Molecular Medicine, New Dimensions in Laboratory Testing and the Looming Challenge of Big Data

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Keynote Address:
G2 Intelligence Lab Institute 2014
Inflection Point for Labs
Washington, DC 17 October 2014

The Imperative to Achieve Sustainability in Healthcare: Societal (Economic) and Individual (Wellness)

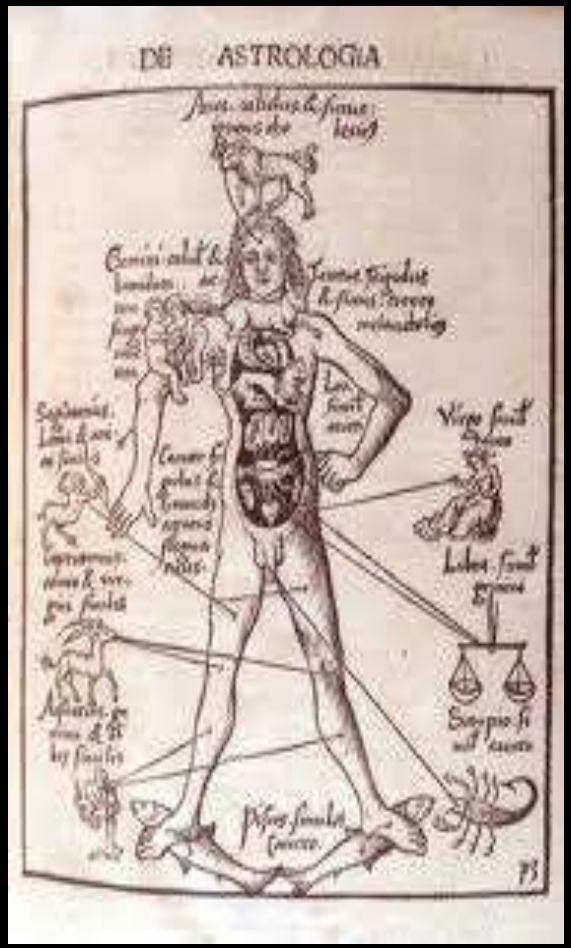
Balancing Infinite Demand Versus Finite Resources in an Era of Economic Constraint

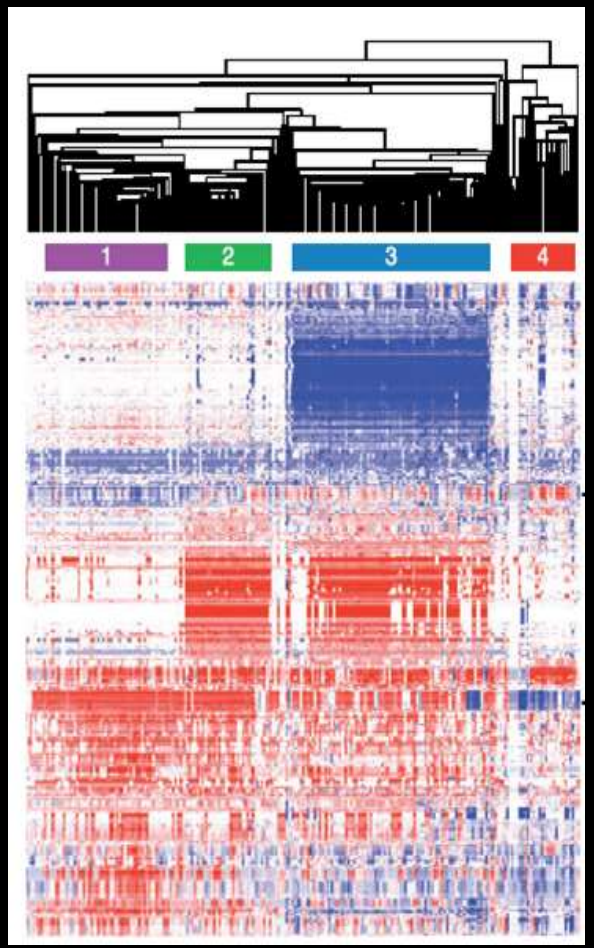
More Effective Management of Chronic Disease in Aging Populations

Shift From a "Do More, Bill More" (FFS) Delivery of Care to Integrated Continuity of Care and Managing Individual Risk to Improve Outcomes and Control Cost

Technology, Innovation and New Value Propositions

Medical Progress:
From Superstitions to Symptoms to Signatures

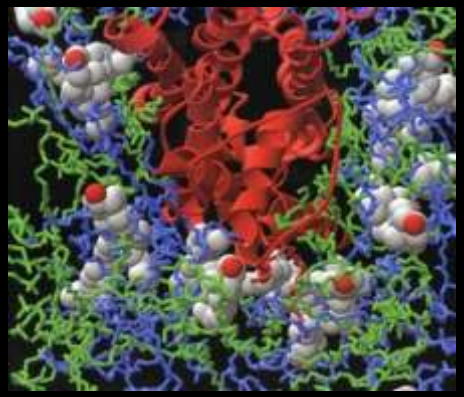




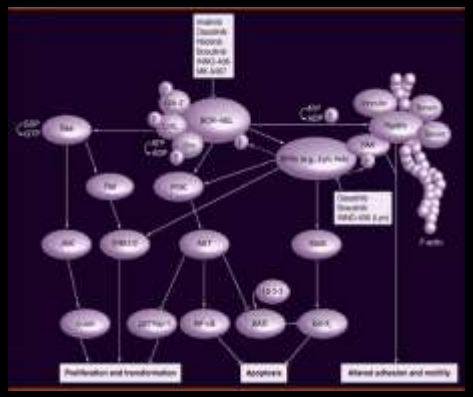
Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

Genomics

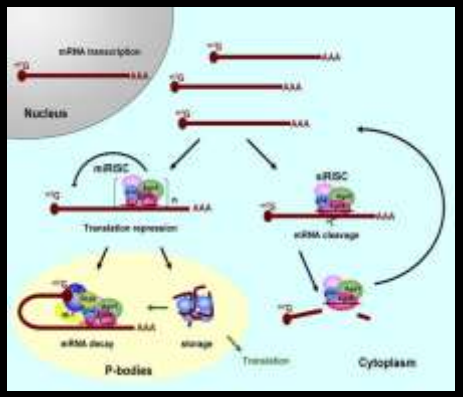
Proteomics

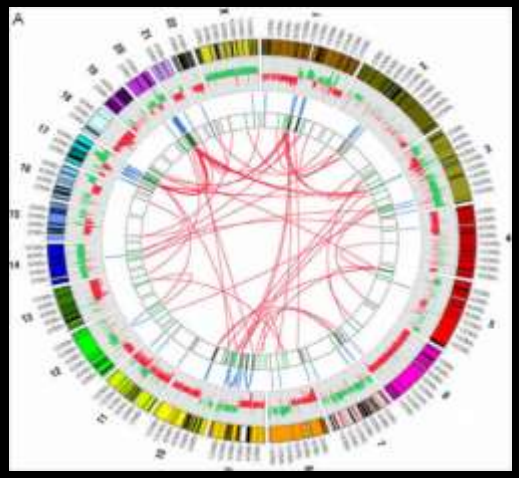


Molecular Pathways and Networks



Network Regulatory Mechanisms

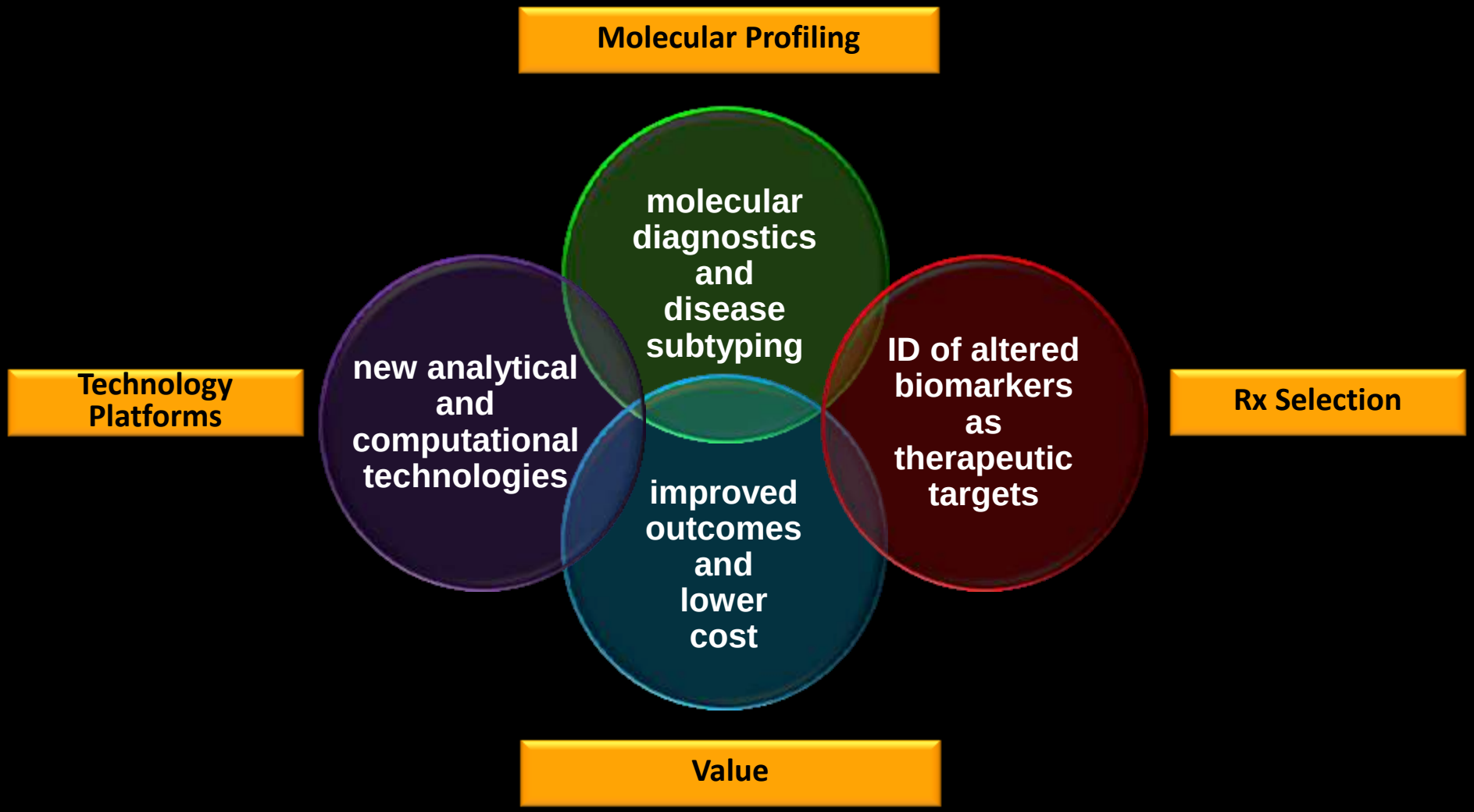




ID of Causal Relationships Between Network Perturbations and Disease

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

Precision Medicine



The Value of the Clinical Laboratory
in the New Healthcare Model

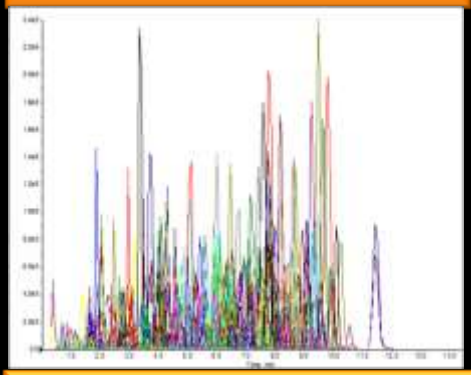
A Central Role for Molecular Diagnostics
in Driving Value-Based Healthcare

Molecular Medicine, Big Data and Clinical Decision Tools:
The New Currencies in the Evolution of Precision Medicine

The Evolution of Clinical Diagnostic Testing in an Era of Molecular Diagnostics and New Sensor and Device Technologies

Unianalyte Tests

Multianalyte Tests

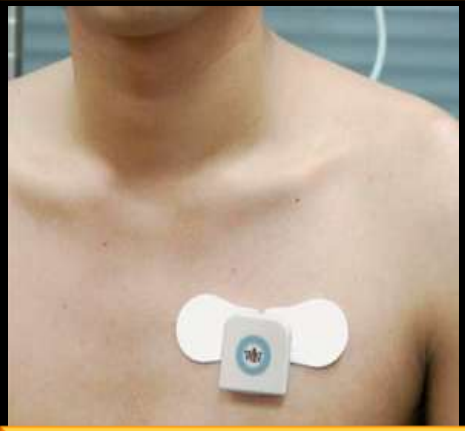


panOmics Profiling

New Regulatory and Reimbursement Policies

Centralized Testing, Large Capital Base Instrumentation

On-Body: In-Body Sensors



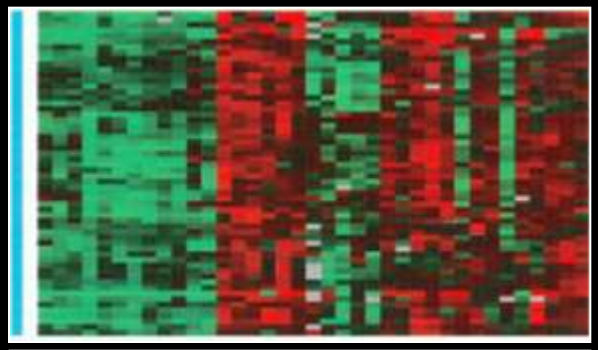
Remote (Virtual) Care

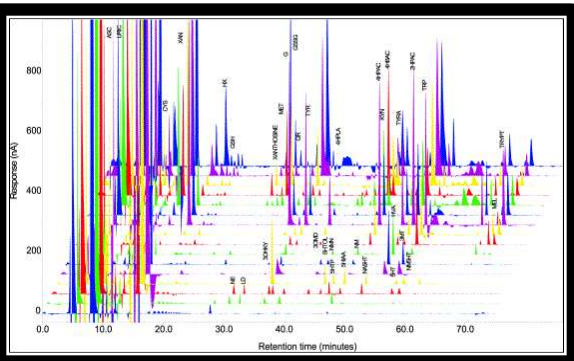
Increasingly Distributed Data Feeds and Real Time Health Monitoring

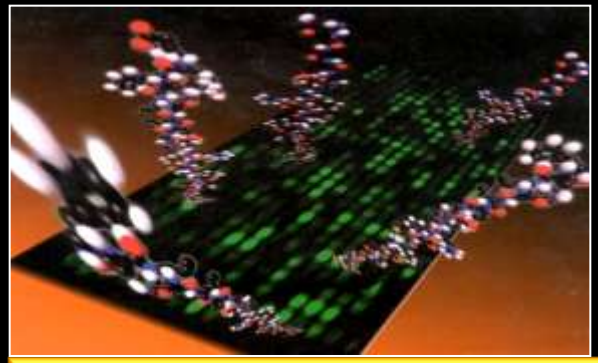
Mapping Molecular (Information) Signaling Pathways in Health and Disease

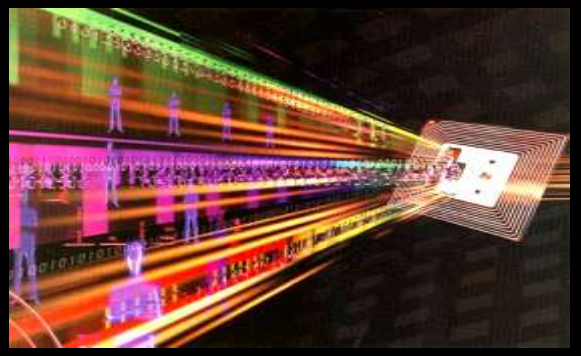
Complex Biosignature Profiling: panOmics

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

Performance Challenges for Clinical Laboratories in an Era of Molecular Profiling and Digital Health

- mastery of constantly changing test menus driven by panOmics and integrated informatics
- erosion of traditional (CPT) code-based reimbursement
- in-laboratory time and cost-per-test will become anachronistic metrics
- new reimbursement models will focus on impact value of tests in improving patient care/cost control
- focus on shorter in-hospital stay will demand faster TAT (life in a perpetual beta-STAT environment)

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

“Traditionally, if a doctor orders a test,
he can presume the test is done right.
Unfortunately, I don’t think we can say
that is necessarily true today
in the era of molecular testing
We honestly don’t know what people are doing.”

