ASU Complex Adaptive Systems Initiative
Arizona State University

PHOENIX CHILDREN'S

# The Strategic Landscape for the US Health Ecosystem and The Evolution of Precision Oncology: Challenges and Opportunities

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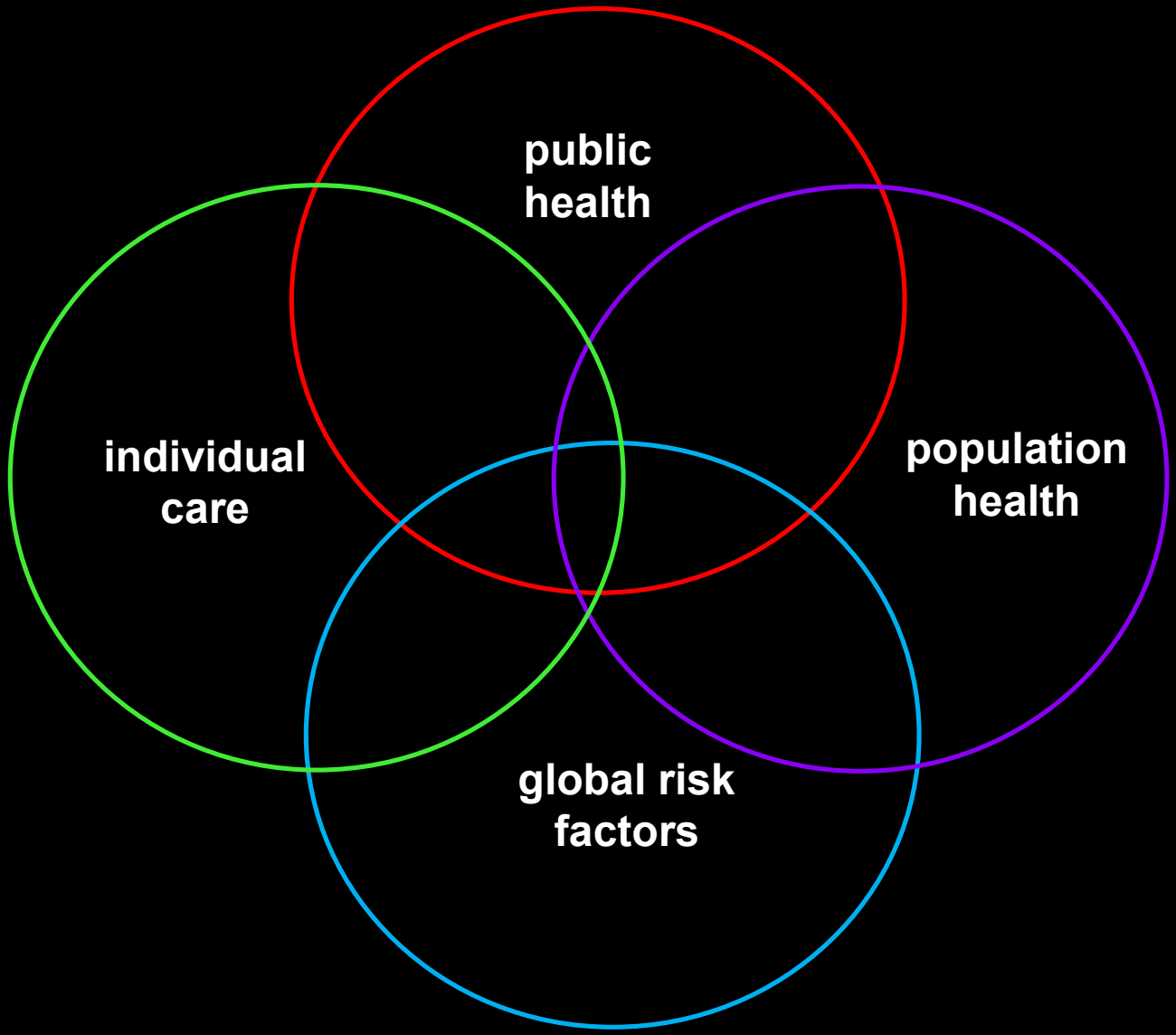
**Division Didactic Session**
**31 May 2022**

# Presentation Outline

- strategic drivers of the evolving healthcare ecosystem
- precision oncology
  - mapping mechanisms of disease at the molecular level
  - new diagnostic and treatment paradigms
- the challenge of ‘big data’ in biomedical research and clinical medicine
- sustaining scientific and clinical competencies in an environment of rapid technological change

# The Health Ecosystem



# The US Healthcare Ecosystem

- the $4.1 trillion US health system (c. 20% GDP) is unmatched in the scale and diversity of organizations and functions
- over 450,000 entities involved in the development and delivery of highly specialized services to heterogenous populations over their lifetimes
- health ranks highest in public and political expectations regarding access, availability and affordability of care

# The US Health Ecosystem

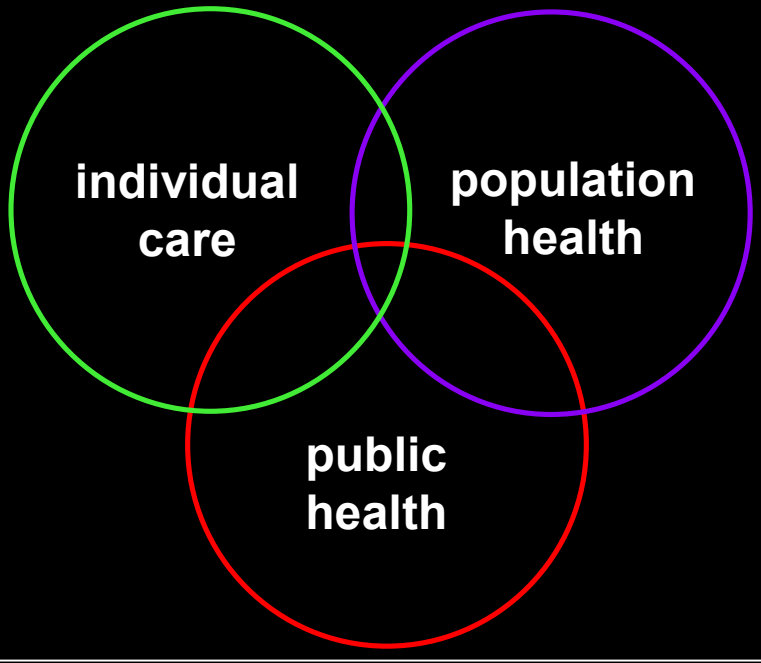
- economically and clinically unsustainable
- domination of care-centric activities (sick care) versus investment in health risk reduction (wellness)
- demographics of an aging society and increased chronic disease burden
    - 50% cost incurred in last six months of life
- disturbing increase in mental illness, SUD, suicide even before the COVID pandemic
- wide variation in clinical practice and outcomes
- disparities in access to care
- poor coordination and continuity of care across the health/health care system
- inefficient integration and analysis of data to drive evidence-based/best practice protocols

# The Imperative for Improved Integration of the Current Fragmented Organization of Health Services

systems vs silos

improved continuity in care

- multiOmics and mapping disease predisposition and progression
- earlier detection and mitigation of health risk




- integration of large-scale diverse data for improved care decisions and use of high-cost health resources

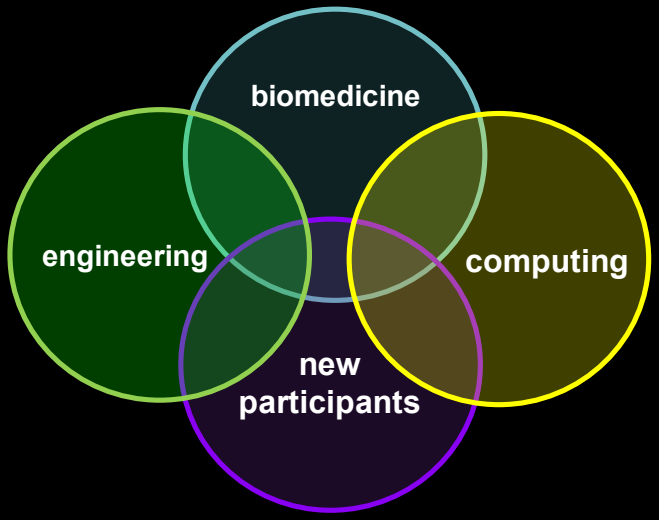
- epidemiology, risk monitoring and demand modeling
- disaster /pandemic preparedness and resilient systems

# Precision Health and Digital Health: Inter-dependent Strategic Drivers in the Evolution of Healthcare Systems, Policies and Priorities

# The Strategic Landscape for the US Health Ecosystem

technology convergence and cross-disciplinary/ cross-sector networks

escalating burden of chronic disease



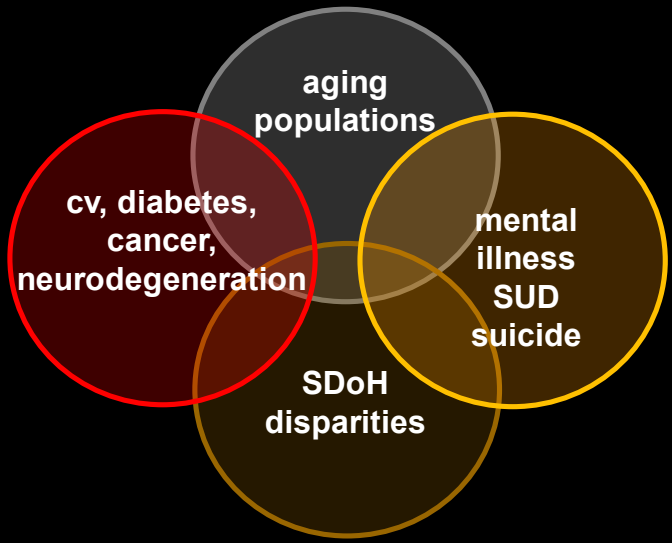

**precision health (PH)**

defining disease at the molecular level

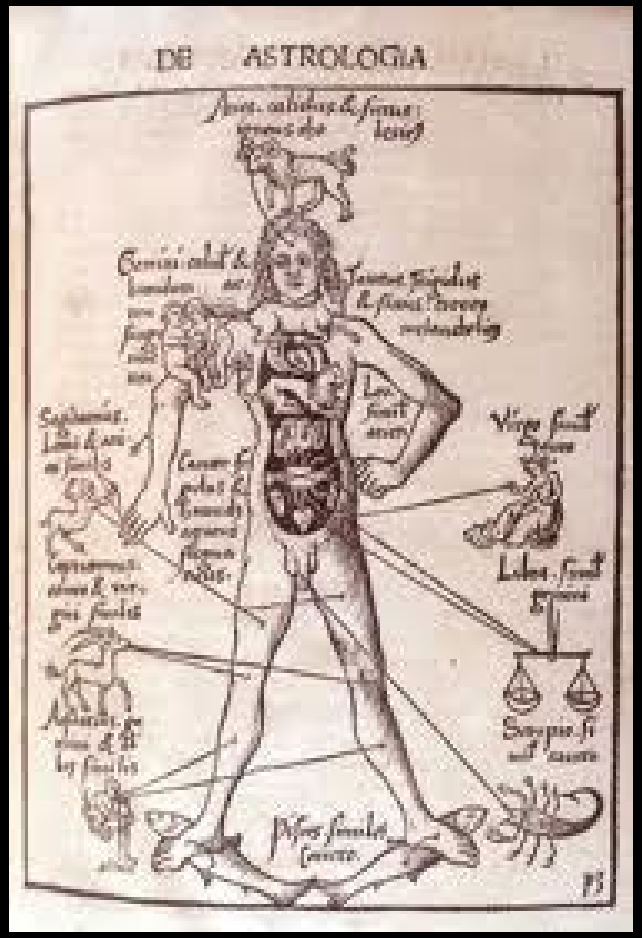
identification of disease risk and mitigation

**digital health (DH)**

data capture and analysis for better care decisions

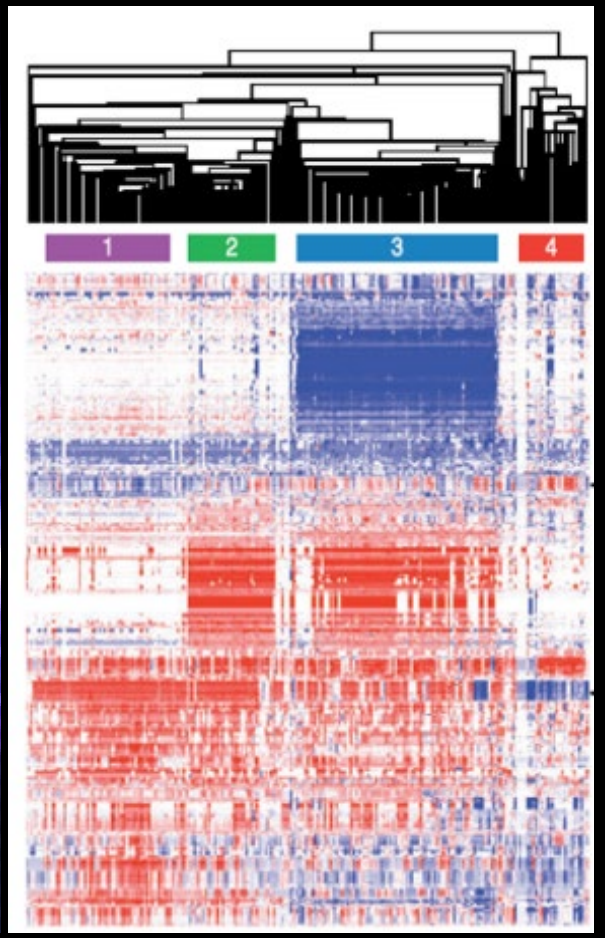


# The Path to Precision Health:
# From Superstitions to Symptoms to (Molecular) Signatures




humors, astrology, shamanism, sin and divine fate

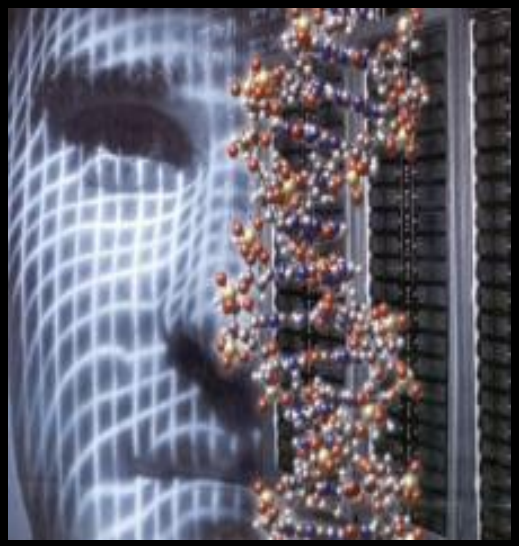
biochemistry and organ-based pathophysiology



