Complex Adaptive Systems Initiative
Arizona State University

THE UNIVERSITY OF ARIZONA Cancer Center

The Evolving Landscape for Precision Oncology: Multidisciplinary Integration, Big Data, Artificial Intelligence and New Collaboration Networks

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Slides Available at: **https://casi.asu.edu/presentations/**

Dr. David Samuel Alberts

1939 - 2023

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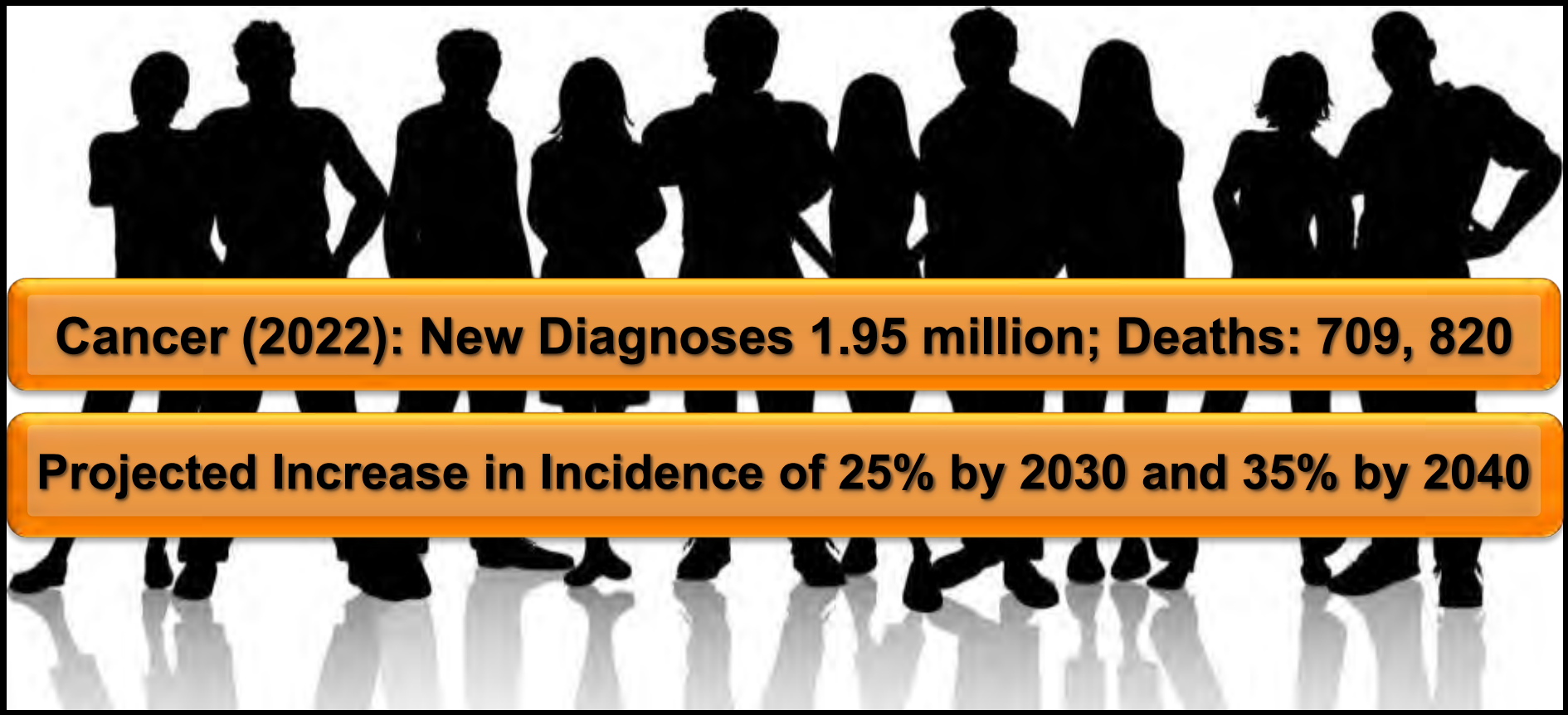
Presentation Outline

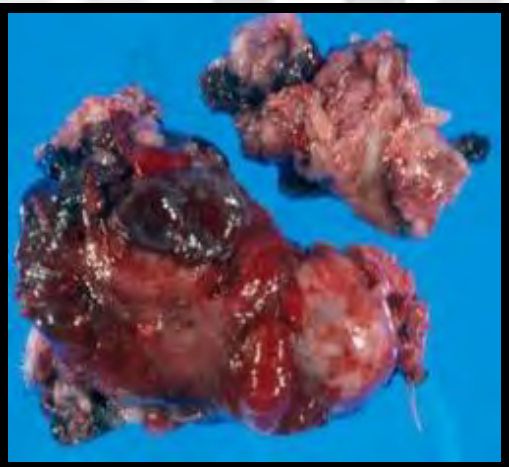
- strategic drivers of the precision oncology ecosystem
- from silos to systems
- the challenge of integration of large-scale, multidisciplinary, multimodal data
  - molecular, clinical, environmental
  - longitudinal profiling of the health to disease continuum
  - new diagnostic and treatment paradigms
- cancer (and all disease) as complex adaptive systems
- ‘big data’ in biomedical research and clinical medicine
- sustaining scientific and clinical competencies in an environment of rapid technological change and escalating complexity

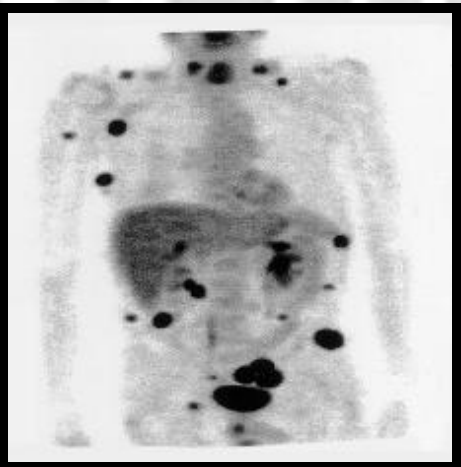
Confronting the Clinical, Economic and Human Toll of Cancer

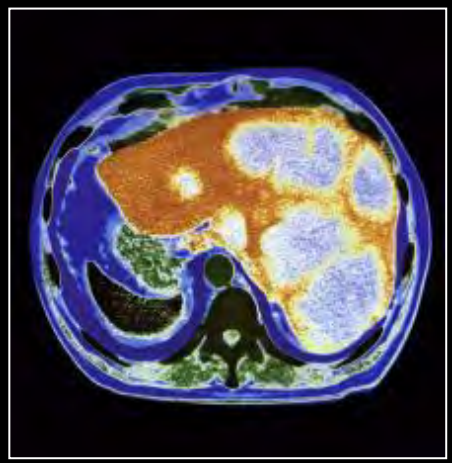


Cancer (2022): New Diagnoses 1.95 million; Deaths: 709, 820

Projected Increase in Incidence of 25% by 2030 and 35% by 2040





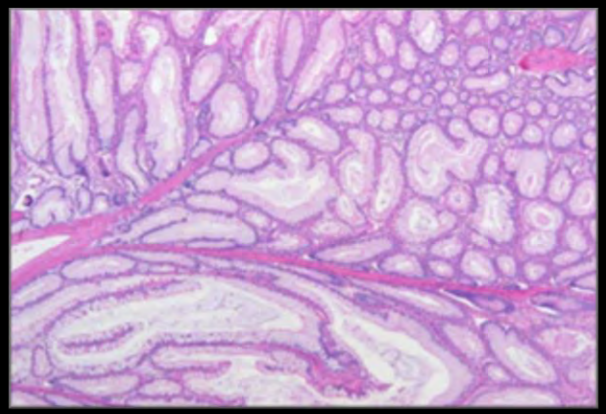


Progress in Cancer Treatment: A Scorecard

- major progress in hematopoietic cancers versus solid tumors
- significant PFS benefits in solid tumors for targeted agents and immunotherapy (alone or more typically in combination) in subsets of patients
  - lack of predictive diagnostics (Dx) to identify responders/non-responders (R/NR) patients
- survival for stage 4 solid tumors
  - modest but uneven improvements for breast, lung, prostate, CRC
  - glacial outcome in improvements for pancreatic, upper GI cancers and glioblastoma
  - disparities in access and affordability of care

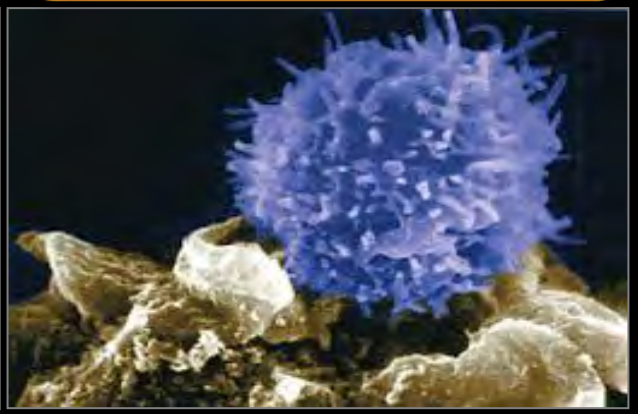
The Complex Biology of Cancer Progression and Treatment Resistance

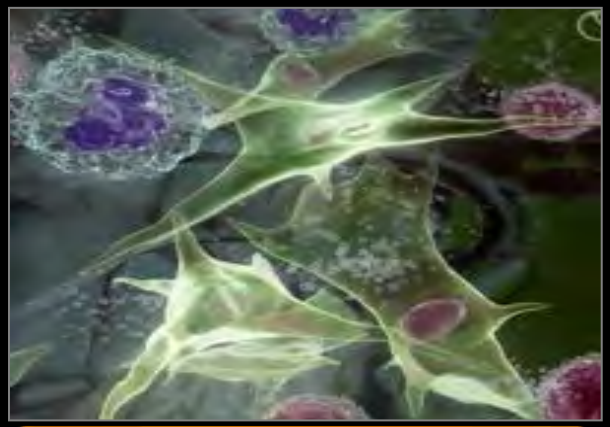
Escape From Controls for Normal Tissue Architecture



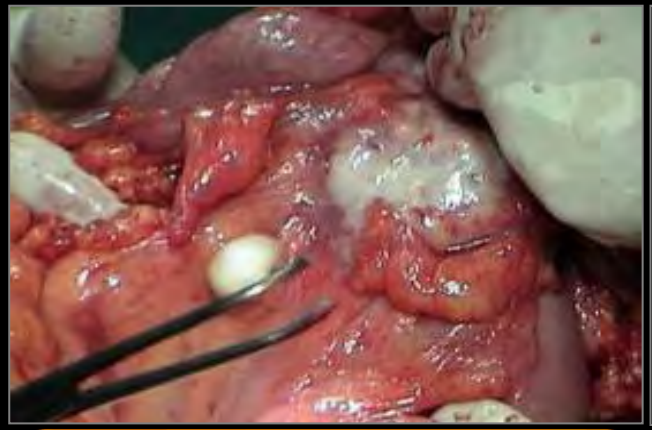
Genome Instability and Emergence of Clonal Variants

Evasion of Detection/ Destruction by Host Immune System

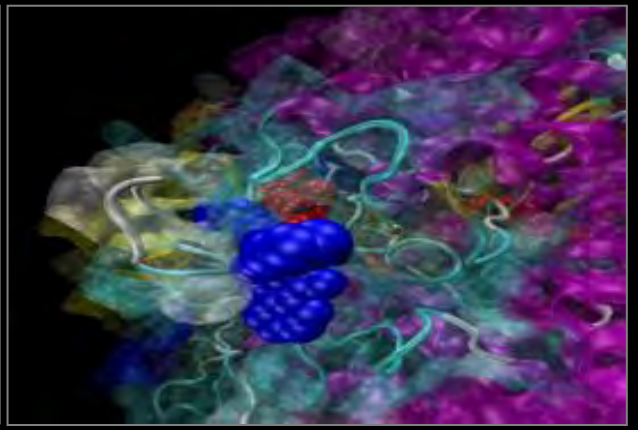




Use of Host Systems to Promote Progression



Invasion and Metastasis



Drug-Resistant Clones: intrinsic, acquired

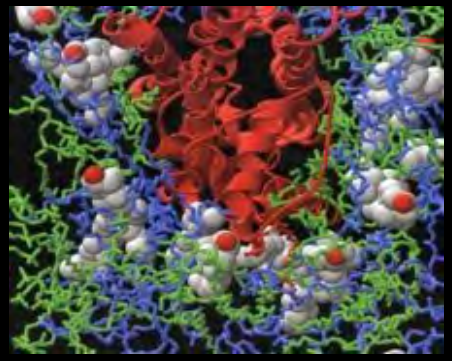
Precision Oncology

The Design of Health Interventions to Reflect the Unique Features of Disease Risk, Onset and Progression in Individuals and Populations

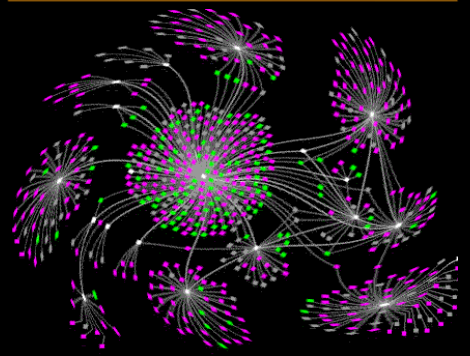
Precision Oncology and Deep Phenotyping: Mapping The Molecular Signatures of Disease as the Intellectual Foundation of Rational Diagnosis and Treatment Selection

(Epi)Genomics

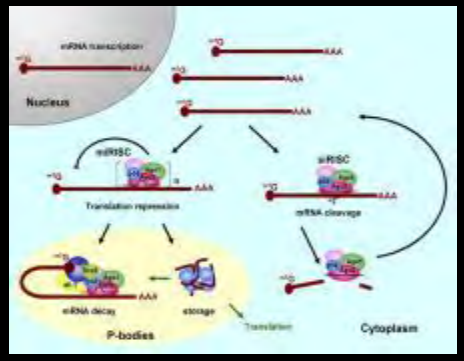
Proteomics

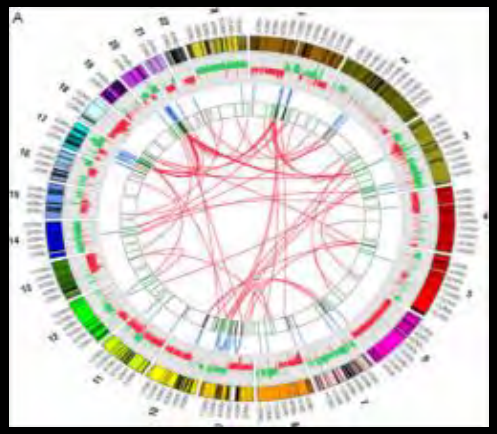


Molecular Pathways and Networks



Network Regulatory Mechanisms





ID of Causal Relationships Between Molecular Network Perturbations and Disease

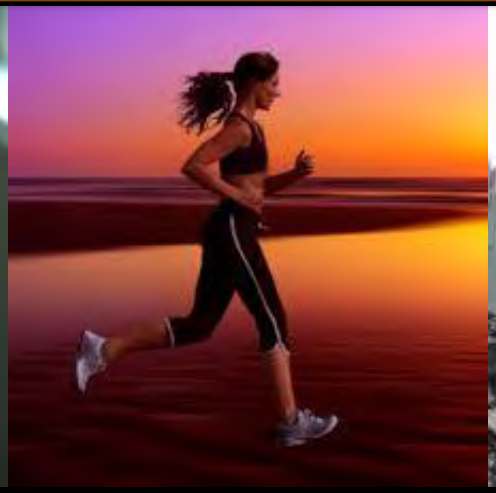
Patient-Specific Disease Signatures: Disease Predisposition; Disease Subtyping; R_x Selection

Deep Phenotyping: “Much More Than MultiOmics”

From Womb to Tomb: Longitudinal Integration of Diverse Health Data

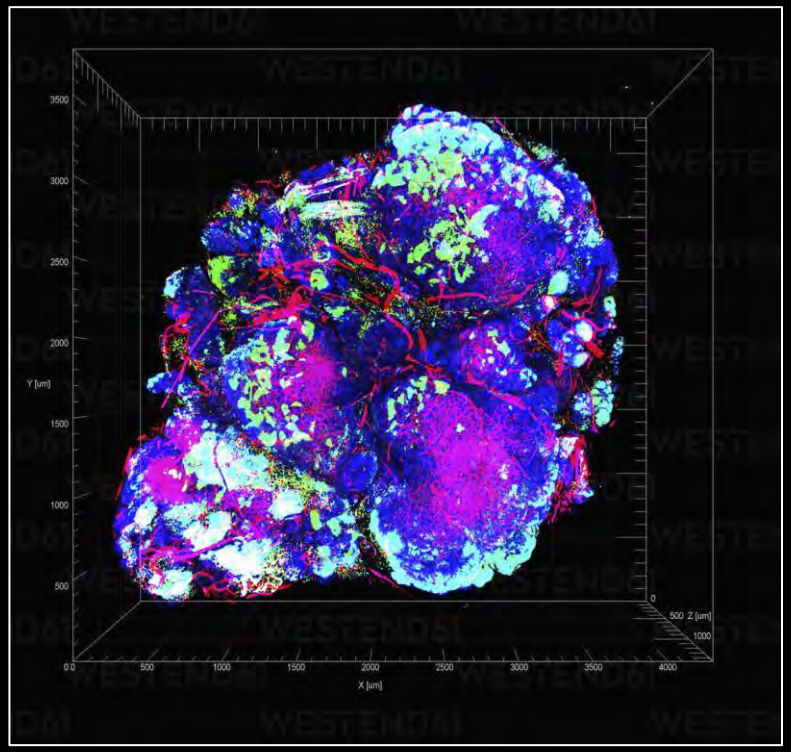



SDoH, Lifestyle, Environment, Health Disparities

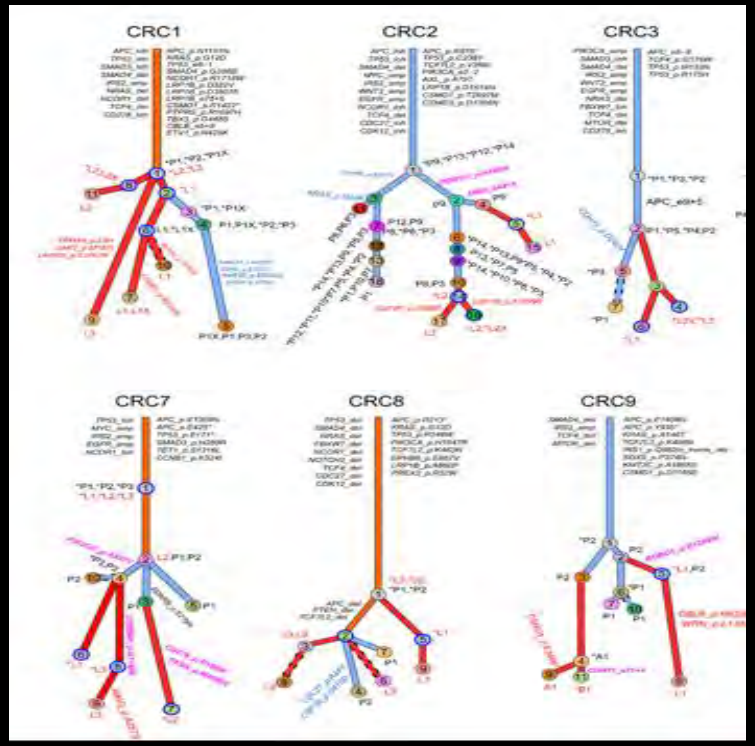
Circumventing Tumor Cell Heterogeneity: The Grand Challenge in Oncology

