



Precision Health and Digital Health: The Inter-Dependent Strategic Drivers of Innovation in Healthcare Delivery

Dr. George Poste, DVM, PhD

Chief Scientist, Complex Adaptive Systems Initiative
and Regents Professor of Health Innovation

Arizona State University

george.poste@asu.edu

www.casi.asu.edu

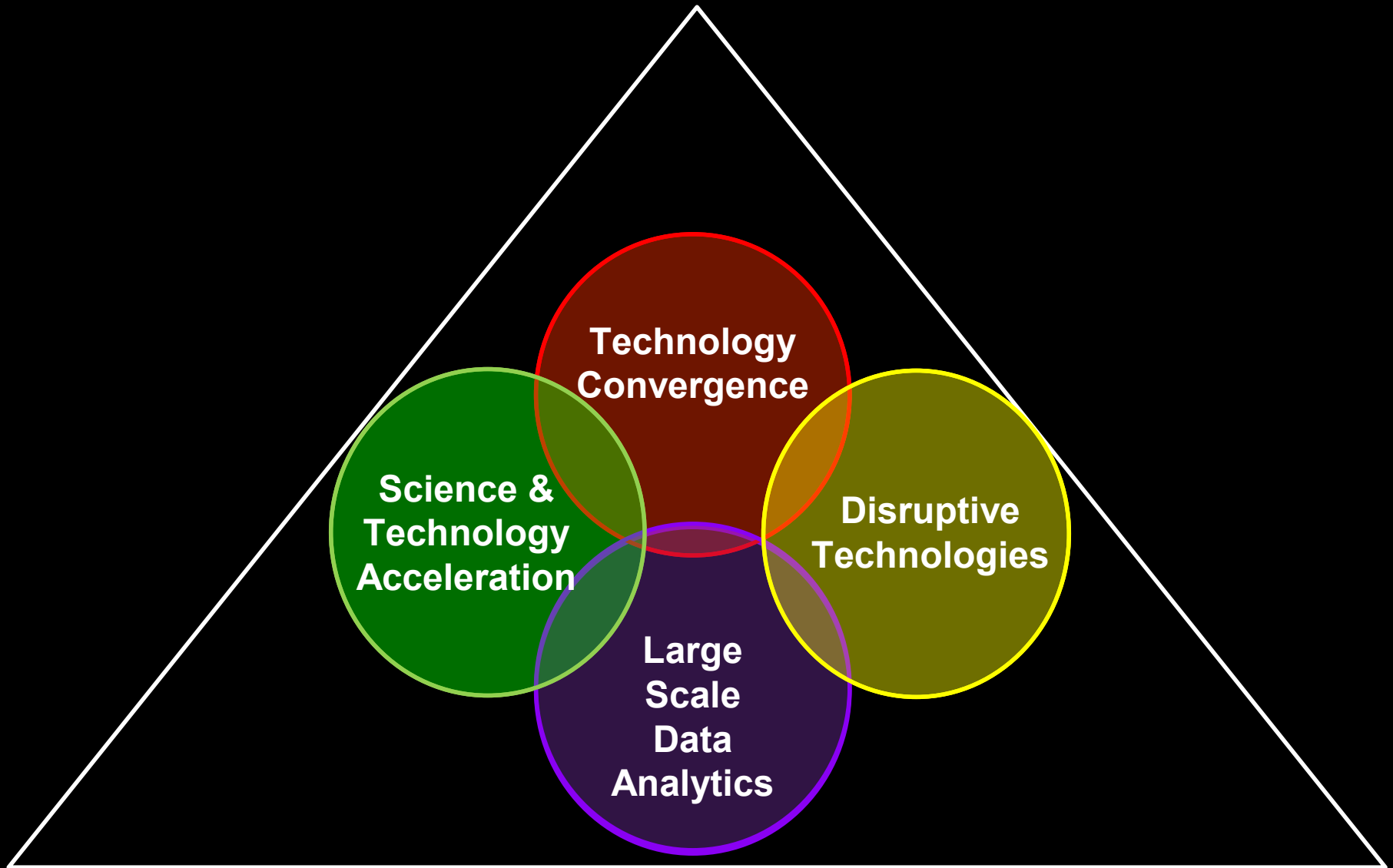
EMED 227/127: HEALTH CARE LEADERSHIP

Stanford University School of Medicine

Li Ka Shing room 130

22 January 2020

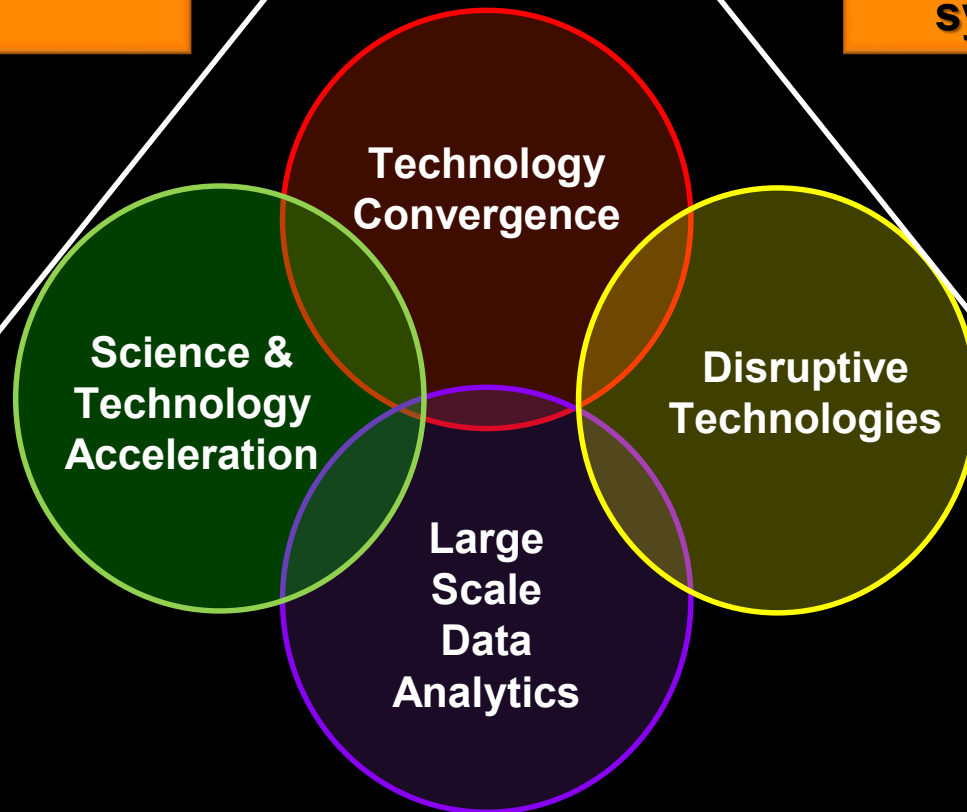
Precision Health and Digital Health: The Strategic Drivers of Biomedical Research and Healthcare Delivery



The Strategic Environment for Biomedical Research and Healthcare Delivery

- ageing populations
- chronic disease
- SDoH
- new patterns of care delivery

- reduce cost of care
- improve clinical outcomes
- learning healthcare systems



a complex multi-dimensional, multi-stakeholder ecosystem

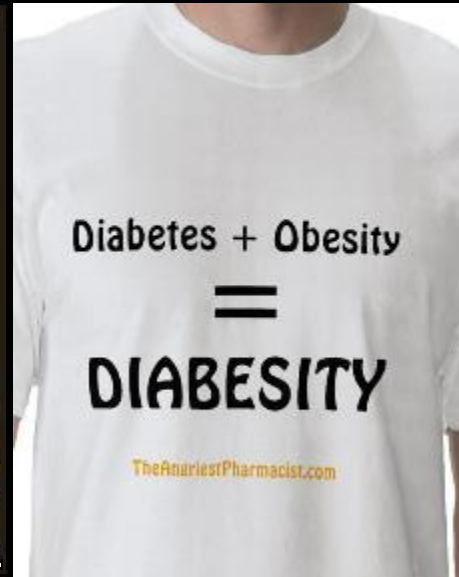
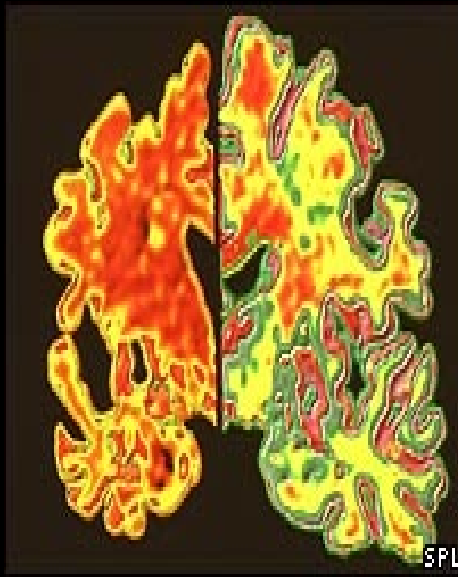
The Growing Burden of Chronic Disease

cancer

neurodegeneration

cardiovascular/
metabolic disease

mental illness



- economic unsustainability of current care systems
- insufficient clinical infrastructure
- disparities in access to care and patterns of care
- inadequate health information systems and poor coordination and continuity of care
- cost of innovation (Rx price as political target)
- rise of consumerism in healthcare and entry of new corporate players

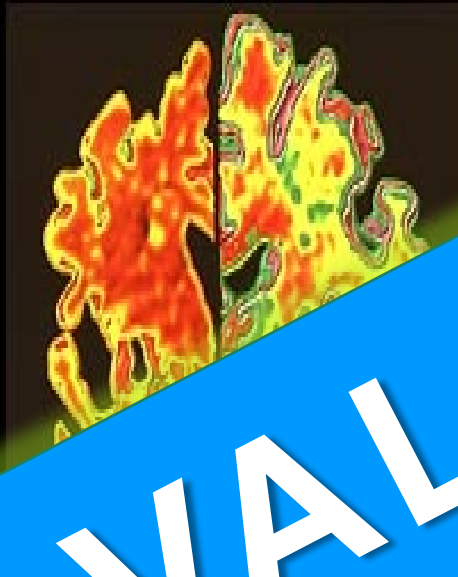
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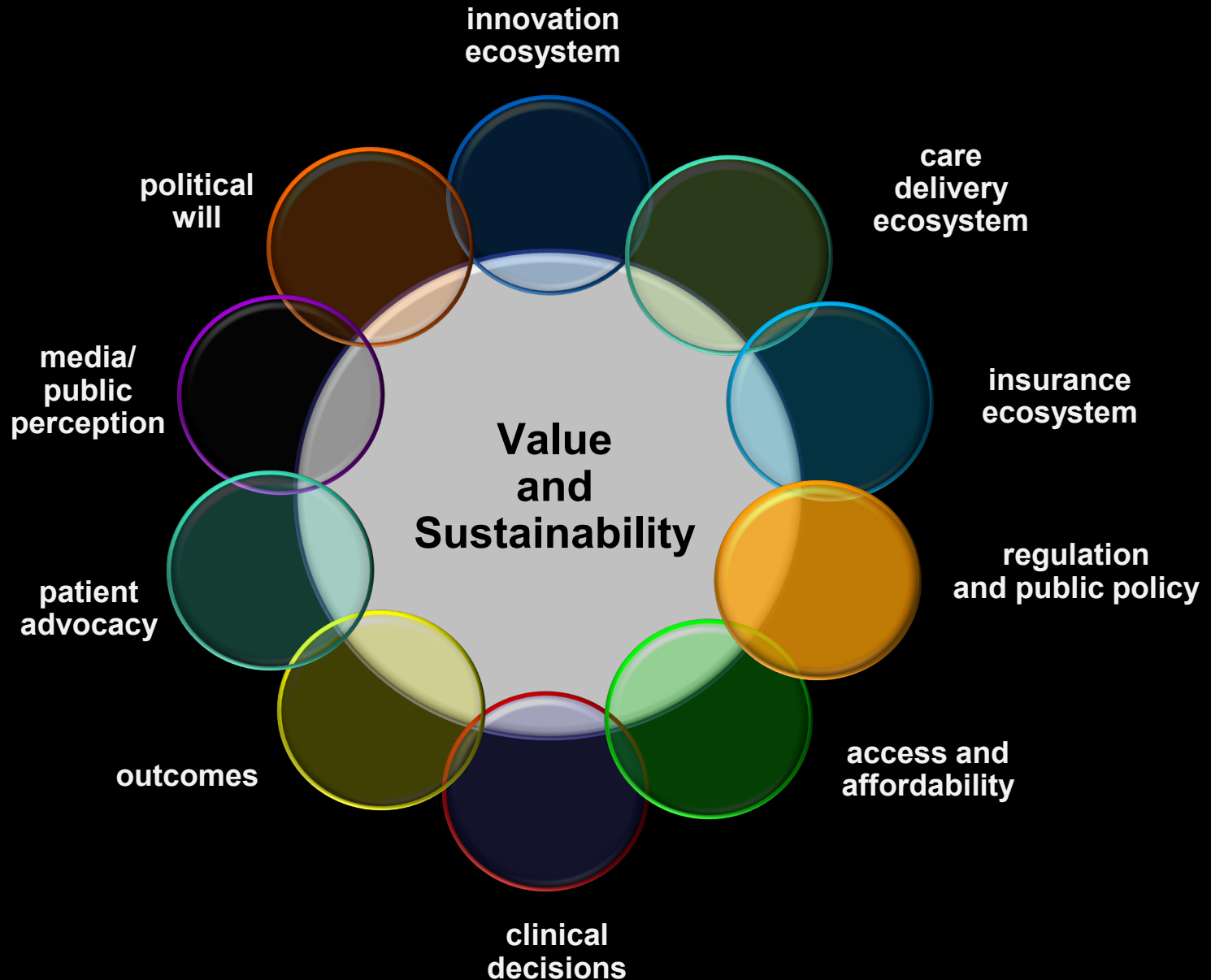
mental illness



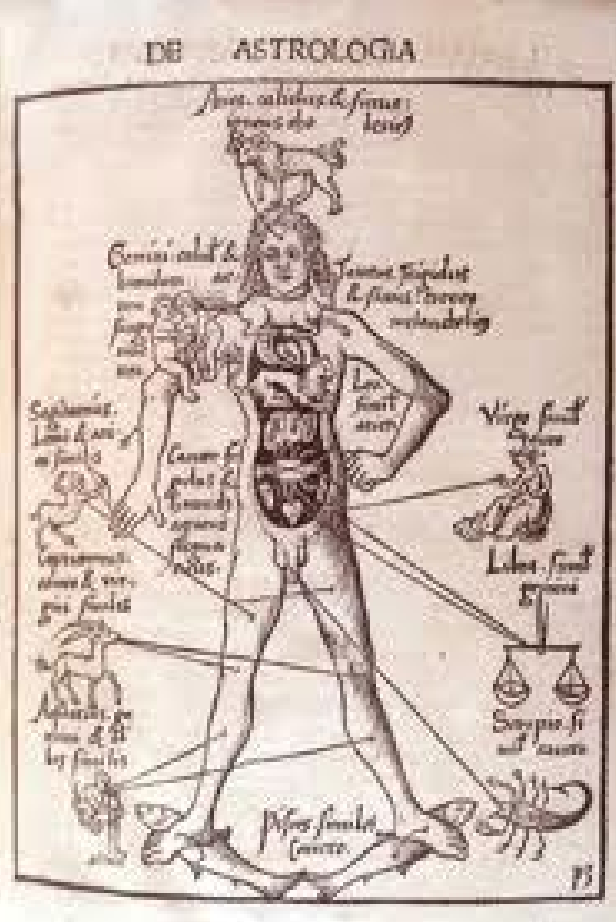
VALUE

- economic burden on health care systems
- fragmented care
- fragmented care structure
- fragmented access to care and patterns of care
- inadequate health information systems and poor coordination and continuity of care
- cost of innovation (Rx price as political target)
- rise of consumerism in healthcare and entry of new corporate players