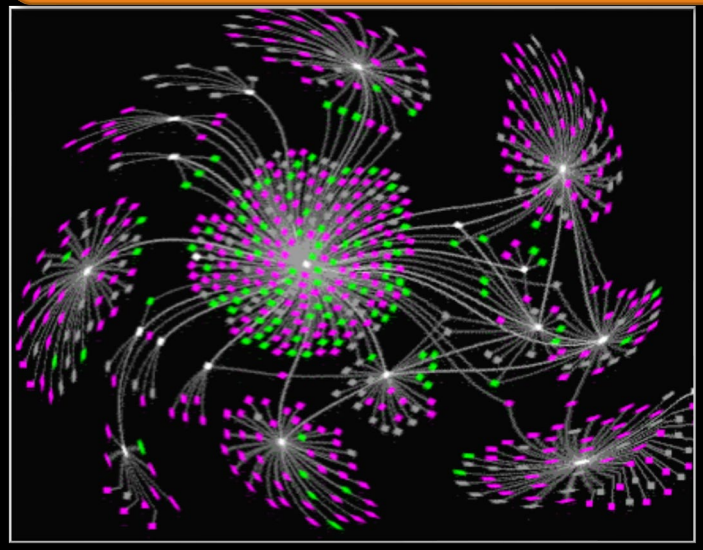

molecular biology and multiOmics profiling

# Precision Health

**(Epi)Genomics and MultiOmics Profiling**



**Detection of Altered Molecular Signaling Networks in Disease: A New Taxonomy of Disease and Subtype Classification**



- terabytes per individual
- zettabyte – yottabyte population databases

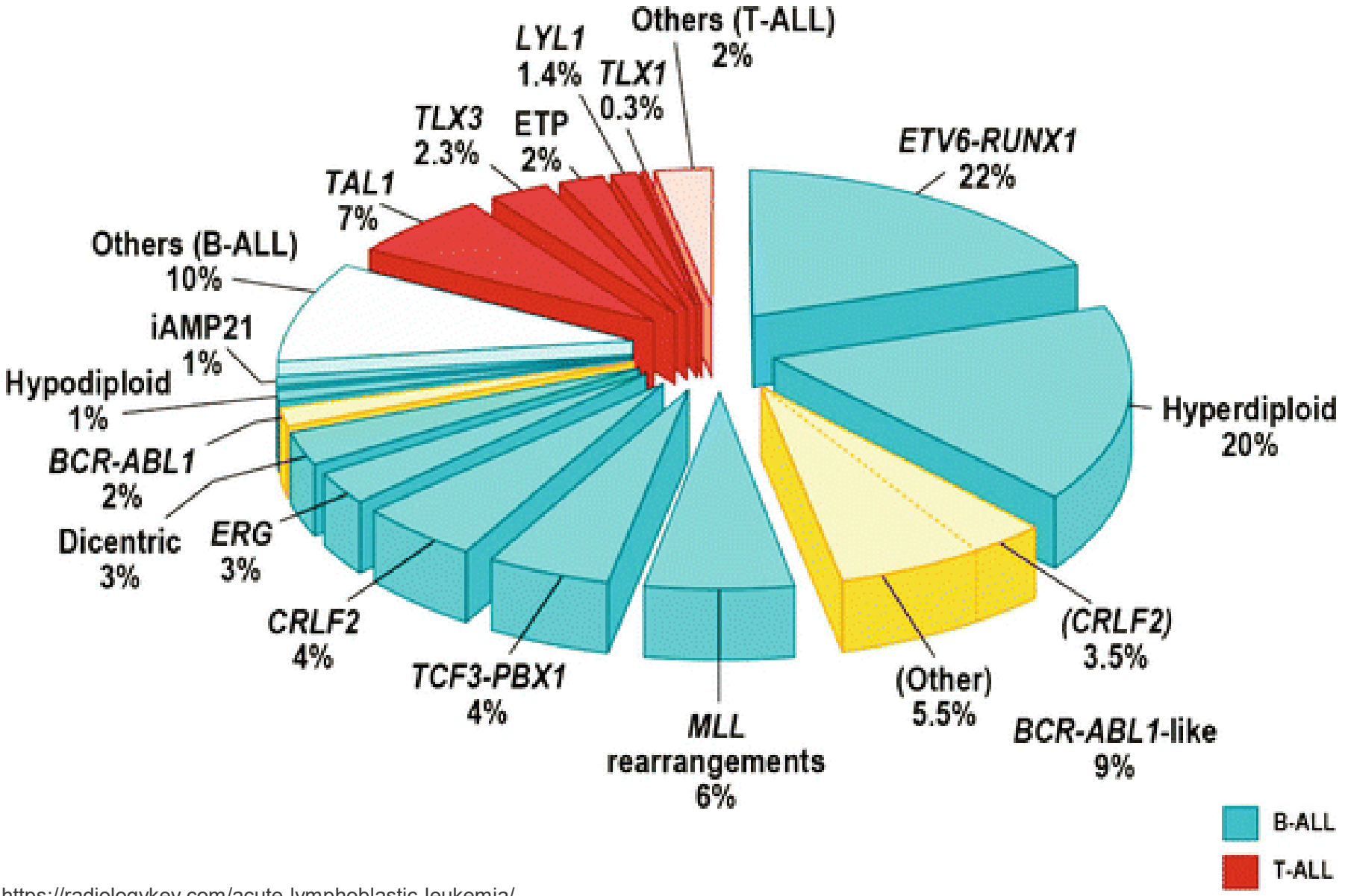
**MDx Signatures of Disease Predisposition and Subtyping of Overt Disease for Optimum Rx Selection**

**The Challenge of Big (Messy) Data**

# MultiOmics Profiling Technologies

- disease risk prediction and monitoring
  - germ line, CH, acquired somatic mutations/epigenetics
- disease diagnosis and prognosis
  - subtyping (endophenotypes), staging
- Rx target ID, Rx selection (precision therapeutics) and pharmacogenetics (drug interactions/AEs)
- disease progression
  - monitoring, Rx resistance and adaptive Rx
  - cf/ctDNA, cell-based transcriptomics (liquid biopsy)
- MRD

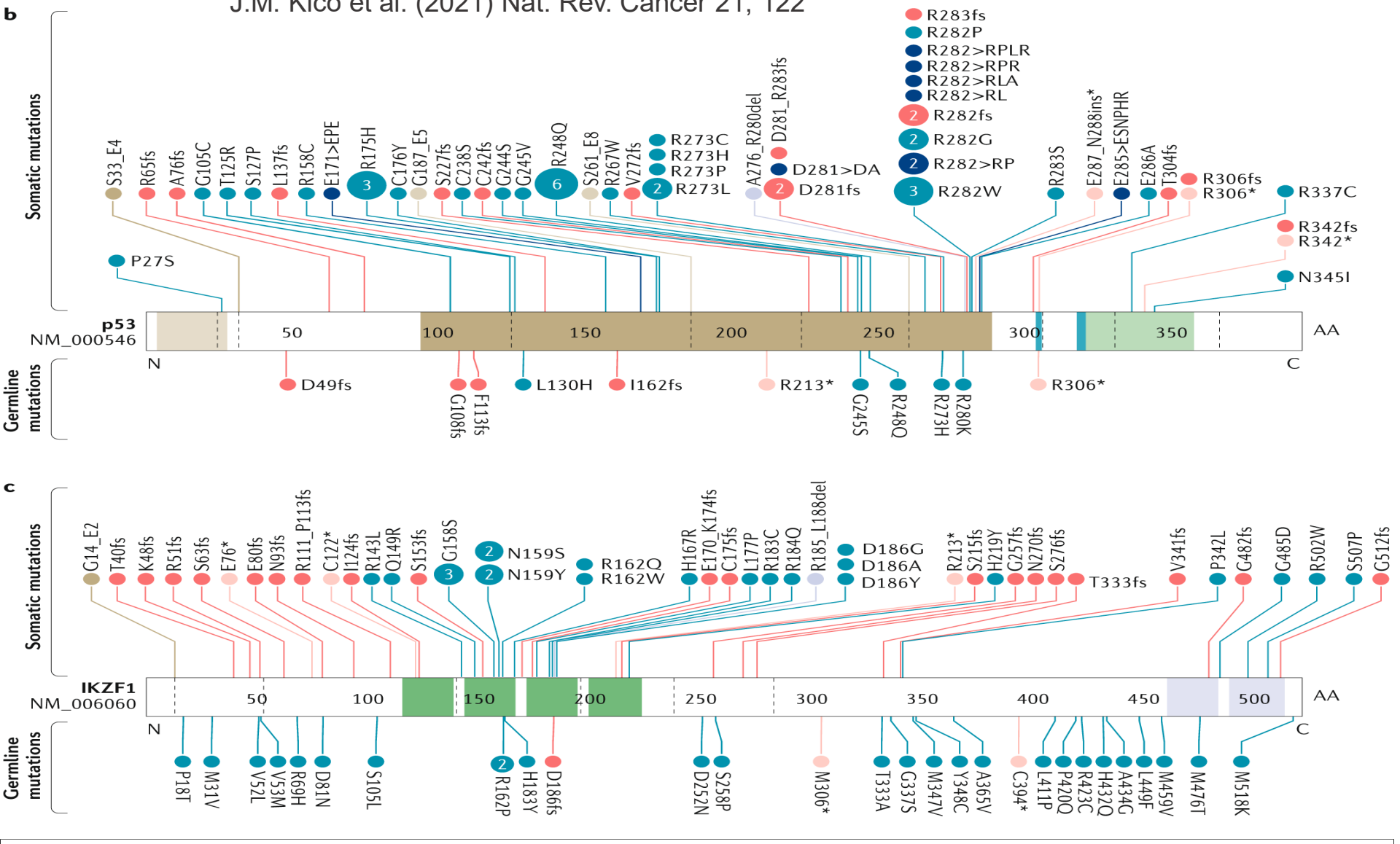
# Frequency of Cytogenetic Subtypes of Pediatric ALL




https://radiologykey.com/acute-lymphoblastic-leukemia/

# Somatic and Germline Mutations in Pediatric ALL

J.M. Klco et al. (2021) Nat. Rev. Cancer 21, 122



# MultiOmics Profiling Meets the Real World of Clinical Medicine and Care Delivery

- oncology in the vanguard in clinical adoption

**BUT**

- stark dichotomy in understanding/adoption in community oncology settings versus academic medical centers/large provider networks
  - estimated only 15% pts in community settings receive profiling
- continued escalation of technical and conceptual complexities
  - Board certification, CME, MD/HCP curricula
- validation and adoption of ML/AI algorithms for clinical decisions
  - legal implications for use/non-use in clinical care

# Deep Phenotyping:
# "Much More Than Omics"- Overcoming the Curse of Reductionism

## From Womb to Tomb: Systematic Integration of Diverse Health Data




## SDoH, Lifestyle, Environment, Health Disparities




# Expanding the “Care Space” in Healthcare

**Healthcare Beyond The Clinic**

**Remote Health Status Monitoring**

**Smartphones, Wearables, Devices and Digital Services**

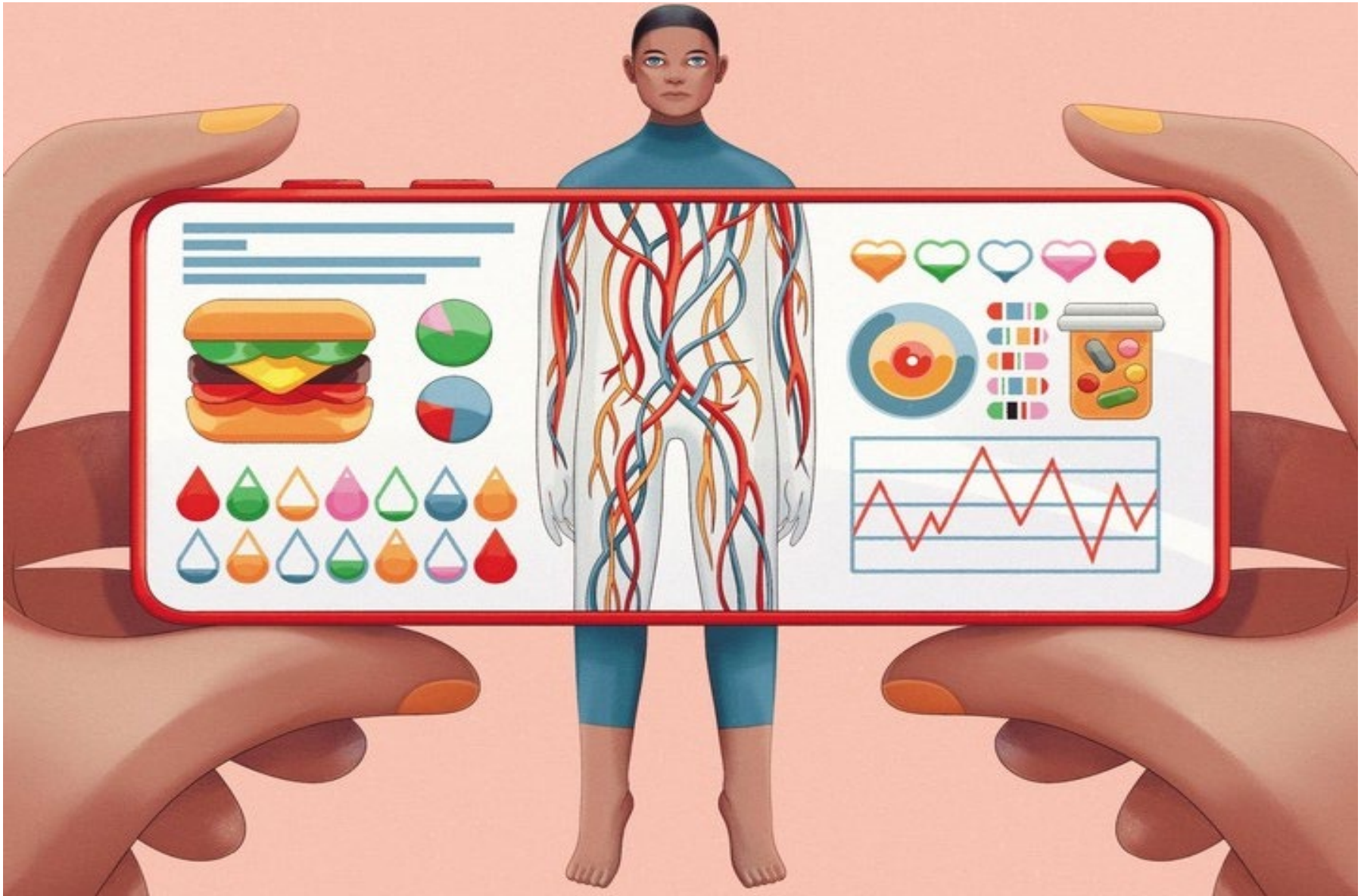
**M4: Making Medicine More Mobile**

**AORTA: Always On, Real Time Access**

# Wellness Apps for Fitness, Diet and Exercise



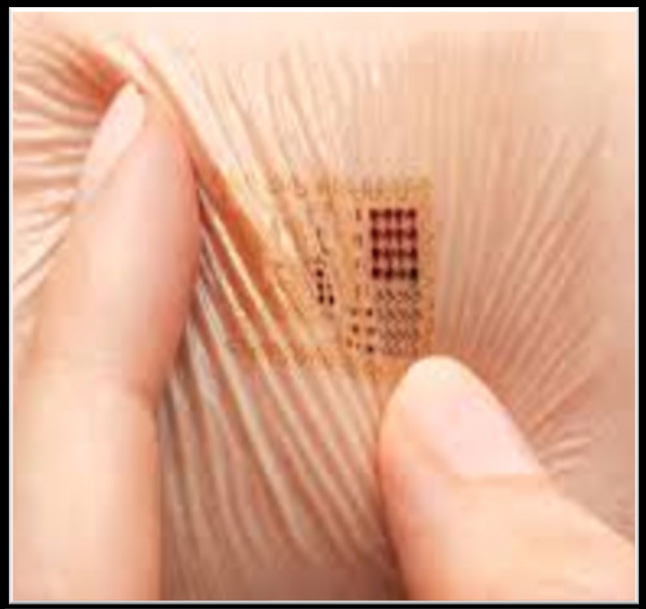
# Wearables and Mobile Devices: From Fashionable Trend to Routine Component of Remote Health Status Monitoring



