ASU Complex Adaptive Systems Initiative
Arizona State University

# A Status Report on Biomarkers: biomarkers that are not; standards that are forgot; and the need to transform the system we've got!


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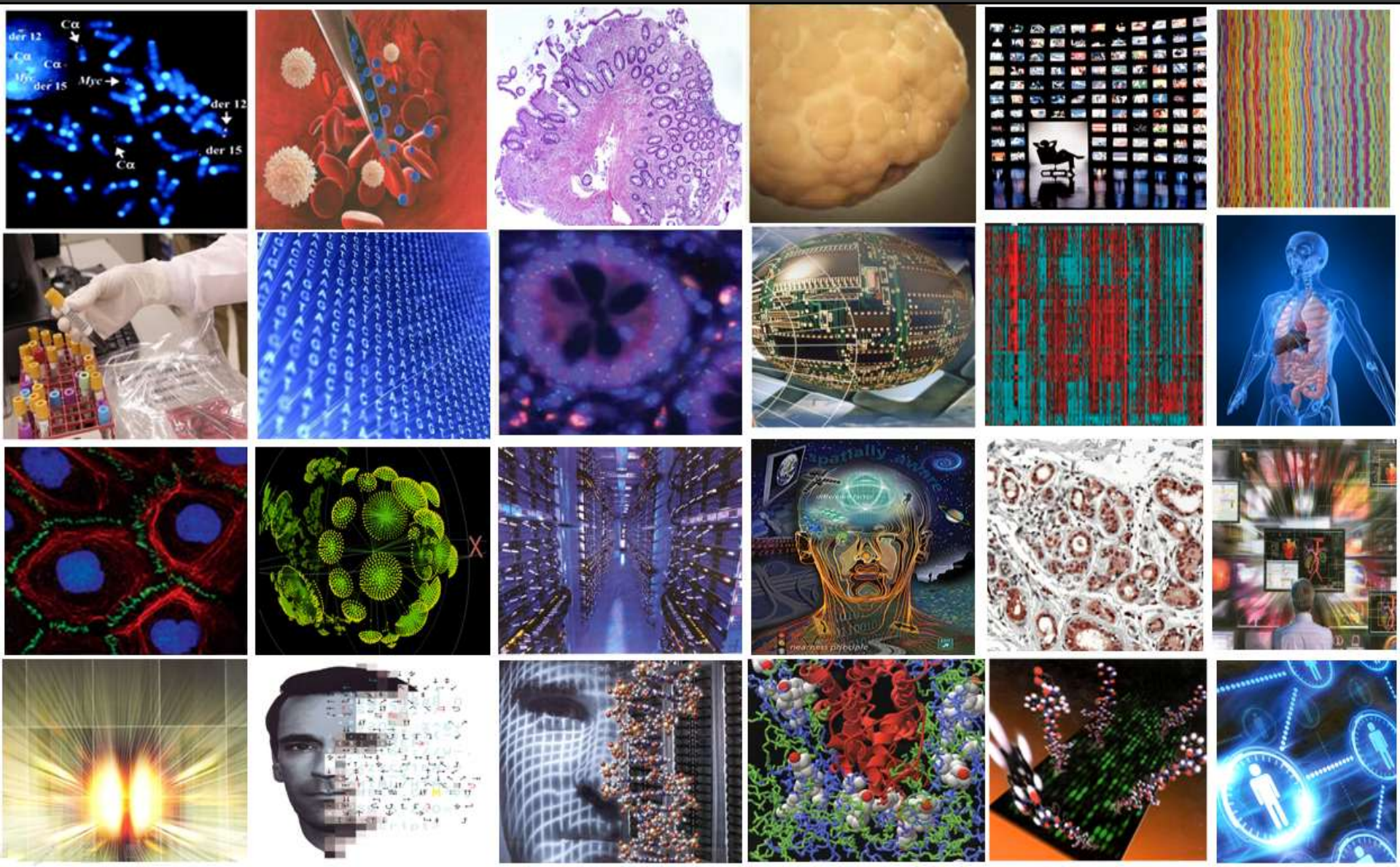
Presentation at: National Biomarkers Development Alliance
JW Marriott Camelback Inn, Scottsdale, Arizona
December 13, 2012

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



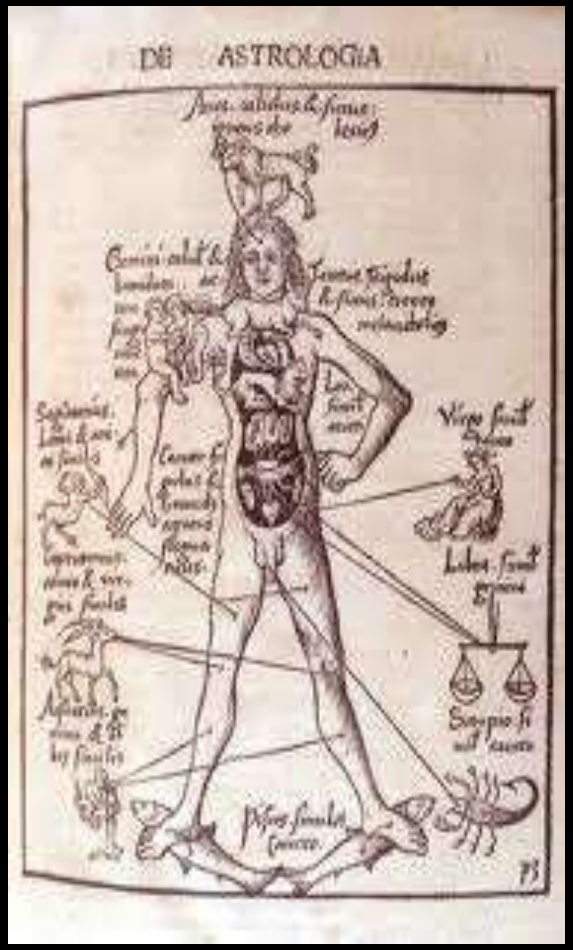
**Healthcare: An Expensive Menu Without Prices**

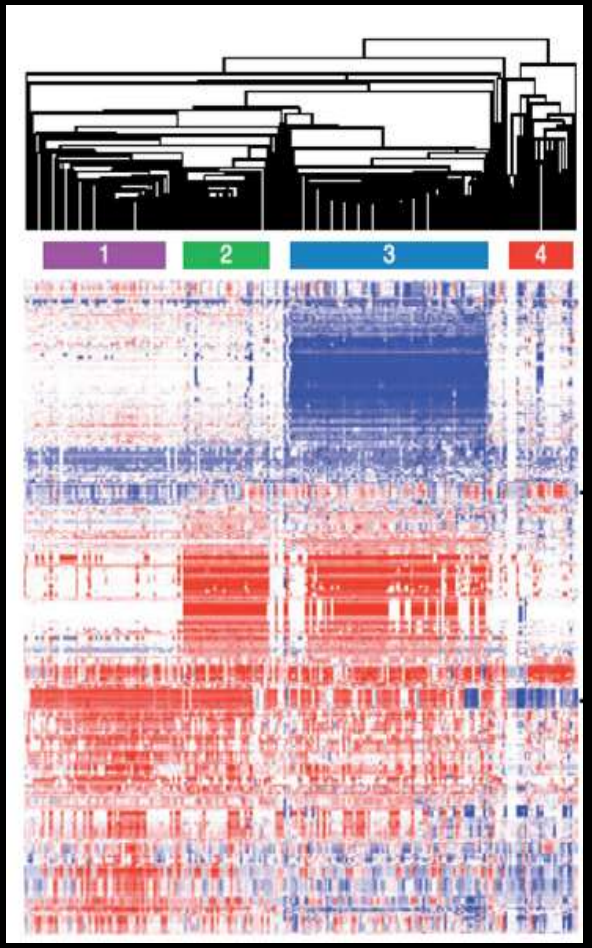
**Managing the Demands of an Aging Society and Chronic Disease Burden in an Era of Economic Constraint**

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

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

# Medical Progress:
# From Superstitions to Symptoms to Signatures

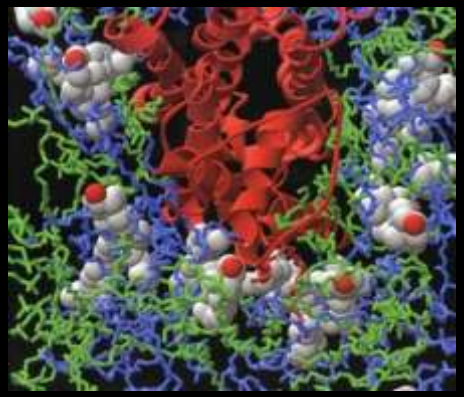


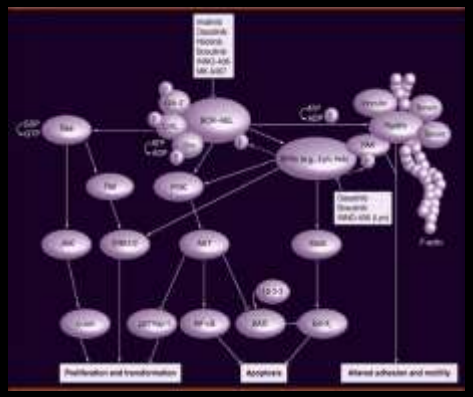
# Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

**Genomics**

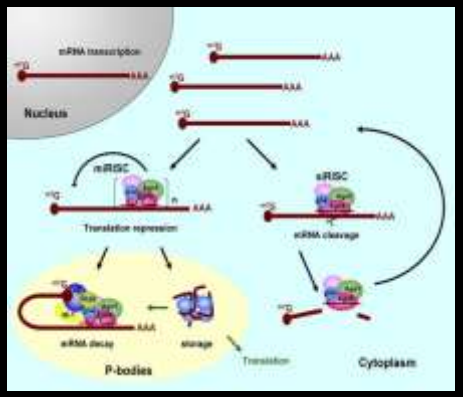
**Proteomics**

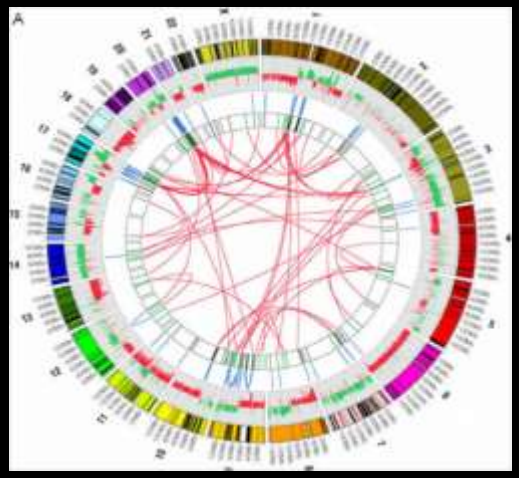


**Molecular Pathways and Networks**



**Network Regulatory Mechanisms**



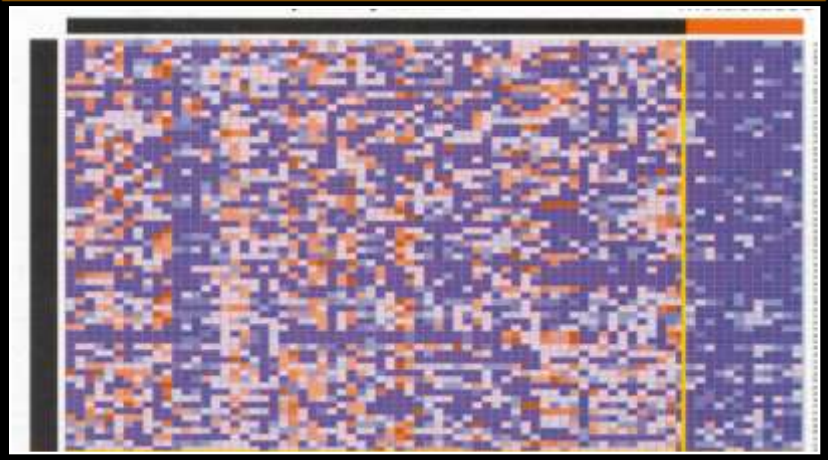



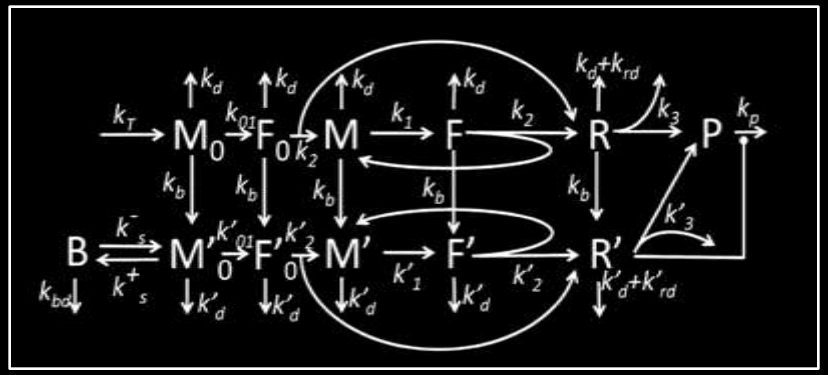
**ID of Causal Relationships Between Network Perturbations and Disease**

