Molecular Diagnostics: Multiplexity, Complexity and Ambiguity

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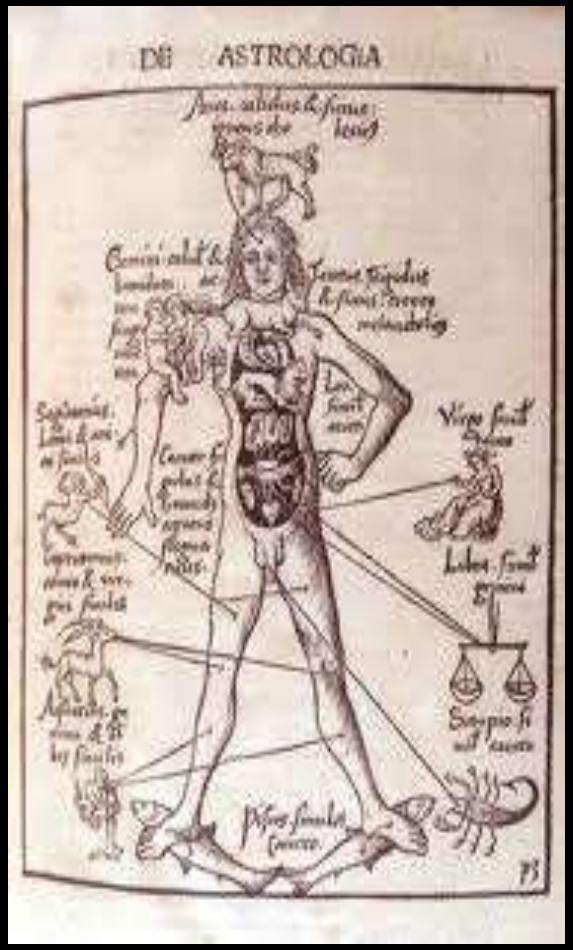
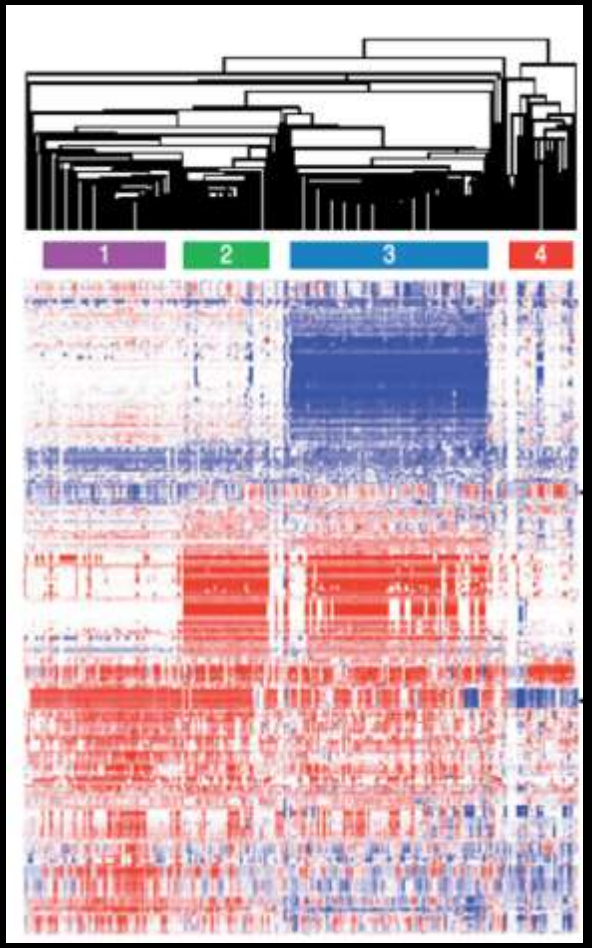
on Molecular Diagnostics, Reimbursement and Regulation
Scottsdale, Arizona • 17 April 2015

Medical Progress:
From Superstitions to Symptoms to Signatures

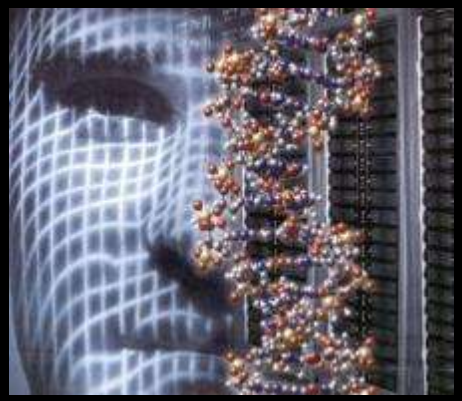




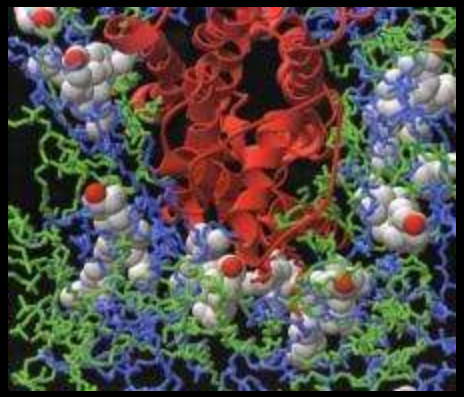
The Path to Precision (Personalized) Medicine

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

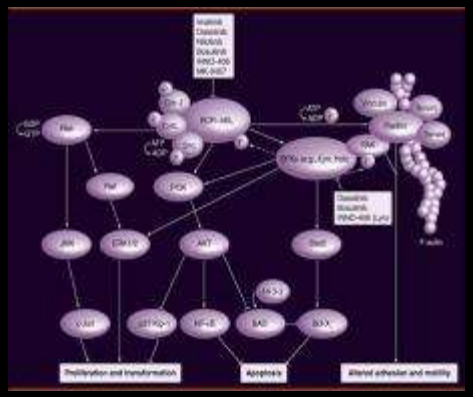
(Epi)Genomics



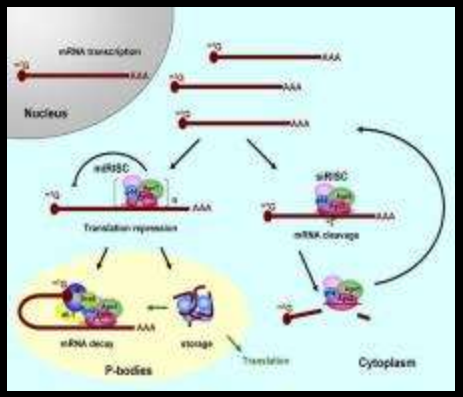
Proteomics

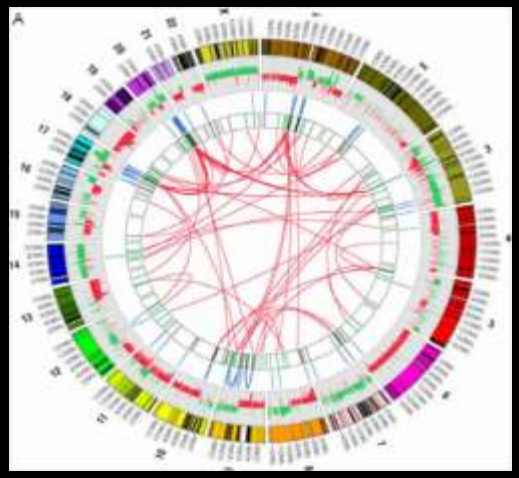


Molecular Pathways and Networks



Network Regulatory Mechanisms





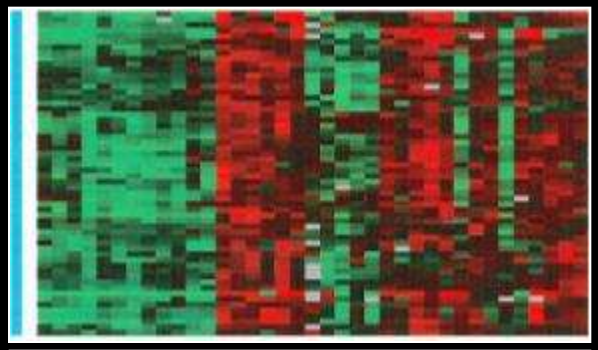
ID of Causal Relationships Between Network Perturbations and Disease