Michael Kolodziej
Director, Oncology Strategy, Aetna
CEN 24 Feb 2014, p. 20

Genetics in Medicine (2013) 15, 9, Pgs. 733

ACMG clinical laboratory standards for next-generation sequencing

Heidi L. Rehm, PhD[1,2]
Kerry K. Brown, P
Madhuri R. Hegde, P
Medical

Disclaimer: These American C
clinical laboratory geneticists to ha
not necessarily assure a successf
exclusive of other procedures and
the clinical laboratory geneticist sh
Clinical laboratory geneticists are
in conformance with these Standa
relevant medical and scientific info

JAMA. 2014;311(10):1035-1044.
doi:10.1001/jama.2014.1717

Original Investigation

Clinical Interpretation and Implications of Whole-Genome Sequencing

Frederick E. Dewey, MD; Megan E. Grove, MS
Jonathan A. Bernstein, MD, PhD; Hassan Cha
Gregory M. Enns, MB, ChB; Sean P. David, MD
Colleen Caleshu, MS; Kerry Kingham, MS; Ter
Matthew T. Wheeler, MD, PhD; Atul J. Butte,
John P. A. Ioannidis, MD, PhD; Alan C. Yeung,
Michael Snyder, PhD; Euan A. Ashley, MRCP,

Nature (2014) 508, 469
doi:10.1038/nature13127

Guidelines for investigating causality of sequence variants in human disease

D. G. MacArthur[1,2], T. A. Manolio[3], D. P. Dimmock[4], H. L. Rehm[5,6], J. Shendure[7], G. R. Abecasis[8], D. R. Adams[9,10], R. B. Altman[11], S. E. Antonarakis[12,13], E. A. Ashley[14], J. C. Barrett[15], L. G. Biesecker[16], D. F. Conrad[17], G. M. Cooper[18], N. J. Cox[19], M. J. Daly[1,2], M. B. Gerstein[20,21], D. B. Goldstein[22], J. N. Hirschhorn[2,23], S. M. Leal[24], L. A. Pennacchio[25,26], J. A. Stamatoyannopoulos[27], S. R. Sunyaev[28,29], D. Valle[30], B. F. Voight[31], W. Winckler[2]† & C. Gunter[18]†

The discovery of rare genetic variants is accelerating, and clear guidelines for distinguishing disease-causing sequence variants from the many potentially functional variants present in any human genome are urgently needed. Without rigorous standards we risk an acceleration of false-positive reports of causality, which would impede the translation of genomic research findings into the clinical diagnostic setting and hinder biological understanding of disease. Here we discuss the key challenges of assessing sequence variants in human disease, integrating both gene-level and variant-level support for causality. We propose guidelines for summarizing confidence in variant pathogenicity and highlight several areas that require further resource development.

Ignoring Biological Complexity

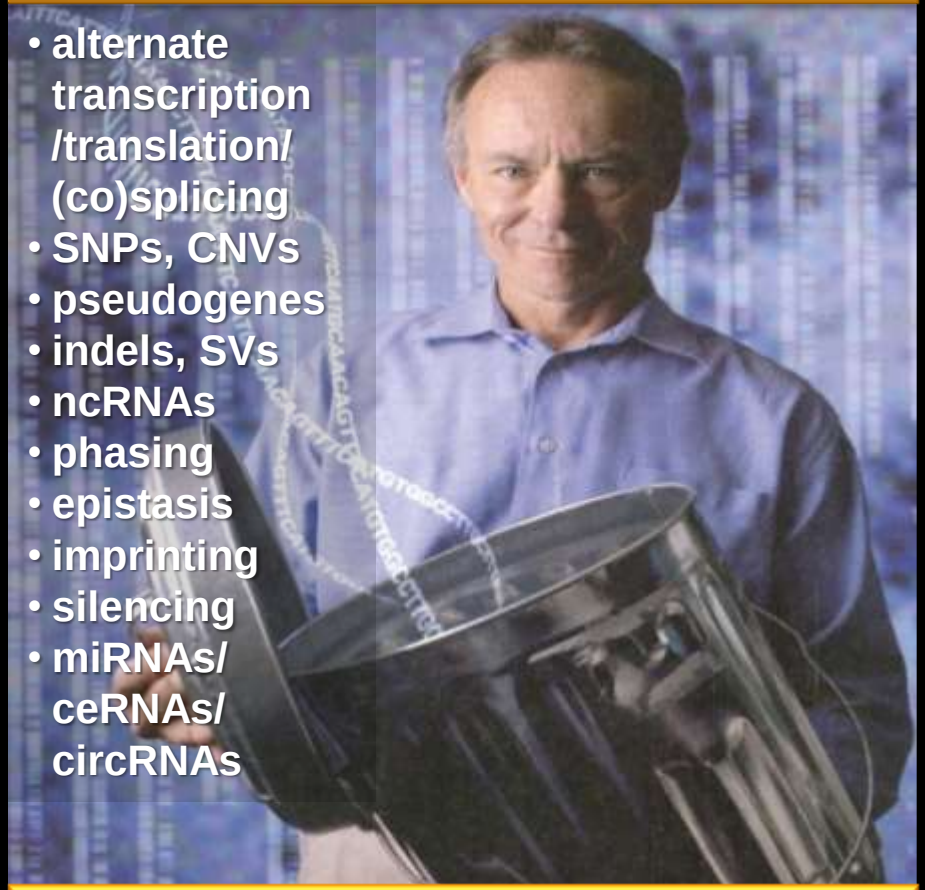
Genes For ….
The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective

Biology is More Than the Germ Line and Somatic Genomes

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

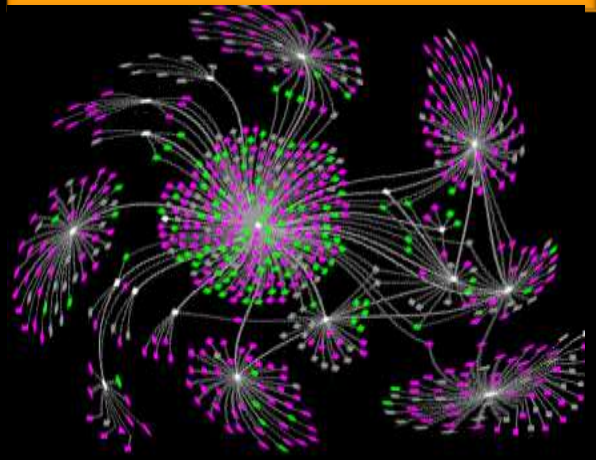
Junk No More: Pervasive Transcription



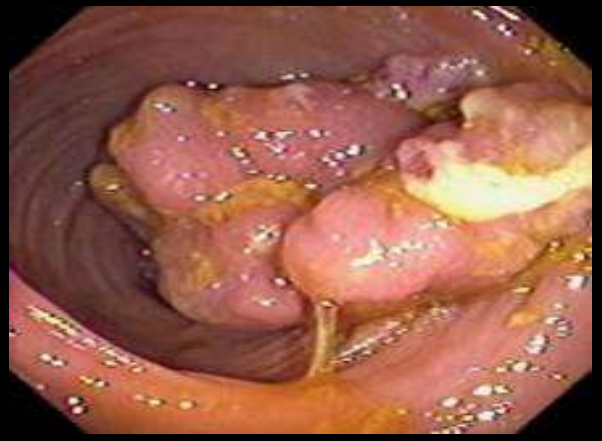
- alternate transcription /translation/ (co)splicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- ncRNAs
- phasing
- epistasis
- imprinting
- silencing
- miRNAs/ ceRNAs/ circRNAs

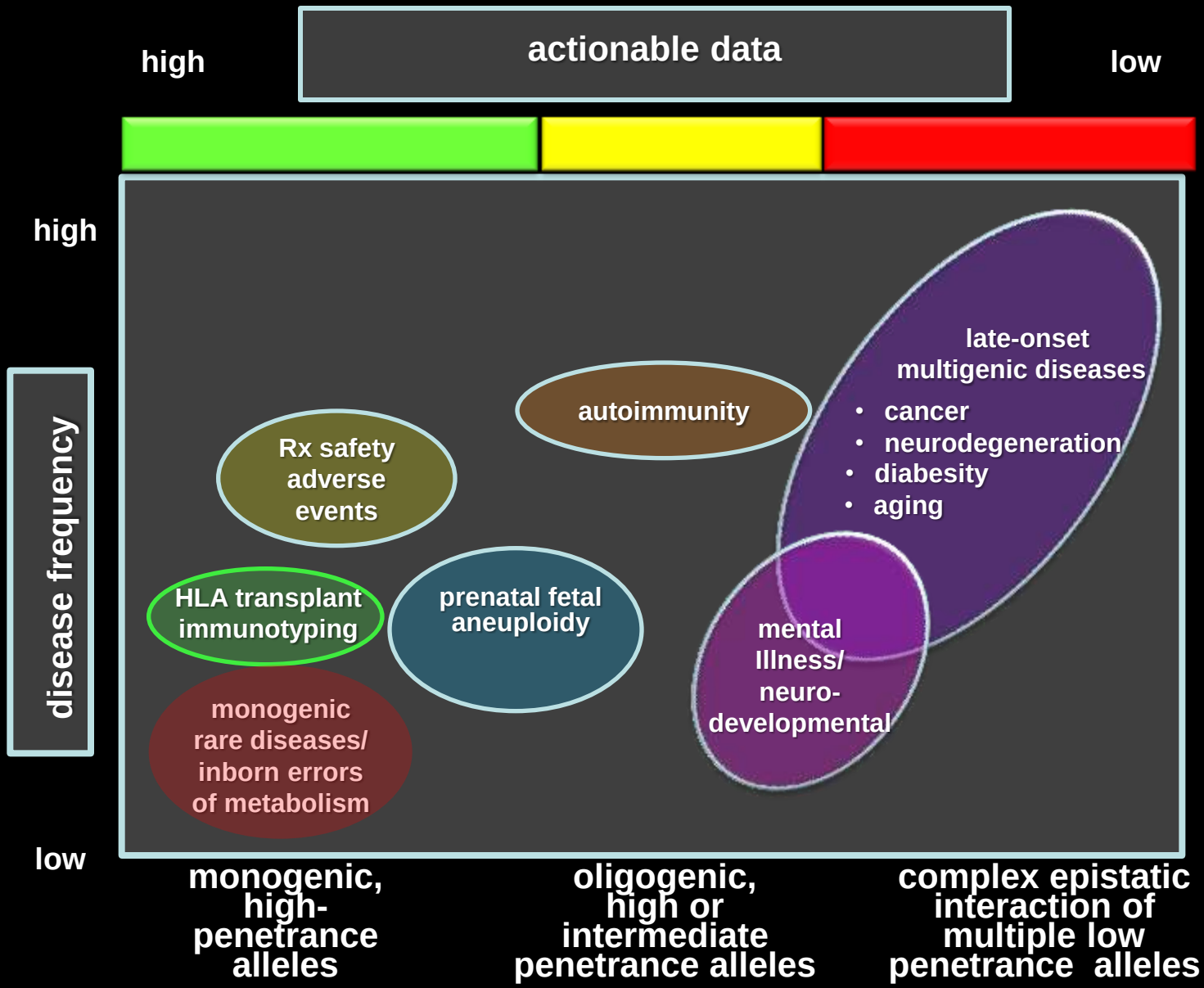
recognition of genome organizational and regulatory complexity

