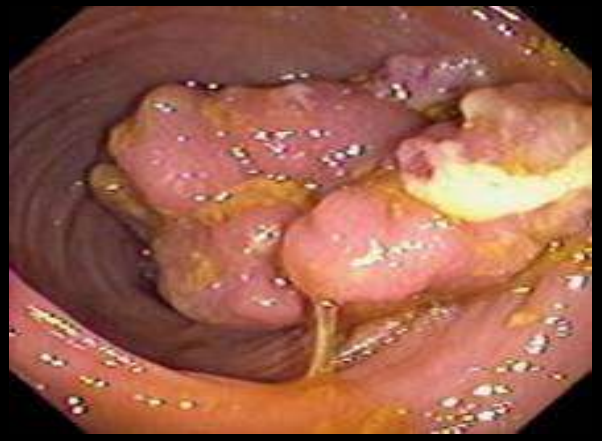
- alternate transcription /translation/ (co)splicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- ncRNAs
- phasing
- epistasis
- imprinting
- silencing

recognition of genome organizational and regulatory complexity

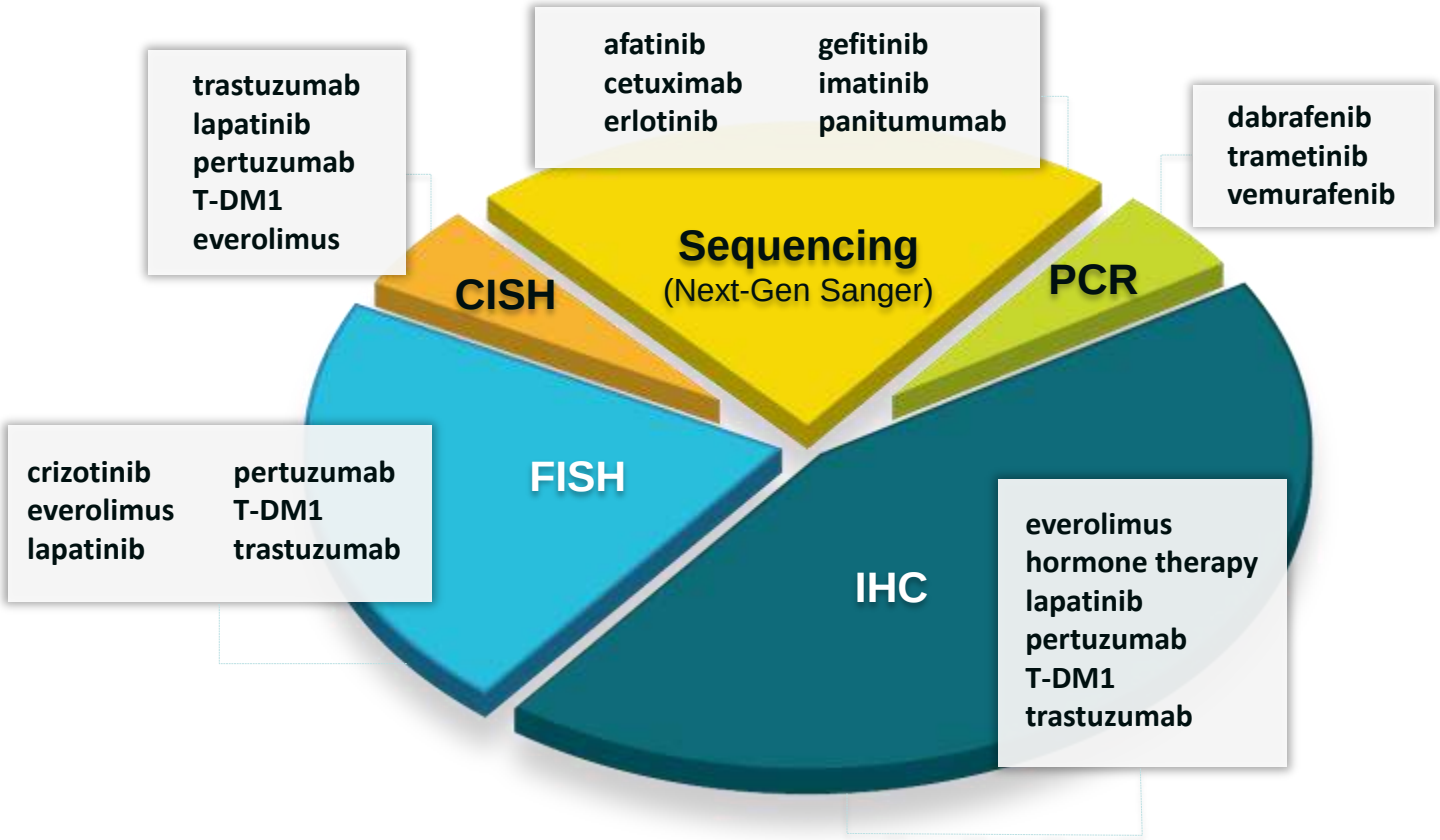
Cell-specific Molecular Interaction Networks



Perturbed Networks and Disease



The Need for Multi Molecular Diagnostic Platforms to Maximize the Number of Actionable Drug: Target Associations to Guide Therapeutic Decisions



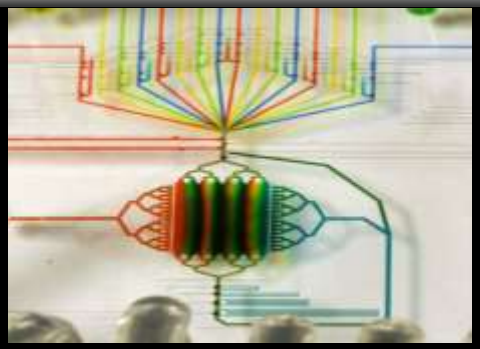
FISH = fluorescent in situ hybridizaiton

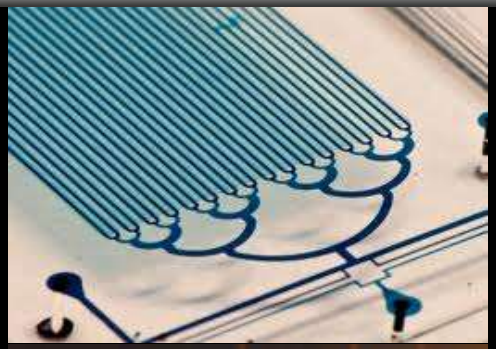
CISH = chronogenic in situ hybrization

IHC = immunohistochemistry

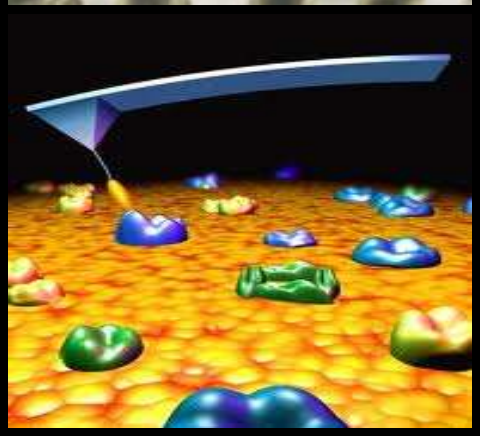
Invasion of the Body Trackers

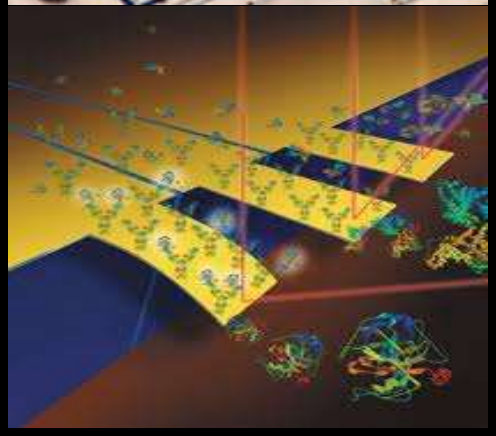
Miniaturization of Analytical Technologies



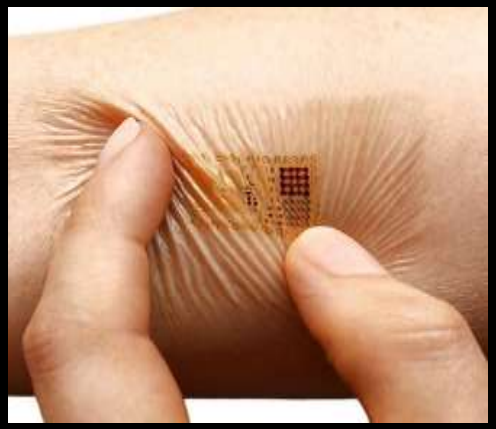


“Lab-on-a-Chip”





“Lab-on-a-Tip”



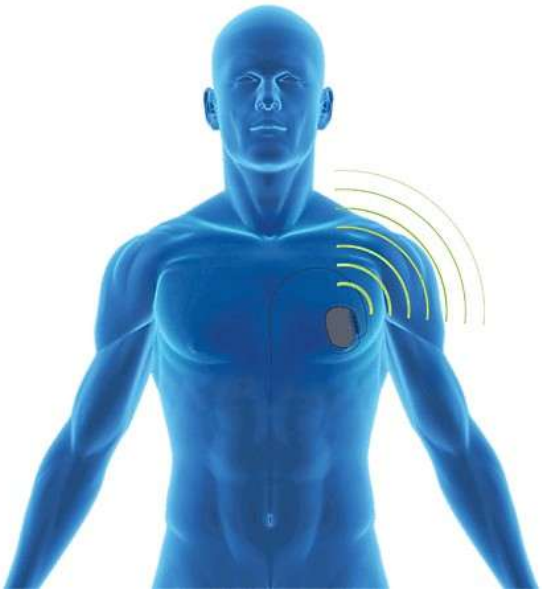
“Lab-Always On”
and
“Lab-On-Me”