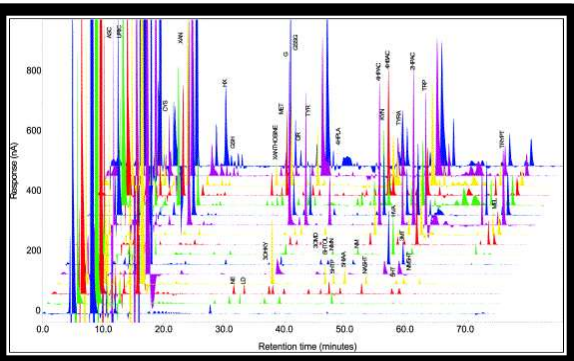
Patient-Specific Signals and Signatures of Disease or Predisposition to Disease

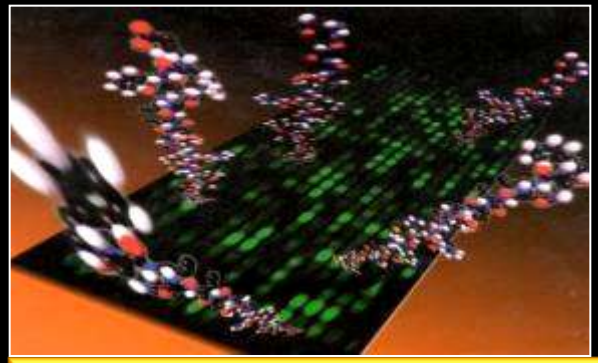
Mapping Molecular (Information) Signaling Pathways in Health and Disease

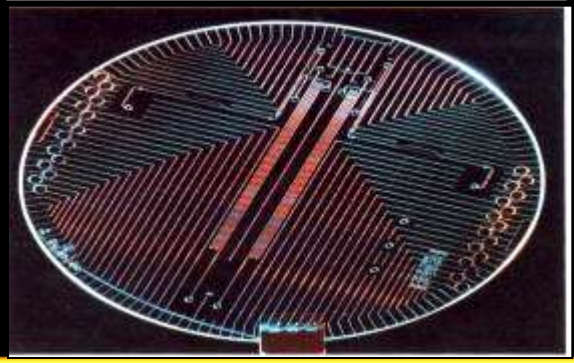
Complex Biosignature Profiling: panOmics

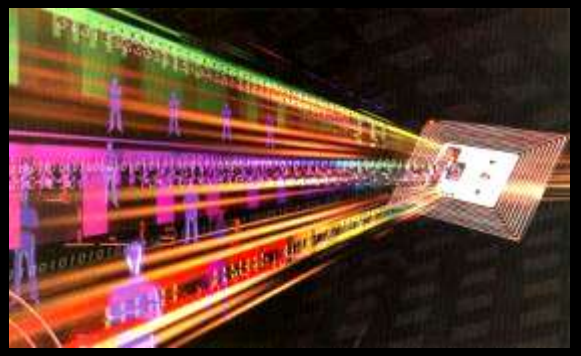
(epi)genomics	proteomics	immunomics











Signature Detection, Deconvolution and Multivariate Analysis

automated, high throughput multiplex assays	novel test formats and devices (POC)	new algorithms for complex signal/deconvolution

Progressive Migration of Diagnostic Profiling from Centralized Large Laboratories to Decentralized POC/PON Platforms and Settings

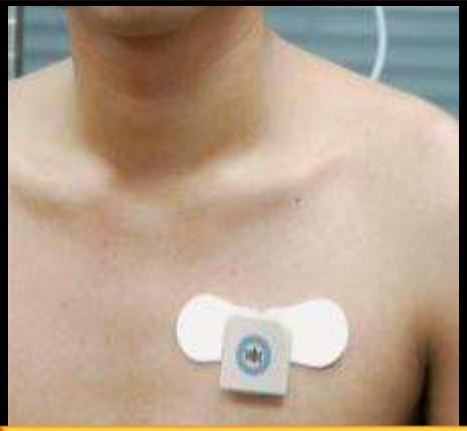
Centralized Testing and Large Capital Base Instrumentation

Economies of Scale for Genome Sequencing

Desktop Integrated Dx

Mobile and Handheld Devices

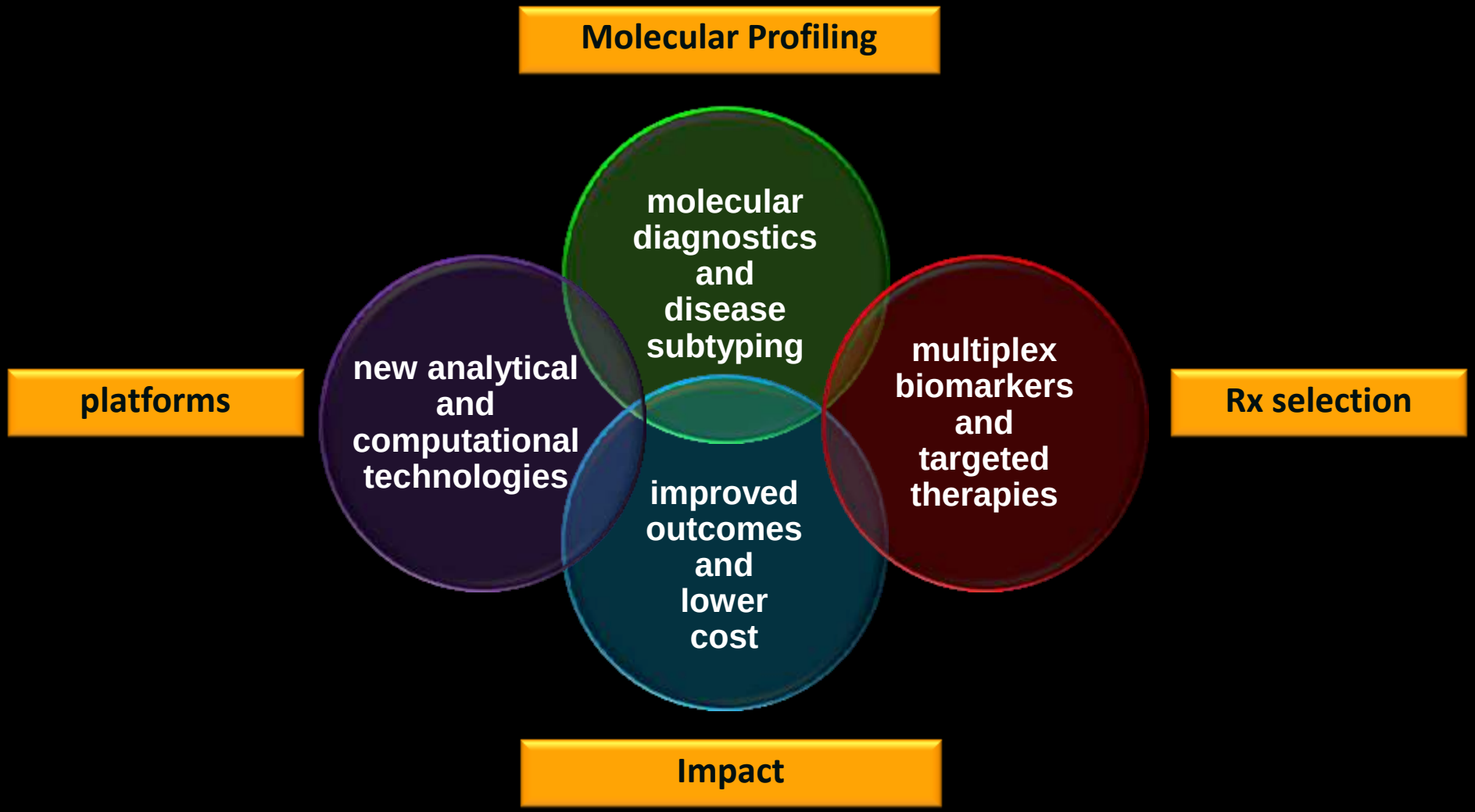
On-Body: In-Body Sensors



Remote (Virtual) Care

Increasingly Distributed and Diversified Data Feeds and Real-Time Health Status Monitoring

