The Complex Strategic Landscape for Precision Medicine

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The Complex Strategic Landscape for Precision Medicine

Cost

Complexity

Computing

Culture

Creative Destruction
(Comfort and Complacency)
Challenges Facing U.S. Healthcare

- Balancing Infinite Demand versus Finite Resources
- From Volume-Based (Do More-Bill More) Fee-for-Service to Value-Based Care
- From Reactive, Episodic Interventions in Advanced Disease to Proactive Identification of Disease Risk and Earlier Detection
- Improving Clinical Outcomes at Lower Cost and Optimizing Wellness
Challenges Facing U.S. Healthcare

Balancing Infinite Demand versus Finite Resources

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

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

Improving Clinical Outcomes at Lower Cost-and Optimizing Wellness

Value

Precision Medicine

Digital Medicine
The Demographics of an Aging Society: Clinical and Economic Challenges to U.S. Healthcare

wellness with longevity and high QOL or multiple co-morbidities and low QOL
Disease Burden: Confronting the Largest Clinical Economic Disruptions and Threats to Sustainable Healthcare

- cancer
- neurodegeneration
- cardio-vascular/metabolic disease
- mental illness
Cost
Health Spending Is Untethered From the Rest of the Economy: Growth in national health expenditures (NHE) and gross domestic product (GDP) and NHE as a share of GDP, 1989–2015

Health Affairs (2017) 17, 166-176

- $3.4 trillion dollar economy
- 17.8% of GDP
- one in seven US workers employed in health sector
Precision Medicine: Not If, But…

- what?
- when?
- how?
- who?
- value?
The Path to Precision Medicine:
From Superstitions to Symptoms to (Molecular) Signatures
Molecular medicine and information-based targeted healthcare.

The Dangers of Techno-Optimism
Still Two Largely Separate Worlds

Precision Medicine
- Research and early clinical adopters
- Slow incremental adoption of technological advances

Routine Healthcare Delivery and SOC
- $10-25 billion (estimated)
- $3.2 trillion (18% GDP)
Precision Medicine:

(Epi)Genomics

Causal Relationships Between Molecular Signaling Network Disruptions and Disease

Patient-Specific Signatures of Disease or Predisposition to Disease

Big (Messy) Data

- terabytes per individual
- zettabyte – yottabyte population databases
Precision Medicine and New Clinical Trial Designs

From RCT to Adaptive, Basket, Umbrella Trials and
New Approaches to RWE Observational Trials and Registries
Addressing the Biopharmaceutical Industry’s Principal Pain Point

• failure of clinical trials
  - unrealized opportunity cost
• cost of failed trials included in pricing of successful Rx
  - fuels political criticism about drug prices
• lack of predictive tools to differentiate responder (R) and non-responder (NR) patients
  - growing payer pressure for value-based reimbursement for guaranteed therapeutic outcomes
  - waste/risk from futile therapy in NR cohorts
Navigating the Coverage Experience and Financial Challenges for Cancer Patients: Affordable Care Act Brings Improvements, But Challenges Remain

By JoAnn Volk and Sandy Ahn

Monthlly and Median Costs of Cancer Drugs at FDA Approval 1965-2016

Monthly Cost of Treatment (2014 Dollars, log scale)

Year of FDA Approval

Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center
What Constitutes a Meaningful Clinical Benefit?

- 71 FDA-approved Rx for solid tumors 2002 to 2012\textsuperscript{a}
  - median PFS (2.1 months) and OS (2.3 months)
- 47 Rx 2014-16\textsuperscript{b}
  - only 19% met ASCO modest OS benefit criterion
- ESMO analysis of 226 randomized trials\textsuperscript{c}
  - only 31% met meaningful benefit criteria

\textsuperscript{a} = T. Fojo et al. (2014) JAMA Otolaryngol. Head Neck Surg. 140, 1225
\textsuperscript{b} = H. Kumar et al. (2016) JAMA Oncology 2, 1238
\textsuperscript{c} = J. C. Del Paggio et al. (2017) Ann. Oncol. 28, 157
The Promise of Immunotherapy: Is Widespread Adoption Economically Feasible?