Intratumoral Clonal Heterogeneity and Different Patterns of Tumor-Host Cell Interactions



https://www.westend61.de/en/imageView/CUF06167/transparent-tumor-tomography-visualising-tumor-microenvironment-showing-a-mouse-model-for-her2-positive-breast-cancer-with-hypoxic-areas-of-cancer-cells-in-green

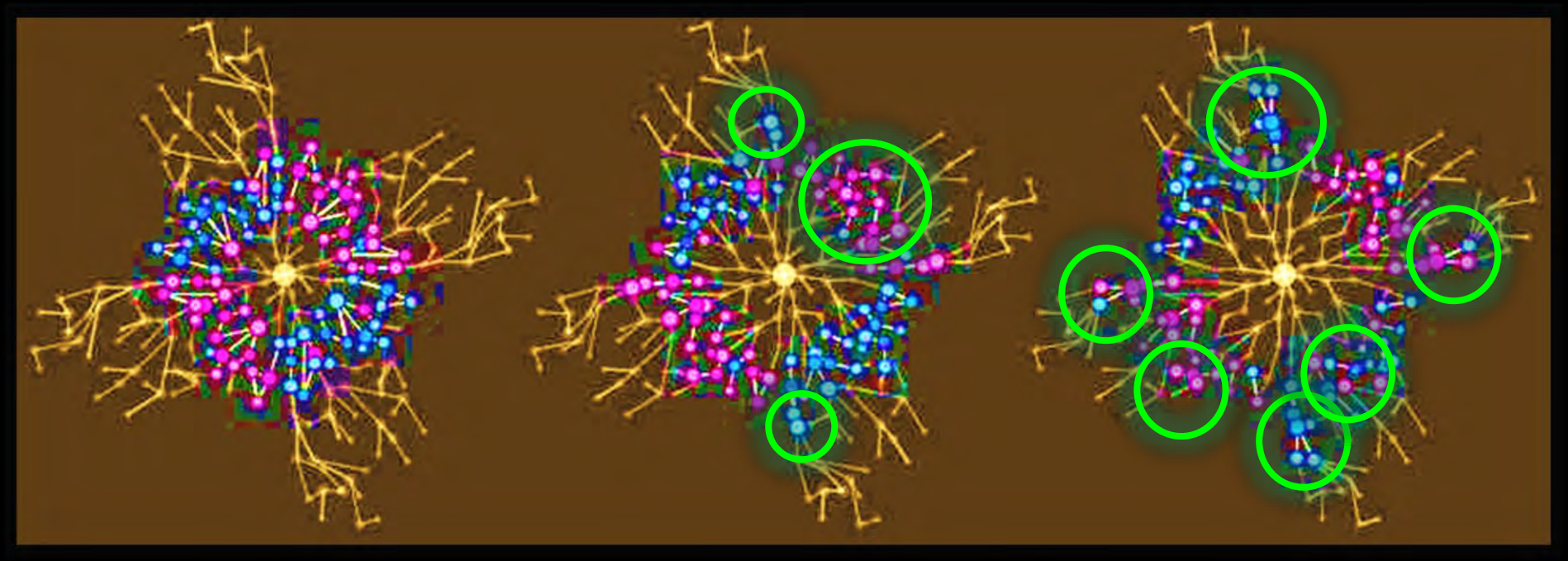
Evolution of Clonal and Subclonal Heterogeneity in Disease Progression and Metastatic Dissemination



H. X. Dang et. al. (2020) Science Advances 6:1-11; doi.org/10.1126/sciadv.aay9691

Understanding Disease Processes as Complex Adaptive Systems: The Core Tenet for Precision Oncology

Cancer as a Complex Adaptive Biological System: System State Shifts (Phenomes) and Cumulative Perturbations in Molecular Signaling Networks in the Health to Disease Continuum

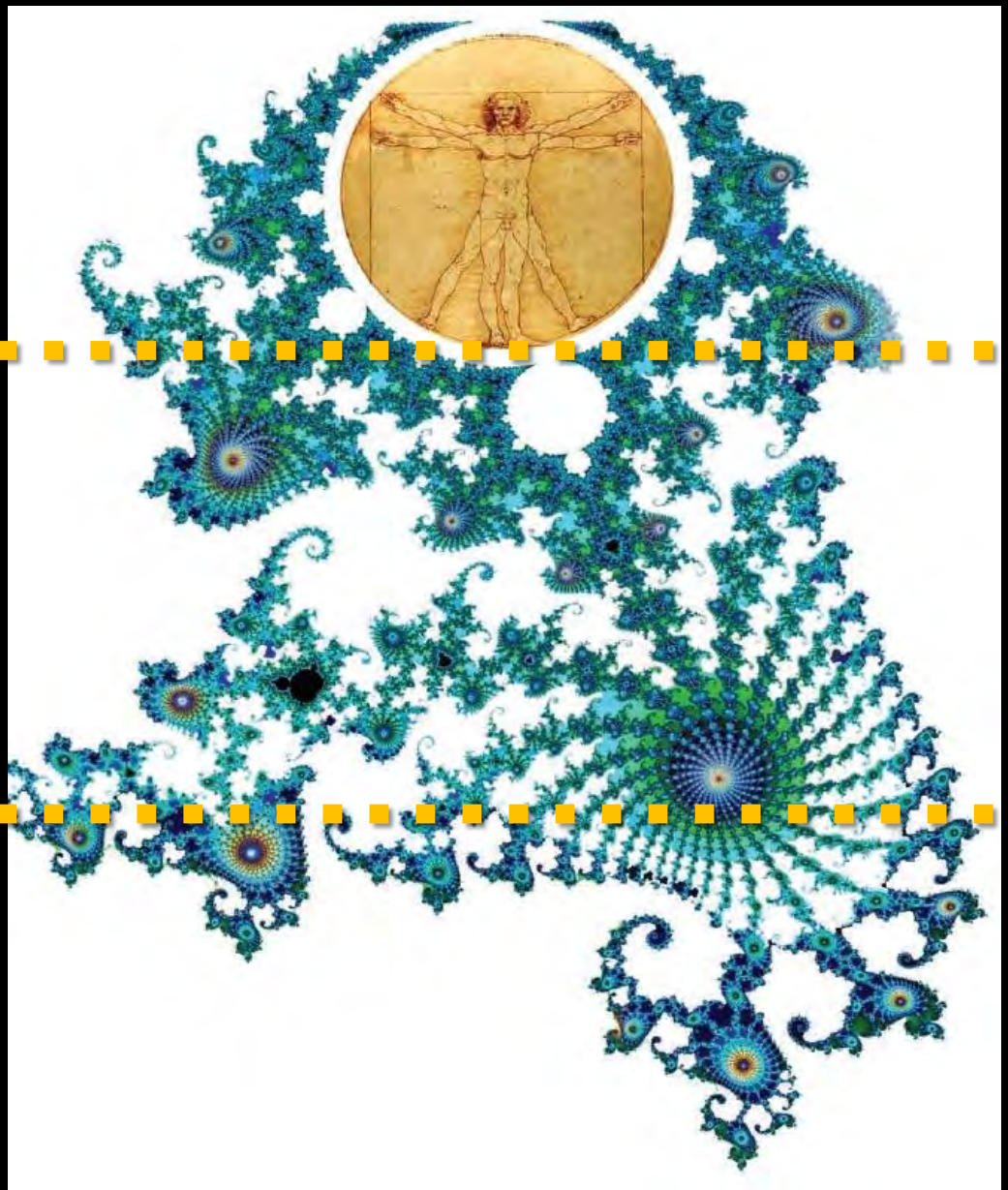


$T_{1(n)}$ health

$T_{2(n)}$ subclinical disease

$T_{3(n)}$ overt disease

The Health to Disease Continuum: Dynamic Geno-phenotypic Transitions in Cell Lineages Across Large SpatioTemporal Scales



physiology
(homeostasis)

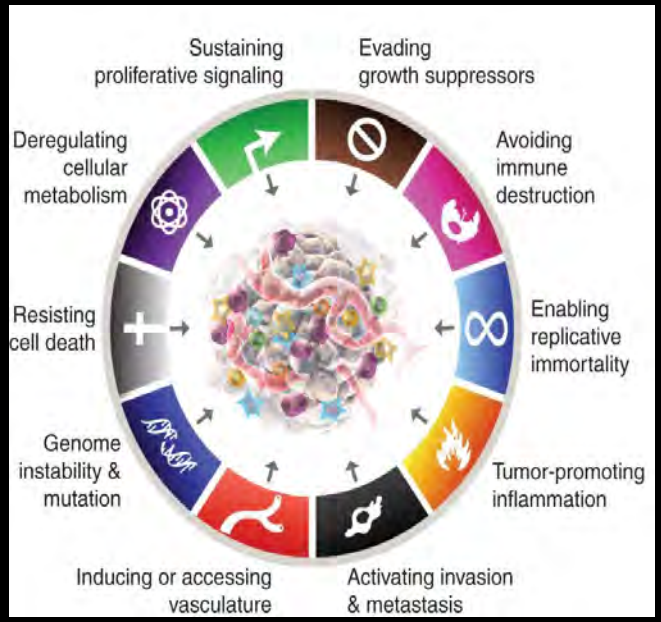
subclinical disease
- disease predisposition
- acquired genomic perturbations

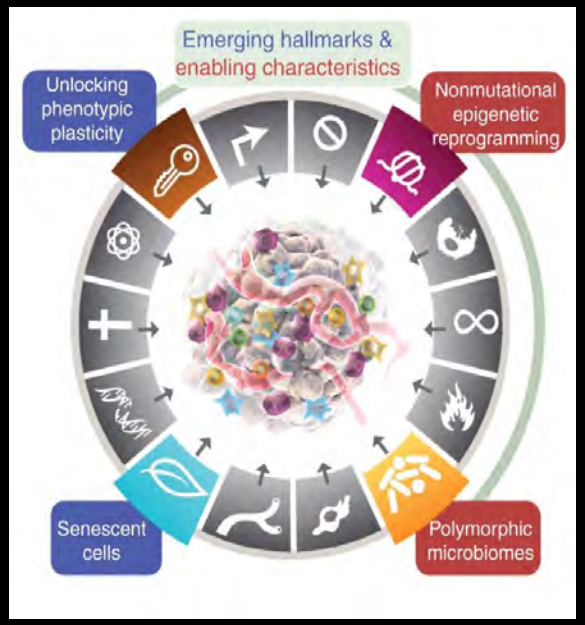
clinical disease
(pathology)
- disease subtypes and phenotypes

Moving Beyond Static Isolated Snapshots to Comprehensive Longitudinal Profiling of Dynamic Transitions in the Health to Disease Continuum

https://www.freepik.com/premium-vector/many-round-clocks-showing-different-times-light-background_38883823.htm

The Confluence of the Hallmarks of Cancer, Aging and Immunosenescence





D. Hanahan (2022) Cancer Discov. 12:31–46; doi.org/10.1158/2159-8290.CD-21-1059

C. Lopez-Otin, et. al. (2013) CELL 153:1194-1217; doi.org/10.1016/j.cell.2013.05.039

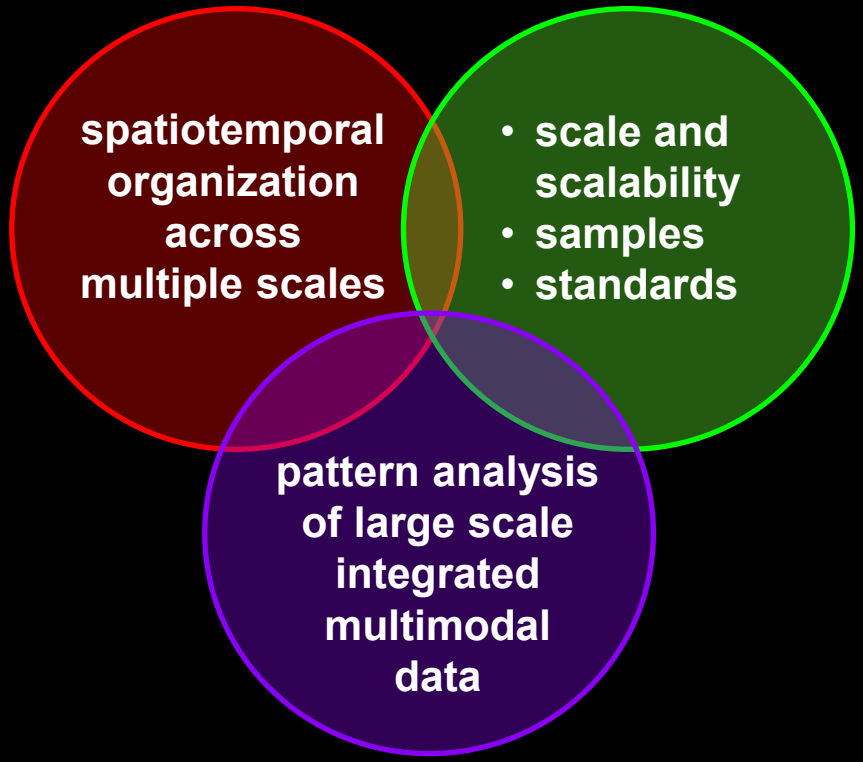
The “Hallmarks” of Complex Adaptive Systems (CAS)

- system state(s) determined by the interactions of multiple subsystem components
- system behavior cannot be predicted from knowledge of the properties of different subsystem components
- many system properties reflect non-linear subsystem interactions
- adaptation and emergence
  - resilient (robust) to commonly encountered evolutionary selection pressures
  - exhibit fragility (instability) in response to novel/infrequent selection pressures
  - extinction (maladaptive loss of fitness) or adaptive system shift to new state space with different properties (emergence)

The Health to Disease Continuum: Dynamic State Transitions in Complex Adaptive Systems