Healthcare: A Complex, Multidimensional, Multi-stakeholder Ecosystem



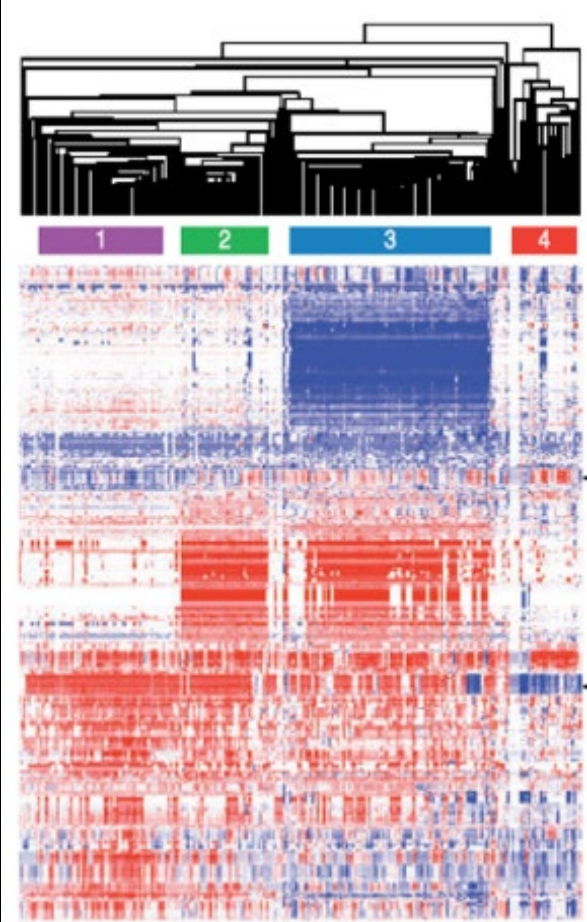
The Path to Precision Medicine: From Superstitions to Symptoms to (Molecular) Signatures



humors; astrology, shamanism, sin and divine fate



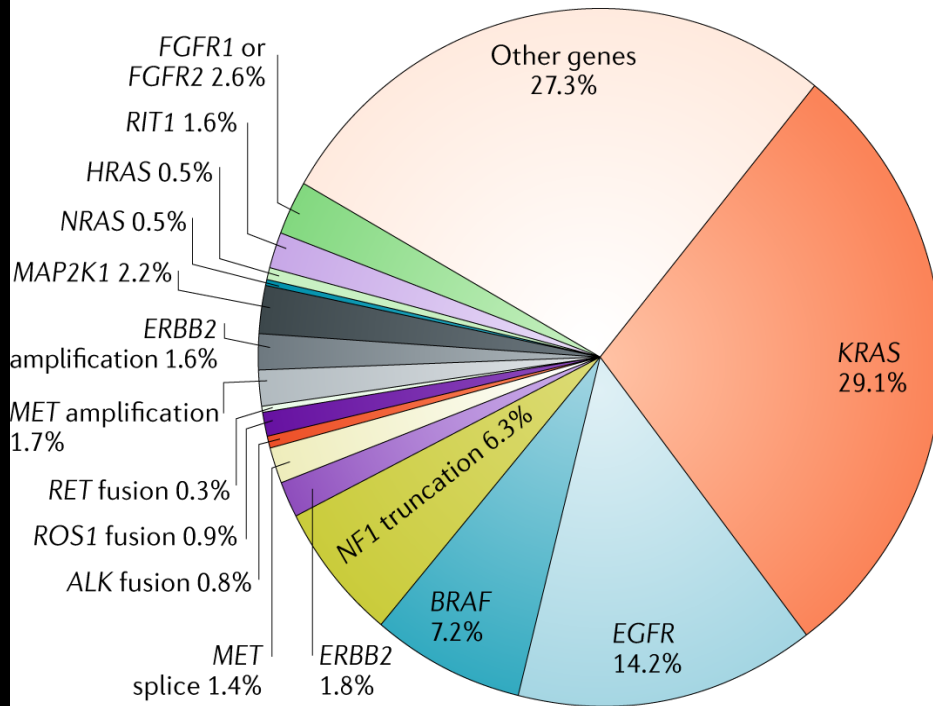
biochemistry and organ-based pathophysiology



molecular biology and multi-omics profiling

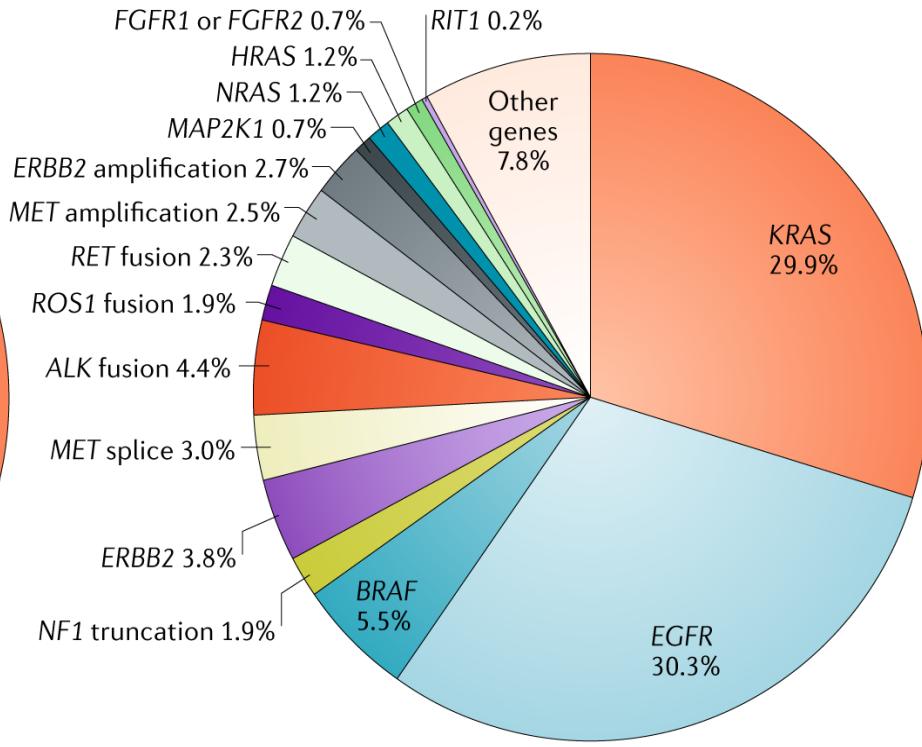
Molecular Classification of NSCLC and Identification of Single, Largely Non-Overlapping Oncogenic Alterations

a Early stage



Data from TCGA (Sanchez-Vega et al.¹⁷⁸, Ellrott et al.¹⁷⁹ and Hoadley et al.¹⁸⁰), Imielinski et al.⁶² and Kadara et al.¹³³ (n = 741)

b Metastatic



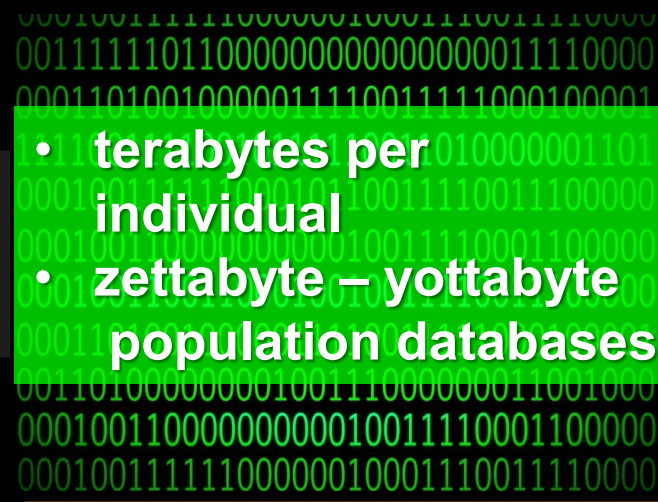
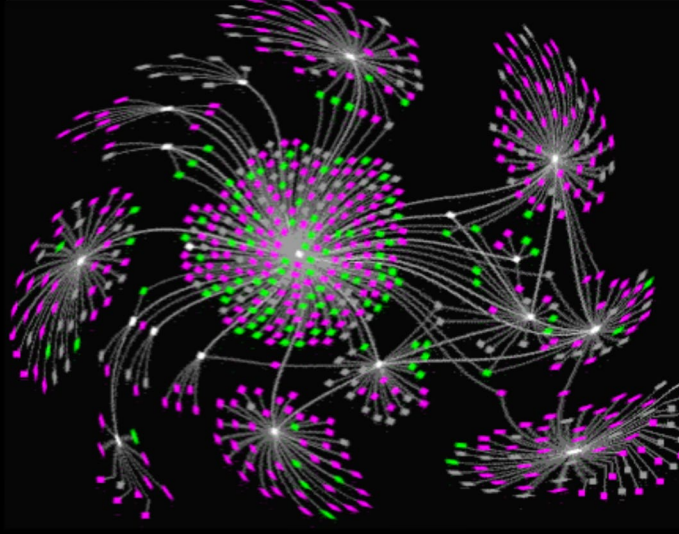
Data from MSK-IMPACT (Jordan et al.⁵⁹) and FoundationOne (Frampton et al.¹⁵) panels (n = 5262)

From: F. S. Koulidis and J. V. Heymach (2019) Nature Rev. Cancer 19, 495

Precision Medicine:

(Epi)Genomics

MultiOmics Profiling of Disrupted Molecular Signaling Networks in Disease:
The New Taxonomy of Disease Subtypes

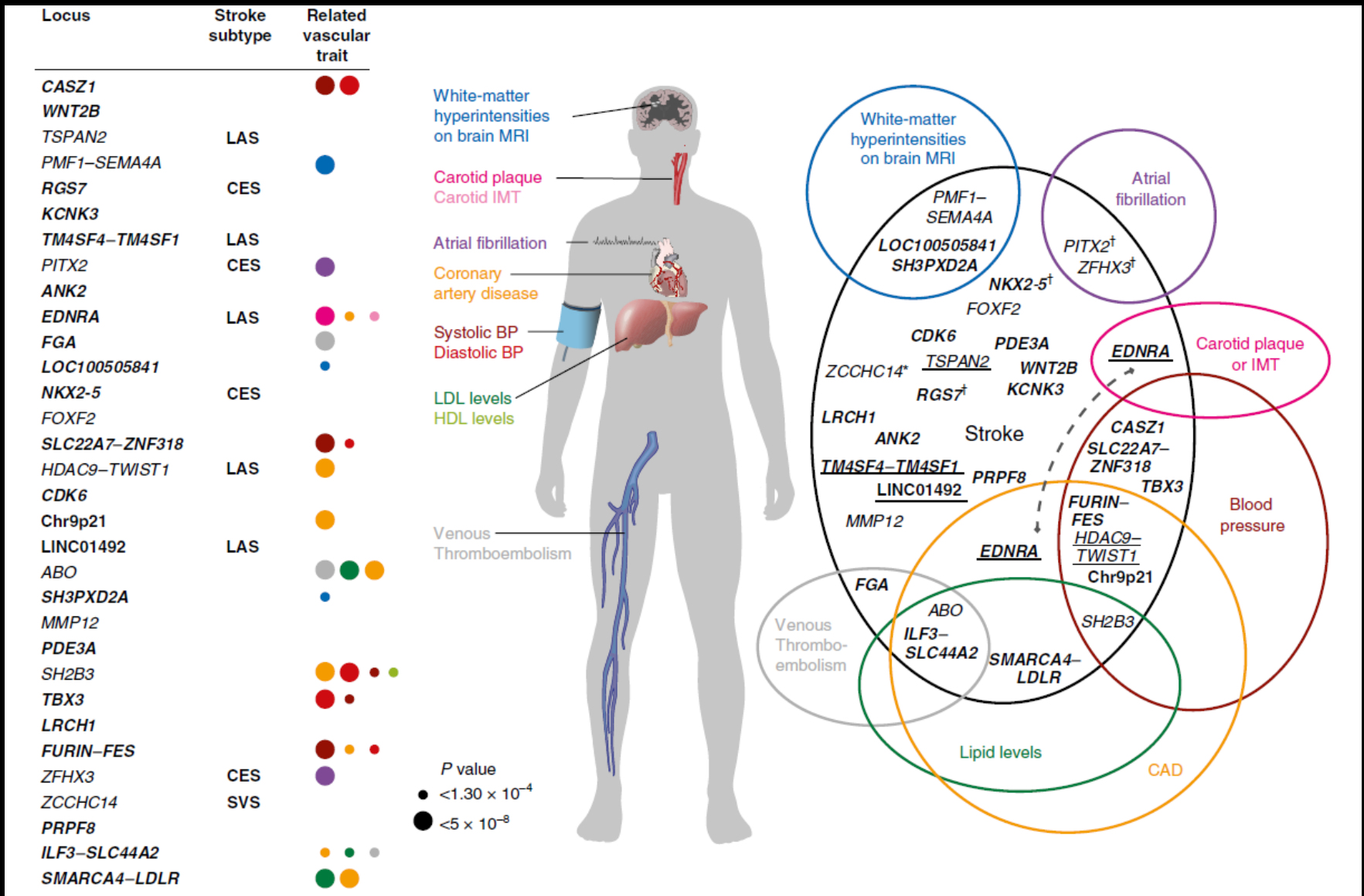


- terabytes per individual
- zettabyte – yottabyte population databases

Patient-Specific Signatures of Disease
and Optimized Treatment Selection for Disease Subtypes

Big (Messy) Data

Genetic Overlap Between Stroke and Related Vascular Traits at 32 Genome Loci for Stroke Profiled in 520,000 Subjects



Molecular medicine and information-based targeted healthcare

[Nature Biotechnology, \(1998\)16 \(Supplement\), 19-21.](#)

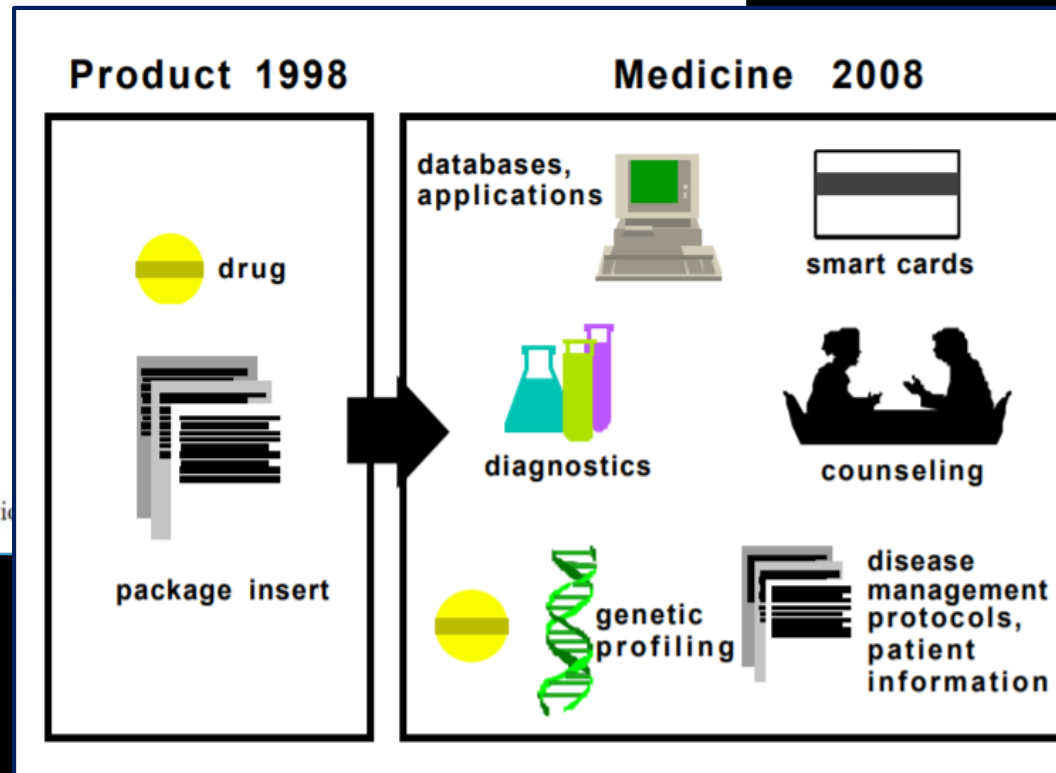
The convergence of genomics and informatics heralds a new era of biomedical research, offering unbridled opportunities for bioentrepreneurs.

