The Biopharmaceutical Industry and the Healthcare Ecosystem: Challenges and Opportunities

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

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The Health Service System and the Business of Healthcare
HSM 502 Spring 2020 McCord Hall 270
6 February 2020

Challenges Facing U.S. Healthcare

Balancing Infinite Demand versus Finite Resources

**From Volume-Based (Do More-Bill More)
Fee-for-Service to Value-Based Care**

**From Reactive, Episodic Interventions in Advanced Disease
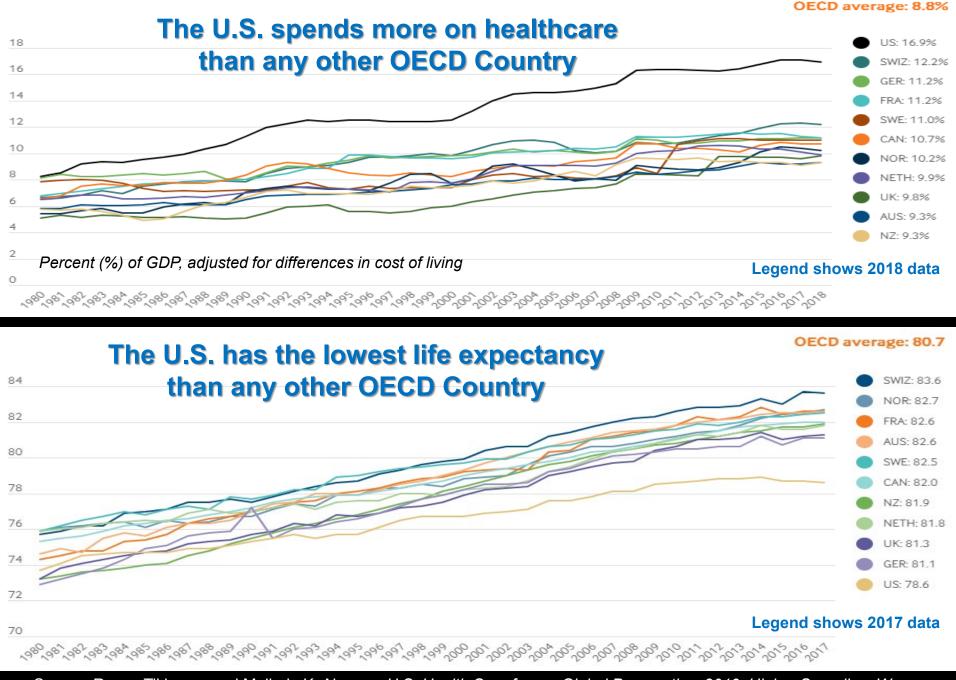to Proactive Identification of Disease Risk and Earlier Detection**

**Improving Clinical Outcomes at Lower Cost
and Optimizing Wellness**

Biomedical Research and Healthcare Delivery: Ecosystems with Pervasive Embedded Inefficiencies Ripe for Creative Destruction

- slow translation of research for patient benefit

- unstainable cost of care

- fragmented and uncoordinated duplication, waste and administrative bloat

- poor use of available information

- slow adoption of advanced IT systems relative to other sectors

- public dissatisfaction and intensified political engagement (Rx, IT)

- health data breaches, privacy violations: techlash

The Healthcare Ecosystem

- **slow technology diffusion and wide variation in clinical care patterns**

- **disparities in access and availability of care**

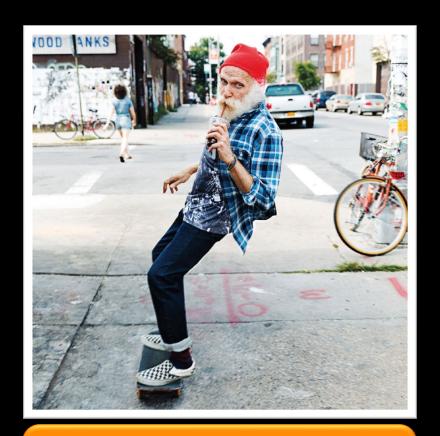   - **national (G20) and international (MIC, LIC)**

The U.S. spends more on healthcare than any other OECD Country

OECD average: 8.8%

Percent (%) of GDP, adjusted for differences in cost of living

Legend shows 2018 data

- US: 16.9%
- SWIZ: 12.2%
- GER: 11.2%
- FRA: 11.2%
- SWE: 11.0%
- CAN: 10.7%
- NOR: 10.2%
- NETH: 9.9%
- UK: 9.8%
- AUS: 9.3%
- NZ: 9.3%

The U.S. has the lowest life expectancy than any other OECD Country

OECD average: 80.7

Legend shows 2017 data

- SWIZ: 83.6
- NOR: 82.7
- FRA: 82.6
- AUS: 82.6
- SWE: 82.5
- CAN: 82.0
- NZ: 81.9
- NETH: 81.8
- UK: 81.3
- GER: 81.1
- US: 78.6

Source: Roosa Tikkanen and Melinda K. Abrams, *U.S. Health Care from a Global Perspective, 2019: Higher Spending, Worse Outcomes?* (Commonwealth Fund, Jan. 2020). https://doi.org/10.26099/7avy-fc29

Health is a One-Sided Marketplace

- **patients receive and pay for a service without typically knowing the price beforehand**
- **no financial tools to spread cost overtime**
  - **ct. mortgage, car loan**

The US Healthcare System: Information Asymmetries

- **patients (consumers) versus payers and providers**
  - decisions about care selection and cost
- **payers versus providers**
  - cost control in care decisions
- **patients and providers versus payers**
  - coverage determinations, OOP-copays, pre-existing conditions
- **patients and payers versus innovators and providers**
  - transparency of cost and effectiveness (outcomes)
- **innovators versus payers and providers**
  - direct cost and indirect cost of integration into workflow
  - generalizability of RTC data to real world effectiveness (RWE)

The Demographics of an Aging Society:
Clinical and Economic Challenges to U.S. Healthcare
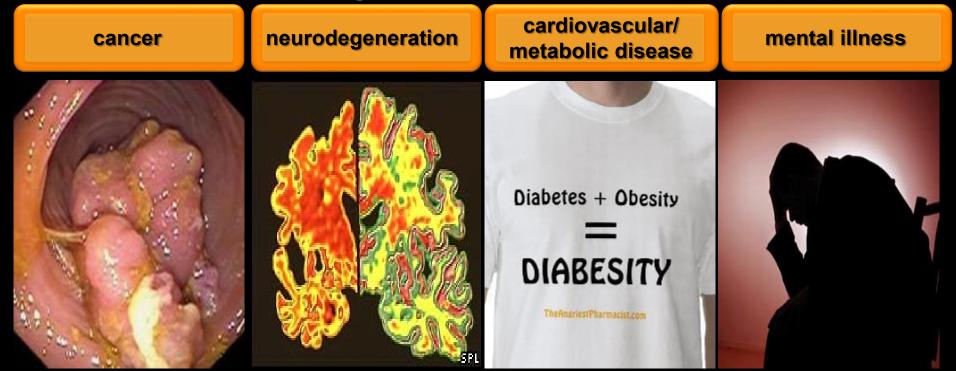
wellness with longevity and high QOL OR **multiple co-morbidities and low QOL**

?　　　　　　　　**?**

The Growing Burden of Chronic Disease

cancer	neurodegeneration	cardiovascular/ metabolic disease	mental illness

Diabetes + Obesity = DIABESITY
TheAngriestPharmacist.com

- economic unsustainability of current care systems

- insufficient clinical resources and infrastructure

- cost of innovation (Rx prices as political target)

- future growth in public and political dissatisfaction with lack of progress in major solutions

The Growing Burden of Chronic Disease
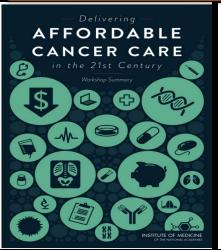
| cancer | neurodegeneration | cardiovascular/ metabolic disease | me...llness |

VALUE

- ec... ...ty of current care systems
- ... resources and infrastructure
- ...ovation (Rx prices as political target)
- future growth in public and political dissatisfaction with lack of progress in major solutions
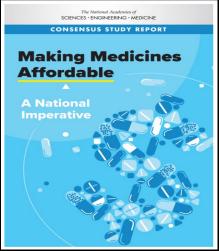
Value

- **clinical outcomes and QOL**
  - QALY, DALY
  - socio-economic metrics: faster return to workplace/school
  - reduced demands on societal support services

- **'downstream' future cost/benefit calculus**
  - reduced demand for future resource use

    versus

  - probability of increased resource use from suboptimal Rx efficacy/increased comorbidity risk
  - cost and management of longer-term Rx toxicity risks (cf. oncology)

Cancer Treatment Cost

Value Framework
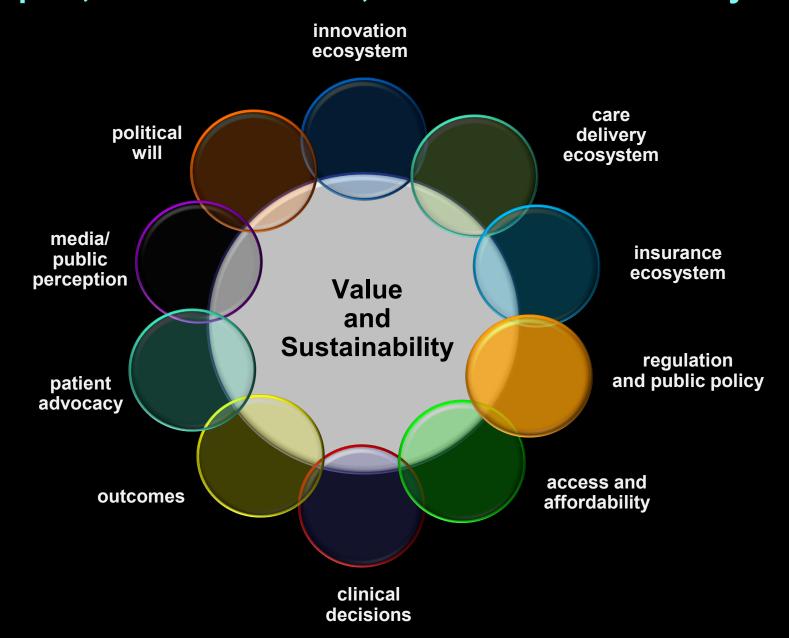
Value

- **disincentives for innovation uptake**

- **cost of adoption of new clinical protocols/HCP training**

- **institutional/HCP revenue loss from displacement of more expensive procedures/facilities utilization**