system dynamics

system profiling

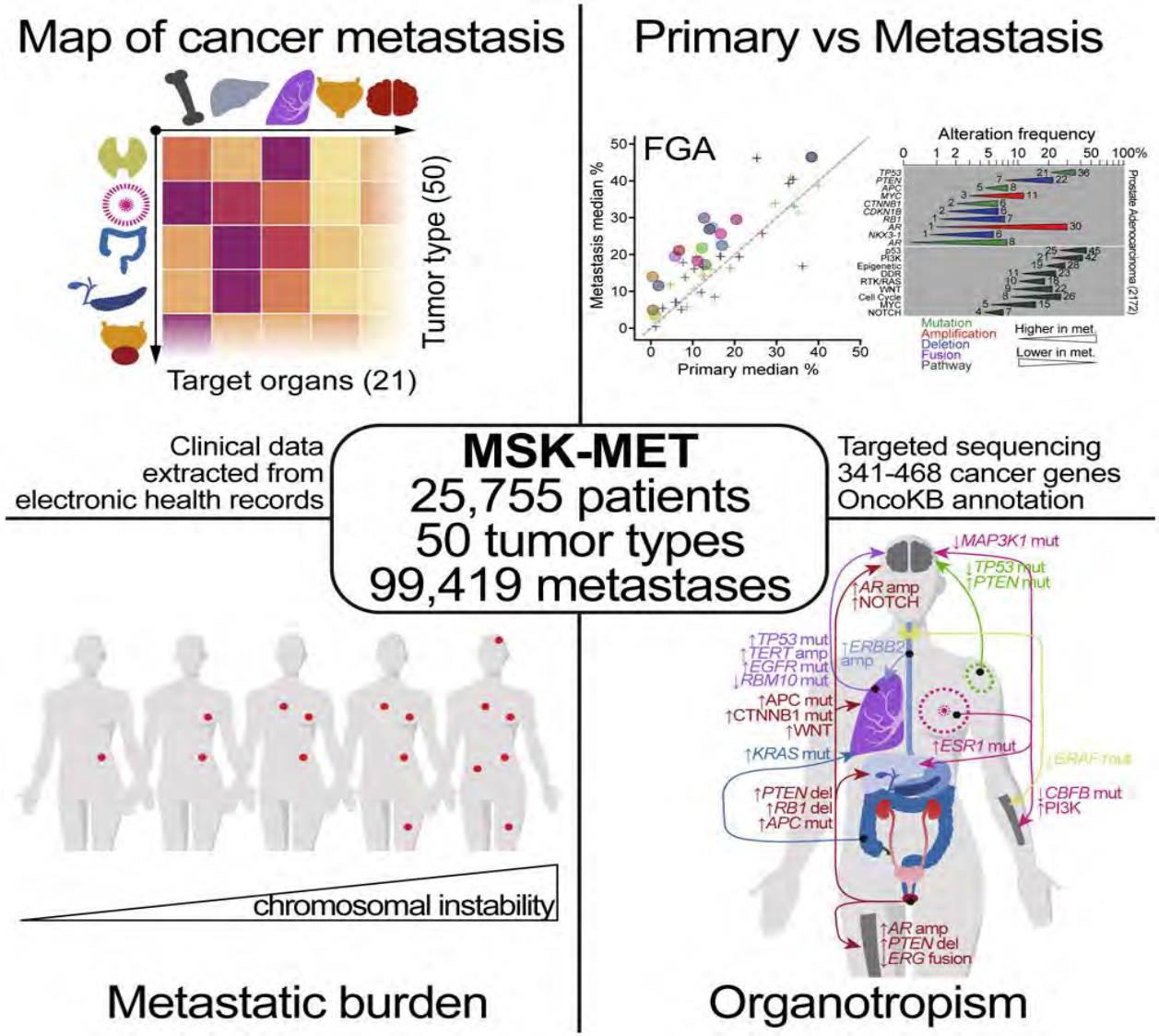


system state(s) and emergent dysregulation

Scale, Samples and Standards

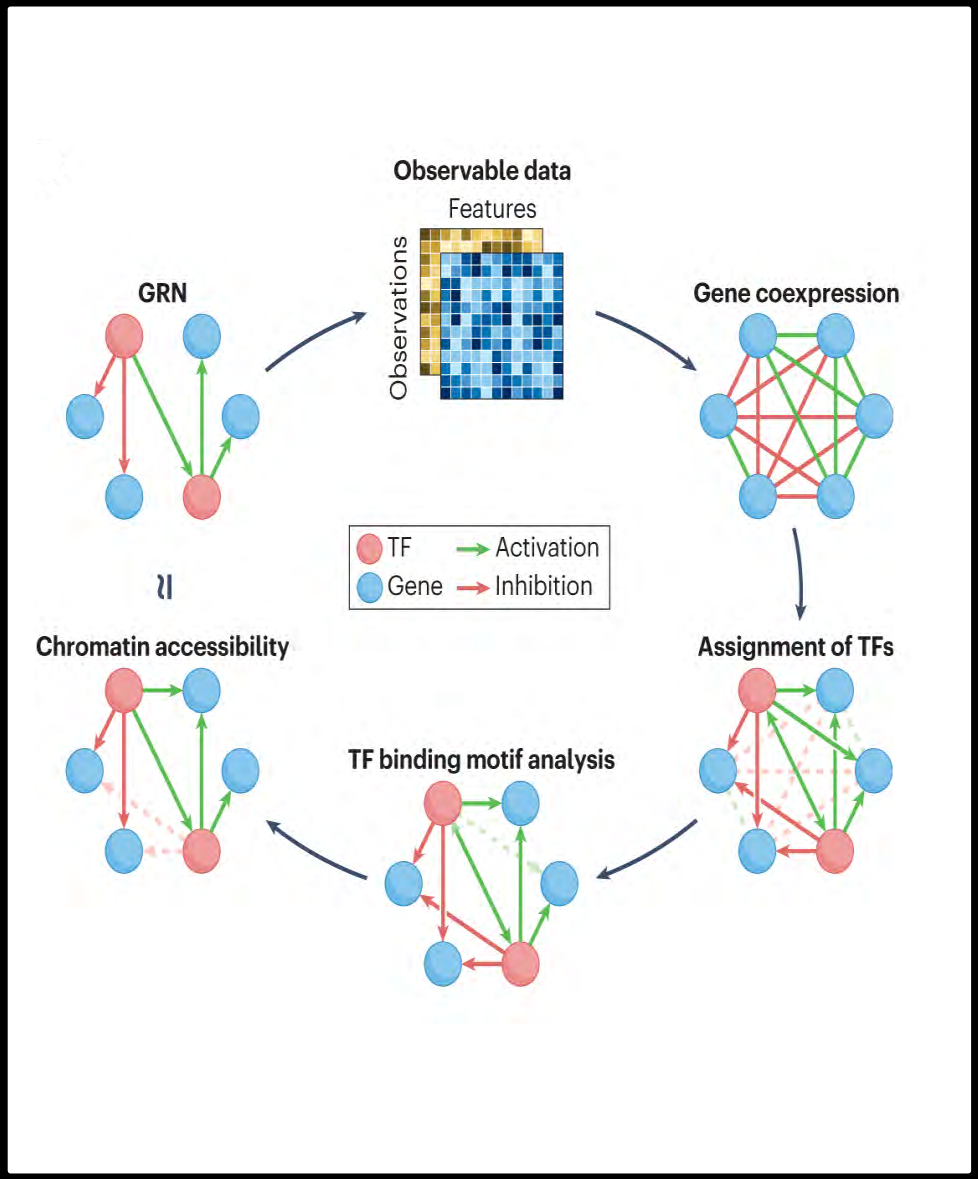
- the reproducibility problem in the biomedical literature
- the multidimensionality curse and overfitting in multiOmics profiling
  - large N analytes (>10^5-10^7)
  - small sample sets (< 10^2-10^3)
- variable (or not reported) preanalytical sample processing protocols
- “samples of convenience” versus samples with defined provenance and clinical data
- poorly characterized geno-phenotypic drift in continuous cell lines grown as 2D monolayers versus homologous cell types in vivo

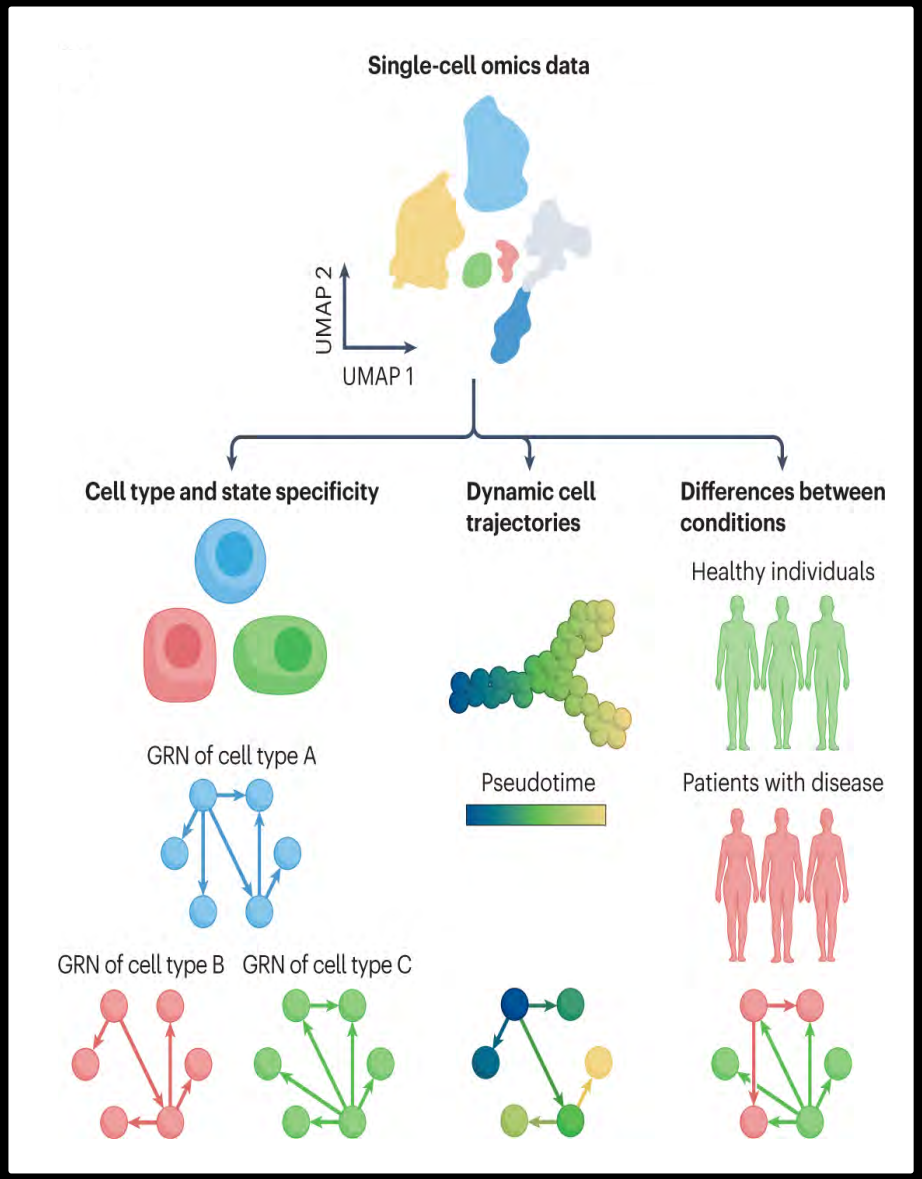
Scale:
Profiling Large N MultiOmics Feature Sets in Large N Samples



B. Nguyen et. al. (2022) CELL 185:563-575.e11; doi.org/10.1016/j.cell.2022.01.003

Elucidation of Gene Regulatory Networks (GRNs) and Characterization of Cell State/Fate Trajectories



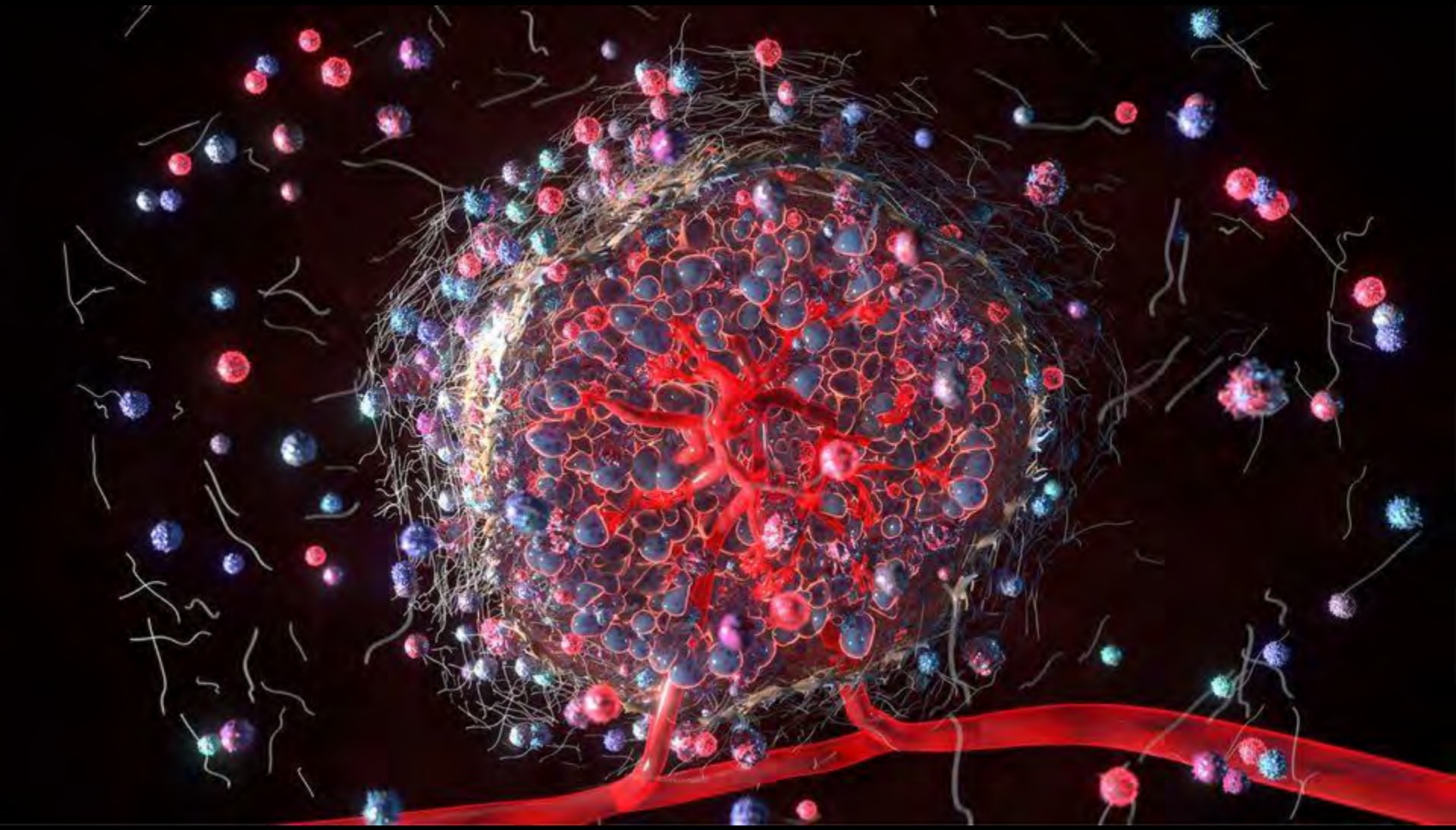


P. Badia-iMompel (2023) Nat Rev Gen 24:739–754; doi.org/10.1038/s41576-023-00618-5

The Next Level of Large-Scale Holistic Data Integration for Comprehensive MultiOmics Profiling

- whole genome sequencing
- cell, tissue and individual-specific differential gene expression and transcription kinetics
- epigenetic modifications: DNA, histones and RNAs
- integrate effects of coding and non-coding regulatory variants across the entire genome
- transcription factor-promoter: enhancer interactions
- protein-RNA interactions
- RNA-RNA interactions
- chromosomal topologies/adjacencies chromatin interactions, gene neighborhoods and other long-range interactions (the 3-D genome)

Mapping Host and Tumor Cell Signatures in the Tumor Microenvironment (TME)



https://www.technologynetworks.com/cancer-research/articles/interrogating-the-complexities-of-the-tumor-microenvironment-367923

Mapping the Spatiotemporal Dynamics of the Complex Cellular Heterogeneity of the Tumor Microenvironment (TME)

- frequency and localization of different cell (sub)types and their functional states
  - host cell populations (resident, migratory)
  - tumor clones and subclones
- inhibitory or permissive microenvironments for proliferation of different tumor subclones
- characterization of the immunosuppressive TME
  - immunoevasion (intrinsic tumor clone phenotypes and acquired Rx resistance)
  - tumor co-option of host cell functions

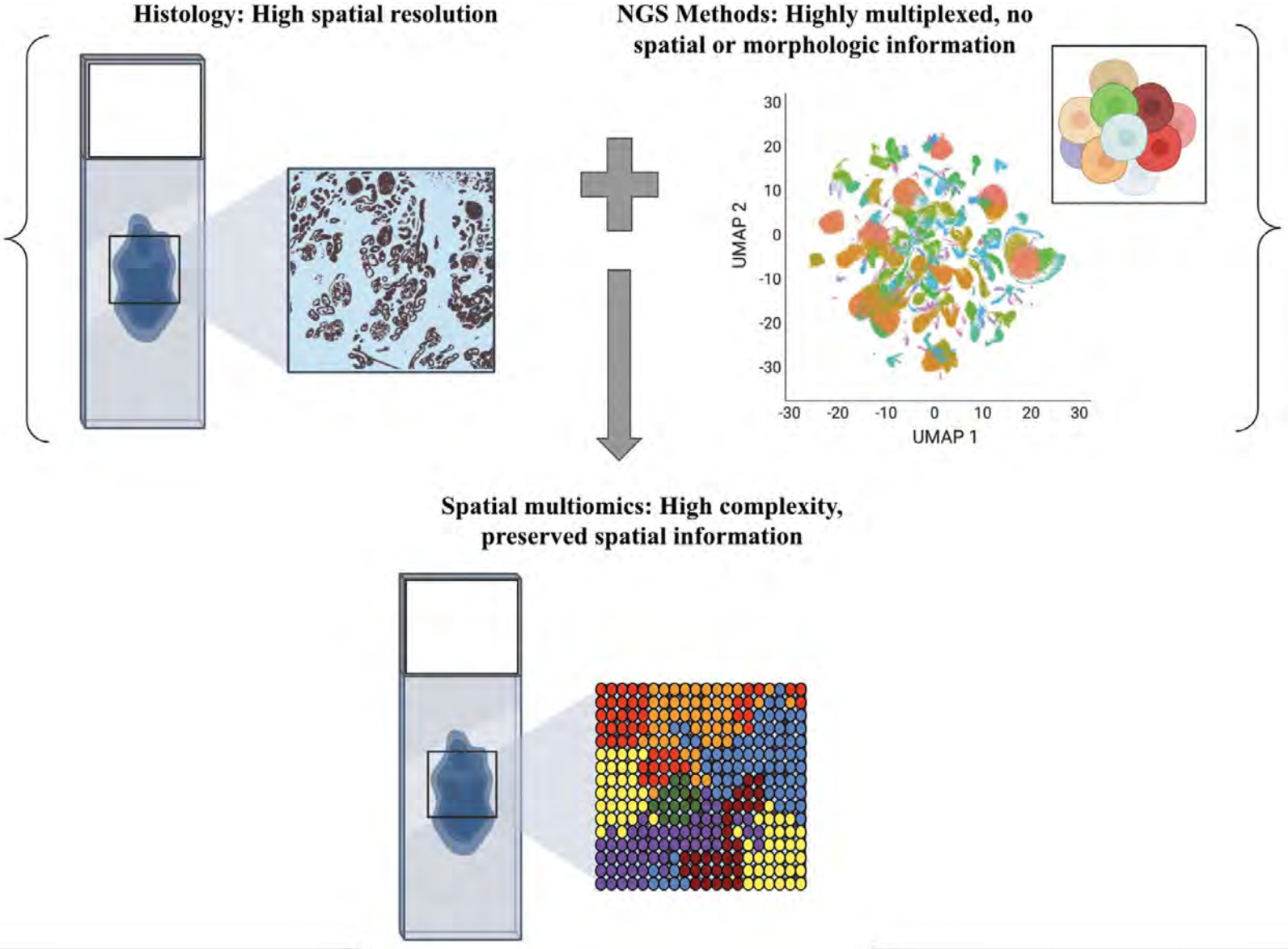
The Challenge of Profiling the TME in Disseminated Metastases

- utility of liquid biopsy?
  - monitoring cf/ctDNA, CK/LKs (plasma) and circulating immune cell subtypes (buffy coat)
  - level of phenotypic fidelity in reflecting the ‘state spaces’ of tumor- host components in the tissue environment?
  - Rx ID of response/resistance phenotypes?

The Evolution of RNA Sequencing (RNAseq) in Gene Expression Profiling

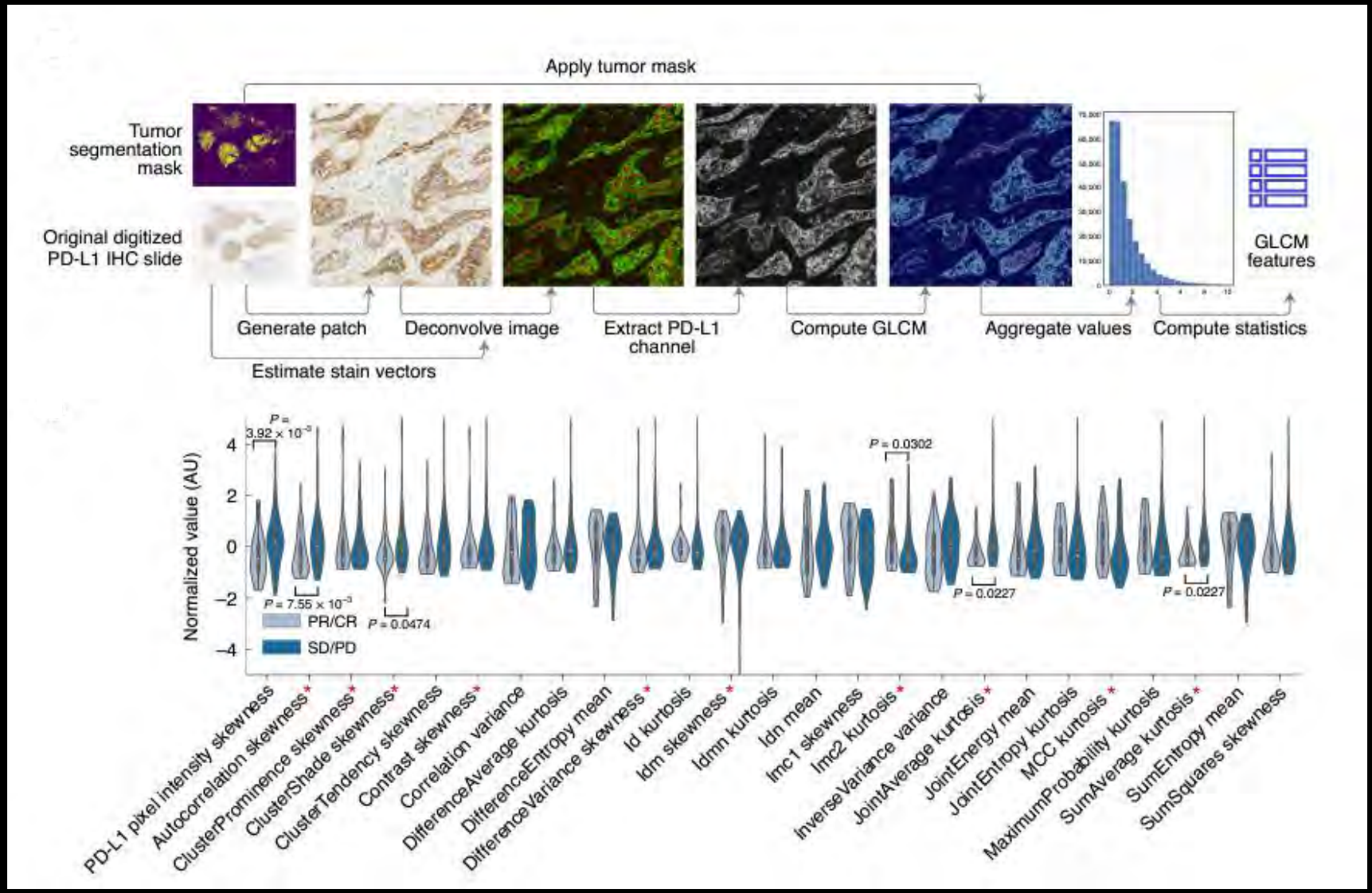
- bulk RNA-seq averages expression profiles
  - masks potentially important patterns of cellular heterogeneity
- single cell RNAseq (scRNAseq) to document cellular heterogeneity
  - but unknown effects of tissue dispersal methods on expression profiles
- spatial transcriptomics and relationship of expression profiles to cellular morphologies, location patterns within tumor foci and frequency homotypic and heterotypic cell interactions (“cell neighborhoods”)