George Poste

The accelerating momentum of technological innovation in the life sciences has been accompanied by equally profound changes in the competitive landscape for industrial R&D. New entrepreneurial companies have emerged on an unprecedented scale to exploit advances in molecular biology, genomics, combinatorial chemistry, robotics, microelectronics, and informatics to generate new products and services for medicine, agri-

The development of informatics tools to annotate, archive, and analyze the vast volume and diversity of data-sets that will be generated will be a key factor in research progress.

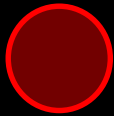
prediction and the prevention



Still Two Largely Separate Worlds

precision medicine

routine healthcare
delivery and SOC



research
and
early clinical
adopters
(largely oncology)

slow incremental
adoption of
technological
advances

\$100-125* billion
(estimated)

\$3.6 trillion
(19% GDP)

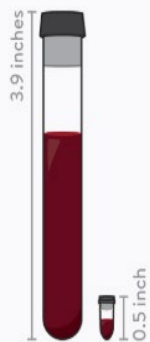
- one-size-fits-all protocols
- wide variation in clinical practice and outcomes
- fragmented continuity of care
- inefficient use of available data

*includes investment in investigational R_x candidates

If It Sounds Too Good To Be True....?

Popular Delusions and The Madness of Crowds: Charles Mackay 1841

Theranos' Nanotainer holds just a drop of blood. As many as 30 lab tests can be done from this one tiny sample.



**Bloomberg
Businessweek**

December 14 • December 21, 2015 bloomberg.com



BAD BLOOD

Secrets and Lies
in a Silicon
Valley Startup

John Carreyrou

Over 100 Companies Pursuing “Liquid Biopsy” for Blood-Based Molecular Biomarkers Precision Medicine

Early Detection / Screening*



Diagnosis



Treatment Selection



Monitoring



Companies in Early Detection / Screening:

- AcuamarkDx
- epigenomics
- freenome
- CHRONIX BIOMEDICAL
- GRAIL
- GUARDANT HEALTH
- MDxHealth
- OncoCyte
- DATAR CANCER GENETICS LIMITED
- exact sciences
- MDNA Life Sciences
- Volition
- exosomed_x

Companies in Diagnosis:

- OncoCyte
- Indi
- epigenomics

Companies in Treatment Selection:

- AccuraGen
- admera
- AnchorDx
- BOREAL GENOMICS
- 华大基因 BGI
- Inivata
- trovogene
- GUARDANT HEALTH
- BIOCARTIS
- FOUNDATION MEDICINE
- biodesix
- 燃石医学 Burning Rock Dx
- PGD
- NEO GENOMICS
- Nevogene
- ARCHER
- Roche
- ThermoFisher SCIENTIFIC
- RESOLUTION BIO
- sysmex
- CellMaxLife
- GENETRON HEALTH
- TEMPUS
- OncoDNA
- SINGLERA GENOMICS
- Biocept
- Agena
- ANGLE
- LIQUID BIOTECH
- Clearbridge BioMedics
- cynvenio
- EPIC SCIENCES™
- BioFluidica
- biodesix
- CARIS LIFE SCIENCES
- exosomed_x
- HELOMICS
- ROSETTAGENOMICS™
- TEMPUS

Companies in Monitoring:

- OncoDNA
- admera
- NANTHEALTH
- NEO GENOMICS
- Roche
- trovogene
- AmoyDx
- RESOLUTION BIO
- natera
- GENETRON HEALTH
- NANTHEALTH
- sysmex
- OncoCyte
- Agena
- cynvenio
- FLUXION
- LIQUID BIOTECH
- MENARINI silicon biosystems
- exosomed_x

Legend

Analytes targeted

- cfDNA
- Other (e.g., exosomes)
- CTCs

Note: *Includes risk stratification (e.g., to determine whether a tissue biopsy is needed) as part of pre-diagnosis process
 Source: DeciBio Liquid Biopsy White Paper, CI Tool

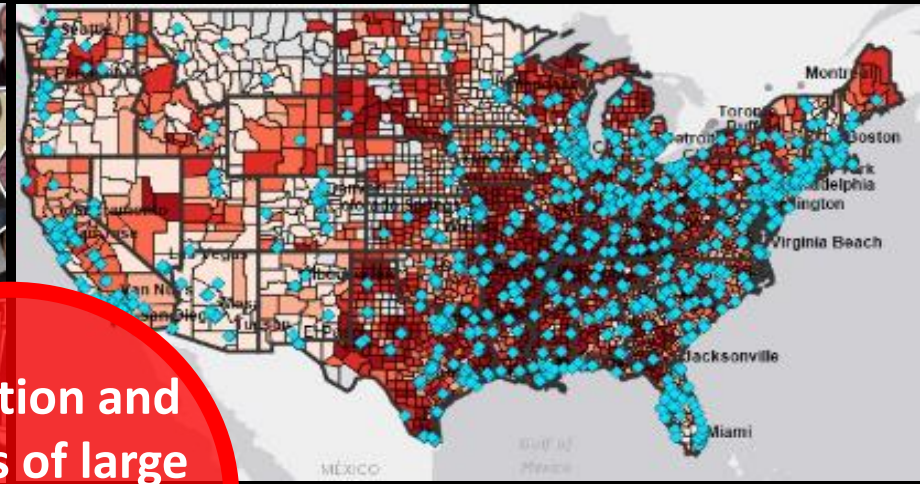


Precision Medicine and Digital Medicine: Evolving Inter-Dependencies

Individual Data



Population Databanks



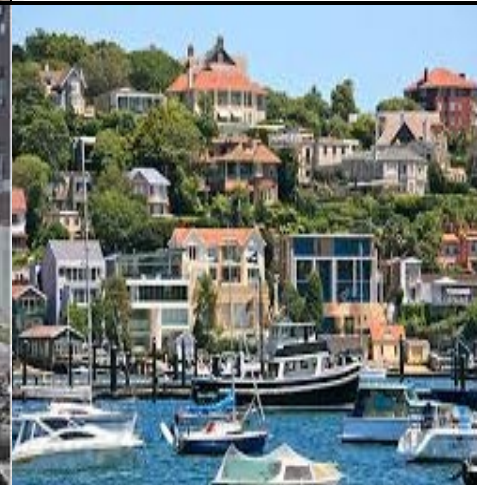
integration and
analysis of large
scale, diverse
data categories

“digital siblings and imputed phenotypes”

- **matching individual profiles to ‘best fit’ data cohorts to identify risk and selection of optimum treatment regimens**

The “Geno-Enviro-Pheno” Triad

Systematic Integration of Diverse Data for Population Health Analytics
Continuity of Care Record: From Womb to Tomb



Behavior

Environment

Social Determinants of Health (SDoH):

U.S. HEALTH IN INTERNATIONAL PERSPECTIVE



NATIONAL RESEARCH COUNCIL AND
INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

CONSENSUS STUDY REPORT

INTEGRATING SOCIAL CARE INTO THE DELIVERY OF HEALTH CARE

MOVING UPSTREAM
TO IMPROVE THE
NATION'S HEALTH

2019

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

CONSENSUS STUDY REPORT



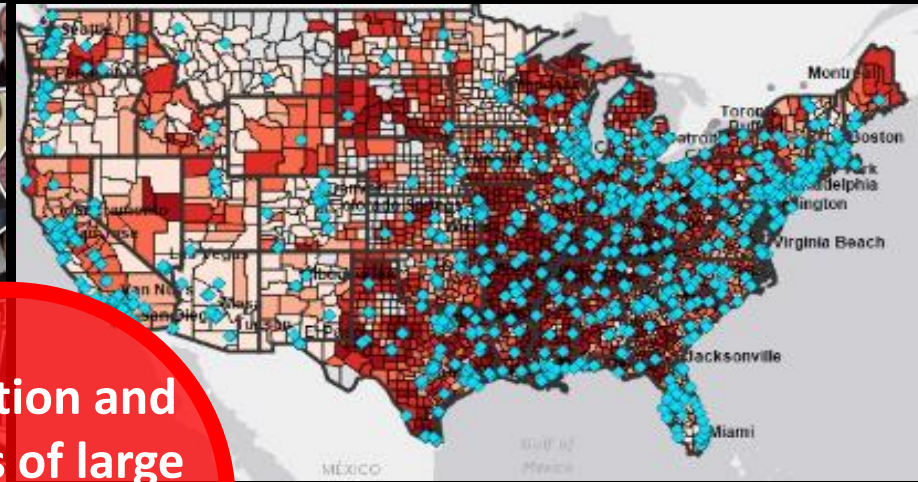
Criteria for Selecting
the Leading Health Indicators
for *Healthy People 2030*

Precision Medicine and Digital Medicine: Evolving Inter-Dependencies

Individual Data



Population Databanks



**integration and
analysis of large
scale, diverse
data categories**

**Deep Phenotyping:
integration of (epi)genomic and multiOmic profiles,
clinical, environmental and socio-behavioral data**

Precision Health and Digital Health

**Expanding 'The Analyte Space'
in Health and Disease**

Monitoring Health Beyond the Clinic

- **the majority of events that influence wellness/disease risk and treatment adherence occur largely outside of formal interactions with the healthcare system**
- **daily decisions by individuals have greater effects on their health than decisions controlled by the healthcare system**

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 and individual risk patterns**
- **the confessional of social media**
- **the blurring of private and public spaces**
- **complex ethical and legal issues**
 - **consent, privacy, security, surveillance**

“People Analytics” and Large-Scale Databanks: Blurring the Boundaries Between Medical Research, Clinical Care and Daily Life

- **every monitored event (clinical and non-clinical) is a potential data point**
- **every individual is a data node**
- **every individual is a research asset**
- **every individual is their own control**

Healthcare Beyond the Clinic

Changing The Touch Points in Healthcare Delivery

Remote Health Status Monitoring

**Smartphones, Wearables, Devices
and Telemedicine Services**

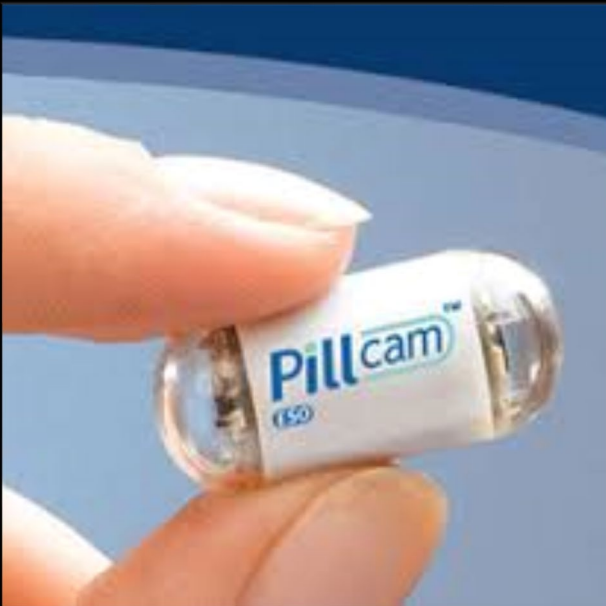
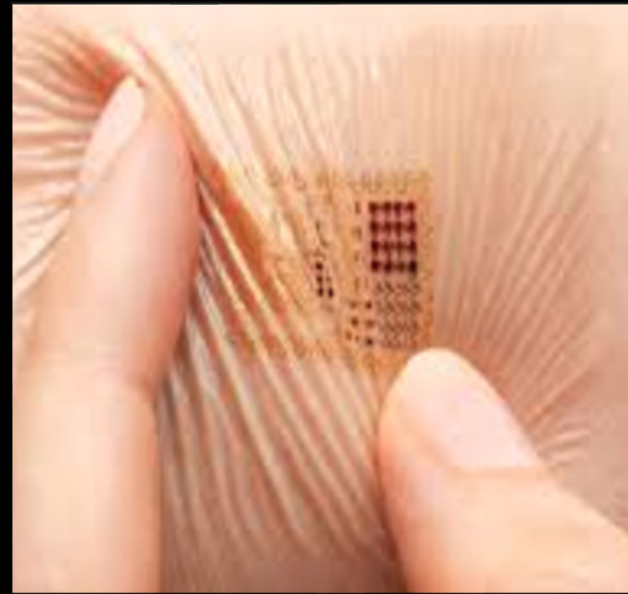
AORTA: Always On, Real Time Access

M4: Making Medicine More Mobile

Wellness Apps for Fitness, Diet and Exercise



Remote Monitoring of Health Status



The Eldercare Gap

10,000

- boomers turn 65 every day

79%

- increase in boomers age 80 or older from 2010 to 2030

1%

- projected increase in number of caregivers aged 45 to 64 from 2010 to 2030

348,000

- projected number of home health aides needed in next decade

Grey Technologies and Ageing in Place: Independent But Monitored Living for Ageing Populations



Rx adherence



**cognitive
stimulation**



**in-home support and reduced
readmissions**



reduced office visits

**Remote Health Monitoring and Reduction
in Hospital Readmissions**

Hospital Readmission Rates

1 CHF (22 - 30%)

**# 2 behavioral health and substance abuse
(20 - 26%)**

3 respiratory (158 - 26%)

4 diabetes mellitus (15 - 22%)

5 acute renal failure (15 - 22%)

Reducing Hospital Readmissions

- **identification and focus on higher-risk, higher-complexity patient**
- **patient coaching/education on discharge instructions and self-management**
- **engage family members**
- **use of transitional care nurses and other care coordination professionals**

Smart Devices for Automated Drug Delivery and Improved Therapeutic Adherence



Propeller Health



Gecko (now Teva)



CapMedic



Biocorp Inspair



Help patients get *onboard* with *onbody* injections

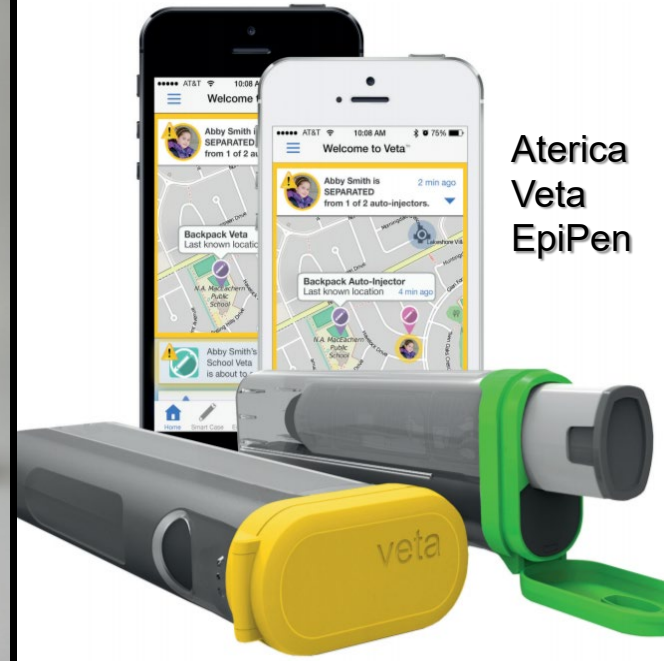
Onbody Trainers
 Device Replication
 Actuation Simulation
 Cartridge Simulation
 Replaceable Device Adhesives
 Injection Speed Simulation



noble

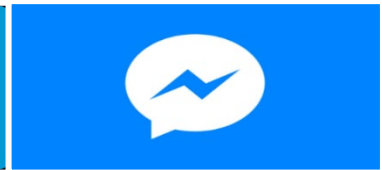
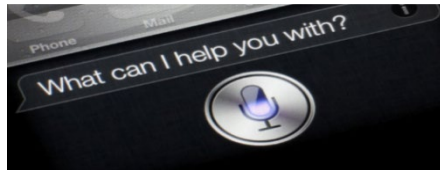
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Aterica
 Veta
 EpiPen

Chatbots and Support Robots in Healthcare



Amazon and Home Care

Development of Third-Party Alexa Apps



Allows seniors to verbally report medical data, get exercise and adherence reminders, call a caregiver, and coordinate transport



Mayo Clinic First Aid

"Tell me about spider bites"

"Help for a burn"



Ask My Buddy

"Alexa, ask My Buddy to alert everyone."

