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

Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative and Regents Professor of Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

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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

- Public Health
- Population Health
- Global Risk Factors
- Individual Care
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
  - multiOomics 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
- individual care
- population health
- public health
  - 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

- Biomedicine
- Engineering
- Computing
- New participants
- Aging populations
- CV, diabetes, cancer, neurodegeneration
- SDoH disparities
- Mental illness
- SUD
- Suicide
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

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

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
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

- Collection of Analytes
  - Patient tumor
  - Plasma
  - Cell line
  - PDX/organoid models
- Data Generation
  - Gene/Methylation arrays
  - High-throughput sequencing
  - Functional genetic screens
  - Drug-repurposing screens
  - Pharmacological screens
- Computational Analysis
  - Mutation detection
  - Fusion and SV Detection
  - Mutational Signatures
  - Tumor Classification
  - Systems Biology
- Clinical Research
  - Cancer Predisposition
  - Precision therapy
  - Patient stratification
  - Novel clinical trials and designs
- Prevention and Surveillance
  - Longitudinal studies
  - Therapy-induced disease

Translation to clinic

- Pediatric Cancer
- Diagnosis
- Therapy
- Outcome
- Remission
- Survivor

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 (ENCODER) 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
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

<table>
<thead>
<tr>
<th>Fusion</th>
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<tr>
<td>ALK</td>
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<tr>
<td>ROS-1</td>
<td>crizotinib, entrectinib</td>
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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

Number of clinical trials

Combination type
- Immuno-oncology
- Targeted therapy
- Chemotherapy
- Radiotherapy
- Chemoradiotherapy
- Multi-way combo.
- Others
- Monotherapy

Pembrolizumab
Nivolumab
Durvalumab
Atezolizumab
Avelumab
Cemiplimab
Dostarlimab
Other PDx

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

Conventional CAR T cells (e.g., CD19, CD22, and TSLPR)

Bispecific CAR T cells (co-expression) (e.g., CD19/CD22)

Bispecific CAR T cells (bivalent) (e.g., CD19/CD22)

Inotuzumab Epratuzumab

Rituximab

Alemtuzumab

CD2

CD5

CD7

B-ALL

T-ALL

B-ALL and T-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
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

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

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, Homogeneous “Universal” CAR T Cell Manufacture

Healthy Donor Cells

- c-MYC, OCT3/4, SOX2, KLF4

Multiplex CRISPR Editing

iPSC pool

- 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
• 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

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)
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 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
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

- Google
- Amazon
- Apple
- Microsoft
- ORACLE
- CVS
- Aetna
- United Healthcare
- Optum
- Blue Cross Blue Shield
- Walgreens
- Walmart

- the metaverse land grab
- blockchain platforms
Precision Health and Digital Health: Building the Learning Health System

- Qualitative, descriptive information of variable quality and provenance
- Complex ecosystem of largely unconnected data sources
- Quantitative data of known provenance and validated quality
- Evolving, inter-connected networks of data sources for robust decisions and improved care
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

- ‘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
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
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

- Silo busting:
  - Improved continuity in care

- Precision health:
  - Integration and analysis of large-scale data to optimize decisions
  - Physicians, pts, payors
  - Consumer/pt expectations/Ux

- Digital health:
  - New technologies for health risk identification and mitigation
  - SDoH and health

- Improved outcomes and economic sustainability:
  - New quantitative performance metrics
  - Intensified focus on VALUE

- Telemedicine, RHM and decentralization of care services
The Evolving Systemic Landscape for Optimizing Health

- silo busting
- precision health
- digital health
- improved outcomes and economic sustainability

- 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
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