Whole Slide Imaging and Spatial Omics



D. Pucciarelli et. al. (2023) GEN Biotechnology 2:360-371; doi.org/10.1089/genbio.2023.0029

Spatial Mapping of NSCLC Cell Morphologies and Prediction of Response to ICB

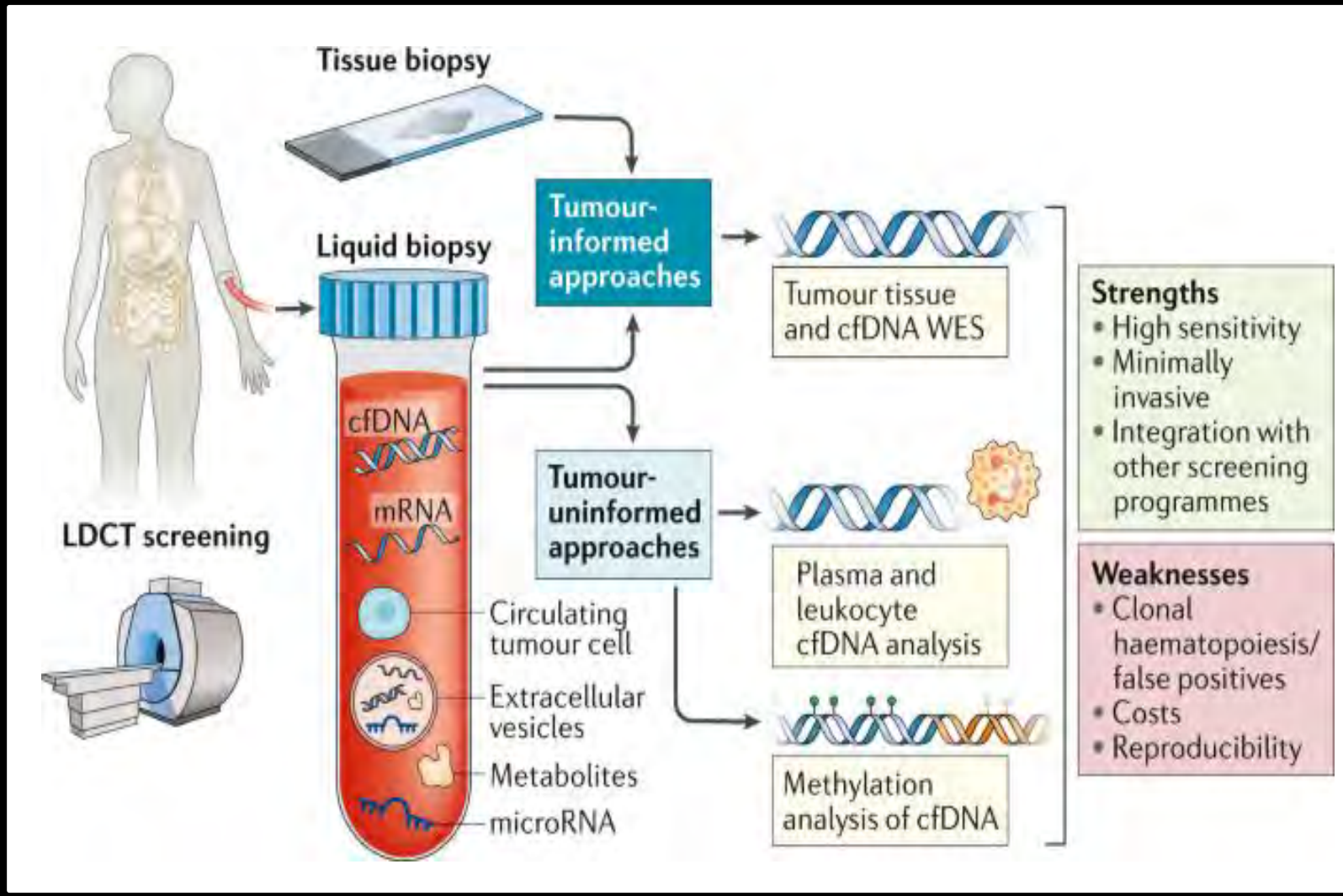


Vanguri RS, et. Al. Nat Cancer.(2022) 3; 10; 1151-1164. doi:10.1038/s43018-022-00416-8

Large Scale Biobanks: A Core Resource for Precision Medicine

- consent
  - broad to allow de-identified reuse
  - opt-out provision
  - recontact provision
- biospecimens
  - provenance and processing standards
  - tissue and Whole Slide Imaging (WSI)
  - blood/serum/plasma/bloodspot; saliva; microbiome
- multimodal data integration
  - imaging data
  - multiOmics, immunOmics, metabolOmics
  - digital pathology and spatial multiOmics
  - age, sex, race, ethnicity clinical history and socioeconomic factors
  - gaps in clinical history
  - GWAS, PheWAS and ICD-EHR codes
  - ML/AI platforms for unstructured but potentially informative data

Detection of Blood-based Tumor Biomarkers (Liquid Biopsy): A Potentially Transformative Platform for Cancer Screening and Improved Clinical Case Management



C. Rolfo & A. Russo (2020) Nat Rev Clin Onc 17:523–524; doi.org/10.1038/s41571-020-0393-z

Blood-Based Liquid Biopsy: Early Detection Tests

- expand screening to broader range of cancers than current USPSTF recommendations for population-based cancer screening
  - breast, cervical, colorectal, lung
- increase screening uptake (convenience, minimally invasive and reduced disparities)
- objective to shift clinical/economic burden from advanced stage III/IV cancers to earlier detection and intervention
  - assay performance in detection of stage I/II cancers
  - specificity, sensitivity, NPV, PPV
  - detect tissue of origin

Large Scale Multi-Institutional Initiatives on Validation of Blood-Based Liquid Biopsy in Cancer Detection and Treatment

FRIENDS of CANCER RESEARCH

MCED MULTICANCER EARLY DETECTION CONSORTIUM

BLOODPAC

NCI

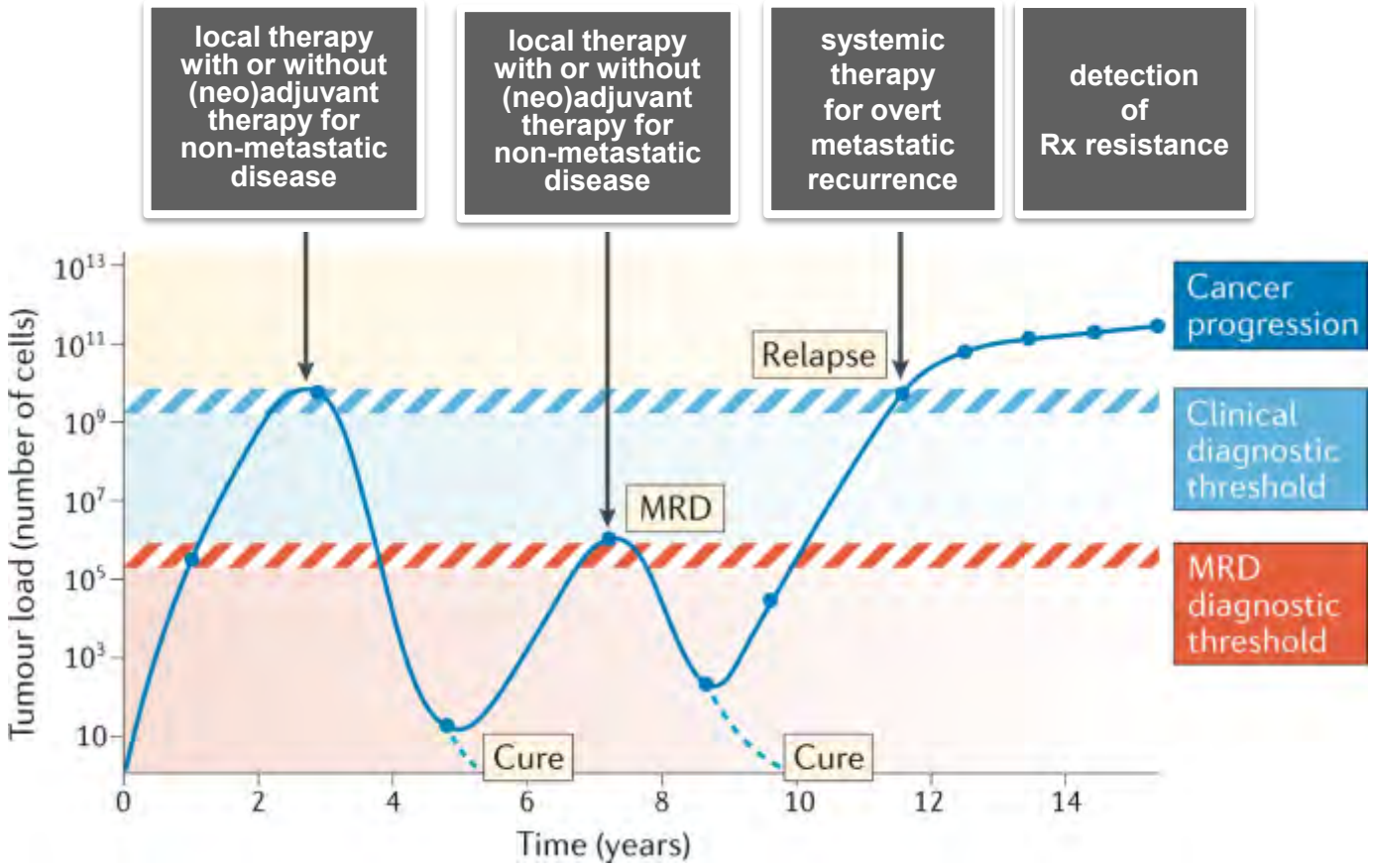
NCI Vanguard Study: Cancer Screening Research Network

- driven by non-profit entities but extensive membership from private sector companies
  - prospective clinical trial design and endpoints
  - harmonization of assay standards and interoperability
  - regulatory issues
- reported performance
  - low sensitivities (25 – 40%) for stage I/II cancers
  - major differences in ctDNA shedding in different malignancies

Blood-Based Multicancer Early Detection (MCED) Tests
The Benefit: Harm Calculation

- acceptable levels of false positives and negatives?
- importance of tissue-of-origin specificity in guiding follow-up on positive test results
- costs for clinical evaluation of false positives
  - immediate evaluation
  - protocols for follow-up testing: frequency/duration
  - sociopsychological impact
- risk of overtreatment of indolent (slow growing) cancers detected by MCED tests
- merits of population screening versus focused profiling of individuals with known predisposition risk or symptomatic patients referred for potential cancer diagnosis

The Use of Cancer Liquid Biopsy Assays in Clinical Case Management



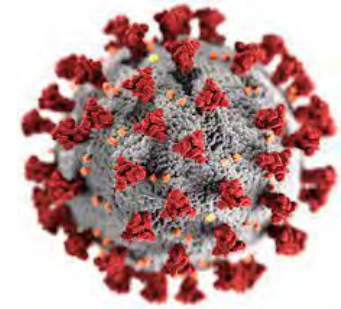
Adapted from: K. Pantel & C. Alix-Panabieres (2019) Nat Rev Clin Onc volume 16:409–424; doi.org/10.1038/s41571-019-0187-3

The Changing Landscape for Regulatory Oversight of High Complexity MultiOmics Diagnostic Tests

theranos

23andMe

consumer genomics profiling for disease predisposition



EUA and withdrawal of COVID-19 tests

New Proposed Rule (Sept. 2023) for Regulation of Laboratory Developed Tests (LDTs)

- amend FDA regulations to expand oversight of LDTs by classification as medical devices
- replace current oversight by CMS of LDTs developed in CLIA-certified laboratories
- concern that historical mechanisms developed for single analyte LDTs are insufficient to validate the performance and reproducibility of 'higher complexity' multianalyte diagnostics (e.g., multiOmics)
  - use in management of life-threatening diseases and decisions on Rx selection
  - many vendors use LDT pathways to avoid Agency review for marketing
  - lack of standards and potential harm to patients

The Search for New Therapeutic Targets and New Drug Classes with Novel Mechanisms of Action

Moore's Law and Eroom's Law
The New Drug Pipeline Productivity Dilemma

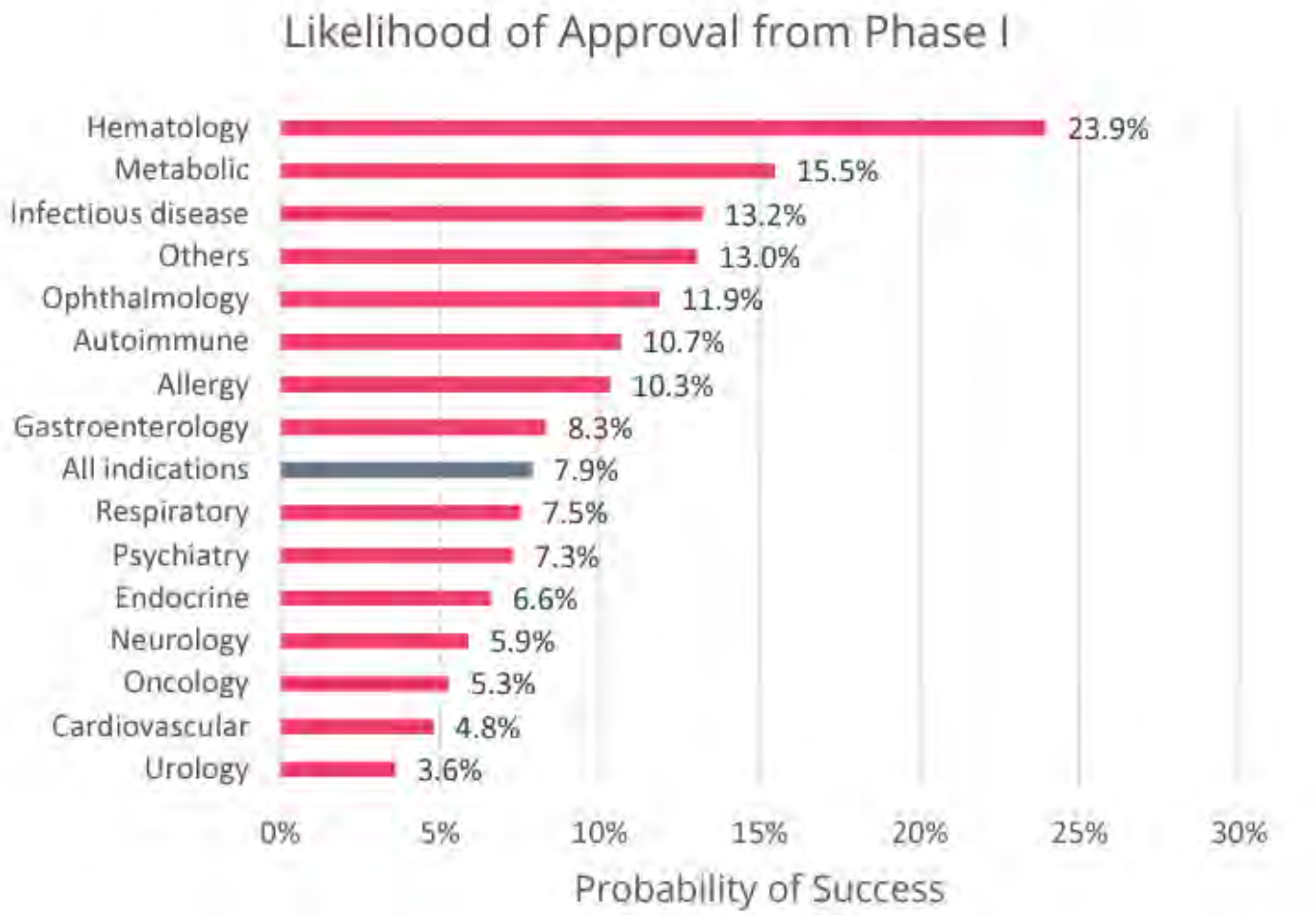
Moore's Law (Gordon Moore, Intel 1965)

- number of transistors on an integrated circuit doubles every two years (originally one year)
- dramatic increase in computing power performance at lower costs and rapid growth of IT-based industries

Eroom's Law (Sanford Bernstein 2012 Nature Rev. Drug Disc. 11,191)

- Moore's Law in reverse
- drug discovery and development are becoming slower and more expensive despite impressive technology advances
- average cost of successful NDA/BLA now $1 to 3.8 billion
- inflation-adjusted cost roughly doubles every nine years

Overall Likelihood of Approval by Disease Area



https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf?_gl=1*8s30b5*_gcl_au*MTIxNjI0OTA1NS4xNjk3NjY0MTU0&_ga=2.102983811.2083123613.1697664154-1374498054.1697664154

Investigational Clinical Trials in Oncology: Derisk R&D Investment and Improve Patient Access to Innovative Rx

- reduce high failure rate, particularly for high-cost Phase III trials
- shorten overall completion time for trials and regulatory approval
  - inflation Reduction Act (IRA) and new windows for post-approval market exclusivity
  - improved predictive methods to identify responder: non-responder patients/cohorts for accelerated enrollment
- multiOmics profiling and new clinical trial designs
- reduce high rate of protocol deviations and patient dropouts

Identification of Novel Molecular Targets for New Classes of Cancer Therapeutics

- diversification of product classes in the therapeutic portfolio
- small molecules
  - transition from cytotoxics to targeted agents
- biologicals
  - monoclonal antibodies, ADCs, biospecifics, T-cell engagers
  - PROTACs, molecular glues
  - immunotherapeutics
- cell and gene therapies
- cancer vaccines against tumor neoantigens
- new molecular probes for improved in vivo imaging and radiomics