Digital Platforms in Behavioral Health

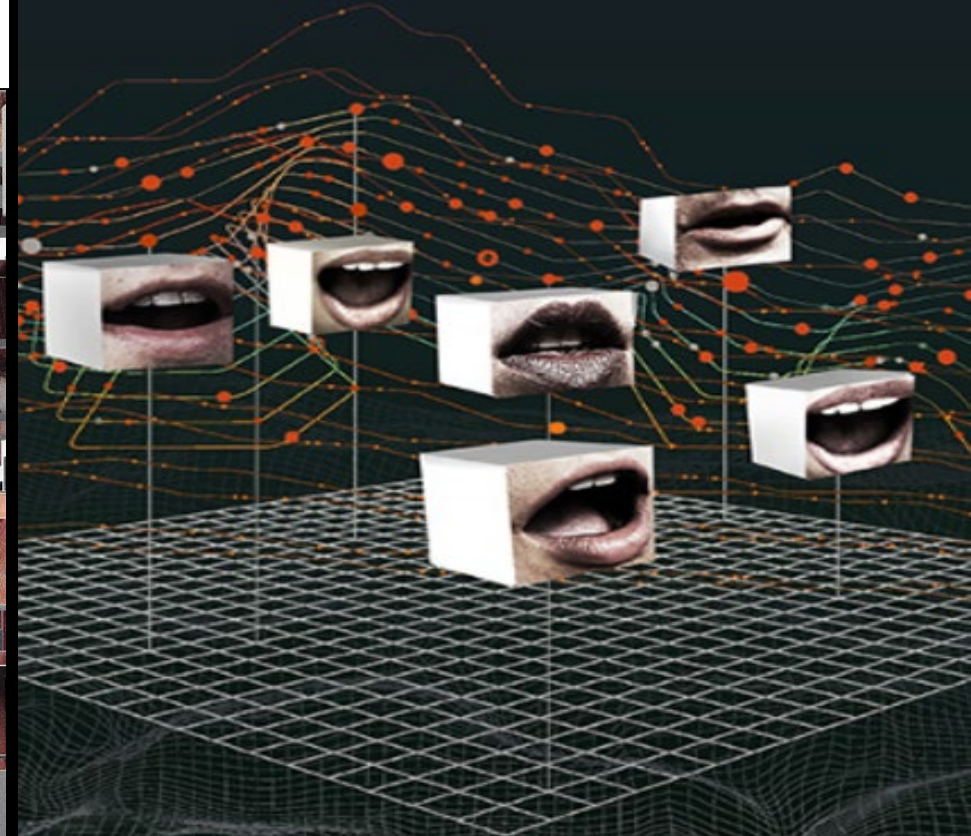
Growing Demand: Increased ED Presentations of Behavioral Health Emergencies

- **reported range of 8-25% of ED volume (outliers higher)**
- **70% of behavioral health patients also have one or more co-morbidities**
- **opioid-related visits tripled between 2005-16**
- **approx. 1 in 4 individuals with serious mental illness also have SUD**
- **60% of adolescents in community-based SUD treatment programs also meet diagnostic criteria for mental illness**

***mental illness and substance use disorder (SUD)**

Digital Psychiatry: Digital Psychometrics and Evaluation of Mental Illness

- (micro)saccades
- facial dynamics



- speech prosody (rhythm, tone, volume)
- semantic construction
- stimulus response and interaction speed

Digiceuticals: Software as Therapy



“We envision empowering individuals with digital therapeutic solutions that address underlying motivational and technical deficits by deciphering neural pathways that support motivation, decision-making and reinforcement to prompt health.”

**Dr. Ben Wiegand
Global Head, Janssen R&D
World Without Disease Accelerator
PharmaVoice 2017**

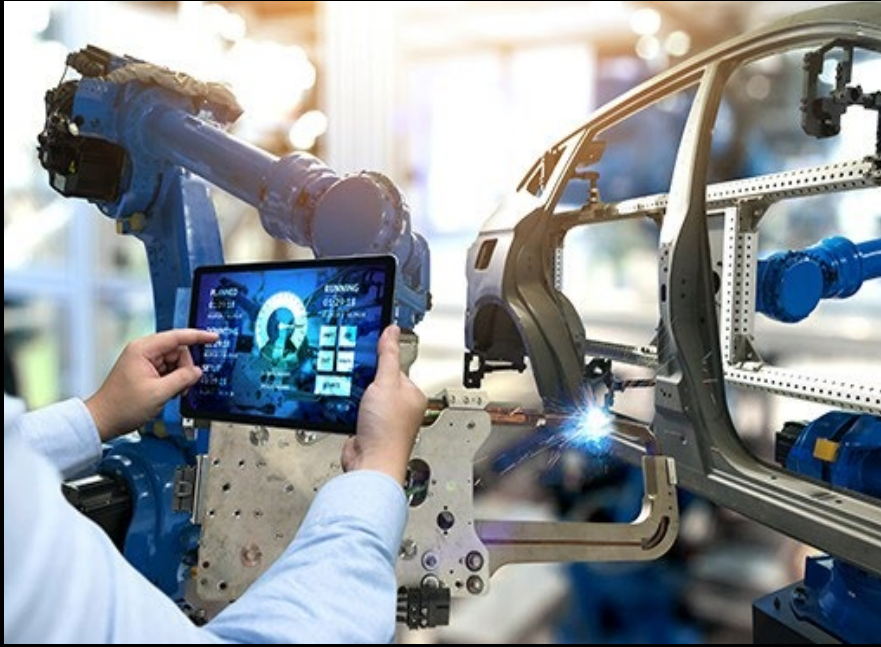
Digital Therapeutics Alliance



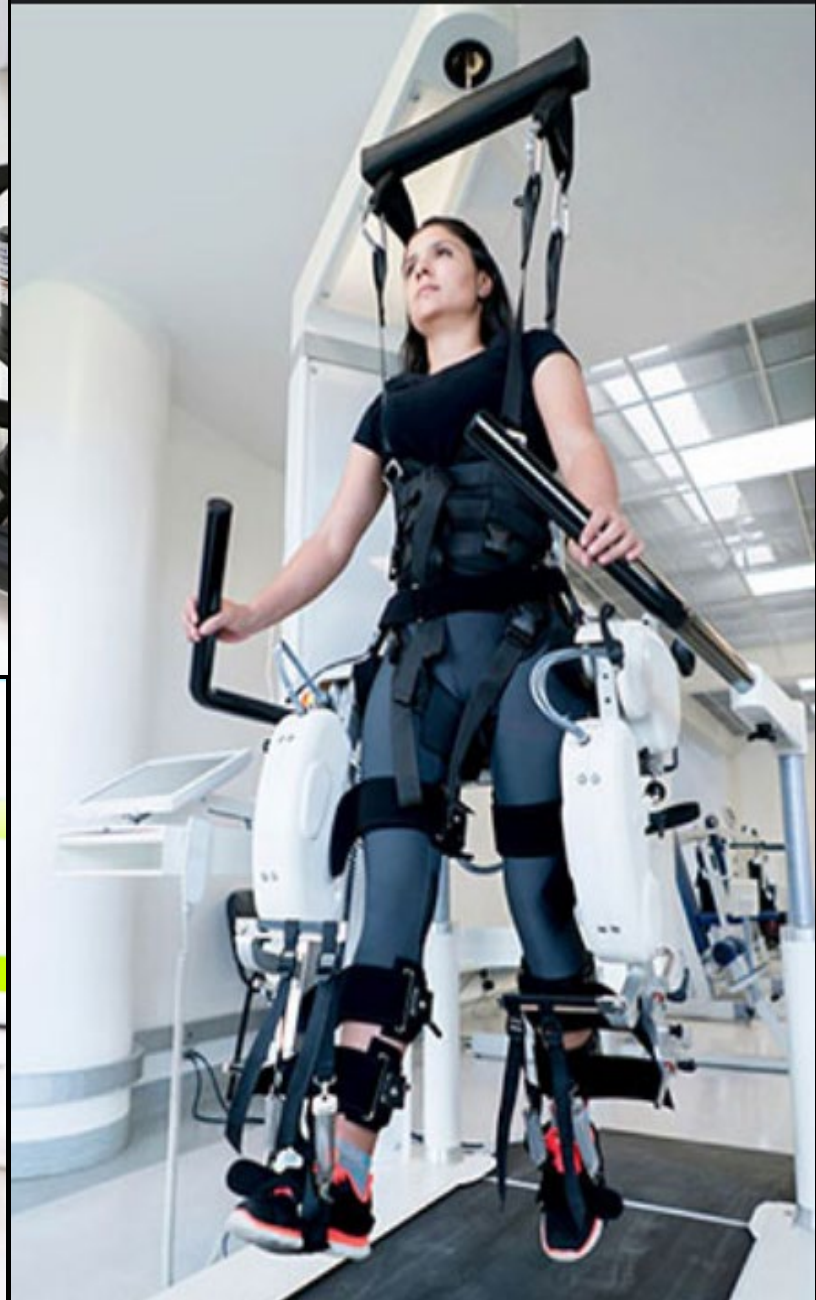
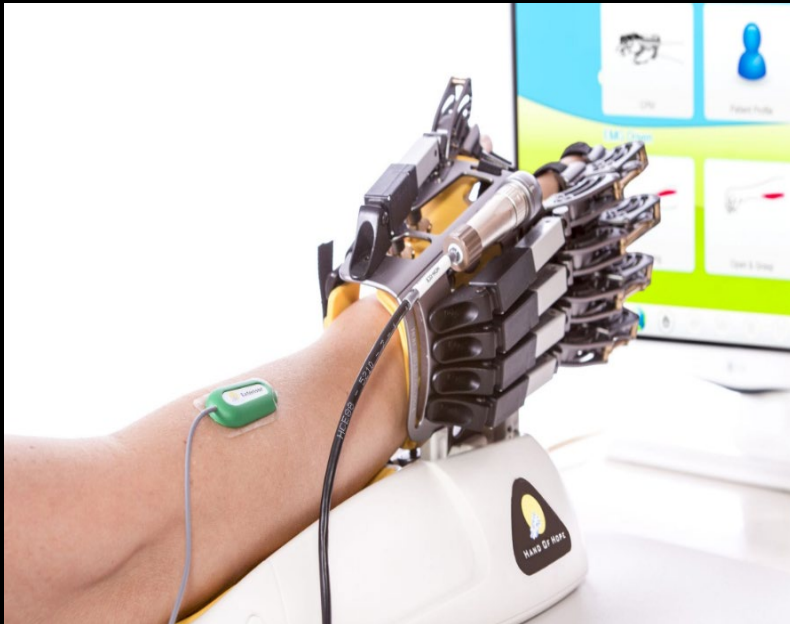
Robotics and Human-Machine Interactions

**Brain-Machine Interface Technologies and
Augmented Sensory, Motor and Cognitive Functions**

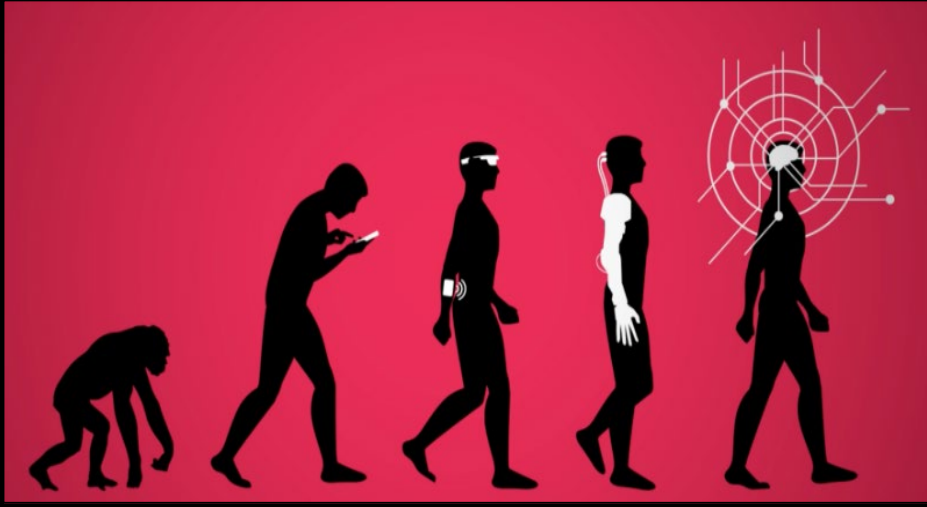
Robot-Human Directed Interactions



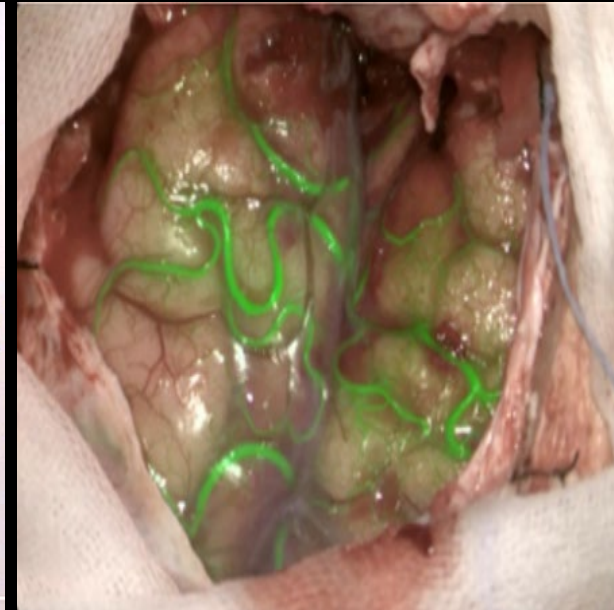
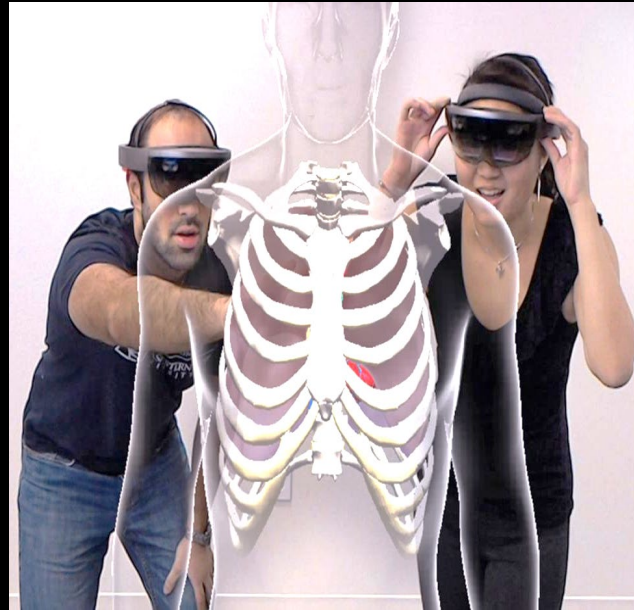
Robotic Assist Systems and Exoskeletons for Rehabilitation



Co-evolution of Human-Machine Interactions, Robotics and Augmented Cognition



VR/AR/MR and Preparation for Complex Procedures



VR/AR and Neuromodulation



- promote behavior change via altered sensory inputs and feedback
- mental illness: PTSD, physical rehabilitation, substance abuse and pain control



Next-Generation Non-Surgical Neurotechnology (N³) Program

- brain-machine (computer) interface technologies
- non-invasive interfaces
- “minimally invasive” technologies
 - ingest chemical compounds that enable external sensors to read brain’s activity
- bidirectional information links





“Do you solemnly swear to have no involvement in your own care?”