Healthcare:
A Complex, Multidimensional, Multi-stakeholder Ecosystem

Infinite Demand and No Limits to Care

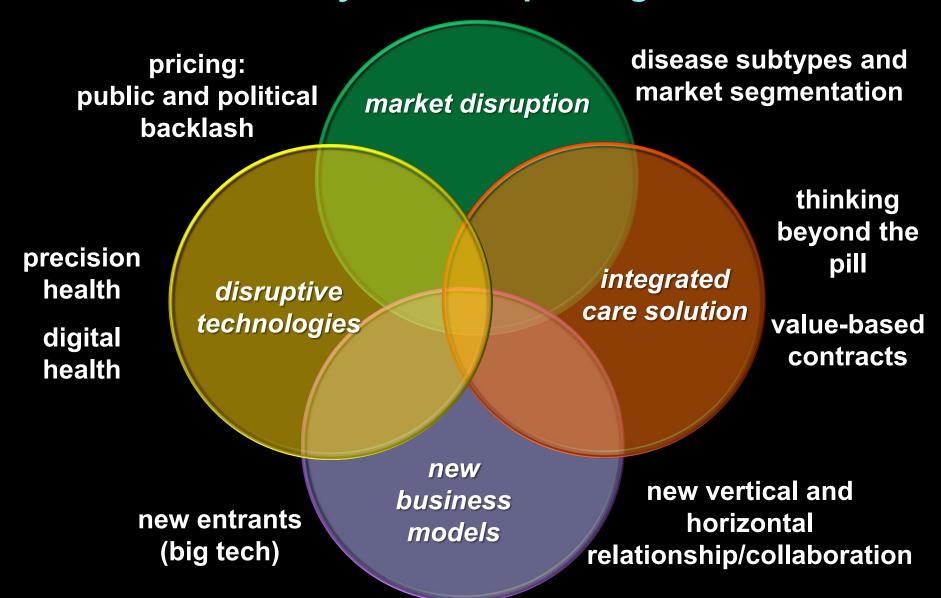**Welcome to the Age of One-Shot Miracle Cures That Can Cost Millions**

MIT Technology Review — The precision medicine issue

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

Should you?

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

Global Biopharmaceuticals:
Highest R&D Investment as % Sales of Any Industry Sector
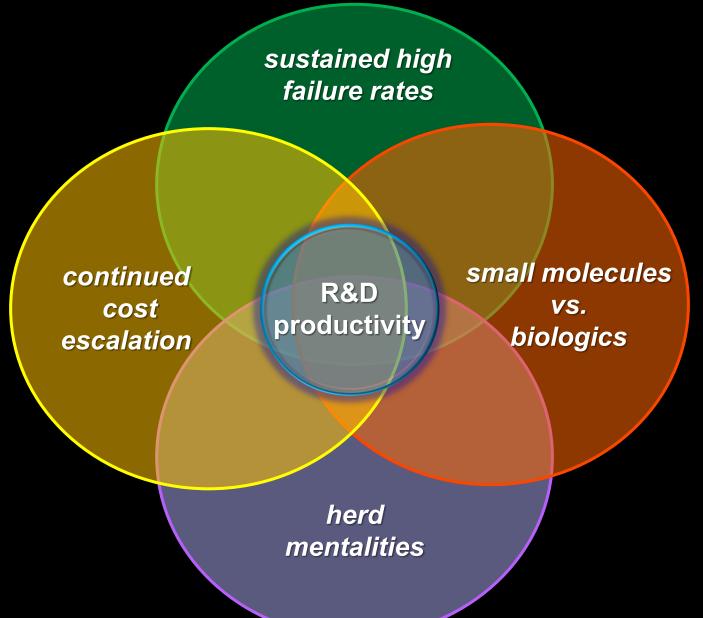
		Rx Sales*	R&D spend*
1	**Pfizer** NEW YORK, NEW YORK [PFIZER.COM]	$45.302	$7.962
2	**Roche** BASEL, SWITZERLAND [ROCHE.COM]	$44.552	$9.803
3	**Novartis** BASEL, SWITZERLAND [NOVARTIS.COM]	$43.481	$8.154
4	**Johnson & Johnson** NEW BRUNSWICK, NEW JERSEY [JNJ.COM]	$38.815	$8.446
5	**Merck & Co.** KENILWORTH, NEW JERSEY [MERCK.COM]	$37.353	$7.908
6	**Sanofi** PARIS, FRANCE [SANOFI.COM]	$35.121	$6.227
7	**AbbVie** NORTH CHICAGO, ILLINOIS [ABBVIE.COM]	$32.067	$5.093
8	**GlaxoSmithKline** BRENTFORD, ENGLAND [GSK.COM]	$30.645	$4.987
9	**Amgen** THOUSAND OAKS, CALIFORNIA [AMGEN.COM]	$22.533	$3.657
10	**Gilead Sciences** FOSTER CITY, CALIFORNIA [GILEAD.COM]	$21.677	$3.897

Source: EvaluatePharma® May 2019, Evaluate Ltd, www.evaluate.com
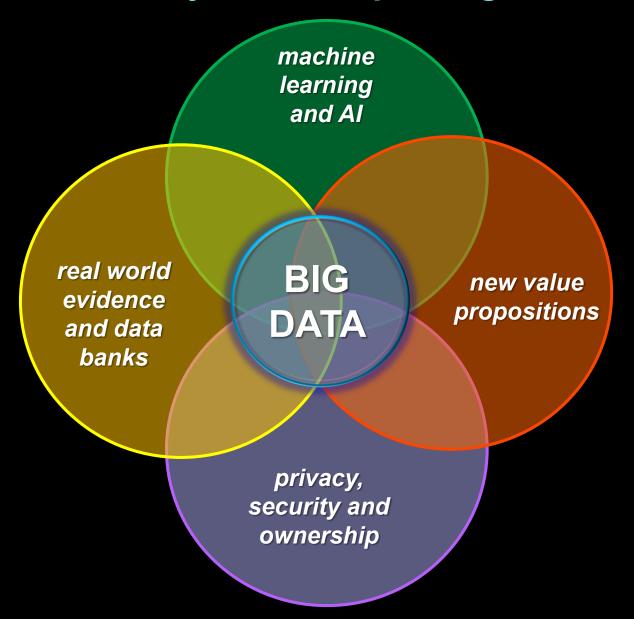
What Does/Should Keep the Biopharmaceutical Industry C-Suite Up at Night?

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Biopharmaceuticals

- one of the most efficient and cost-effective solutions to illness?

or

- overpriced and major contributor to rising healthcare costs (society) and the affordability crisis (society and individuals)?
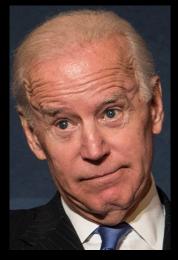
"Unconscionable Rx Price Increases and Price Gouging"

**Overly Simplistic Legislation
and
Emotions Run High
(State of the Union Address
4 Feb 2020)**

The Politically Expedient Search for Unidimensional 'Quick Fixes' to Multi-dimensional Problems and the Law of Unintended Consequences

"For Every Complex Problem There Is an Answer That is Clear, Simple and Wrong."

- H.L. Mencken

Drug Pricing

Pelosi Rx Pricing Bill Offers Big Savings, Big Drop In Drug Development – CBO

Pink Sheet (21 October 2019)

- cost shifting of financial risk to patients/consumers is the most publically visible endpoint in the opaque universe of 'drug spend'

- adverse patient/consumer financial impact as the 'lightning rod' for public and political ire and negative image of both innovator and generic companies

- poor advocacy and communication of multi-dimensional complexity by biopharma-industry

- negative image reinforced by legacy and current marketing practices

- **are financial returns on biopharmaceutical products excessive?**

- **is the biopharmaceutical industry receiving a 'free ride' by exploiting taxpayer-funded biomedical research?**

- **should medicines be viewed as an essential public social good and subject to provisions to ensure their availability and affordability?**

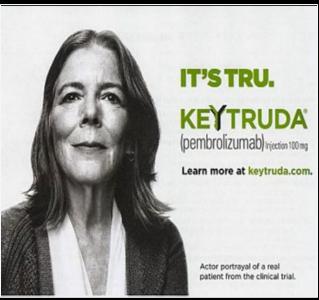- **do individuals have a 'right' to unlimited healthcare services?**

- how are Rx price(s) determined?

- what is a fair price to reward risk and sustain innovation?

- who profits and how much?

- how are value and access determined, by whom and for whom?

- how can affordability be balanced with incentives to sustain R&D investment in new Rx innovation?

- is the pace and cost of overall innovation outstripping our ability to afford certain categories of care?