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

# Mapping Causal Perturbations in Biological Networks in Disease: Defining the Molecular Taxonomy of Disease

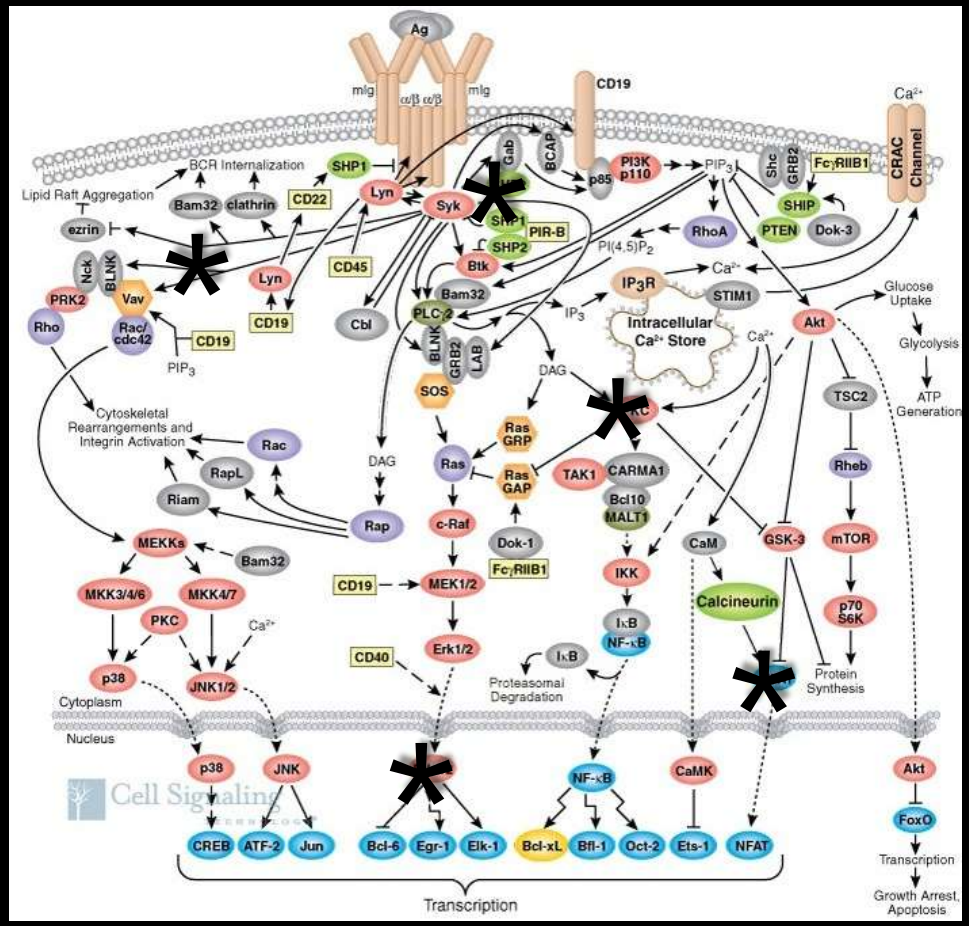
## iOmics Profiling to Identify Disease Subtypes (+ or - Rx Target)





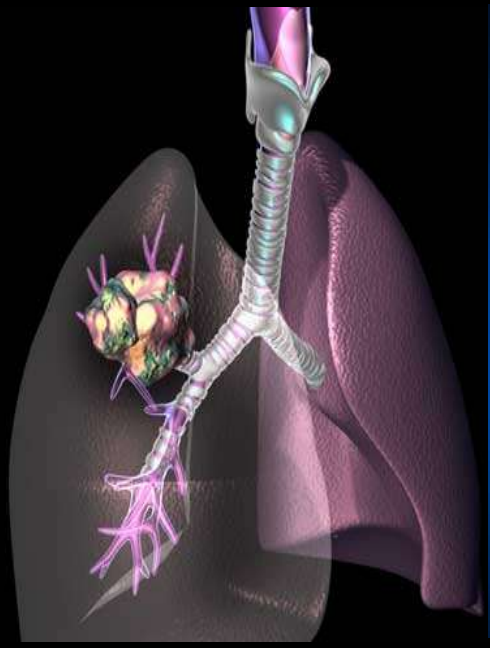

## Modeling Information Flow in Biological Networks

## Altered Network Structure and ID of 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)

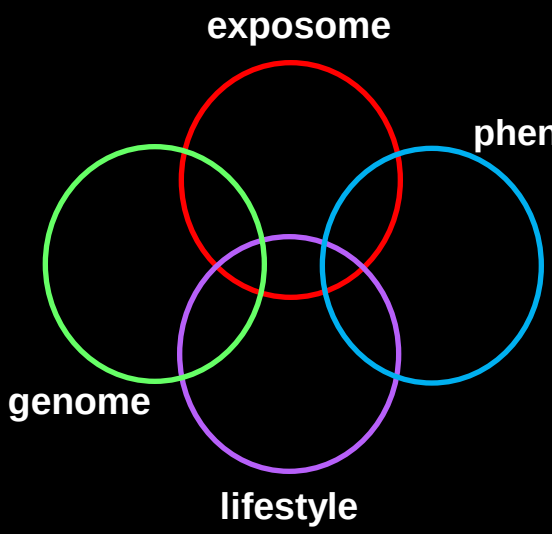


EML4-ALK
(Xalkori)

KRAS
(Erbitux)
(Vectibix)

BRAF-V600
(Zelboraf)

# Molecular Profiling of Disease and the Trajectory for Data-Intensive Healthcare




data annotation, formats, curation and analysis

risk identification and mitigation + decision-support systems

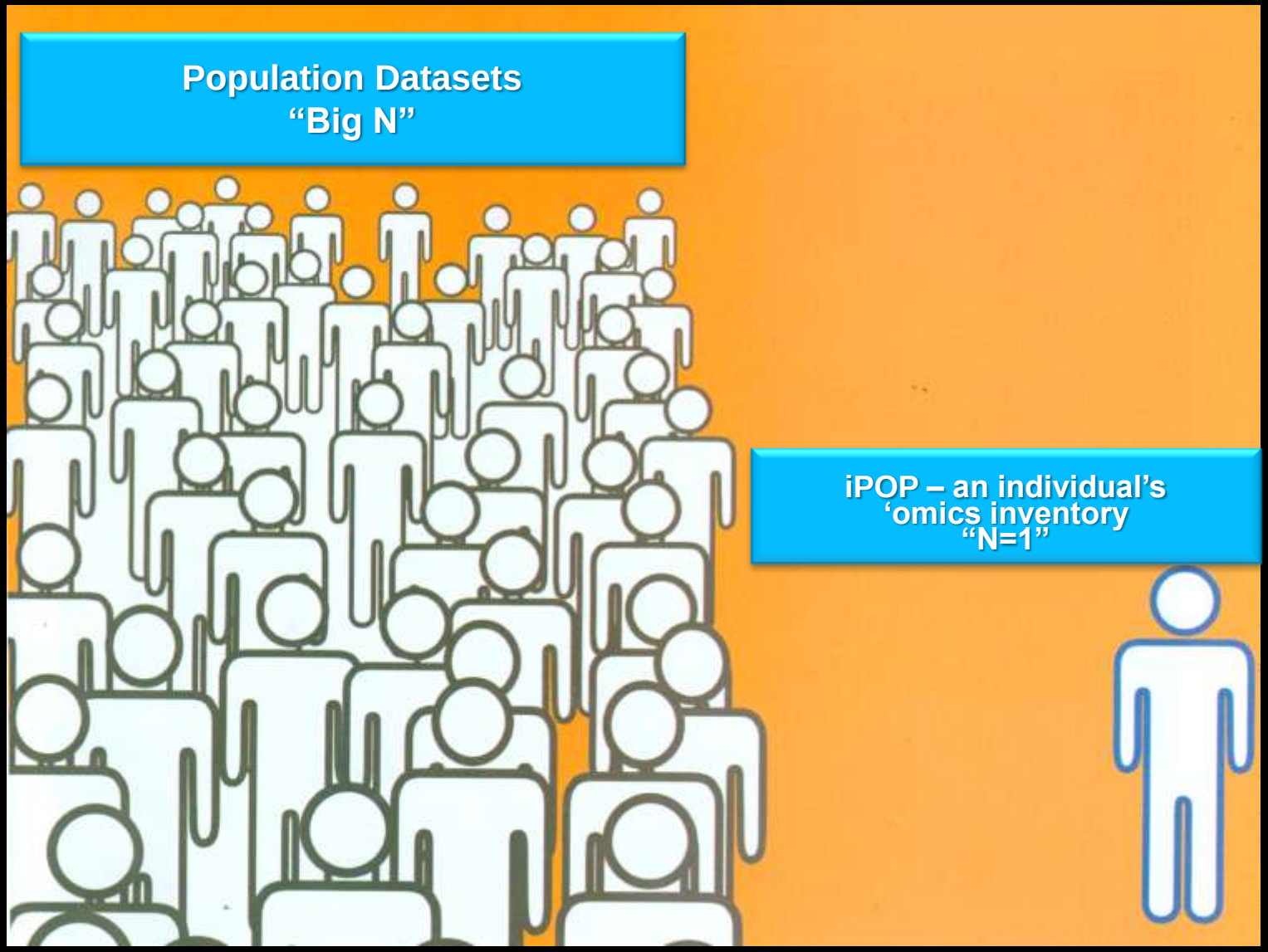
- earlier detection of disease
- disease subtypes and rational Rx
- monitoring of health status
- predisposition risk
- integrated, continuity of care
- optimized resource allocation

profiling

analysis

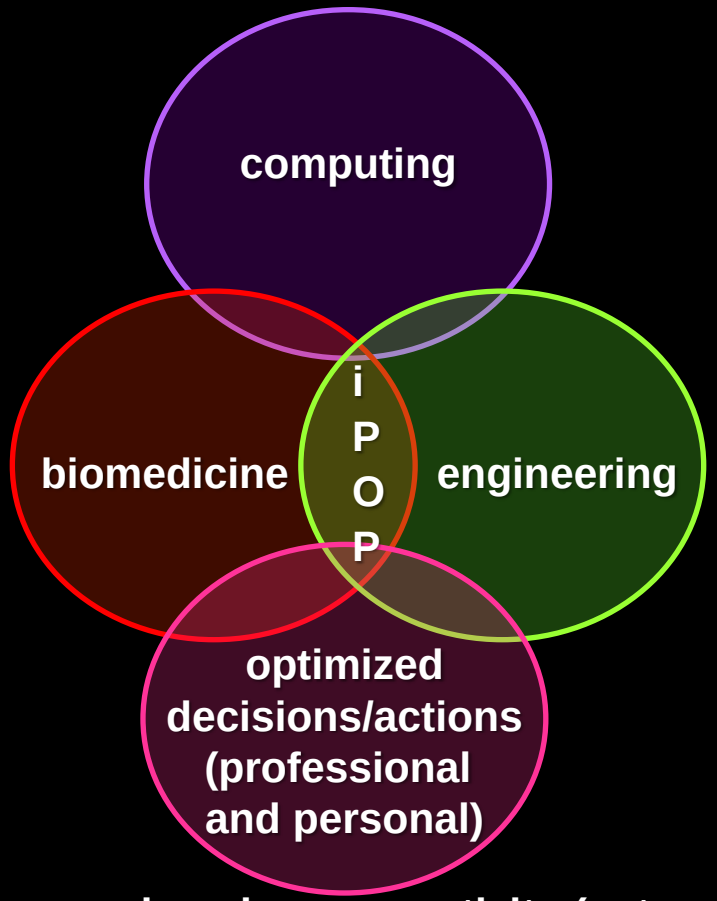
actionable information and knowledge-driven decisions

# The Integrative Personal Omics Profile (iPOP)



# Technology Convergence and the Trajectory for Molecular Medicine

- informatics, statistics, mathematics, modeling
- big data: analytics and infrastructure




- iPOP
- systems-based processes

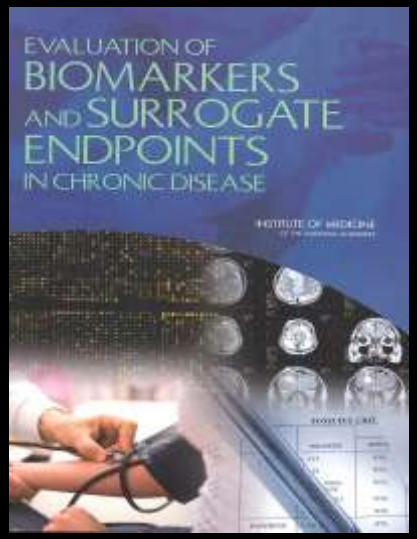
- devices
- sensors
- m.Health

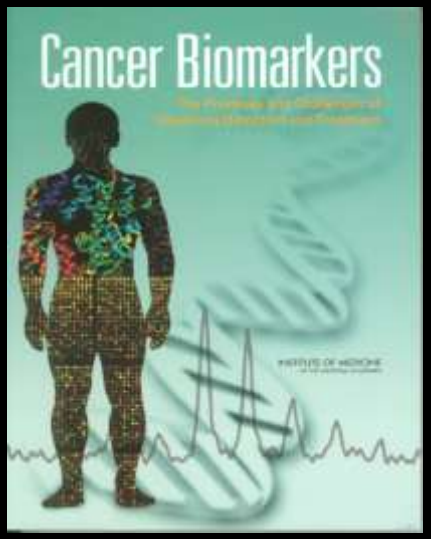
- comprehensive connectivity (networks)
- integrated data • continuity of care
- risk management and maximizing wellness

# Translating Molecular Profiling into Clinical Medicine and Healthcare Delivery

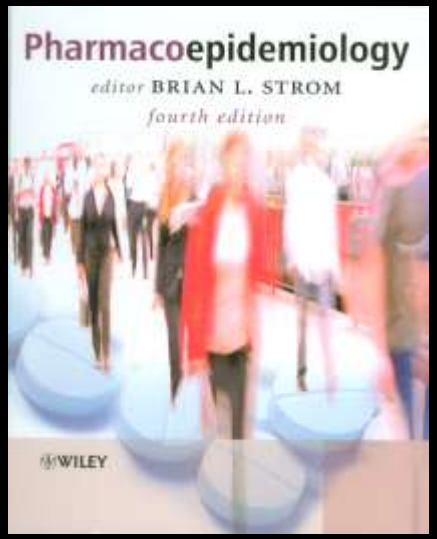
- what is the best biospecimen for the intended use?
- how will the biospecimen be profiled and when?
- who will conduct the profiling?
- what will be reported?
- how will profiling information be used to support a clinical decision and/or clinical decision support system?
- how will MD/HCPs be trained/supported in interpretation of complex profiling data
- how will profiling results be incorporated into EHR/EMR and/or aggregated into larger databanks
- how will profiling assays be regulated and reimbursed?