Empowered Patients: Social Networking Sites (SNS) and Their Role in Clinical Care

- **logical extension to healthcare of rapid rise of web/apps in mainstream culture**
- **increasingly proactive and engaged consumers/patients/families**
- **greater access to information on treatment options, cost and provider performance**
- **new clinical practice tools to optimize physician-patient relationships**
- **Ux and formation of senior executive level Chief Patient Experience Officer posts in large provider organizations**

The Principal Forces Shaping Biomedical R&D and Healthcare Delivery

- sensors
- smart implants

engineering and device-based medicine

- remote health monitoring
- telemedicine
- robotics

molecular (precision) medicine

- panOmics profiling
- analysis of disruption in biological networks

information-based healthcare

- m.health/e.health
- data- and evidence-based decisions and Rx selection

BIG DATA

outcomes-based healthcare and sustainable health

new value propositions, new business models and services

THE DIGITAL HOSPITAL: 100+ COMPANIES REINVENTING THE PRACTICE OF MEDICINE

CARE MANAGEMENT



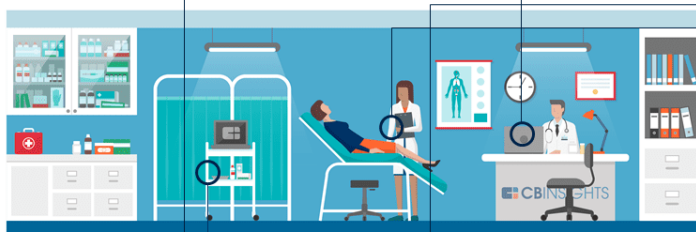
EMR/ PRACTICE MANAGEMENT



COMMUNICATION



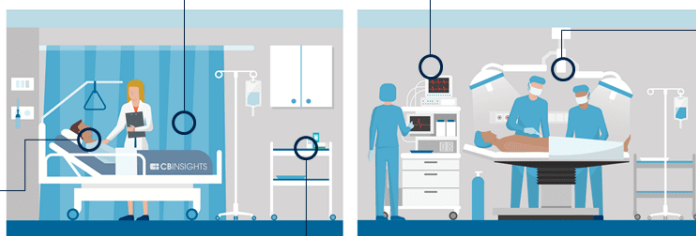
RADIOLOGY



DIAGNOSTICS



PATIENT MONITORING



SURGERY



PHARMACY



APPOINTMENTS & REFERRALS



HOSPITAL NAVIGATION



READMISSIONS/ EMERGENCY DEPARTMENT



INFECTION CONTROL



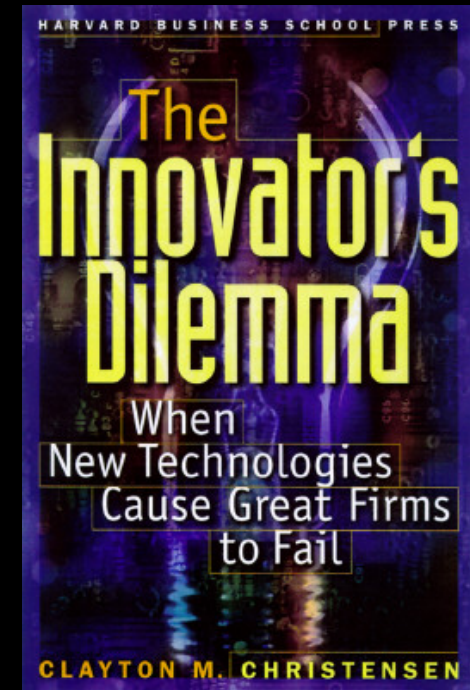
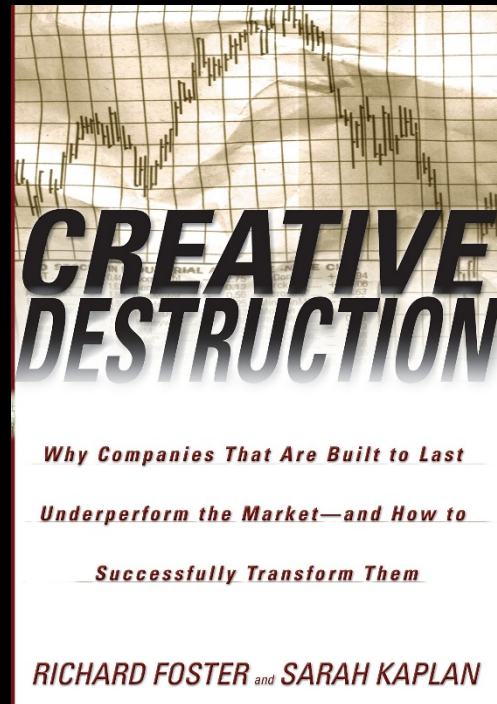
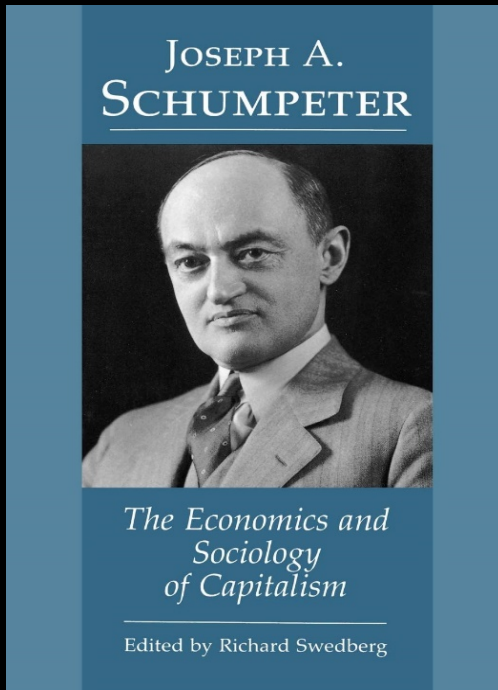
PATIENT EXPERIENCE



CLINICAL DECISION SUPPORT



Creative Destruction and Disruptive Innovation



- radical disruption always occurs at the margins of existing fields or at points of convergence between previously separate fields
- history shows that the competitive threat posed by disruptive vectors of innovation are typically denied by the then current leading institutions/companies/public sector plans



100 Years of America's Top 10 Companies



1917



U.S. Steel
\$46.4B



American Telephone & Telegraph
\$14.1B



Standard Oil of N.J.
\$10.7B



Bethlehem Steel
\$7.1B



Armour & Co.
\$5.8B



Swift & Co.
\$5.7B



International Harvester
\$4.9B



E.I. du Pont de Nemours
\$4.9B



Midvale Steel & Ordnance
\$4.8B



U.S. Rubber
\$4.6B

1967



International Business Machines
\$258.6B



American Telephone & Telegraph
\$200.5B



Eastman Kodak
\$177B



General Motors
\$171.2B



Standard Oil of N.J.
\$106.5B



Texaco
\$82.3B



Sears, Roebuck
\$64.6B



General Electric
\$63.9B



Polaroid
\$58B



Gulf Oil
\$58B

2017



Apple
\$898B



Alphabet
\$719B



Microsoft
\$644B



Amazon
\$543B



Facebook
\$518B



Berkshire Hathaway
\$452B



Johnson & Johnson
\$374B



Exxon Mobil
\$350B



JPMorgan Chase
\$340B



Wells Fargo & Co.
\$266B

Mkt. Val. (\$ bn) as of November 10th, 2017

Assets (\$ bn) Inflation adjusted September 2017

Mkt. Val. (\$ bn) Inflation adjusted September 2017

Industry

- Tech
- Conglomerate
- Medical
- Oil & Gas
- Financial Services
- Film
- Rubber

- Retail
- Autos
- Telecom
- Steel
- Foods
- Chemicals
- Heavy Equipment

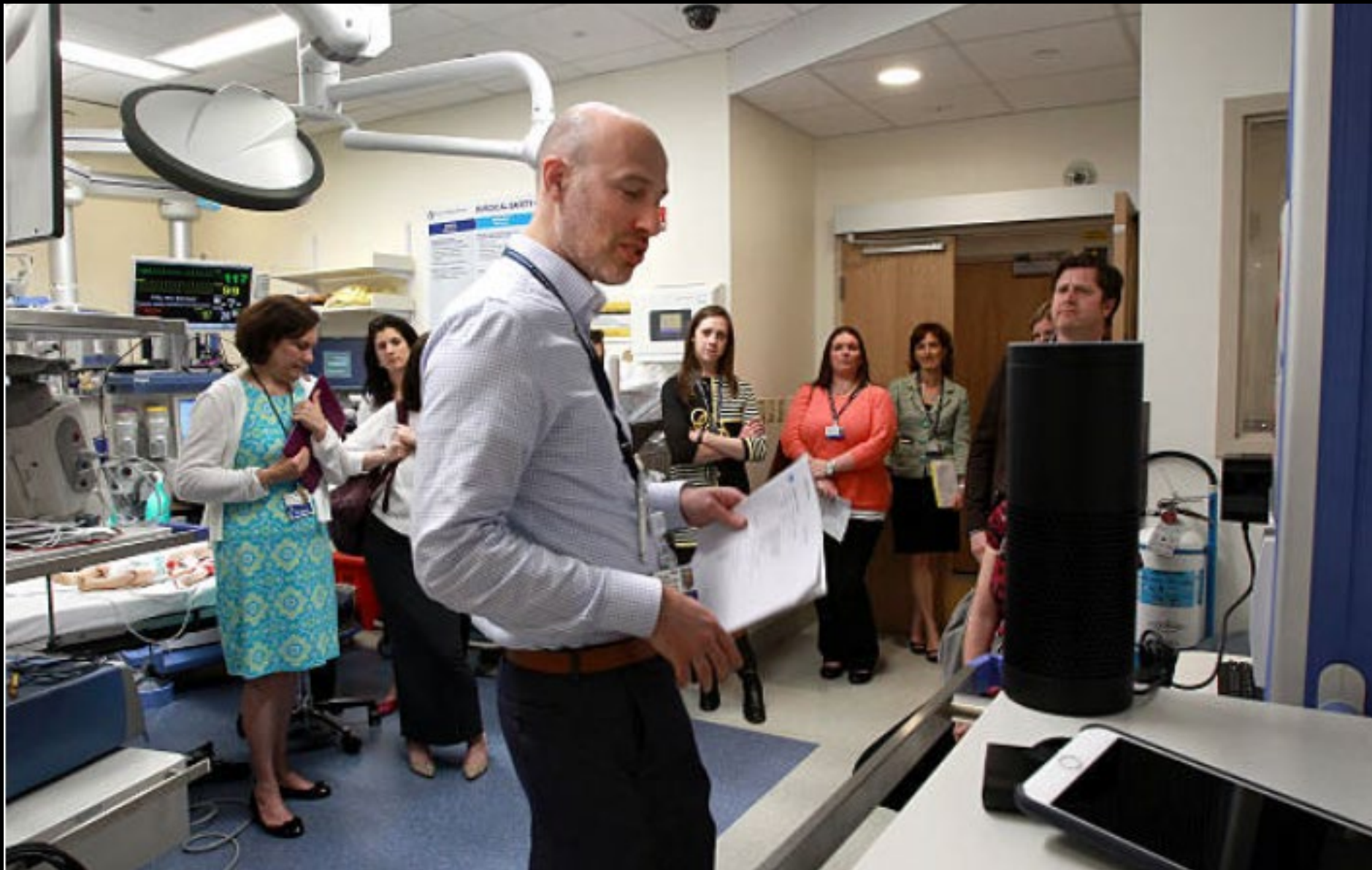


HAVEN

Amazon and Healthcare



HIPAA-Complaint Intelligent Agents



The Next Competitor for Amazon ?

Walgreens



Microsoft

Economies of Scale and Convenience Come to Primary Care



Turning Data Into Decisions



“Data!, Data!, Data!”

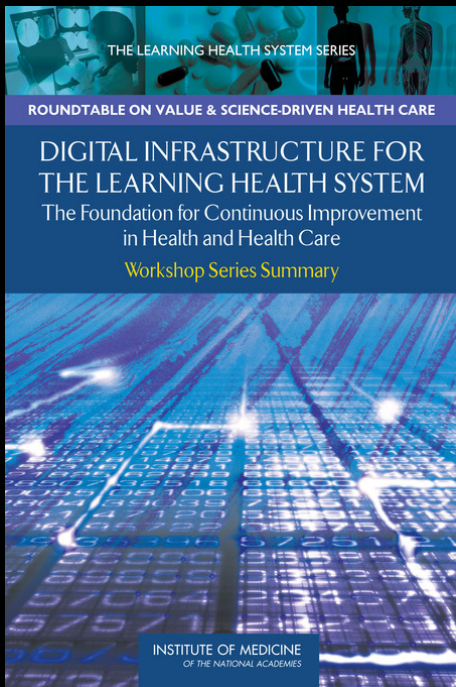
Holmes cried impatiently

“I can’t make bricks without clay.”