Antibody-Drug Conjugates

- higher ORR than same Rx as single agent
  - validation in adjuvant setting
  - lower toxicity due to targeted intracellular Rx release versus non-targeted drug
- anticipated progression to first line indications and replace chemo in multiple settings
- major investment momentum
  - over 200 trials registered in ClinicalTrials.gov
  - 51 M&A/BD investments in 2022 and 1H/2023

Immune Checkpoint Blockade and Cancer Immunotherapy

- a seminal advance in cancer treatment
  - varied efficacy against different tumor lineages and significant fraction of non-responder patients
  - lack of predictive markers for proactive identification of responders/non-responders
- FDA criticism of proliferation of ‘follower’ checkpoint inhibitors for solid malignancies with limited therapeutic differentiation

CAR-T Cell Therapy

- impressive efficacy of CAR-T therapies in hematological cancers
  - 6 products approved for relapsed and/or refractory B cell indignancies
- efficacy of CAR-T in solid tumors still uncertain
- high cost, complex clinical management protocols
  - acute AEs and unknown long-term sequelae

Genomic Reprogramming of T Cells to Induce More Durable Anti-Tumor Efficacy in Adoptive Cell Therapy

- anti-tumor activity declines under chronic antigenic stimulation (exhaustion)
- differentiate into dysfunctional states
  - expression of inhibitory receptors (PD-1, LAG3, TIM-3)
  - reduced cytokine production
  - altered transcriptome and chromatin landscapes
- engineer therapeutic T cells to improve durable anti-tumor response (fitness)

Genomic Reprogramming of T Cells to Induce More Durable Anti-Tumor Efficacy in Adoptive Cell Therapy

- unbiased gene-wide screens to identify new Rx targets
- tune CAR-T regulation/signaling via promoter regulation of endogenous TCR alpha construct (TRAC)
- CRISPR-Cas9 ablation of genes that restrict durable anti-tumor activity
  - loss-of-function screens
- CRISPR activation gain-of-function screens and knock-in screens
- novel synthetic surface receptors that alter tonic responses to external signals

*see F. Blaeschke et al. (2023) Cell 186, 4216

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-b3t4D4AhUAAAAAHQAAAAQAw

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

Patient-derived (autologous) T-cells

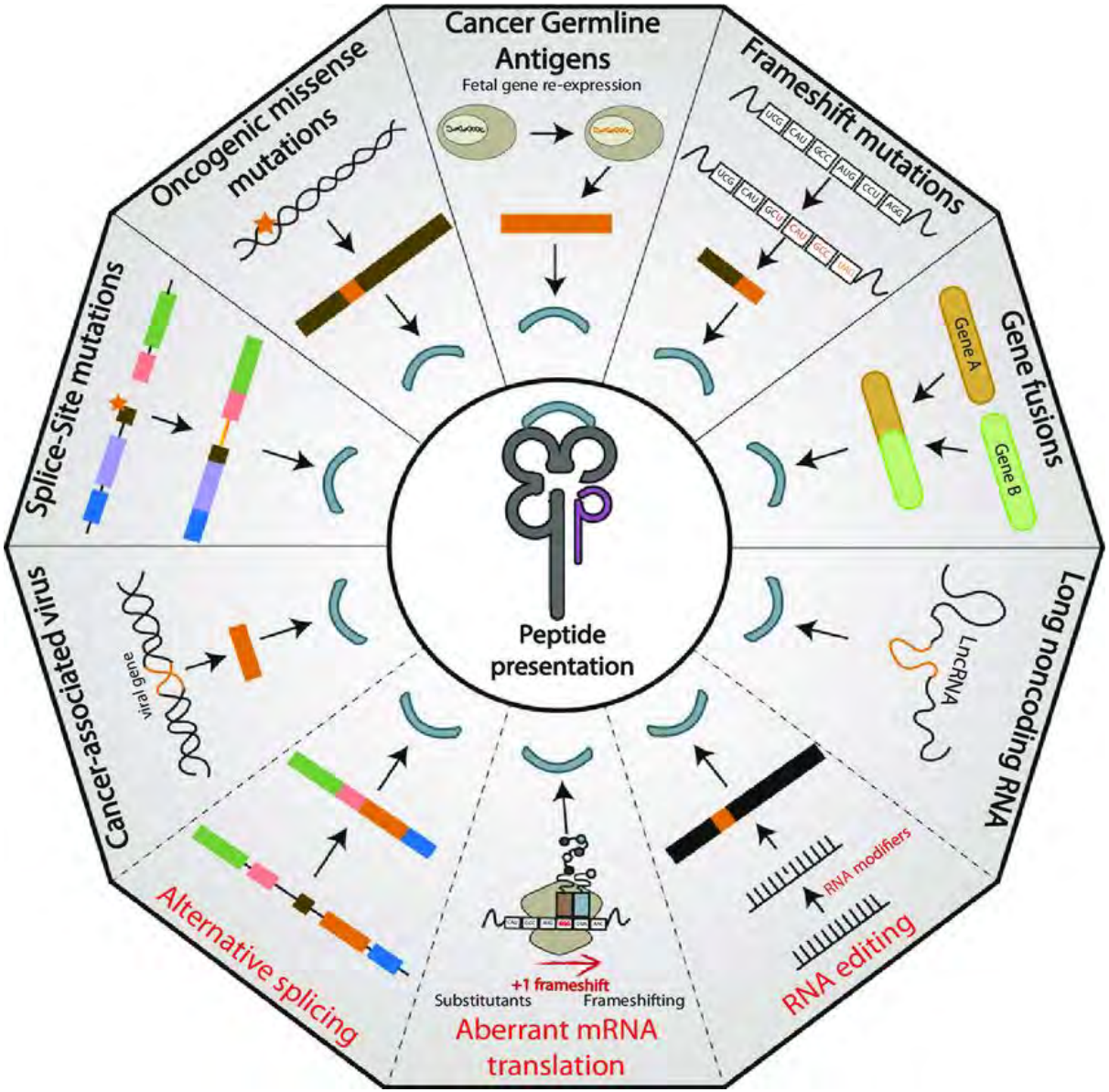
- ⊕ Host compatibility, FDA approved
- ⊖ Cell quantity and quality concerns
- ⊖ Time-consuming and costly manufacturing process

Healthy Donor (allogeneic) T-cells

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

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

New Strategies for Immune-Mediated Targeting of Cancer Neoantigens



R. Nagel et. al. (2022) Cancer Research 82:3637-3649; doi.org/10.1158/0008-5472.CAN-22-1525

Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer

Luis A. Rojas, Zachary Sethna, Kevin C. Soares, Cristina Olcese, Nan Pang, Erin Patterson, Jayon Lihm, Nicholas Ceglia, Pablo Guasp, Alexander Chu, Rebecca Yu, Adrienne Kaya Chandra, Theresa Waters, Jennifer Ruan, Masataka Amisaki, Abderezak Zebboudj, Zagaa Odgerel, George Payne, Evelyna Derhovanessian, Felicitas Müller, Ina Rhee, Mahesh Yadav, Anton Dobrin, Michel Sadelain, ... Vinod P. Balachandran + Show authors

BioNTech:Genentech

Nature **618**, 144–150 (2023) | Cite this article

Personalized anti-cancer vaccine combining mRNA and immunotherapy tested in melanoma trial

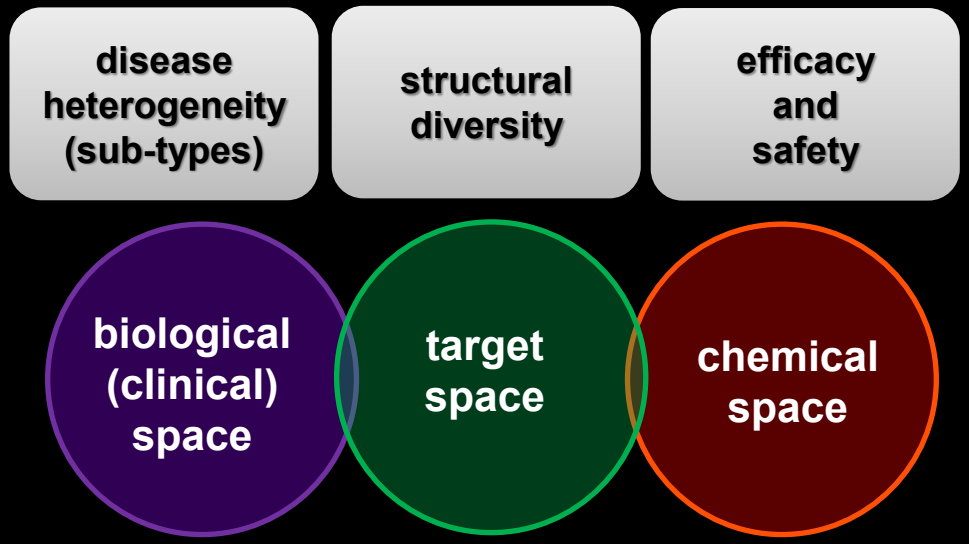
Nature Medicine **explores the latest translation and clinical research news, with a phase 3 trial from Merck and Moderna testing mRNA-4157 combined with pembrolizumab in melanoma.**

T. Carvalho (2023) Nature Medicine 29:2379

The Druggability Challenge

AI and Accelerated Drug Discovery: Hype or Reality?

The Druggability Challenge:



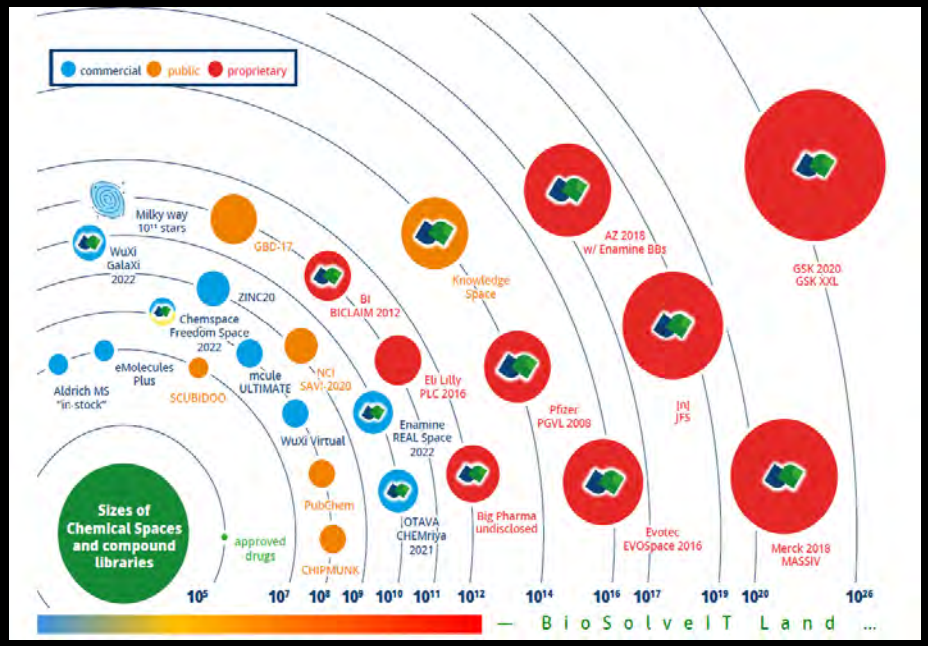
- network dysregulation
- coding and non-coding elements
- specificity
- ADME
- CMC
- IP/FTO

digital information space

- new concepts in data science to enhance selection of drug candidates for major improvements in clinical trial success

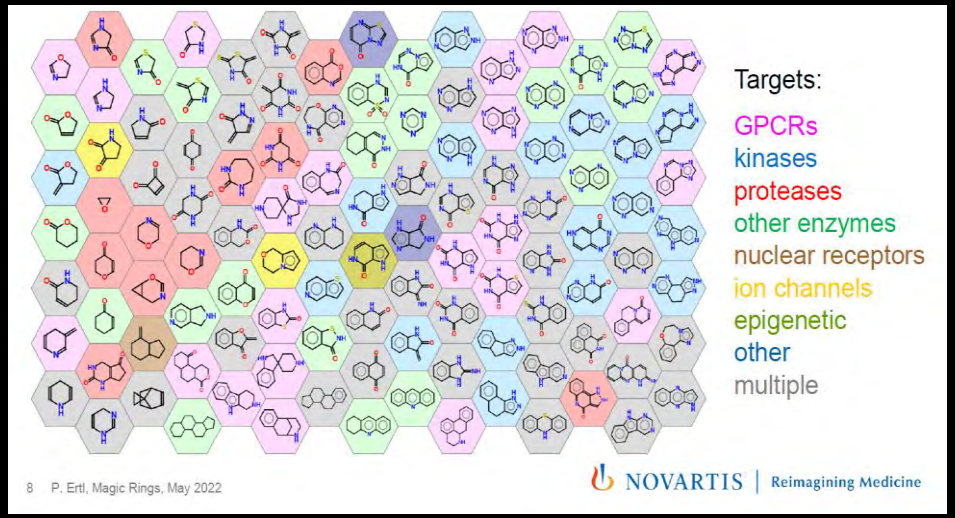
“Intelligent Informatics in Drug Discovery”
Reducing Very Large Structural
Reaction Space to Experimentally Tractable Opportunities

Chemical Space and Compound Libraries



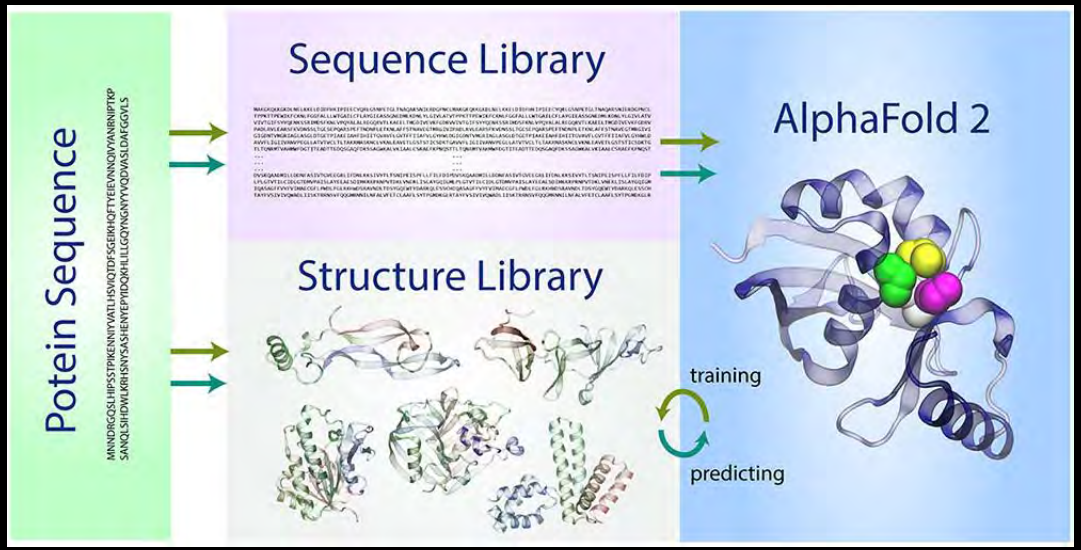
https://www.biosolveit.de/2022/06/17/recap-drugspace-symposium-2022-recordings-and-slides-available/

Small Molecule Bioactive Structural Domains



https://www.biosolveit.de/2022/06/17/recap-drugspace-symposium-2022-recordings-and-slides-available/

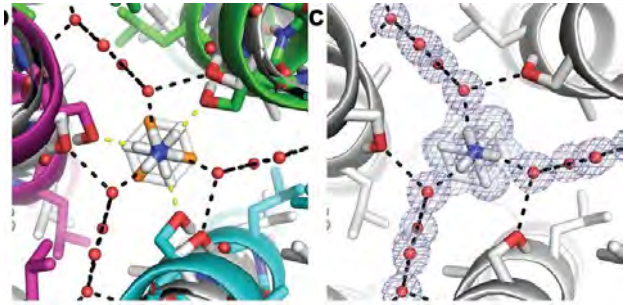
AI and Protein Design:
From 1-D Code to 3-D Complexity
The Next Dimension in Rational Drug Design



Genome-Wide Prediction of Pathogenic Missense Mutations

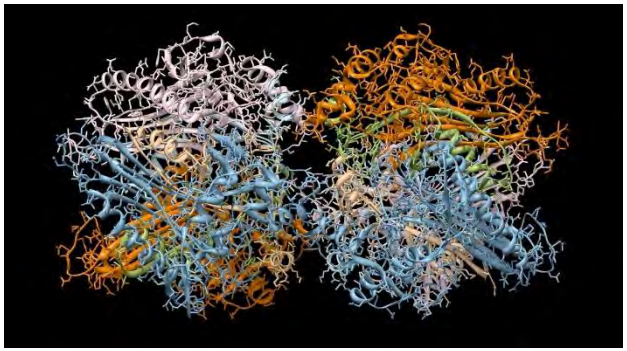
- 650 million-parameter protein language model
- predict estimated 450 million possible missense variants in the human genome
- outperformed earlier models in classifying 150,000 clinVar/HGMD missense variants as pathogenic or benign
- 2 million variants predicted as damaging only in specific protein isoforms

Use of ML-AI Protein Structure Prediction in Drug Discovery and Synthetic Biology



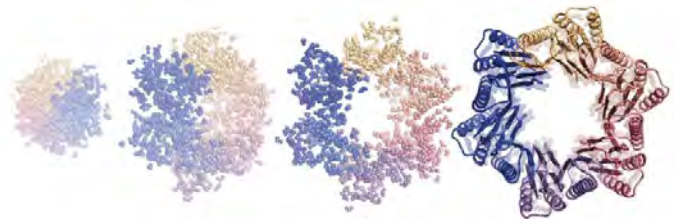
J. Park et. al. (2019) Elife doi.org/10.7554/eLife.47839

- Improved Drug-Pocket Affinities and Expanded Modulation of Allosteric Sites



https://www.cnet.com/science/biology/googles-deepmind-ai-predicts-3d-structure-of-nearly-every-protein-known-to-science/

- Design of Protein-Protein Interactions



E. Callaway (2023) Nature 619:236-238; doi.org/10.1038/d41586-023-02227-y

- Expanded Inventory of Novel Protein Structures, Designer ADME, Targeting Systems for Drug Delivery and Cellular Therapy

Now Comes the Hard Part!