Industry Critics

- sales and marketing 1.2 to 2.3X higher than R&D

- direct-to-consumer (DTC) advertising

  – drive up Rx use

  – high cost 'glam-mercials'

  – notice everyone is healthy, active and affluent

- shift from print to TV to social media

  – identification of high prescriber MDs

  – identification of patients and new tools to ensure 'brand stickiness'
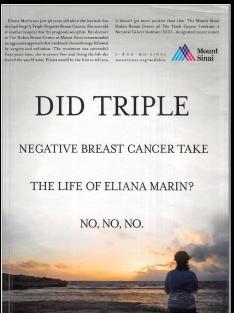
  – first amendment rights upheld

Expensive DTC Campaigns

Hype Versus Hope: A Delicate Ethical Balance
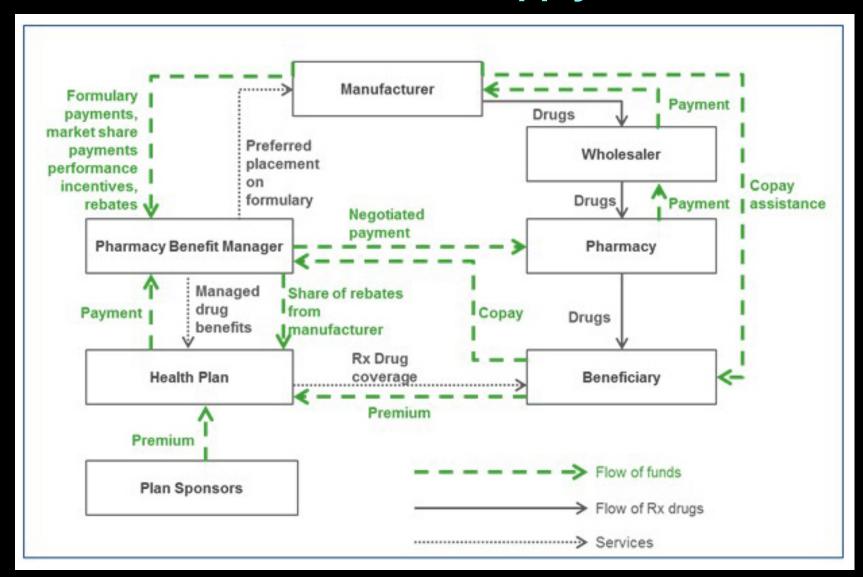# Come and Be Cured by Us: (Go Elsewhere at Your Peril)!

- the sale and pricing of biopharmaceuticals (and much else in healthcare) do not conform to free market principles

- the pricing of drugs and all aspects of healthcare financing are shaped by myriad sectorial inefficiencies and perverse information asymmetries that render the true costs and profit distribution across the supply chain opaque

  – Rx companies, wholesalers, PBMs, pharmacies, GPOs, payers, providers

  – specialized services : dialysis

  – geographies : MD office vs hospital; 340B legislation

Transactional Relationships in the Pharmaceutical Distribution and Supply Chain

N. Sood, et al. (2017) Health Affairs Blog, 13 June
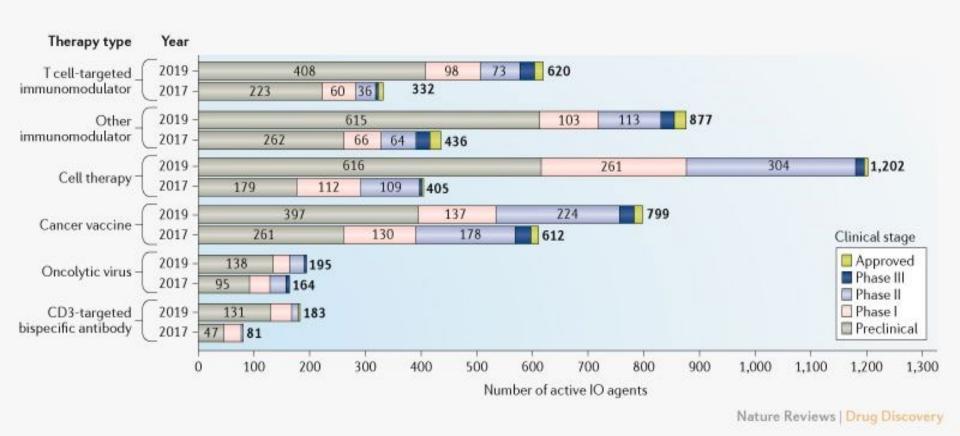
Why Should Price Vary With Location?

- price for oncology drugs administered in hospital versus typically double price paid for community clinic
- Herceptin
  - hospital/hospital outpatient $5,350
  - independent clinic $2,740
- Avastin
  - clinic ($6,620), hospital ($14,100)
- incentive for trend for purchase of community clinics by hospital systems and reclassification as 'hospital outpatient clinics' and eligible for 340B discounts

Are Oncologists Financial Incentives Misaligned with Optimum Treatment?

- **high cost of new oncology drugs (US)**
  - **$100K-250K/year**
- **estimated 80% annual income for community oncologists tied to R_x use**
- **no incentives to select less expensive R_x or palliative care**
- **physician/payer refuge in slow pace of change in SOC guidelines to incorporate obligate molecular diagnostic profiling for R_x selection**
- **unacceptable levels of use of new R_x regimen(s) in last two weeks of life**

How Many Agents With the Same MOA Can the Market Support?

3,876 active IO agents in the current global drug development pipeline

Nature Reviews | Drug Discovery

Policy Choices in Government Price Controls for Biopharmaceuticals

- median index pricing from G8 'basket' prices
- expanded CMS negotiation of 'best price'
- FDA to include value pricing metrics in comparable fashion to EU in regulatory approval
- inflation-based capitation
- reference pricing
- indication-based pricing
- march-in rights and compulsory licensing
- GoCo initiatives for public sector manufacturing (generics)

Hypothetical Scenarios for Indication-Based Drug Pricing

Drug and Indication	Median Survival Gain In Years	Current Monthly Price	Price Based On Indication With Most Value
Abraxane (Celgene)			
Metastatic breast cancer	0.18	$6,255	$6,255
Non-small cell lung cancer	0.08	$7,217	$2,622
Pancreatic cancer	0.15	$6,766	$448
Tarceva (Roche/Astellas)			
First-line treatment metastatic non-small cell lung cancer	0.28	$6,292	$6,292
Pancreatic cancer	0.03	$5,563	$1,556
Erbitux (BMS/Lilly)			
Locally advanced squamous cell carcinoma of head/neck	1.64	$10,319	$10,319
First-line treatment recurrent or metastatic squamous cell carcinoma of head/neck	0.23	$10,319	$471
Herceptin (Roche)			
Adjuvant treatment breast cancer	1.99	$5,412	$5,412
Metastatic breast cancer	0.40	$5,412	$905

Source: JAMA article by Peter Bach, Oct. 3, 2014

Outcomes-Based Pricing:
More Complicated Than It Might Seem

- pre-specified clinical outcomes
- robustness of efficacy endpoints
- design of observational/RCT protocols and registries
  - eligible patients
  - duration
- risk that administrative overhead and monitoring costs erode potential savings
- PhRMA proposal of safe-harbor from Federal anti-kickback penalties for manufacturer medication adherence programs

Reference Pricing

- **uniform pricing of Rx deemed "clinically comparable"**

- **how should "clinically comparable" be defined?**

- **instructive precedents?**

  – **demise of antibiotic R&D**

  – **immuno-oncology drugs with apparent common MOA but different efficacy (Opdivo™ vs Keytruda™ in NSCLC)**

Application of the Public Utility Model for Essential Public Goods Products to Pharmaceuticals

- water, electricity, gas, critical infrastructure
- regulated pricing plus periodic price increases
- commodity products/services with known performance characteristics and markets
- how would R&D risk (failure) be amortized in pricing of pharmaceuticals?
- what fraction of revenues would be reinvested to sustain next cycle of innovation
- competitiveness of US industry versus EU/PRC/FSU

How to Identify and Quantify the Contributions of Taxpayer-Funded Research to Commercial Products

- intellectual lineages of conceptual or technological advances are diffuse and diverse
- how to demarcate (and reward?) research done in overseas research laboratories
- biomedical R&D is increasingly dependent on innovations originating in industry
- reciprocal industry entitlement to recoup investments based on public funded research that cannot be reproduced or failed to fully characterize the proposed Rx target?
  - the reproducibility crisis in academic biomedical publications

Why Focus on Pharmaceutical R&D as a Beneficiary of Taxpayer-Funded Research and Exclude Other Industrial Sector Beneficiaries?
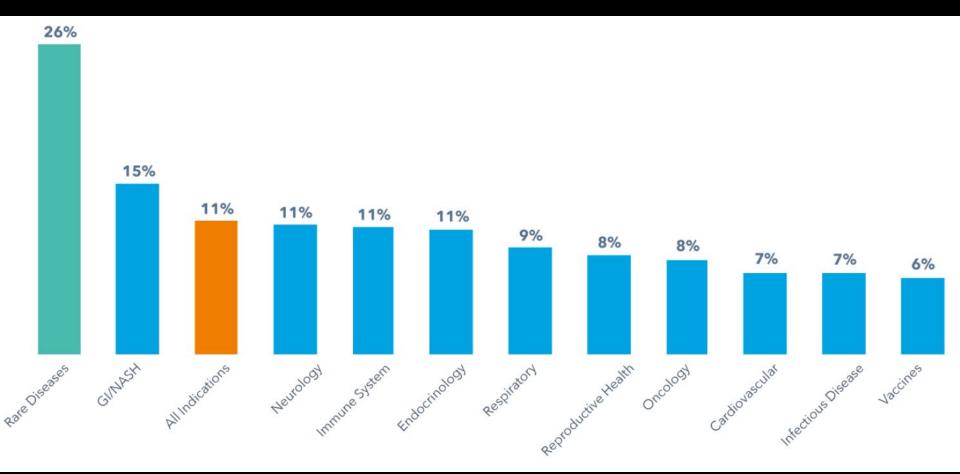
Telcoms	GPS	Computing	Internet	Social Media

Novel Materials	Geophysics	Robotics	3D printing	Biotechnology

R&D Costs Continue To Increase In An Increasingly Cost-Sensitive Market

The Imperative to Improve the Efficiency of the R&D Process

Precision Medicine and Implications for Biopharmaceutical R&D and Pricing

R&D Composite Success Rate in 2018 by Therapeutic Area

Therapeutic Area	Success Rate
Rare Diseases	26%
GI/NASH	15%
All Indications	11%
Neurology	11%
Immune System	11%
Endocrinology	11%
Respiratory	9%
Reproductive Health	8%
Oncology	8%
Cardiovascular	7%
Infectious Disease	7%
Vaccines	6%

Failure of Investigational Drugs in Clinical Trials

- **50% fail on insufficient efficacy**

- **30% fail on safety issues**

    - **8% on known concerns**

    - **22% on new unexpected AEs**

- **20% fail on lack of differentiation**

    - **16% on inadequate efficacy**

    - **4% on safety profile**

Addressing the Biopharmaceutical Industry's Principal Pain Point

- **amortization of cost of failed trials in pricing of successful agents**
  - **political liabilities**
- **lack of predictive tools to differentiate responder (R) and non-responder (NR) patients**
  - **growing payer pressure for value-based reimbursement for guaranteed therapeutic outcomes**
  - **waste/risk from futile therapy in NR cohorts**

The Promise of Immunotherapy: Is Widespread Adoption Economically Feasible?