The Adventure of the Copper Beeches

Sir Arthur Conan Doyle

Strand magazine June 1892



THE LEARNING HEALTH SYSTEM SERIES

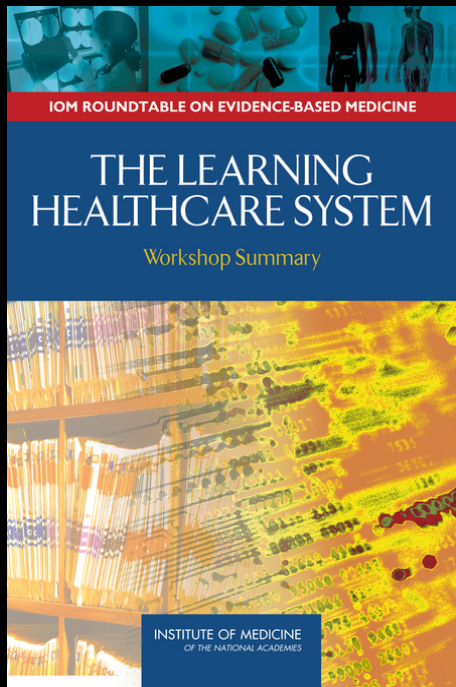
ROUNDTABLE ON VALUE & SCIENCE-DRIVEN HEALTH CARE

DIGITAL INFRASTRUCTURE FOR THE LEARNING HEALTH SYSTEM

The Foundation for Continuous Improvement in Health and Health Care

Workshop Series Summary

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

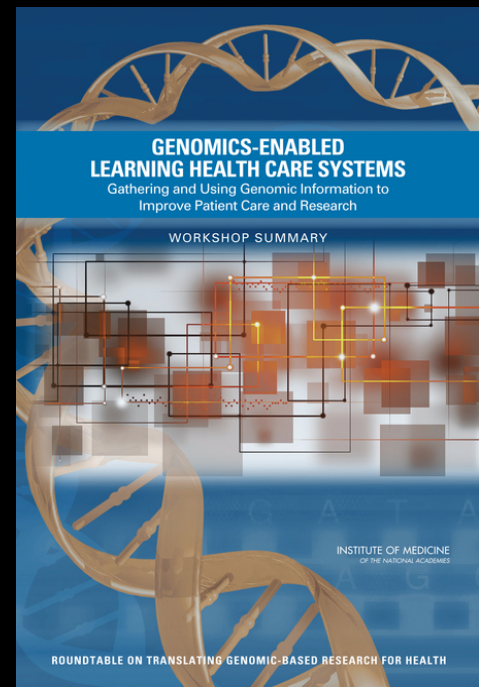


IOM ROUNDTABLE ON EVIDENCE-BASED MEDICINE

THE LEARNING HEALTHCARE SYSTEM

Workshop Summary

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES



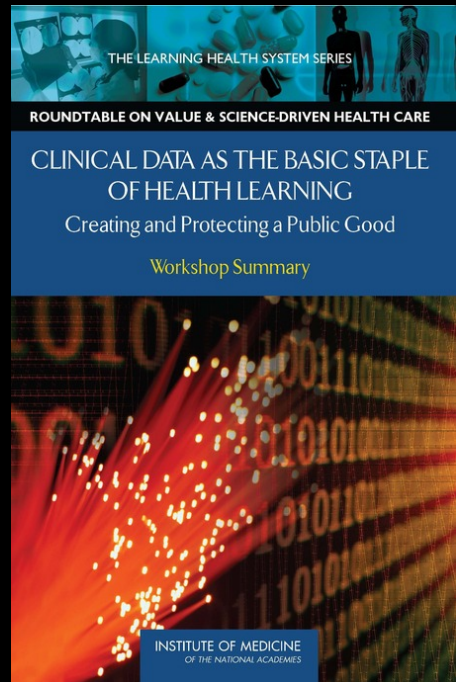
GENOMICS-ENABLED LEARNING HEALTH CARE SYSTEMS

Gathering and Using Genomic Information to Improve Patient Care and Research

WORKSHOP SUMMARY

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

ROUNDTABLE ON TRANSLATING GENOMIC-BASED RESEARCH FOR HEALTH



THE LEARNING HEALTH SYSTEM SERIES

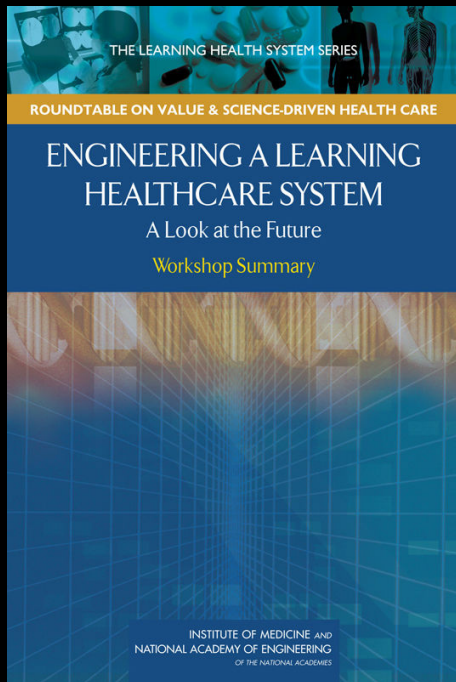
ROUNDTABLE ON VALUE & SCIENCE-DRIVEN HEALTH CARE

CLINICAL DATA AS THE BASIC STAPLE OF HEALTH LEARNING

Creating and Protecting a Public Good

Workshop Summary

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES



THE LEARNING HEALTH SYSTEM SERIES

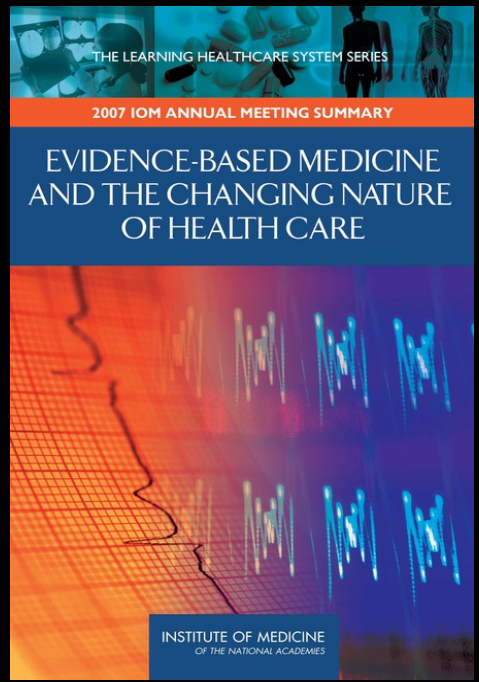
ROUNDTABLE ON VALUE & SCIENCE-DRIVEN HEALTH CARE

ENGINEERING A LEARNING HEALTHCARE SYSTEM

A Look at the Future

Workshop Summary

INSTITUTE OF MEDICINE AND
NATIONAL ACADEMY OF ENGINEERING
OF THE NATIONAL ACADEMIES



THE LEARNING HEALTHCARE SYSTEM SERIES


2007 IOM ANNUAL MEETING SUMMARY

EVIDENCE-BASED MEDICINE AND THE CHANGING NATURE OF HEALTH CARE

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Now Comes the Hard Part!

**Driving Precision Medicine and Data-Driven Healthcare
Into Routine Clinical Practice**



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



**Welcome to
The World of
Biomedical Research
and
Healthcare Information Systems**

The Health Information Supply Chain

- **fragmented, disconnected, incomplete and inaccurate data**
- **incompatible data formats as barrier to data integration and sharing**
- **obstacles to EHR integration of new data classes (multi-Omics; wearables; IoMT)**
- **legislative barriers to data transfer based on well intentioned privacy protections (HIPAA)**
- **organizational, economic and cultural barriers to open data sharing**
- **static episodic snap shots of complex dynamic systems (patients and delivery channels)**

Precision Medicine and Digital Health: Building a Learning Healthcare System

**qualitative,
descriptive
information of
variable quality and
provenance**



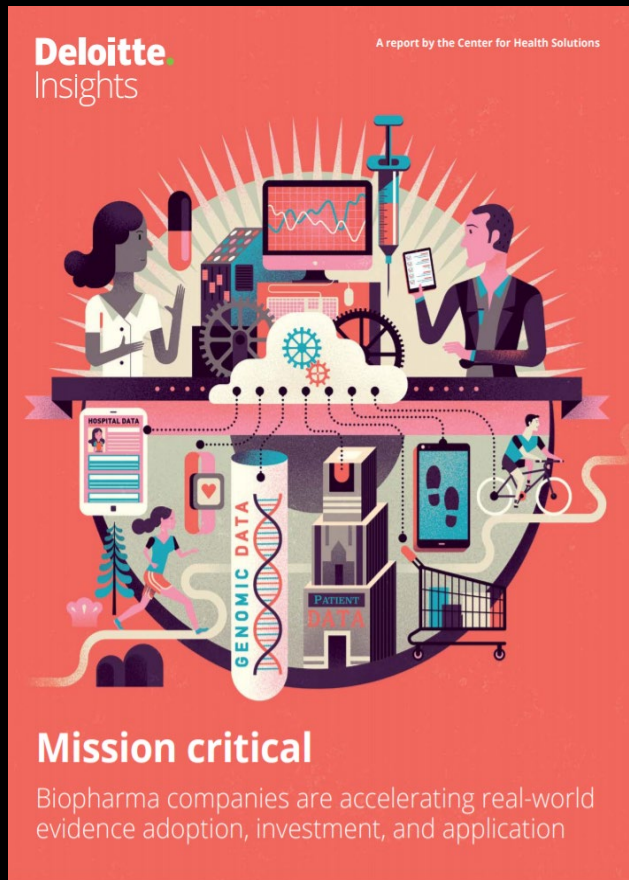
**quantitative data
of known
provenance and
validated quality**

**complex ecosystem
of largely
unconnected
data sources**



**evolving,
inter-connected
networks of data
sources for robust
decisions and
improved care**

The Increased Importance of Real World Data (RWD) and Evidence (RWE)



- **expanded payer requirements to demonstrate efficacy/utility/value in intended-use population(s) with different characteristics to trial population(s) studied in investigational clinical trials**
 - **age, co-morbidities, polypharmacy**
 - **clinical setting (AMCs, community hospitals, primary care)**
- **analyze treatment outcomes in sub-populations**
- **quantify treatment outcomes for value-based contracting**

Bloomberg Businessweek

December 16, 2019

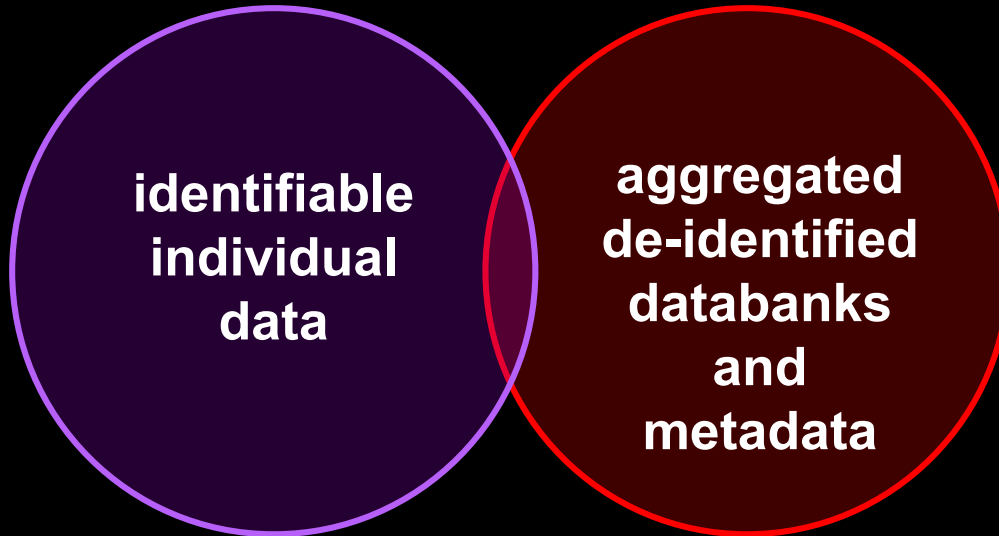
Alexa, What's Privacy?

"Smart" devices
are listening—and
so are humans



Protection and Privacy Provisions for Personal Healthcare Data

- informed consent
- legal provisions/penalties for breach

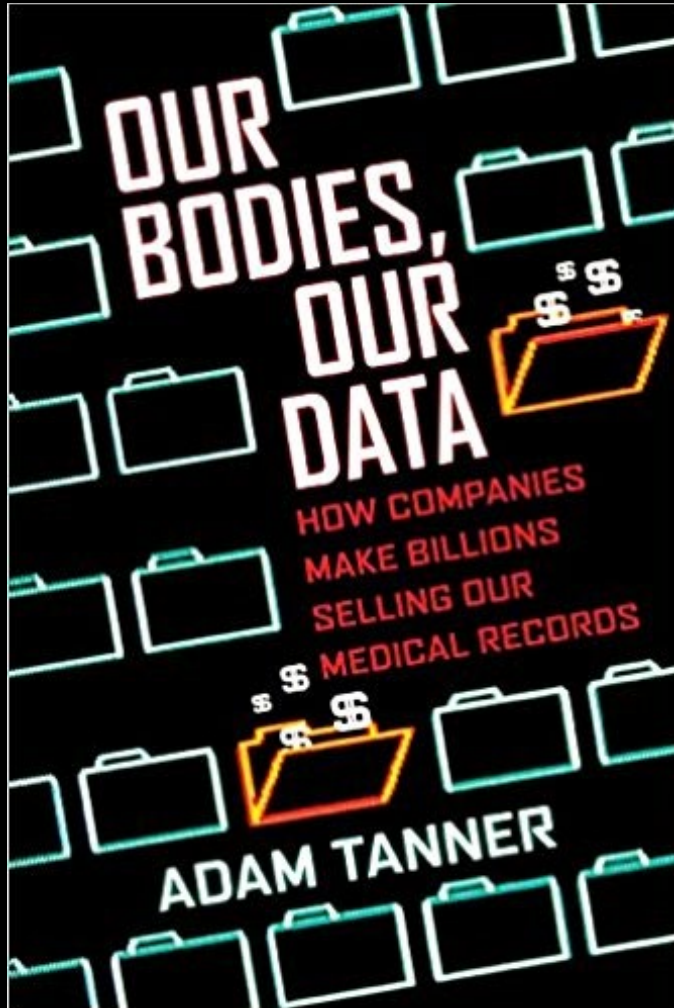


- variable levels of consent
- probabilistic, multi-parameter individual 'match'

Google Ascension Partnership Fuels HIPAA Privacy Debate(1/2020)



Data Brokers and ‘Selling-On’



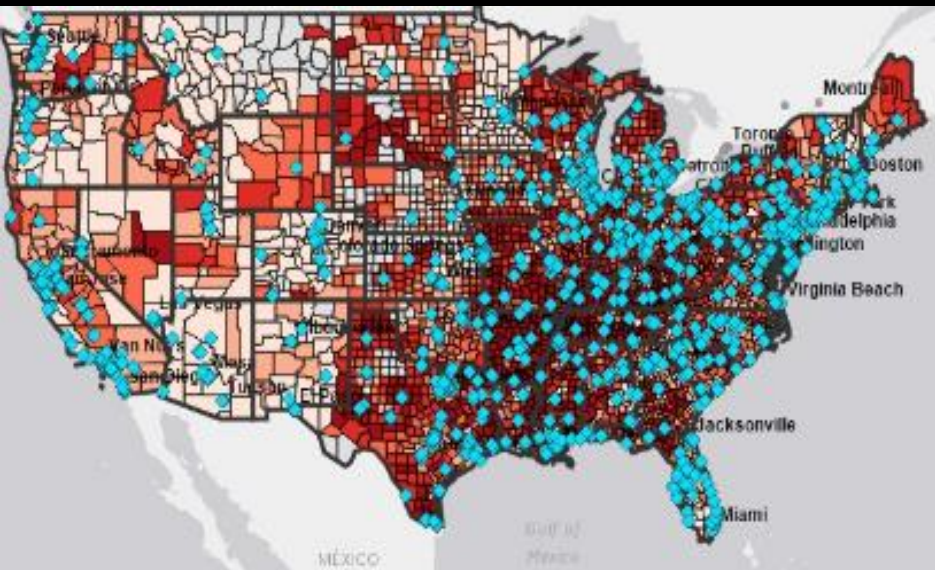
23andMe, moving beyond consumer DNA tests, is building a clinical trial recruitment business

By REBECCA ROBBINS @rebeccadrobbins / SEPTEMBER 26, 2019



National Security Implications of Genome Data on Populations

Population Databanks



Individual Profiles



Foreign Access to Data



Data Security





OFFICE OF THE SECRETARY OF DEFENSE
1000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-1000

DEC 20 2019

MEMORANDUM FOR: SEE DISTRIBUTION

SUBJECT: Direct-to-Consumer Genetic Testing Advisory for Military Members

It has come to the attention of the DoD that some direct-to-consumer (DTC) genetic testing companies are encouraging DoD personnel to purchase genetic ancestry and health information through the offering of military discounts or other incentives. These DTC genetic tests are largely unregulated and could expose personal and genetic information, and potentially create unintended security consequences and increased risk to the joint force and mission.