Driving Precision Oncology and Large Scale Data Analytics into Routine Practice

New Competencies, Processes and Organizational Structures

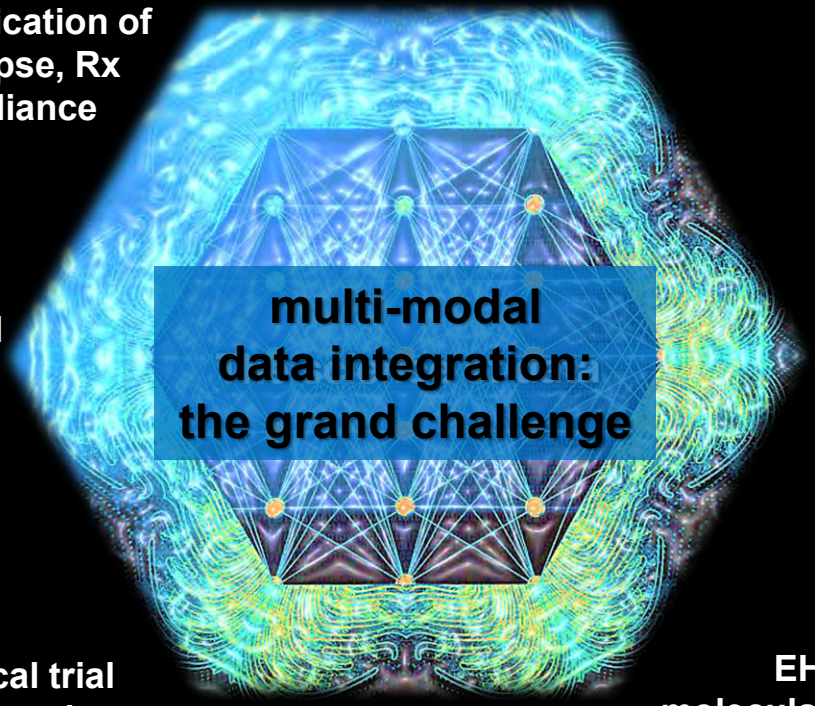
New Participants and New Models for Research and Care Delivery

Precision Health and Digital Health: The Evolution of a Data-Centric Ecosystem

multiOmics and mapping biological information networks

remote health status monitoring (IoMT) and earlier identification of clinical relapse, Rx non-compliance

biological network deconvolution and disease associations



patient match: "digital twins" and optimized clinical interventions

spatio-temporal dynamics of disease progression

new clinical trial designs based on multiOmics disease subtyping

clinical regimens and outcomes

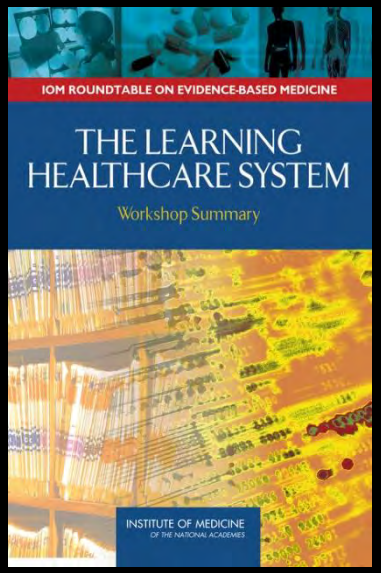
EHR integration of molecular, imaging, clinical and SDoH data

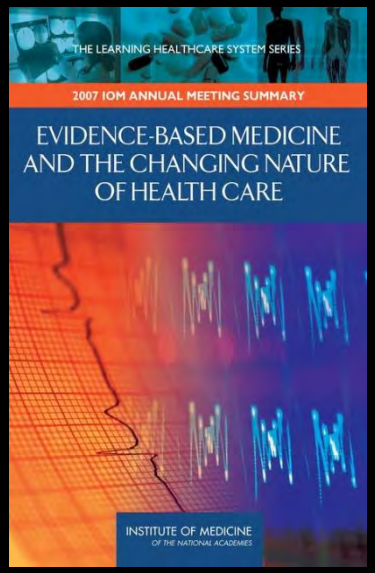
Big Biology and Biomedicine Meets Big Data

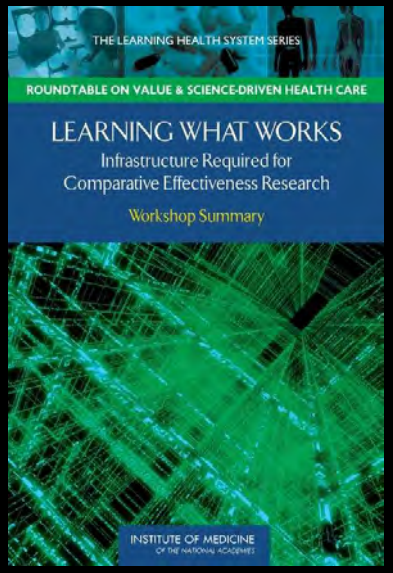
The Pending Zettabyte Era
1,000,000,000,000,000,000,000

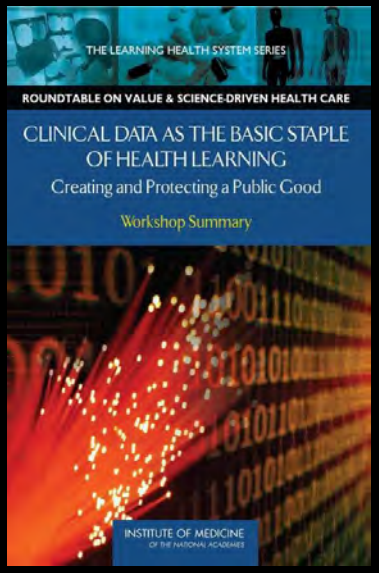
Integration of Large Scale, Multi-Disciplinary Datasets Will Not Be a Simple Extrapolation from Current Bioinformatics and HIT Platforms

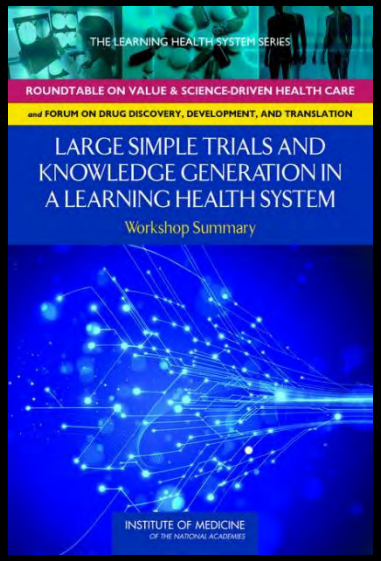
The Learning Healthcare System

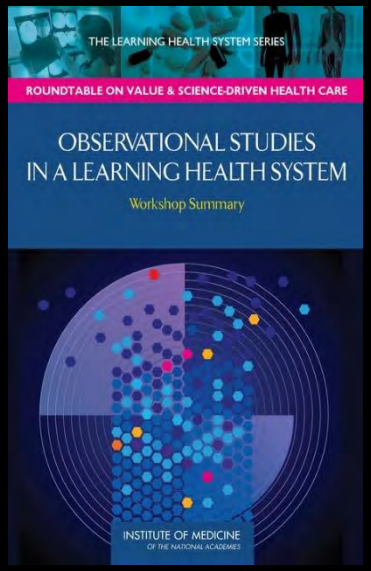


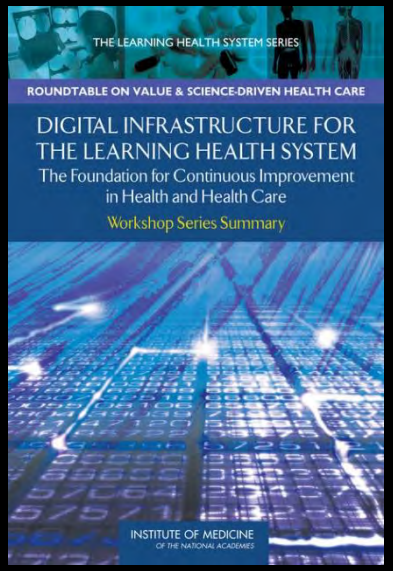


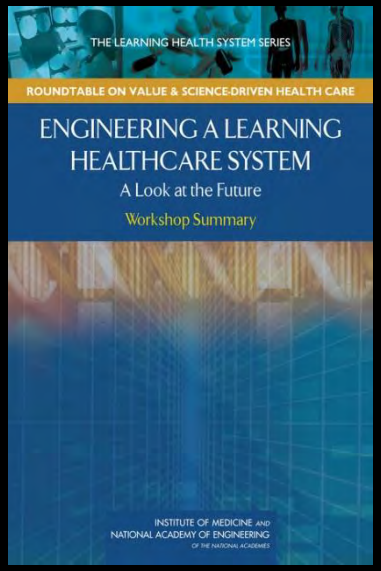












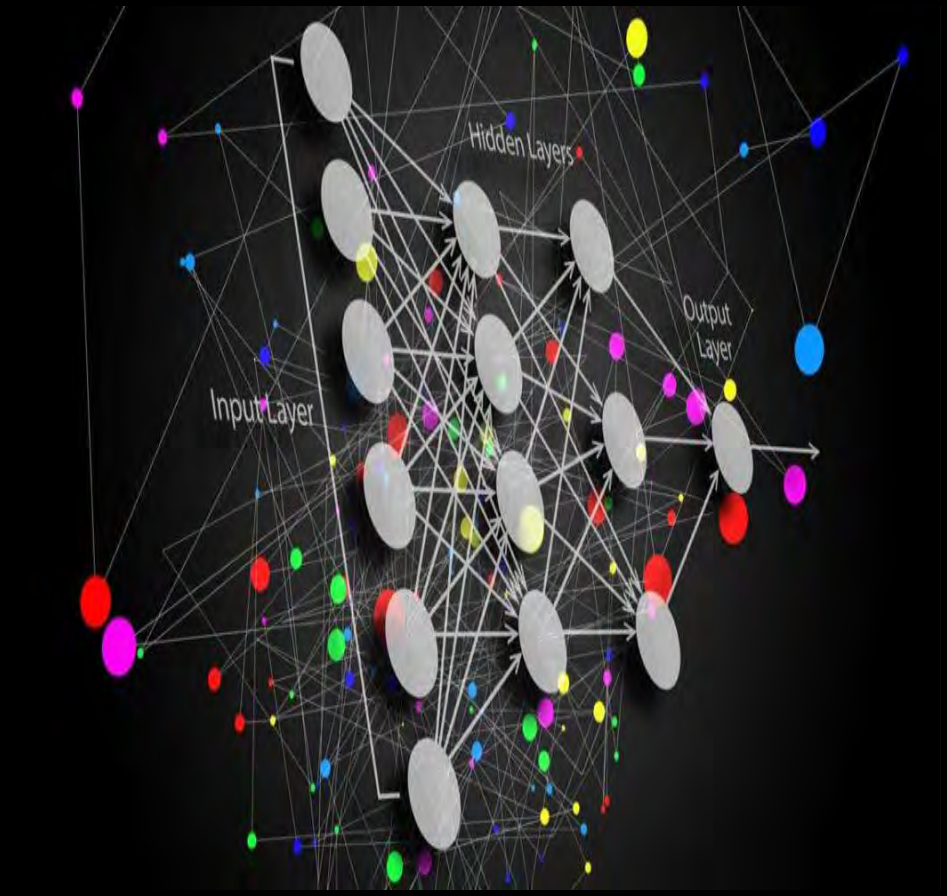
Welcome to The World of Biomedical Research and Healthcare Information Systems

Biomedical Data: Vast, Growing Rapidly But Poorly Used

- 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 dynamics in disease progression
- major impediments to research productivity, optimum clinical decisions and continuity-of-care for patients

ML-AI Large Language Models (LLMs): Transformation of the Research Process and Clinical Decision-Making

GAI and Transformer Platforms

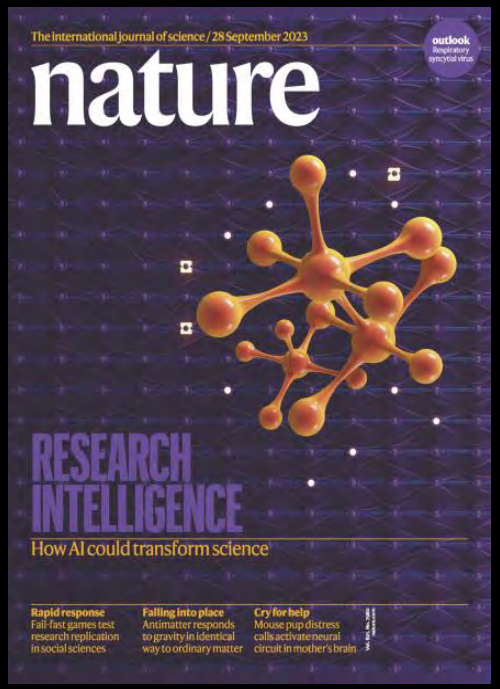


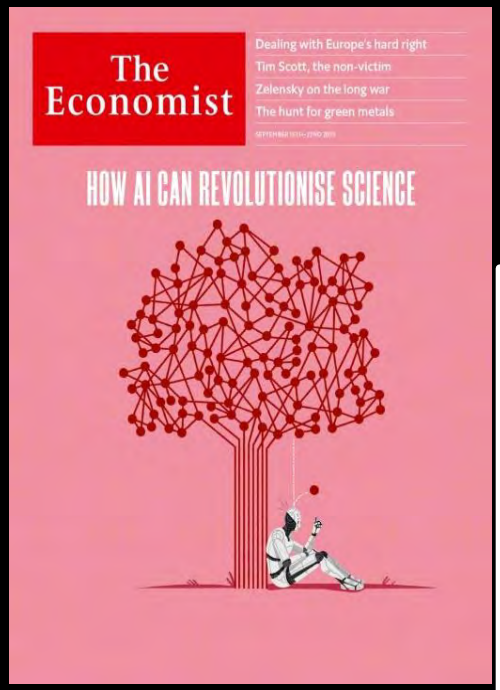
https://insidebigdata.com/2023/10/01/video-highlights-vicuna-gorilla-chatbot-arena-and-socially-beneficial-llms-with-prof-joey-gonzalez/

Deep Learning and Pattern Analysis in Multi-model Data Integration

https://techxplore.com/news/2023-07-chatgpt-people-surprisehere-technologies-difference.html

AI and LLM Platforms and Disruptive Transformation of Biomedical Research and Healthcare Delivery





Meta PyTorch, LLaMA (24 Feb.)

Google DeepMind Palm (10 March) BARD ANTHROP\C

OpenAI GPT4 (14 March) Microsoft Bing (7 March)

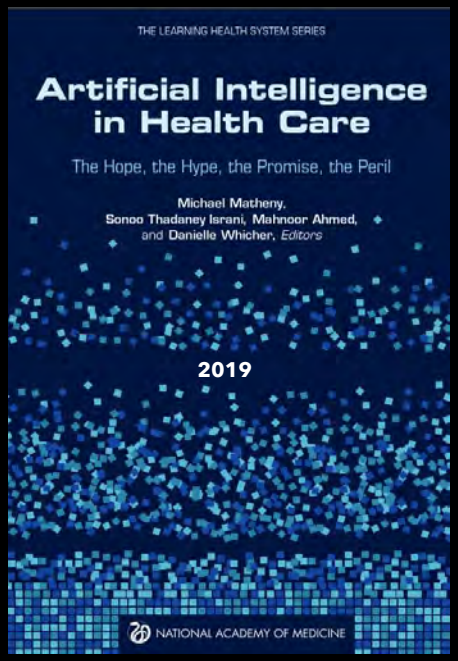
Baidu ERNIE (15 March)

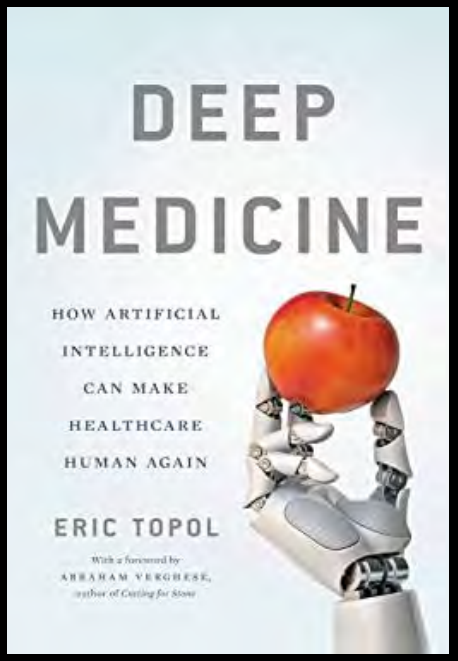
Microsoft GitHub Copilot X (22 March)

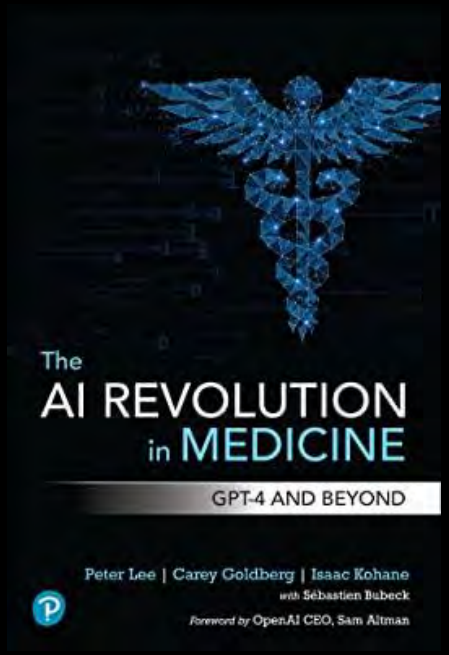
aws expand partnerships Hugging Face ANTHROP\C

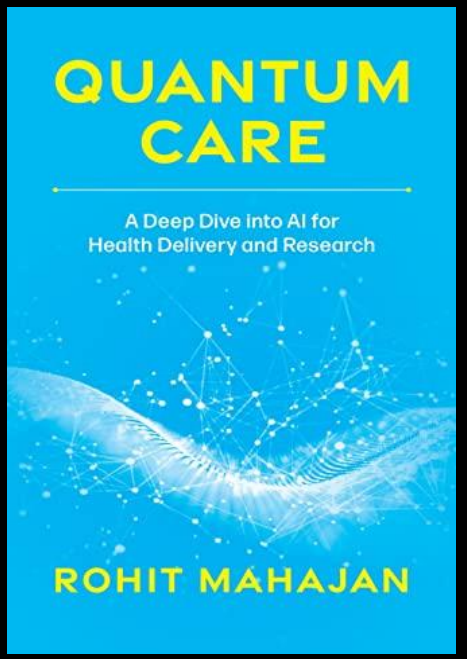
salesforce ChatGPT app added its Slack and Einstein platforms

Generalized Artificial Intelligence and Healthcare







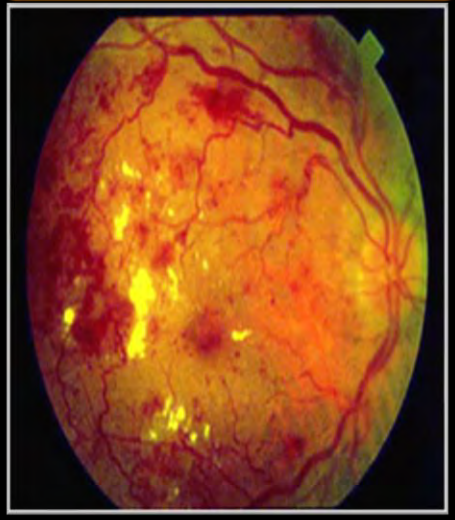


No Shortage of Commentaries on the Potential of AI for Limitless Benefits or the Road to Dystopian Futures and Machine Control?