APRIL 4, 2016

TIME

What if your immune system could be taught to kill cancer?

Inside the brutally selective, hugely expensive, lifesaving trials of immunotherapy.

By Alice Park

- **unit Rx cost (> $100K)**
- **indirect care cost**
- **escalating cost of combination Rx regimens (> $200K)**
- **extravagant cost of cell-based therapies ($500K - $1.5 million)**
- **complex clinical management challenges and compatibility with community oncology services**

40-80% patients fail to respond even with I/O – I/O combinations
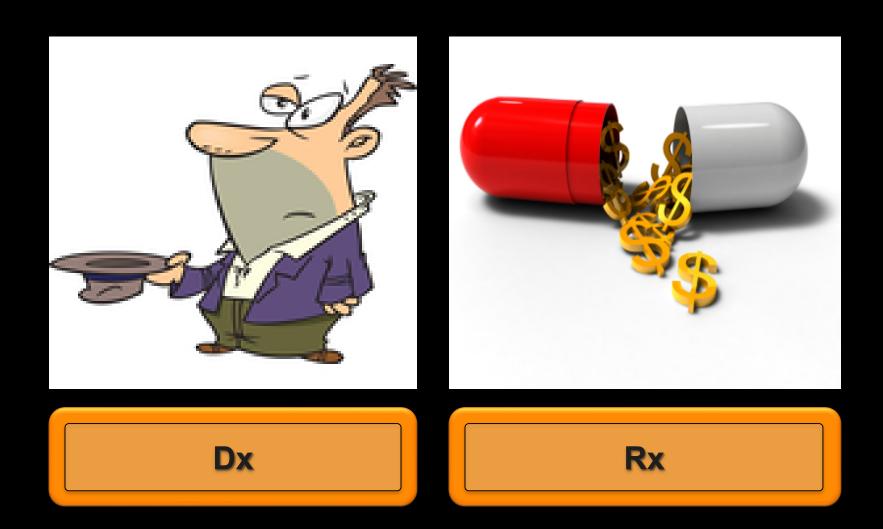
Performance-Based Contracts and Pricing: The Inevitable Future Landscape for Cancer Therapy?
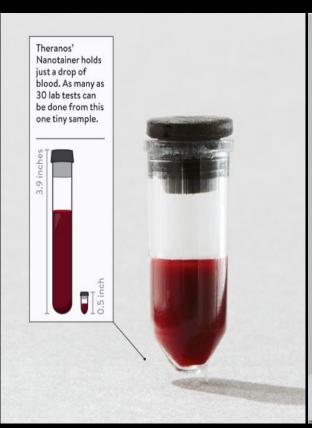
A Pricing and Reimbursement Dichotomy

Dx

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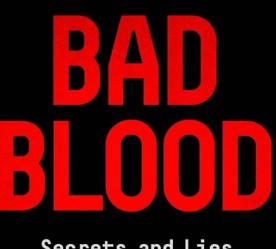
Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology

MDx and Multi-Omics Profiling

SOC Rx guidelines

Disease Subtyping and ID of Rx-Responsive Cohorts

High Cost Rx Without Subset Profiling

Precision Diagnosis and Rational Treatment Selection

Propagation of Therapeutic Regimens With Variable Response Rates

If It Sounds Too Good To Be True….?
Popular Delusions and The Madness of Crowds: Charles Mackay 1841
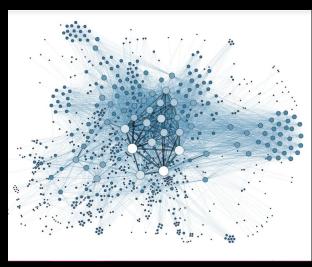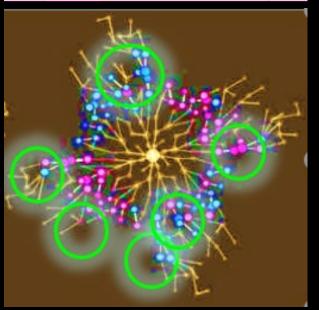
Drug Discovery

- the low hanging fruit have been picked
- major unmet medical needs:
    - late-onset chronic diseases
    - mental illness
- identification of new targets or Rx action
    - mapping underlying perturbations in molecular signaling networks (wiring diagrams)
    - GxE: interplay between genes (G) and environment (E) in disease predisposition risk and progression patterns

The Search for New Drug Targets: Mapping Disease –Associated Perturbations in Molecular Information Networks
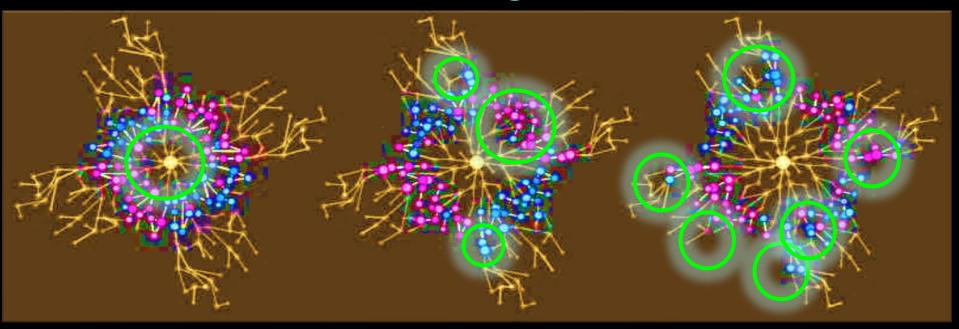
- **'It's the Network, stupid!"**

- **most major diseases involve complex perturbations at multiple points in the network or hits on key control nodes**

Understanding Perturbations in Molecular Signaling Networks and Rx Target Identification
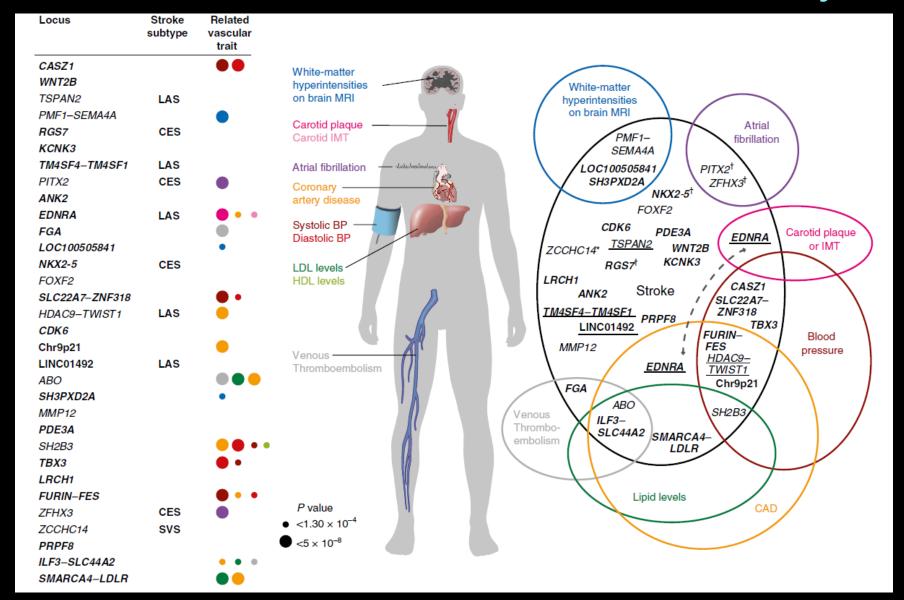

'Single Hit' Diseases

- single target or master control target
- foreign target (m/organisms)
- replacement therapy (insulin)
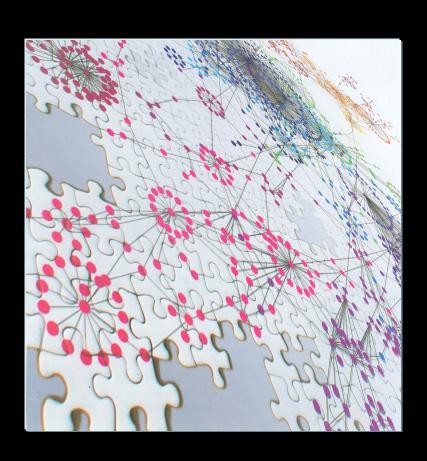- no/low interpatient variation

'Multi-Hit' Diseases

- varied 'excursions' from physiological topologies
- variable GxG interactions
- GxE (SDoH) interactions
    - high inter-patient variation

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

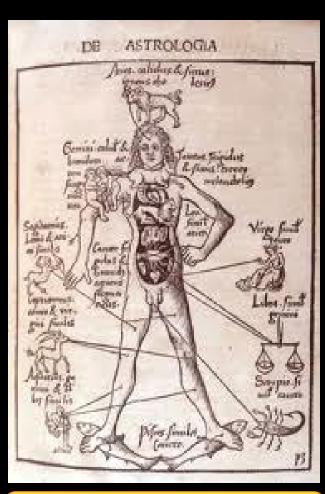From: R. Malik et al. (2018) Nature Genetics 50, 524

An Ugly but Fundamental Question:
Is Unifocal Rx Modulation of Complex Network Dysregulation in Advanced Chronic Diseases Feasible or a Delusion?
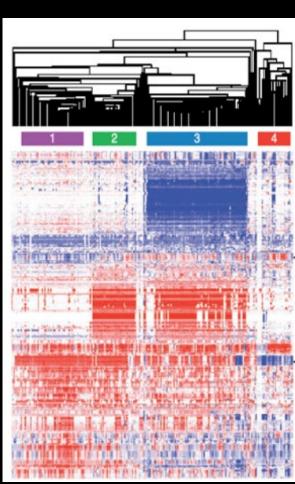

- "too disrupted for homeostatic reset?"