https://www.economist.com/technology-quarterly

# Remote Monitoring of Health Status and Rx Adherence



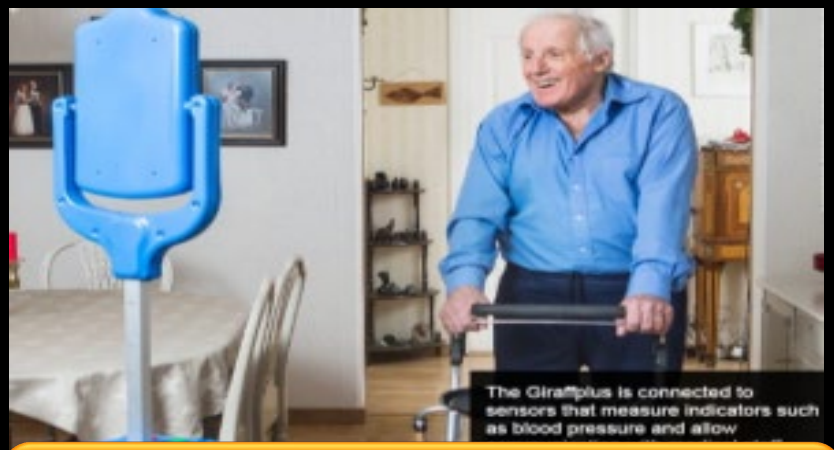



# Grey Technologies and Ageing in Place: Independent But Monitored Living for Ageing Populations

**Rx adherence**

**cognitive stimulation**


**in-home support and reduced readmissions**



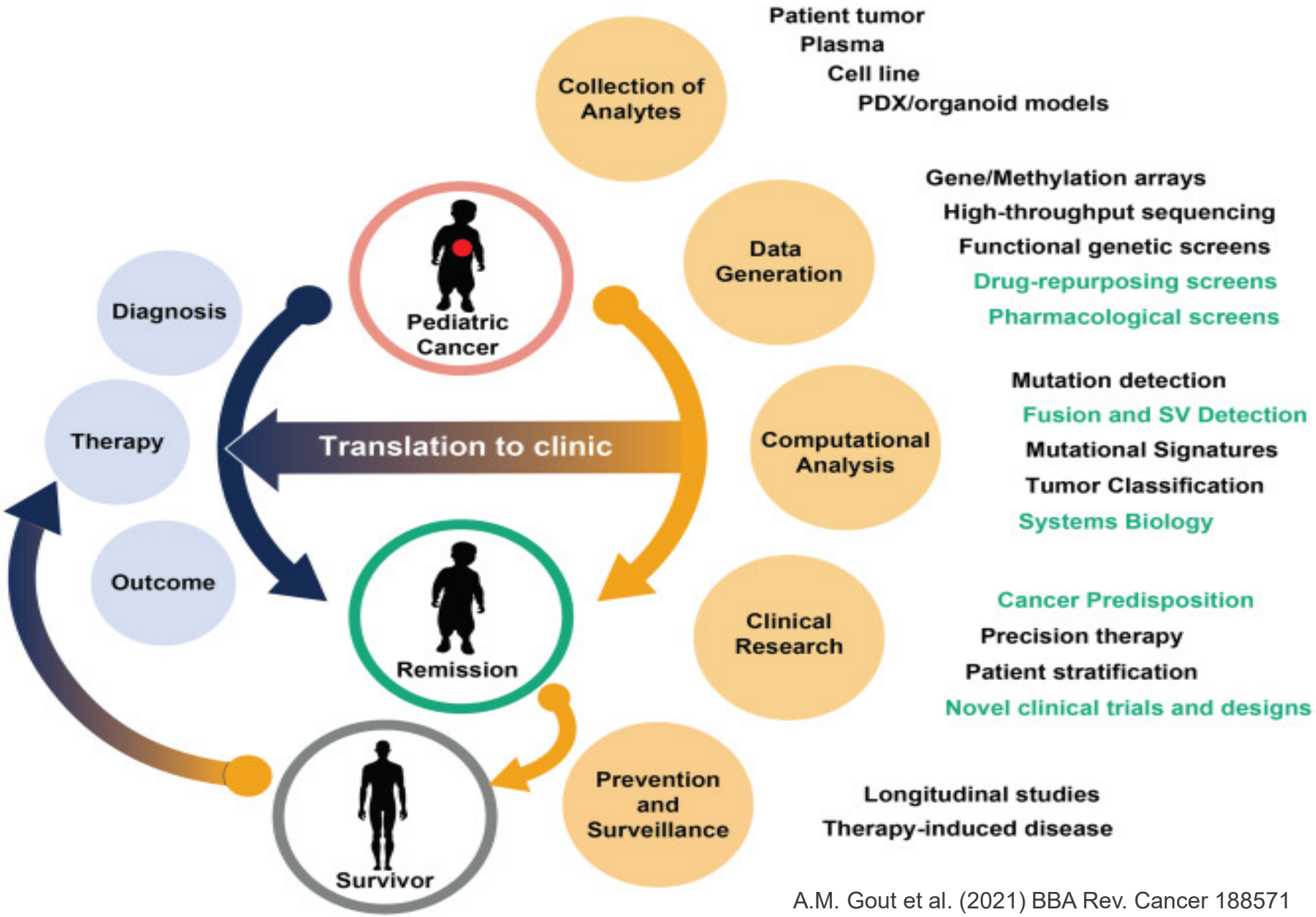

**reduced office visits**

# Precision Oncology

# The Evolution of Precision Oncology: Hematological Cancers (H) Versus Solid Tumors (S)

- shared MultiOmics analytical platforms for molecular phenotyping
- levels of clonal heterogeneity in advanced disease (S>H)
- different challenges in clinical management, MDx/Rx protocols and clinical trial design
- pediatric/adolescent patients vs adult patients

# The Landscape of Translational Science in Pediatric Cancer




A.M. Gout et al. (2021) BBA Rev. Cancer 188571

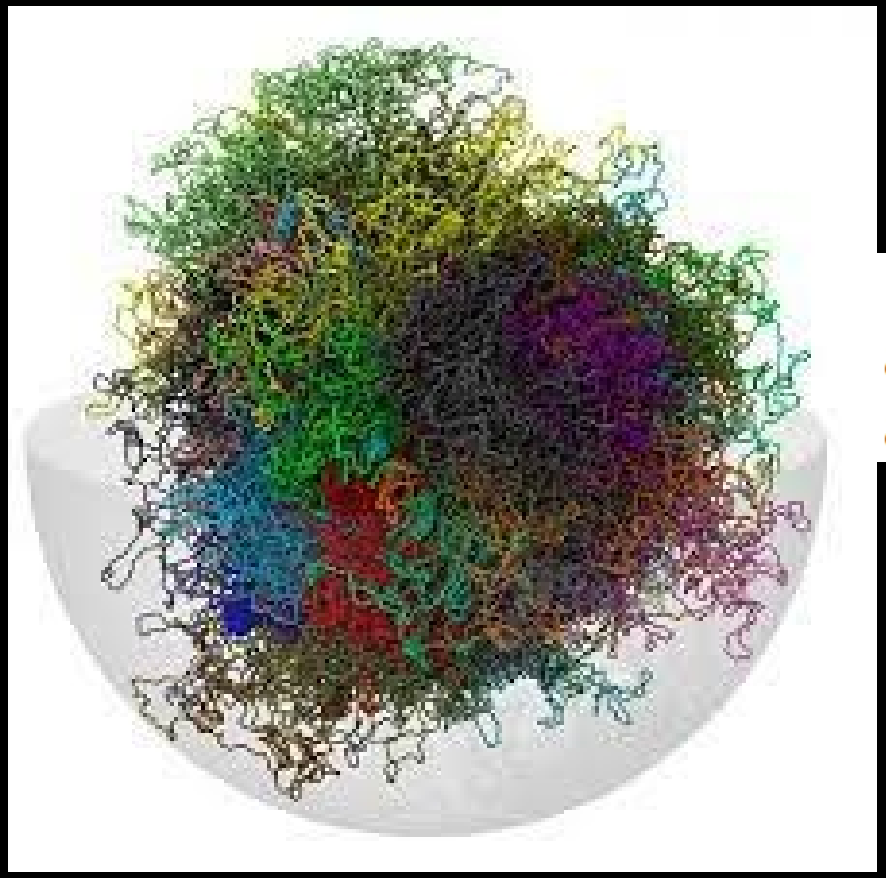
# The Transition to Routine Whole Genome and Transcriptome Sequencing in Cancer

- expansion of germ line predisposition loci
- growing recognition of the extravagant repertoire of gene fusions and splice variants detected by WTS vs RT-PCR
- role of non-coding variants in gene expression and RNA regulation
- long range/cross-chromosomal effects due to rearranged topology of nuclear chromosome packing
- microbiome-mediated effects on immune responses and cancer Rx efficacy

# Increasing Recognition of the Role of Noncoding Genetic Variants in Cancer

- Encyclopedia of DNA elements (ENCODE) and Epigenome Map
  - most noncoding variants located inside regulatory elements (promoters, enhancers, silencers)
- role of noncoding variants in regulation/modulation of local and distal gene transcription
  - challenge to identify target genes
  - enhancers can function upstream or downstream of target genes up to 1 million bp via chromatin looping

# The 4D Genome:
# Mapping Topologically Associating Domains (TADs) and Long-Range Genomic Interactions



Nature Genetics (2022) 54,170

Noncoding genetic variation in *GATA3* increases acute lymphoblastic leukemia risk through local and global changes in chromatin conformation

# Precision Oncology and the Evolution of Cancer Therapies

# The Evolution of Cancer Therapies

- chemotherapy
- targeted therapies
- biologics
  - antibodies and derivatives (ADCs, bispecifics)
  - cell and gene therapy
  - cancer vaccines
- delivery systems
  - optimize Rx localization to disseminated lesions
  - improve pharmacokinetics and/or reduce AEs

# Lineage-Agnostic Biomarker-Driven Targeted Molecular Therapies in Cancer

- inhibitors of kinase fusion-driven cancers
- immune checkpoint inhibitors
- novel gene fusions and new Rx targets
- ongoing clinical trials to study benefit demonstrated in adult cancers in pediatric cancers with same molecular markers

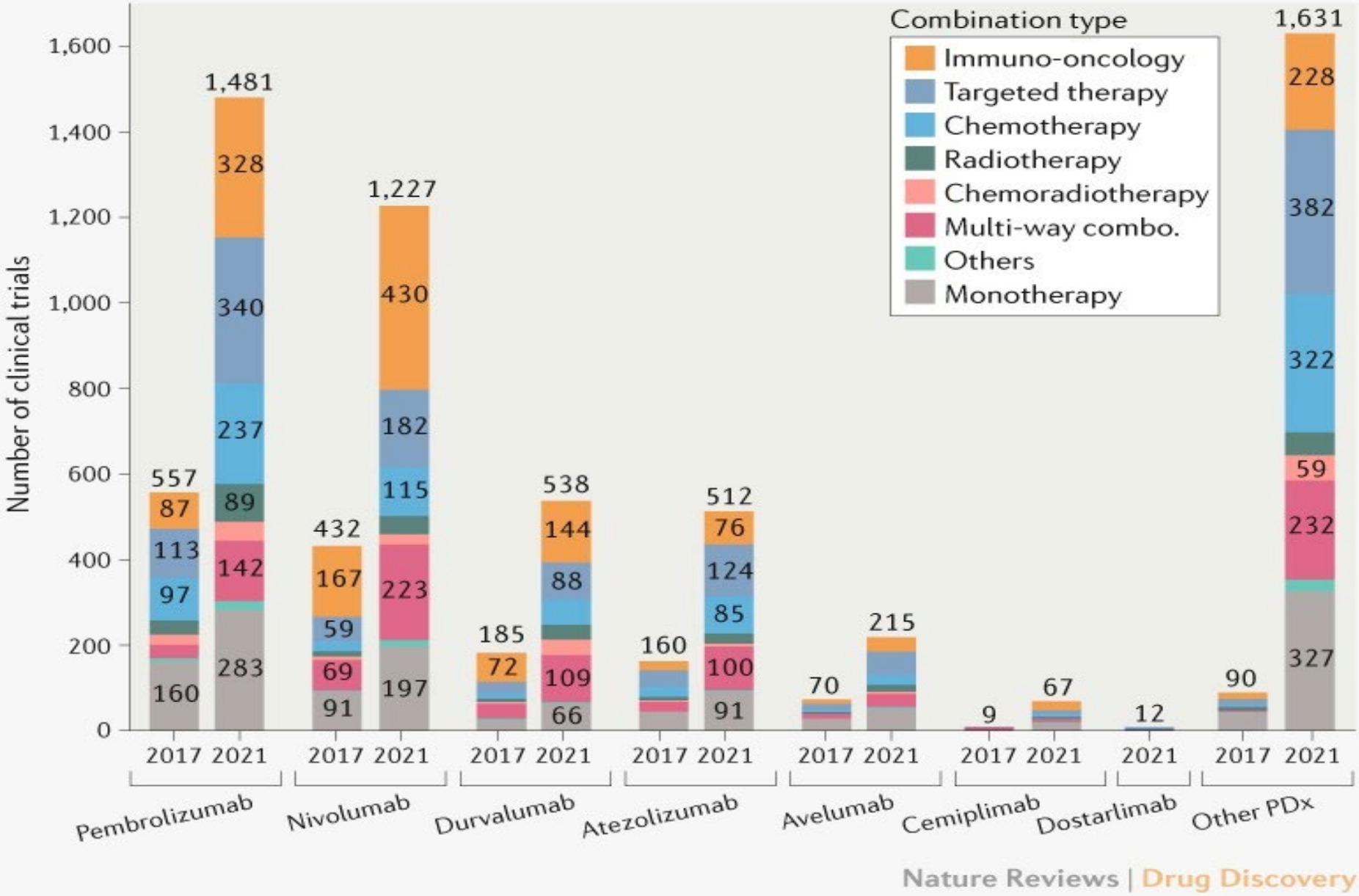
# High Response Rates in TKI Therapy of Pediatric Cancers With Kinase-Driven Fusions

| Fusion | Therapy |
|---|---|
| ALK | crizontinib, ceritinib, entrectinib |
| NTRK | larotrectinib, entrectinib |
| BCL-ABL | imatinib, dasatinib, nilotinib |
| ROS-1 | crizotinib, entrectnib |

# Cancer Immunotherapy

- impressive efficacy of CAR T therapies in hematological cancers
- efficacy of CAR T in solid tumors still uncertain
- valuable impact of immune checkpoint blockade Rx in solid malignancies
  - non-responder (NR) fraction still substantially higher than responders (R)
  - lack of biomarkers for pre-therapy ID of R and NR cohorts
- high cost, complex clinical management protocols
  - acute AEs and unknown long-term sequelae