OCTOBER 30, 2023

FACT SHEET: President Biden Issues Executive Order on Safe, Secure, and Trustworthy Artificial Intelligence

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

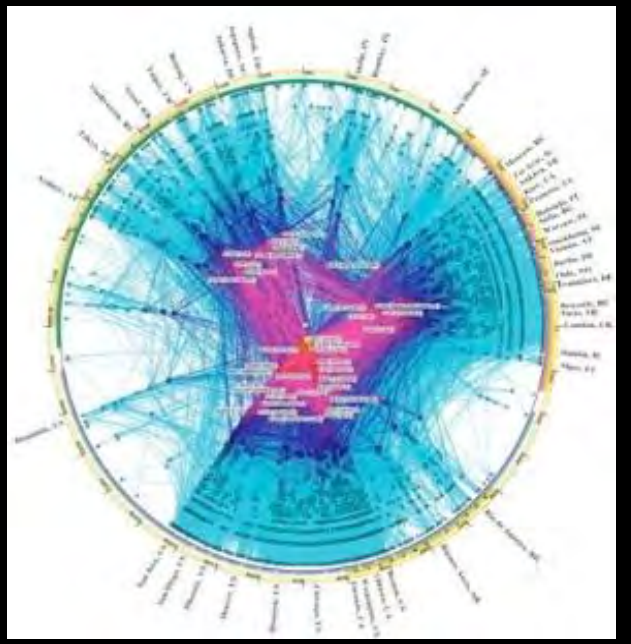
The Adoption of ML- AI Platforms in Clinical Medicine

- from early applications in image analysis to assembly and interpretation of multi-modal deep phenotyping data to define ‘signatures’ of individual health status and risk prediction

The Emergence of Big Data and ML-AI Platforms Changes the Questions That Can Be Asked

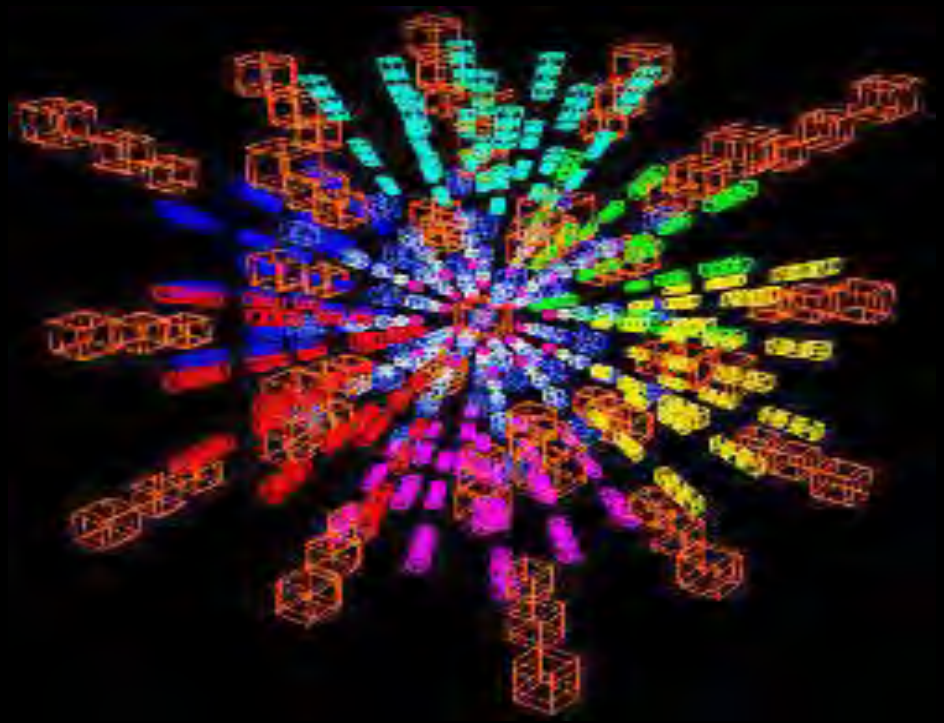
Isolated Siloed Data

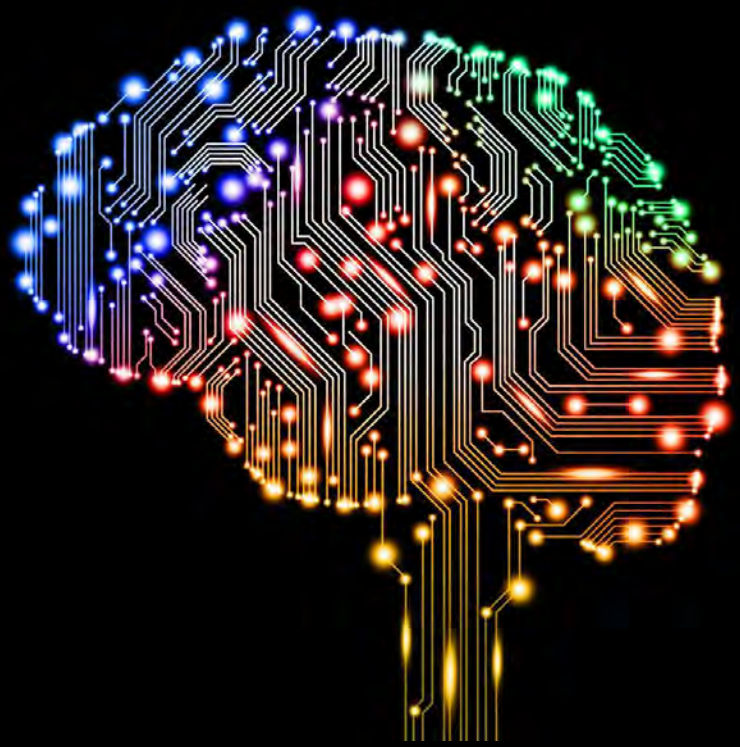
Complex Networked Data



Complex Computational Data

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**

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

Individual Data

Population Databanks

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

Will ML-AI Alter the Fundamental Intellectual Framework for Research Investigation and Decisions?

- large-scale data analytics and pattern recognition for hypothesis-free analysis

- validation of LLM/GAI decision-support tools
- new hypothesis generation from orthogonal vectors

Large-Scale Data Science, Creation of New Research Paradigms and the Entry of New Private Sector Enterprises Into the Biomedical Ecosystem

Implications for the Future Organization, Conduct and Funding of Research, Care Delivery, Education and Training

- private sector dominance?
  - compute scale and analytical algorithms
  - proprietary datasets
  - talent
- new academic-industry collaborations
  - multi-scale research questions
  - funding education and training to create talent pipeline

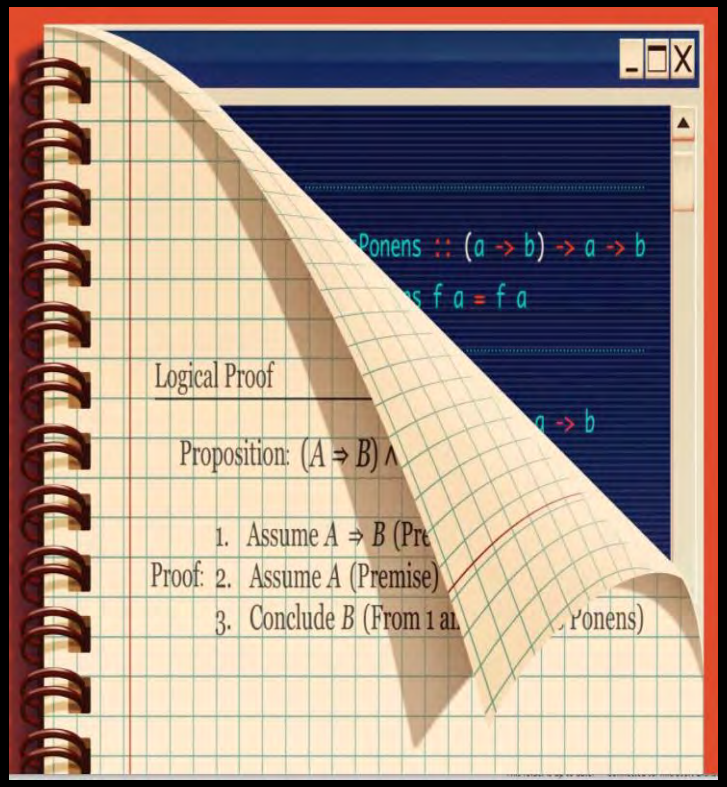
P. Webster (2023) Nat. Med. 29:1034-1037;
doi.org/10.1038/s41591-023-02290-y

Just What the Data Ordered

ML-AI LLM
Algorithms for Clinical Diagnosis
and Treatment Decisions

Black Box Medicine?

Regulatory Oversight and Validation of Large Language Model (LLM) AI Platforms in Biomedicine



- most LLMs released globally but international harmonization guidelines yet to be defined
- new validation complexities not addressed by current regulatory criteria for pre-LLM machine learning algorithms
  - FDA: software as medical device (SaMD)
- availability of regulatory expertise and resources to accommodate pace of adoption of GPT platforms?
  - integration of next wave of multi-modal data will exacerbate the challenge
  - voice-to-text, video
  - AR/VR/XR platforms

MITRE

FDA

AHRQ Agency for Healthcare Research and Quality

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

NIH

MAYO CLINIC

OPTUM

The Office of the National Coordinator for Health Information Technology

sas

Microsoft

Google

Stanford University

Duke UNIVERSITY

UCSF University of California San Francisco

VANDERBILT UNIVERSITY

JOHNS HOPKINS UNIVERSITY

Berkeley UNIVERSITY OF CALIFORNIA

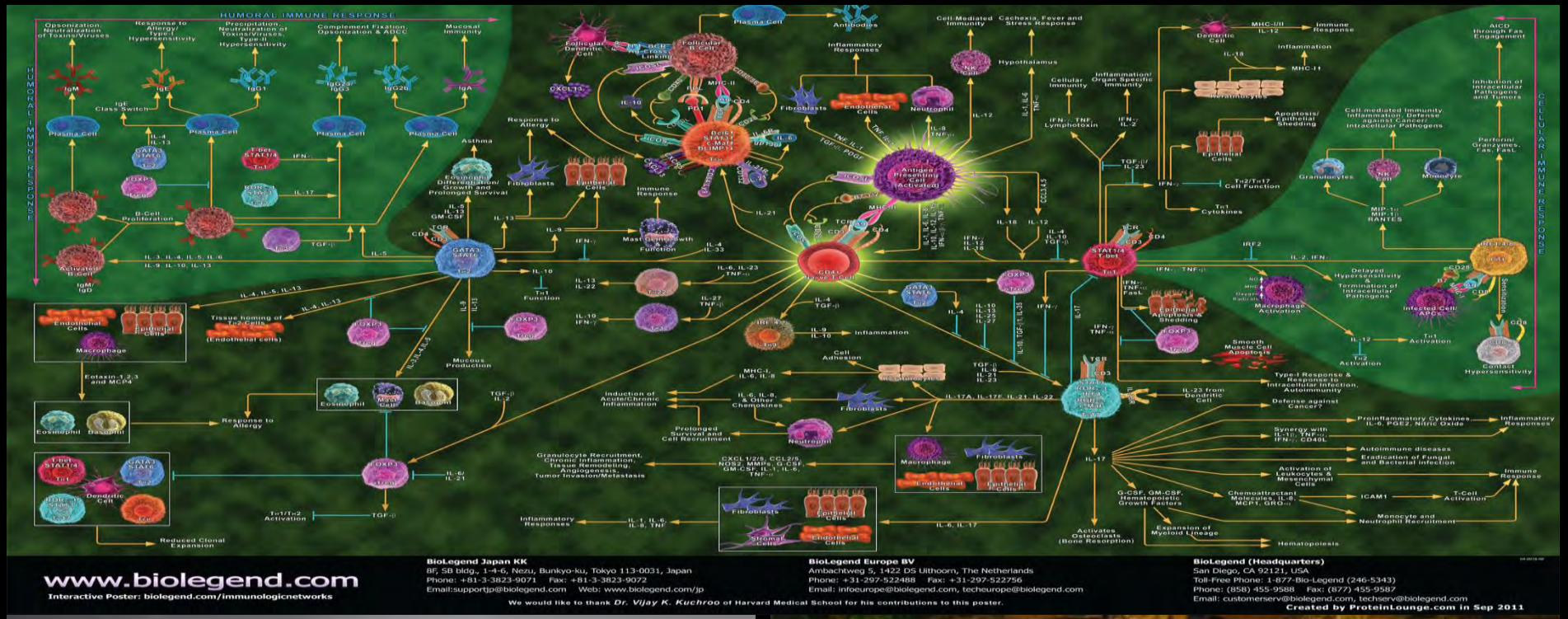
PARTNERSHIP ON AI

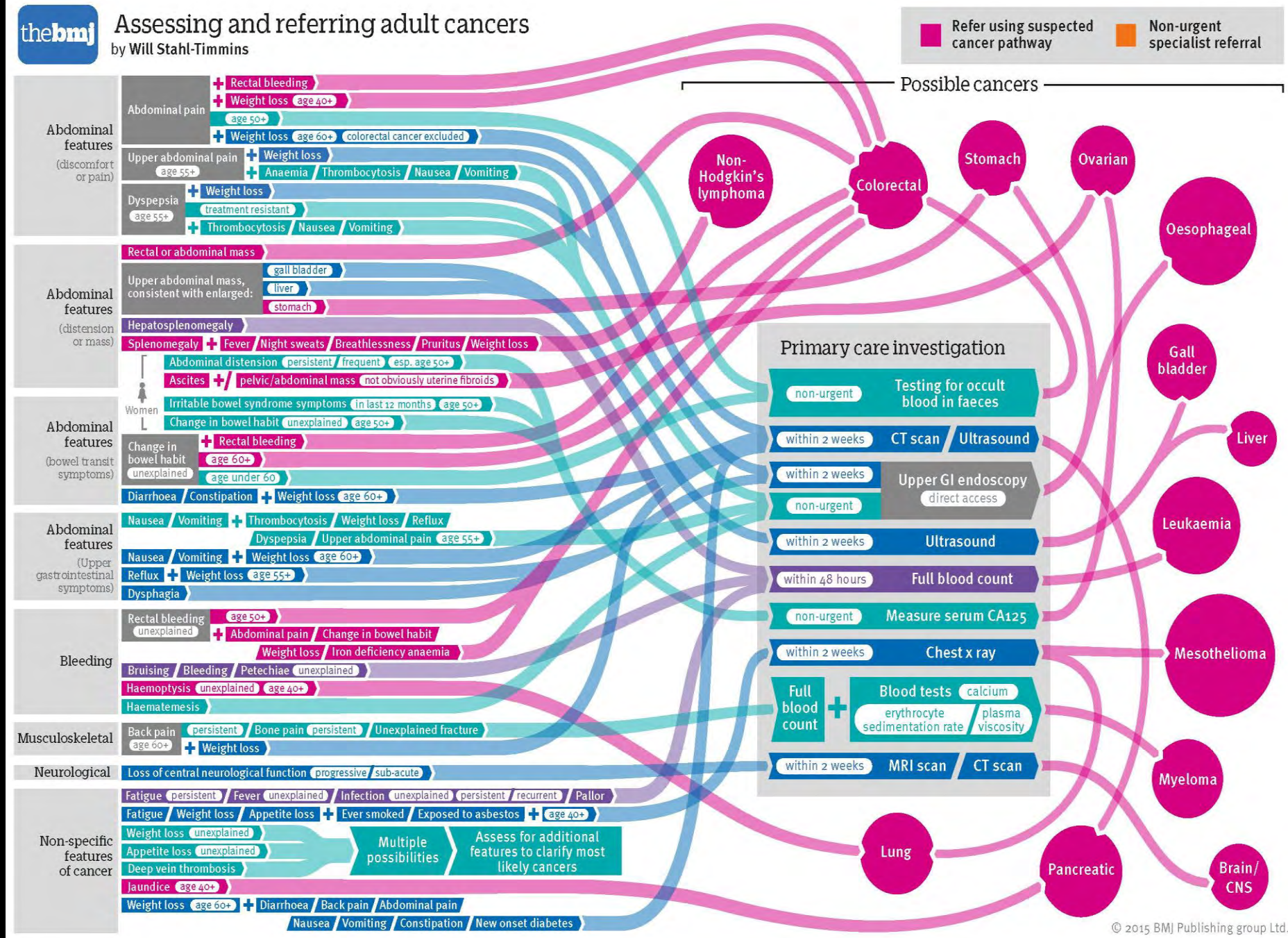
GORDON AND BETTY MOORE FOUNDATION

Inadvertent Disclosure Risks in GPT Platforms

- all data (prompts) provided to GPT platforms are not confidential and not HIPAA complaint
- employees asking ChatGPT to draft text/PowerPoint presentations using confidential and/or unpublished data creates potential risk of exposure to third party prompts to retrieve the deposited information
  - Samsung data breach (April 2023)
- physician inputs patient's name and condition into ChatGPT to draft a letter to insurance company justifying treatment
  - third party can then ask ChatGPT what clinical condition(s) does 'patient X' have and the bot could answer breaching patient confidentiality
- Verizon, JP Morgan Chase, USG agencies and several US states prohibit employee use at work