Precision (Personalized) Medicine



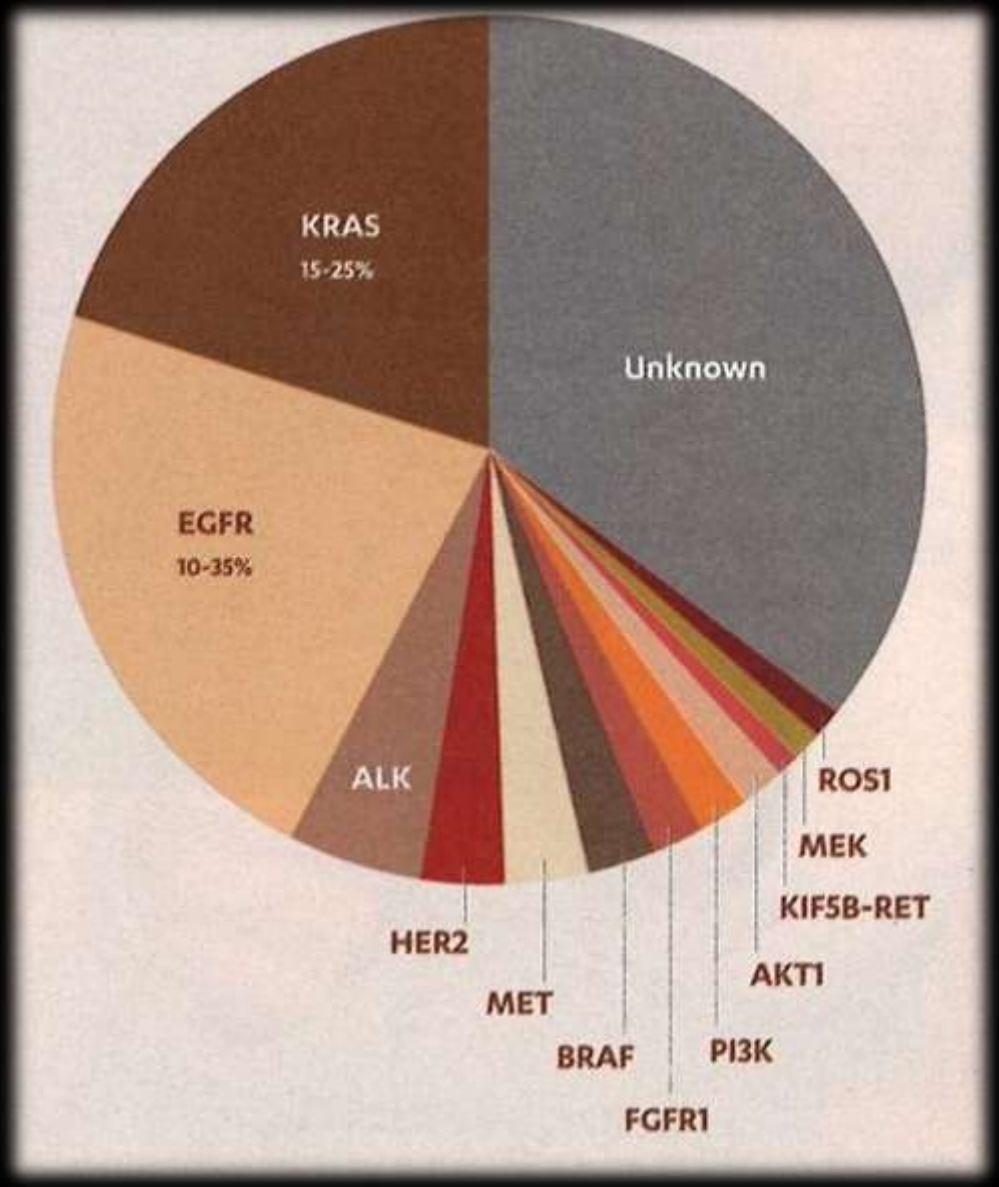
Multiplex Molecular Profiling (panOmics)

A New Taxonomy for Disease Classification

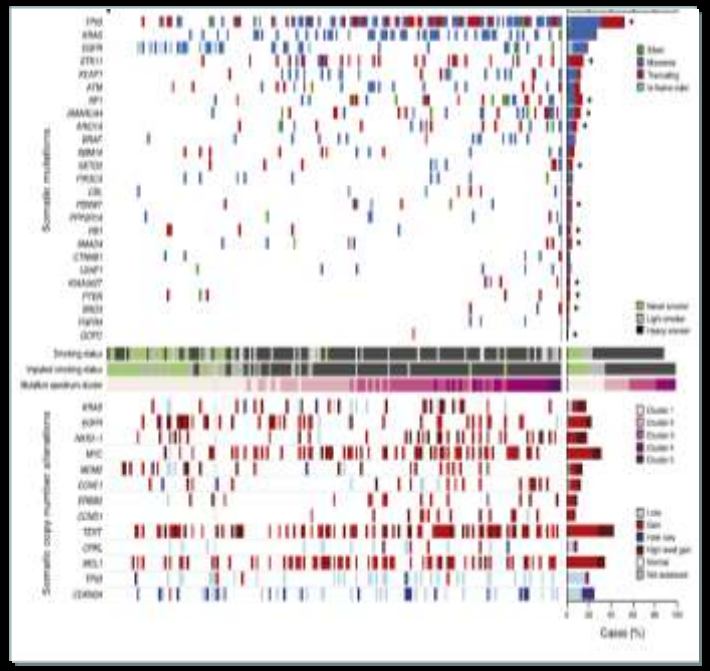
Revealing the Underlying Complexity and Diversity of Disease Mechanisms

Disease Subtypes, Different Molecular Pathway Perturbations and the Phenotypic and Clinical Diversity of Disease Pathology, Progression and Rx Responses

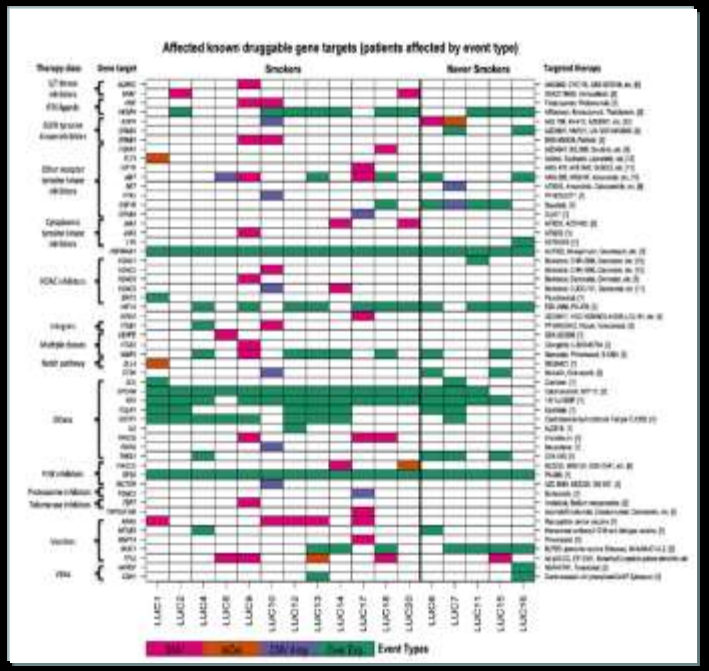
Molecular Biomarkers in NSCLC



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 Rx and development of new Rx

Are We There Yet?
Personalized (Precision) Medicine: Seemingly Always on the Threshold of Mainstream Adoption

What Applications of NGS/panOmics Profiling Technologies Are Ready Now for Routine Clinical Adoption?

The Central Challenge in the Validation/Qualification of Multiplex Biomarkers, panOmics Profiling and Molecular Diagnostics