Invasion of the Body Trackers

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

Remote Health Status Monitoring

m.Health



Real Time Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

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

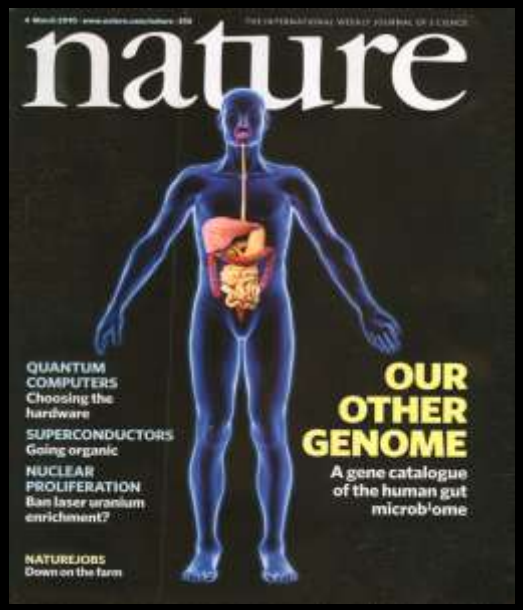
- extend reach and continuity in care
- each individual becomes their own control
- better real time patient-specific data and decision-support tools
- new patterns (touch points) of patient engagement with the health system
  - AORTA: Always-On-Real Time Access
  - new delivery channels and services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

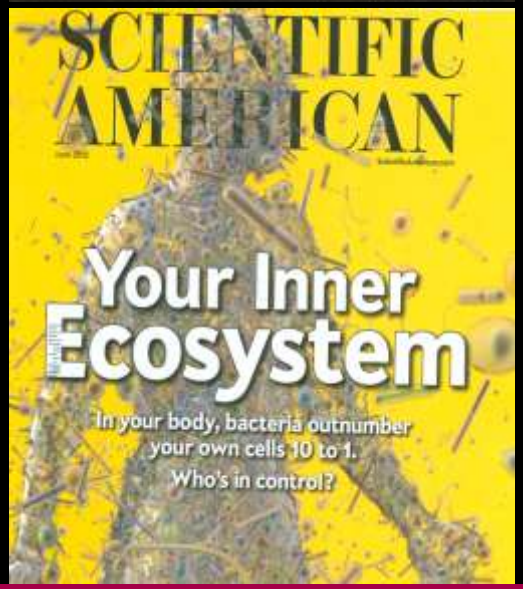
The Microbiome

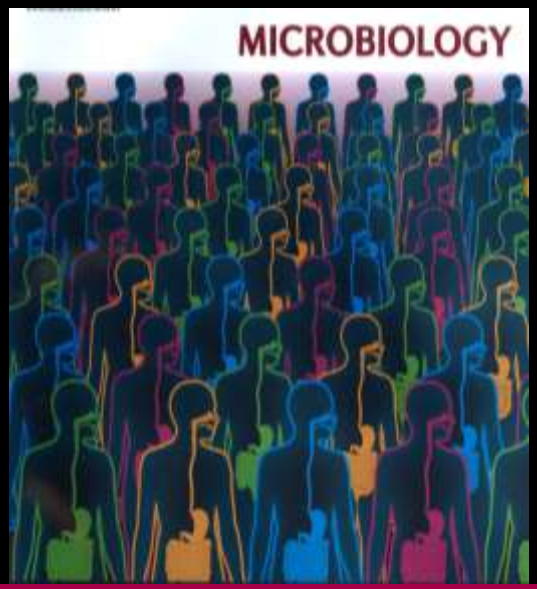
We Are Not Alone!

The Growing Recognition of the Importance of the Body's Commensal Bacterial Population in Health and Disease

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

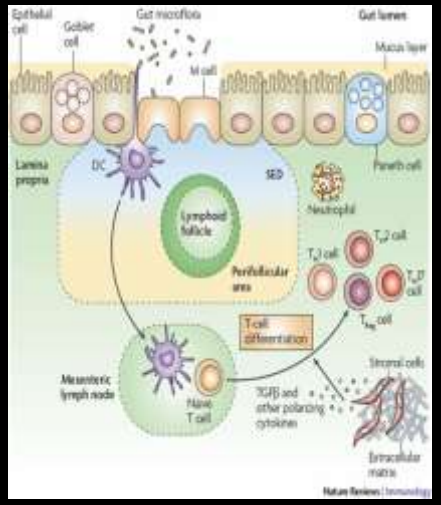


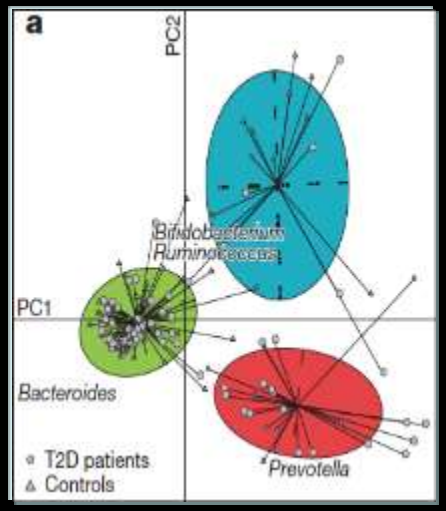


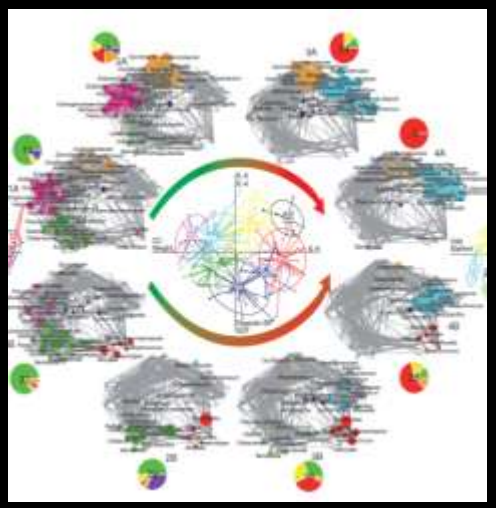


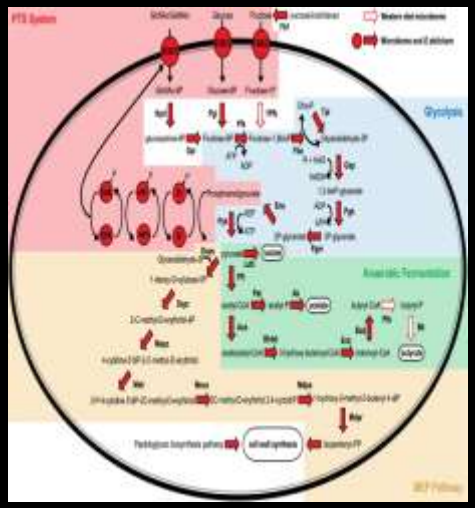
Commensal Microbiomes: The "Frenemy Within" An Additional Dimension to Biomarker Profiling

Metagenome-wide Association Studies (MGWAS)



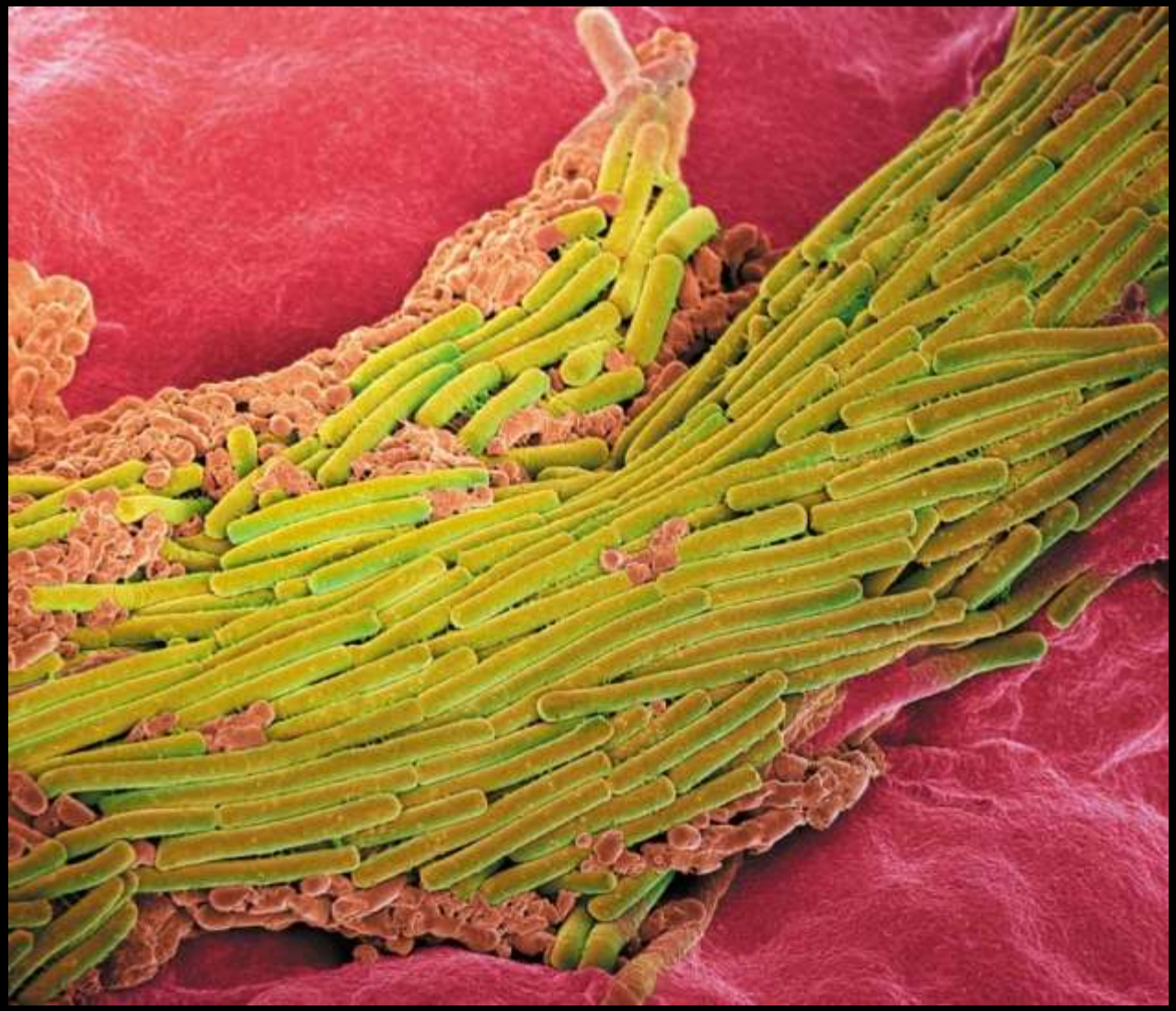






Immune-Mediated GI Diseases	Type 2 Diabetes Profile	Aging Metabolism and Fragility	Metabolic Activation of Carcinogens/ Pollutants