- unit Rx cost (> $100K) before cost of clinical care
- escalating cost of combination Rx regimens (> $200K)
- extravagant cost of cell-based therapies ($500K - $1.5 million)
- 40-80% NR in most solid tumors
- TML, MSI, MMR as potential ‘R’ predictors
Hype Versus Hope - A Delicate Ethical Balance: Come and Be Cured by Us: (Go Elsewhere at Your Peril)!
Impact of Pembrolizumab Dosing Regimen on Treatment Cost (75kg Patient)

- 2017 price $46.54/mg
- initial FDA approval 2mg/kg every 3 weeks
  - $121,000/yr.
- subsequent FDA approval 200mg dose every 3 weeks
- 10mg/kg dose used in multiple publications
  - $586,000/yr.
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Pending I/O combinations: Aargh!!
“Unconscionable Price Increases and Price Gouging”: The Biopharmaceutical Sector and Reputational Damage
Precision Medicine and Predictive Identification of Rx Responder (R) and Non-Responder (NR) Patients

- the single most important opportunity for the Rx industry in confronting political attacks about pricing?
- high cost immunotherapy as the inflection point?
- proactive industry engagement or imposition by payers?
Conflicts and Contrasts in Reimbursement Policies for Therapeutics (Rx) and Molecular Diagnostics (MDx) in Oncology

- **Rx**
  - high Rx non-responders plus Rx-resistance
  - limited improvement in PFS/OS (non-I/O Rx)
  - reimbursement for one-size-fits-all Rx regimens

- **MDx**
  - multi-omics and rational Rx selection
  - cost-based versus value-based reimbursement policies
  - reimbursement policies as disincentive for investment in MDx
## Multigene Test Reimbursement Policies for Five Largest US Private Insurers (Enrollment 112 Million Lives)

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<th>Payer</th>
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<th>% Policies Covering All Included Tests</th>
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</table>

Policy Options to Incentivize Development of Diagnostic Assays to Identify Rx Responders (R) and Non-Responders (NR)

- impose progressive Rx price reduction over five year post-launch period until R-NR assay introduced
  - annual reduction based on projected cost of documented futile Rx in NR patients
- payers guarantee premium pricing and formulary placement for positive outcomes in R patients
- accelerated regulatory review for Rx submitted with companion Dx (CoDx) versus Rx without CoDx
Complexity
The Over-Simplified Perspective That
While Exome-and Whole Genome-Sequencing
Will Reveal the Etiology of Disease Pathogenesis

Ignoring Biological Complexity
Large Scale Genome Sequencing Projects: Siloed Data or Purposeful Integration with Multi-Omics and Phenotypic Data?
Individual Variation, (Epi)Genome Complexity and the Challenge of Genotype-Phenotype Predictions

Junk No More: Pervasive Transcription

- alternate transcription/translation/(co)splicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- phasing
- epistasis
- imprinting
- cis-and trans regulation
- RNA universe

(epi)genome organizational and regulatory complexity

Cell-specific Molecular Interaction Networks

Perturbed Networks and Disease
(Epi)Genome Plus Environment (Exposome) Determines the Dynamics of Cellular (Information) Signaling Networks (System States)

Longitudinal Quantitative Data: A Major Knowledge Gap in Patient Histories

Behavior

Environment
consistent ID of alterations in a modest number of genes/pathways and/or their regulation in disease
  – “core genes”, “drivers”
  – role in disease predisposition/onset

variants in multiple ‘peripheral’ genes with non-zero effects affect penetrance of core/driver gene sets
An Emerging ‘Omnigenic’ Model for Epistatic Gene Networks in Driving Complex Phenotypes
A. Boyle et al. (2017) Cell 169, 1177