Cell-specific Molecular Interaction Networks



Perturbed Networks and Disease



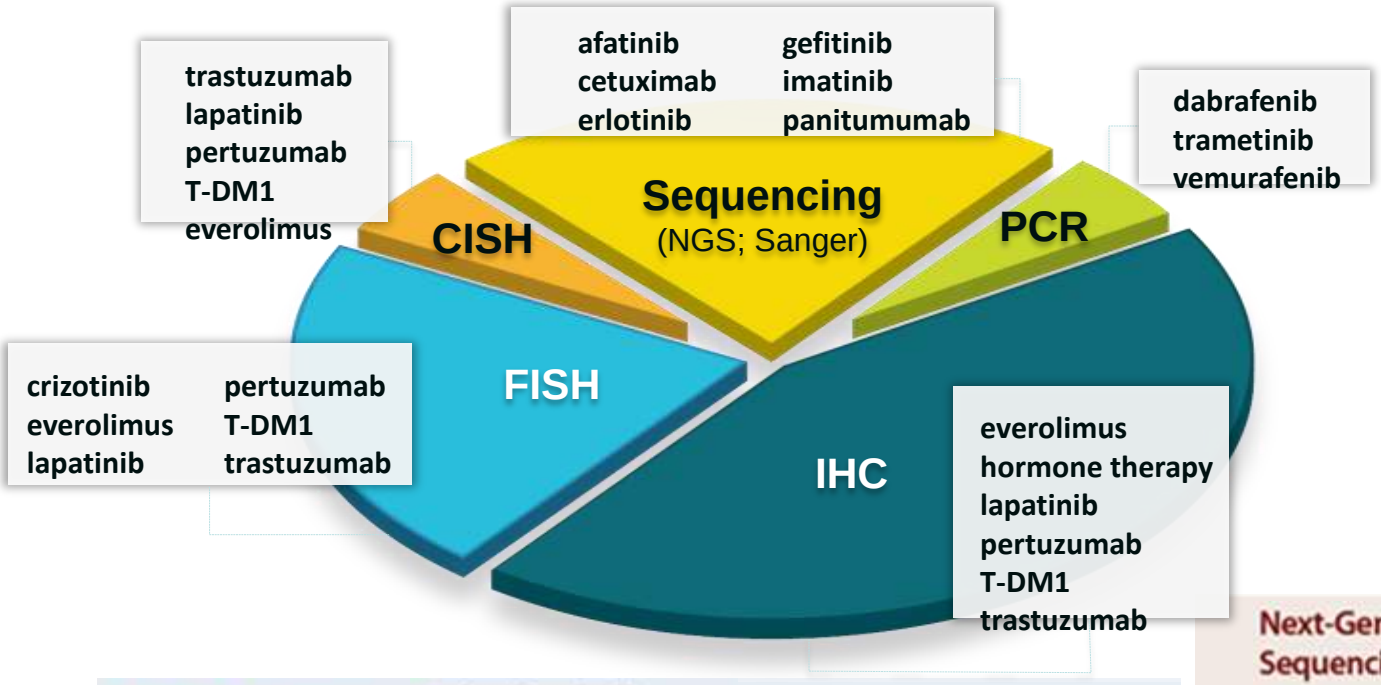

high
actionable data
low
high
disease frequency
low
Rx safety adverse events
autoimmunity
late-onset multigenic diseases
• cancer
• neurodegeneration
• diabesity
• aging
HLA transplant immunotyping
prenatal fetal aneuploidy
mental Illness/ neuro-developmental
monogenic rare diseases/ inborn errors of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

- depending on the disease and clinical context genome sequence data alone will not provide a sufficiently complete picture for either Dx or Rx decisions

- for late onset, multigenic diseases the underlying pathology is a complex, dynamic multi-component process

- mapping the patterns of disruption in molecular signaling pathways requires profiling of multiple aspects of both genotypic and phenotypic (molecular and clinical) changes

The Need for Multiple Molecular Diagnostic Platforms for Comprehensive Profiling of Actionable Drug: Target Associations to Guide Therapeutic Decisions in Oncology



55 Actionable Drug/Target Associations

- Next-Generation Sequencing *(NGS)*
- Fluorescence in situ Hybridization *(FISH)*
- Chromogenic in situ Hybridization *(CISH)*
- Immunohistochemistry *(IHC)*
- Sanger Sequencing
- PryoSequencing
- Fragment Analysis
- Quantitative Polymerase Chain Reaction *(qPCR - cobas®)*

abarelix	ceritinib	docetaxel	fluorouracil	irinotecan	nab-paclitaxel	sunitinib	trametinib
abiraterone	cetuximab	doxorubicin	flutamide	lapatinib	oxaliplatin	tamoxifen	trastuzumab
afatinib	cisplatin	enzalutamide	fulvestrant	letrozole	paclitaxel	T-DM1	triptorelin
anastrozole	crizotinib	epirubicin	gefitinib	leuprolide	panitumumab	temozolomide	vandetanib
bicalutamide	dabrafenib	erlotinib	gemcitabine	liposomal-doxorubicin	pemetrexed	temsirolimus	vemurafenib
capecitabine	dacarbazine	everolimus	goserelin	lomustine	pertuzumab	topotecan	vincristine
carboplatin	degarelix	exemestane	imatinib	megestrol acetate	procarbazine	toremifene	

Next-Generation Sequencing *(NGS)*

19 Actionable Drug:Target Associations

afatinib	oxaliplatin
carboplatin	panitumumab
cetuximab	sunitinib
cisplatin	temozolomide
dabrafenib	temsirolimus
dacarbazine	trametinib
erlotinib	trastuzumab
everolimus	vandetanib
gefitinib	vemurafenib
imatinib	

panOmics, Clinical Microbiology and Public Health

Proven Utility Today!


AMBULANCE


FACE MASK

Out of Sight: Out of Mind!

Comfort and Complacency:
The Cocoon of How Quickly We Forget
Past Epidemics and Their Toll

Reduced Investment in Biosurveillance, Public Health and Biosecurity: False Economies

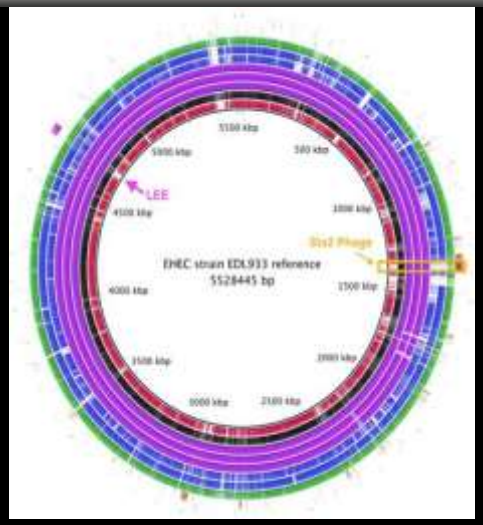
Faster Detection and Accurate Diagnosis Saves Lives

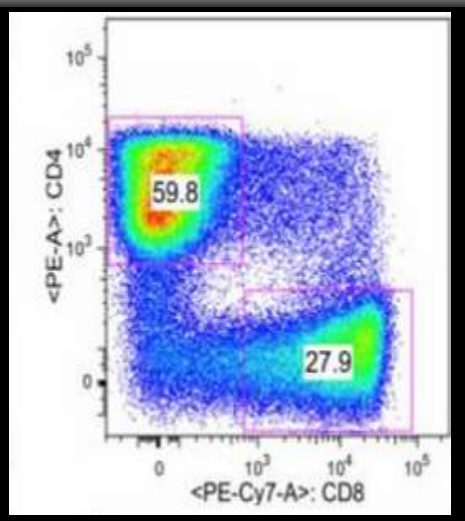
Biosurveillance: Faster Detection and Accurate Diagnosis Saves Lives

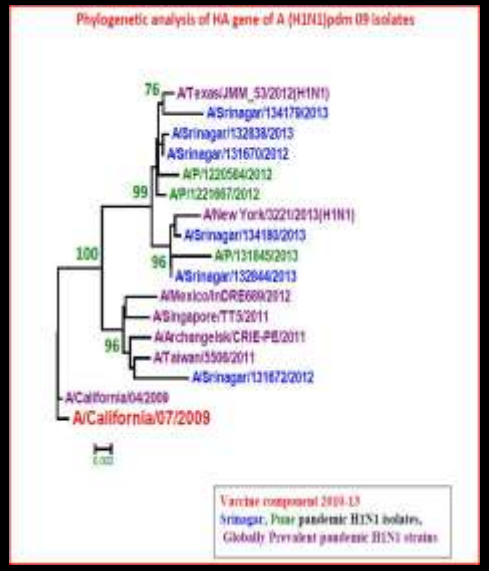
Ebola: West Africa 2013-14

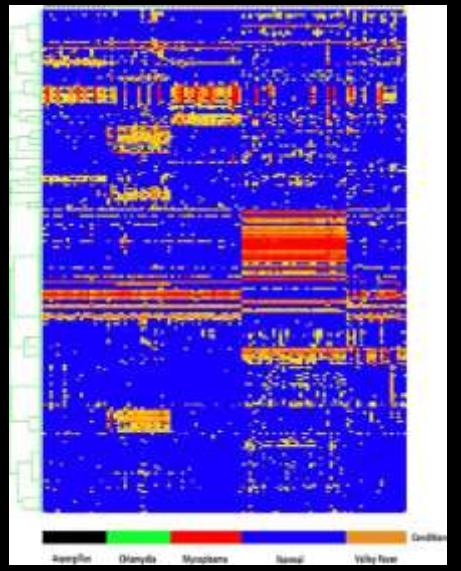
- index case December 2013
- confirmation as Ebola March 2014
- WHO declaration of Int. Health Emergency, August 2014

panOmics and Clinical Microbiology









Genomics and Epidemiology	MALDI-TOF Organism ID	Cytokine Panels	Immunosignatures

The Changing ‘Touch Points’ in Healthcare Delivery

Sensors, Smart Devices, Social Media and New Distributed Channels for Health Monitoring

Mobile Devices, Sensors and Remote Health Status Monitoring: The Changing 'Care Space' and Improved Continuity in Care Provision

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

to

- distributed- and virtual-architectures linking multiple providers, home, work and the internet

expanded 'points-of-touch' with the health systems

improved continuity of care and data integration

- from reactive, incident-centric, poorly coordinated and sequential referrals and inefficient post-incident follow-up(s)

to

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

Retail Healthcare:
New Services and Value-Based Shopping for Healthcare

“The fourth site of care is going to be the Internet.”

George Halvorson
CEO, Kaiser Permanente
Statement at ONC 2012 Annual Meeting

The Engaged Digital Consumer: Technology Beyond the Exam Room (Televox Survey 294)

- 86% US consumers view e.mail, text and voicemail from providers as valuable as F2F or phone contact
- 33% consumers admit greater honesty in responding to automated prompt systems
- 3/10 consumers consider e.communications from providers as valuable in cultivation of trust

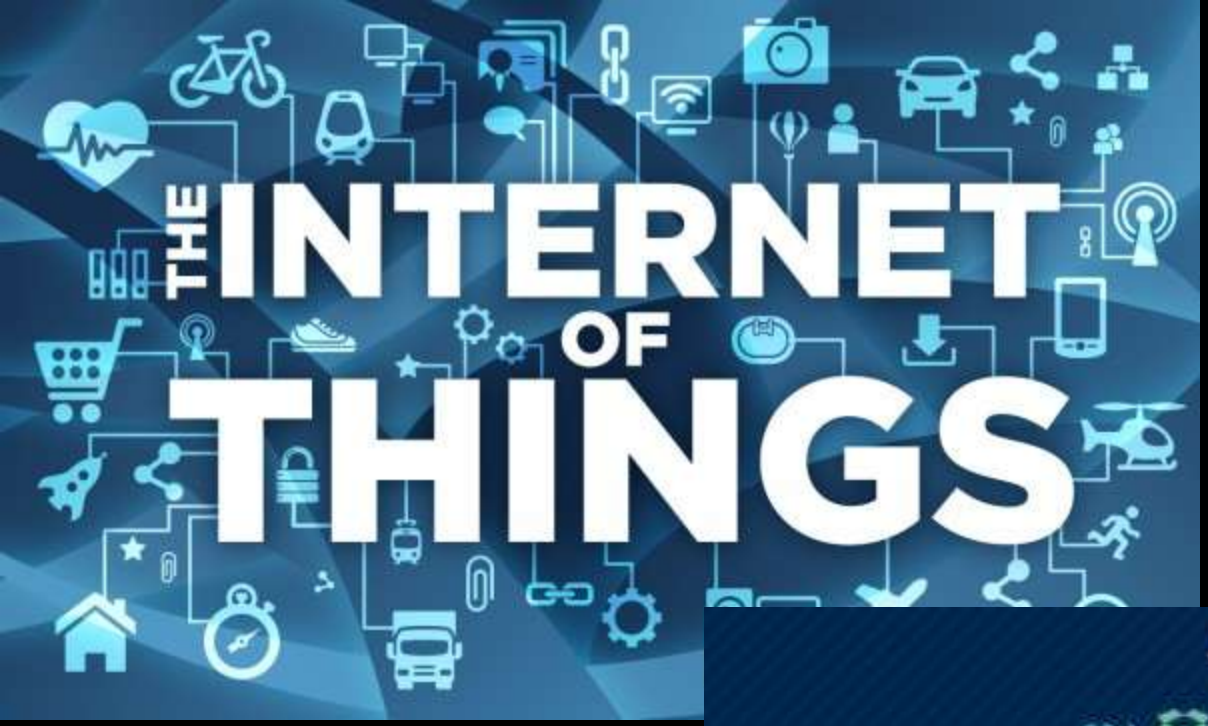
Digital Health: Early Days But Profound Implications for Disruption of Current Practices

Invasion of the Body Trackers

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

Remote Health Status Monitoring

M4: Making Medicine More Mobile


THE INTERNET OF THINGS


Moto 360
Google Glass
Sony SmartWatch 3
Pebble Steel
Sony SmartBand Talk
RFC Ring
Fitbit Flex
SYNC Buni