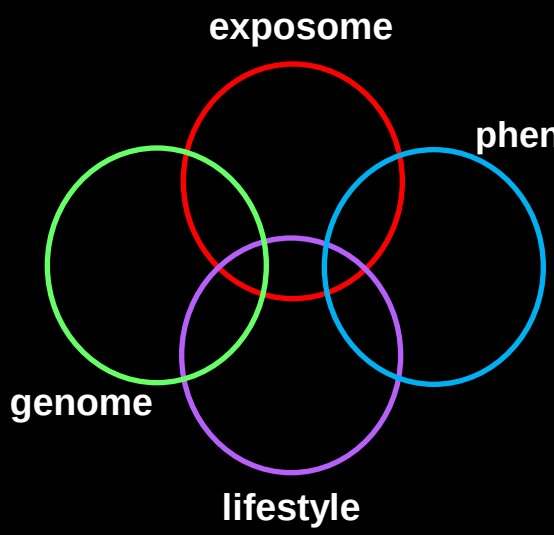
Regulation of Human Fecal Transplants: Biological Drug or Cell Therapy or Tissue?



C. difficile **infection and refractory infection**
Nature (2014) 506, 290

Science Photo Library

Information-Based Services for Increased Precision in Managing Risk in Healthcare



data curation and analysis

risk identification and mitigation + decision-support tools

- earlier detection of disease
- rational Rx
- monitoring of health status
- predisposition risk
- risk pre-emption

profiling → **analysis** → **informed decisions**

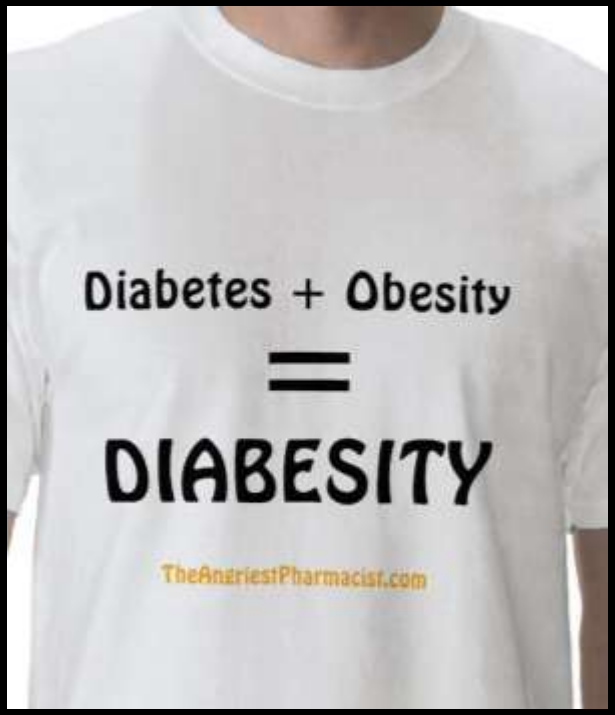
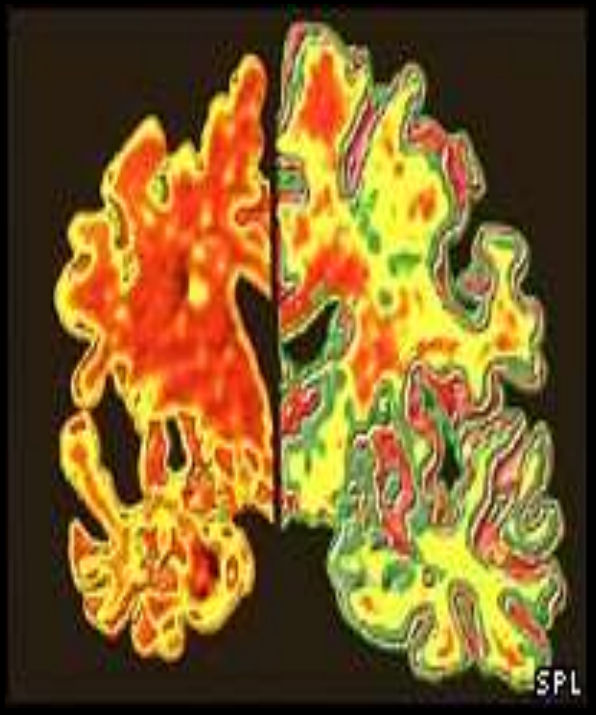
Keeping Pace With Technical Advances

- Regulatory Science
- Health Technology Assessment
- Clinical Guidelines and Standard-of-Care (SOC)
- Reimbursement
- Defining Value

If You Build It, Will They Pay?
If It Isn't Billable, It Won't Happen!

- #1 will test alter patient management?
  - reduce cost of care
  - improve outcomes
- #2 what additional resources/services/training are affected by test adoption?
- #3 perception of RCT as only 'gold standard'
  - narrow interpretation that discounts value of observational studies
- #4 payer demand for regulatory approval to be eligible for reimbursement or CED
- #5 mindset of 'lab data' as low cost (<1% total cost) despite role in most treatment decisions (>85%)
  - unianalyte versus multiplex tests
  - outdated US reimbursement codes

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

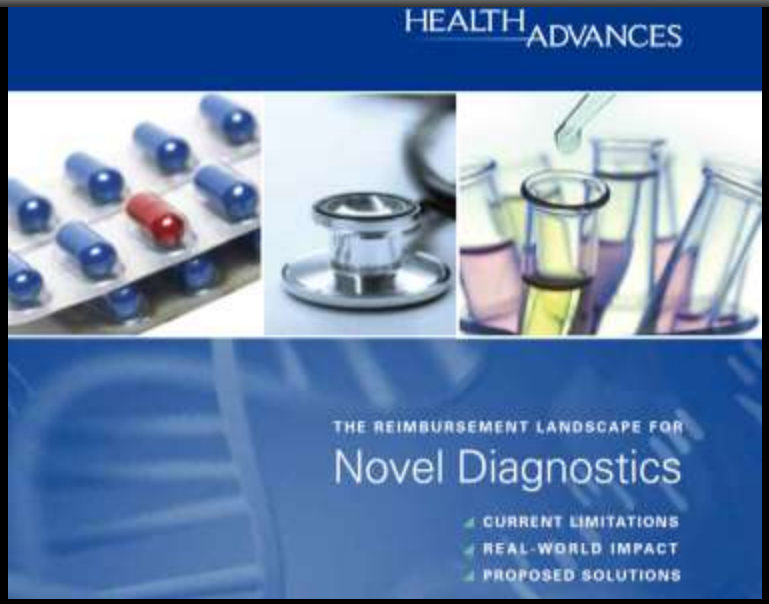
Cancer Detection Before Metastasis	Cardiovascular/ Metabolic Diseases	Neurodegenerative Diseases
		
Early Diagnosis and Curative Surgery	Lifestyle Changes and/or Rx to Limit Risk	The Dilemma of Early Diagnosis Without Rx

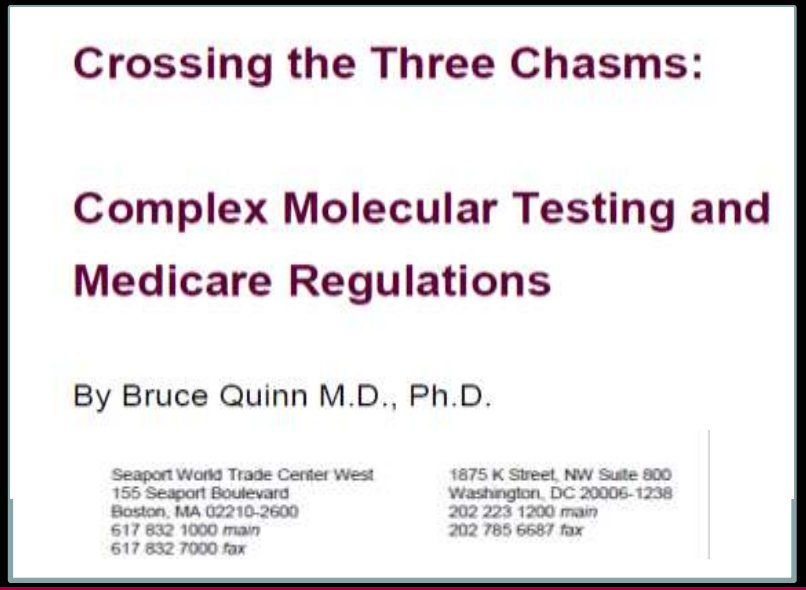
Circumventing The Reimbursement Problem

New Yorker 23 Jan. 2012

“When I grow up, I want to go into medicine and help people who can pay out of pocket.”