- dynamic shifts in composition/modularity of molecular networks/subnetworks engages different collections of peripheral (modulating) genes
- resulting spectrum of overlapping disease phenotypes based on different core-peripheral gene combinations
It’s The Network Stupid!
Deconvolution of the Topology and Regulatory Dynamics of Molecular (Information) Networks
Understanding Network Organization and Regulatory Dynamics in Complex Adaptive Systems

- "health"
- homeostasis
- subclinical disease
- graded threshold states
- overt clinical disease
- diverse phenomes

X (health) ➔ X' (subclinical disease) ➔ X (d) (rational therapy)
Understanding Network Organization and Regulatory Dynamics in Complex Adaptive Systems

new analytical tools for proactive monitoring of systems state space(s) and timely intervention(s) to channel emergent behavior to most desired trajectories

\(X\) (health)
\(X'\) (subclinical disease)
\(X\) (d) (rational therapy)
Are We Approaching the End of Identification of New Rx Targets Associated with the Coding Genome?

Will Future MDx and Rx Discovery Be More Productive By Identification of Novel Targets in Non-Coding Regulatory Elements (Regulome)?
Recurrent and functional regulatory mutations in breast cancer

Genomic analysis of tumours has led to the identification of hundreds of cancer genes on the basis of the presence of recurrent mutations in protein-coding regions. By contrast, much less is known about cancer-causing mutations in non-coding regions. Here we perform deep sequencing in 360 primary breast cancers and develop computational methods to identify significantly mutated promoters. Clear signals are found in the promoters of three genes. FOXA1, a known driver of hormone-receptor positive breast cancer, harbours a mutational hotspot in its promoter leading to overexpression through increased E2F binding. MNF1R and NEAT1, two non-coding RNA genes, carry mutations that affect protein binding to their promoters and alter expression levels. Our study shows that promoter regions harbou recurrent mutations in cancer with functional consequences and that the mutations occur at similar frequencies in coding and non-coding regions. Power analyses indicate that more such regions remain to be discovered through deep sequencing of adequately sized cohorts of patients.

Nature (2017) 547, 55

An imprinted non-coding genomic cluster at 14q32 defines clinically relevant molecular subtypes in osteosarcoma across multiple independent datasets

High-confidence coding and noncoding transcriptome maps
Bo-Hyun You, Sang-Ho Yoon, and Jin-Wu Nam

The advent of high-throughput RNA sequencing (RNA-seq) has led to the discovery of unprecedentedly immense transcriptomes encoded by eukaryotic genomes. However, the transcriptome maps are still incomplete partly because they were mostly reconstructed based on RNA-seq reads that lack their orientations (known as unstranded reads) and certain boundary information. Methods to expand the utility of unstranded RNA-seq data by predetermining the orientation of the reads and precisely determining the boundaries of assembled transcripts could significantly improve the quality of the resulting transcriptome maps. Here, we present a high-performing transcriptome assembly pipeline, called CAFE, that significantly improves the original assemblies by orienting and/or unstranded RNA-seq data, by orienting unstranded reads using the maximum likelihood estimation and by integrating information about transcription start sites and cleavage and polyadenylation sites. Applying large-scale transcriptome sequencing comprising 220 billion RNA-seq reads from the ENCODE, Human BodyMap 2.0, The Cancer Genome Atlas, and GTEx projects, CAFE enabled us to predict the directions of about 220 billion unstranded reads, which led to the construction of more accurate transcriptome maps, comparable to the manually curated map, and a comprehensive lncRNA catalog that includes thousands of novel lncRNAs. Our pipeline should not only help to build comprehensive, precise transcriptome maps from complex genomes but also to expand the universe of noncoding genomes.