Phone-Based Health and Medical Apps

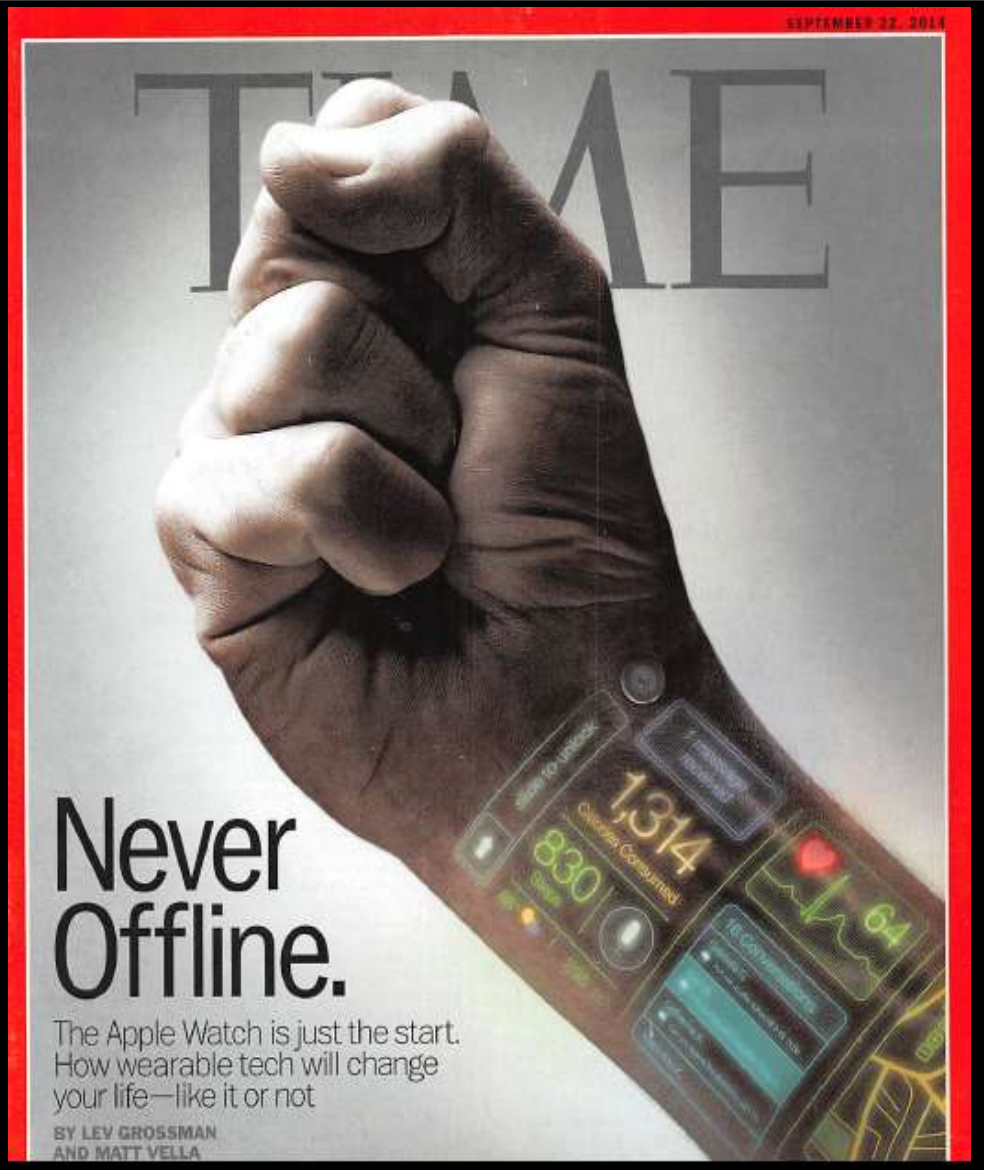
m.Health

Real Time Remote Health Monitoring and Chronic Disease Management

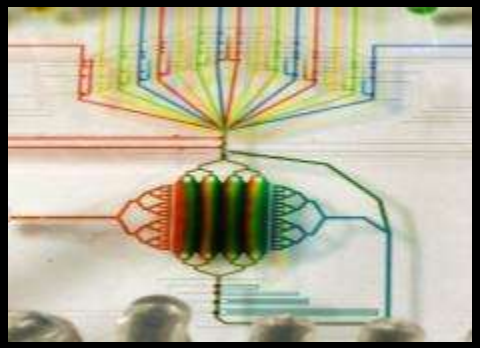
Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

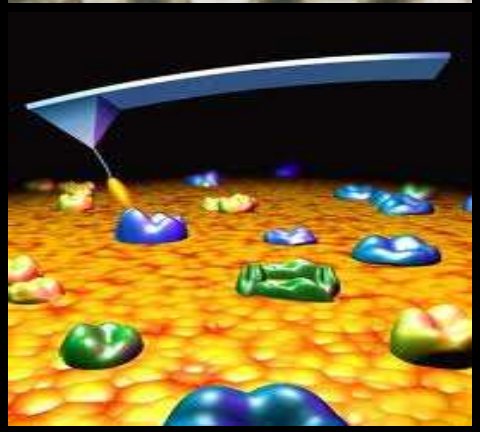
“Medical Selfies”: The Proliferation of Mobile Devices in Healthcare

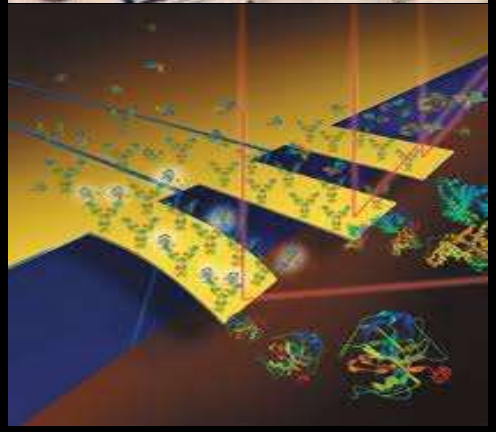

SEPTEMBER 22, 2014
TIME
Never Offline.
The Apple Watch is just the start. How wearable tech will change your life—like it or not
BY LEV GROSSMAN AND MATT VELLA
1,314
830
64

Miniaturization of Analytical Technologies

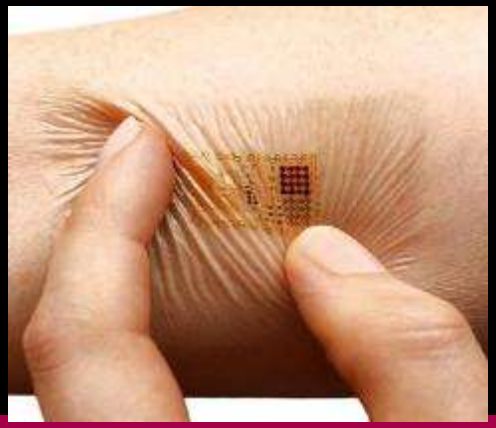


“Lab-on-a-Chip”





“Lab-on-a-Tip”



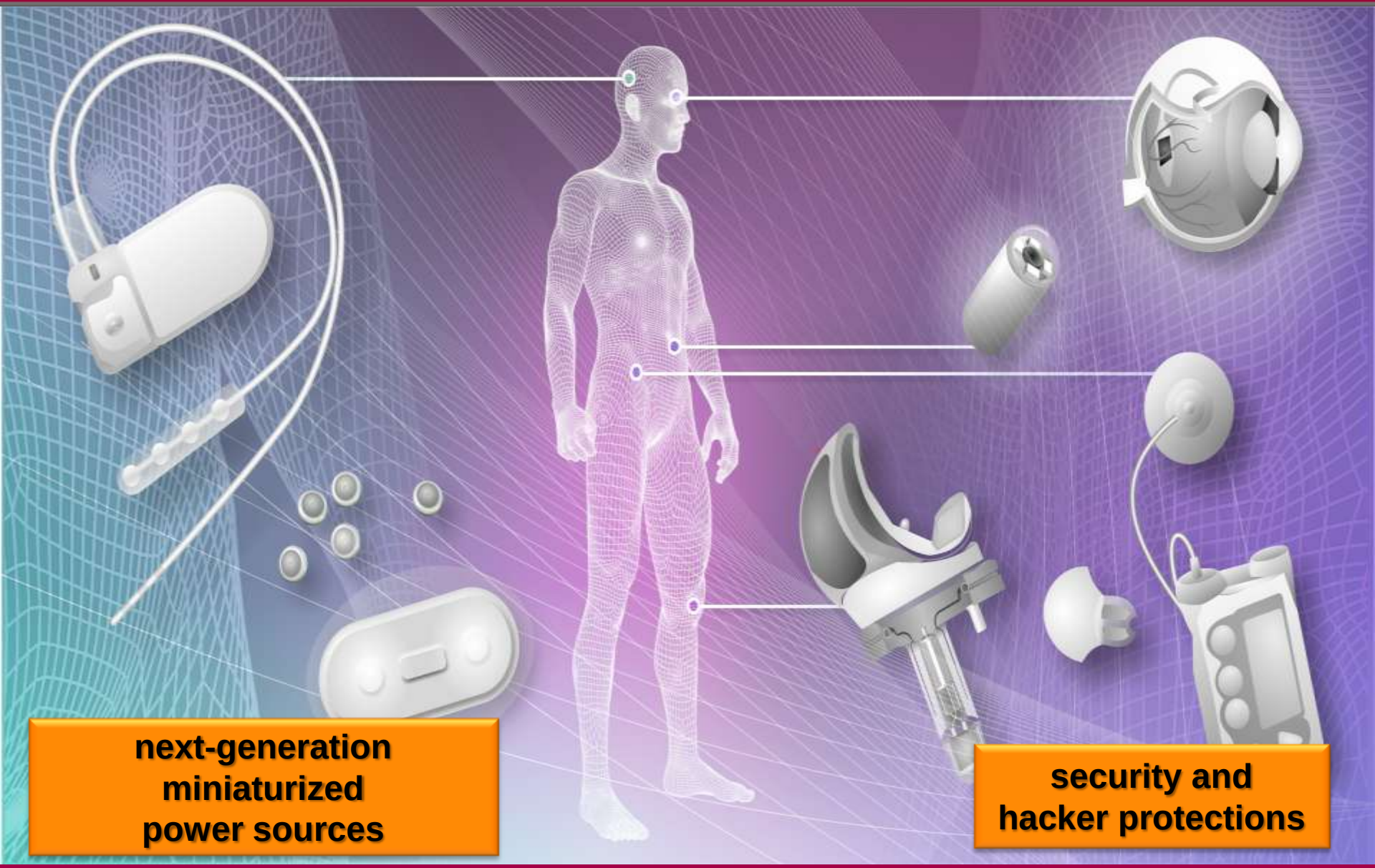
“Lab-Always On”
and
“Lab-On-Me”

Wireless Smart Bandages, Pills, and Contact Lenses

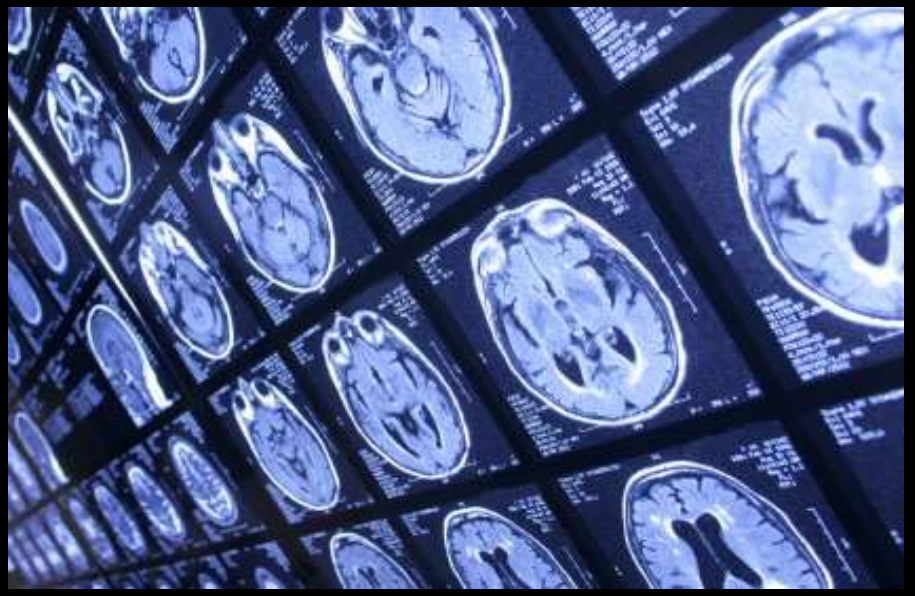
Vital Signs Monitoring

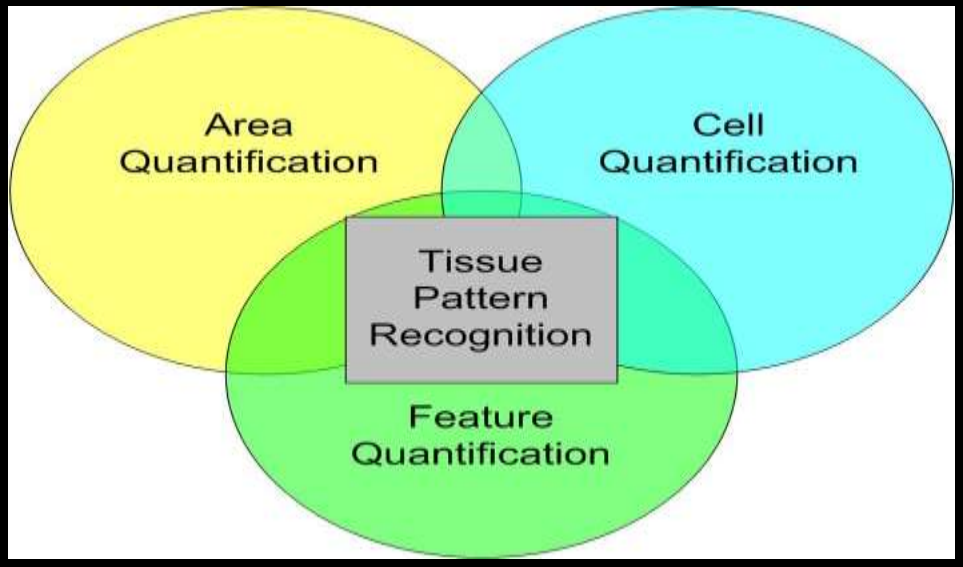
Gastroenterology | Pills with Chips | Glucose Monitoring

Implantable Devices and Wireless Monitoring (and Modulation)



Teleradiology and Telepathology





Mobile Devices and Telemedicine

Robotics: Telemedicine and Distributed Healthcare

RP-VITA Remote Presence Robot:
(iRobot Corp) FDA 510(k) clearance 1/24/13

What Happens When We All Live to 100?