# The Landscape of Anti-PD1/PDL1 mAb Clinical Trials

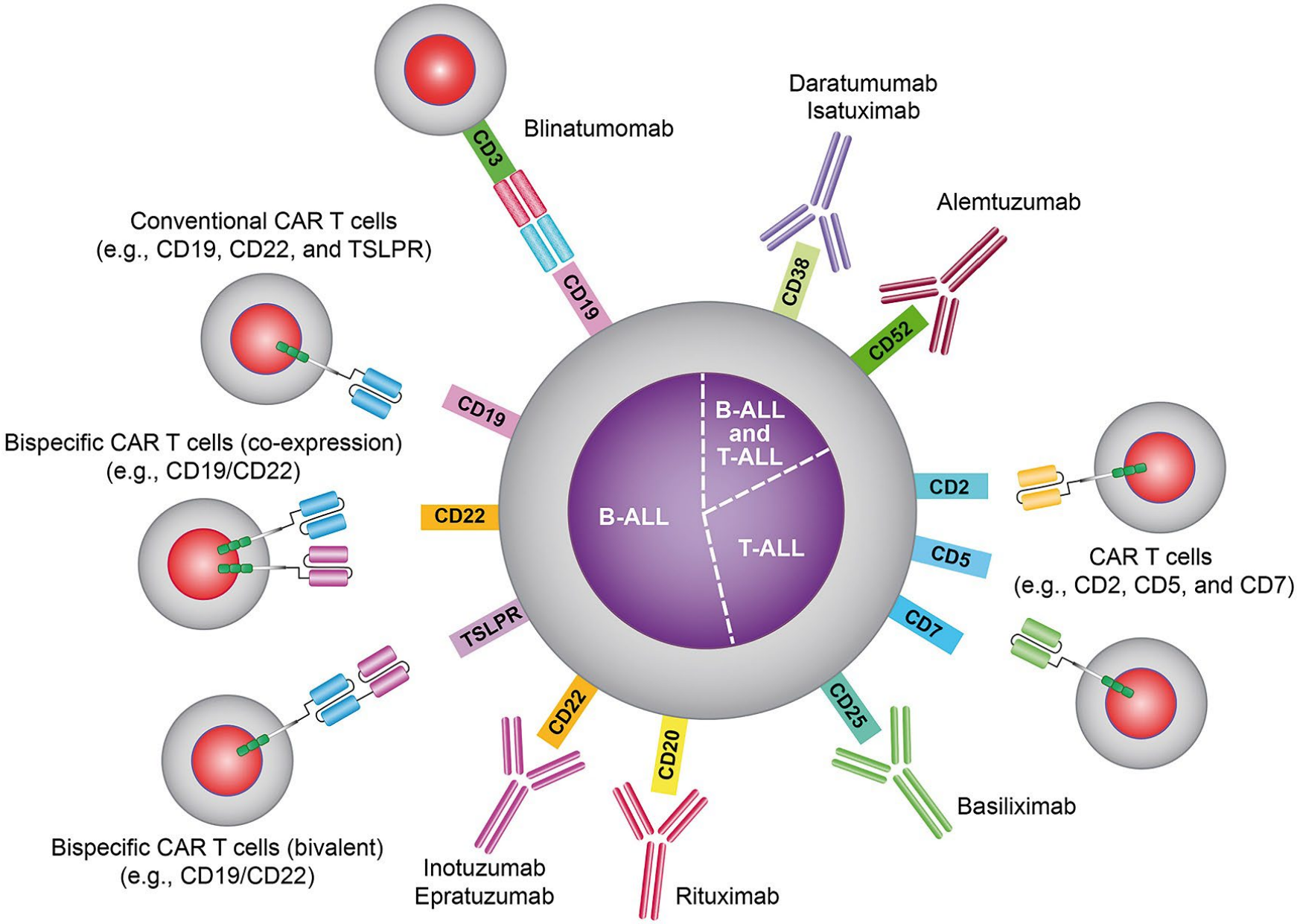



https://www.nature.com/articles/d41573-022-00030-4

# Cancer Immunotherapy

- FDA criticism of plethora of ‘follower’ I/O checkpoint inhibitors for solid malignancies
- new wave of multi-agent combination clinical trials
  - I/O + I/O, I/O + targeted Rx, I/O + I/O + targeted Rx
- flying blind
  - inadequate insights into dose selection, frequency, Rx sequence and duration

# Immunotherapy in ALL




H. Inaba and C.G. Mulligan (2020) Haematologica 105, 2524

# CAR T Therapy in Hematological Cancers

- 5 FDA products for relapsed and/or refractory B cell malignancies
- currently approval only after disease progression on two prior lines of treatment and infusion at approved center
- ongoing evaluation of earlier identification of eligible patients for first line
- quality and suitability of harvested T cells impacted by prior treatments
- exploration of apheresis and cryopreservation prior to additional lines of therapy that might reduce T cell fitness

# GMP Manufacturing for Cell and Gene Therapy

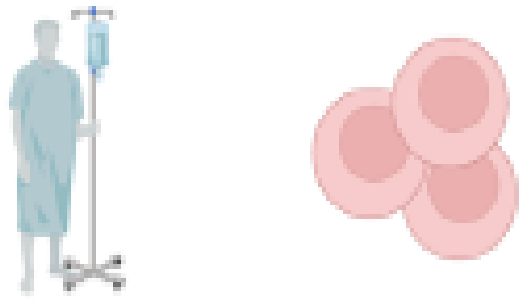

Right: https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.bio-techne.com%2Fresearch-areas%2Fcell-and-gene-therapy&psig=AOvVaw3KfhndHuP4DKci1R6Xcydh&ust=1653766881363000&source=images&cd=vfe&ved=0CA4Q3YkBahcKEwi4q-b3t4D4AhUAAAAAHQAAAAAQAw

# Vein-to-Vein Autologous CAR T Cell Manufacturing Timelines

- typically ≤ 2 weeks but typically extended by complexity of release criteria
  - transduction efficiency, # viable cells, sterility testing
  - logistics of shipping apheresis products
- enrollment to infusion time in major trials
  - ELIANA (45 days:  Tisagenlecleucel)
  - ZUMA-1 (17 days:  Axicabtagene ciloleucel)

# Trends in Design of CAR-T Therapies
# The Shift from Autologous to Allogeneic T-Cells

## Ameliorate issues with autologous cell starting material



Patient-derived (autologous) T-cells

- ⊕ Host compatibility, FDA approved
- ⊖ Cell quantity and quality concerns
- ⊖ Time-consuming and costly manufacturing process

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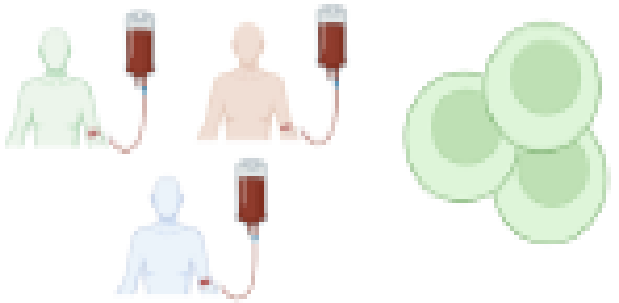


Healthy Donor (allogeneic) T-cells

- ⊕ Unlimited pool of healthy donors
- ⊕ Reduced cost and manufacturing timeline eases patient access
- ⊖ GvHD and rejection

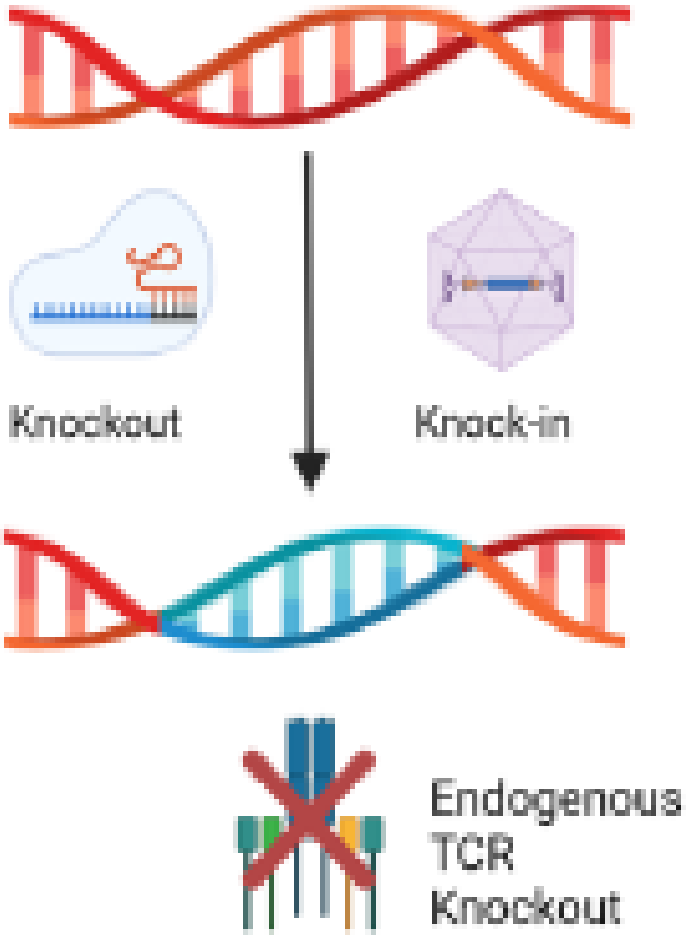
→ Addressed using CRISPR-Cas9 technology

Adapted From: A. Dimitri et al. (2022) Molec. Cancer 21, 78

# The Shift from Autologous to Allogeneic CAR T Cell Therapies

- how many doses can be produced consistently from a single apheresis from a healthy donor?
- manufacturing techniques to increase cell number also increase time in culture and potential for exhaustion and decreased potency
- engraftment and proliferation challenge versus autologous cells may necessitate more intense lymphodepletion chemotherapy regimen

# Trends in Design of CAR T Therapies
# CRISPR-Cas 9 Mediated TRAC Site-Specific Genome Editing




**CAR directed to *TRAC* locus**

- Non-random integration unlike traditional lentiviruses
- Uniform CAR Expression at *TRAC* locus with endogenous promotor
- No donor TCR-induced alloreactivity
- Low level of tonic signaling

*TRAC*: T cell receptor α constant locus

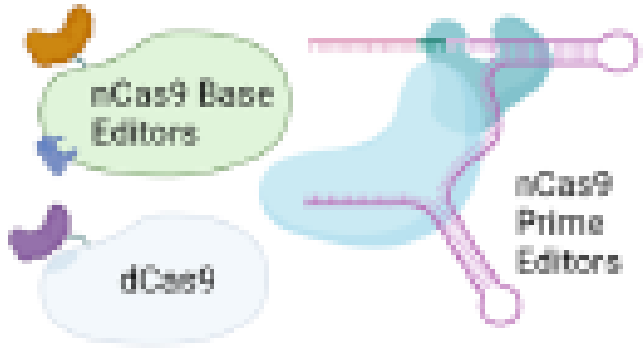
Adapted From: A. Dimitri et al. (2022) Molec. Cancer 21, 78

# Trends in Design of CAR T Therapies
# Multiplexed CRISPR-Cas 9 Editing to Enhance CAR-T Antitumor Efficacy

PD-1, CTLA-4, LAG-3, Fas

- Restrained differentiation
- Less exhaustion, greater persistance
- Reduced apoptosis

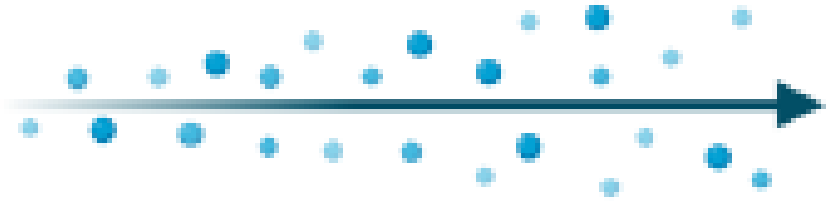
Cas9 variants to fine-tune transcriptional and epigenetic regulation




TRAC, B2M

- No GvHD
- No rejection
- Allogenic 'off-the-shelf' option

Enhanced Cytokine Profile

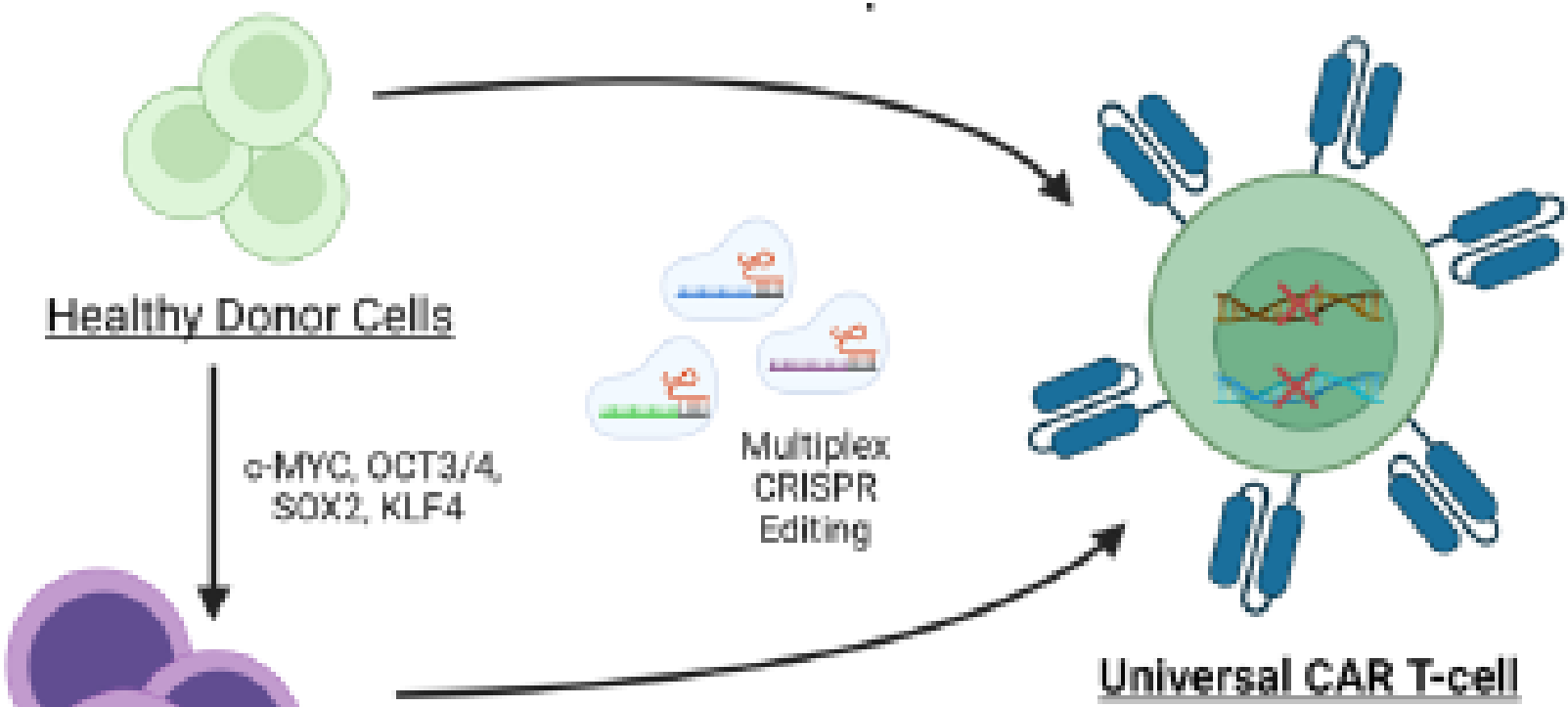


⊕ IL-7, IL-12, IL-15, IL-18

⊖ GM-CSF, IL-6, less inhibited by immunosupressive factors in TME

Adapted From: A. Dimitri et al. (2022) Molec. Cancer 21, 78

# Trends in Design of CAR T Therapies
# Editing of Clonal Master iPSC Cell Lines for Large Scale, Homogeous "Universal" CAR T Cell Manufacture