- multi-point/multi-module/ multi-subnetwork dysregulation

- low feasibility of multi-Rx intervention against multiple targets

- even lower probability of design of promiscuous multi-target action in a single Rx molecule

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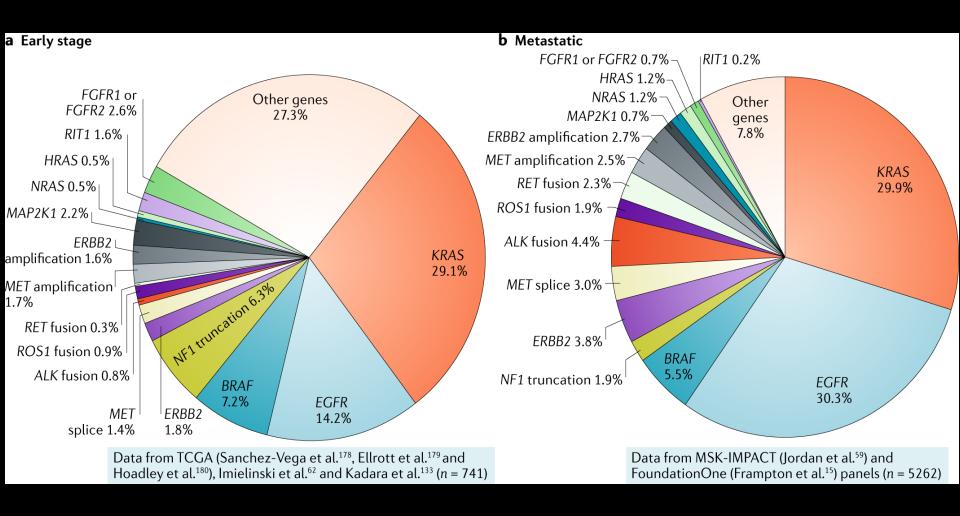# From Superstitions to Symptoms to (Molecular) Signatures

humors; astrology, shamanism, sin and divine fate

biochemistry and organ-based pathophysiology
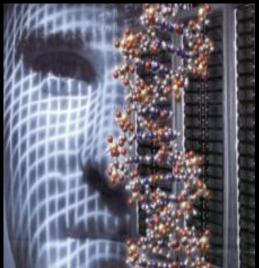
molecular biology and multi-omics profiling

Molecular Classification of NSCLC Subtypes

a Early stage

FGFR1 or FGFR2 2.6%
RIT1 1.6%
HRAS 0.5%
NRAS 0.5%
MAP2K1 2.2%
ERBB2 amplification 1.6%
MET amplification 1.7%
RET fusion 0.3%
ROS1 fusion 0.9%
ALK fusion 0.8%
MET splice 1.4%
ERBB2 1.8%
BRAF 7.2%
NF1 truncation 6.3%
EGFR 14.2%
KRAS 29.1%
Other genes 27.3%

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

FGFR1 or FGFR2 0.7%
RIT1 0.2%
HRAS 1.2%
NRAS 1.2%
MAP2K1 0.7%
ERBB2 amplification 2.7%
MET amplification 2.5%
RET fusion 2.3%
ROS1 fusion 1.9%
ALK fusion 4.4%
MET splice 3.0%
ERBB2 3.8%
NF1 truncation 1.9%
BRAF 5.5%
EGFR 30.3%
KRAS 29.9%
Other genes 7.8%

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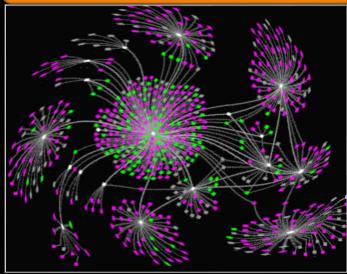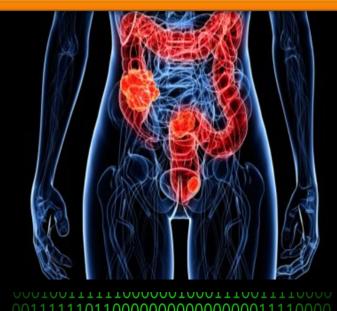
Precision Medicine:

(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

Still Two Largely Separate Worlds

precision medicine

routine healthcare delivery and SOC

research
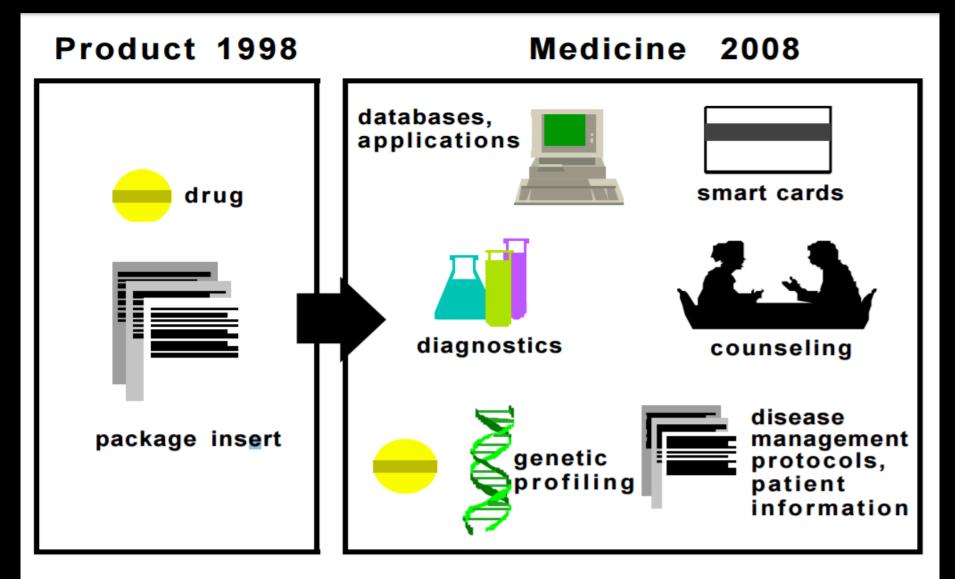and
early clinical
adopters
(largely oncology)

slow incremental adoption of technological advances

- one-size-fits-all protocols

- wide variation in clinical practice and outcomes

- fragmented continuity of care

- inefficient use of available data

$100-125* billion (estimated)

$3.6 trillion (19% GDP)

*includes investment in investigational R$_x$ candidates

The Dangers of Techno-Optimism

Molecular medicine and information-based targeted healthcare.
G. Poste (1998) Nature Biotechnol. 16, p 19-21

Precision Medicine and Digital Medicine: Evolving Inter-Dependencies

Individual Data

Population Databanks

integration and analysis of large scale, diverse data categories
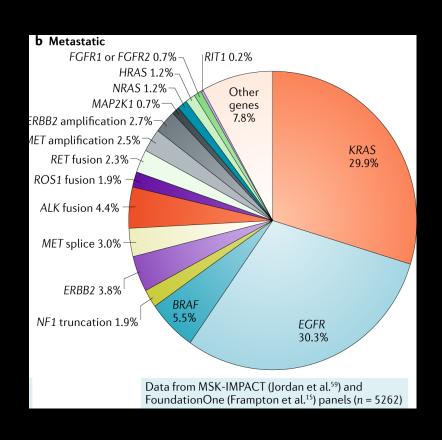
"digital siblings and imputed phenotypes"

- **matching individual profiles to 'best fit' data cohorts**

to identify risk and selection of optimum treatment regimens

Precision Medicine, Disease Subtyping and Market Segmentation into Ever Smaller Niche Domains

b Metastatic

- FGFR1 or FGFR2 0.7%
- RIT1 0.2%
- HRAS 1.2%
- NRAS 1.2%
- MAP2K1 0.7%
- ERBB2 amplification 2.7%
- MET amplification 2.5%
- RET fusion 2.3%
- ROS1 fusion 1.9%
- ALK fusion 4.4%
- MET splice 3.0%
- ERBB2 3.8%
- NF1 truncation 1.9%
- BRAF 5.5%
- EGFR 30.3%
- KRAS 29.9%
- Other genes 7.8%

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

- **from 'all-comer' RTC to stratified trials of Rx-target positive patients**
- **cost and time to find eligible patients**
- **narrow regulatory labeling**
- **increased ROI risks**
- **oncology: short-lived Rx eligibility with rapid emergence of Rx resistance**

The "Geno-Enviro-Pheno' Triad

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

Behavior

Environment

Precision Medicine and Digital Medicine: Evolving Inter-Dependencies

Individual Data

Population Databanks

integration and analysis of large scale, diverse data categories

Deep Phenotyping:
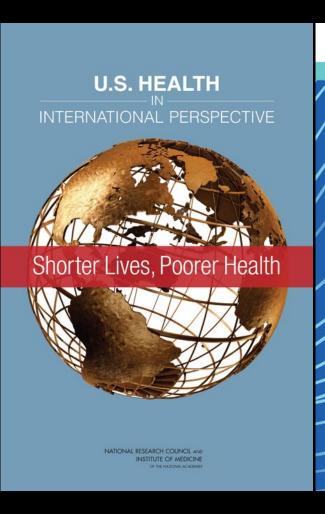
integration of (epi)genomic and multiOmic profiles,

clinical, environmental and socio-behavioral data

Social Determinants of Health (SDoH):

Invasion of the Body Trackers: Expanding the "Care Space" in Healthcare

Healthcare Beyond The Clinic

Remote Health Status Monitoring

Smartphones, Wearables, Devices and Digital Services

M4: Making Medicine More Mobile

AORTA: Always On, Real Time Access

- 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

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

Smart Devices for Automated Drug Delivery and Improved Therapeutic Adherence
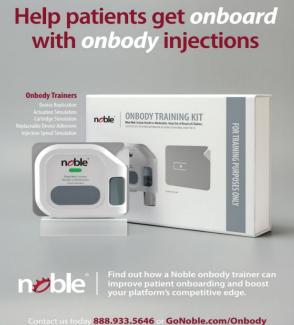
Propeller Health

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 | ONBODY TRAINING KIT

FOR TRAINING PURPOSES ONLY

noble®

Find out how a Noble onbody trainer can improve patient onboarding and boost your platform's competitive edge.