Aging-in-Place:
The Connected Senior in the Connected Home

- dignity, independence
- cost and logistics of alternate care sites
- 29% of Americans aged 65 or older live alone
- 8 in 10 seniors own a cell phone
- 22% own tablets
- 59% use e.mail or the internet

Gray Technologies:
Independent But Monitored Living for Aging Populations

Rx compliance

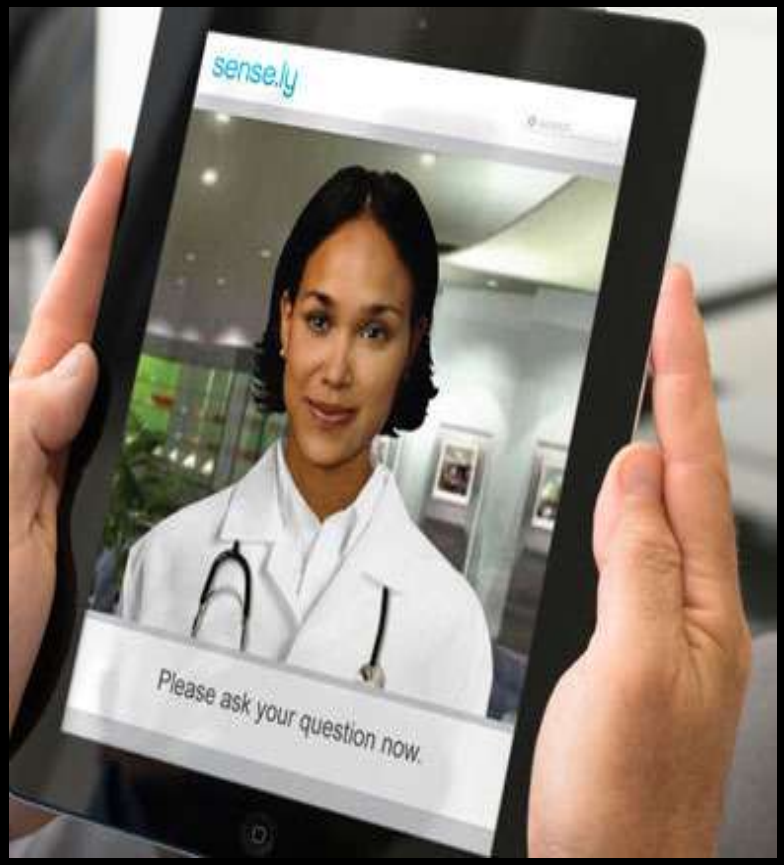
cognitive stimulation

Fujitsu's 'smart walking stick'

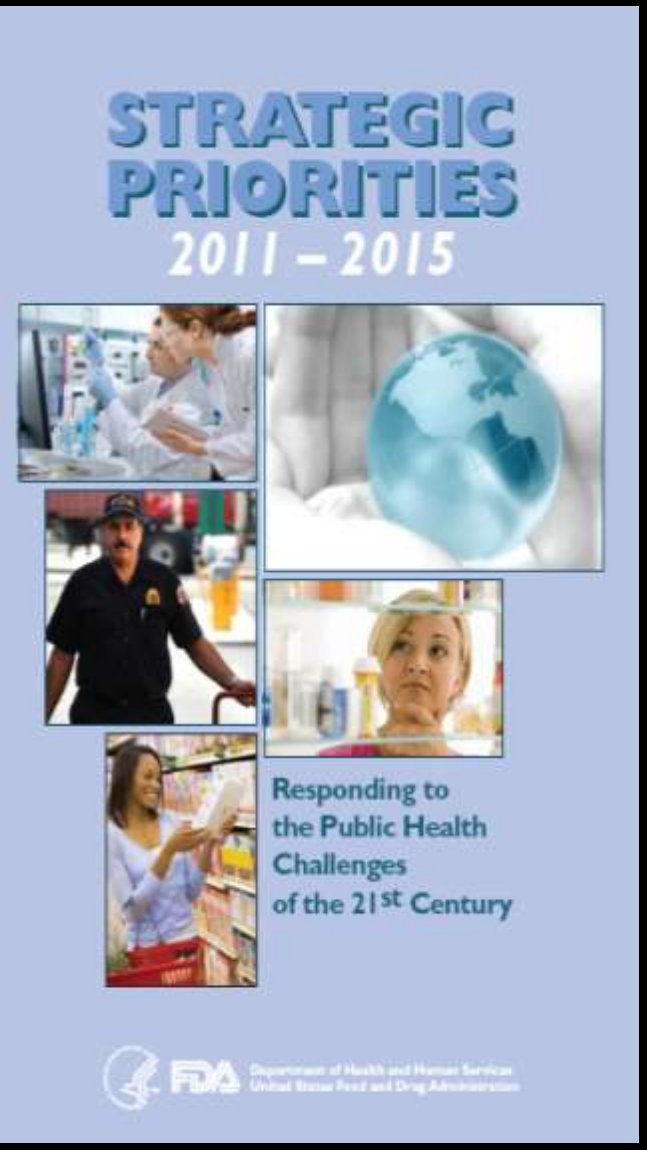
early alerts

use of appliances

Avatars and Robotics for Home Healthcare



Regulatory Science



In Vitro Companion Diagnostic Devices

Guidance for Industry and Food and Drug Administration Staff

The draft of this document was issued on July 14, 2011.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or elizabeth.mansfield@fda.hhs.gov; for questions for CBER contact Office of Communication, Outreach and Development (OCOD) at 240-402-7800 or 1-800-835-4709, or ocod@fda.hhs.gov. For questions for CDER, contact Christopher Leptak at 301-796-0017, or christopher.leptak@fda.hhs.gov.

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

Content of Premarket Submissions for Management of Cybersecurity in Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document Issued on: October 2, 2014

The draft of this document was issued on June 14, 2013.

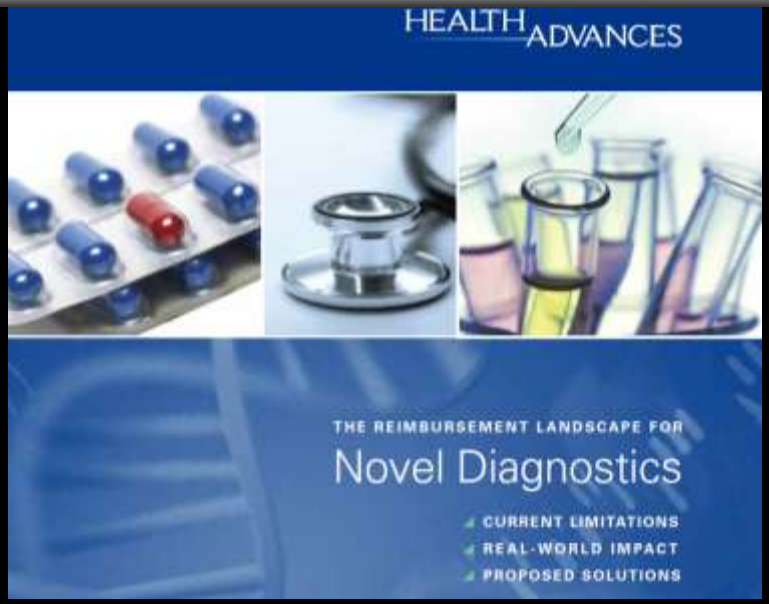
For questions regarding this document contact the Office of Device Evaluation at 301-796-5550 or Office of Communication, Outreach and Development (CBER) at 1-800-835-4709 or 240-402-7800.

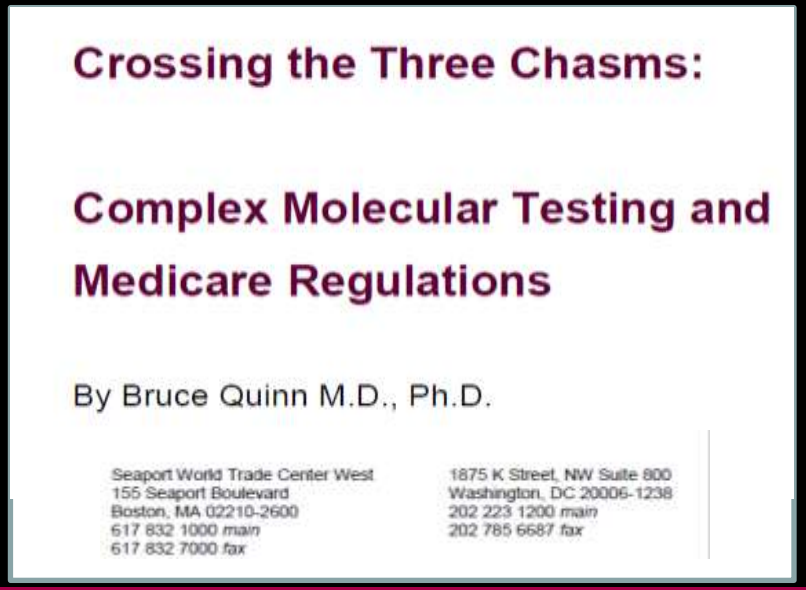
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of In Vitro Diagnostics and Radiological Health
Center for Biologics Evaluation and Research

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

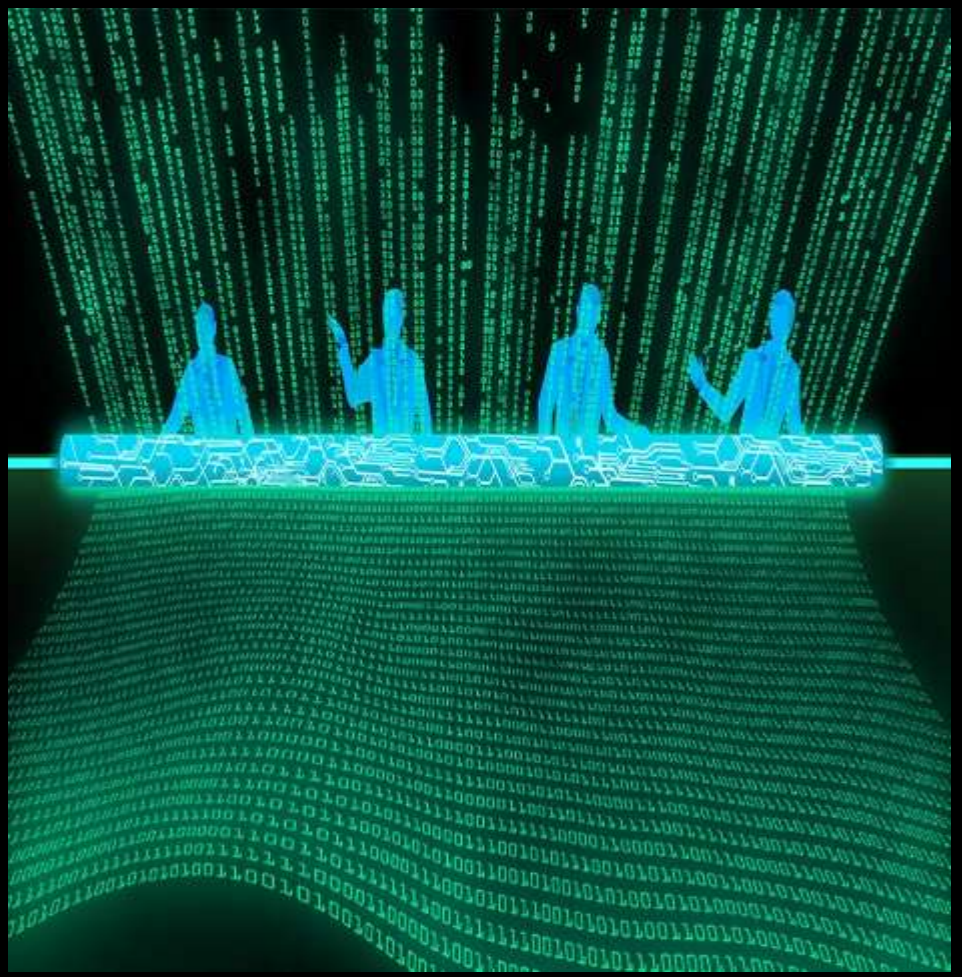
- ceding decision authority to computerized support systems
- culturally alien to professionals in their expertise domain but accept in all other aspects of their activities
- who will have the responsibility for diligence and oversight of critical assumptions used in decision tree analytics?

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





Data: The Fastest Growing Resource in Biomedicine



The Graduate: Fast Forward 1967 to 2014

Mr. McGuire: I want to say two word to you. Just two words.

“ Big Data”

Benjamin: Exactly how do you mean?

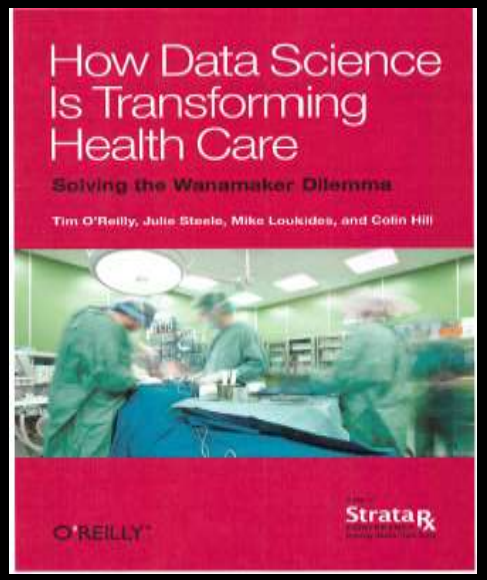
Mr. McGuire: There's a great future in Big Data. Think about it. Will you think about it?