Exposing sensitive genetic information to outside parties poses personal and operational risks to Service members. DTC genetic tests that provide health information have varying levels of validity, and many are not reviewed by the Food and Drug Administration before they are offered, meaning they may be sold without independent analysis to verify the claims of the seller. Possible inaccuracies pose more risk to DoD military personnel than the public due to Service member requirements to disclose medical information that affects readiness (see DoD Instruction 6025.19, "Individual Medical Readiness"). Testing outside the Military Health System is unlikely to include a clear description of this risk.

Moreover, there is increased concern in the scientific community that outside parties are exploiting the use of genetic data for questionable purposes, including mass surveillance and the ability to track individuals without their authorization or awareness.

Until notified otherwise, DoD military personnel are advised to refrain from the purchase and/or use of DTC genetic services.

Joseph D. Kernan
Under Secretary of Defense for Intelligence

James N. Stewart
Assistant Secretary of Defense for Manpower
and Reserve Affairs, Performing the Duties
of the Under Secretary of Defense for
Personnel and Readiness



Bayesian approach to incorporating different types of biomedical knowledge bases into information retrieval systems for clinical decision support in precision medicine

Saeid Balaneshinkordan, Alexander Kotov*

Department of Computer Science, Wayne State University, Detroit, MI 48202, USA

How to Read Articles That Use Machine Learning Users' Guides to the Medical Literature

Yun Liu, PhD; Po-Hsuan Cameron Chen, PhD; Jonathan Krause, PhD; Lily Peng, MD, PhD

Reinforcement learning in artificial and biological systems

Emre O. Neftci^{1,3} and Bruno B. Averbeck^{2,3*}

Human Molecular Genetics, 2018, Vol. 27, No. R1 R63–R71

doi: 10.1093/hmg/ddy115
Advance Access Publication Date: 10 April 2018
Invited Review

INVITED REVIEW

Deep learning of genomic variation and regulatory network data

Amalio Telenti^{1,*}, Christoph Lippert², Pi-Chuan Chang³ and Mark DePristo³

¹Scripps Translational Science Institute, The Scripps Research Institute, La Jolla, CA 92037, USA, ²Max Delbrück Center for Molecular Medicine, 13125 Berlin, Germany and ³Google Inc., Mountain View, CA 94043, USA

*To whom correspondence should be addressed at: The Scripps Research Institute, La Jolla, CA 92037, USA. Tel: +1 8582324424; Email: atelenti@scripps.edu

High-performance medicine: the convergence of human and artificial intelligence

Eric J. Topol

Predicting the clinical impact of human mutation with deep neural networks

Lakshman Sundaram^{1,2,3,6}, Hong Gao^{1,6}, Samskruthi Reddy Padigepati^{1,13}, Jeremy F. McRae¹, Yanjun Li³, Jack A. Kosmicki^{1,4}, Nondas Fritzilas¹, Jörg Hakenberg¹, Anindita Dutta¹, John Shon¹, Jinbo Xu⁵, Serafim Batzoglou¹, Xiaolin Li³ and Kyle Kai-How Farh^{1,4*}

Deep learning sequence-based ab initio prediction of variant effects on expression and disease risk

Jian Zhou^{1,2,3}, Chandra L. Theesfeld¹, Kevin Yao³, Kathleen M. Chen³, Aaron K. Wong³ and Olga G. Troyanskaya^{1,3,4*}

Opportunities and obstacles for deep learning in biology and medicine

Travers Ching^{1,1}, Daniel S. Himmelstein², Brett K. Beaulieu-Jones³, Alexandr A. Kalinin⁴, Brian T. Do⁵, Gregory P. Way², Enrico Ferrero⁶, Paul-Michael Agapow⁷, Michael Zietz², Michael M. Hoffman^{8,9,10}, Wei Xie¹¹, Gail L. Rosen¹², Benjamin J. Lengerich¹³, Johnny Israeli¹⁴, Jack Lanchantin¹⁷, Stephen Woloszynek¹², Anne E. Carpenter¹⁸, Avanti Shrikumar¹⁵, Jinbo Xu¹⁹, Evan M. Cofer^{20,21}, Christopher A. Lavender²², Srinivas C. Turaga²³, Amr M. Alexandari¹⁵, Zhiyong Lu²⁴, David J. Harris²⁵, Dave DeCaprio²⁶, Yanjun Qi¹⁷, Anshul Kundaje^{15,16}, Yifan Peng²⁴, Laura K. Wiley²⁷, Marwin H. S. Segler²⁸, Simina M. Boca²⁹, S. Joshua Swamidass³⁰, Austin Huang³¹, Anthony Gitter^{32,33} and Casey S. Greene²

AAIH Founding Members: Unified Vision for Healthcare



BEYOND LIMITS



Insilico Medicine
英科智能



Numerate

NURITAS



University of
Pittsburgh

Progenics
Pharmaceuticals



RECURSION



90+ Startup AI Companies in Healthcare

INSIGHTS & RISK MANAGEMENT



HEALTHCARE RESEARCH



MEDICAL IMAGING & DIAGNOSTICS



LIFESTYLE MANAGEMENT & MONITORING



NUTRITION



EMERGENCY ROOM & HOSPITAL MANAGEMENT



VIRTUAL ASSISTANTS



MISCELLANEOUS



MENTAL HEALTH



DRUG DISCOVERY



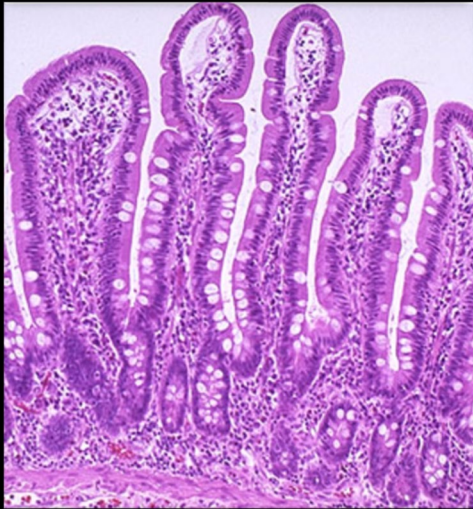
WEARABLES



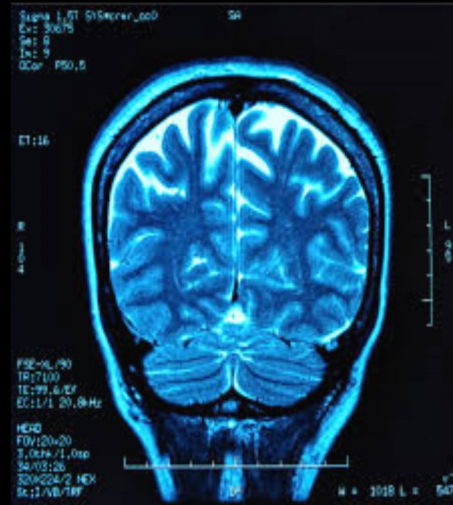
istock.com/hilch

Machine Learning and Image Analysis in Clinical Medicine

pathology



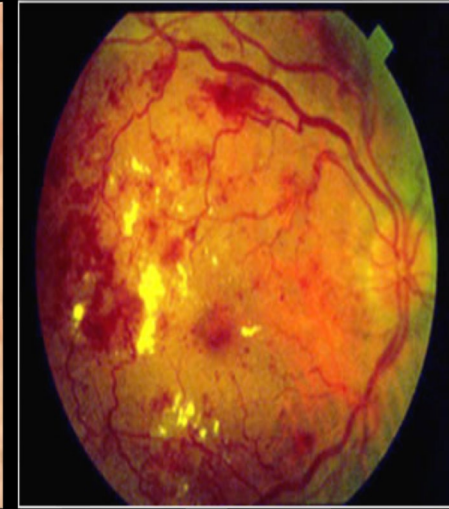
radiology



dermatology



ophthalmology



- large scale training sets and classification parameters
- standardized, reproducible and scalable
- 260 million images/day for \$1000 GPU

Just What the Data Ordered

**Machine Intelligence and Algorithms for
Clinical Diagnosis and Treatment Decisions**

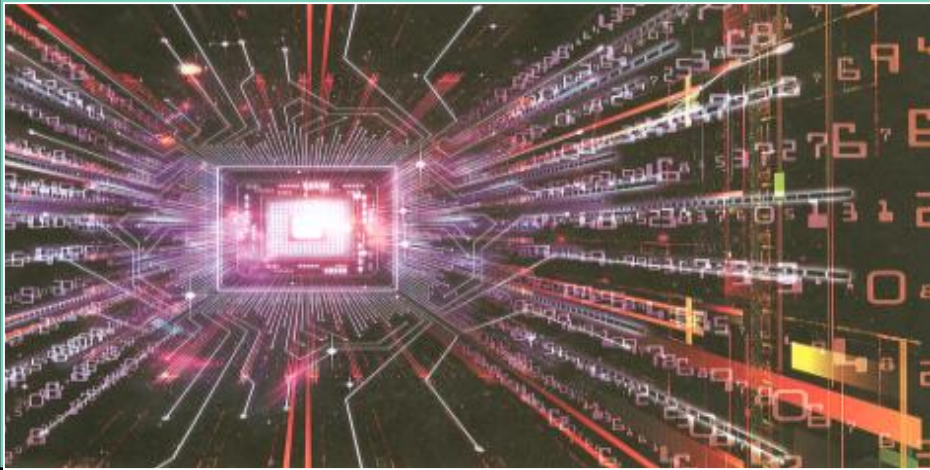
Black Box Medicine?

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

Data Deluge



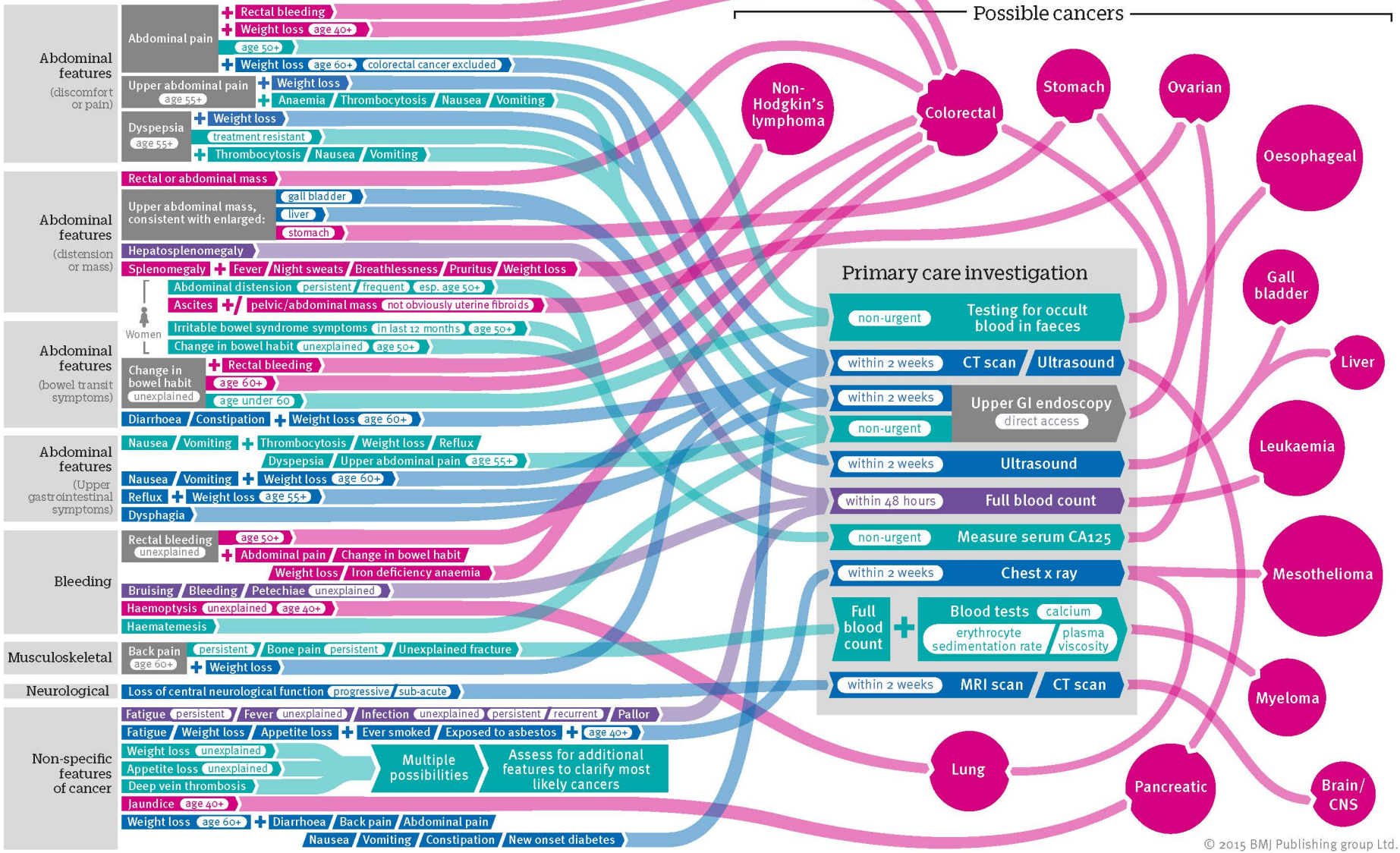
Cognitive Bandwidth Limits



Automated Analytics and Decision Support



Facile Formats for Actionable Decisions



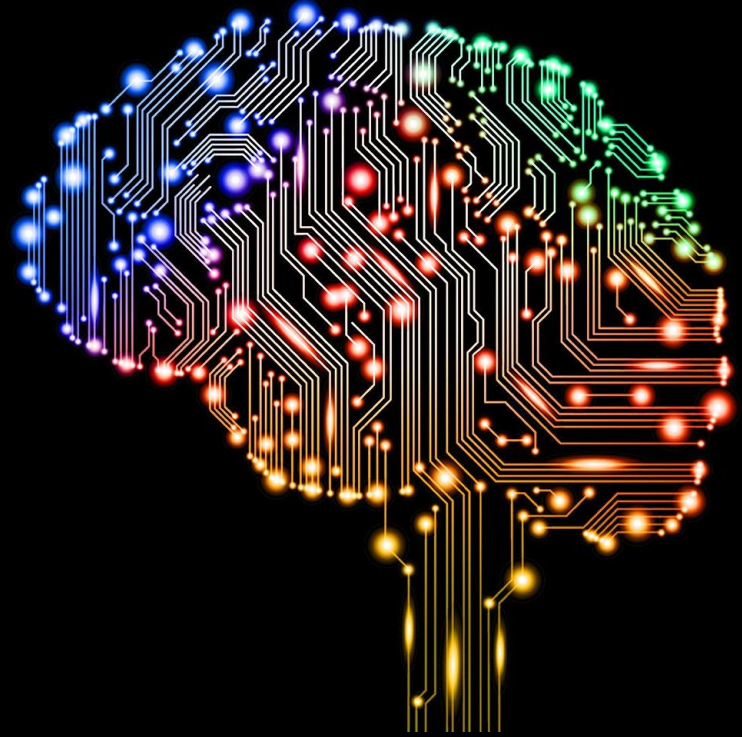
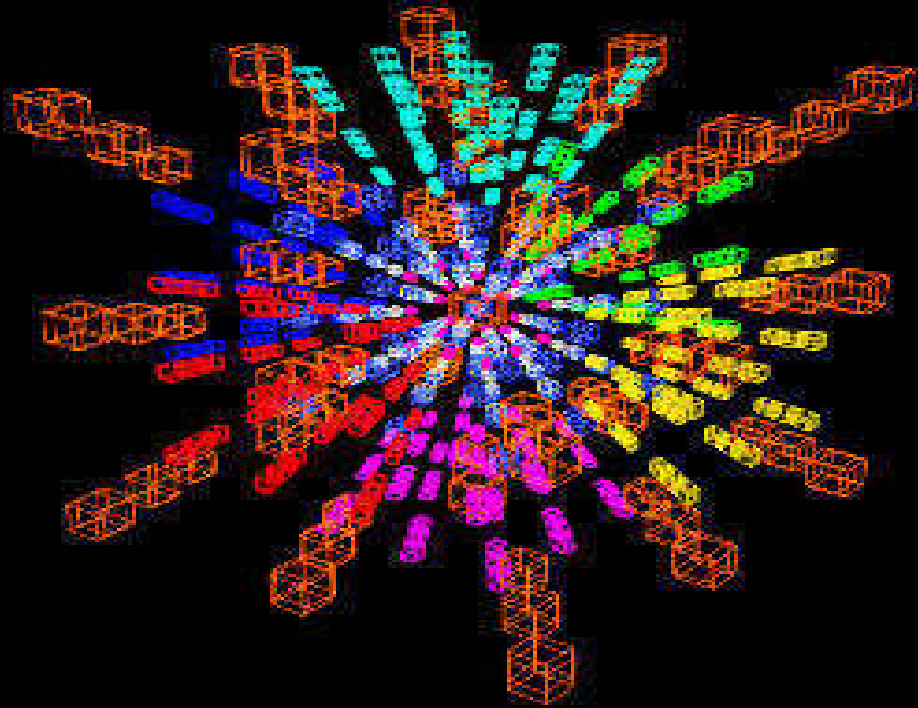
The Future of 'Automated Search' and 'Retrieval'