Educating Payors on the Value of Biomarkers in Healthcare: Shift from Cost-Based Pricing to Value-Based Reimbursement to Incentivize Biomarker R&D



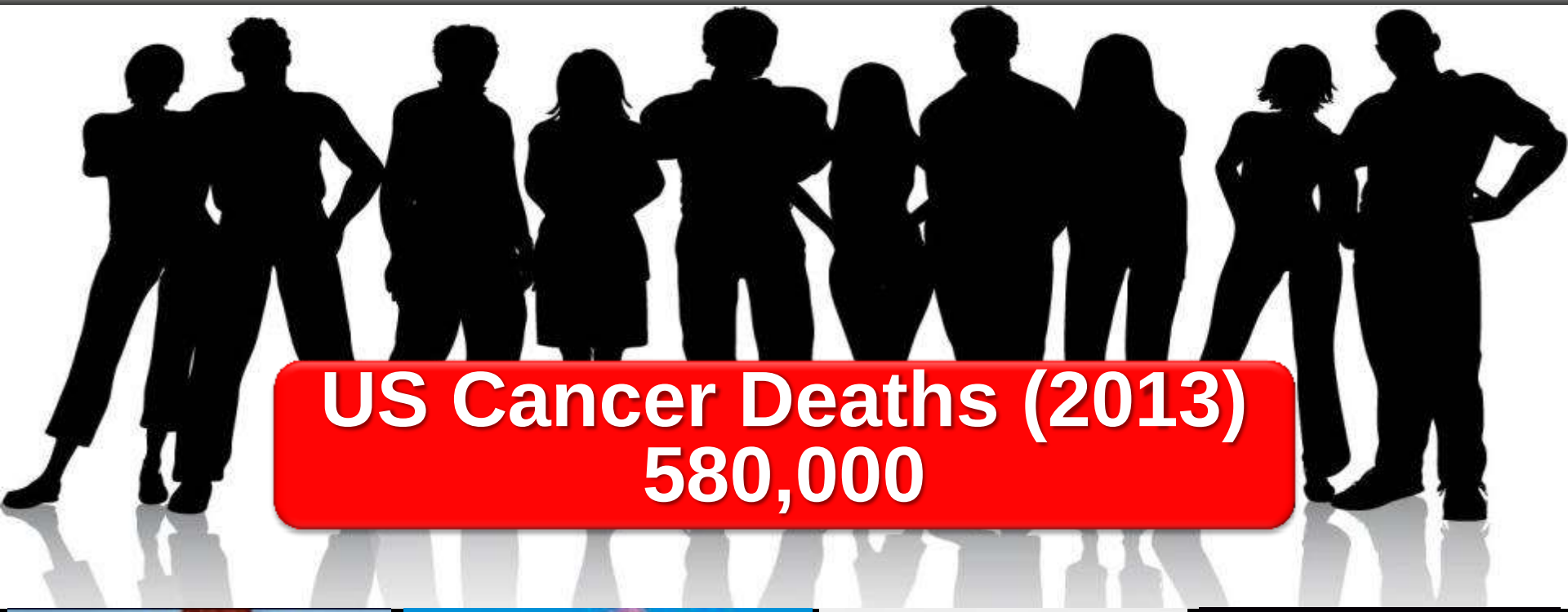


Cancer: A Case Study in Technology Assessment

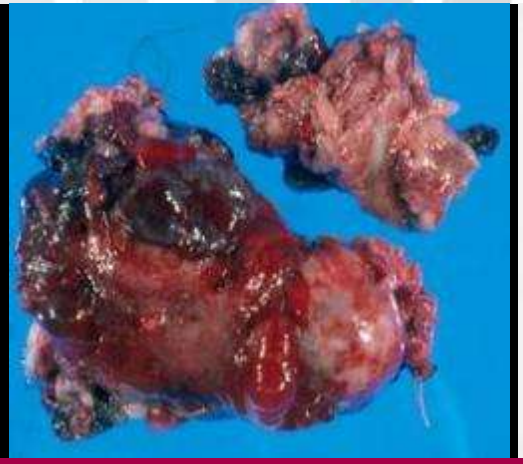
A Study in Reimbursement Policy Contrasts:

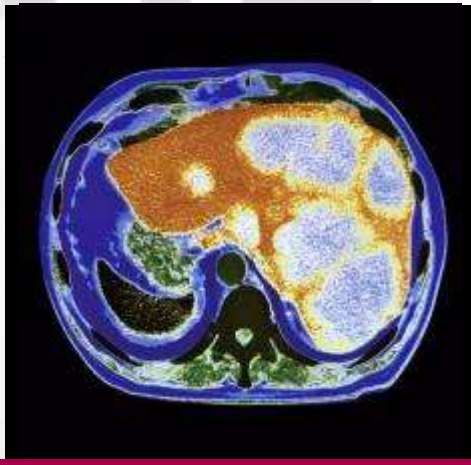
Targeted Therapeutics (Rx) Versus Molecular Diagnostics (MDx) in Oncology

Confronting the Clinical, Economic and Human Toll of Cancer



US Cancer Deaths (2013)
580,000



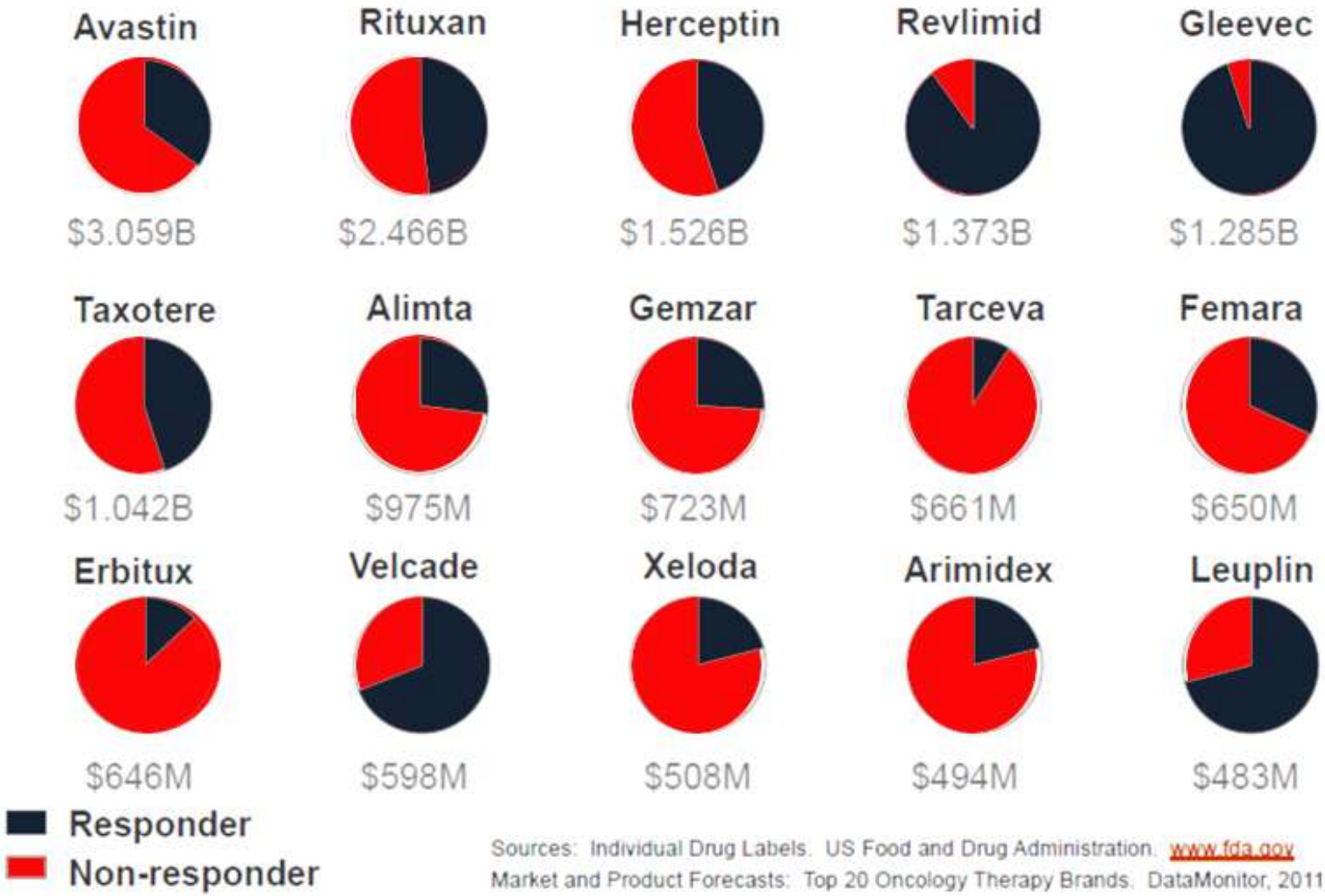


The Projected Increase in US Cancer Cases (2010 to 2020)