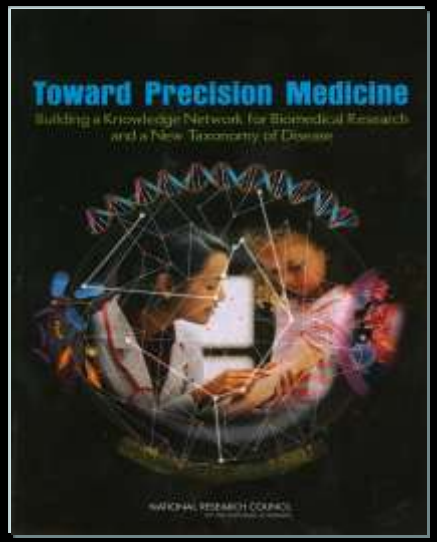
# Biomarkers and Personalized Medicine: Promises, Pitfalls and Unrealized Potential

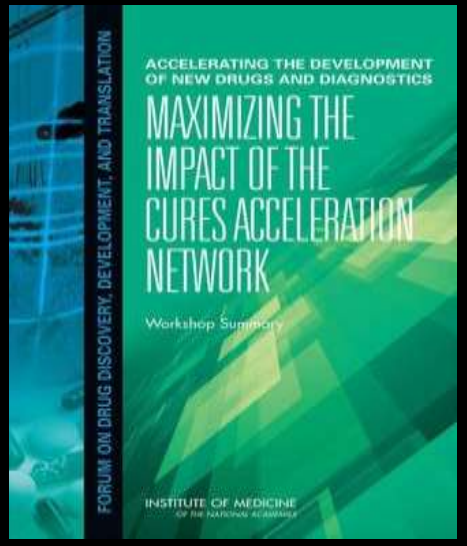






# Garbage Data, Fragmented Data, Selfish Data and Untapped Data: Pervasive Deficits in the Conduct and Organization of Academic Research

- disturbing low reproducibility of biomarker publications
- poor access to rigorously annotated biospecimens from stringently phenotyped sources
- insufficient control of pre-analytical parameters and variable analytical standards
- idiosynchratic, ‘lab-specific’ analytical methods
- ‘small N’ studies lacking statistical power
- chaotic incompatible data reporting formats and poor dbase interoperability
- pressure to publish and poor compliance with funding agency/journal policies on open data sharing
- failure to work to (or understand) industry and regulatory standards

# Access to High Quality Biospecimens, Biobanks and DNA Repositories: An Obligate Prerequisite to Productive Validation of Putative Causal Disease Markers

requisite
scale
and
stringent
QA/QC
standards

or

academic
anecdotes
and
wasted
investment

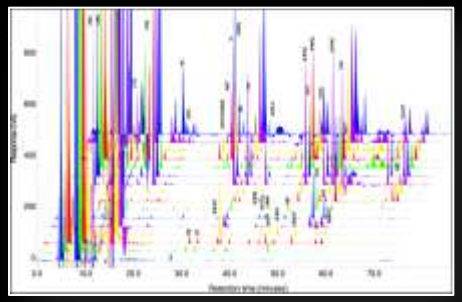
# The Dismal Productivity of Biomarker R&D

**Legacy of Failure to Embrace Multidisciplinary Expertise and Adopt Stringent QA/QC Processes**

**The Complexity of Biomarker Discovery, Validation and Clinical Adoption is Comparable to (Bio)Pharmaceutical R&D**

**In Common With R&D for Drugs and Vaccines Success Demands a Systems-Based Approach**

# Building Large Scale, Standardized Resources for Biomarker 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

# Blood-Based Biomarkers

- obvious appeal of low cost, minimally invasive sampling and ease of repeat sampling
- DNA banking and WES/WGS of germ line variants and disease predisposition/PGX profile
- current major knowledge gaps
  - lability of different molecular species in different pre-analytical process protocols (intended use setting)
  - biomarker(s) abundance, dynamic range and intra- and inter-patient variation
  - detection threshold(s) for different analytical platforms
  - relationship between stage of disease progression, (sub)clinical phenotype and intravascular biomarker shedding kinetics

# Omics Profiling, Informed Consent and the Incidentalome

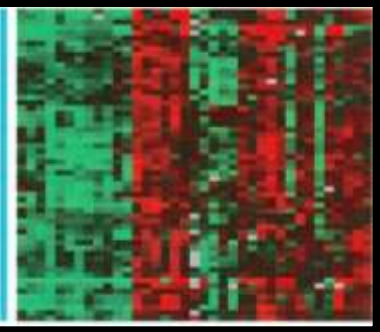
- new informed consent provisions in an era of Omics profiling and DNA banking
  - broad (future proof) versus narrow (explicit) research investigations
  - flexibility to address personal preferences
- dynamic consent:  e.consent tools and regular updating
  - EnCoRe, Indivo, PrivateAccess
- separate informed consent for sample banking for PGx testing versus MDx and PDx and clinical trial stratification?
- the ‘incidentalome’ and recontact criteria

# Questions Not Raised Often Enough by Study Sections and the EDRN

- are the phenotypes and profiled molecular pathways of cell lines and 2D cell cultures so unrepresentative of the situation in vivo to render them irrelevant and pose blind avenues for diagnostic/therapeutic discovery?
- can the biology of metastasis and MDx biomarkers for metastasis and new Rx targets be elucidated by the analysis of non-metastatic cells?
- how representative are circulating tumor cells (CTC) of the metastatic phenotypic and the extravagant inter-patient and intra-patient heterogeneity of cancer cell phenotypes?

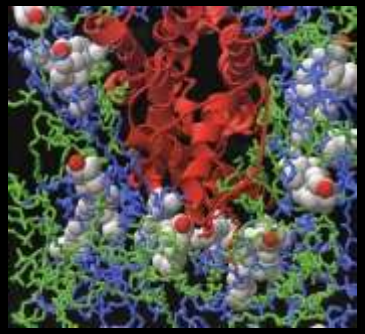
# Analytical Platforms for Biomarkers and Biosignatures: Setting Stringent QA/QC Standards

Gene Expression

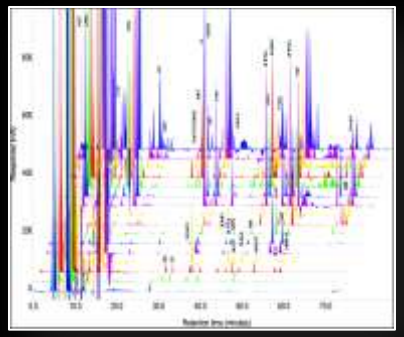


WES/WGS

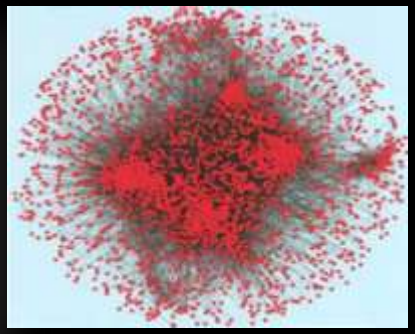
Proteomics



Metabolomics



Biological Network Regulation



- massively parallel multiplex assays (global profiling)
- automated, miniaturized, high throughput
- novel test formats and data formats
- escalating data volume, velocity and variety (V3)
- complex deconvolution of low signal to noise signatures
- big data, analytics and infrastructure

# Implications of the Underlying Distribution of the Dataset and Selection of Classification Algorithms

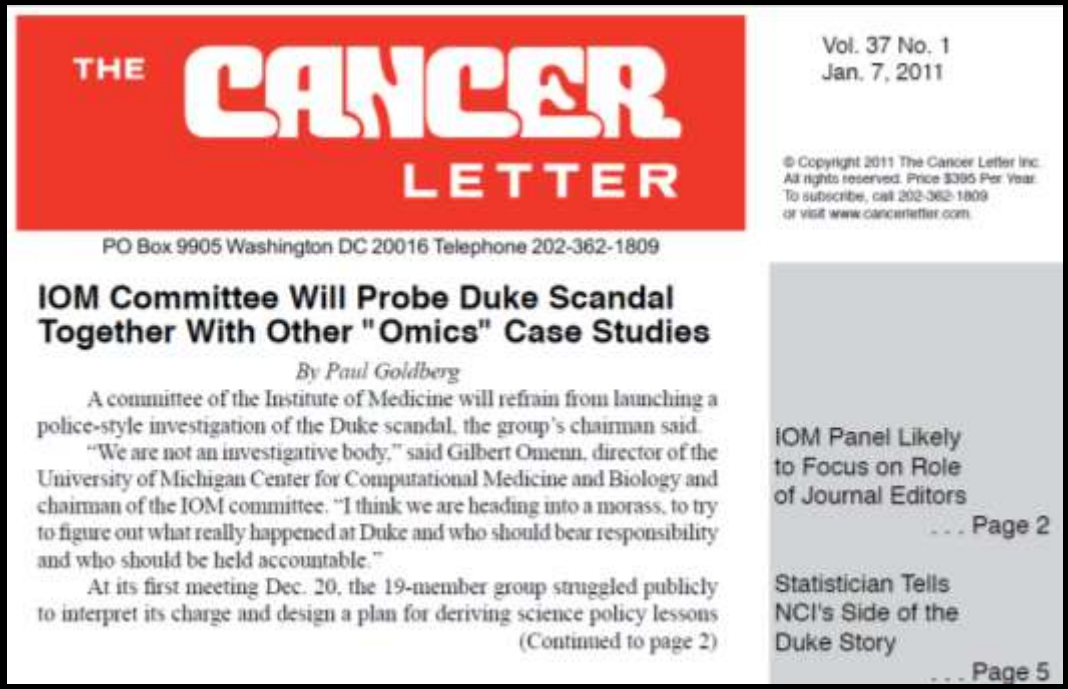
- large scale, molecular datasets differ fundamentally from traditional biological and clinical datasets
- traditional clinical/epidemiological datasets
  - small number of variables (p) tracked across a proportionately larger number (n) of samples (n>p)
- molecular datasets
  - the high dimensionality problem: number of variables measured per sample ($10^5$ – $10^9$ analytes/WGS) far exceeds the typical number of samples ($10^1$ – $10^2$) (p>>n)
- without detailed understanding of the biology of cellular network regulation impossible to know whether any or all of the measured features (genes/proteins) are related in a linear or non-linear fashion
  - difficult to demonstrate non-linear relationship in incompletely-characterized biological systems

# Standards, Complexity and New IRB Competencies

Duke UNIVERSITY

NATIONAL® CANCER INSTITUTE

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES



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**IOM Committee Will Probe Duke Scandal Together With Other "Omics" Case Studies**

*By Paul Goldberg*

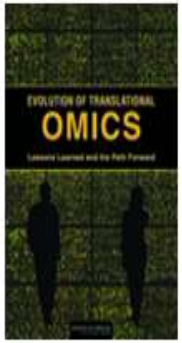
A committee of the Institute of Medicine will refrain from launching a police-style investigation of the Duke scandal, the group's chairman said.

"We are not an investigative body," said Gilbert Omenn, director of the University of Michigan Center for Computational Medicine and Biology and chairman of the IOM committee. "I think we are heading into a morass, to try to figure out what really happened at Duke and who should bear responsibility and who should be held accountable."

At its first meeting Dec. 20, the 19-member group struggled publicly to interpret its charge and design a plan for deriving science policy lessons

(Continued to page 2)



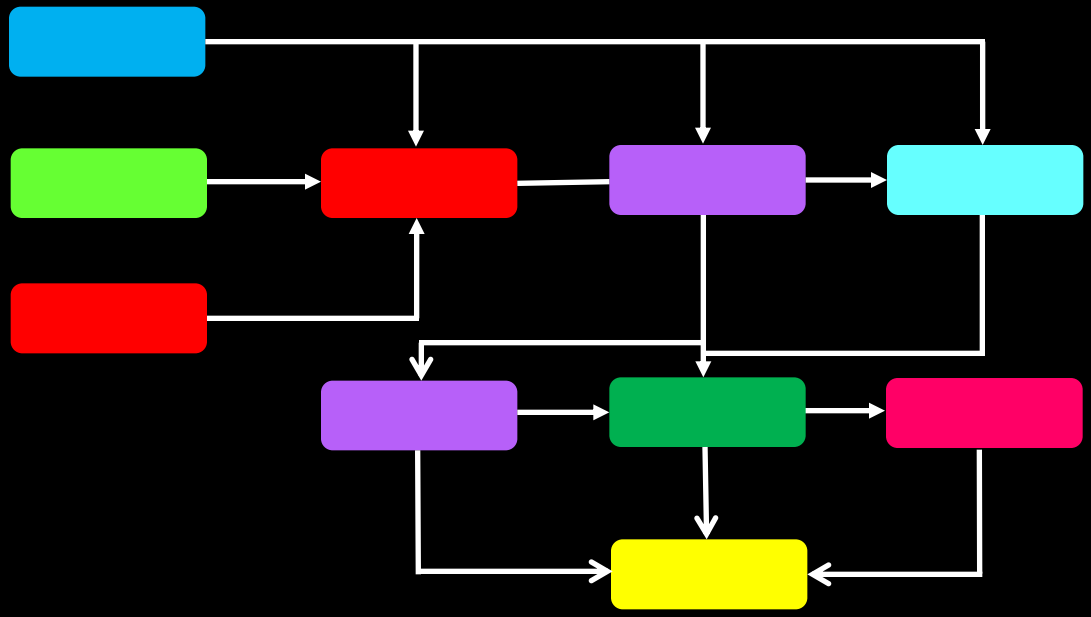



## Evolution of Translational Omics: Lessons Learned and the Path Forward

Released: March 23, 2012
Type: Consensus Report
Topics: Biomedical and Health Research, Health Services, Coverage, and Access
Activity: Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials
Board: Board on Health Care Services

**Quality happens only when someone is responsible for it**

# Sophisticated Project Management Systems and Automated Workflow Systems



- visual modeling of multi-step processing and analysis
- automated documentation:  ID, tracking and provenance
- integration of disparate software tools, edits and provenance
- automated translation to required formats
- longitudinal data integration (from discovery to EHR/EMR)
- regulatory compliance and inspection audits