Contact us today **888.933.5646** or GoNoble.com/Onbody

Aterica Veta EpiPen

Chatbots and Support Robots in Healthcare

Amazon and Home Care

Development of Third-Party Alexa Apps

LIFE | HEALTH | FREEDOM
LIBERTANA®

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

MAYO CLINIC

Mayo Clinic First Aid

"Tell me about spider bites"
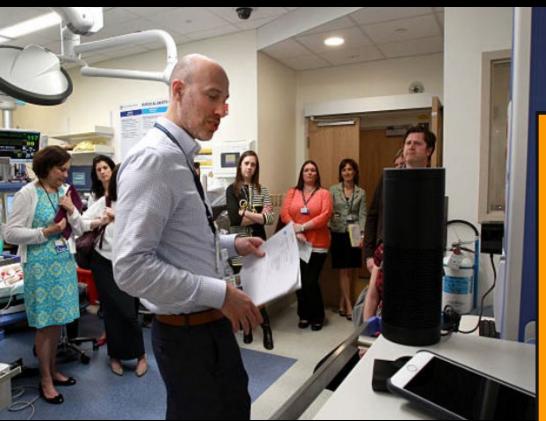
"Help for a burn"

Ask My Buddy

"Alexa, ask My Buddy to alert everyone."

https://www.cbinsights.com/research/report/amazon-transforming-healthcare/

HIPPA-Compliant Intelligent Agents
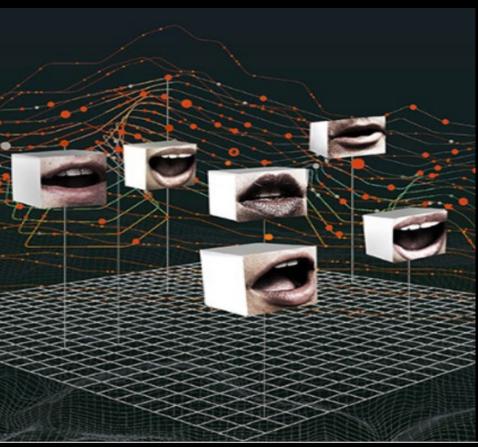
Digital Psychiatry:
Digital Psychometrics and Evaluation of Mental Illness

- (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

VR/AR and Neuromodulation

- **promote behavior change via altered sensory inputs and feedback**

- **mental illness: PTSD, physical rehabilitation, substance abuse and pain control**

Digital Therapeutics Alliance

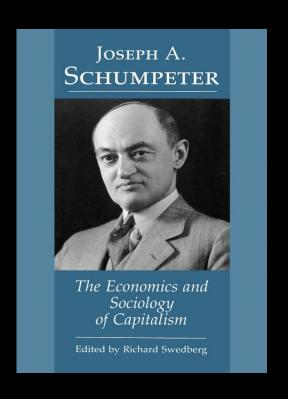# The Precision Medicine: Digital Medicine Convergence

Meeting the Needs of the Expanded Care Space
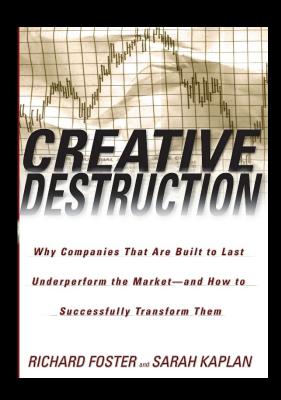# Created by the Precision Medicine: Digital Medicine Convergence

- mobile
- in-home
- social media analysis
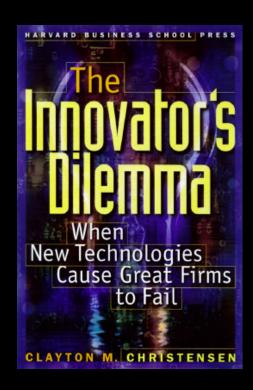- improved continuity in care
- earlier detection of risk and mitigation

the expanded care space

new product classes, services and new industry alliances/entrants

- Dx-Rx
- Dx-Rx-Ix
- Dx-Rx-Device
- DigRx
- brain-computer interactions
- intelligent agents
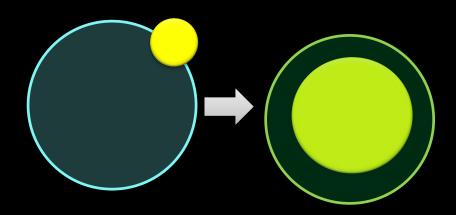
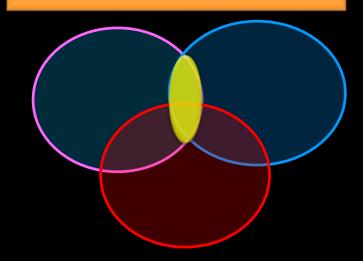# Creative Destruction and Disruptive Innovation

- 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

Technology Innovation and Creative Destruction

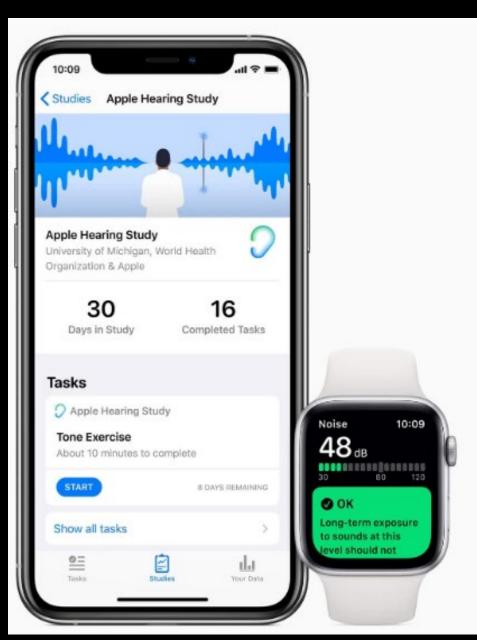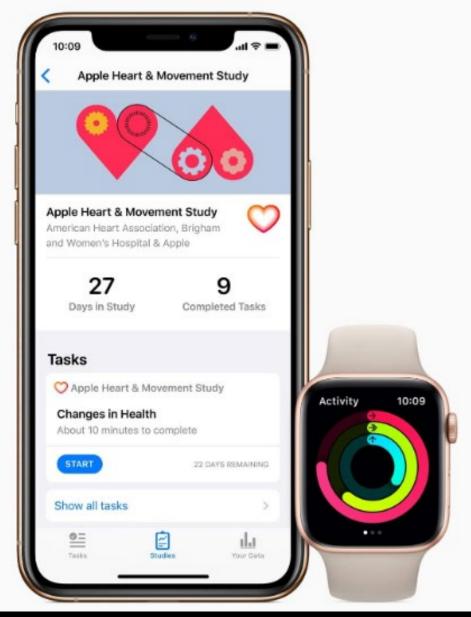| emergence at margin of an existing domain | emergence by convergence of previously separate domains |

biotechnology 1980-present
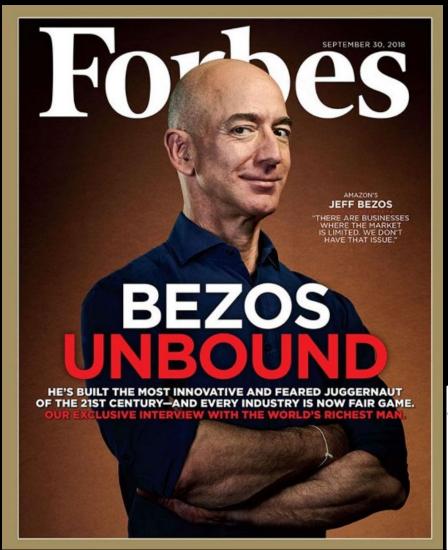
- multi-Omics and precision medicine
- big data, AI and digital medicine

https://www.techspot.com/news/82781-apple-launches-research-app-opens-three-health-studies.html

Amazon and Healthcare

The Next Competitor for Amazon ?

Walgreens

Microsoft

Economies of Scale and Convenience Come to Primary Care

CVS Launch of Transform Oncology Care™ (December 2019)

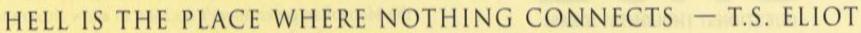- genome sequencing at diagnosis
- align therapeutic selection to NCCN guidelines
- automatic prior authorization approval
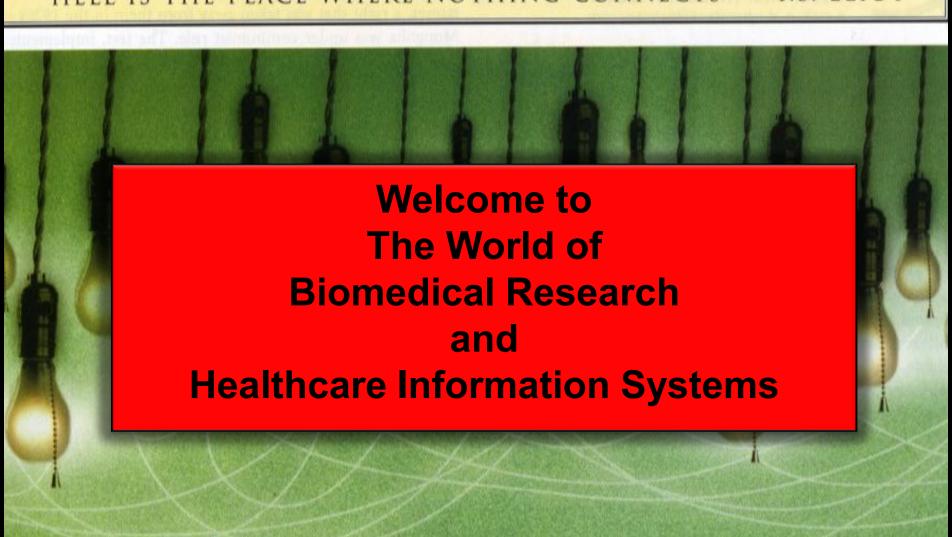- faster patient access to Rx including high cost specialty Rx

Now Comes the Hard Part!