Navigation of Escalating Scientific and Clinical Complexities





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

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

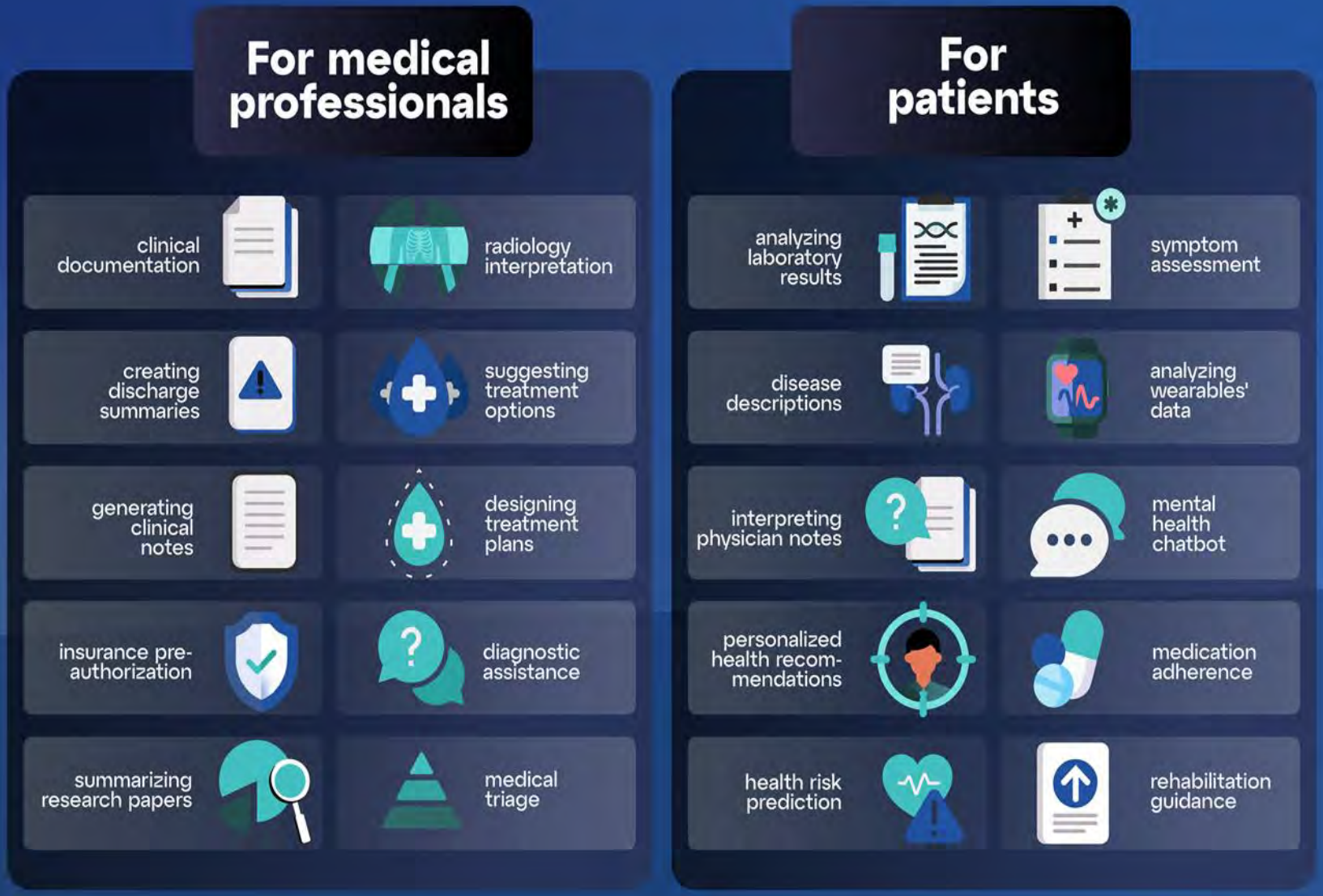
Data Deluge

Cognitive Bandwidth Limits

Automated Analytics and Decision Support

Facile Formats for Actionable Decisions

GAI and the Rise of Chatbots in Healthcare

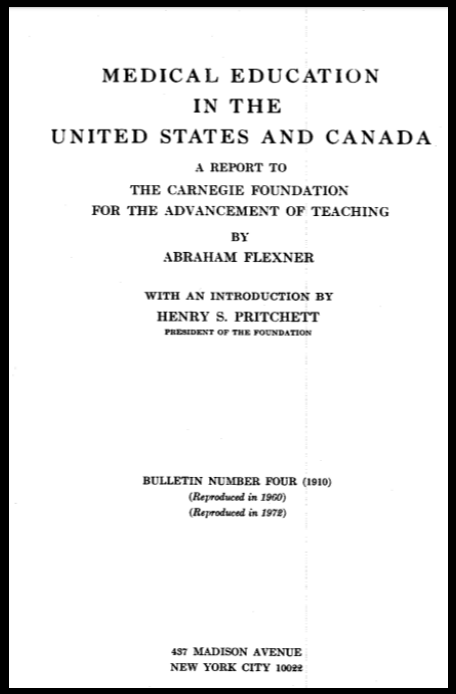


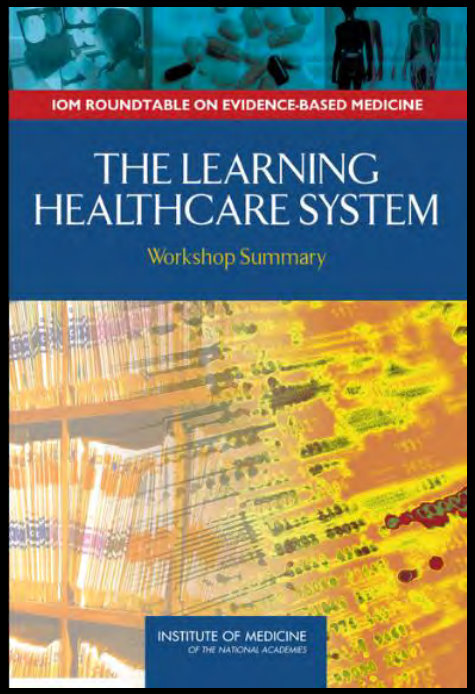
B. Meskó & E. J. Topol (2023) NPJ Dig Med 6:120; doi.org/10.1038/s41746-023-00873-0

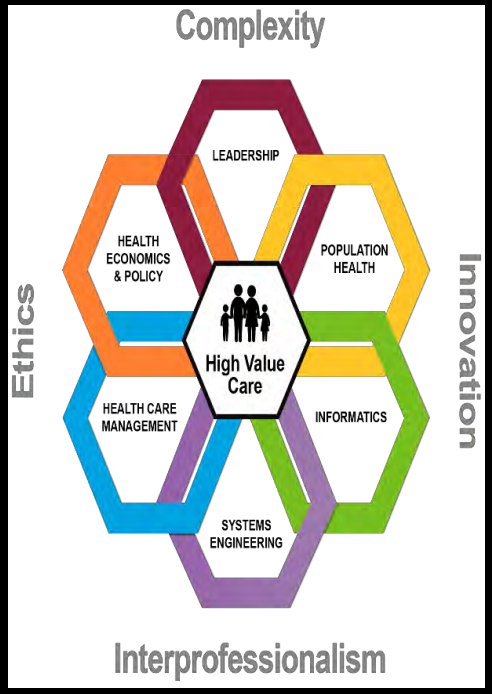
Regulatory Oversight and Validation of Large Language Model (LLM) AI Platforms in Biomedicine

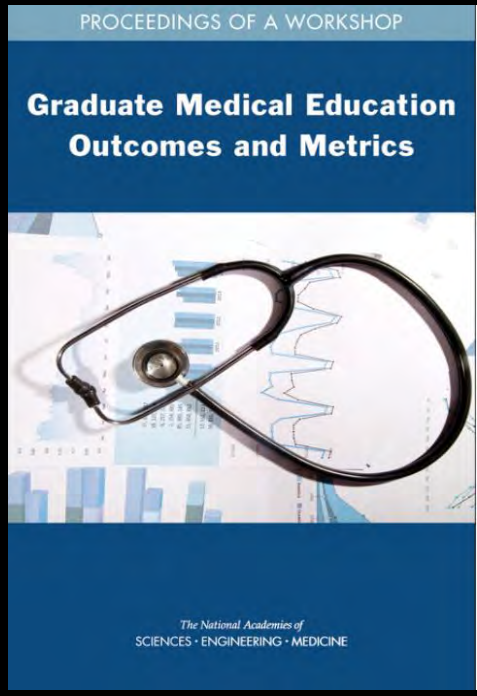
- transparency and patient informed consent when AI tools used in their care
- malpractice liabilities
  - harm from use (platform developers, HCPs, or the health systems which approved adoption)
  - harm from failure to use or ignored recommendations when AI-decision support systems are integrated into SOC, professional guidelines or regulatory labeling

Major Transitions in Medical Education and Healthcare









1910 - present | **2000 - present** | **2015 - ?**

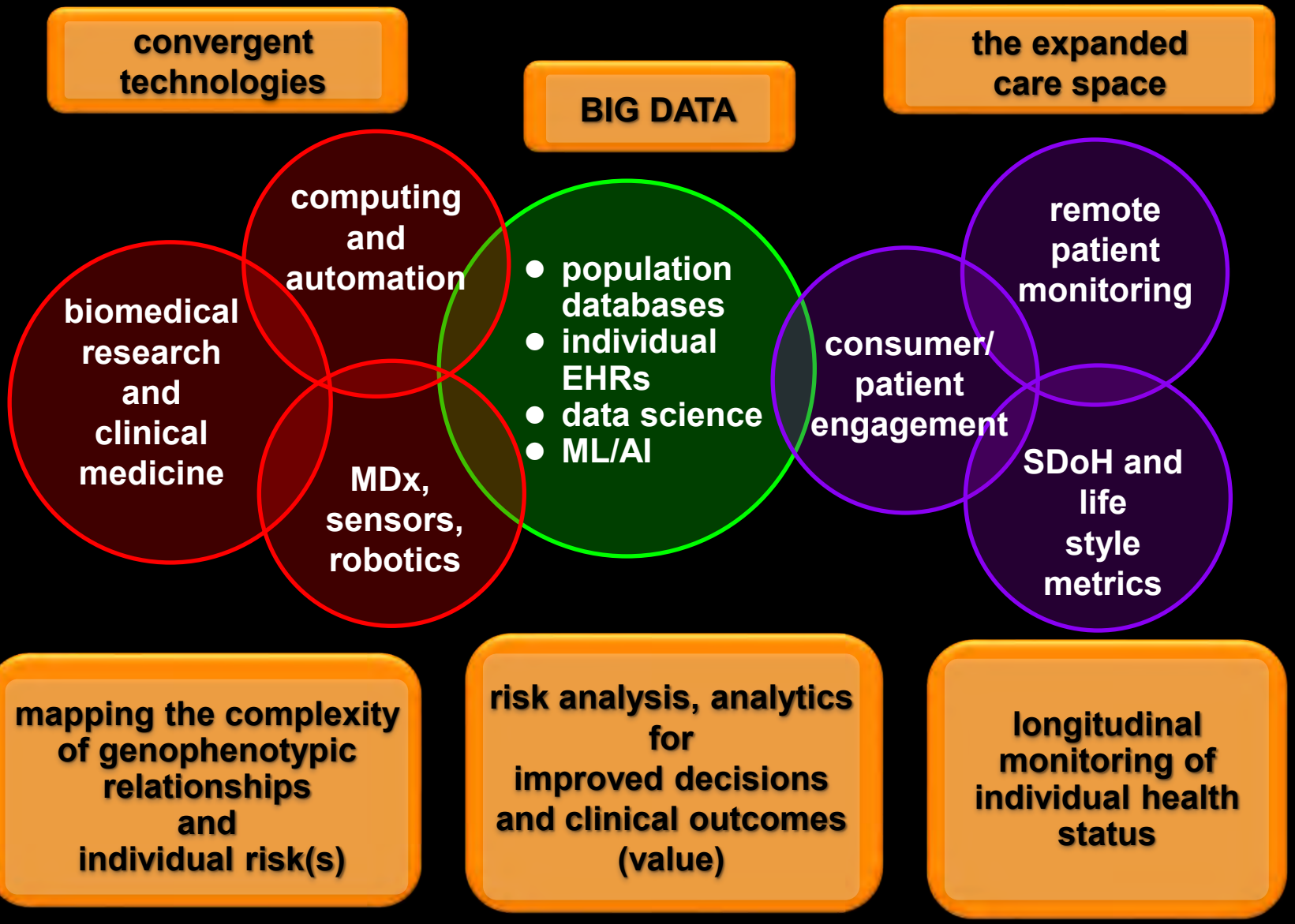
(science-centric)	healthcare as a learning system (data-centric)	mastery of escalating complexity and massive data (network-centric)

New Patterns of Learning

"Digital Darwinism": A Looming Digital Divide

- understanding data structure and its productive application/customization for acceleration of research and clinical care 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 Co-Evolution of Precision Health, Digital Health: Making Learning Healthcare Systems A Reality



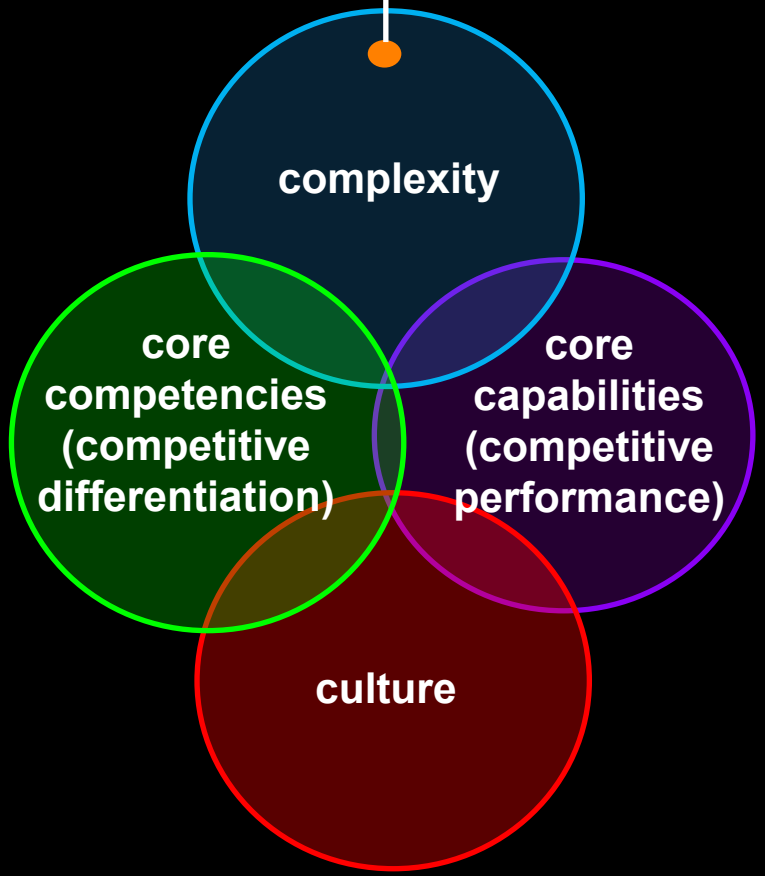
The Innovation Ecosystem

the strategic landscape

- unmet needs
- societal expectations
- conceptual trends
- new analytical platforms
- new cross-sector convergence
- new participants
- big data

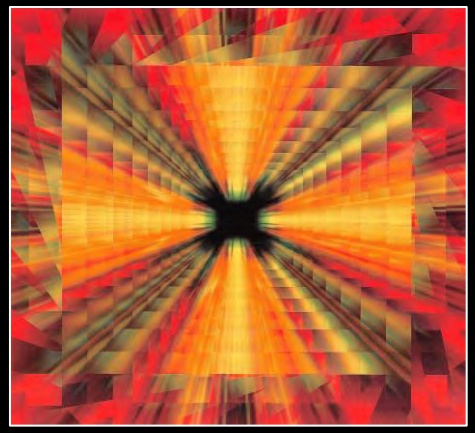
the organizational landscape

- unavoidable requirement for scale
- new collaboration networks
  - multidisciplinary, multi-institutional, multi-sector
- adaptive agile reconfiguration of expertise needs as the problem morphs



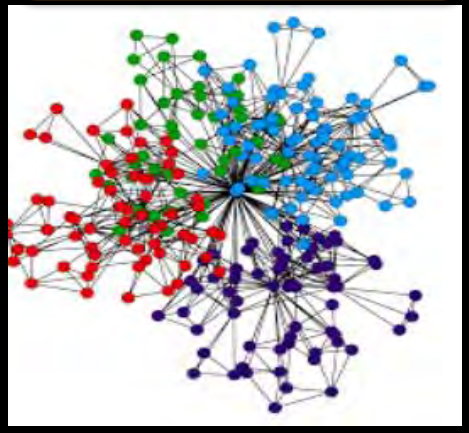
The Evolution of Data-Intensive Precision Health

Technology Convergence and Acceleration

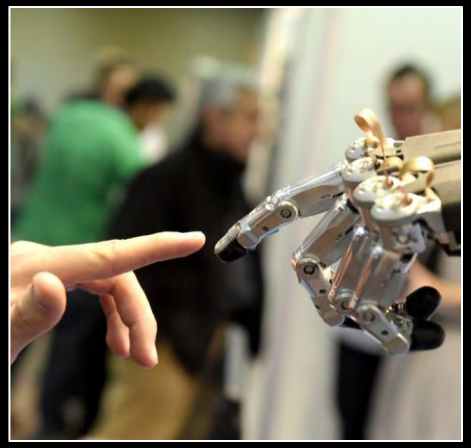


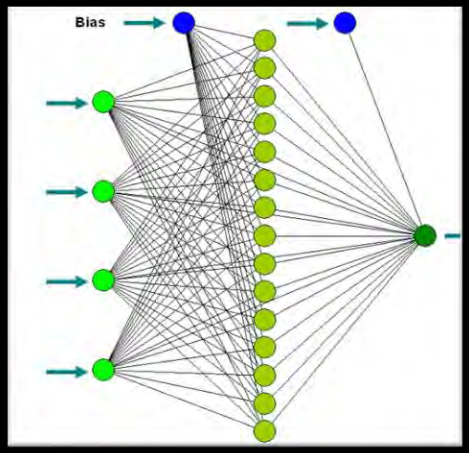
Mapping Geno-Phenotype Complexity

Topology of Biological Information Networks



Big Data





Data Security and Privacy

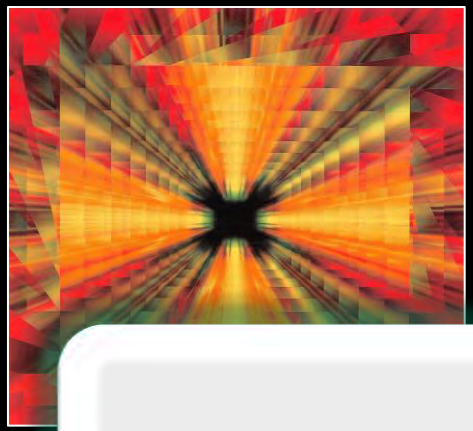
Artificial Intelligence and Decision Support

Robotics and Human Machine Interactions

Public Policy: Ethics, Risk and Regulation

The Evolution of Data-Intensive Precision Health

Technology Convergence and Acceleration



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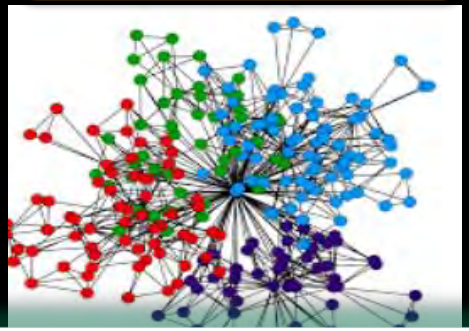
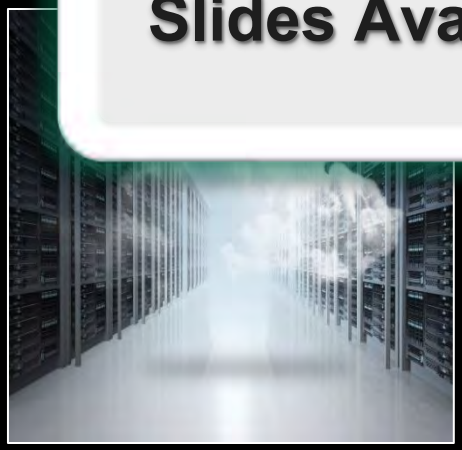
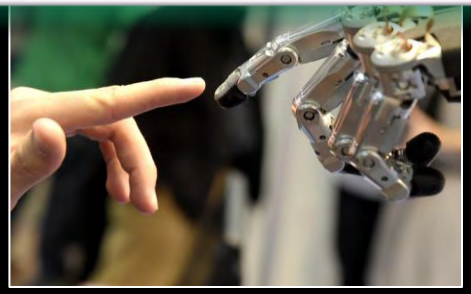
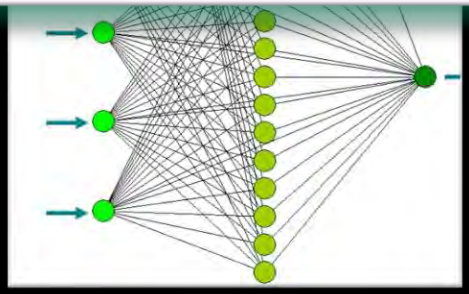


Big Data

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







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