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

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

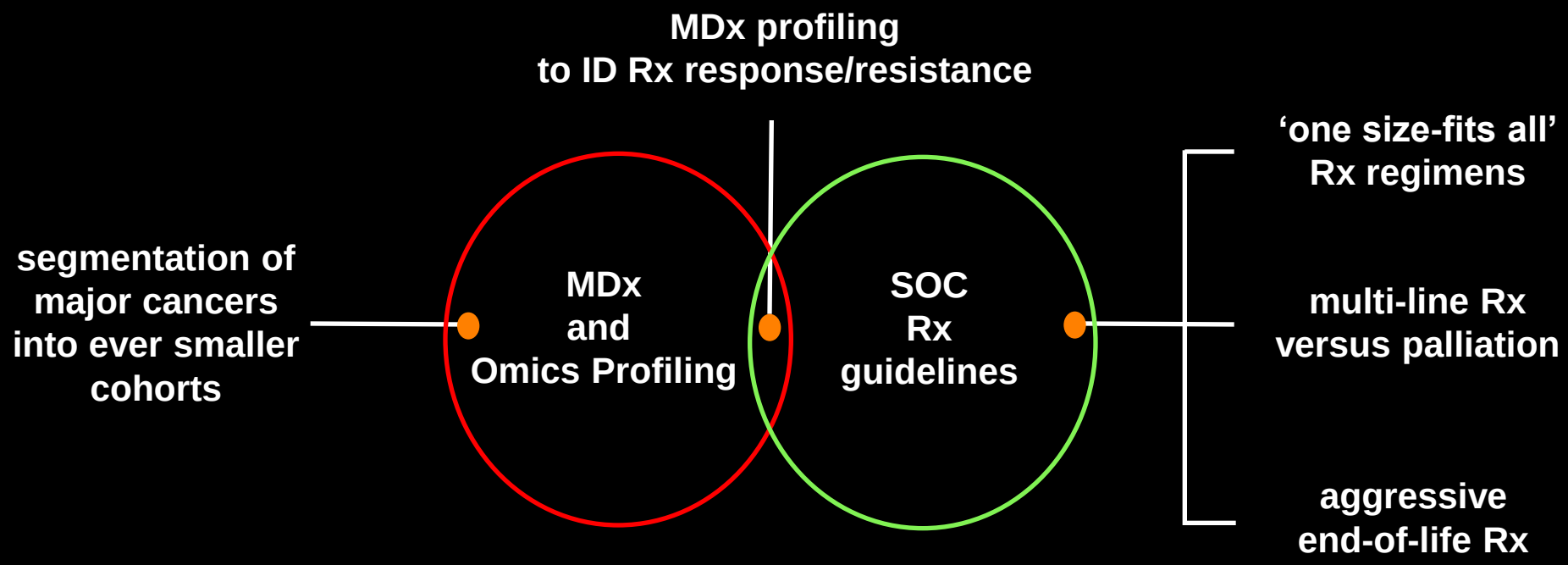


Sources: Individual Drug Labels. US Food and Drug Administration. www.fda.gov
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

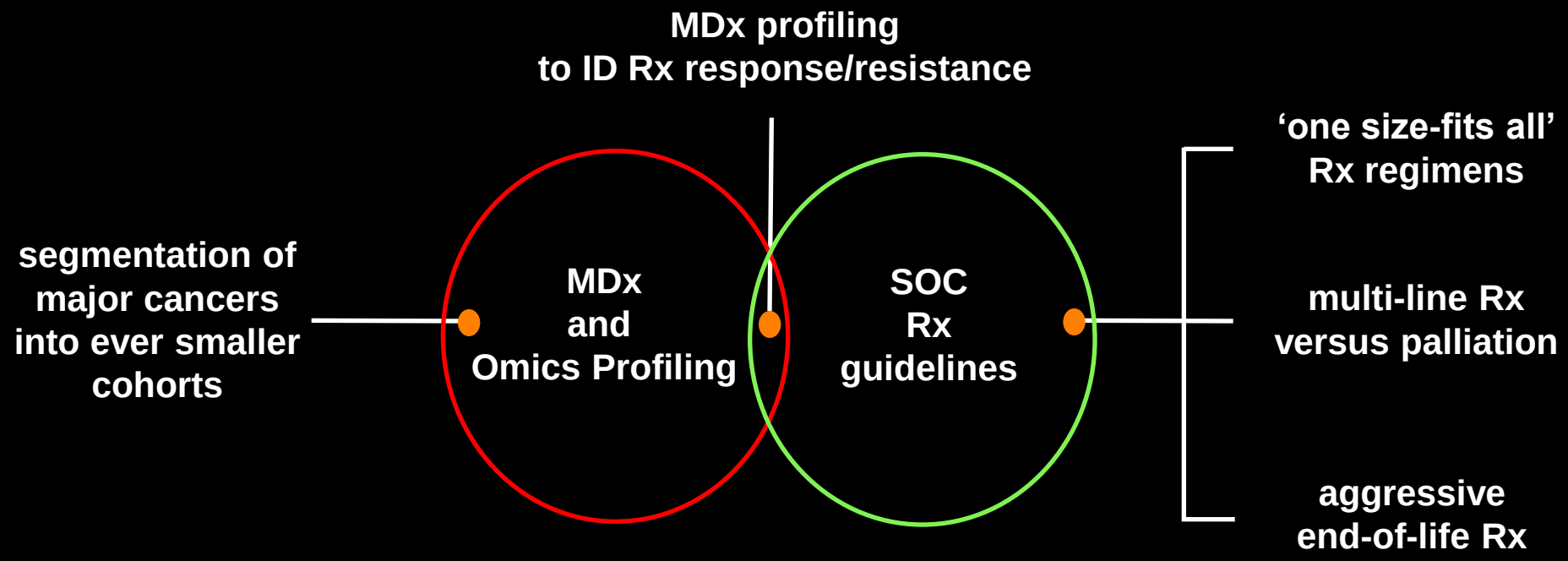
Cost of Recently Approved Anti-Cancer Drugs

- brenfuximab (Adcetris) $216,000/course
- ipilimab (Yervoy) $123,000/year
- cabazitaxel (Jevtana) $96,000/year
- sipuleucel-t (Provenge) $93,000/year
- vismodegib (Erivedge) $75,000/course
- petuzumab (Perjeta) $70,800/year
- vemurafenib (Zelboraf) $61,000/year
- abiraterone (Zimiga) $60,000/year
- premetrexed (Alimta) $30,000/course

Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology



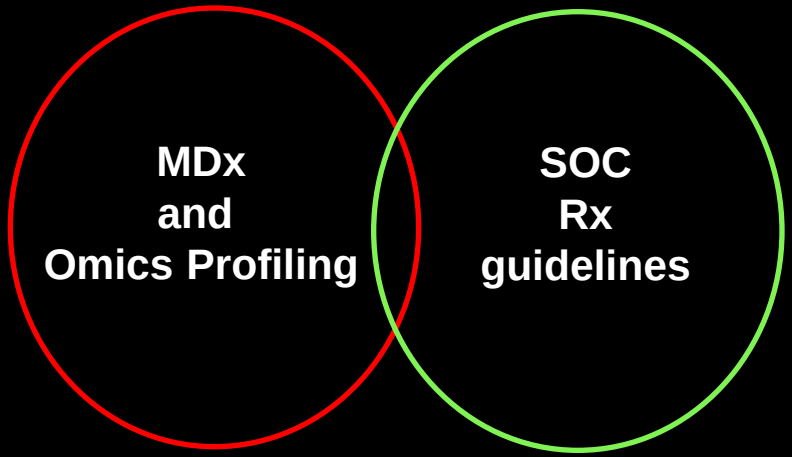
Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology



Foundation for Precision Diagnosis and Rational Treatment Selection

Propagation of Irrational Therapeutic Strategies With Limited Effectiveness

Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology

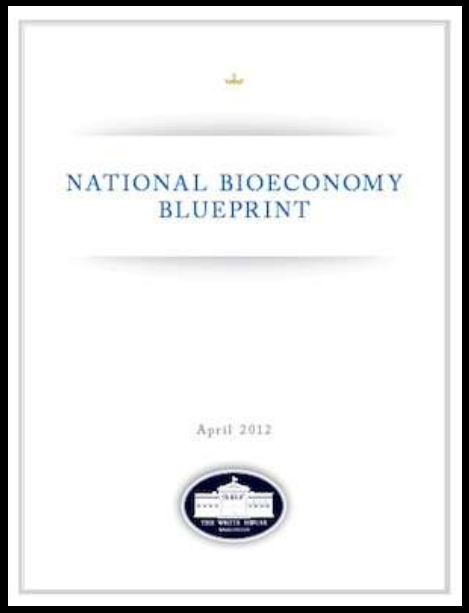


- Cost-Based Versus Value-based Pricing
- Uncritical Acceptance of Rx Pricing
- Barriers to Innovation and Recovery of Increasing R&D Cost
- Incentives to Sustain Inadequate Rx Discovery Strategies

Reimbursement for Molecular Diagnostics and Related Omics Profiling Tests

- current payment policies based on earlier era of comparatively simple (low technical complexity) tests
  - time and materials used to conduct test
  - no premium for cost recovery for escalating test complexity/R&D investment for next-generation “Omics” tests
- failure of CPT coding to match pace of technical advances in MDx/WES/WGS
- inadequate HTA/reimbursement/business models for value-based pricing of next-generation diagnostic platforms

CMS Coverage with Evidence Development (CED)



"CMS…..believes that the lessens learned during the initial implementation of CED can inform its more frequent use and create predictable incentives for innovation while providing great assurance that new technologies in fact fulfill their initial claims of benefit."

National Bioeconomy Blueprint
The White House, April 2012

Reimbursement for Multi-Analyte Algorithmic Tests

- FDA: In Vitro Diagnostic Multivariate Index Assay (IVDMIAs)
- AMA/CMS: Multi-Analyte Assays with Algorithmic Analysis/(MAAA)

"Medicare does not recognize a calculated or algorithmically derived rate or result as a clinical laboratory test since the derived rate or result alone does not indicate the presence or absence of a substance or organism in the body."