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

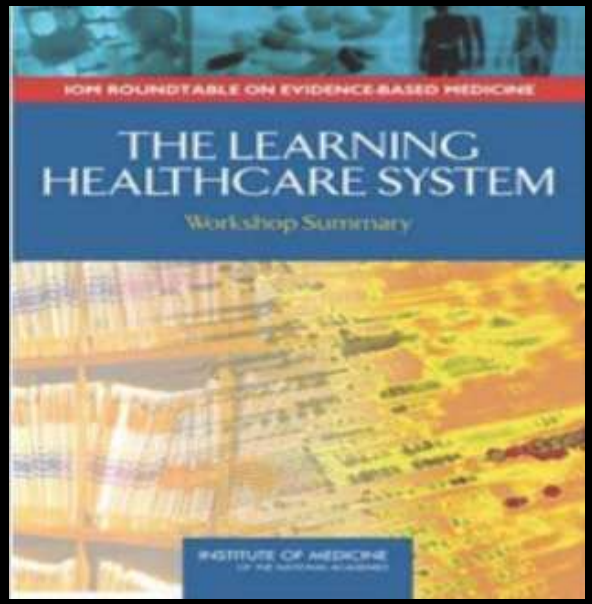
Managing Big Data in Biomedicine is Not a Simple Extrapolation from Current Practices

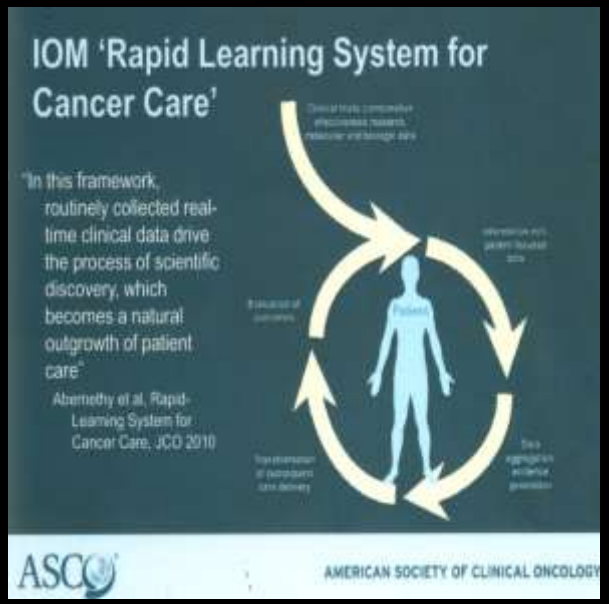
Current Institutional Structures and Competencies Are Ill-Prepared for Pending Disruptive Change

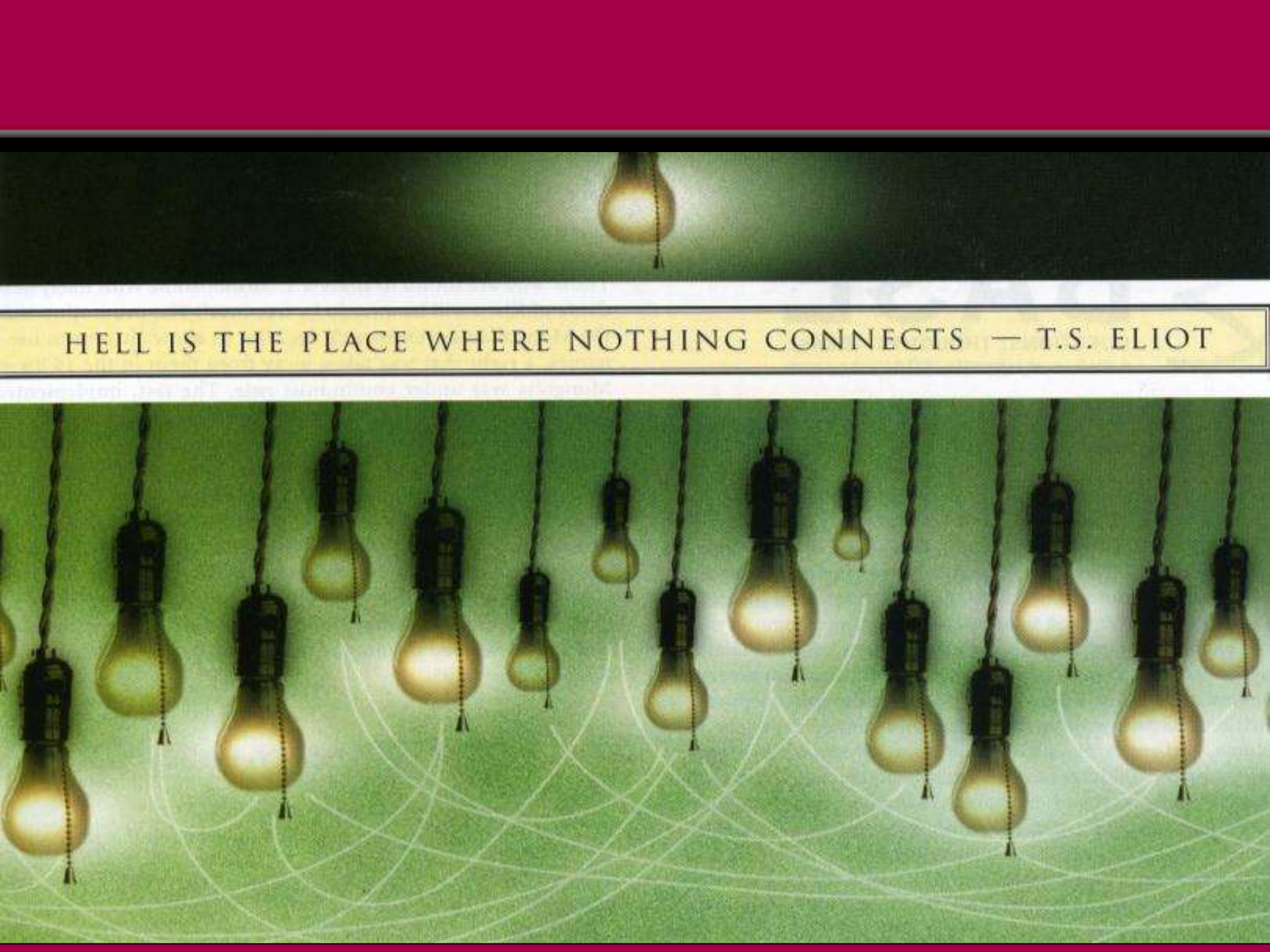
Big Data and Healthcare: No-Shortage of Opinions



Now Comes the Hardest Part: Driving Molecular Medicine and IT-Centric Capabilities Into Routine Clinical Practice

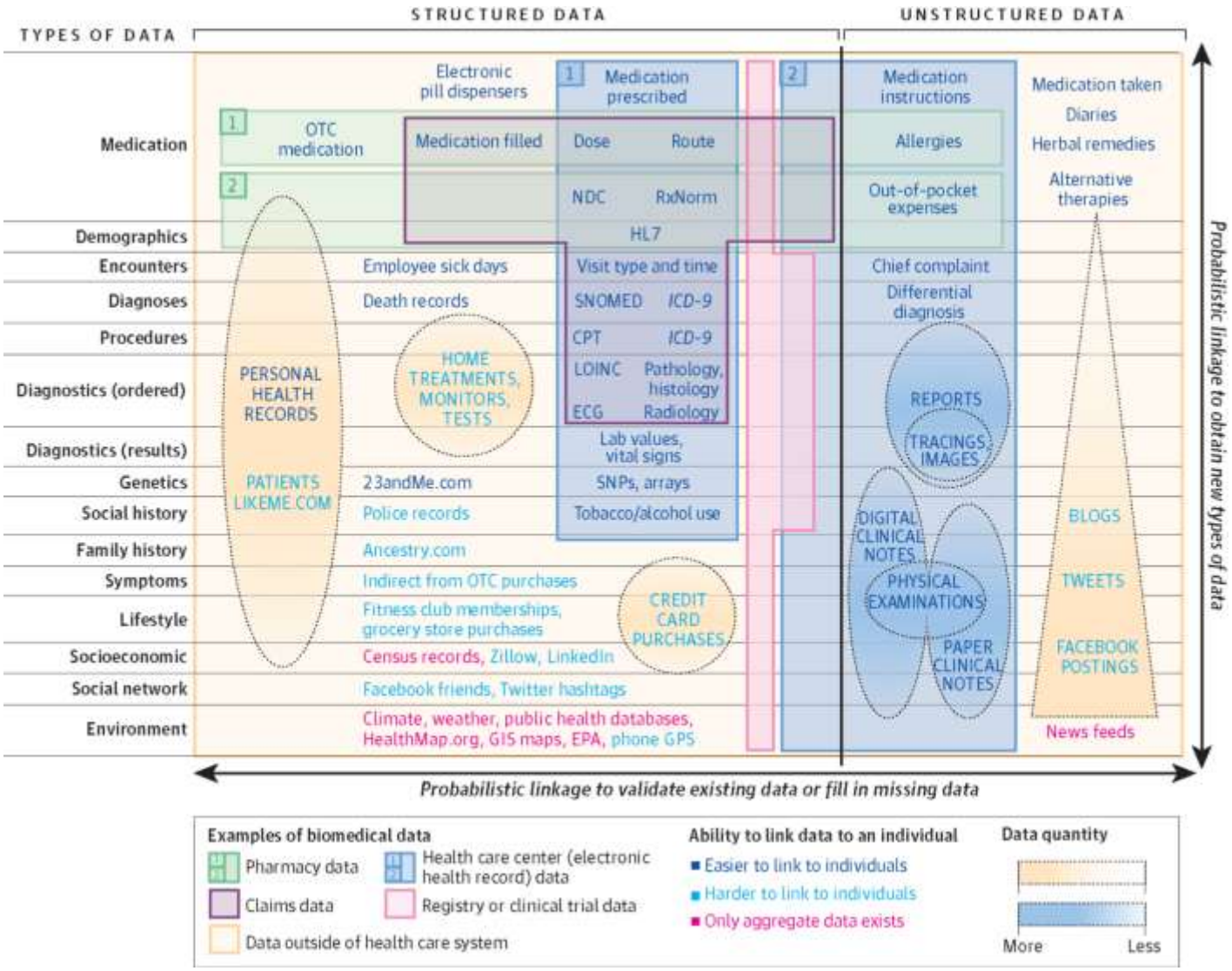





HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT

Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo

The Diversity of High Value Data Sources in Healthcare: The Integration Challenge



G. M. Weber et al. JAMA. 2014;311(24):2479-2480. doi:10.1001/jama.2014.4228

Healthcare as a Complex Information Ecosystem

From Fragmented Silos of Reactive Incident-Centric Care to Systems-Based Integrated Frameworks for increasing Proactive Management of Individual Risk

Stage 2 Meaningful Use: 2014

- 30% of lab orders entered into EHR via CPOE
- 55% of orders to be received in a structured format
  - Logical Observation Identifiers Names and Codes (LOINC)
- provide more than 50% patients with electronic copy of health information upon request
  - lab test results, problem lists
- EHRs must be able to transmit structured lab result to providers of ambulatory care
- use lab results to promote compliance, referral to education resources and health reminders

Progress (?) in Implementation of HITECH Act

- very few hospitals have achieved MU Stage 2 (MU2)
- further delay in MU2 compliance timeline
- stage 3 concepts elicited major pushback
- CMS granting hardship extensions for hospitals and eligible professionals
- easing 2014 EHR certification enables inept products and developers to survive
- GAO reports lack of strategy, prioritized actions and milestones
- PCAST and JASON reports on need for major architecting effort (reboot!)
- delays in implementation of ICD-10

The Design Challenge for Next Generation HIT Systems

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

“Stop talking about EHRs!

EHRs are part of a much bigger HIT ecosystem.

They are like leaves on a tree.

These must also be branches, a trunk and roots.

There are networks and hundreds of other HIT systems that support ancillary organizations and activities, population health and healthcare.”