Genome Research (2017) 27, 1050

Recurrent noncoding regulatory mutations in pancreatic ductal adenocarcinoma
Michael E. Feigin, Tyler Garvin, Peter Bailey, Nicola Waddell, David K Chang, David R Kelley, Shimin Shuai, Steven Gallinger, John D McPherson, Sean M Grimmel, Eka Khurana, Lincoln D Stein, Andrew V Biainkel, Michael C Schatz, David A Tuveson

Nature Genetics (2017) 49, 825
Defining Short- and Long-Range Cis- and Trans- Regulation of Gene Networks

Chromosomal Neighborhoods: Understanding the 3-D and 4-D Genome

ChromEMT Mapping of Chromatin Ultrastructure and DNA Packing

From: International School of Advanced Studies (SISSA) [October 26, 2016]

From: H. D. Ou et al. (2017) Science eaaag.0025
The Deconvolution of Biological Complexity: The Shift from Reductionism to Systems-Based Concepts

- fifty years of reductionist biology
- vital legacy but now ill-suited to address the daunting complexity of biological network dynamics in physiology and pathology
- big biology (analogy with big physics)
  - multi-disciplinary, multi-institutional, multi-sector
  - increased investment and dependency on methods from industry sectors hitherto uninvolved in healthcare
Convergence

Convergence of Advances in Biomedicine, Materials Science, Engineering, Telecommunications, Advanced Computing and Data Science

Blurring the Boundaries of Biomedicine
Most Events That Affect Our Health Occur Outside of the Healthcare System And Are Not Monitored

Need for Continuity of Care Record: From Womb to Tomb

Behavior

Environment
Precision Medicine: Healthcare Beyond The Clinic

- Daily decisions by individuals have greater effects on their health than decisions controlled by the healthcare system.
- Building HIT systems to better monitor health status and treatment adherence.
Microbiome Profiling:
The Gut-Immune-Brain Axis in Health and Disease

- influence of microbial metabolites
  - nutrition
  - obesity
  - brain function/mood
  - drug metabolism
  - autoimmunity; immune system responsiveness
WE’VE MAPPED THE WORLD.
NOW LET’S MAP HUMAN HEALTH.
Personal, Dense, Dynamic Data Clouds: Comprehensive Profiling of Health Status of 108 Individuals Over 9 Months


- WGS
- daily physical and sleep activities
- 3 month blood, saliva, urine and stool analysis
- 643 metabolites
- 262 proteins

- cost
- scalability
- data interpretation
- clinical utility
“[Brings] health monitoring to new heights or depths, depending on how you look at it.”
- Eric Topol, Scripps Institute

"…lack of sparkling findings. All these tests cost a lot of money and it’s not exactly clear what we are getting out of them.”
- Atul Butte, UCSF

“when you link it [profiling] to companies offering this as a service, that is where we start getting into trouble.”
- Jonathan Berg, UNC

Reports in the August issue of *Nature Biotechnology* that dozens of the participants turned out to have undiscovered health risks, including prediabetes and low vitamin D, which the coaching helped them address.

Hood says the findings justify commercializing the monitoring, in a service costing thousands of dollars a year. But some colleagues disagree. The effort takes health monitoring "to new heights, or depths, depending on how you look at it," says Eric Topol, director of the Scripps Translational Science Institute in San Diego, California.

Entrepreneur Clayton Lewis (left) and biologist Leroy Hood (right) offer a data-heavy approach to health monitoring through their company, Arivale.

Berg, a physician scientist who studies cancer and genetics at the University of North Carolina School of Medicine in Chapel Hill, considered that project "thrilling." But, he adds, "when you link it to companies offering this as a service, that is where we start getting into trouble."

The problem, Berg says, is that "we don't have any idea at all how this information should be used clinically." Topol agrees, noting that he had comparable concerns about a similar barrage of tests on presumably healthy people, including genome sequencing and a full-body MRI scan, from a company launched by another genome legend, J. Craig Venter.
Invasion of the Body Trackers: Expanding the “Care Space” in Healthcare

- Smartphones, Wearables, Devices and Digital Services
- M4: Making Medicine More Mobile
Remote Health Status Monitoring
Wearables and Tracking Physical Activities

Nature (2017) 547, 13

Giant health studies try to tap wearable electronics

Google spin-off explores combining data from smart devices with other health metrics.