# Improved Conduct and Reporting of Biomarker Validation Studies and QI Standards for Biobanking, Analysis and Publication

- CONSORT
- AMSTAR
- AGREE
- STROBE

- REMARK
- BRISQ
- EGAPP
- STREGA
- MIAME (loc.cit)

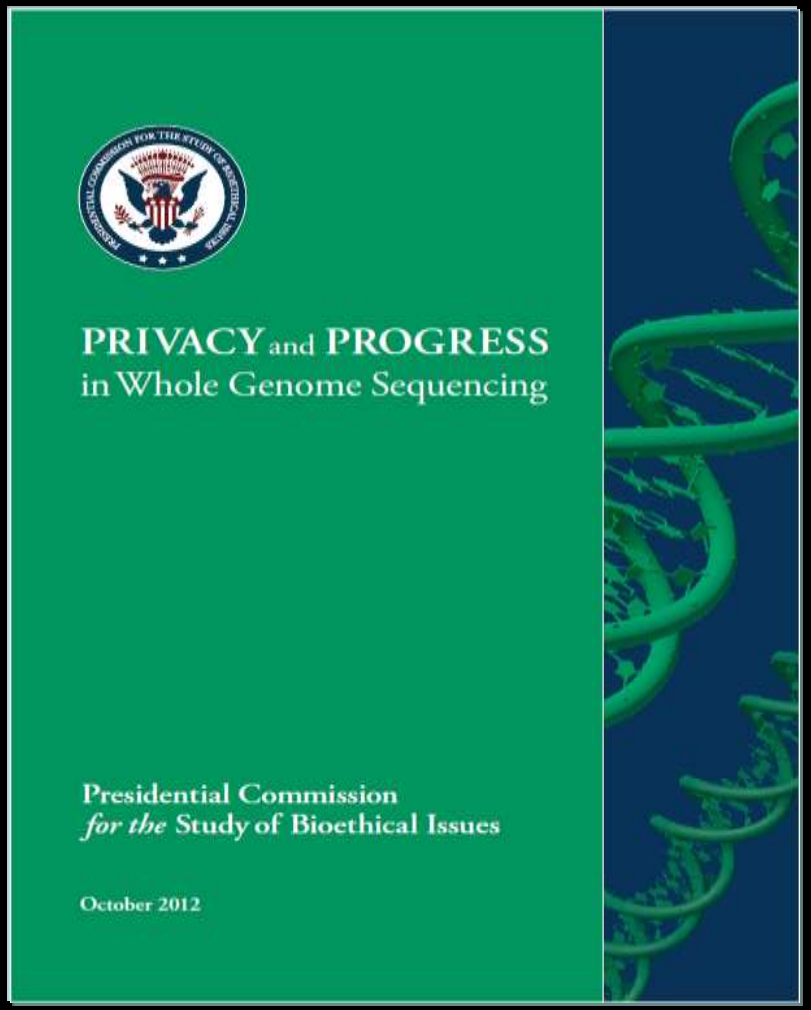
- Biospecimen Reporting for Improved Study Quality
- Best practices:  NCI, OECD, UK, Australia, Canada
- Int. Society for Biological and Environmental Repositories

**Reinforcement by Funding Agencies and Journals of Reporting Formats and Open Data Submission**

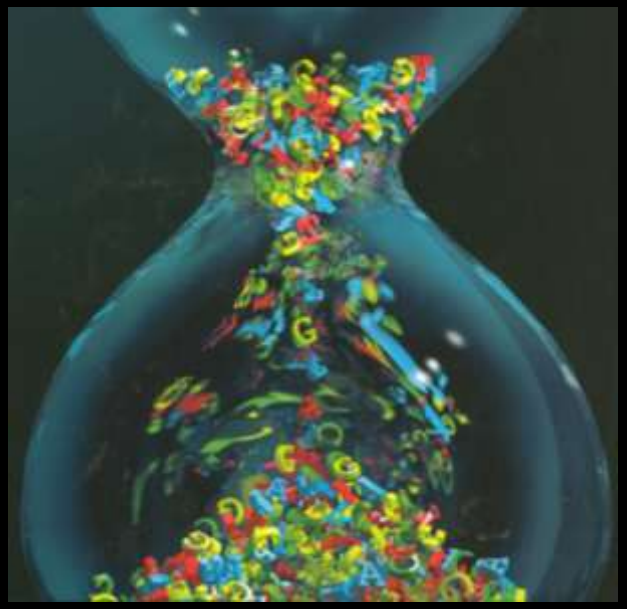
# IHE-LAW
# A Major Advance for Integration of Diagnostic Laboratory Automation, Information Systems and Electronic Health Records

- partnership between Integrating the Healthcare Enterprise (IHE) and In Vitro Diagnostics Connectivity Consortium (IICC)
- IHE-LAW (Laboratory Analytical Workflow) standard
  - uniform IT connectivity standards for LIS, automation systems, middleware, CPOE and EHR
  - use of ISO HL7 messaging
- participation of leading instrument manufacturers
  - Abbott, BD, Beckman Coulter, BioMerieux, Ortho, Roche, Siemens
- projected final standard in collaboration with The Clinical and Laboratory Standards Institute (CLSI) in 2013

# Will Low Cost Whole Genome Sequencing Change Everything?

# Current Chokepoints and Challenges in Adoption of Personal Omics Profiling Data for Clinical Decisions



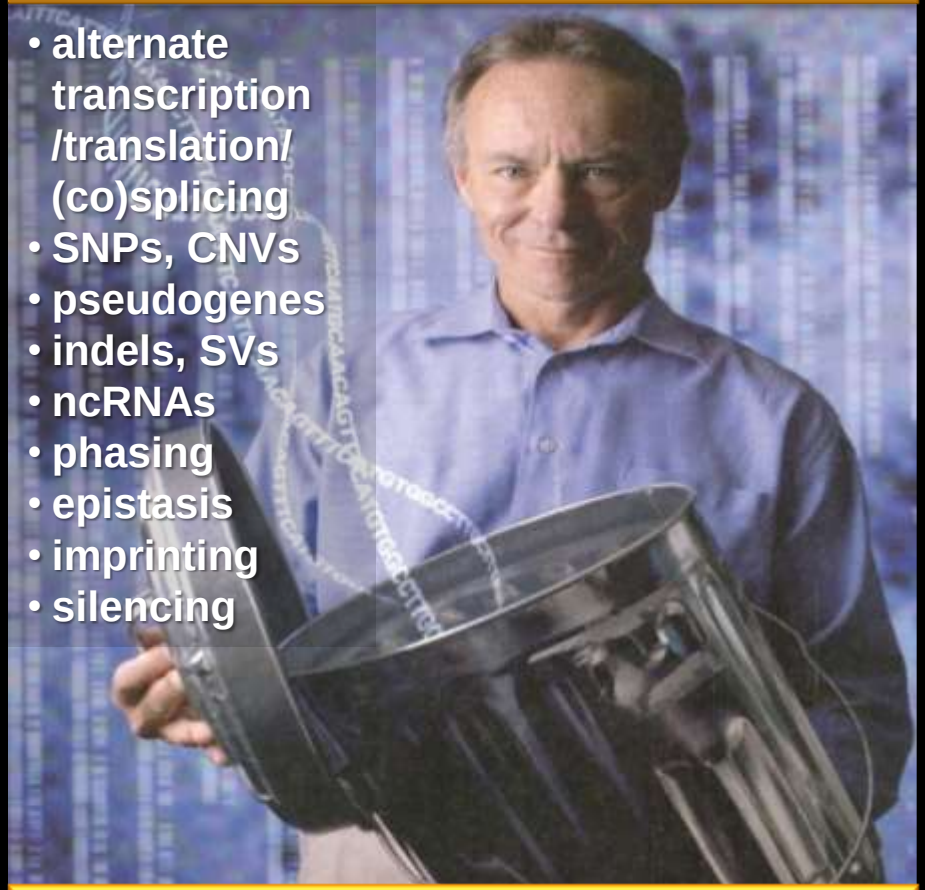
- production of sequencing data outstripping interpretational capacities
- CLIA compliance, RUO materials and other regulatory requirements for clinical decisions
- confusing maze of base calling, alignment, assembly and analysis tools
- many software tools insufficiently robust and/or customized for one type of data or sequencing platform
- variation in clinical significance predictions from different algorithms using well known algorithms (SIFT, PolyPhen, LRT, MAPP, VarioWatch)
- (comparable data standardization/ validation problems in large scale proteomics)

**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**

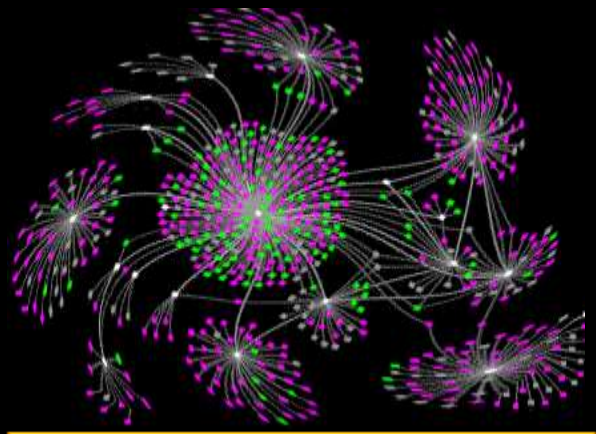
# Individual Variation, Genome Complexity and the Challenge of Genotype-Phenotype Predictions

## Junk No More: Pervasive Transcription

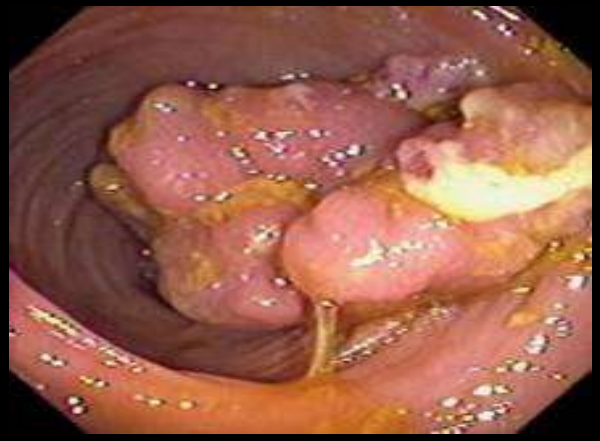



**recognition of genome organizational and regulatory complexity**

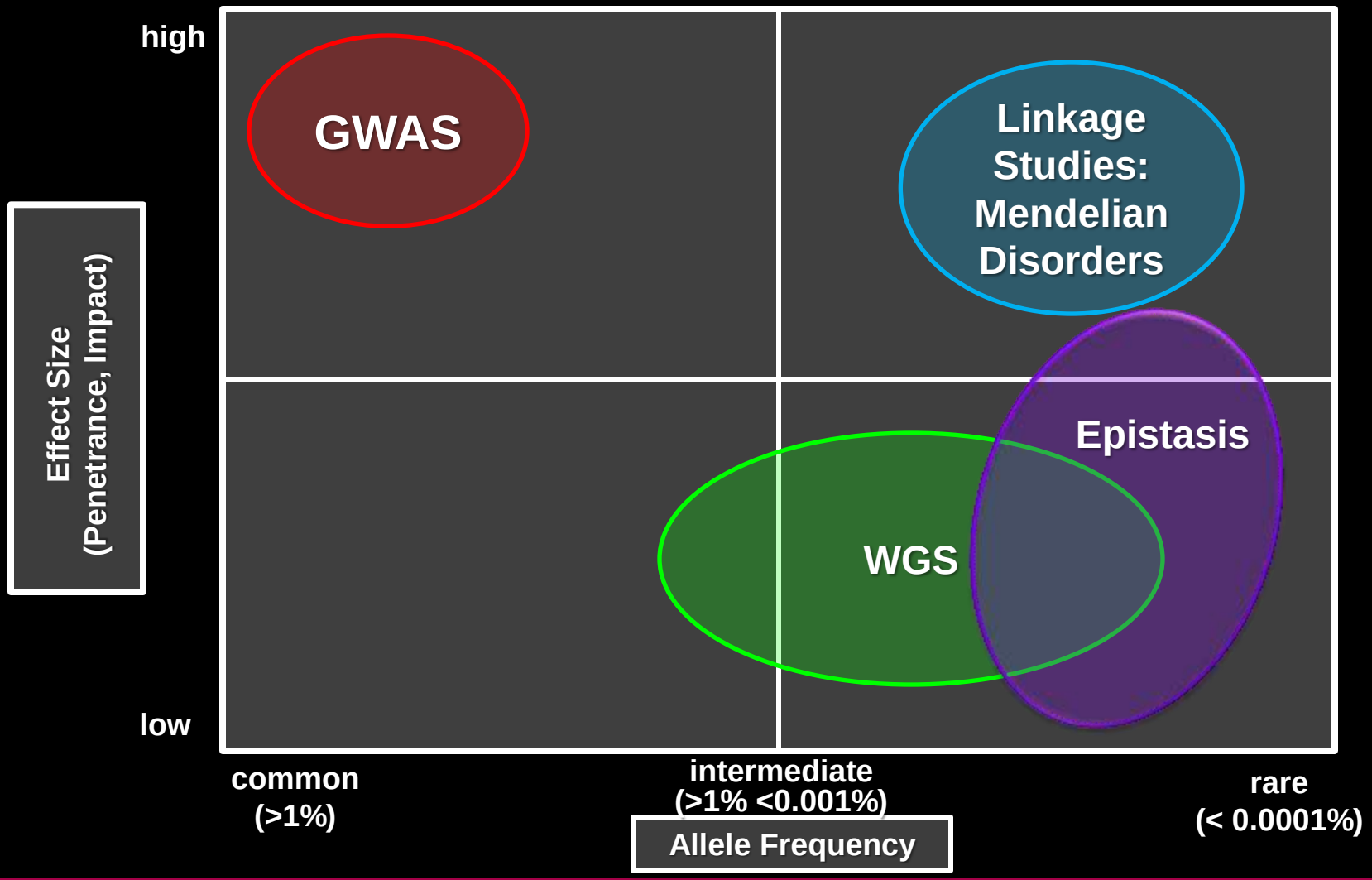
## Mapping Cell-specific Molecular Interaction Networks