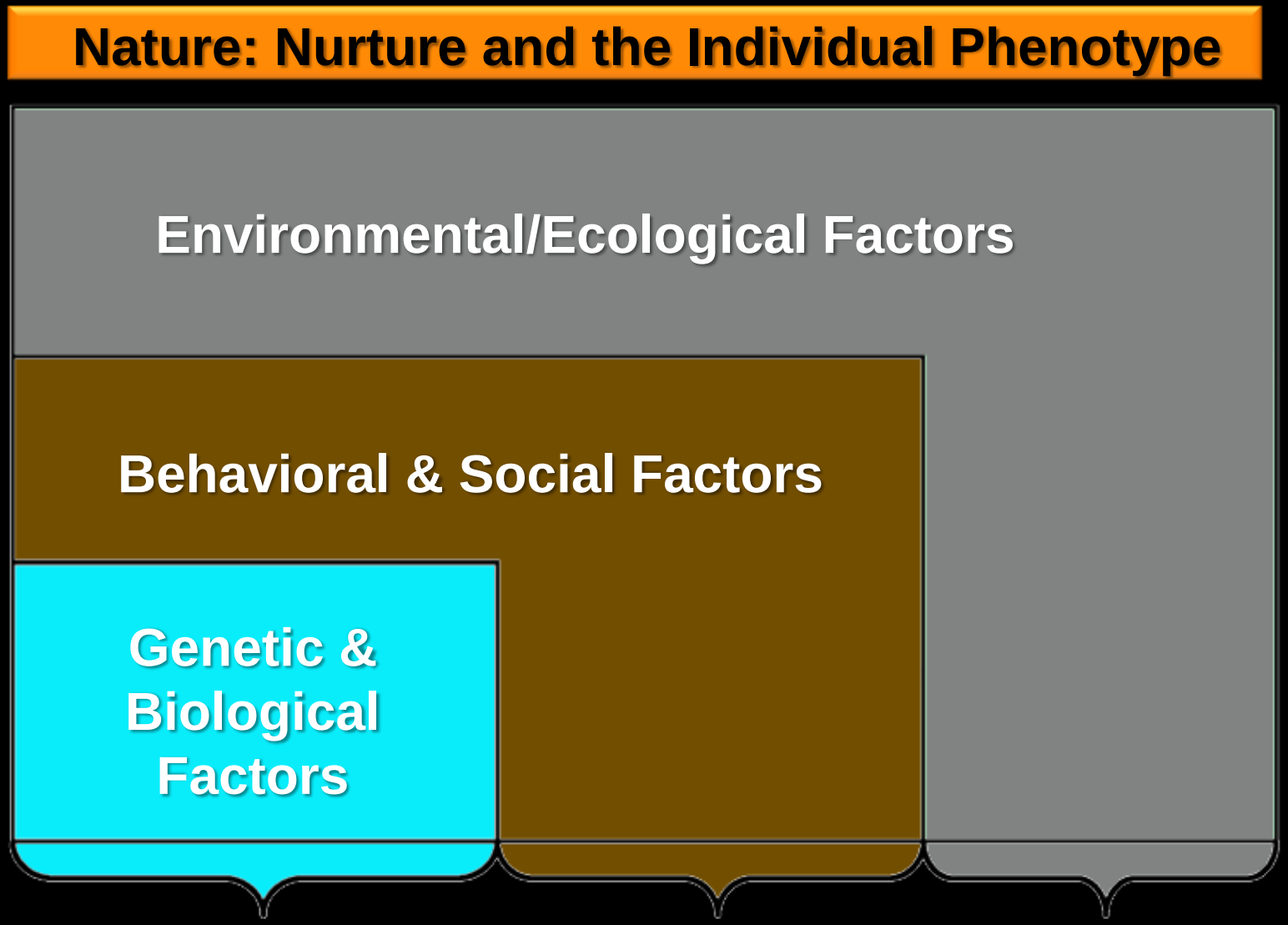
John Loonsk

Health IT News July 2014 p,14

Previous Director, Interoperability and Standards, ONC

Jan. 2006-Dec. 2009

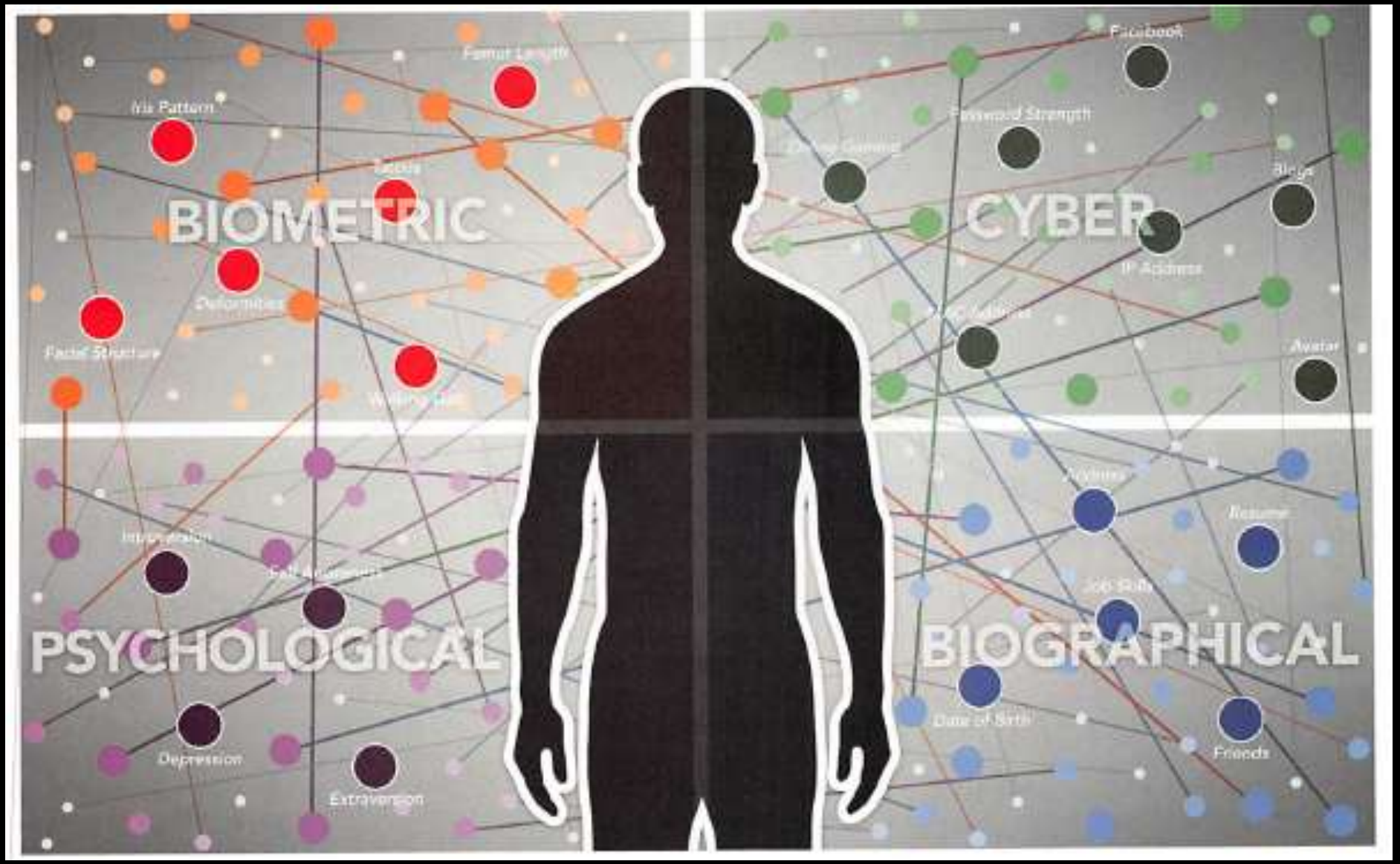
The Challenge of the Capture of Comprehensive Information Relevant to Disease Risk, Progression and Outcomes



Social Spaces Become Quantifiable

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

Computational Tag, Track and Locate (TTL): Applications for Healthcare Meta-Analytics



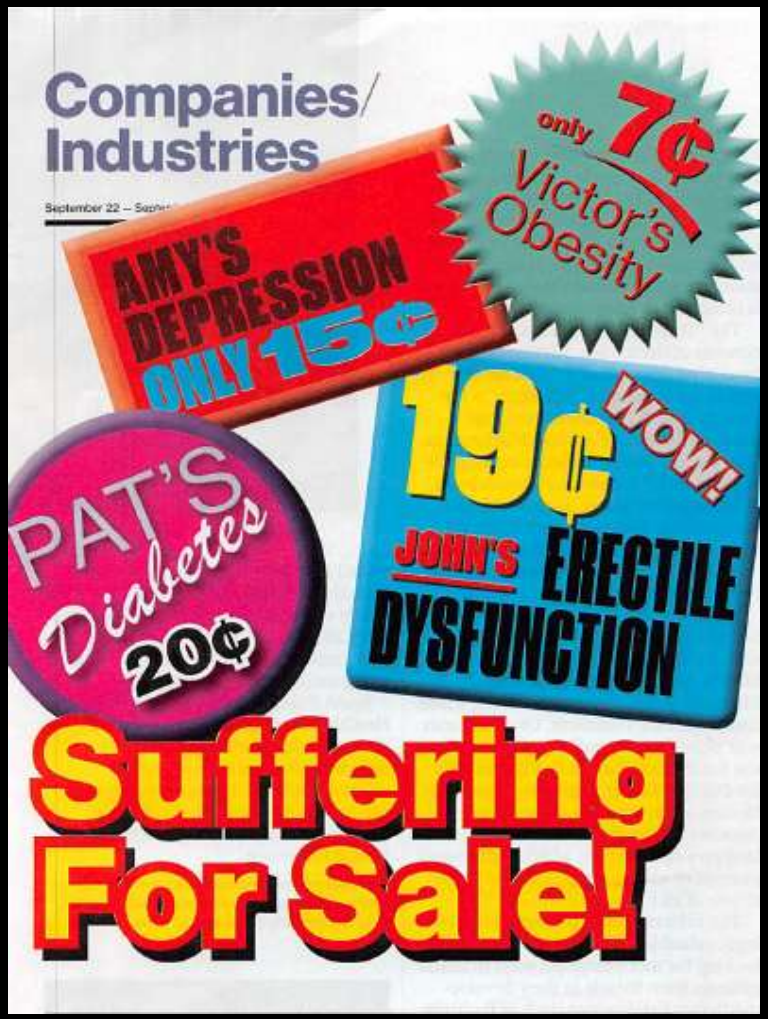
“The paradox of a wearable device is that it gives you control and takes it away at the same time”

Time 22 September 2014

Outside HIPAA: Data Brokers and Mining Health Information

- non-consented meta-analytics
- searching for healthcare information
- use of medical/disease social networks
- on-line purchases of health products
- GPS-location of use of retail stores/pharmacies
- diet, smoking and alcohol purchases
- predictive modeling of physical and mental health

Consumer Data Brokers and New Vulnerabilities in Healthcare Privacy



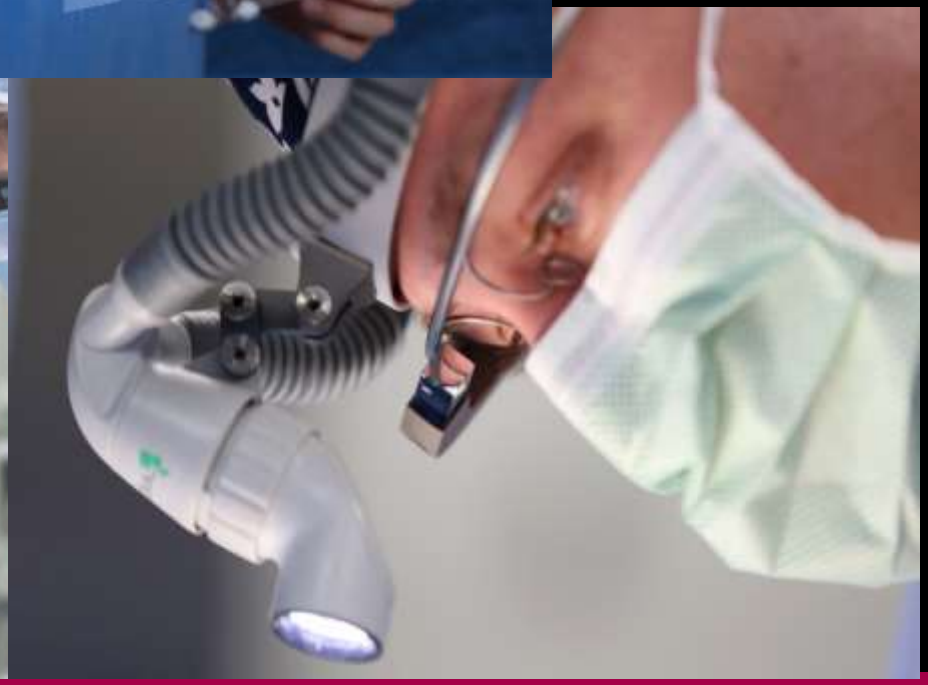
ACXIOM
datalogix
CoreLogic
eBureau
id:analytics
INTELIUS
peekyou
RapLeaf
Recorded Future

Bloomberg Businessweek
22 Sept 2014

FEDERAL TRADE COMMISSION
PROTECTING AMERICA'S CONSUMERS
100 YEARS

We Are A Visual Species!

New Visualization Tools: Interactive Interfaces and Customization Formats



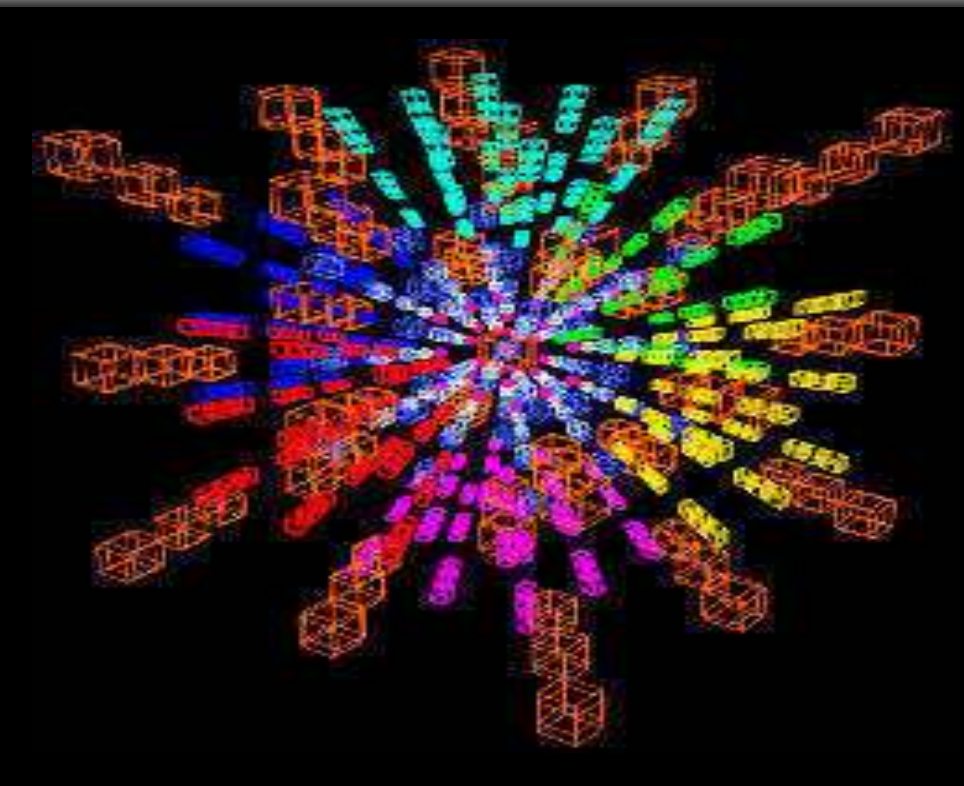
The Pending Era of Cognitive Systems: Overcoming the "Bandwidth" Limits of Human Individuals

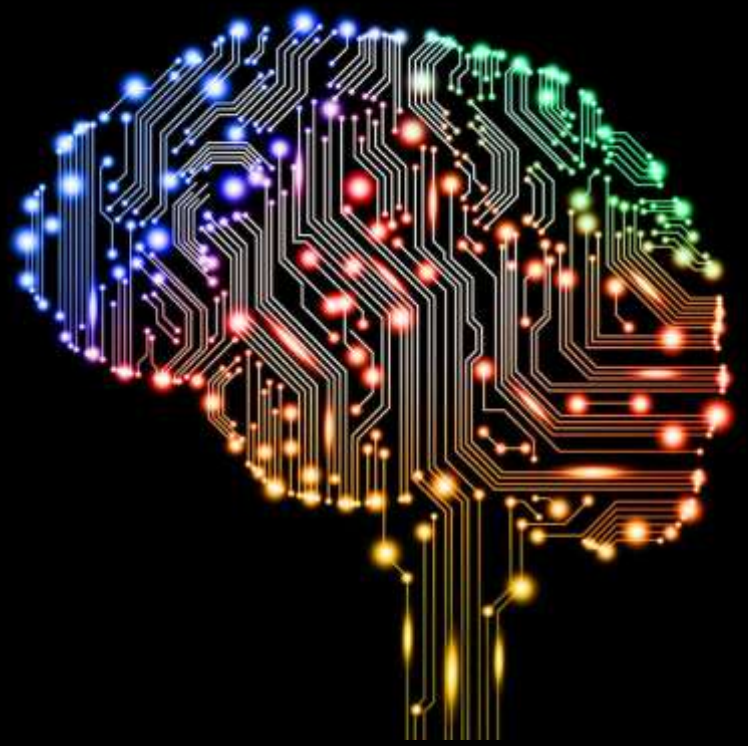
- limits to individual expertise
- limits to our multi-dimensionality
- limits to our sensory systems
- limits to our experiences and perceptions
- limits to our objective decision-making

Future Trajectories for Mining and (Meta)Analysis of Big Data: The Rise of Increasingly Automated Decision Tools