Driving Precision Medicine and Large Scale Data Analytics into Routine Clinical Practice

New Incentives and New Delivery Models

New Participants and New Business Models

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

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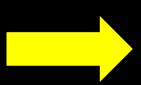
The Health Information Supply Chain

- 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

The Big Data Challenge
Data Standards, Validation, Provenance and Security

I-3

1. infrastructure
2. investment
3. intelligent systems
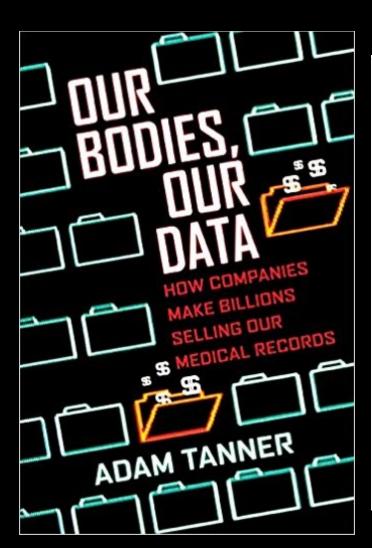
V-7

1. volume
2. velocity
3. variety
4. veracity
5. visualization
6. virtualization
7. VALUE !

D-3

1. dynamic
2. distributed
3. decision-support

Data Brokers and 'Selling-On"

OUR BODIES, OUR DATA
HOW COMPANIES MAKE BILLIONS SELLING OUR MEDICAL RECORDS
ADAM TANNER

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

By REBECCA ROBBINS @rebeccadrobbins / SEPTEMBER 26, 2019

23andMe
Welcome to you
saliva collection kit

Big Tech: Big Provider Linkups
Fuel HIPAA Privacy Debate

National Security Implications of Genome Data on Populations

Population Databanks

Individual Profiles

Foreign Access to Data

Data Security

DEC 20 2019

MEMORANDUM FOR: SEE DISTRIBUTION

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

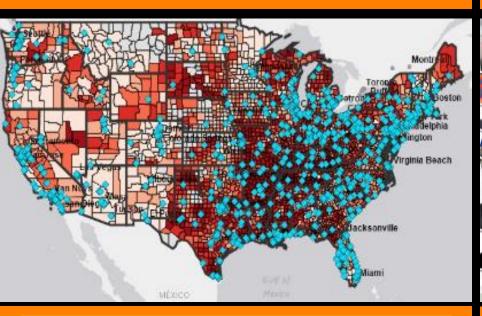It has come to the attention of the DoD that some direct-to-consumer (DTC) genetic testing companies are encouraging DoD personnel to purchase genetic ancestry and health information through the offering of military discounts or other incentives. These DTC genetic tests are largely unregulated and could 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

AAIH Founding Members: Unified Vision for Healthcare
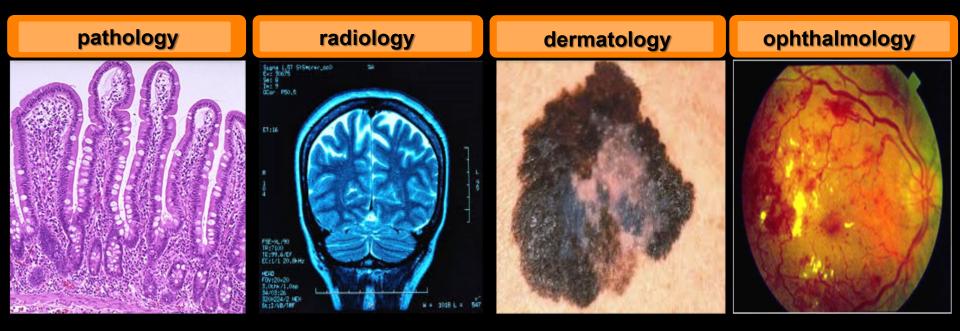
Leading
IT and Tech Corporations / AI Companies / Pharma Corporations
Advanced AI in Healthcare and Drug Discovery

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

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

Assessing and referring adult cancers
by Will Stahl-Timmins

the bmj

Legend:
- ■ Refer using suspected cancer pathway
- ■ Non-urgent specialist referral

Possible cancers

Abdominal features (discomfort or pain)

Abdominal pain
- + Rectal bleeding
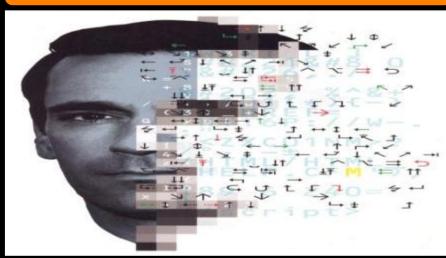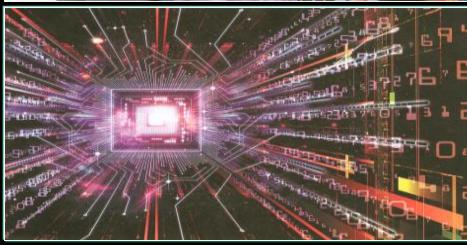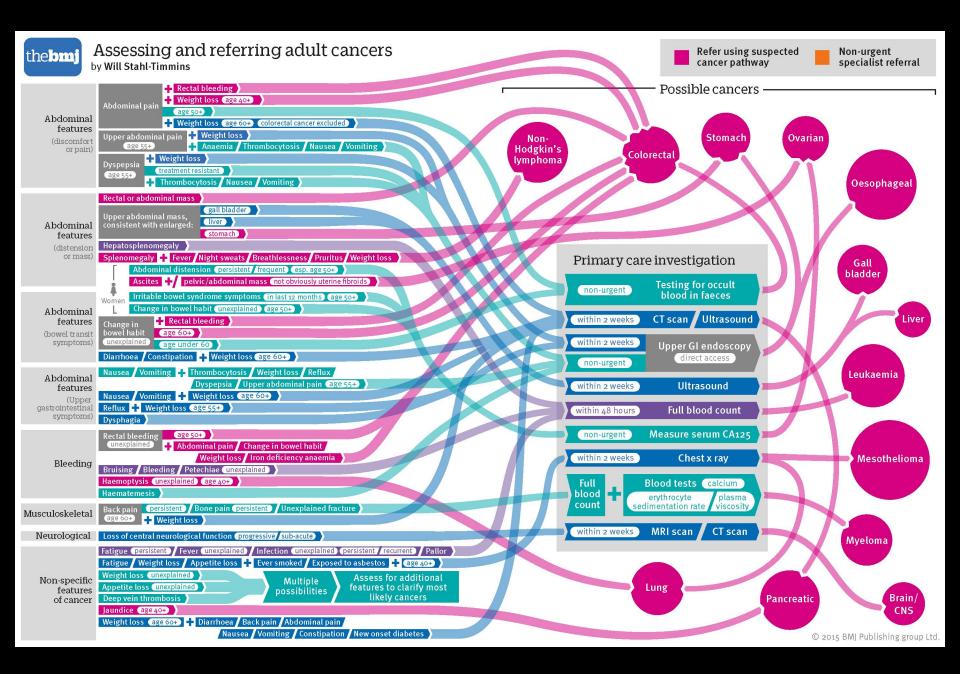- + Weight loss (age 40+)
- age 50+
- + Weight loss (age 60+) (colorectal cancer excluded)

Upper abdominal pain (age 55+)
- + Weight loss
- + Anaemia / Thrombocytosis / Nausea / Vomiting

Dyspepsia (age 55+)
- + Weight loss
- treatment resistant
- + Thrombocytosis / Nausea / Vomiting

Abdominal features (distension or mass)

- Rectal or abdominal mass
- Upper abdominal mass, consistent with enlarged: gall bladder / liver / stomach
- Hepatosplenomegaly
- Splenomegaly + Fever / Night sweats / Breathlessness / Pruritus / Weight loss
- Abdominal distension (persistent / frequent) (esp. age 50+)
- Ascites +/ pelvic/abdominal mass (not obviously uterine fibroids)

Women

Abdominal features (bowel transit symptoms)

- Irritable bowel syndrome symptoms (in last 12 months) (age 50+)
- Change in bowel habit (unexplained) (age 50+)
- Change in bowel habit (unexplained)
  - + Rectal bleeding
  - age 60+
  - age under 60
- Diarrhoea / Constipation + Weight loss (age 60+)

Abdominal features (Upper gastrointestinal symptoms)

- Nausea / Vomiting + Thrombocytosis / Weight loss / Reflux
- Dyspepsia / Upper abdominal pain (age 55+)
- Nausea / Vomiting + Weight loss (age 60+)
- Reflux + Weight loss (age 55+)
- Dysphagia

Bleeding

- Rectal bleeding (age 50+) (unexplained)
- + Abdominal pain / Change in bowel habit
- Weight loss / Iron deficiency anaemia
- Bruising / Bleeding / Petechiae (unexplained)
- Haemoptysis (unexplained) (age 40+)
- Haematemesis

Musculoskeletal

Back pain (age 60+)
- persistent / Bone pain (persistent) / Unexplained fracture
- + Weight loss

Neurological

- Loss of central neurological function (progressive / sub-acute)

Non-specific features of cancer

- Fatigue (persistent) / Fever (unexplained) / Infection (unexplained) (persistent / recurrent) / Pallor
- Fatigue / Weight loss / Appetite loss + Ever smoked / Exposed to asbestos + (age 40+)
- Weight loss (unexplained)
- Appetite loss (unexplained)
- Deep vein thrombosis
- Jaundice (age 40+)
- Weight loss (age 60+) + Diarrhoea / Back pain / Abdominal pain
- Nausea / Vomiting / Constipation / New onset diabetes

Multiple possibilities → **Assess for additional features to clarify most likely cancers**

Primary care investigation

- non-urgent — **Testing for occult blood in faeces**
- within 2 weeks — **CT scan / Ultrasound**
- within 2 weeks / non-urgent — **Upper GI endoscopy** (direct access)
- within 2 weeks — **Ultrasound**
- within 48 hours — **Full blood count**
- non-urgent — **Measure serum CA125**
- within 2 weeks — **Chest x ray**
- **Full blood count** + **Blood tests** (calcium / erythrocyte sedimentation rate / plasma viscosity)
- within 2 weeks — **MRI scan / CT scan**