STANDARDS

STANDARDS

STANDARDS

Genome Sequencing: A Disruptive Technology

Clinical Utility: Not If, but When, What and How

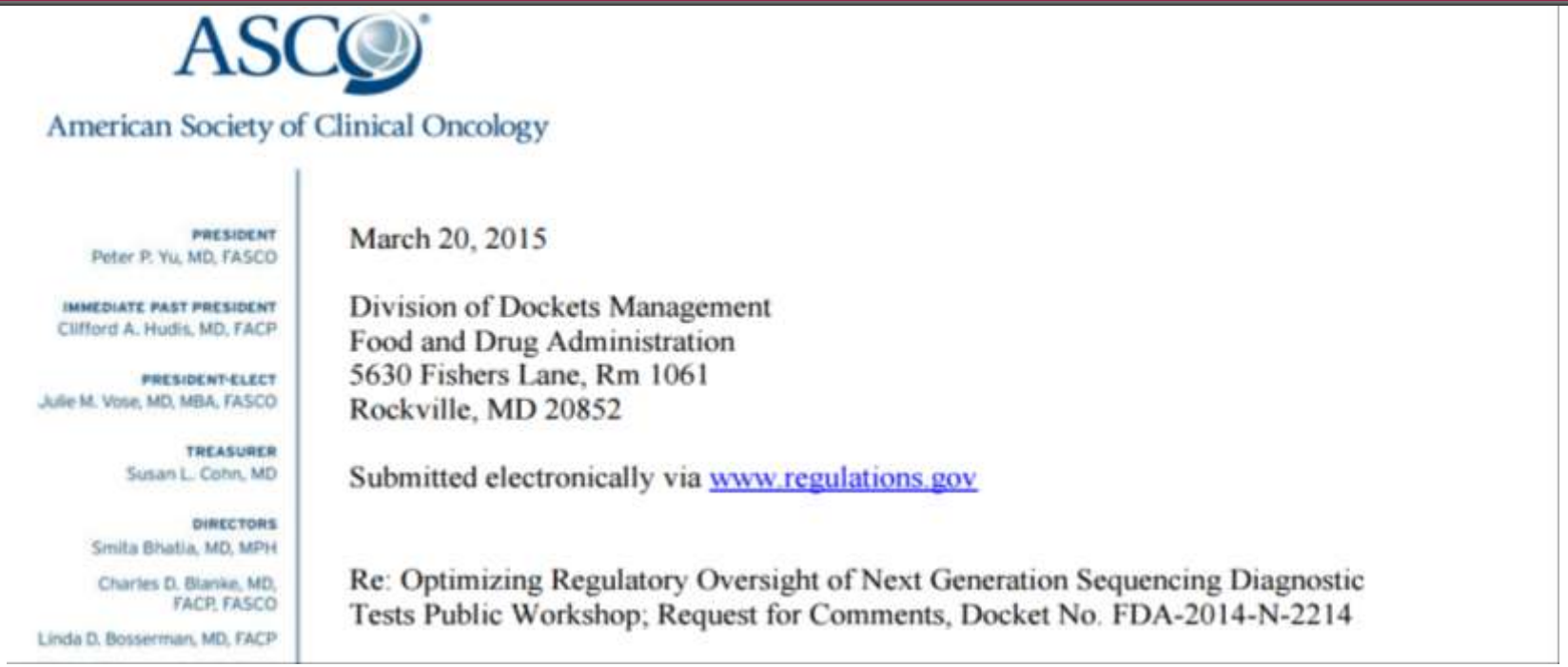
Use of NGS and Clinical Care

- because we can?
- because it is useful?

Meeting the ‘Fit-for-Purpose’ Standard

The Urgent Imperative to Define Analytical and Interpretation Standards for Clinical Grade Genome Sequencing

Sequences and Consequences



ASCO

American Society of Clinical Oncology

March 20, 2015

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Submitted electronically via www.regulations.gov

Re: Optimizing Regulatory Oversight of Next Generation Sequencing Diagnostic Tests Public Workshop; Request for Comments, Docket No. FDA-2014-N-2214

"Failure of such tests to perform as intended can lead to patients receiving inappropriate and potentially harmful treatments or, alternatively, not receiving a treatment that has the potential to benefit them."

"These are significant risks in reporting tumor or genetic variants as being "actionable" in association with non-FDA-approved indications, or those which are not listed in CMS-approved compendia."

"Such reports have the potential to mislead physicians and expose patients to undue risk."

http://www.asco.org/sites/www.asco.org/files/asco_ngs_comments_03.20.2015.pdf

Current Issues Related to the Accuracy and Quality of WGS for Clinical Applications

- error rate
- sequence completeness
- sequencing depth
- instrument platform variation
- base calling algorithms
- aligning real algorithms
- adequacy of reference genomes
- annotation, analysis and curation of large scale data

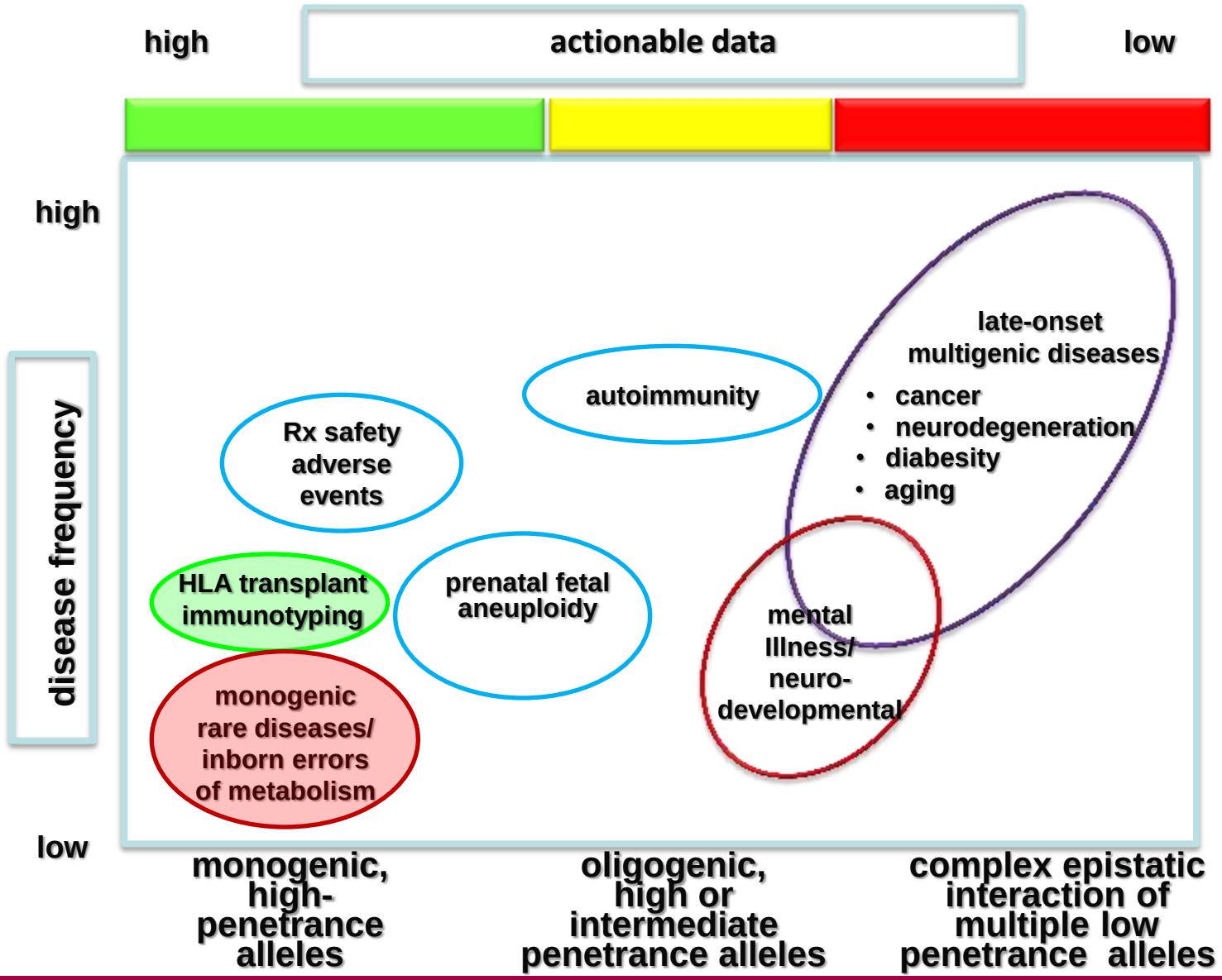
Lack of Consistent Technical Standards and Ill-Defined Regulatory Frameworks

Accuracy of Identification of Sequence Variation Calls in Next Generation Sequencing