## Perturbed Networks and Disease



# Defining Human Genetic Variation



# From Genotype to Phenotype: Understanding Genetic Architecture and Biological Networks in Health and Disease

- what are the network epistatic interactions between causal and modifying genes that define expressivity, penetrance and ultimate phenotypic impact?
  - genesis of a likely continuum of clinical phenotypes
  - potential spectrum of subtle to severe disease generated by graded perturbations within- and between- molecular pathways and networks in the same cell type/organ

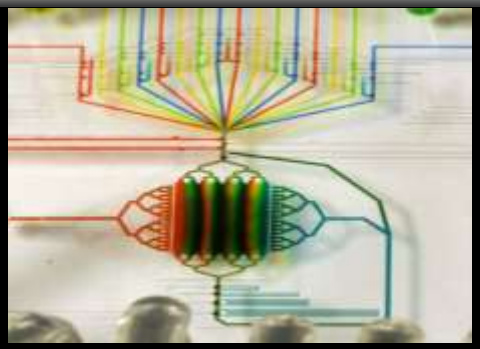
# Diversity of the Human Variome and Role of Rare/Private Disease-Associated Variants

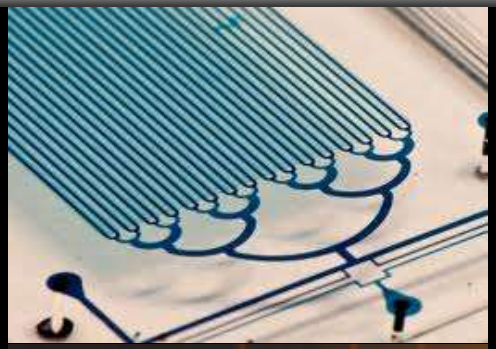
- implications for cohort selection for profiling studies
  - clinically relevant/medically actionable variants may be heavily weighted toward recent rare/ private variants (clan/pedigree/individual)
  - ethnic factors and study design
- implications for genoprofiling
  - deep sequencing (>100X coverage) of 20,000 or more individuals to link variants/variant combinations to disease phenotype(s)
- cancer presents unique challenges
  - extravagant scale of causal somatic mutations plus rapid progression of intra-and inter-lesional heterogeneity in advanced disease

# Biomarkers for Disease Subtyping and Improved Design of Clinical Trials and Enrollment Efficiency

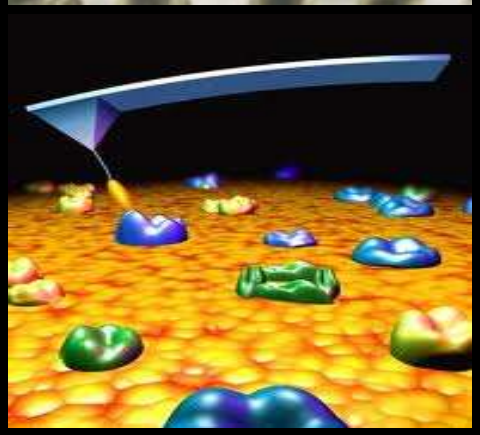
- imperative to reduce cost/time of high failure rate of investigational drugs
- targeted Rx and stratification of cohorts based on target BM (and/or other Rx response marker)
  - enrichment trials and adaptive trials
  - faster trials?
  - greater regulatory clarity?
- logistics:  time, cost and scale of screening to ID $BM^+$ cohort(s) (frequency dependent e.g. ALK)
- social media and accelerated enrollment

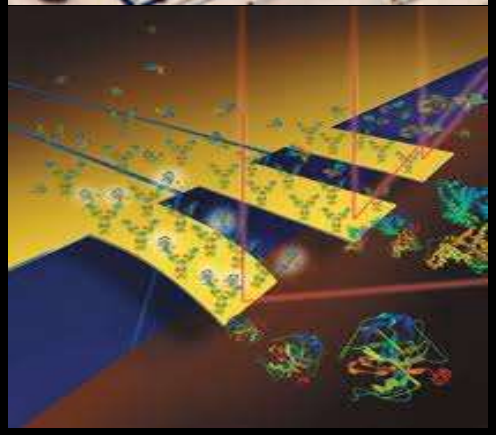
# Miniaturization of Analytical Technologies



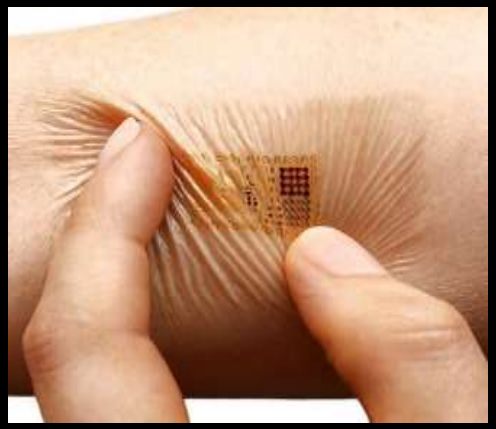


“Lab-on-a-Chip”





“Lab-on-a-Tip”



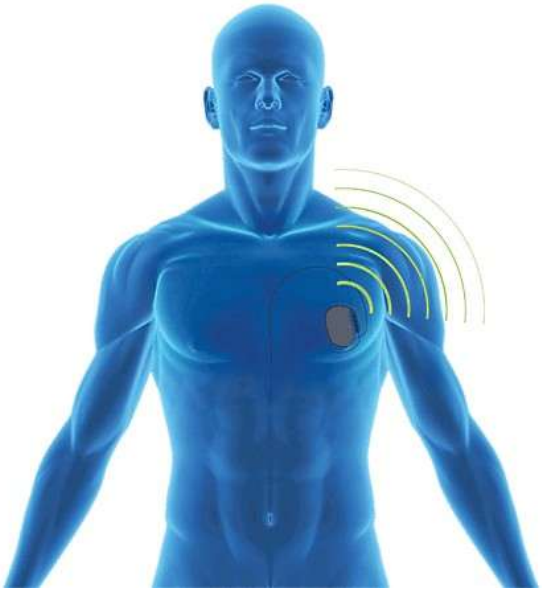
“Lab-Always On”
and
“Lab-On-Me”

# Invasion of the Body Trackers

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

**Remote Health Status Monitoring**

# m.Health



**Remote Health Monitoring and Chronic Disease Management**

**Lifestyle and Fitness**

**Information for Proactive Health Awareness (Wellness)**

# Proactive Engagement of Patient Communities in Investigational Clinical Trials and Observational Outcomes Studies

- Collate, Annotate and Curate Clinical Trial Data with Genomic Information from the Comparator Arms of Industry- and Foundation-Sponsored Clinical Trials
- Building a Site for Sharing Data and Models to evolve better Disease Maps.

Partnering for Cures | A FasterCures Meeting

CYCORE CYber-infrastructure for COmparative Effectiveness REsearch

CW PHS CENTER FOR WIRELESS & POPULATION HEALTH SYSTEMS

PURPOSE

To improve **cancer-related comparative effectiveness research** by better capturing data on physiological, behavioral and psychological status from research participants at home and as the go about their daily lives.

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

CYCORE


caBIG cancer Biomedical Informatics Grid®

army of women

LOVE/AVON Going Beyond a Cure

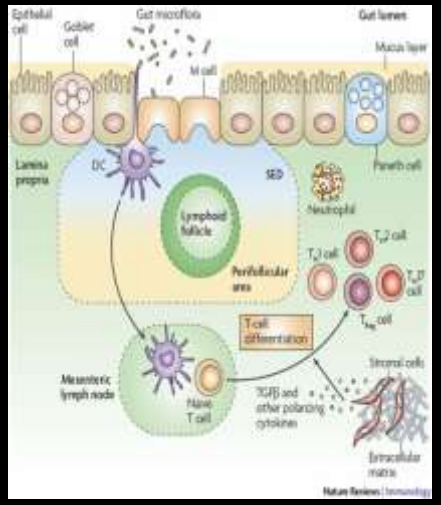
# Framingham Redux!
# Longitudinal Sampling of Populations to Assemble Biomarker/Biosignature Correlates of Health Outcomes

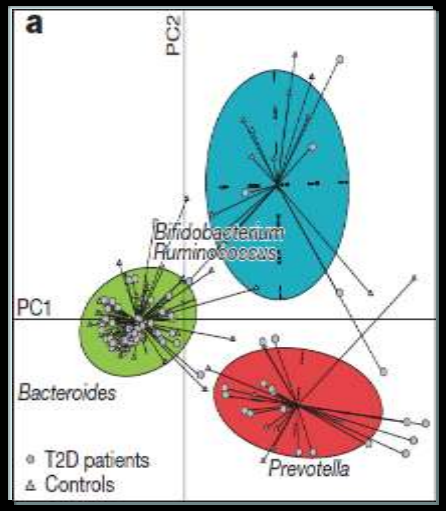
ASU Arizona State University

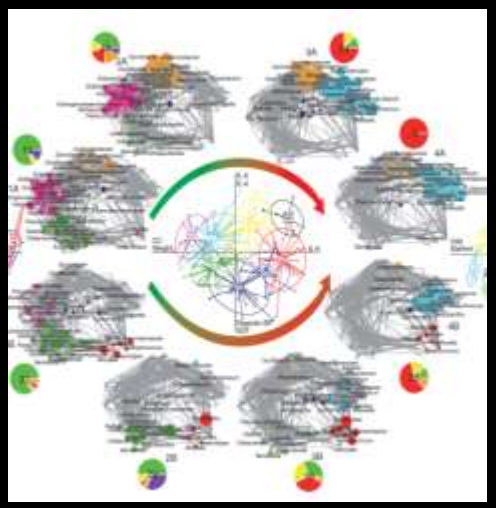
- 73,000 undergraduates
- 10% enrollment for longitudinal monitoring
- bi-annual blood profile
- progressive expansion of WES/WGS datasets
- broad and portable informed consent
- upload to PHR/EHR plus reciprocal consent for epidemiological analysis

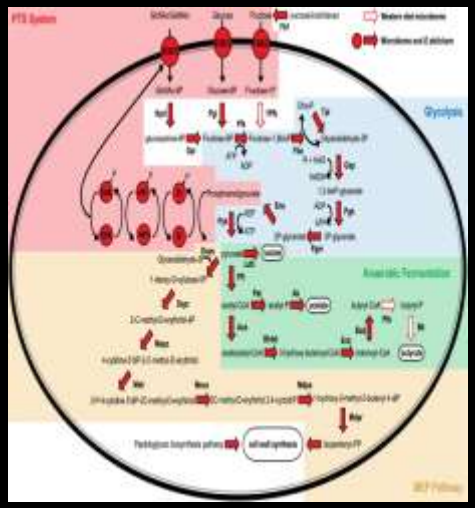
# Commensal Microbiomes: The Frenemy Within. An Additional Dimension to Biomarker Profiling

## Metagenome-wide Association Studies (MGWAS)






| Immune-Mediated GI Diseases | Type 2 Diabetes Profile Shift | Aging, Metabolism and Fragility | Metabolic Activation of Xenobiotics |
|---|---|---|---|

# Oversight and Regulation of Diagnostic Tests: Emerging Gaps and Ambiguities

**enforcement**

- FDA or CMS or both?

**new technologies and new analytical complexities?**

- Dx-Rx combinations and patient stratification for adaptive trials
- multiplex assays and validation of complex statistics/software
- genome sequencing (WGS, exome, transcriptome)
- RUO vs. clinical use (reagents/instruments)
- international harmonization

**new marketing issues**

- no system for post-market surveillance of Dx performance
- DTC advertising and testing
- internet sales
- social media

# New Locations and New Services in Primary Healthcare

## What Was

## What Will Be


From: S. Burrill

# Evolution of CLIA-Waived POC/PON Devices

## Decentralized Primary Care



## Low Cost Fieldable Units: DCs/FOBs

DIAGNOSTICS FOR ALL

- paper-based assays
- hepatoxicity of retroviral therapy
- malaria
- dengue
- pre-eclampsia
- mHealth Apps

HEALTH ADVANCES

THE REIMBURSEMENT LANDSCAPE FOR

# Novel Diagnostics

- CURRENT LIMITATIONS
- REAL-WORLD IMPACT
- PROPOSED SOLUTIONS

UnitedHealth®
Center for Health Reform & Modernization

# Personalized Medicine:
*Trends and prospects for the new science of genetic testing and molecular diagnostics*

Working Paper 7
March 2012

PMC Personalized Medicine Coalition

*Issue Brief*

# The Adverse Impact of the US Reimbursement System on the Development and Adoption of Personalized Medicine Diagnostics

By David Parker, Ph.D, Boston Healthcare

BOSTON HEALTHCARE

# Crossing the Three Chasms:

# Complex Molecular Testing and Medicare Regulations

By Bruce Quinn M.D., Ph.D.