B. Malone (2013) Clinical Lab News 39 (1)

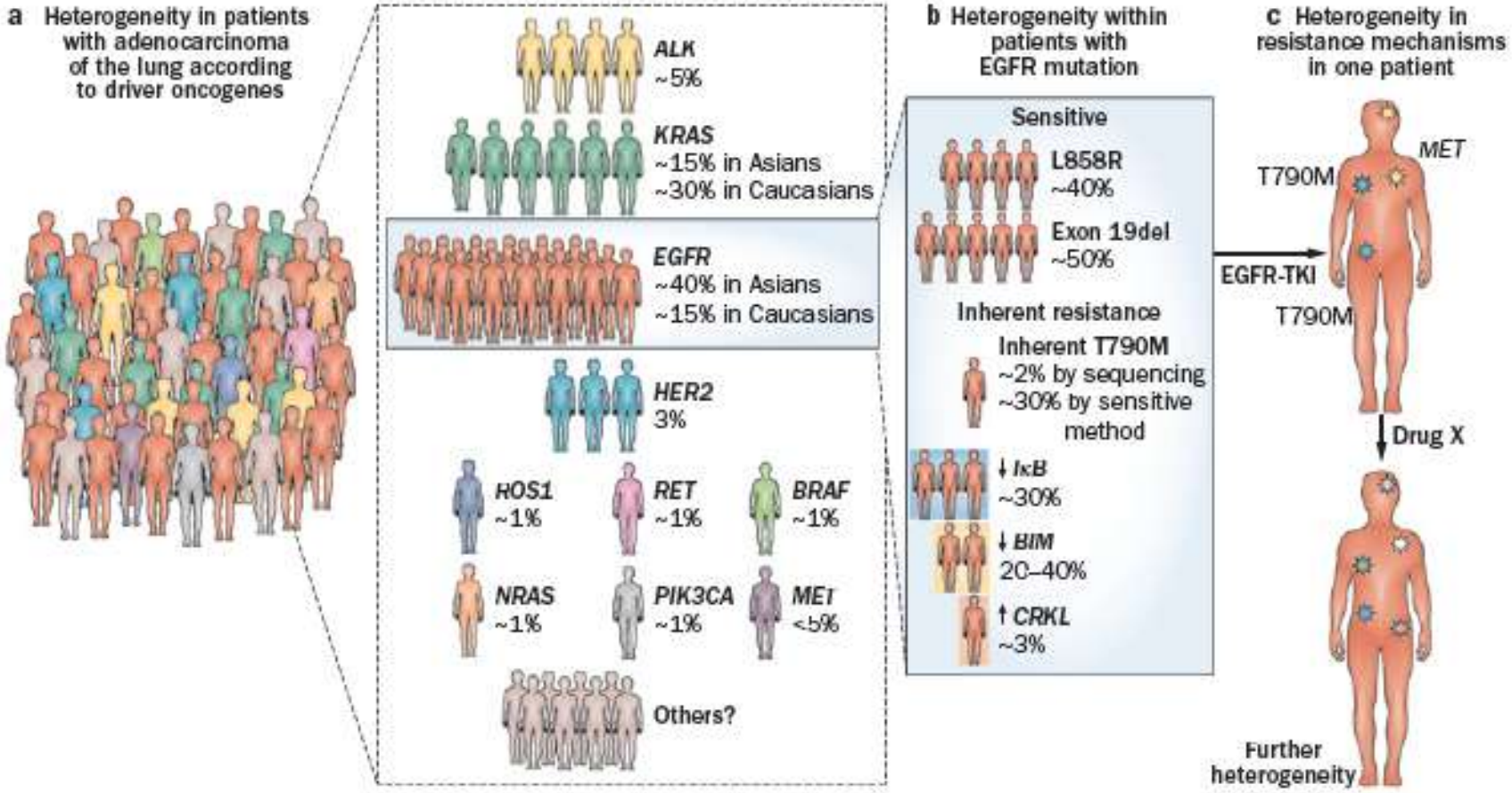
Segmentation (Stratification) of Patient Cohorts by Molecular Profiling and Clinical Trials

Can Large Scale, “All Comers”, Randomized Clinical Trials Be Justified in an Era of Clinical Profiling?

New Regulatory and Reimbursement Issues

Design of Post-Approval/Observational Studies to Support Reimbursement Decisions

Heterogeneity of Driver Oncogenes in NSCLC



From: T. Mitsudomi et al. (2013) Nat. Rev. Clin. Oncol. 10, 235

Enrichment and Adaptive Trials Using MDx-Stratified Patients: Consequences of Foregoing Phase III RCTs

- faster trials and patient access to promising Rx (terminal diseases)
- less definitive evidence regarding safety and efficacy (smaller ‘N’)
- accelerated approval should require reciprocal agreement for market withdrawal if confirmatory trials are negative
  - “fast on, fast off”
  - lessons from Avastin

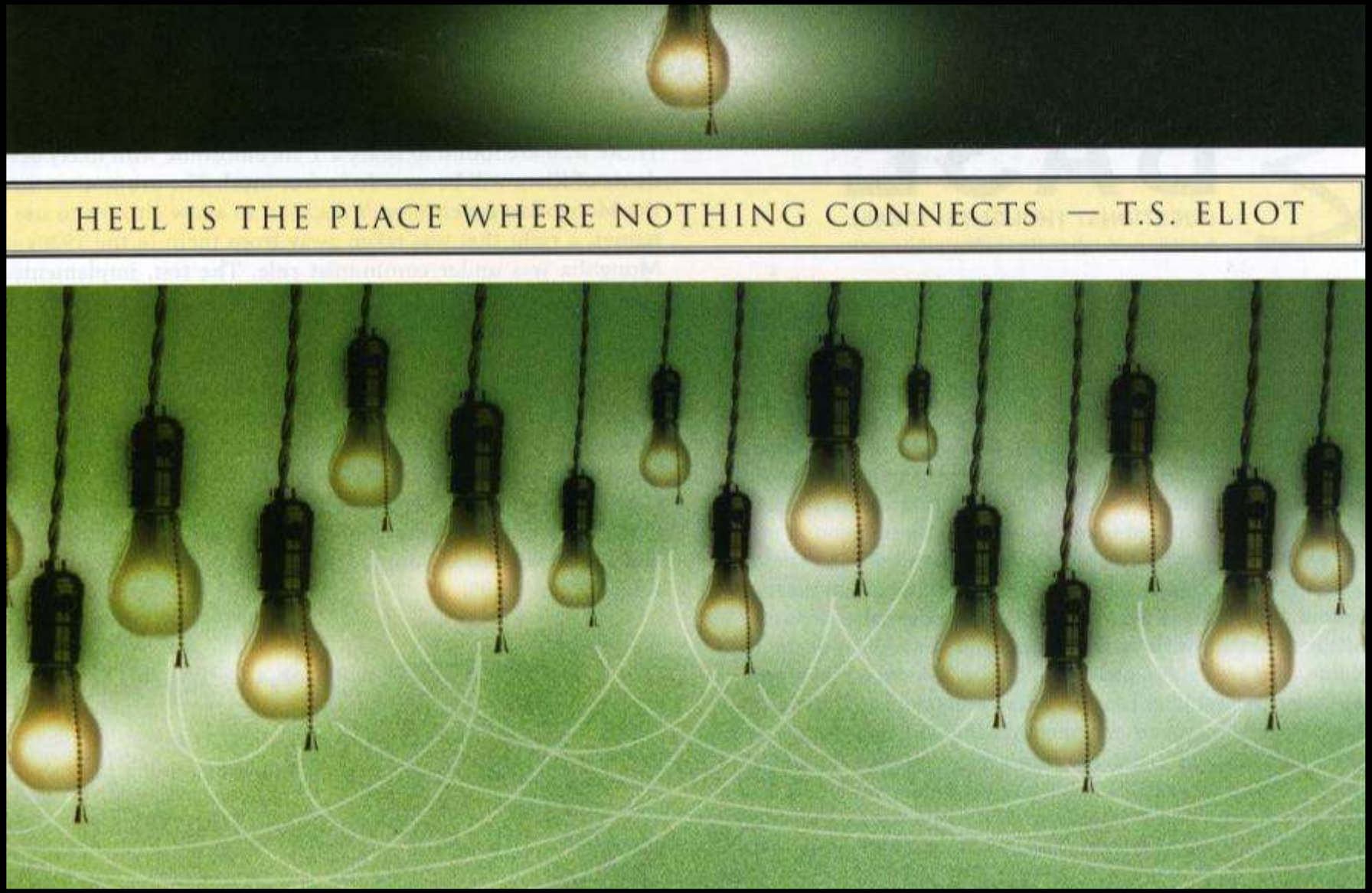
The Challenge of Escalating Technical Complexity and Massive Data Streams

"In God we trust,
all others must bring data"