- Cultured indefinitely, no continuous healthy donor aphereses needed
- CRISPR edits maintained, producing consistent downstream differentiated T-cells

Adapted From: A. Dimitri et al. (2022) Molec. Cancer 21, 78

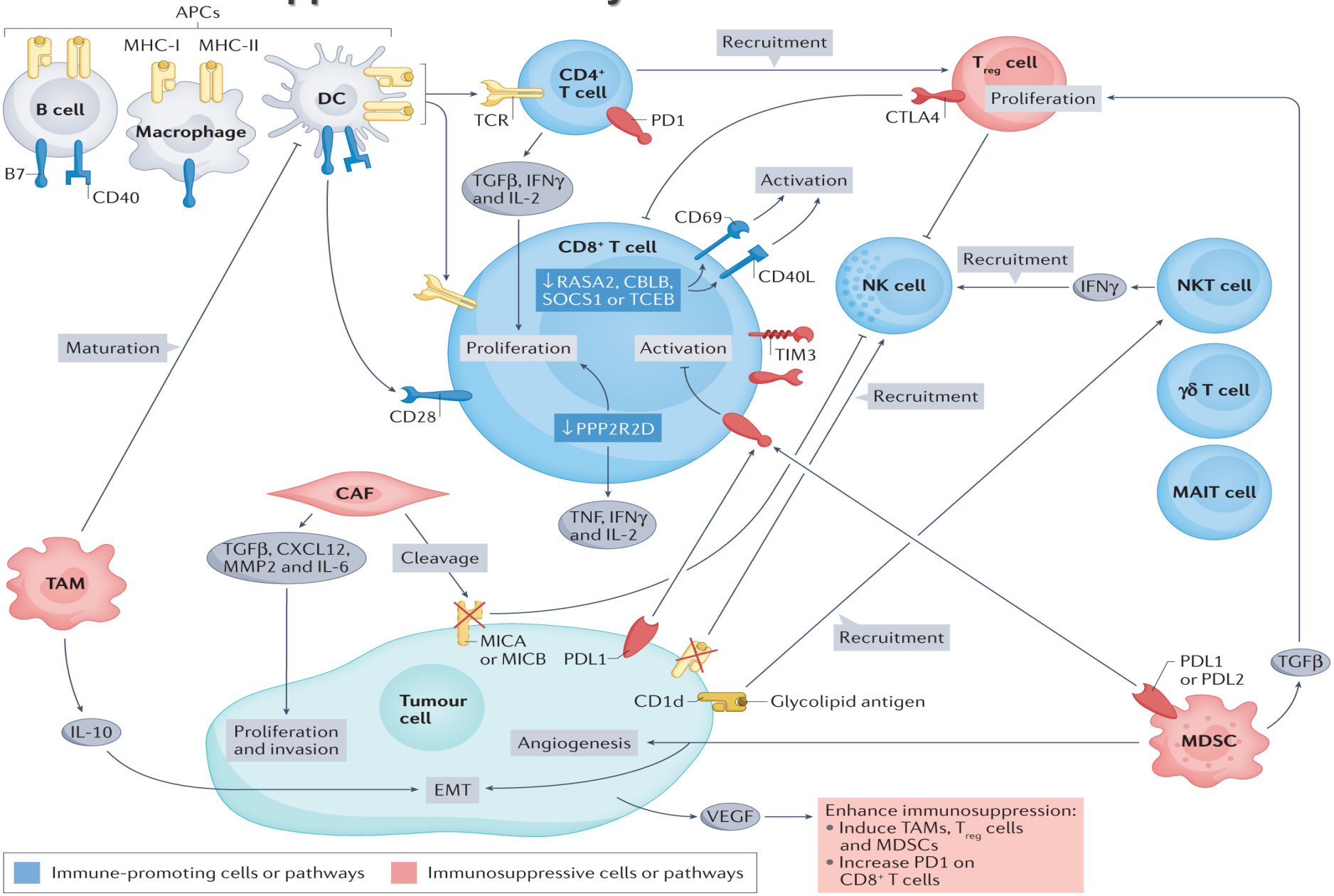
# Draft Guidance for Therapeutic Gene Editing and Drug Products (2022)

- focus on off-target effects
- first-in-human (FiH) studies should only enroll those with no other treatment options
- 15 year follow up

**Future Progress in Immunotherapy Requires New Levels of Systems-Based Analysis of Tumor-Immune Cell Interactions**

**Mapping the Biological Complexity and Dynamics of the Tumor Microenvironment (TME)**

# The Complex Interplay of Immune-Promoting and Immunosuppressive Pathways in the Tumor Microenvironment



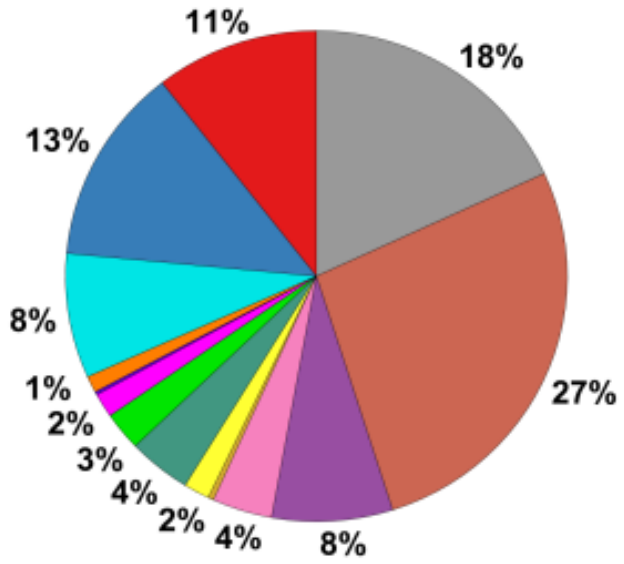

S. Kalaora et al. (2022) Nat. Rev. Cancer 22, 195

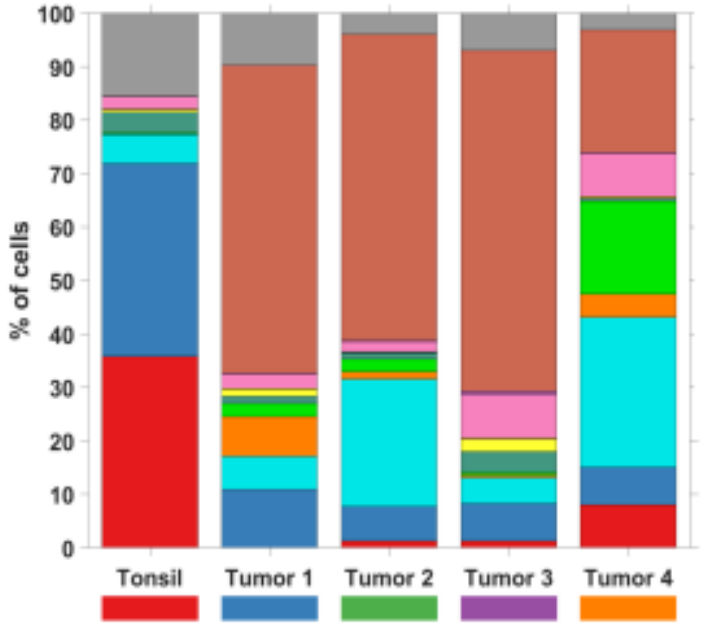
# Tumor-Host Immune System Interactions and Rational Design of Novel Cancer Immunotherapies (I/O)

- new analytical platforms for mapping the TME
  - genomic and transcriptomic biomarkers
  - cellular phenotypes (tumor and host)
  - spatial feature sets
- challenge of profiling TME in disseminated metastases
- liquid biopsy
  - monitoring cf/ctDNA, CK/LKs (plasma) and circulating immune cell subtypes (buffy coat)
  - fidelity in reflecting the ‘state spaces’ of tumor-host components in the tissue environment and/or Rx ID of response/resistance phenotypes ?

# Profiling of 835,823 Cells in FFPE Oropharyngeal Squamous Cell Carcinoma Reveals 14 Distinct Cell Types and Four Tumor Regions (Zonal Heterogeneity)

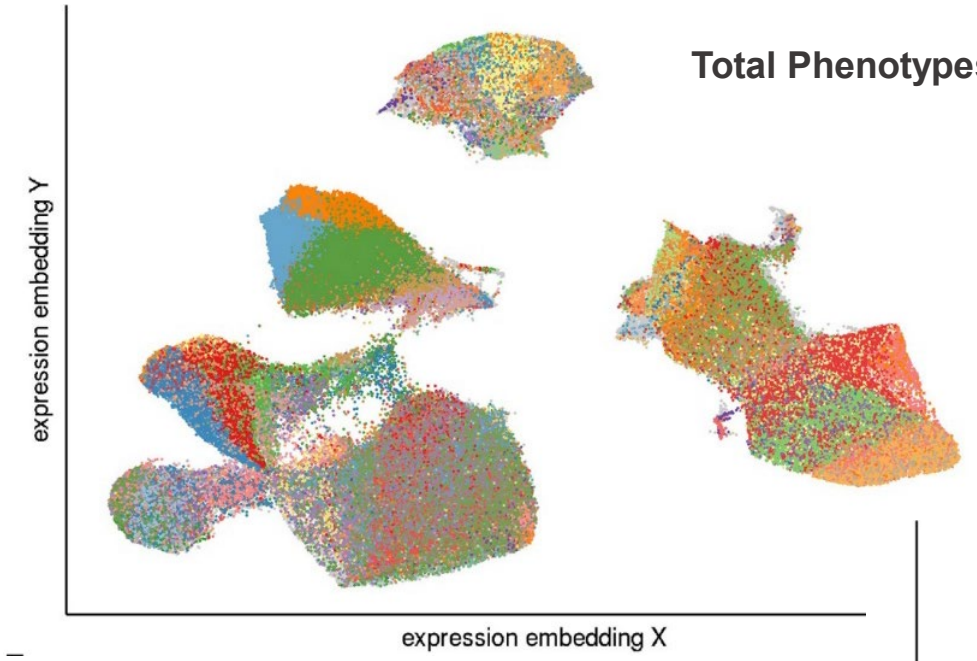

| cell type | |
|---|---|
| B cells | M1 Macrophages |
| CD4 T cells | M2 Macrophages |
| CD8 T cells | Ducts |
| Dendritic cells | ESMG |
| Monocytes | Squamous Epithelium |
| NK cells | Tumor cells |
| Proliferating | Vasculature/Lymphatic |

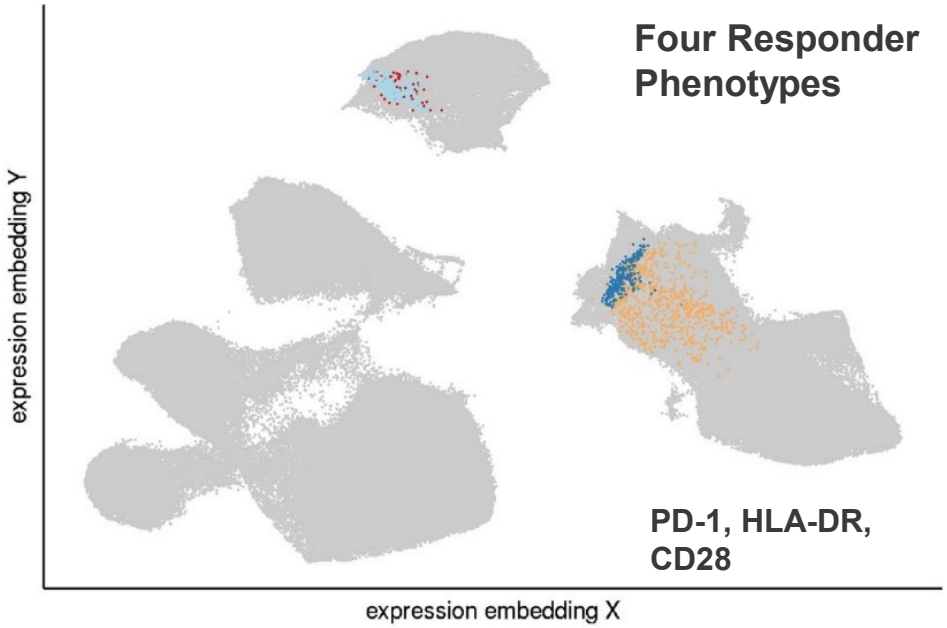



Akoya Biosciences PhenoCyclo-Fusion (2022)

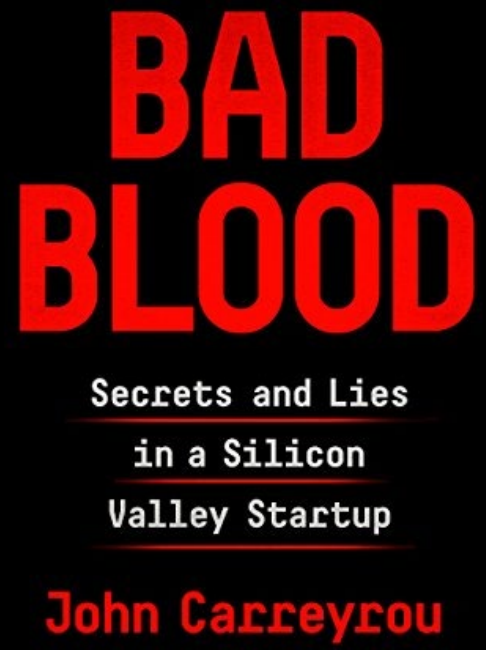
# High Dimensional Multiparameter FACS Immunophenotyping of Non-Responder and Responder anti-PD-1 Therapy in Pre-treatment Blood Mononuclear Cell Samples in Merkel Cell Carcinoma




Adapted From: E. Greene et. al (2021) Patterns 2, 100372

# The ‘Theranos Debacle’ and the Case for FDA Oversight of New High Complexity Molecular Diagnostic Assays

# Oversight of Molecular Diagnostics: FDA or CMS?

- evolution of high complexity, multianalyte/MultiOmics tests versus traditional unianalytic LDTs
- validation (fit-for-purpose)
  - preanalytical variation, standards
- analytical validation
  - high dimensional complexity
  - ML/AI algorithms
- the $V_1$, $V_2$…..$V_n$ challenge
  - relentless expansion of multianalyte associations with disease subtypes, incorporation of CDx-Rx combinations in clinical trials and Rx and product approvals

# The Verifying Accurate, Leading-Edge IVCT Development (VALID) Act

- expansion of FDA oversight of Medical Devices (1976) for oversight of high complexity in vitro clinical tests (IVCTs) (aka LDTs)
- bipartisan support of current Senate legislation
- grandfather provision for current LDTs
- major implications for academic/hospital clinical laboratories
  - FDA certification of instrumentation, assays and audit inspections
  - implemented 10/24 if Senate legislation passes

# Defining “Value” in Healthcare Will Intensify

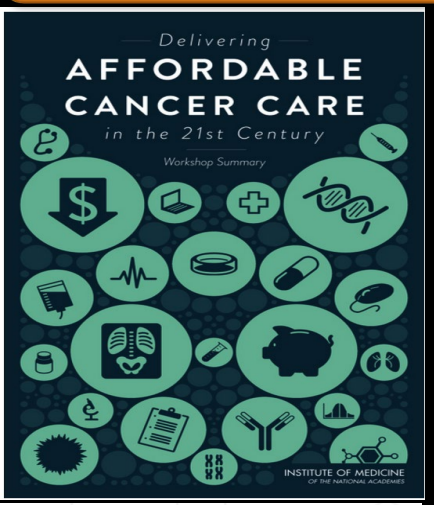
Medicare

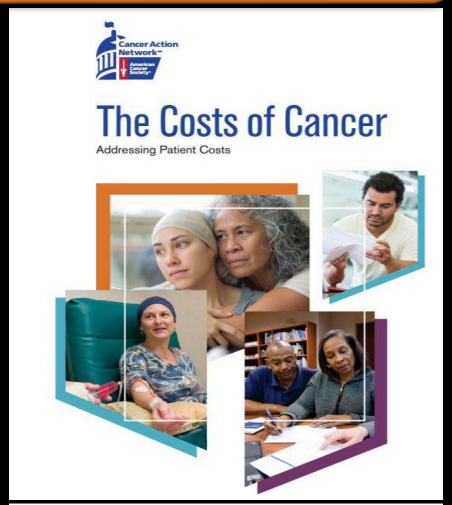

## Medicare limits coverage of $28,000-a-year Alzheimer's drug

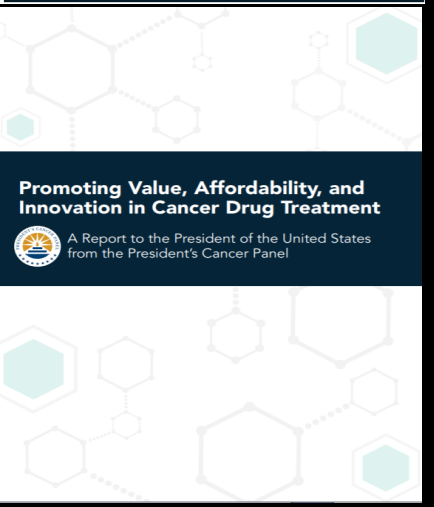
For Medicare to pay, patients will have to be part of clinical trials to assess Aduhelm’s effectiveness against early-stage dementia and its safety.