Seaport World Trade Center West
155 Seaport Boulevard
Boston, MA 02210-2600
617 832 1000 *main*
617 832 7000 *fax*

1875 K Street, NW Suite 800
Washington, DC 20006-1238
202 223 1200 *main*
202 785 6687 *fax*

# Medical Policy and Reimbursement


- ICH, FISH other MDx deemed ‘experimental’


- 14% plans classify MDx as ‘experimental’
- no umbrella coverage; separate-contract for each state


- no adverse policies for MDx
- guidance that NGS will not be reimbursed


- IHC’s not reimbursed


- no adverse policies to MDx


- no adverse policies to MDx

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

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

# Intellectual Property and Molecular Diagnostics

**Essential Protection for Innovation and Incentive to Invest in Increasingly Complex and Expensive MDx Development and Approval?**

**or**

**Inappropriate Patenting of Naturally Occurring Molecules (Biomarkers) and Anti-Competitive Barriers to Adoption of New MDx Services in Medical Centers?**

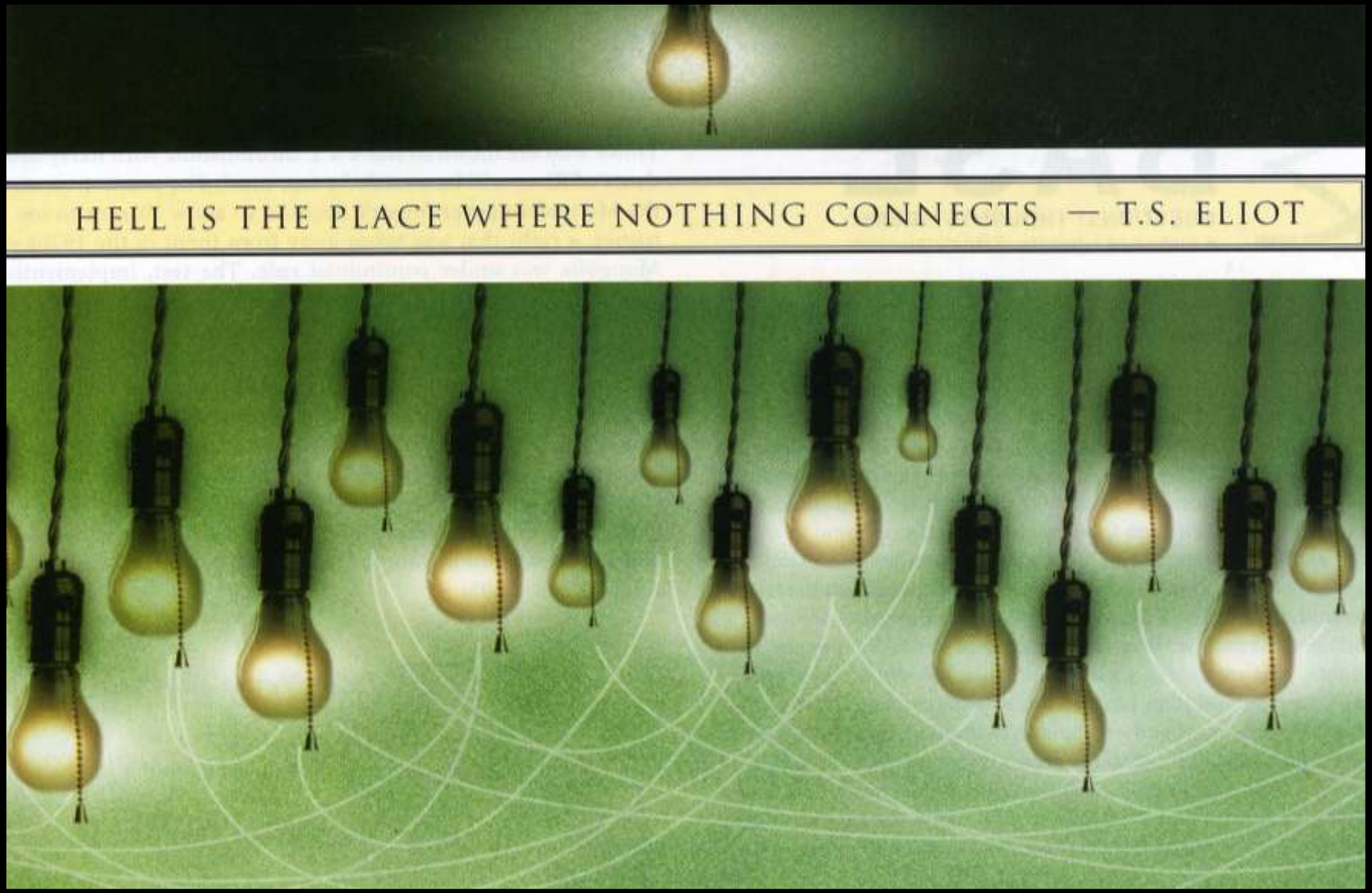
# Now Comes the Hardest Part of All!

**Moving Downstream Beyond Discovery:**

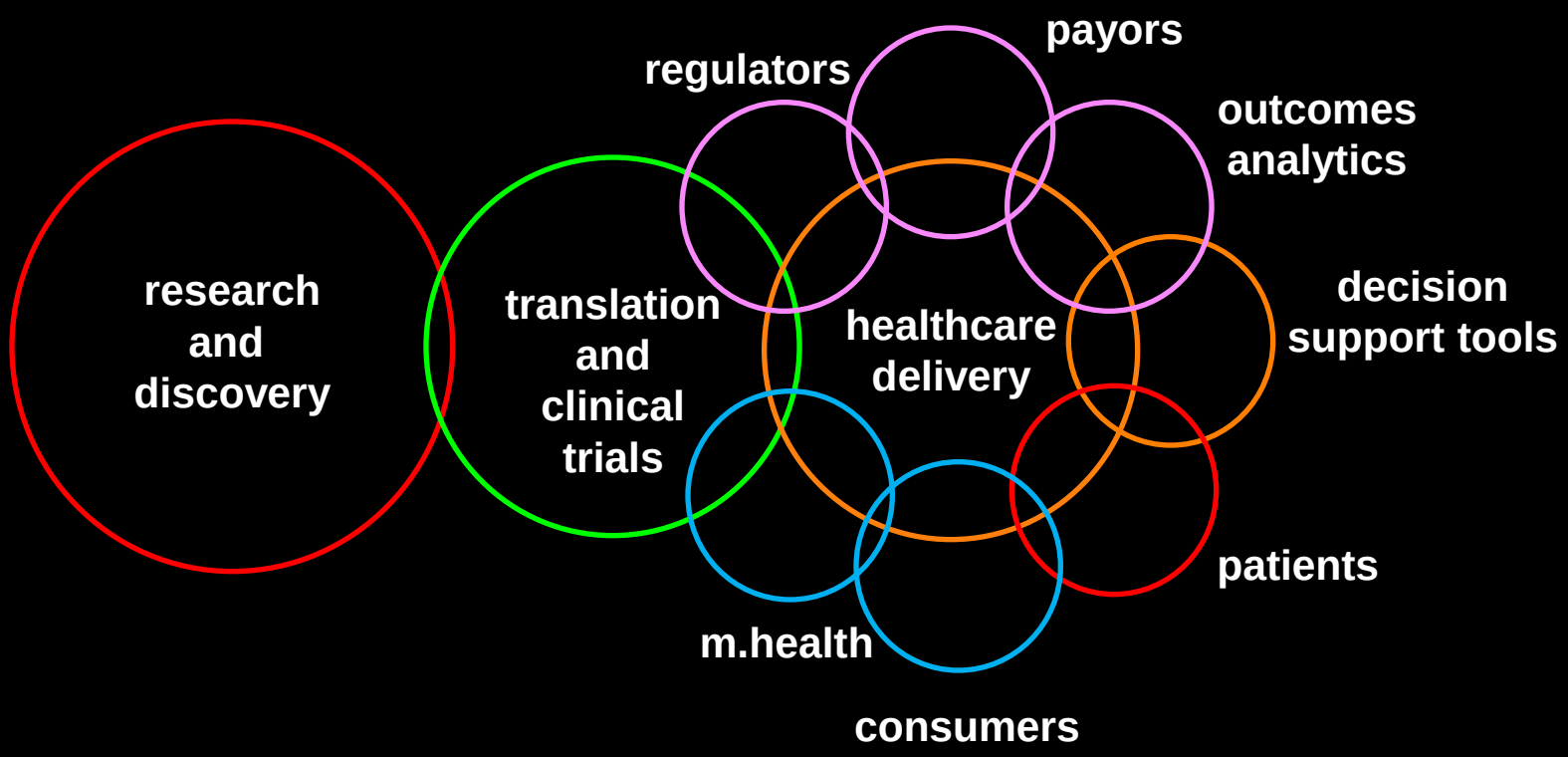
**Driving iOmics and Molecular Medicine and IT-Centric Capabilities Into Routine Clinical Practice**

**The Escalating Scale and Complexity of the Data Stream**

# Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo



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



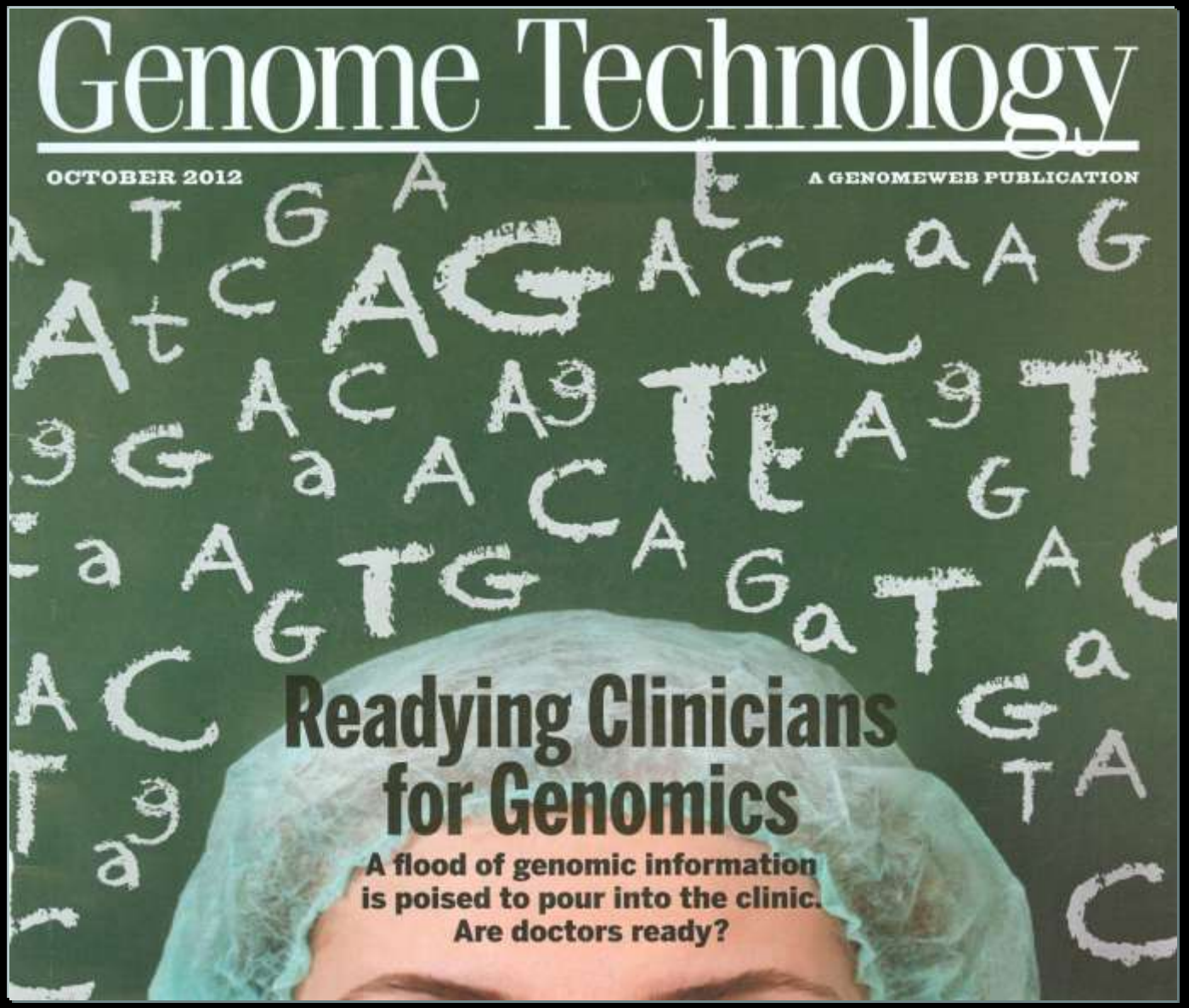
# Representation of Datasets: Formalisms and Abstractions

**Discovery**

- controlled vocabularies and formal ontologies
- quality and provenance checklists and open source repositories
- algorithms and transparent source code for analytical tools

**Translation and Adoption in Routine Care**

- facile exchange formats and semantic interoperability
- cross-domain harmonization/integration/migration/sharing
  - community-driven (eg. SMBL.org, BioSharing catalogue), industry-driven (eg. Pistoia Alliance), regulatory-driven (eg. CDISC), clinical (eg. HL7)
  - reimbursement (CPT, ICD) and HITECH EMR/MU

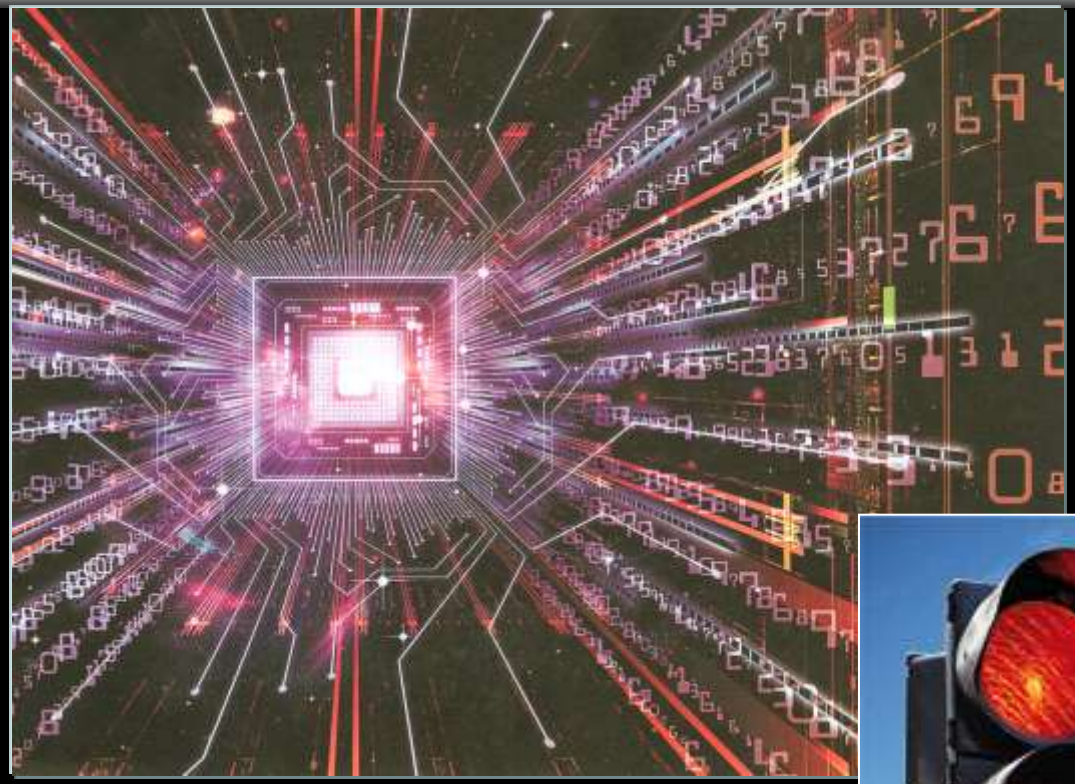

Genome Technology
OCTOBER 2012
A GENOMEWEB PUBLICATION
Readying Clinicians for Genomics
A flood of genomic information is poised to pour into the clinic. Are doctors ready?