- The Future of ‘Search’
- Intelligence at Ingestion
- Deep Learning
- Why Wait for the Slow Brain to Catch Up With the Fast Machine

Automated Context: Data Finding Big Data "Intelligence at Ingestion"





Feature Extraction and Classification

Context Analysis

Persistent Context

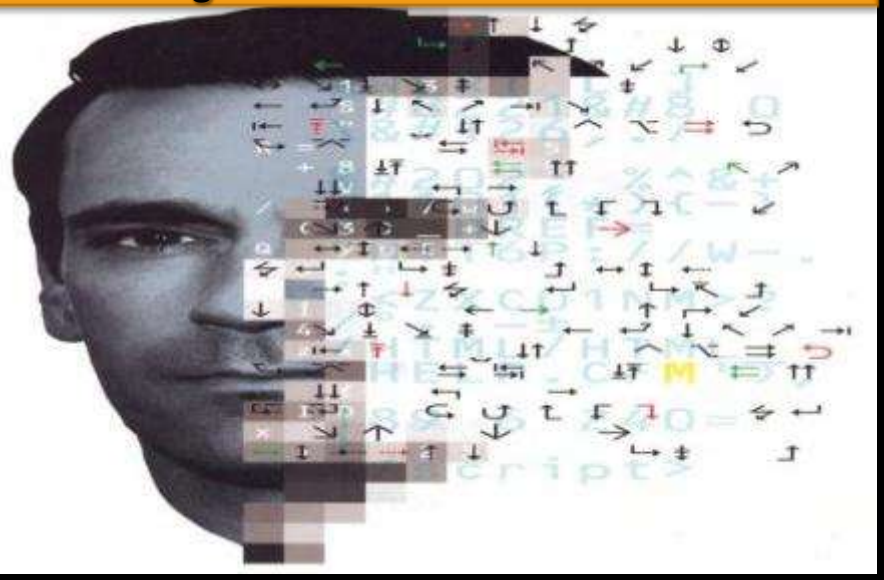
- **Relevance Detection**
- **Situational Awareness**
- **Intelligence**

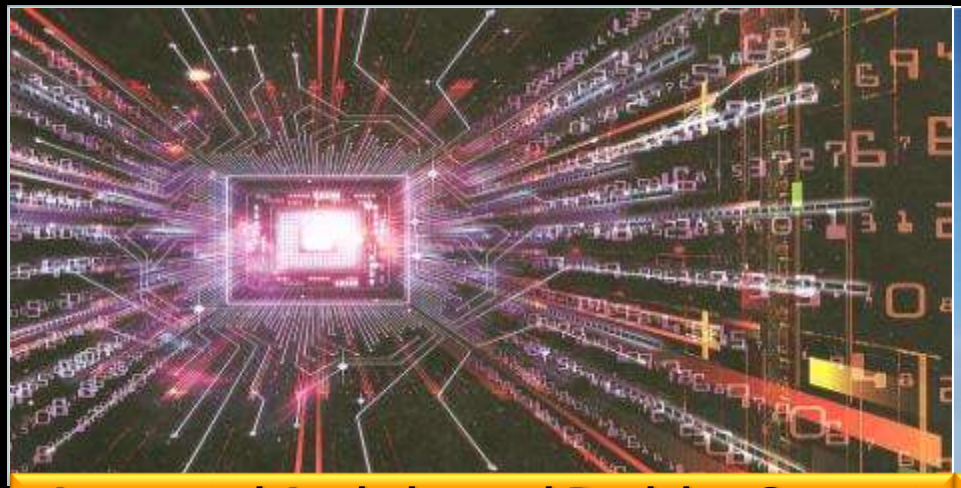
Rapid, Informed Decisions

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

Data Deluge

Cognitive Bandwidth Limits





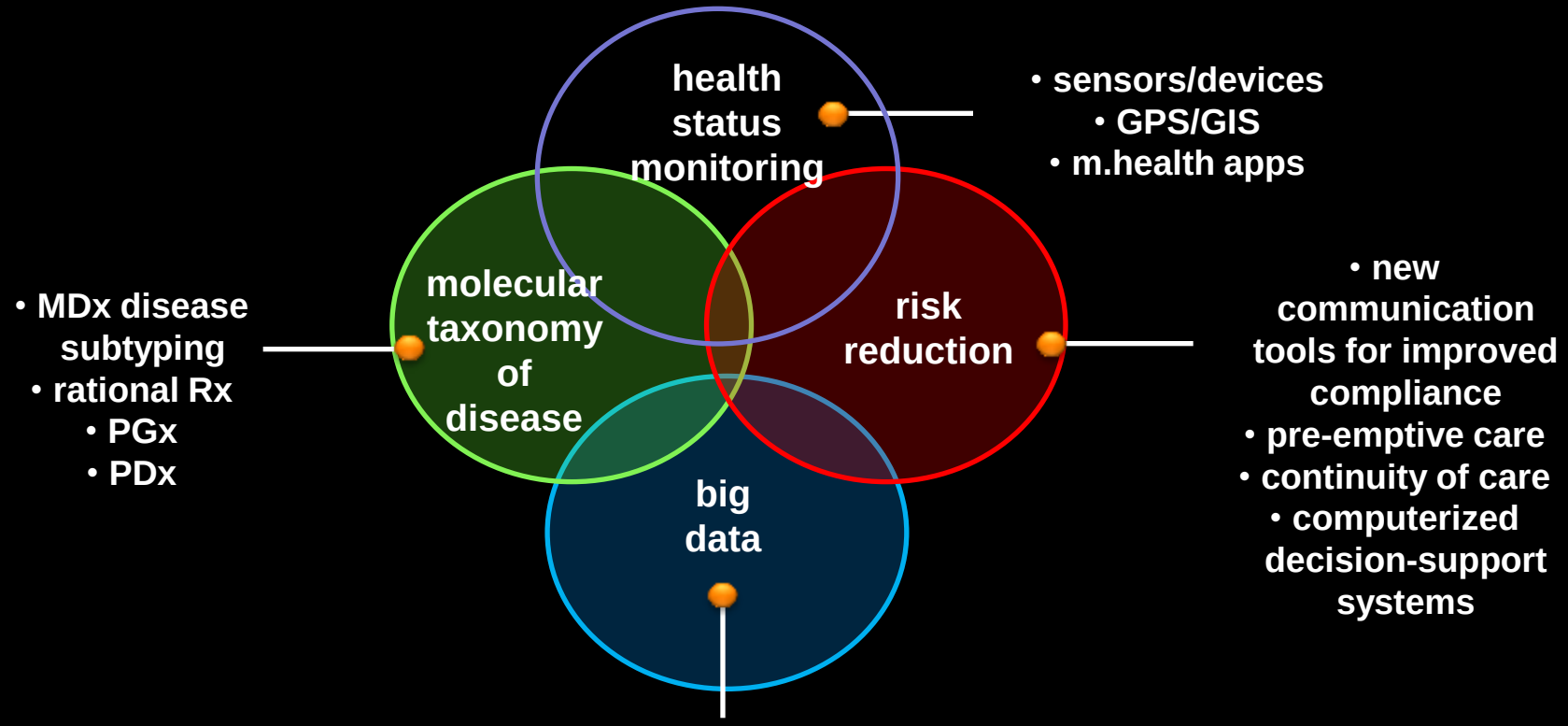
Automated Analytics and Decision Support

Facile Formats for Actionable Decisions

Digital Health, Automation and the Future Work Force

Can Computers and Robotics Can Do Your Job, and Eat Your Lunch?

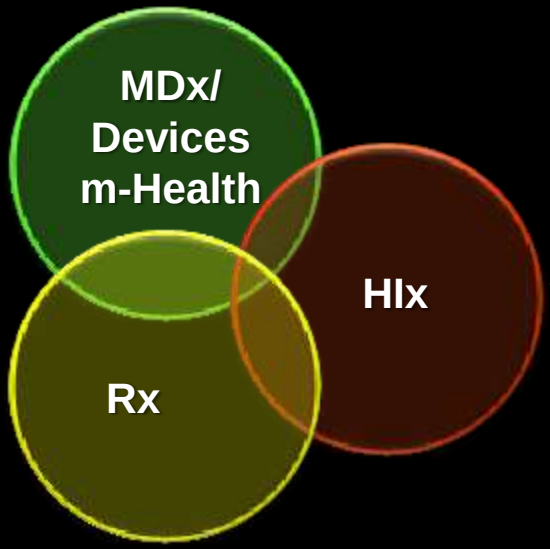
Precision Medicine



Integration of Healthcare Services
Continuity in Care and Optimizing Wellness

A New Healthcare Ecosystem Arising From Technology and Market Convergence

Technology

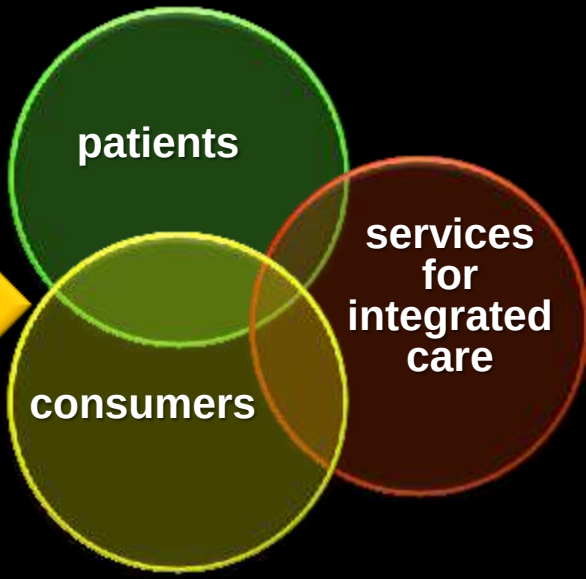


Comprehensive Profiling and Remote, Real Time Monitoring

- passive/active data collection
- analytics and network architecture
- EMR/PMR
- performance and outcomes analysis

Data Mining and Integration Services

Health Services



Increasingly Targeted Care and Efficient Use of Finite Resources

The Changing Analytical and Data 'Spaces' for Clinical Pathology and Laboratory Services

Defining the Future Role of Clinical Pathology and Laboratory Medicine

- primacy as knowledge integrators in making precision medicine a reality?

or

- Darwinian (Schumpeterian) eclipse by new entrants and new service/business models?

“DNR”

- Denial
- Negativity
- Resistance

Incrementalism

Squeezing Savings from Outmoded Processes and Business Models

versus

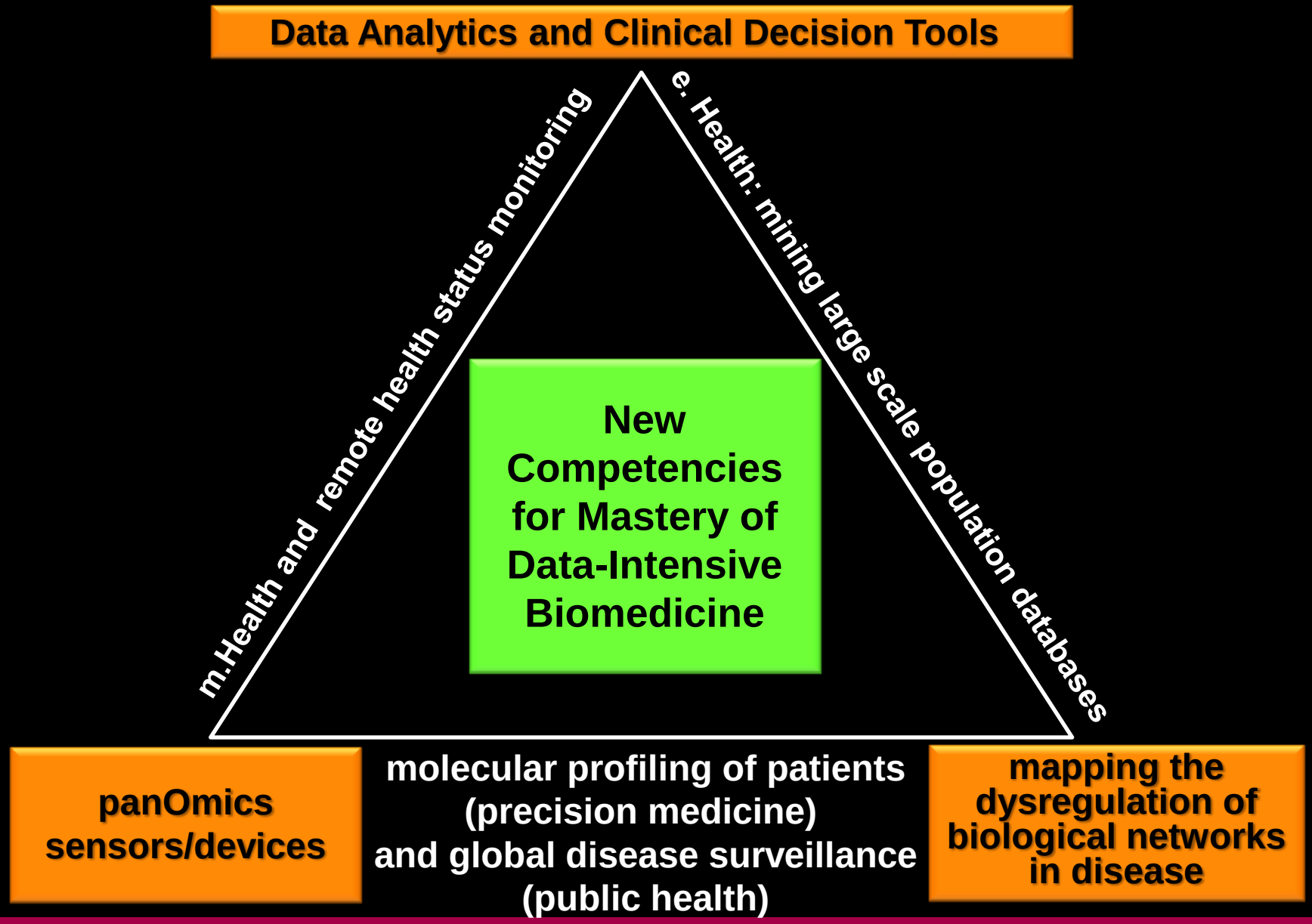
Disruptive Innovation

Yes

No

Fundamental Change in Processes and Business Models for Major Performance Gains, Cost-Effectiveness and ROI

Building Knowledge Networks to Improve Individual Health and Sustainable Healthcare Delivery



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