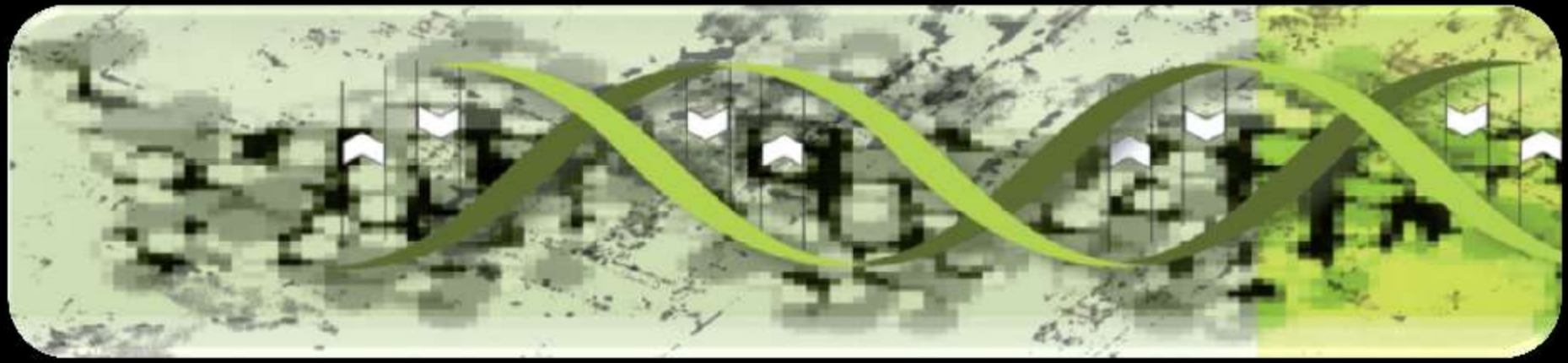
- NGS in its current incarnation(s) estimated to make high-confidence calls for 78% of the human genome
  - J.M. Zook et al 2014. Nat. Biotechnol. 32, 246-51
- c.80% concordance between cells made using different sequencing platforms
  - CAP Today March 2015, p.16
- extensive disagreement between different bioinformatics programs in calling variants on same sequencing data
  - J.A. O'Rawe et al. 2015 Trends. Genet. 31, 61-66

Seeking the 'Needle' of Actionable Clinical Value in the 'Haystack' of Large Scale PanOmics Data

- estimated 3-4 million variants in genome of any individual
- estimated 8-15 protein coding region variants provide 'actionable' information based on current knowledge
- vast majority are Variants of Unknown Significance (VUS)
- anticipated dramatic expansion of individual variant space with resolution of non-coding regions and their regulatory elements
- normal mutation rate will continue to generate a nearly infinite spectrum of genetic variation
  - current population, future generations


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

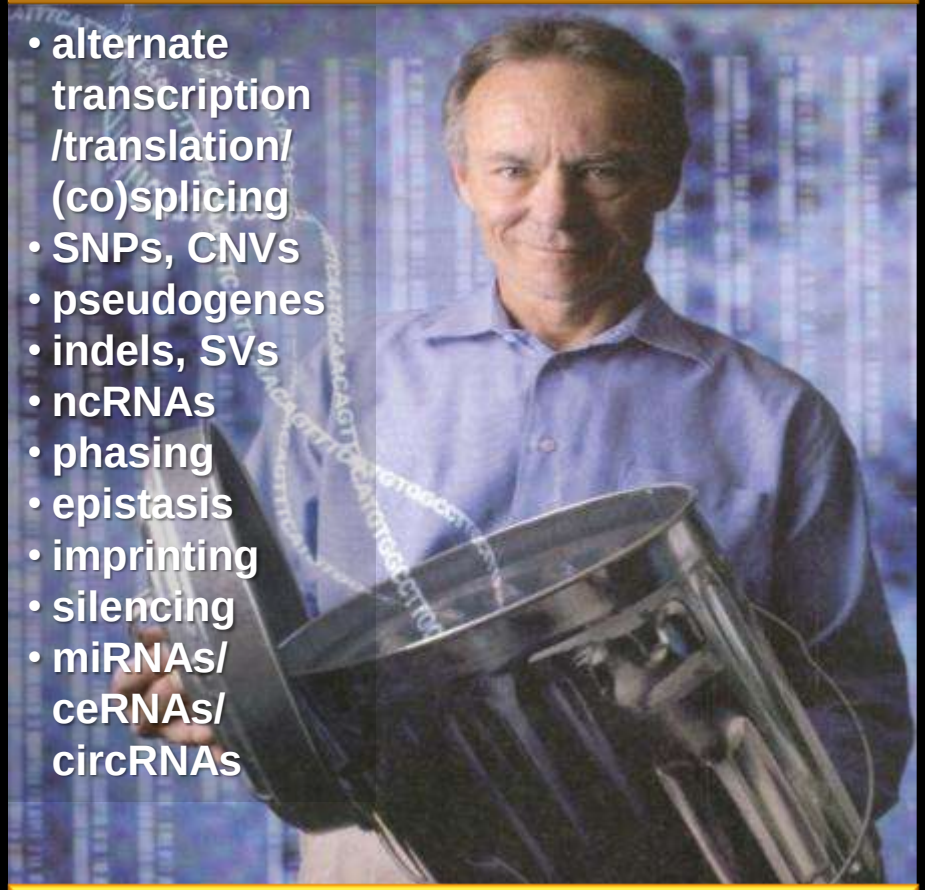
Genes for….
The Over-Simplified Perspective That Whole Exome-and Whole Genome-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis and Transform Treatment Options



- other ‘omes’ matter- the current black box of genome-phenotype relationships
- the epigenome and environmental effects
- the yet unknown dimension of epistatic complexity
- hype, hubris and herd mentalities in uncritical acceptance of value of NGS data in isolation

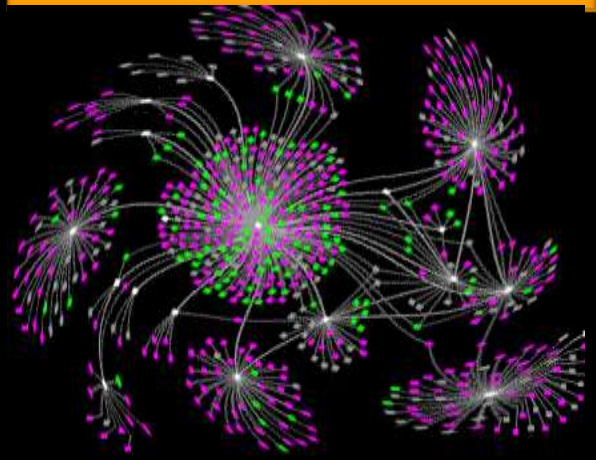
Individual Variation, Genome Complexity and the Challenge of Genotype-Phenotype Predictions