# The Clinical Void in Understanding Laboratory Diagnostic Tests

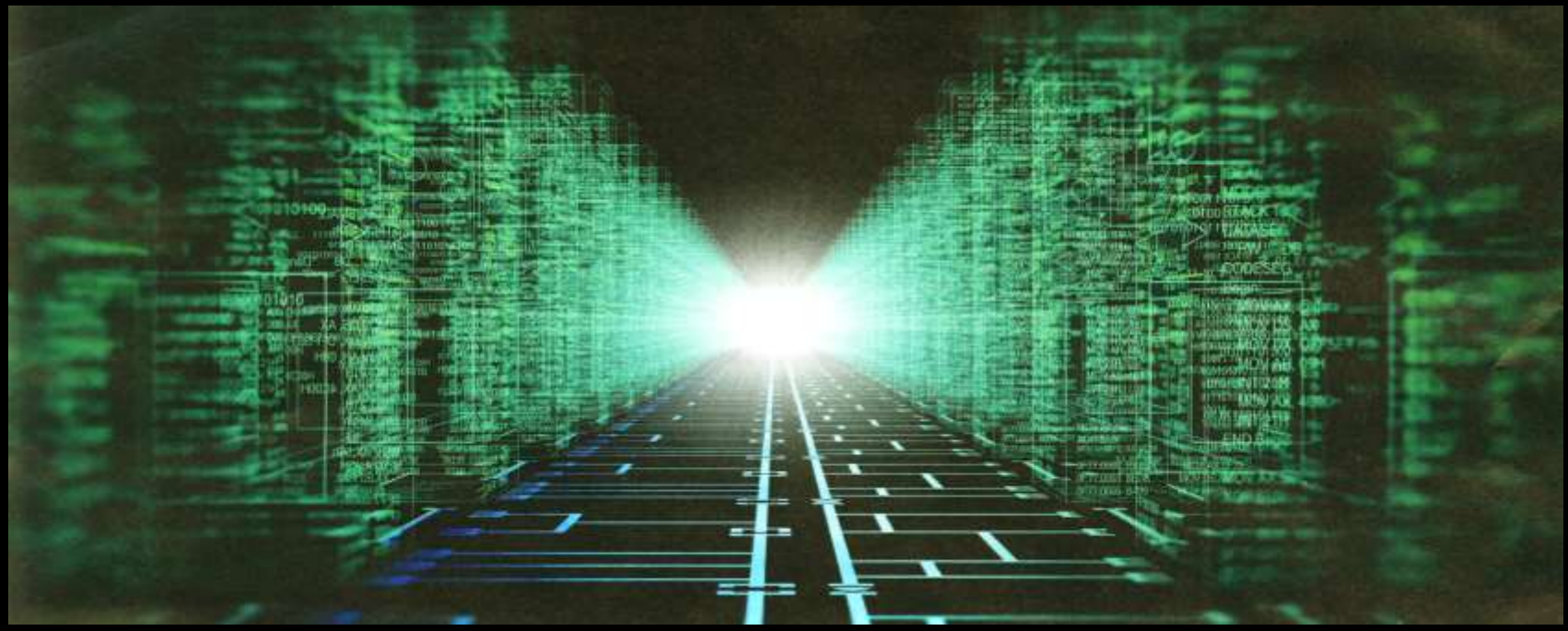
**"We don't teach (medical) students how to interpret lab results or how to pick them.**
**We're spending 61 to 302 hours in anatomic pathology and nine hours teaching laboratory medicine.**
**To pass anatomic pathology you've got to pass a test. There are no tests for lab. medicine."**

**Dr. M. Laposta MD. Ph.D.**
**Executive Vice-Chair of Pathology, Microbiology and Immunology**
**Vanderbilt Univ. School of Medicine**
**Member, CDC Clinical Laboratory Integration Into Healthcare Collaborative (CLIHC)**
**Clin. Lab. News. (2012) Sept. p. 2**

# Reducing Multi-Dimensional Complexity and Diverse Data Sources to End-User Simplicity and Facile Decisions



# The Imminent Arrival of the Zettabyte ($10^{21}$) Era



**The Emergence of Large Scale,
Integrated Data and Knowledge Networks:**

**Profound Consequences for Individuals, Enterprises,
Infrastructure, Investment, Education and Public Policy**

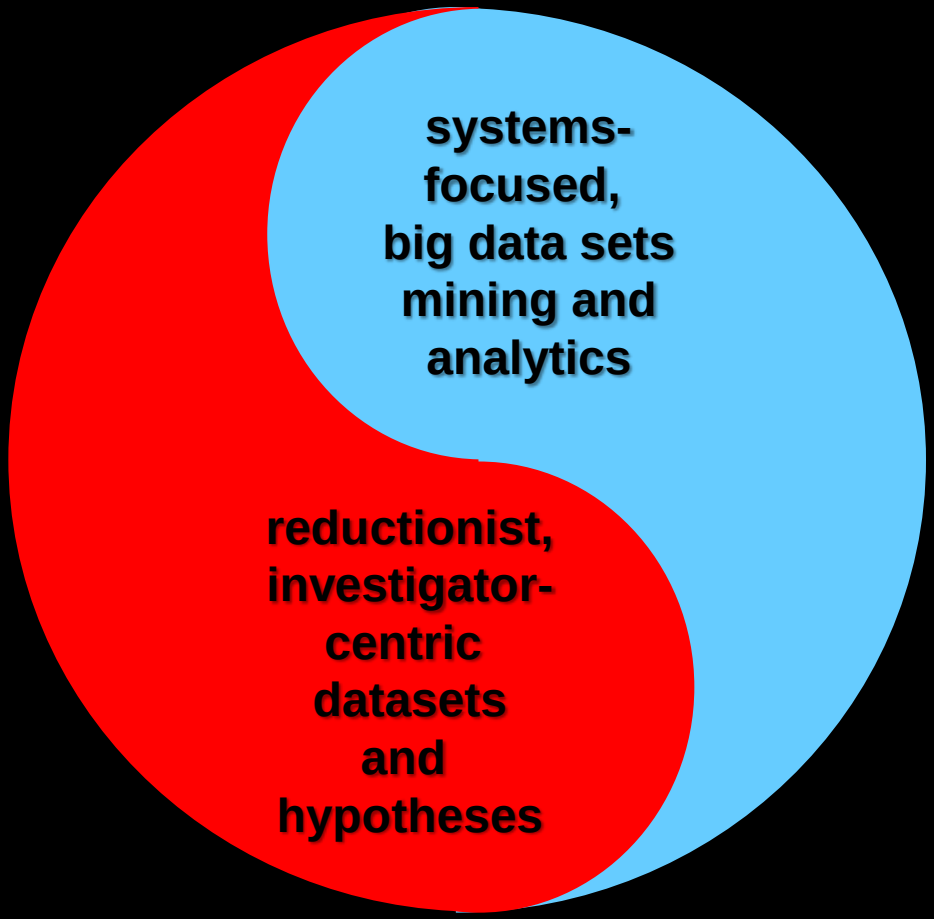
# Managing the Impact of PB and TB-Scale Datasets on Archives, Data Centers and User Communities

- current-approaches for data-access/download not sustainable
- network bandwidth limitations on large scale transfer
- need for rapid access to data in multiple distributed archives
- most end-user local capacities lack power to process large TB/PB datasets
- looming impact of austerity budgets on infrastructure and personnel
- prospect of serious performance degradation/breakdown

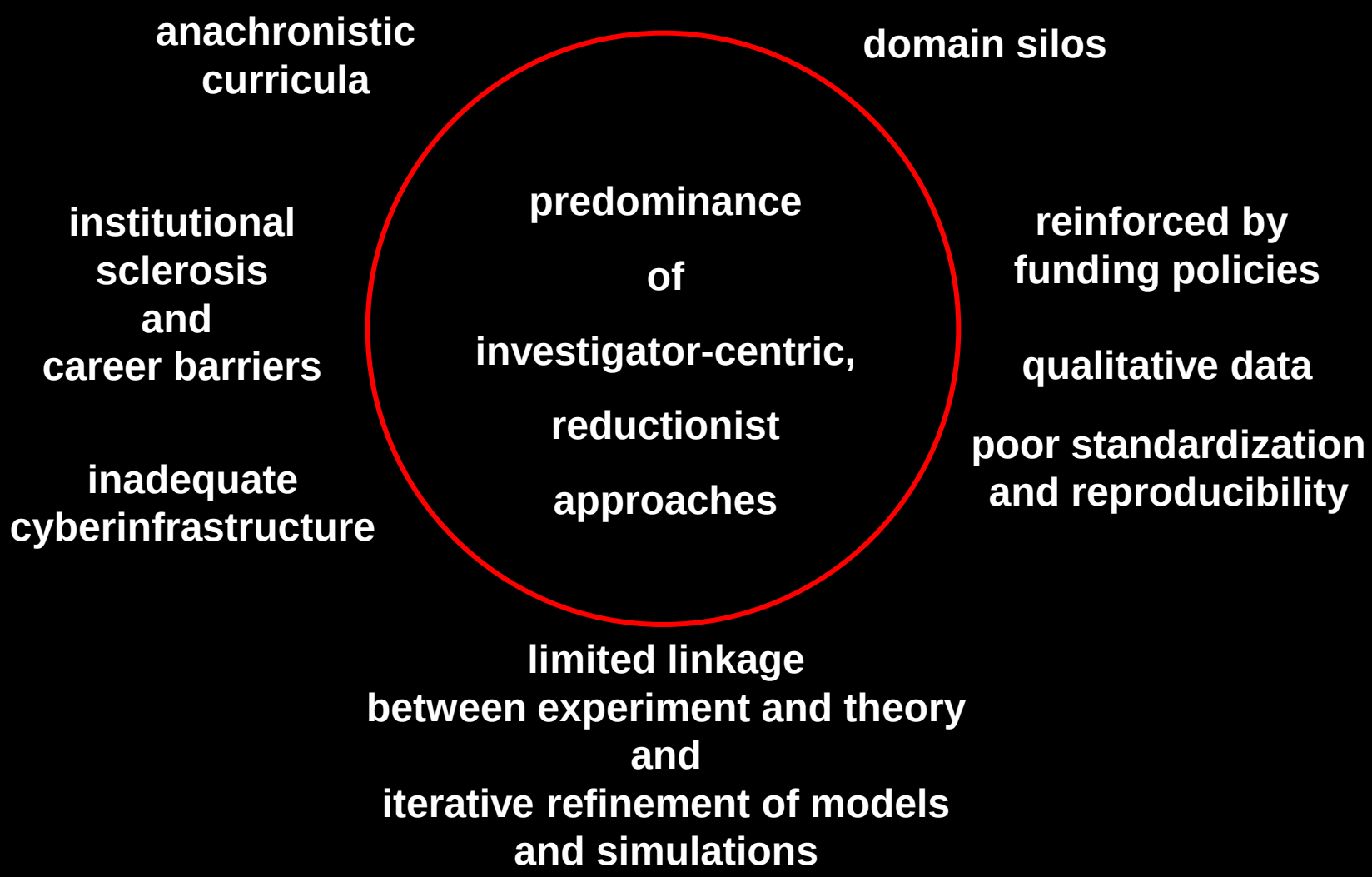
# Data-Driven Knowledge, Intelligence and Actionable Decisions

- changing the nature of discovery
  - hypothesis-driven versus unbiased analytics of large datasets (patterns, rules)
- changing the nature of explanation
  - statistical probabilities versus unitary values
- changing the cultural process of knowledge acquisition
  - large scale collaboration networks, open systems, social media
- changing how knowledge is analyzed and used
  - increased quantification, complex analytics and decision-support systems
- changing education and training