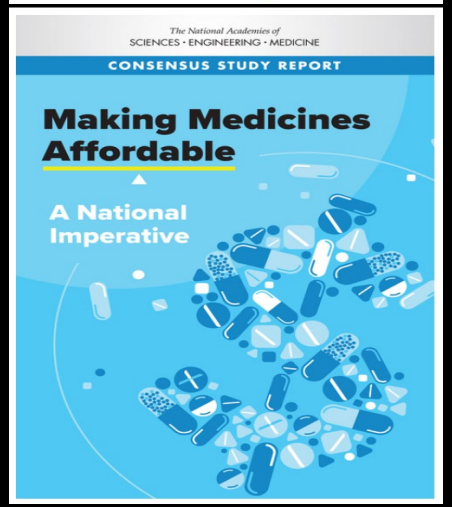
**NCD Decision 1/11/2022**

## Cancer Treatment Cost




## Value Framework





# Now Comes the Hard Part!

**Driving Precision Health and Large Scale Data Analytics into Routine Practice**

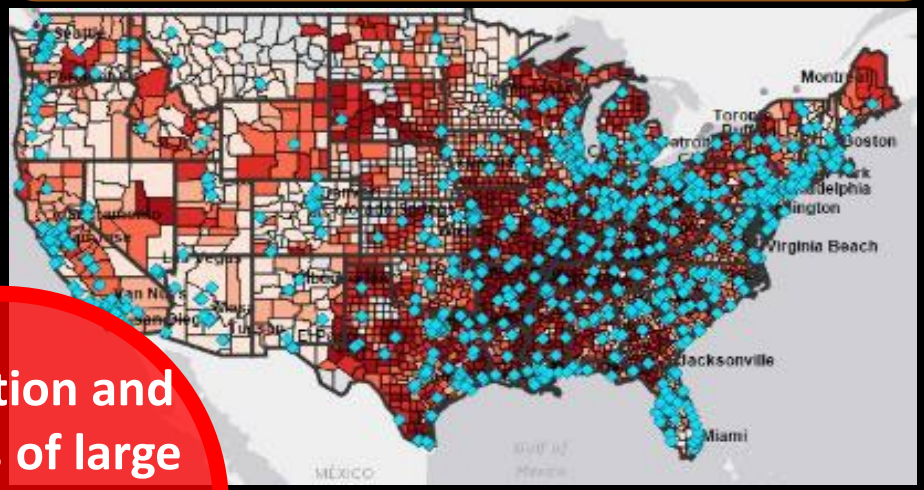
**New Incentives and New Delivery Models**

**New Participants and New Business Models**

# Precision Health and Digital Health: Evolving Inter-Dependencies

## Individual Data

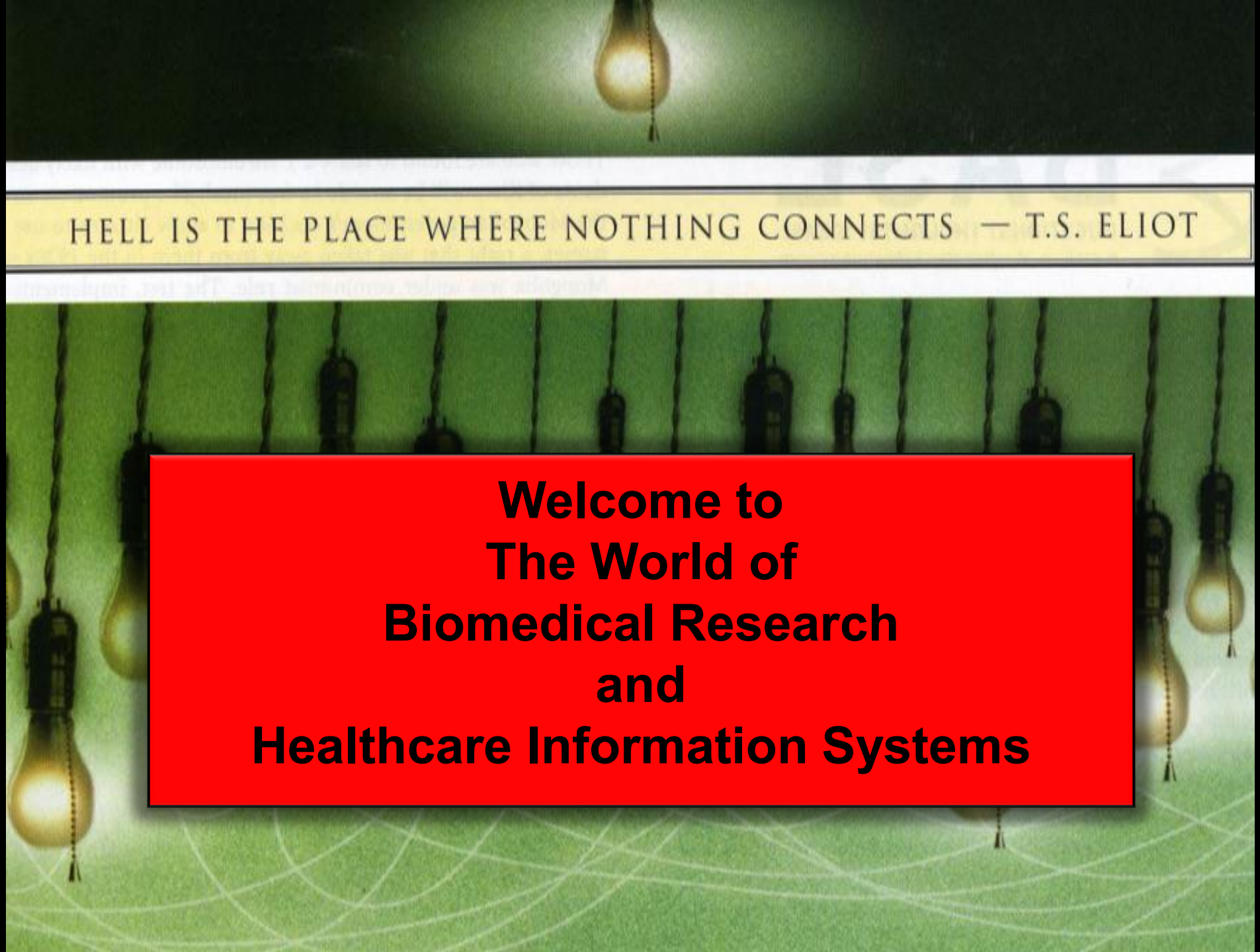
## Population Databanks




integration and analysis of large scale (petabyte, exabyte) diverse data classes

## Deep Phenotyping:

- multiOmics
- clinical history- EHR/PHR
- remote health monitoring
- socio-behavioral data
- environmental exposures




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

# Biomedical Data: Vast But Poorly Utilized

- inadequate standardization
- fragmented, incomplete, inaccurate data and uncertain provenance
- 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
- major impediments to research productivity, optimum clinical decisions and continuity-of-care for patients

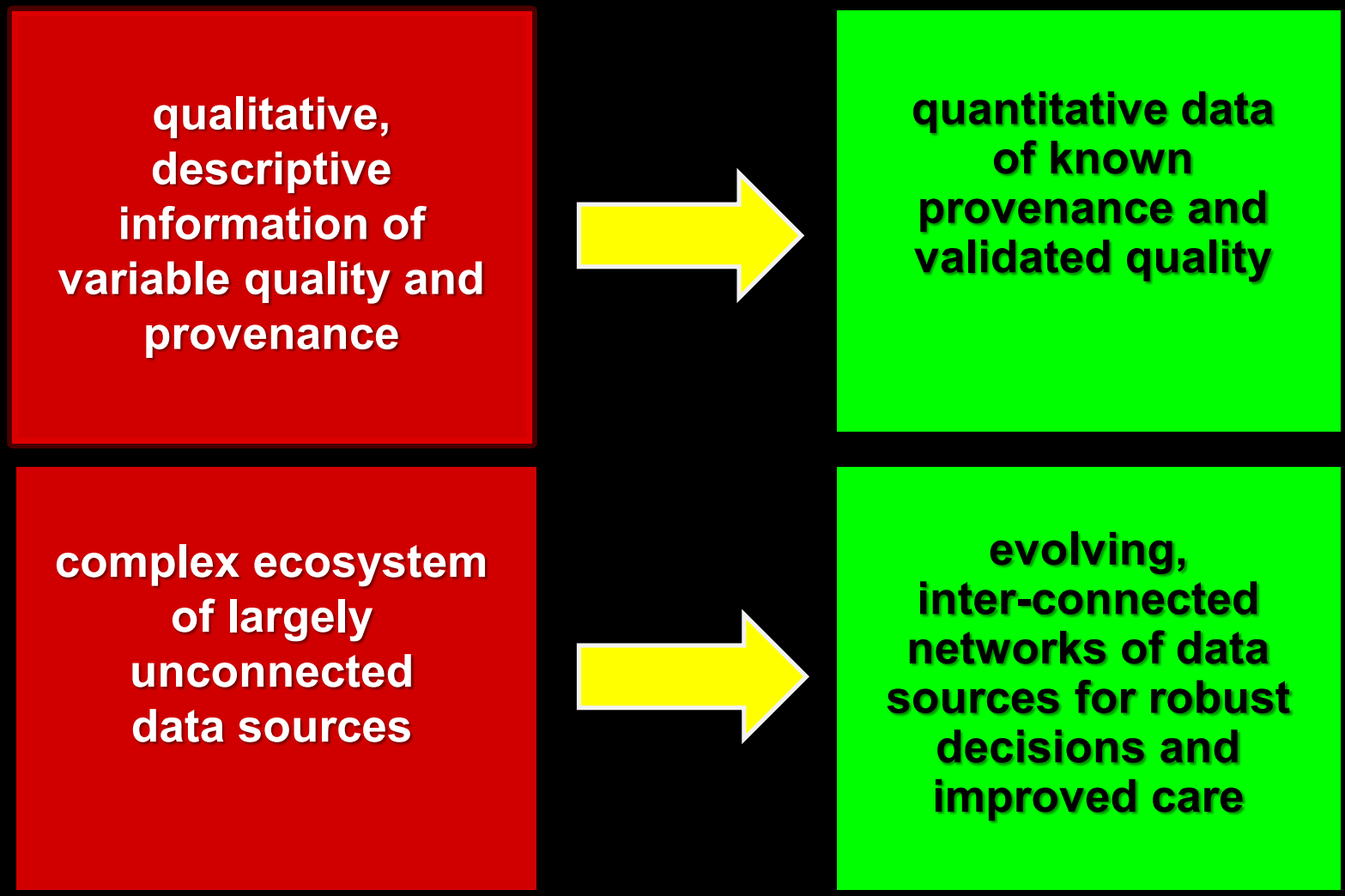
# Big Tech and Health Services: Disruptions Ahead?

# Big Tech: Big Provider: Big Pharmacy: Big Insurers and New Digital Channels for Healthcare Services


the metaverse land grab

blockchain platforms

# Precision Health and Digital Health: Building the Learning Health System



Managing the Data Deluge in Biomedical Research and Healthcare

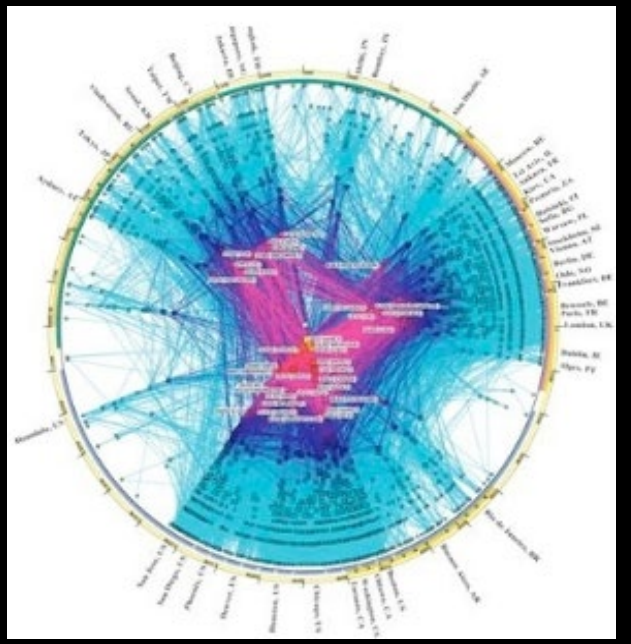
Design, Validation and Adoption of ML/AI for Large Scale Data Analysis

Co-Evolution of Professional Competencies With Advanced Computing and Automated Clinical Decision Systems