Junk No More: Pervasive Transcription

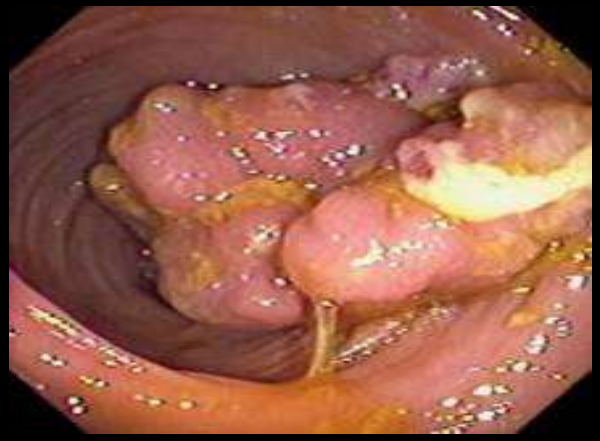


recognition of genome organizational and regulatory complexity

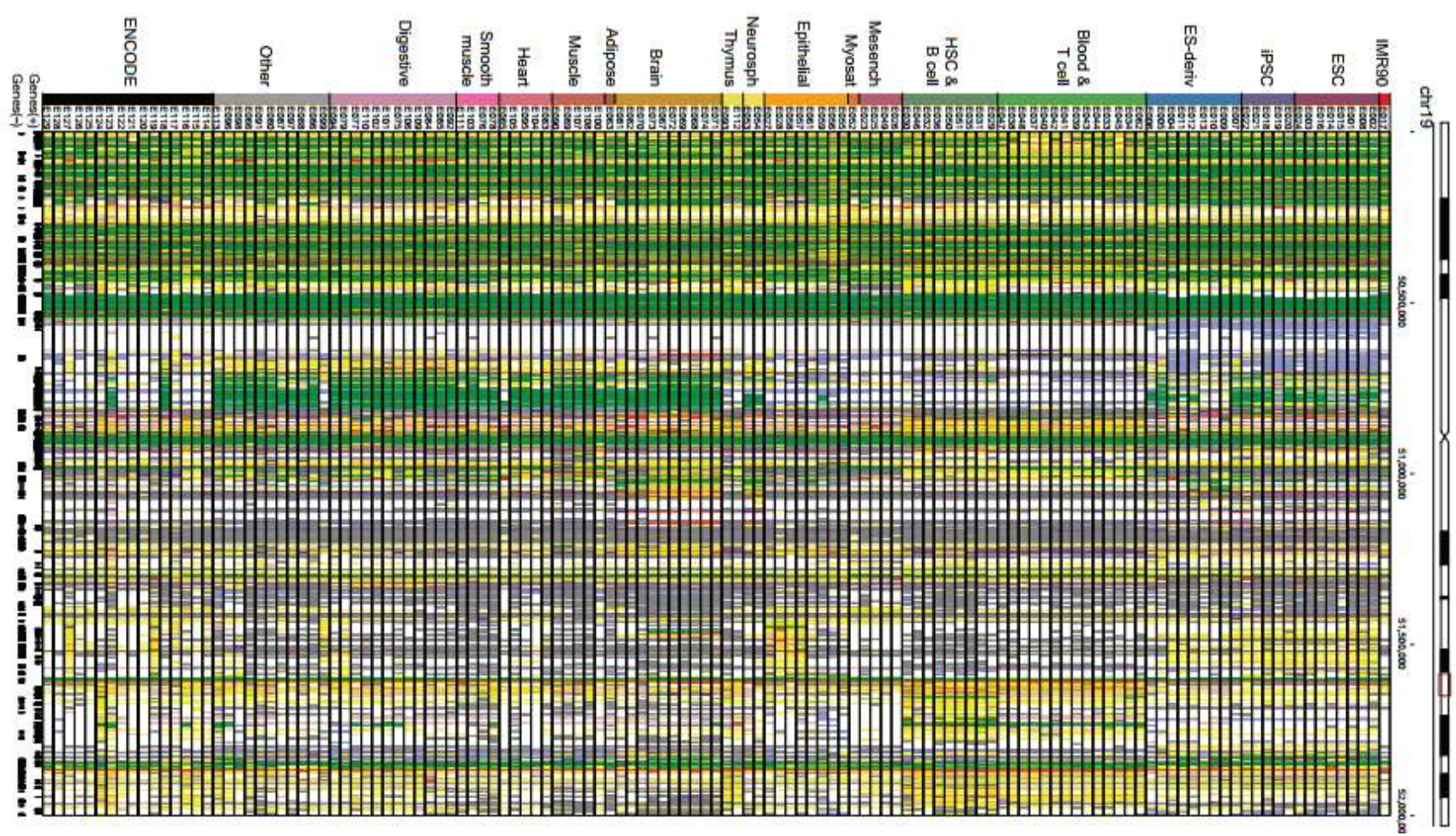
Cell-specific Molecular Interaction Networks



Perturbed Networks and Disease



Large Scale Imputation of Epigenomic Datasets for Systematic Annotation of Diverse Human Tissues



From: J. Ernst & M. Kellis (2015) Nature Biotechnology 33(4), 373

The Need for New Diagnostic Assays to Assess Immunophenotypes

- early evidence indicates that immune checkpoint modulation may offer major PFS gains in several malignancies
- what markers characterize immunorestorative (positive Rx response) and immunoevasive (Rx-resistant) phenotypes?

Proprietary PD-L1 IHC Assays and Clinical Trials and Clinical Decisions Regarding Use of PD-1 and PD-L1 Therapy in Cancer

- at least four Rx companies with proprietary assays
- different antibody clones
- different staining protocols
- different scoring methods

PD-1 and PD-L1 Profiling and Cancer Immunotherapeutics

- multiple drugs acting on same target
- multiple companion diagnostics (CDx) and LDT assays
- multiple FDA-approved CDx for same drug class but each Rx-specific (and proprietary)
  - cost to providers to offer all CDx
  - confusion for MDs/HCPs
- different ‘cut-off’ points in assay interpretation
- scarce biopsy tissue as obstacle to running multiple tests to ID best-in-class Rx recommendation

Patient Stratification by Molecular (panOmics) Profiling, Rx Selection and Need for New Clinical Trial Designs

Molecular Profiling, Disease Subtyping and New Clinical Trial Designs and Regulatory Review Frameworks

- the demise of the “all-comers” RCT design?
- new trial designs based on biomarker-selected patient cohorts and Rx response evaluation
  - enrichment trials, adaptive trials, basket trials
  - multi-agent trials and more agile shifts in combination Rx
- statistical sophistication of protocol design and criteria for switching between trial arms
- proactive regulatory engagement in trial design
- new regulatory policies for review of Rx^n:MDx^n combination dossiers and labeling issues

The Internet of Things
Expanding the Diversity and Scale of Multiplex Signatures

On-Body: In-Body Sensors, Mobile Health and Telemedicine

Real-time Transmission of Multiplex Signatures on Health Status and Treatment Compliance

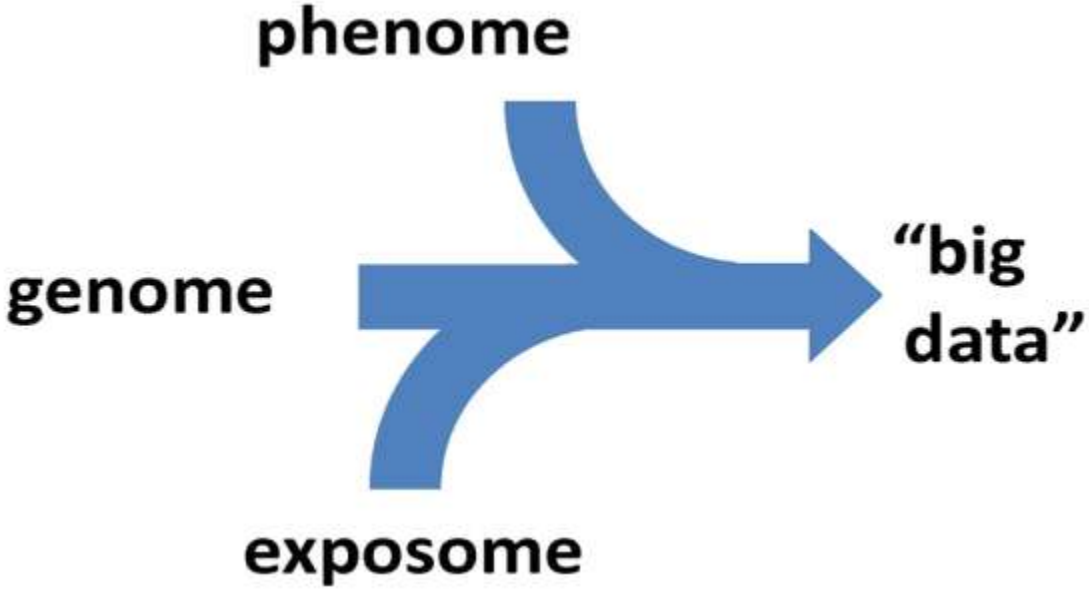
New Challenges in Clinical Monitoring, Health Records, Regulation and Reimbursement


Units
WebMD
MediMath
PALS
BAC Calc
MedCalc
BLACKBAG
Evernote
Phone
Contacts


TIME
Never Offline.
The Apple Watch is just the start. How wearable tech will change your life—like it or not
BY LEV GROSSMAN AND MATT VELLA

From Static Population-Based Indices of Diagnostic Ranges to Dynamic Longitudinal Monitoring of Individuals Who Each Serve as Their Own Controls

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



Integration of Multiplex panOmics Data into Electronic Medical Records

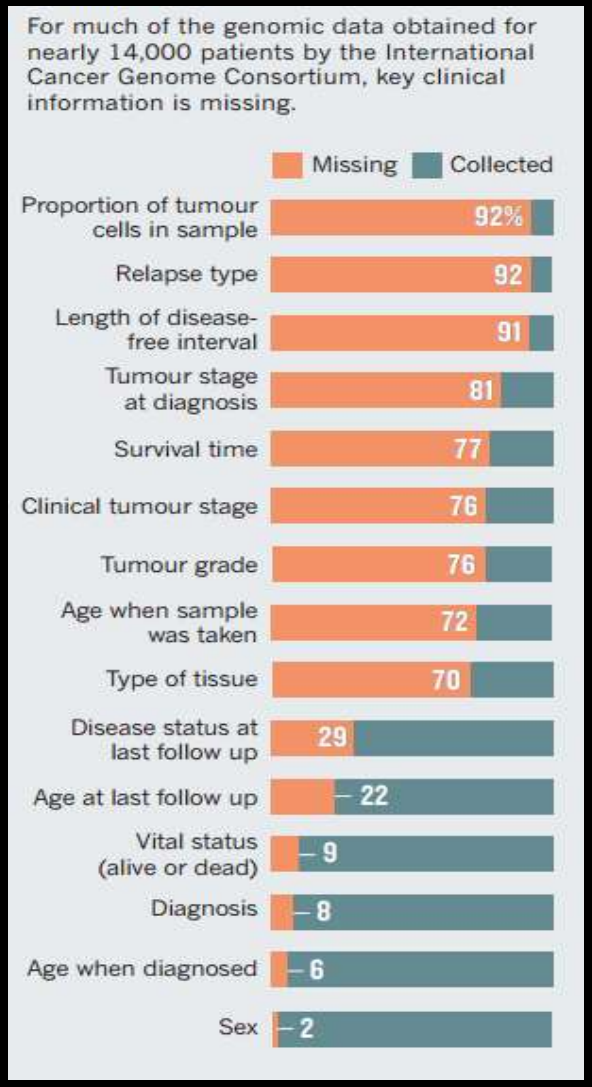
Standards for Data, Formatting, Database Architecture and Analytics

Design of Facile Interfaces for Cross Vendor, Cross-Institution Data Interoperability!