W. Edwards Deming, Statistician

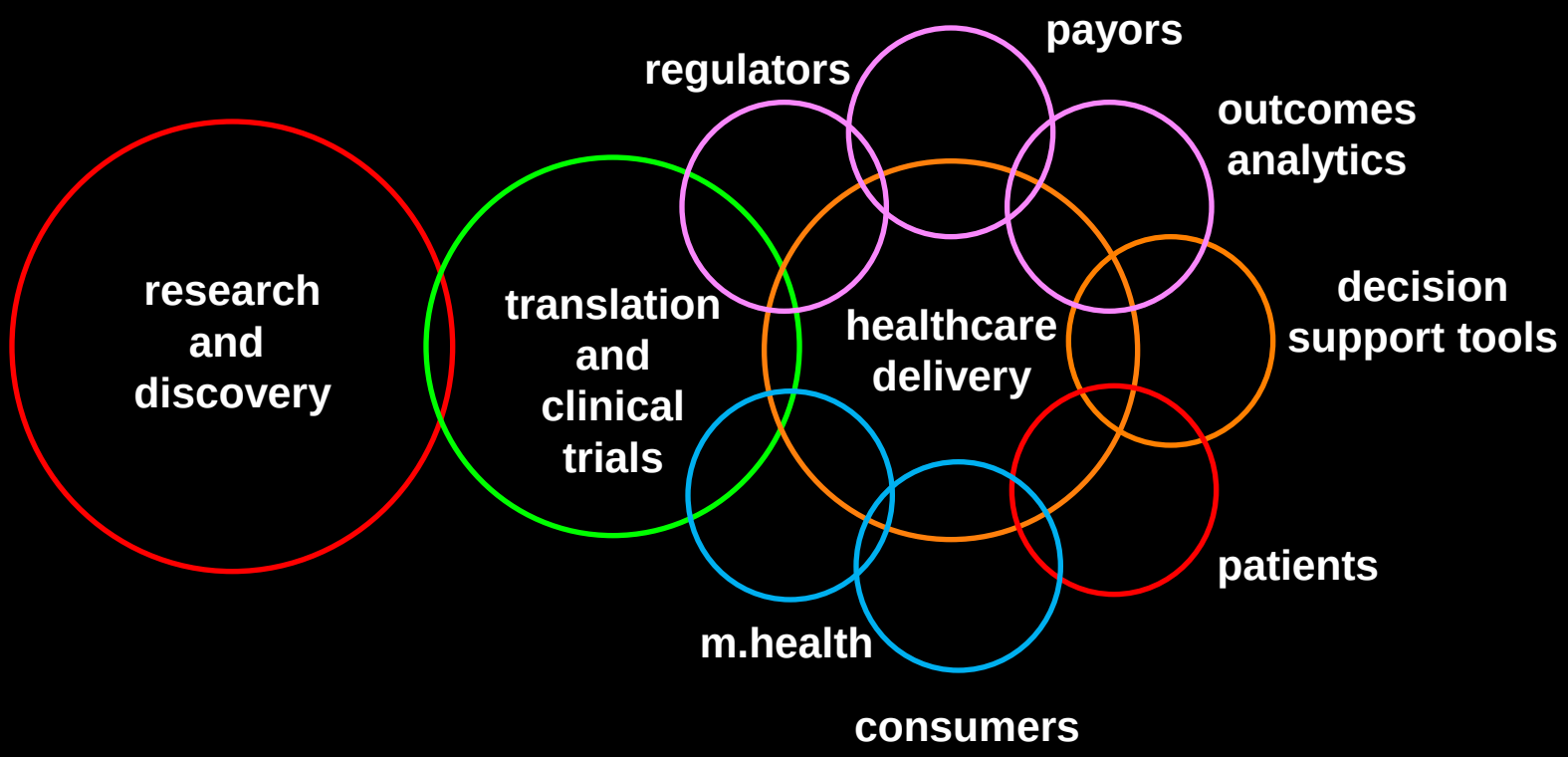
- validated data
- actionable data
- accessible data
- integrated data for knowledge-driven decisions

Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo



Data Silos and Data Tombs

The Need for Facile, Seamless Data Exchange Formats for Large Scale Biomedical Data Systems



The Pending Zettabyte Era
1,000,000,000,000,000,000,000

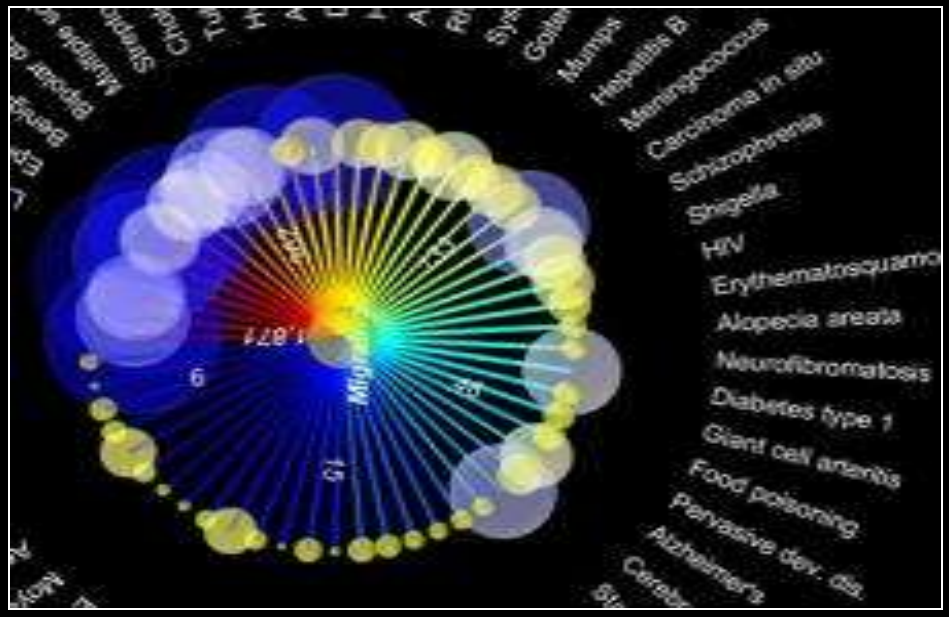
Managing Big Data in Biomedicine is Not a Simple Extrapolation from Current Practices

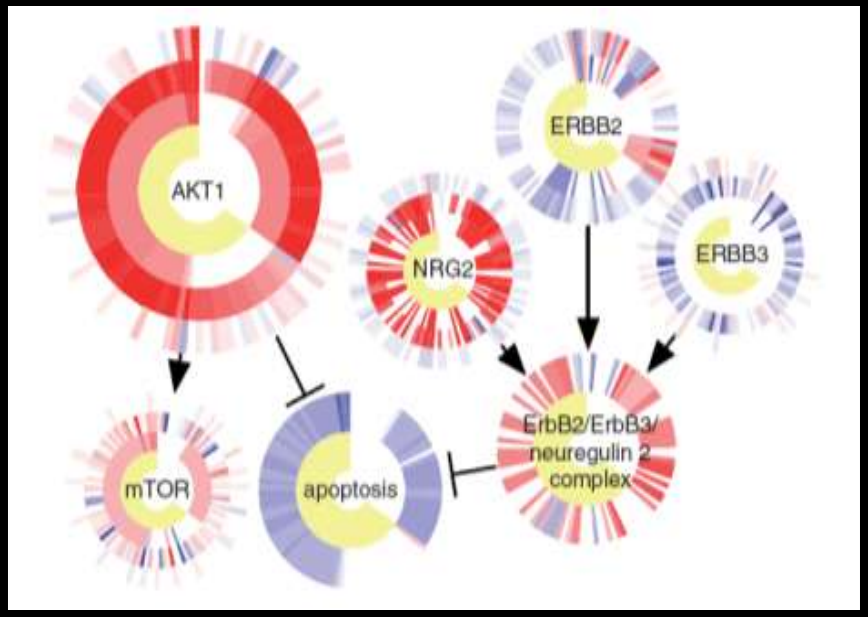
Current Institutional Structures and Competencies Are Ill-Prepared for Pending Disruptive Change

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

The Growing Education and Knowledge Gaps in Comprehension of Molecular Medicine Concepts Among Healthcare Professionals





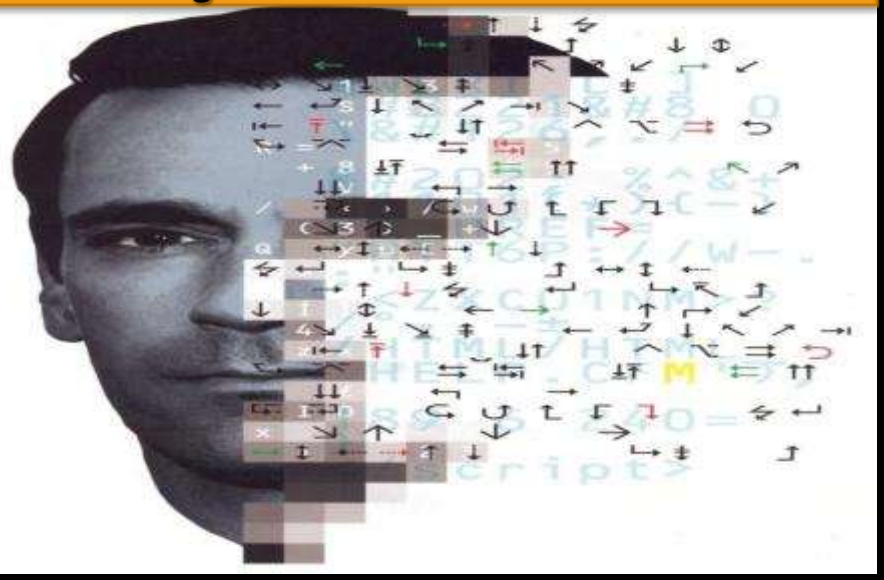
Education in Molecular (Precision) Medicine and a Looming Skills Gap

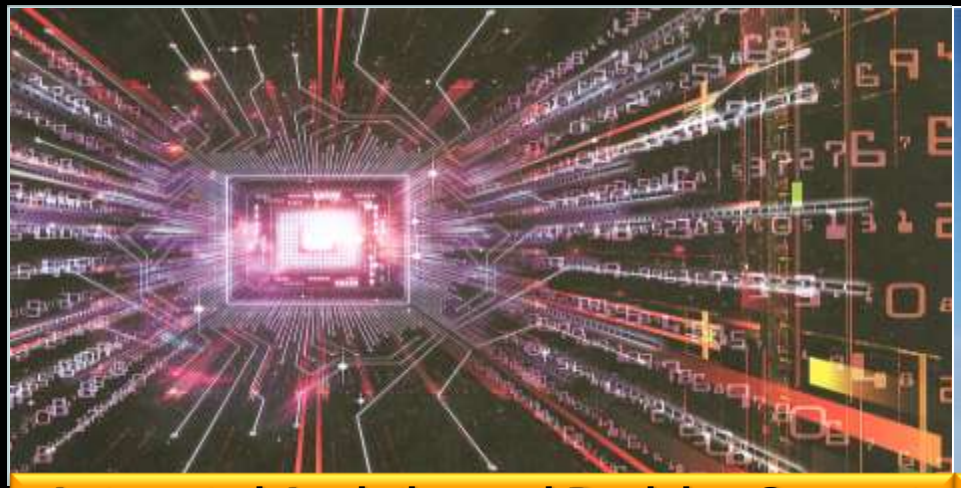
- clinical specialists with panOmics expertise
  - molecular genetics, pathology, genetic counseling
  - “molecular medicine 101” and CME for healthcare professionals
- informaticians
  - informatics (analytics)
  - database design and curation for optimized data flows for clinical decisions
  - data customization and visualization for different end-users
- social media and medical apps.