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

Isolated Data

Complex Networked Data



Complex Computational Data

# Building Personalized 'Digital Twins': Matching Individual Deep Phenotypes to 'Best Fit' Cohorts

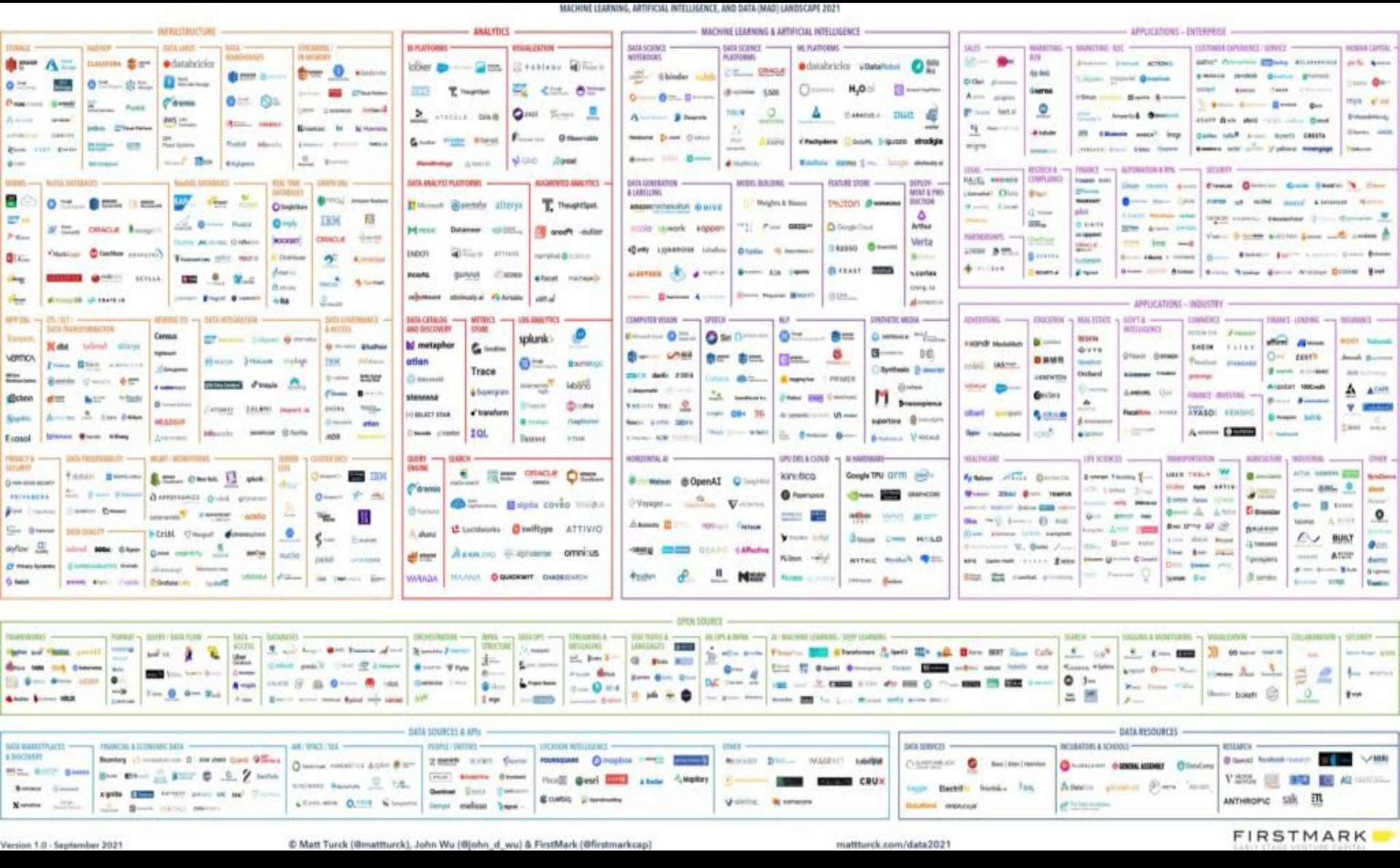
**Individual Data**

**Population Databanks**

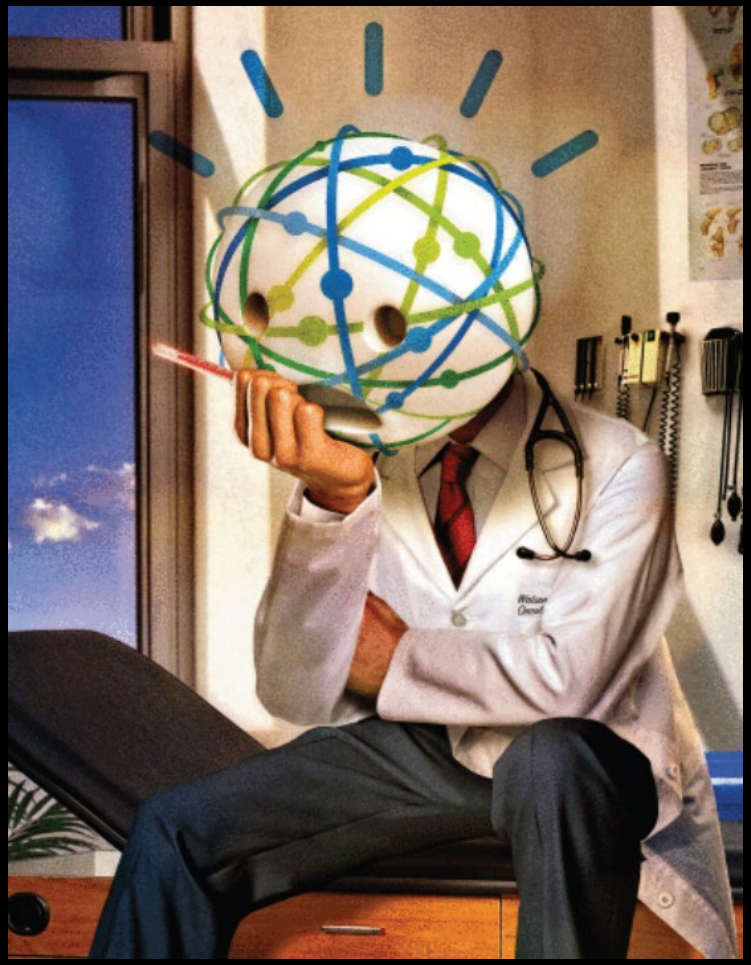
- 'digital twins and siblings' and imputed phenotypes
- disease predisposition and prevention
- earlier detection of subclinical disease and intervention
- selection of optimum treatment regimen for overt disease
- improved outcomes and QOL

# Machine Learning (ML) and Artificial Intelligence (AI): Massive Infusion of Private-Sector Funding and Entrepreneurial Activities

https://mattturck.com/data2021/

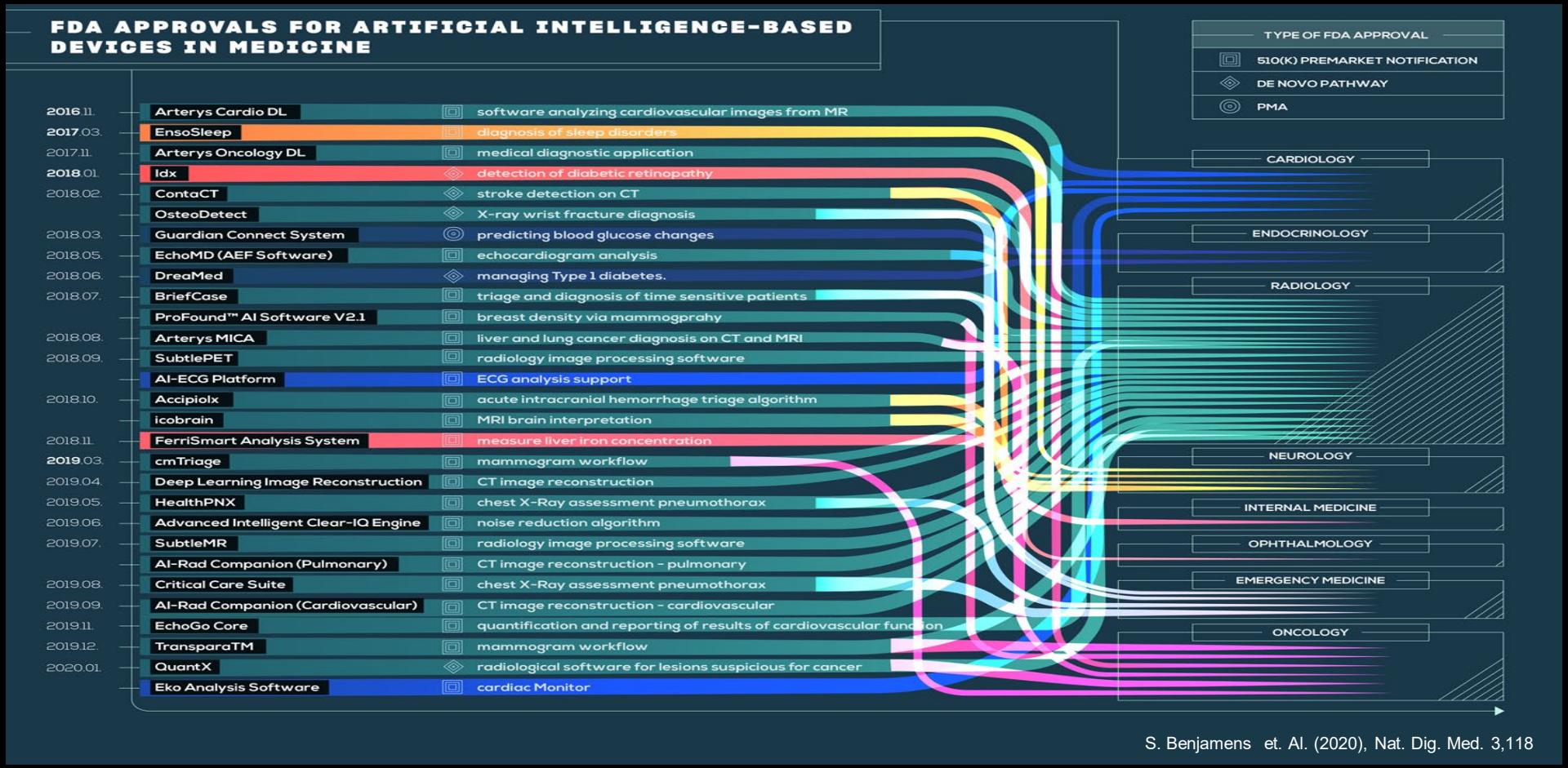


# Bias: The Omnipresent Danger in ML/AL Datasets
# IBM Watson and Cancer Care: A Classic Case Study



- overpromised and underdelivered
- underpowered training sets
- institution-specific data and bias
- risk to patients
- instructive precedent for more stringent AI validation standards

# 29 FDA Approved ML/AI-Based Medical Technologies




S. Benjamens et. Al. (2020), Nat. Dig. Med. 3,118

# How Will ML-AI Algorithms/Decision Analytics Be Validated and Regulated?




- how will regulators accommodate accelerating pace of changes in inputs, outputs and code construction in ML/AI algorithms ($V_1$, $V_2$, $V_n$….)?

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

- which clinical specialties/processes will be at risk of disruption 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
- how will ML-AI platforms alter payment schemes ?
- what new malpractice liabilities will emerge from failure to interpret and/or adopt ML-AI platforms?

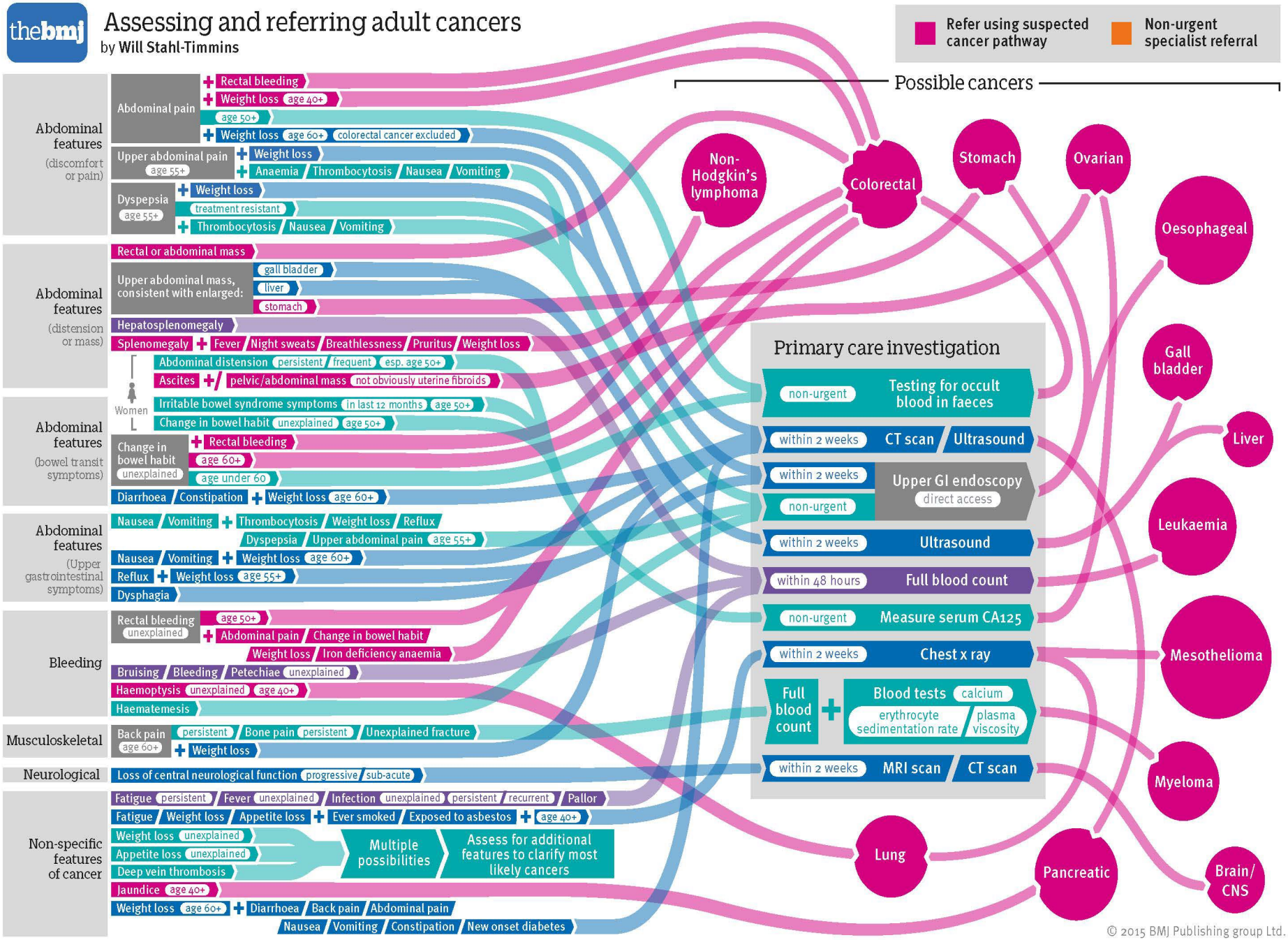
# Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Medical Education

## Data Deluge

## Cognitive Bandwidth Limits

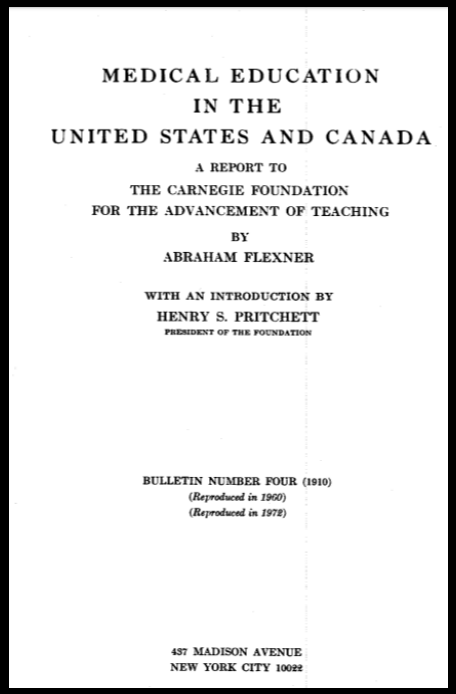
## Automated Analytics and Decision Support