Data Access Will Become a Critical Factor in the Accuracy and Safety of Clinical Decisions Using NGS and panOmics Patient Profiling Platforms

- anticipated expansion of data profiles on millions of individuals
- value will reside in robust correlation with individual risk and clinical outcomes and demonstration of clinical utility
- escalating complexity of informatics and algorithms for data mining with concomitant improvements in risk management and outcomes
  - transitioning from the current VUS black box to increased capture of clinically actionable information

Missing Metrics in Linking NGS Data and Clinical Phenotypes



From: M. A. Rubin (2015) Nature 520, 291

Data Access Will Become a Critical Factor in the Accuracy and Safety of Clinical Decisions Using NGS and panOmics Patient Profiling Platforms

- how to establish open-source ‘data commons’ of requisite scale?
- major implications for viability of single segment (data-poor) versus integrated (systems) entities
  - clinical decisions and patient safety
  - database standards and inter-operability
  - scale matters!
  - IP
  - competitive business models

“The present framework for regulating the genetic testing industry does not address the need for competing providers of test-related services to have access to data resources to support state-of-the-art interpretation of genetic tests.”

Barbara J. Evans,
University of Houston Law Center
J. Law Med. Ethics Supplement Fall 2014, p.51

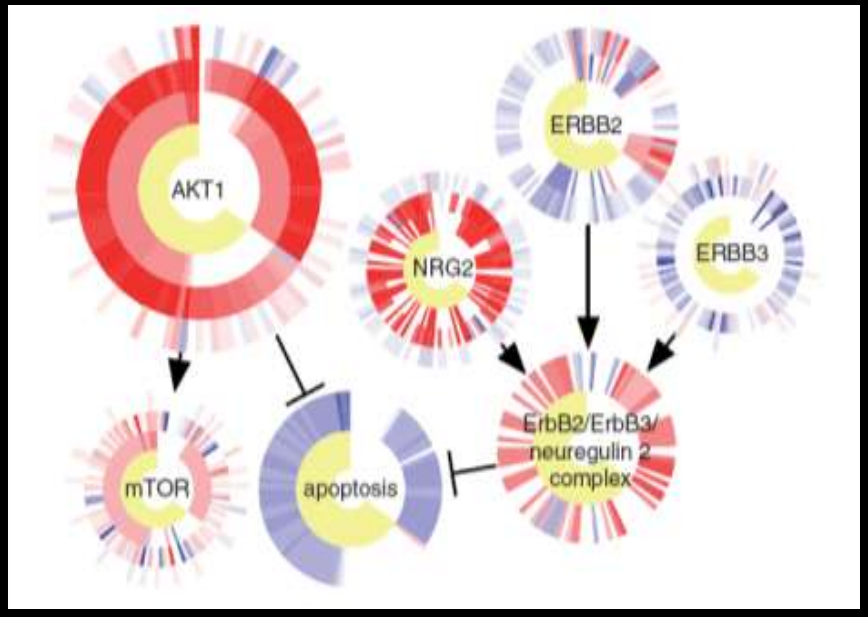
"Modularity"
The Economic and Regulatory Framework for Access to Complementary Products and Services*

- markets with mix of integrated and single segment providers
  - telecommunications, public utilities, natural gas industry
- market structure able to interoperate through public, non-discriminatory and well-understood interfaces

*J. Farrell and P.J. Weiser (2003) Harvard J. Law Tech. 17(1), 85-134 at 95

Assimilation of Concepts of Molecular Medicine into Routine Clinical Practice and Health Records

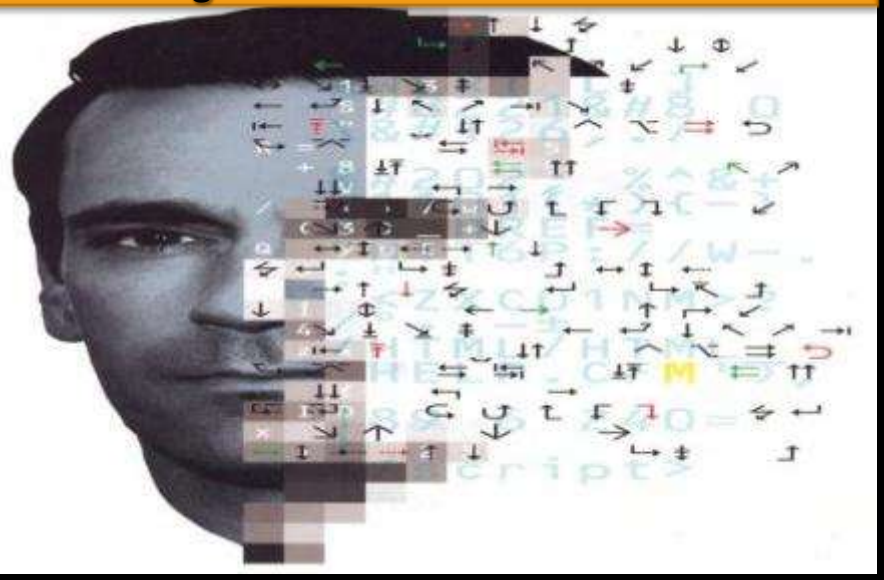
ASCO CANCER·LINQ™
Learning Intelligence Network for Quality