Possible cancers

- Non-Hodgkin's lymphoma
- Colorectal
- Stomach
- Ovarian
- Oesophageal
- Gall bladder
- Liver
- Leukaemia
- Mesothelioma
- Myeloma
- Lung
- Pancreatic
- Brain/CNS

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The Emergence of Big Data Changes the Questions That Can Be Asked

Isolated Data

Complex Networked Data

Complex Computational Data

Just What the Data Ordered

Machine Intelligence and Algorithms for Clinical Diagnosis and Treatment Decisions
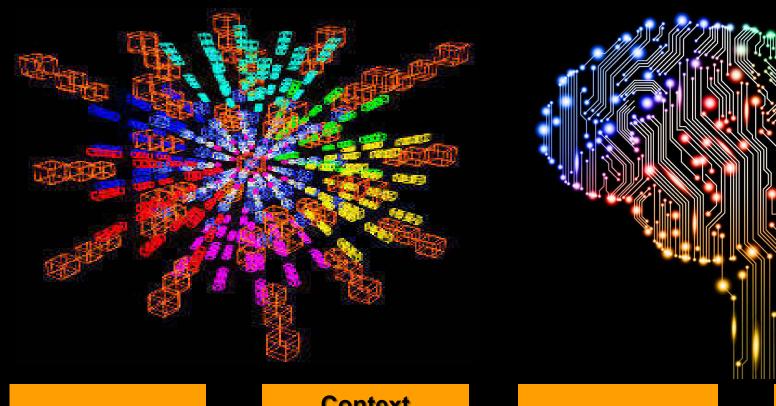
Black Box Medicine?

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

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 claimed expertise domain but they accept in all other aspects of their lives

- who will have the responsibility for validation and oversight of critical assumptions used in decision tree analytics for big data?

  - regulatory agencies and professional societies?

  - humans?

  - machines?

Machine Learning (ML), Artificial Intelligence (AI) and Healthcare
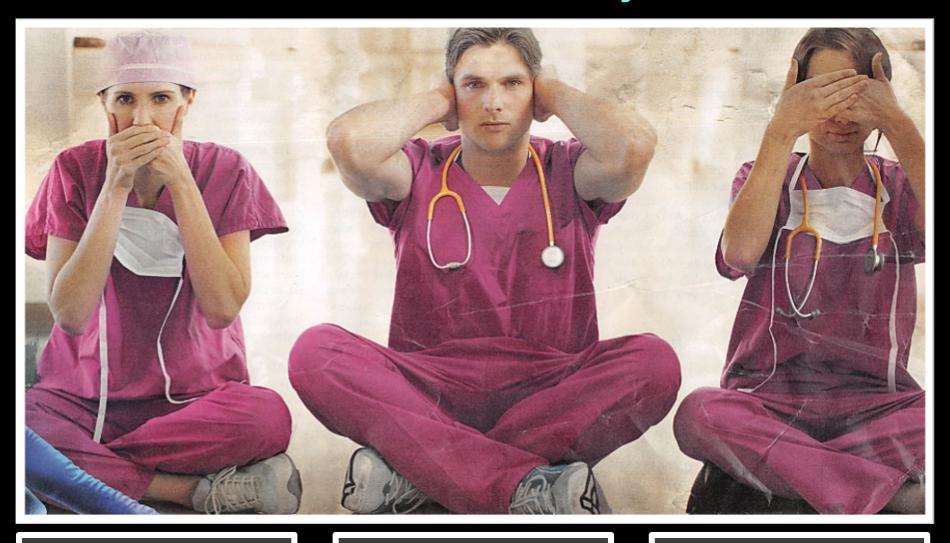
- which clinical specialties/processes will be at risk of replacement by ML-AI and when?

- 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

New Patterns of Learning

DNR: Is the Current Healthcare System Terminal?

Denial

Negativity

Resistance
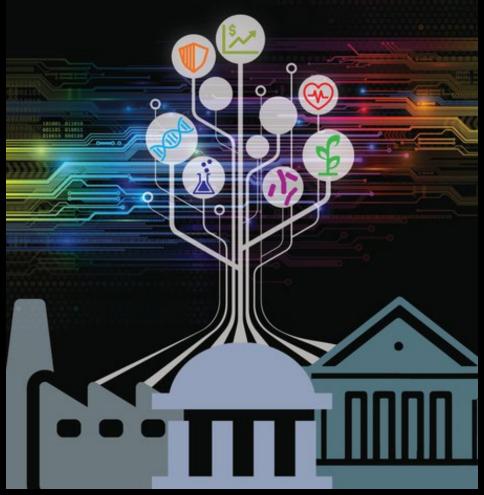
"Digital Darwinism": A Looming Digital Divide

- 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
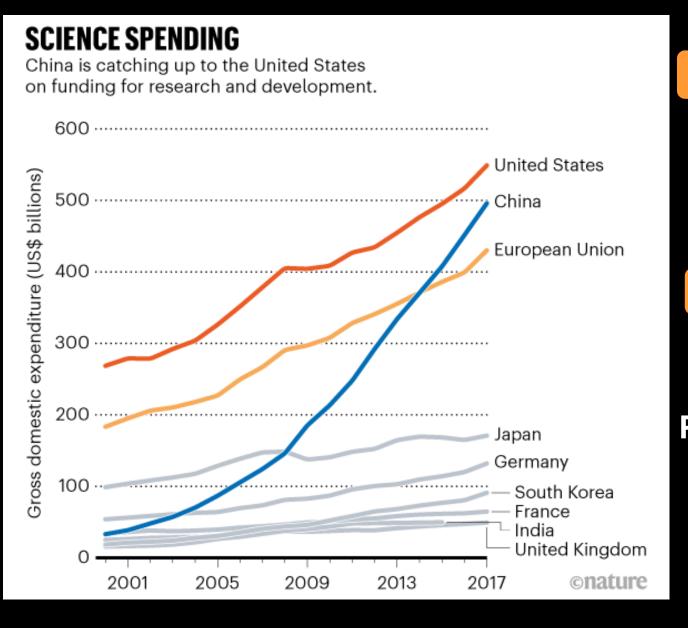
The National Academies of
SCIENCES · ENGINEERING · MEDICINE

CONSENSUS STUDY REPORT

SAFEGUARDING
the BIOECONOMY

NSF Biennial Science and Engineering Indicators (2000-2017)

SCIENCE SPENDING
China is catching up to the United States on funding for research and development.

Gross domestic expenditure (US$ billions)

- United States
- China
- European Union
- Japan
- Germany
- South Korea
- France
- India
- United Kingdom

©nature

ACGR

US = 4.3%
PRC = 17%

World R&D

US = $2.2 Trillion
= 25%
PRC = 23%

Threats to the U.S. Research Enterprise: China's Talent Recruitment Plans

STAFF REPORT
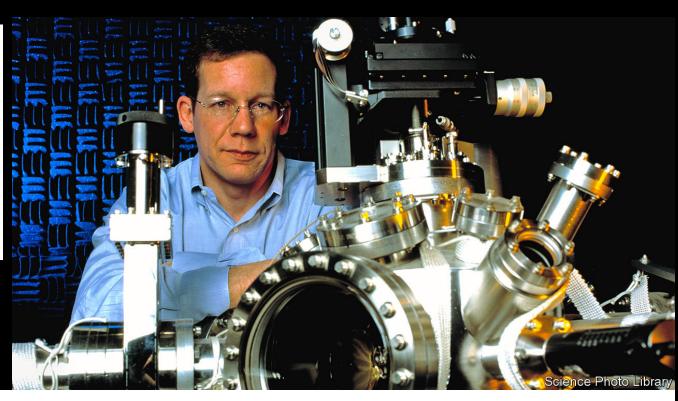
PERMANENT SUBCOMMITTEE ON INVESTIGATIONS

UNITED STATES SENATE

The Arrest of Charles Lieber, Chair, Dept. of Chemistry, Harvard University (28 January 2020)

Science Photo Library

Global Biosecurity
A Neglected Consequence of Comfort and Compliancy

The Challenge of Legislative Technical Literacy in an Era of Escalating Complexity

- **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**

- **novel threats from dual-use technologies and complex ethical and legal issues**

Unidimensional "Quick Fixes"
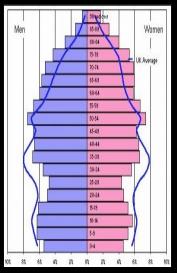
"The greatest danger in times of turbulence,
is not the turbulence,
it is to act with yesterday's logic."

- Peter Drucker

"Strategic Design Spaces"
Exploring the Architecture and Dynamics of Complex Networks

Precision Medicine Biotechnology, Synthetic Biology

Population Demographics and Disease Burden

IoT: Ubiquitous Sensing and Sensor Networks

Big Data Analytics, Machine Learning

Escalating Complexity

"Bio-Space"

"Unmet Need Space"

"Connected and Monitored Space"

"Decision Space"

"Opportunity Space"

New Patterns of Technology Convergence, Evolution and Adoption

New Knowledge Networks
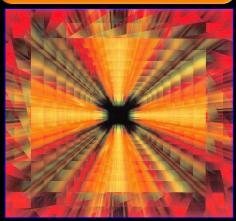
New Participants

New Organizational Models

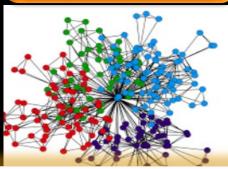# The Evolution of Data-Intensive Precision Health
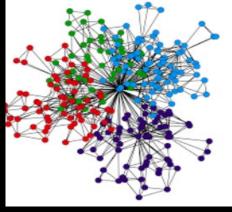
The Evolution of Data-Intensive Precision Health

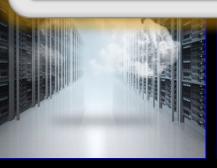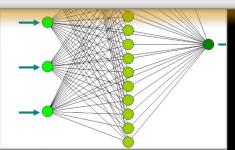| Technology Convergence and Acceleration	Mapping Geno-Phenotype Complexity	Topology of Biological Information Networks	V7 Big Data

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