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

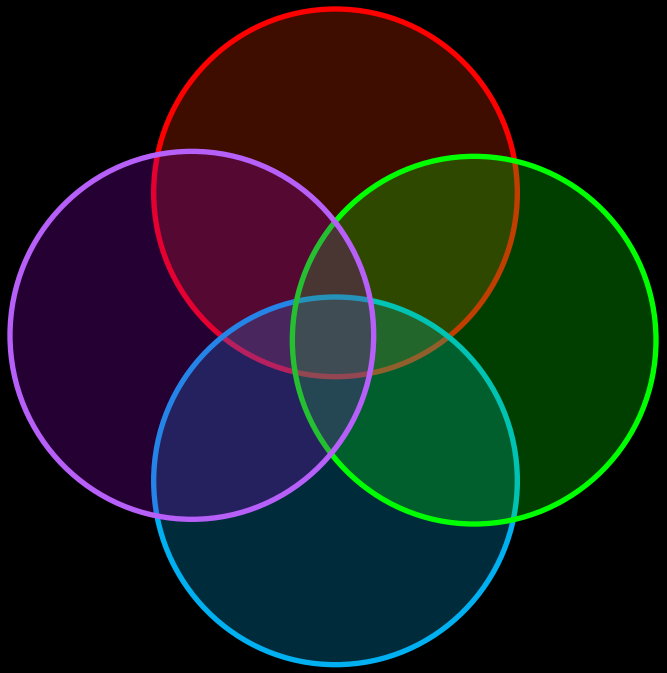
Facile Formats for Actionable Decisions

The Principal Forces Shaping Biomedical R&D and Healthcare Delivery

- sensors and m.health

device-based medicine

- remote health monitoring



molecular medicine

- panOmics

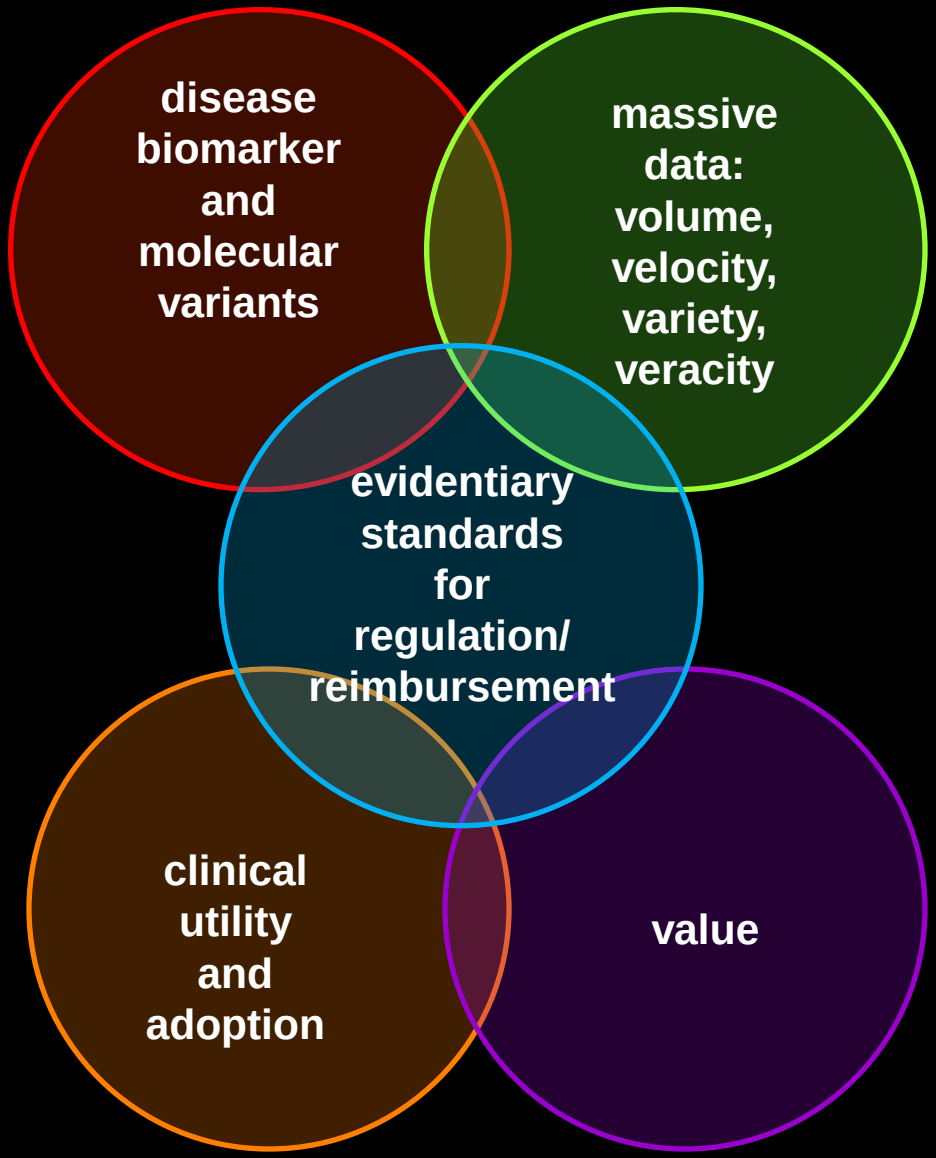
information-based healthcare

- m.health/e.health

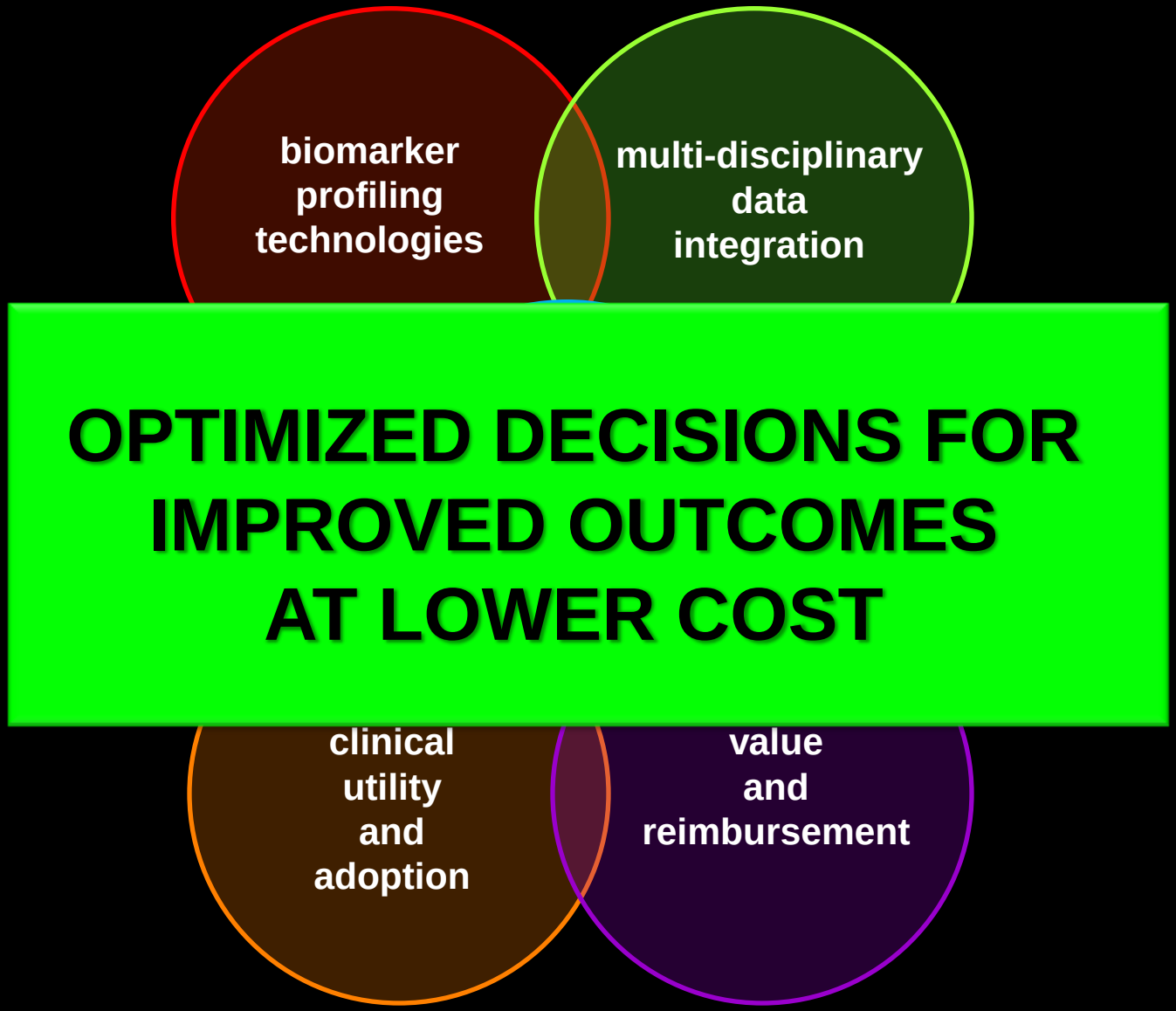
outcomes-based healthcare and sustainable health

new value propositions, new business models and services

Analytical and Clinical Validation of Molecular Determinants of Disease, Treatment Options and Predisposition Risk



Identification and Validation Biomarkers: A Complex, Multi-Dimensional Challenge



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