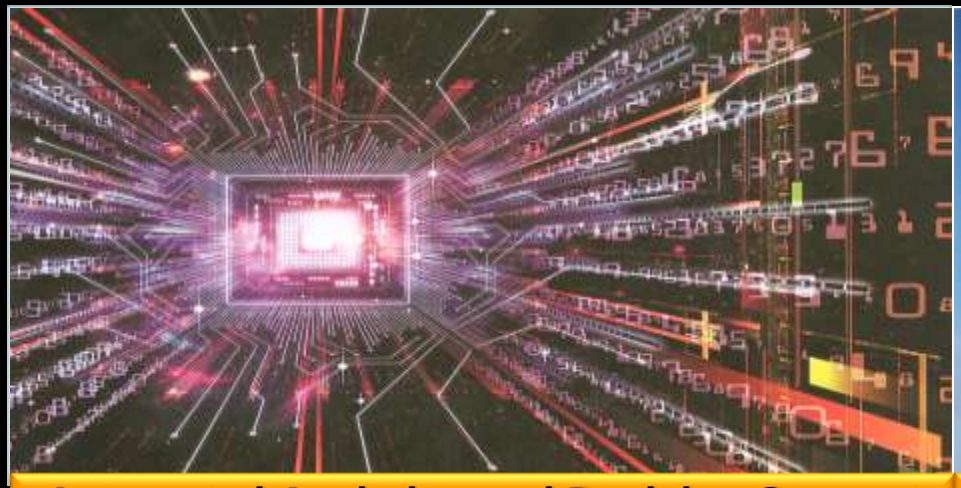


Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula

Data Deluge

Cognitive Bandwidth Limits





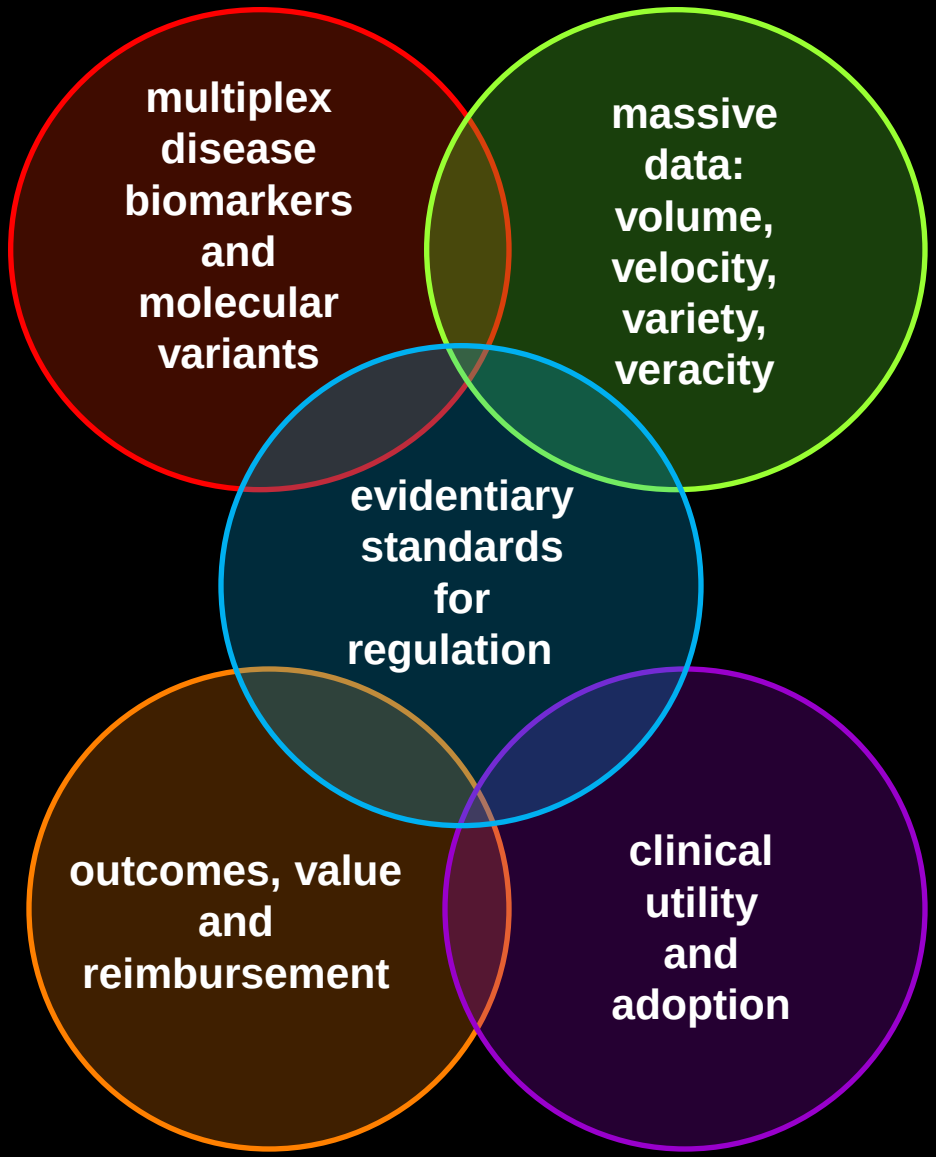
Automated Analytics and Decision Support

Facile Formats for Actionable Decisions

Living in a World Where the Data Analytics and Interpretation Algorithms Are Obscure to the End User

- ceding decision authority to computerized support systems
- culturally alien to professionals in their expertise domain but accept in all other aspects of their activities
- who will have the responsibility for diligence and oversight of critical assumptions used in decision tree analytics?

Analytical and Clinical Validation of Molecular Determinants of Disease (Subtypes) and Treatment Options



For the Purpose of Notification to Congress Only

Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

This document provides the anticipated details of the *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* that FDA intends to issue in 60 days, and is being provided to Congress pursuant to section 1143 of the Food and Drug Administration Safety and Innovation Act of 2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of In Vitro Diagnostics and Radiological Health

Center for Biologics Evaluation and Research

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of *In Vitro* Diagnostics and Radiological Health

Center for Biologics Evaluation and Research

Reimbursement for Molecular Diagnostics and Emerging Molecular Profiling Tests

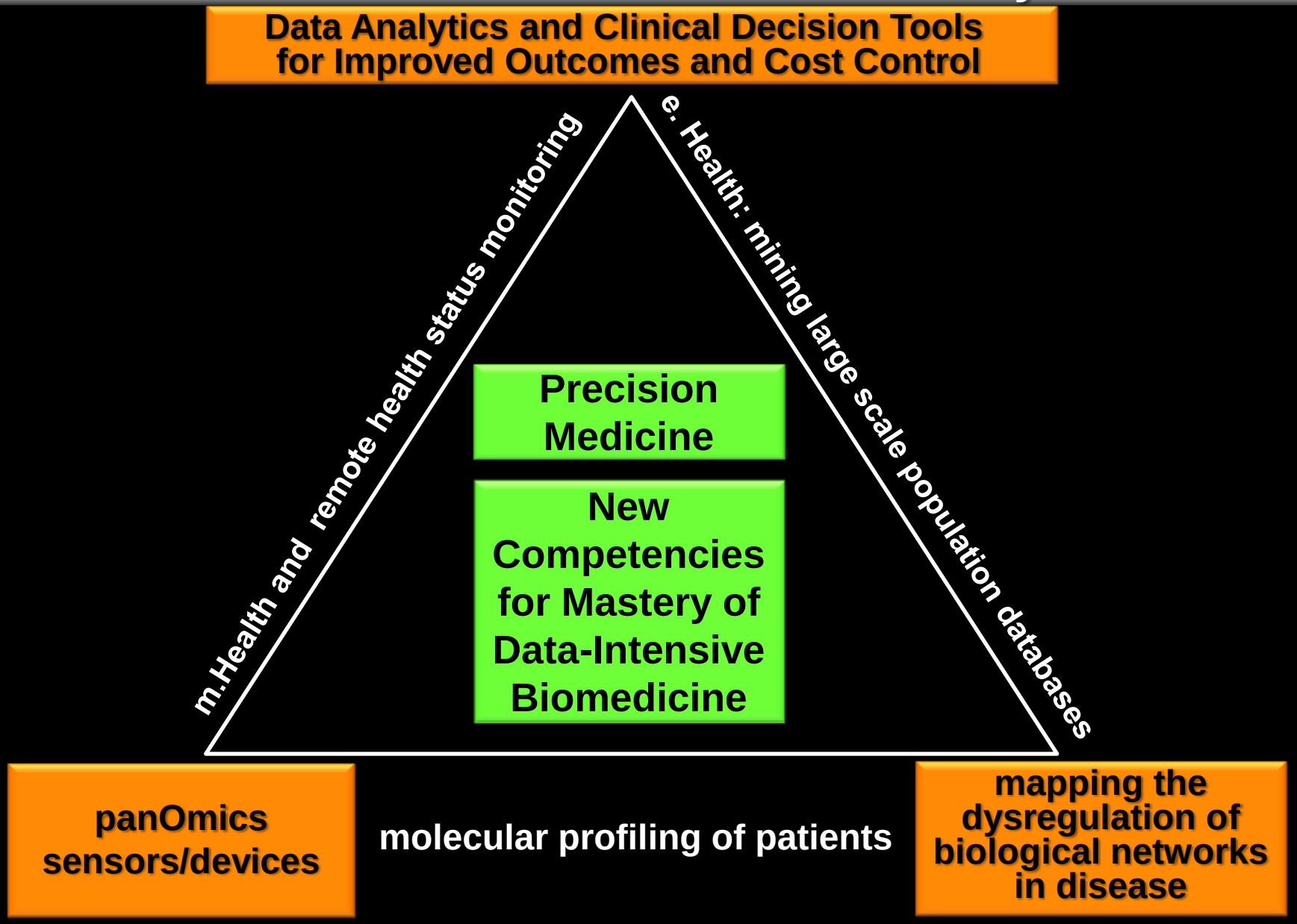
- current payment policies based on earlier era of comparatively simple (low technical complexity) tests
  - cost-based pricing: time and materials used to conduct test
- no premium for cost recovery for escalating technical complexity/R&D investment need to qualify panOmics profiling tests
- failure 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 as value drivers of improved clinical outcomes and cost savings


CHANGE
is good
you go first

Precision Medicine is a Disruptive Technology

- conflicts with systems, incentives and practices of multiple constituencies in the healthcare 'ecosystem'
  - providers
  - regulators
  - payors
- absent new incentives and alternatives to sustain financial viability these groups "won't vote themselves off the Island"
- patients/consumers not yet sufficiently well informed about availability/value of precision medicine to demand faster adoption

Building Knowledge Networks to Improve Individual Health and Sustainable Healthcare Delivery



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