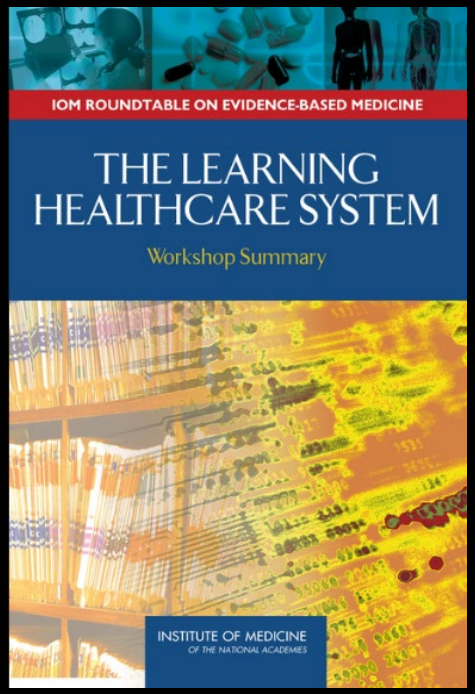
## Facile Formats for Actionable Decisions



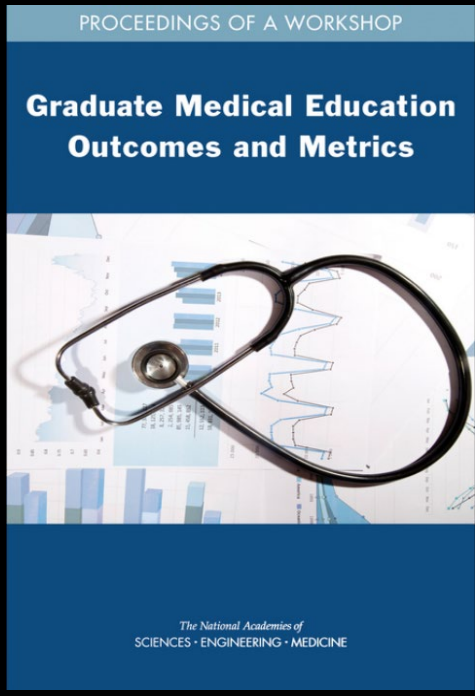

https://www.bmj.com/content/bmj/suppl/2015/07/17/bmj.h3044.DC1/adult_cancer_NICE_graphic_v3.1.pdf

# Major Transitions in Medical Education and Healthcare








**1910 - present** (science-centric)

**2000 - present** healthcare as a learning system (data-centric)

**2015 - ?** mastery of escalating complexity and massive data (network-centric)

# New Patterns of Learning

The Strategic Landscape for the US Health Ecosystem and the Evolution of Precision Oncology

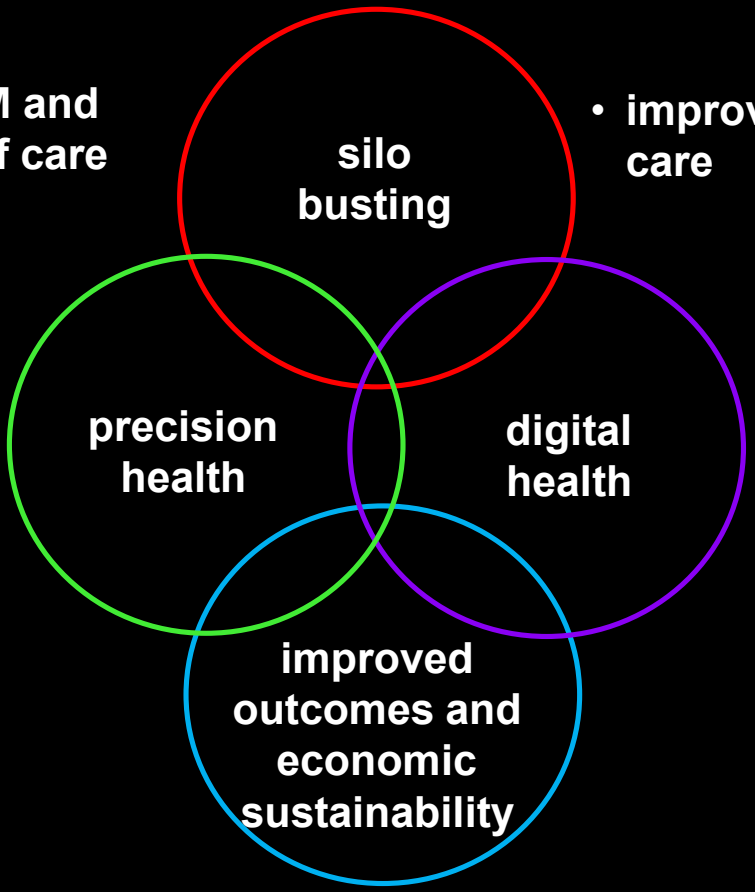
Challenges and Opportunities

# The Evolving Systemic Landscape for Optimizing Health

- telemedicine, RHM and decentralization of care services

- improved continuity in care

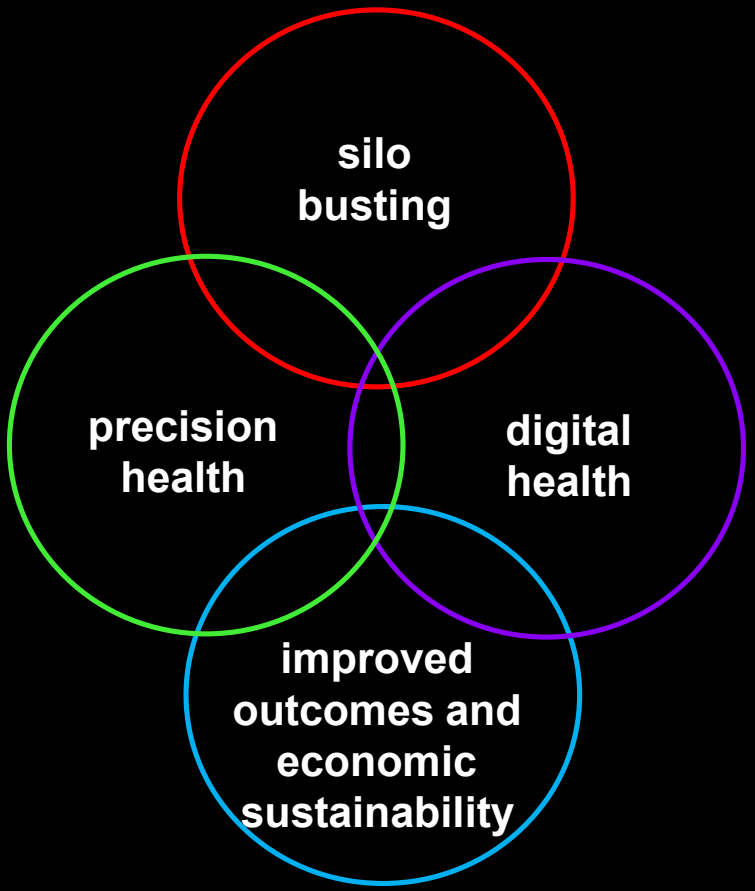
- new technologies for health risk identification and mitigation
- SDoH and health




- integration and analysis of large-scale data to optimize decisions – physicians, pts, payors
- consumer/pt expectations/Ux

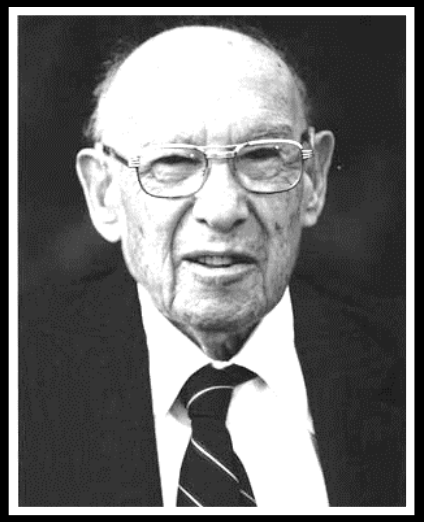
- new quantitative performance metrics
- intensified focus on VALUE

# The Evolving Systemic Landscape for Optimizing Health




- sustaining professional competencies in an era of accelerating technological change
- navigating the co-evolution of professional competencies and the rise of cognitive computing platforms in biomedical research and clinical medicine

# Unidimensional “Quick Fixes”

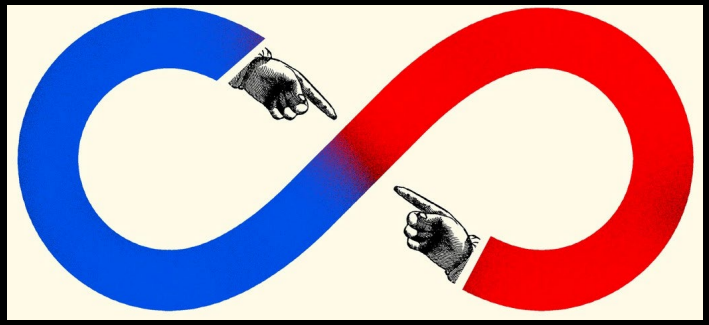


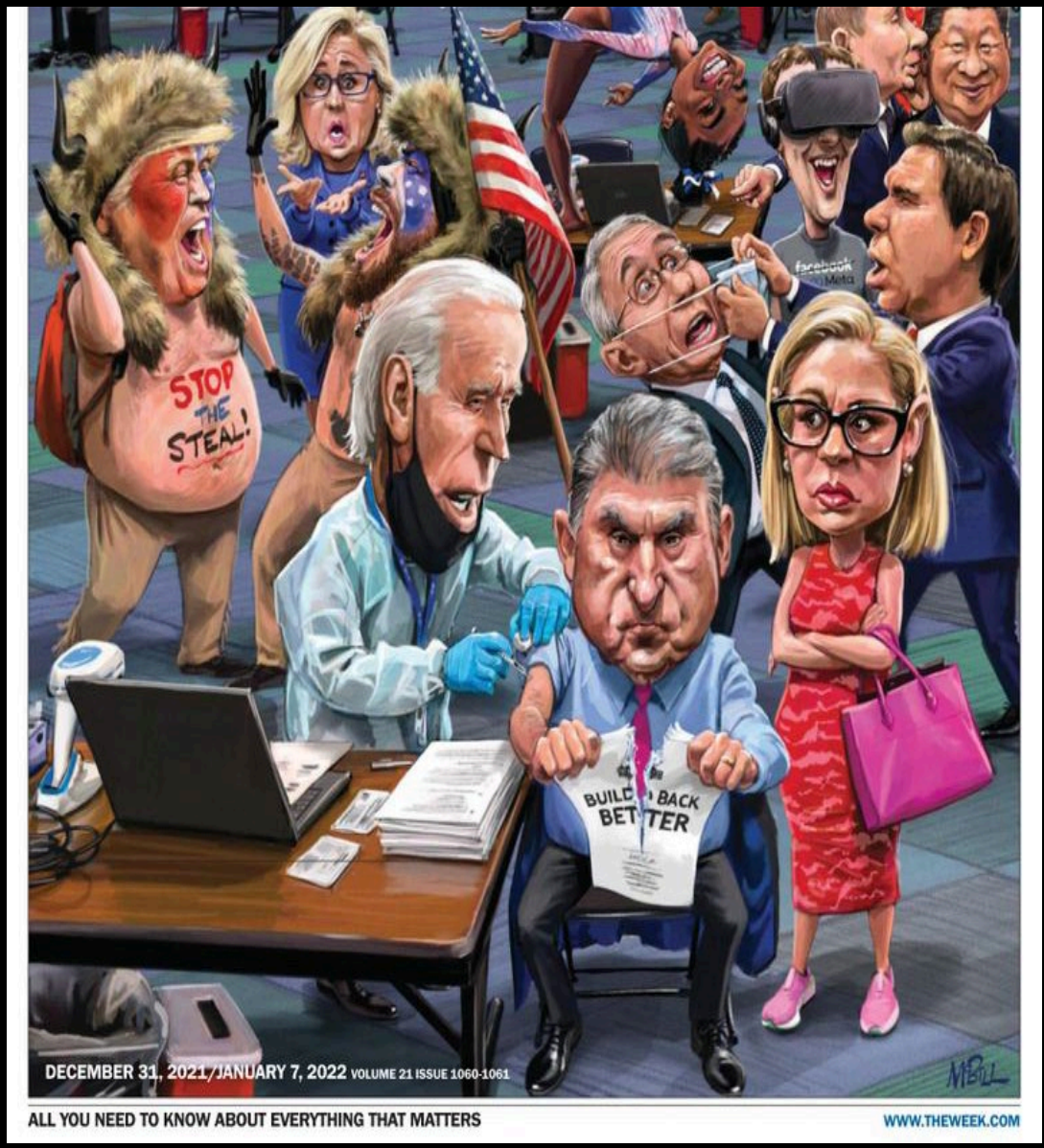
“The greatest danger in times of turbulence,
is not the turbulence,
it is to act with yesterday’s logic.”

- Peter Drucker

# The Challenge of Charting Health Policy in a Climate of Increased Social Divisions and Legislative Paralysis

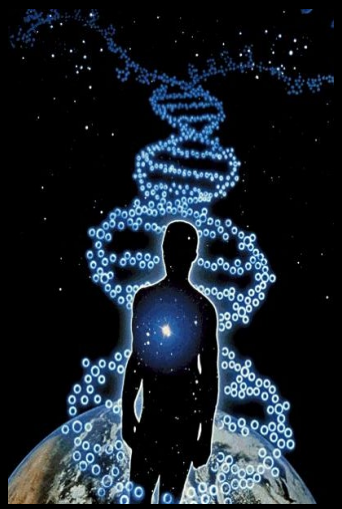
- Dysfunctional National Governance, Lack of Bipartisanship and Legislative Paralysis
- Legislative Technical Illiteracy, Retreat from Complexity and Short-Term 'Quick-Fixes'
- Dangerous Societal Divisions on Multiple issues
- Implications Well Beyond Healthcare: A Threat to National Security and Technological Competitiveness ?



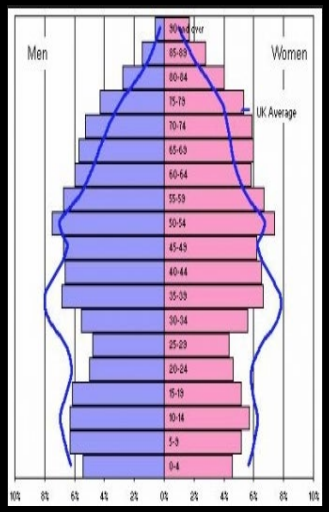


# Strategic Drivers in the Evolution of Health Care

**Precision Health Biotechnology, Synthetic Biology**



**Population Demographics and Disease Burden**




**IoMT: Ubiquitous Sensing and Sensor Networks**

**Big Data Analytics, Machine Learning and AI**

**Technology Convergence, Acceleration and Escalating Complexity**

**Identification of Health Risk and Mitigation**

**Defining "Value" in Healthcare Will Intensify**

**New Knowledge Networks**

**New Participants**

**New Organizational Models**

# Strategic Drivers in the Evolution of Health Care

Precision Health Biotechnology, Synthetic Biology

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**Slides available @ casi.asu.edu/presentations**

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