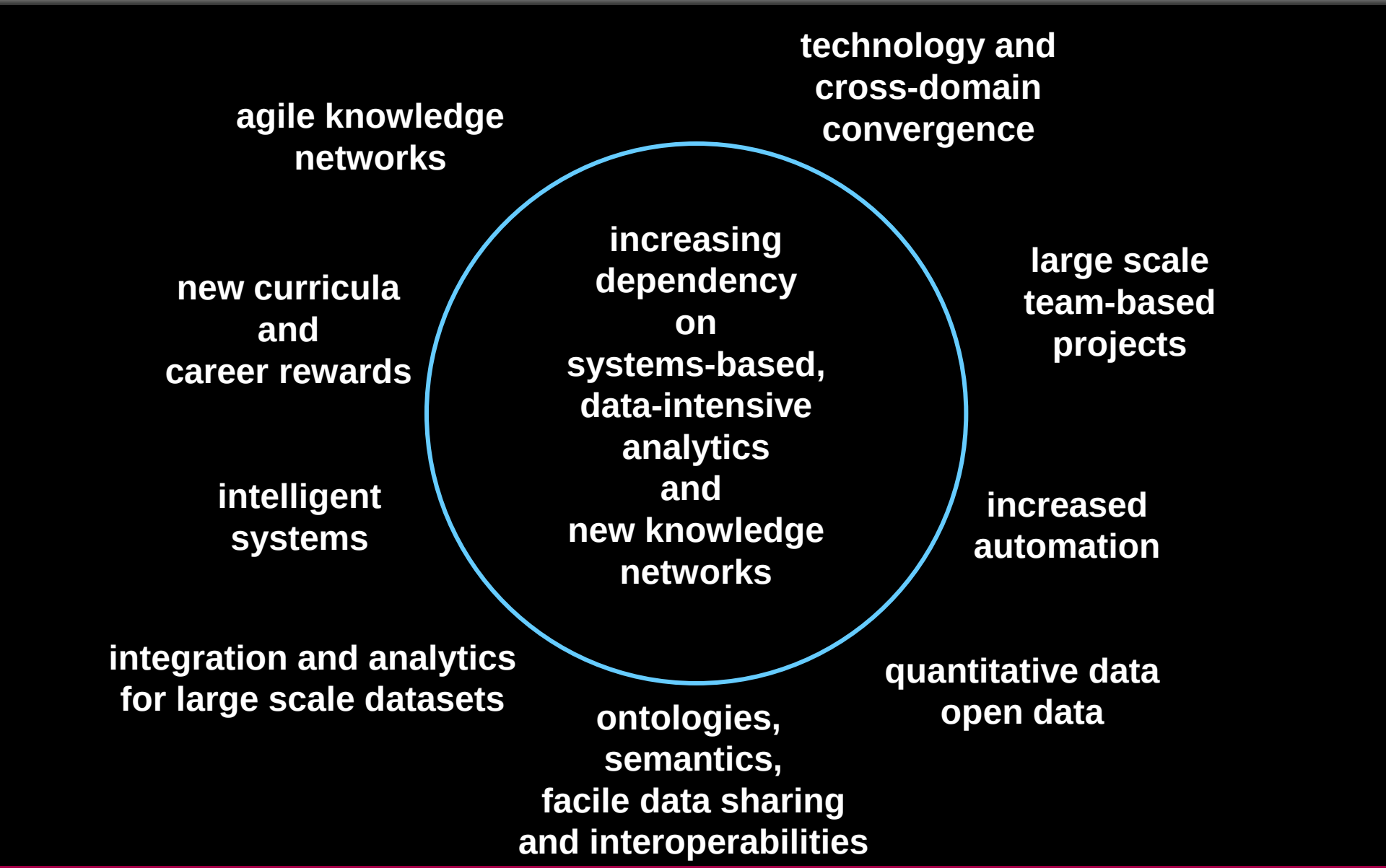
# Cross-Domain Convergence, Complexity and Increasing Dependency on Data-Intensive Methods and New Knowledge Networks



# Silos Subvert Solutions: The Slow Response of Biomedicine to Technology Convergence and Cross-Disciplinary Requirements



# New Conceptual, Methodological and Organizational Frameworks for Data-Intensive Biomedical R&D



# Sustainable Health: Societal and Individual
# The Complex Path to Proficient, Personalized Healthcare

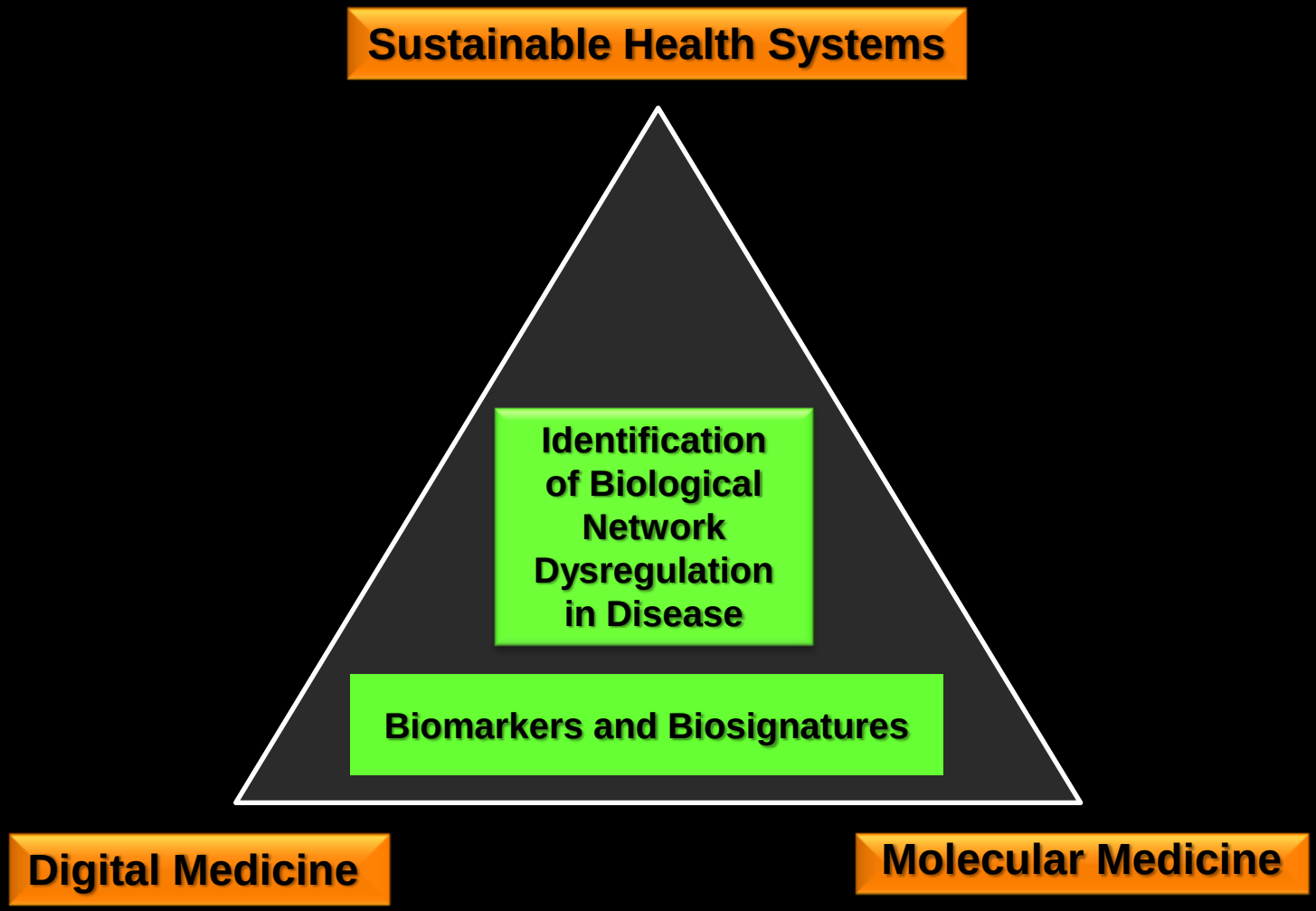
- the potential economic and health benefits from biomarkers for molecular diagnostic profiling, rational treatment selection and continuous health monitoring transcend any other current category of healthcare innovation

- realization of this potential will depend not only on technological advances but equally on overcoming entrenched cultural, institutional and economic interests

# Sustainable Health: Societal and Individual - The Complex Path to Proficient, Personalized Healthcare

- realization of this potential will not be straightforward and will require:
  - improved technical standards for biomarker R&D
  - sophisticated integration of complex multidisciplinary expertise (from silos to systems)
  - proactive (inter)national leadership to establish comprehensive resources for biobanks, cyberinfrastructure and HIX data inter-operability
  - new clinical trial designs for Rx/MDx combinations
  - streamlined updating of SOC guidelines to reflect disease subtypes, patient heterogeneity and predisposition risk

# The Primacy of Biomarkers and Biosignatures in Charting a New Ecology for Healthcare



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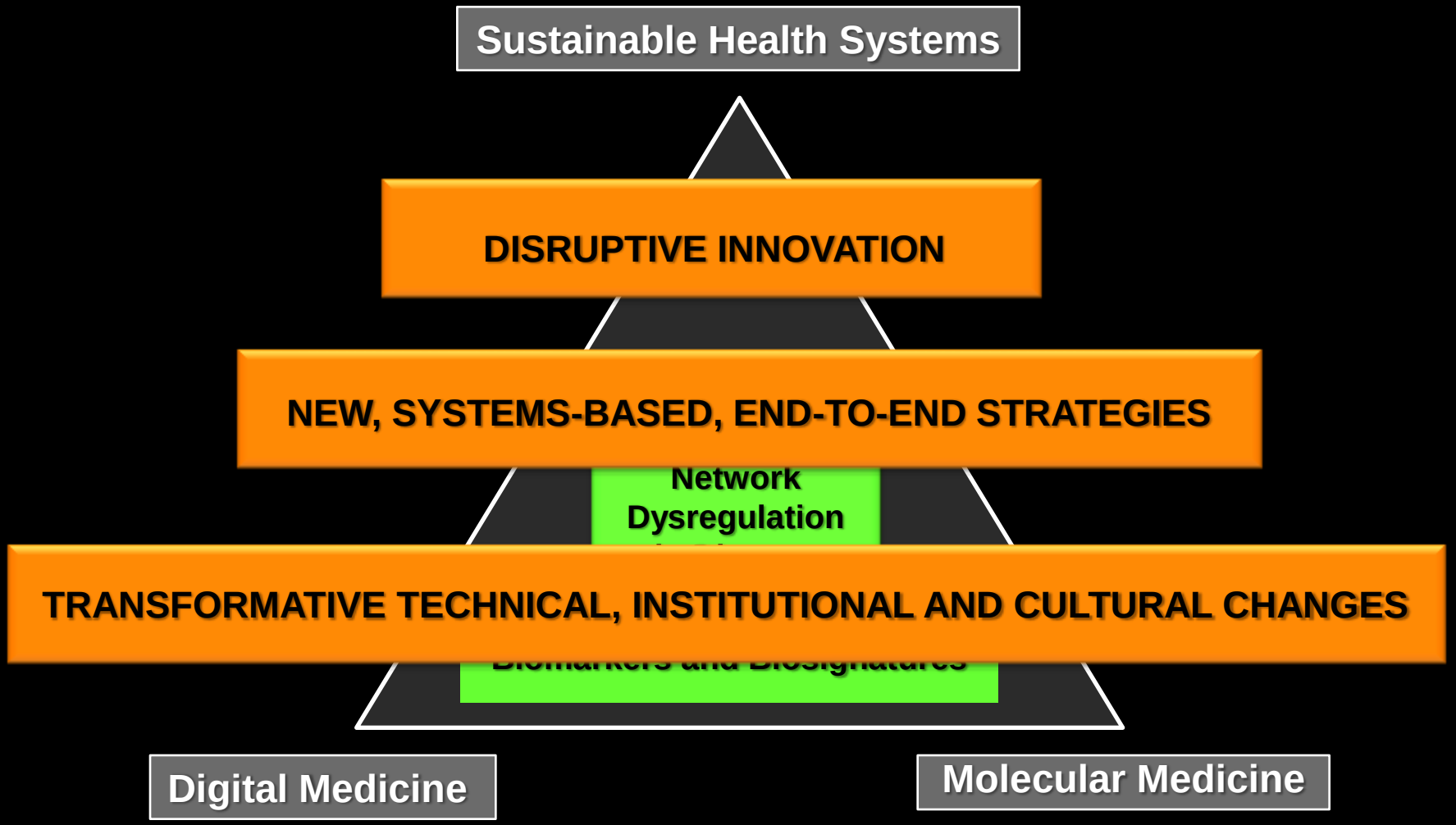
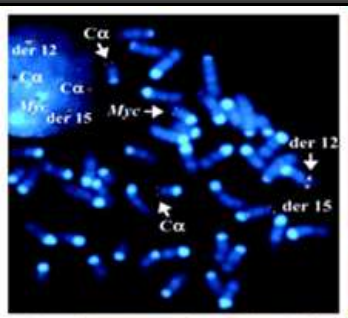
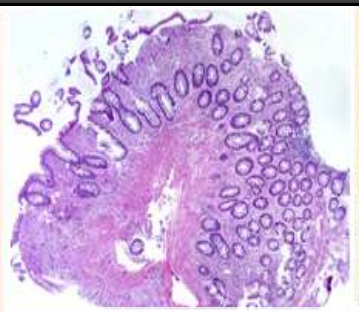


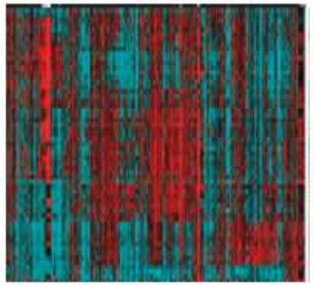
# Slides available @ http://casi.asu.edu/

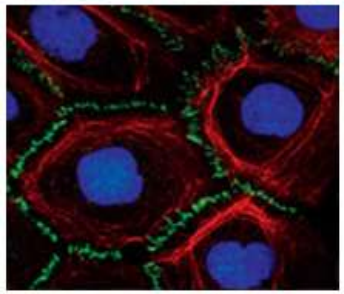
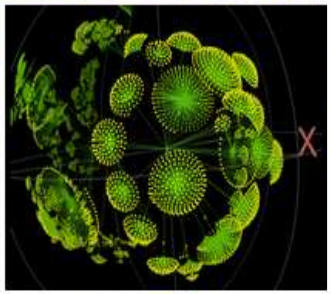
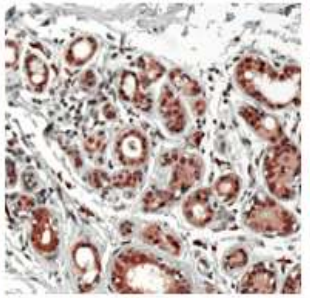


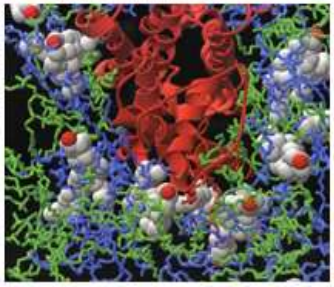
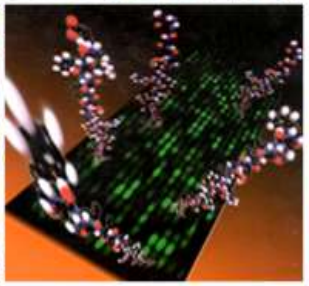






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