Deep Understanding of Content and Context

Collapse Time to Decision: Intelligence at Ingestion

**Automated and Proactive Analytics:
Why Wait for the Slow Brain to Catch Up to the Fast Machine**

Automated Context: Data Finding Data “Intelligence at Ingestion”



**Feature
Extraction
and
Classification**



**Context
Analysis**

**Persistent
Context**



- **Relevance
Mapping**
- **Learning
Systems**



- **Situational
Awareness**
- **Rapid,
Robust
Decisions**



Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)

Discussion Paper and Request for Feedback



Machine Learning (ML), Artificial Intelligence (AI) and Healthcare

- **which clinical specialties/processes will be at risk of replacement by ML-AI and when?**
- **how will professional competencies in using ML-AI decision-support tools be developed and sustained?**
 - **MD curriculum, CME**
 - **non-medical data science professionals**
- **what new malpractice liabilities will emerge by failure to use/interpret ML-AI platforms**

The Future of Work and The Future Workforce



COUNCIL ON FOREIGN RELATIONS

Independent Task Force Report No. 76

The Work Ahead Machines, Skills, and U.S. Leadership in the Twenty-First Century

John Engler and Penny Pritzker, Chairs
Edward Alden, Project Director
Laura Taylor-Kale, Deputy Project Director

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

CONSENSUS STUDY REPORT

THE
NEXT GENERATION OF
BIOMEDICAL AND
BEHAVIORAL SCIENCES
RESEARCHERS

Breaking Through

PROCEEDINGS OF A WORKSHOP

**LEARNING FROM THE SCIENCE
OF COGNITION AND PERCEPTION
FOR DECISION MAKING**

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

**Cognitive
Diversity:
AI & The
Future
of Work**

AI

TATA COMMUNICATIONS

World Health Organization

Global strategy on
human resources
for health:
Workforce 2030

PROCEEDINGS OF A WORKSHOP

MOTIVATION NATIONAL ARTIFICIAL SKILLS
RECRUITMENT SECURITY INTELLIGENCE GROWTH
ANALYSIS TEAM SCIENCE KNOWLEDGE CAREER
COMMUNICATION ABILITIES NETWORK AUTOMATION
SELECTION EXPERIENCE INTELLIGENCE SENSEMAKING
GROWTH MANAGEMENT ANALYSIS TRAINING
DIVERSITY CAREER LEADERSHIP ABILITIES
WORKFORCE SKILLS TEAMWORK EDUCATION

**WORKFORCE DEVELOPMENT
AND INTELLIGENCE
ANALYSIS FOR NATIONAL
SECURITY PURPOSES**

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

New Patterns of Learning



“Digital Darwinism”: A Looming Digital Divide

- **understanding data structure and its productive application/customization for improved decisions and clinical outcomes will become a critical institutional competency**
- **major skill gaps and personnel shortages in biomedicine**
- **training of a new cadre of data scientists (medical and non-medical)**
- **institutions lacking adequate computational infrastructure and critical mass in data analytics will suffer ‘cognitive starvation’ and relegation to competitive irrelevance**



Welcome to the Age of
One-Shot Miracle Cures
That Can Cost Millions

MIT
Technology
Review

T The precision
medicine issue

VOL. 321 NOV/DEC 2018 \$9.99 USD \$10.99 CAD

**\$2 million
would save her life.
Could you pay?**



Should you?

Medicine is becoming hyper-personalized, hyper-accurate ... and hyper-unequal. »

The AIs taking over from
doctors

Curing cancer with
customized vaccines

How to plan your digital
afterlife

p. 22

p. 45

p. 78

Healthcare and the Washington Asylum



- aging demographics and the chronic disease burden
- Affordable Care Act
- “Medicare-for-All”
- drug prices and importation
- opioids, fentanyl(s), SUD, PTSD and suicide
- cybersecurity and data protection
- neglect of global public health as a national security risk
- ethical and legal issues for dual-use technologies



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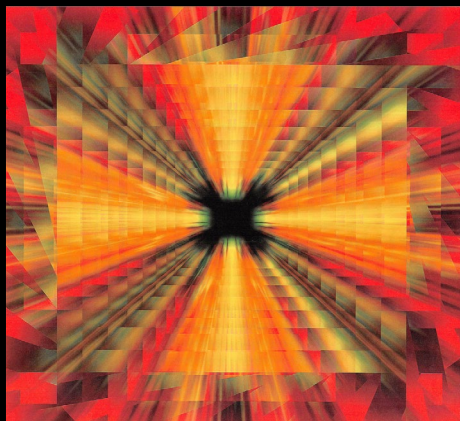


OUR MOST
VALUABLE
RESOURCE SITS
63 FEET AHEAD.

C241

The Evolution of Data-Intensive Precision Medicine

**Technology
Convergence
and Acceleration**



**Mapping
Geno-Phenotype
Complexity**



**Topology of
Biological
Information
Networks**



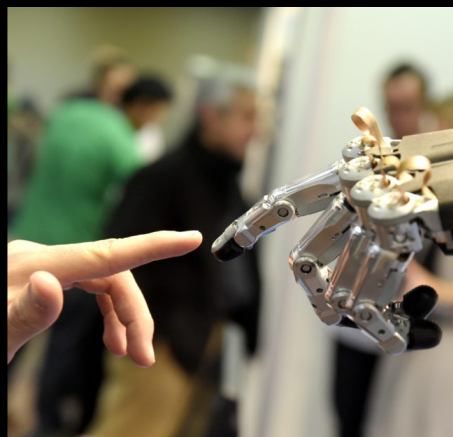
**V7
Big Data**



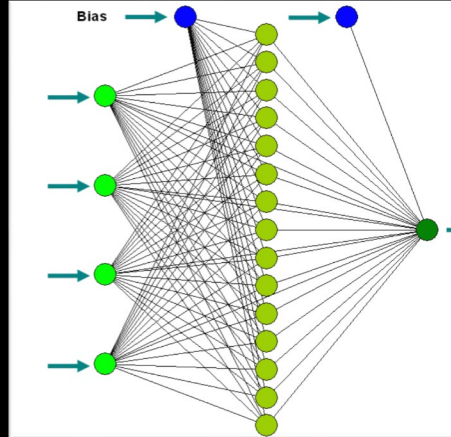
**Data Security
and Privacy**



**Robotics and Human
Machine Interactions**



**Artificial Intelligence
and
Decision Support**



**Public Policy:
Ethics, Risk and
Regulation**



The Evolution of Data-Intensive Precision Medicine

**Technology
Convergence
and Acceleration**



**Mapping
Geno-Phenotype
Complexity**



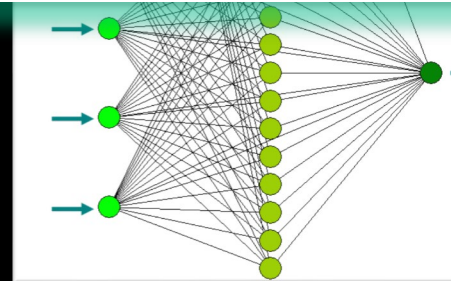
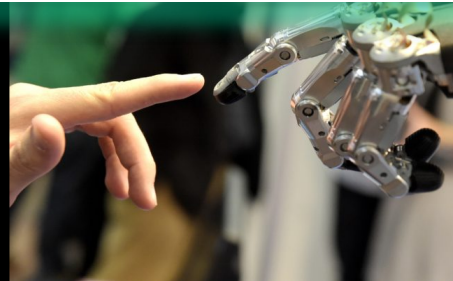
**Topology of
Biological
Information
Networks**



**V7
Big Data**



Slides Available @ <http://casi.asu.edu/presentations>



**Data Security
and Privacy**

**Robotics and Human
Machine Interactions**

**Artificial Intelligence
and
Decision Support**

**Public Policy:
Ethics, Risk and
Regulation**

Industry Career Experience



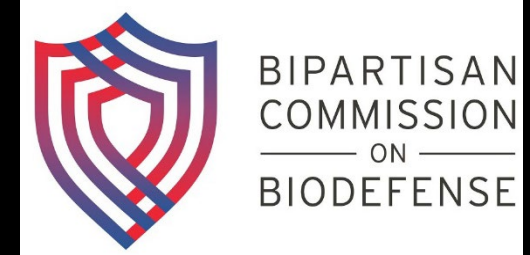
Engagement in National Policy Development in Science and Technology



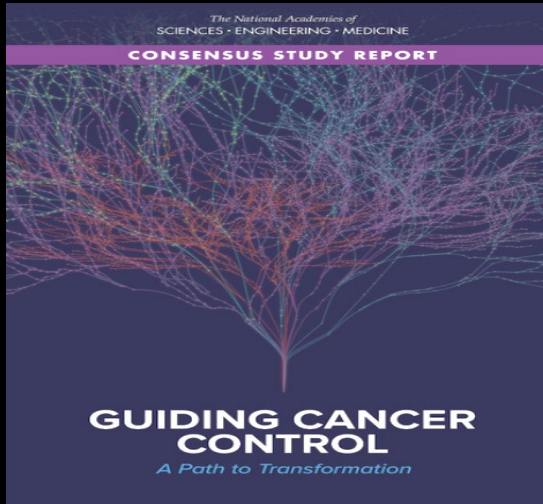
Defense Science Board



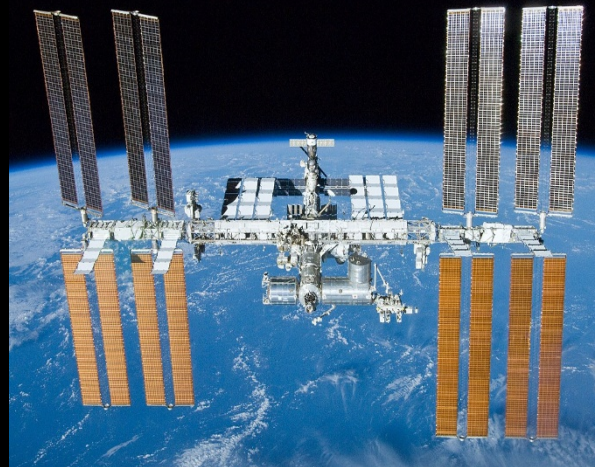
Global Forum on Microbial Threats



Biosecurity



National Academy of Medicine



NASA & Future of the ISS



National Biomarker Development Alliance

New

American

University

Toward 2025 and Beyond





- largest US public university
- fastest growth in research revenues of any US university

ASU Charter

ASU is a comprehensive **public research university**, measured not by whom it excludes, but by **whom it includes** and how they **succeed**; advancing **research and discovery** of public value; and assuming **fundamental responsibility** for the economic, social, cultural and overall health of the **communities** it serves.

Building Unique Value Propositions in Higher Education and Use-Inspired Research

A New American University: Use-Inspired Research on Complex Global Challenges

**Pragmatic
Engagement
with
“Real World
Problems”**

**Leverage
Technology
Convergence
and
Scale**

**Cultural
and
Organizational
Challenges**

“Urgency”

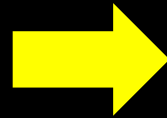
Competitiveness

**Focus, Resolve
Metrics and
Accountability**



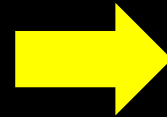
A New American University: A Purposeful, Radical Strategic Redesign

**Party
School**



**Strategic Premise That Many
Features of Contemporary Academia
Lack the Agility to Address
the Forces Reshaping Research
and Education**

**Silos
Subvert
Solutions**



**Ambitious Focus on
Cross-Disciplinary/Cross-Sector
R&D and
Use-Inspired Applications
for Major Unmet Needs**



Design of A New American University

- **15-year transition from a second-tier public university with reputation as a ‘party school’ to highly competitive rankings in both education and research**
- **radical nature of the changes in organization and internal culture would have been far difficult to implement in institutions with long established entrenched cultures and complacency**



Higher Education Research and Development (HERD) Rankings

ASU Rank versus Total Institutions in the NSF Analysis

Total Research Expenditures:

44 of 903

**Total Research Expenditures among
Institutions without a Medical School:**

8 of 747

**HHS (including NIH) Funded Expenditures
among Institutions without a Medical School:**

8 of 417

NSF Funded Expenditures:

22 of 594

Transdisciplinary

3 of 253



Higher Education Research and Development (HERD) Rankings

DOE Funded Expenditures:

28 of 345

NASA Funded Expenditures:

8 of 430

Engineering Expenditures:

18 of 395

Electrical, Electronic, and Communications

Engineering: 9 of 283

Geological and Earth Sciences:

2 of 360

National Science Foundation (NSF)

Higher Education Research and Development (HERD) Rankings

Total Research Expenditures: **44 of 876** ahead of



BROWN



PRINCETON UNIVERSITY

Caltech



University of Colorado Boulder



Total Research Expenditures among Institutions without a Medical School: **9 of 718** ahead of

Caltech



PRINCETON UNIVERSITY

Carnegie Mellon University

THE ROCKEFELLER UNIVERSITY

Science for the benefit of humanity



THE SCRIPPS RESEARCH INSTITUTE



UNIVERSITY OF NOTRE DAME

Non-Medical School Expenditures: **22 of 876** ahead of

Stanford University



COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK



RUTGERS

UNIVERSITY | NEW BRUNSWICK



THE UNIVERSITY OF NORTH CAROLINA
at CHAPEL HILL



#1



in the U.S. for innovation

ASU ahead of Stanford and MIT

- U.S. News & World Report

5 years, 2016-2020

Top 10

in the world for patents

**among universities
granted U.S. patents**

**U.S. National Academy of
Inventors and the Intellectual
Property Owners Association**



- **over 100 new spin-out companies launched from ASU research since 2010**
- **dedicated facility (SkySong) as incubator for translational R&D**
- **40 start-up companies currently reside in the facility**

Top producer of Fulbright students

—Chronicle of Higher Education, 2019

Graduate, Education



A best-in-U.S.: health and well-being programs for students

—Active Minds, 2018

#2

online undergraduate degree program in the nation

—U.S. News & World Report, 2019

Education, U.S. News & World Report



Top 5 campus for sustainability

— Sierra Club, 2018