Pokémon Go: The Latest Fitness App Craze
Gray Technologies and Aging in Place: Independent But Monitored Living for Aging Populations

- Rx adherence
- Cognitive stimulation
- In home support and reduced readmissions
- Reduced office visits
Digital Assistants and Support Robots in Healthcare
AORTA Technologies:
Always-on-Real-Time Access for Health Status Monitoring

- better real time patient-specific data and decision-support tools
- new patterns (touch points) of patient engagement with the health system
  - extend reach and continuity in care
  - ability to monitor larger number of patients
- each individual becomes their own control
Mobile Apps, Wearables, Sensors and Continuous Health Status Monitoring

- who sets the standards?
- who integrates and interprets the data?
- who pays?
- who consents?
- who owns the data?
An Apps-Based Information Economy in Healthcare

- lack of developer access to high quality healthcare data to validate App platforms
- accuracy, reliability, security and privacy
- FDA focus on Apps that transform phone/tablet into a regulated medical device
- renewed FTC interest on Apps making unsubstantiated claims
Computing
Precision Medicine

- molecular classification of disease and elucidation of disease mechanisms
- RWE and learning healthcare systems

early adopters

routine healthcare delivery

subpopulation and individual phenotypes

populations
Precision Medicine and Digital Medicine: Evolving Inter-Dependencies

**Individual Data**

**Population Databanks**

Integration and analysis of large scale, diverse data

Matching individual profiles to “best matched” cohorts for clinical decisions
Social Spaces and Behavior Become Quantifiable

- who knows why people do what they do?
  - the fact is that they do!
- these activities can now be traced and measured with unprecedented precision
- with sufficient data, the numbers reveal increasingly predictable behavior and individual risk patterns
- new ethical and legal issues
  - consent, privacy, surveillance, security
Population Health Research and Precision Medicine: Blurring the Boundaries Between Research and Clinical Care

- every encounter (clinical and non-clinical) is a data point
- every individual is a data node
- every individual is a research asset
- every individual is their own control
“I don’t think of Humana so much as an insurance company as an IT company who is helping us with the data that we need in order to deal with our population health tools.”

Dr. Roy Beveridge, M.D.  
CMO, Humana  
Cited in Fierce Healthcare 9 May 2017
Now Comes the Hard Part!

Driving Precision Medicine and Large Scale Data Analytics into Routine Clinical Practice
The Problem With Real World Data is the Real World
HELL IS THE PLACE WHERE NOTHING ConnectS — T.S. ELIOT
Welcome to The World of Biomedical Research and Healthcare Information Systems
The Worst Supply Chain in Society: The Health Information Supply Chain

- slow transition from paper to electronic systems
- fragmented, disconnected, incomplete and inaccurate data
- incompatible data formats as barrier to data integration and sharing
- EMR integration of new data classes (multi-omics)
- legislative barriers to data transfer based on well intentioned privacy protections (HIPAA)
- organizational, economic and cultural barriers to open data sharing
Culture
“So, as you can see, health care is so complicated you may never get well.”
Adapting to the Rise of Large Scale, Data-Intensive Biomedicine

- exponential technology acceleration
- technology convergence: the exponential of the exponentials
- scale: major implications for investment, organization and culture
The Cultural, Organizational and Economic Implications of the Evolution of Large Scale, Data-Intensive Biomedicine

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Recognizing the Importance of Scale: Multidisciplinary, Multi-Institutional, Multi-Sector Collaborations and Knowledge Networks
A Pending Transition in Research Methods and Clinical Care Decisions?

hypothesis-driven data mining

hypothesis-driven data mining
Cultural Barriers to Systems-Based, Data-Intensive Biomedical Research and Clinical Care

- biomedical communities largely untrained in quantitative data methods and analytics, statistics, computing and data science
- predominance of descriptive, unstandardized, qualitative data generated in fragmented expertise silos
- skepticism about premature, unrealized claims of the transformative impact of “-Omics” platforms
- personal and institutional reluctance for data sharing
The Emergence of Big Data Changes the Questions That Can Be Asked

- Isolated Data
- Complex Networked Data
- Complex Computational Data
### Machine Learning and Image Analysis in Clinical Medicine

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- Large scale training sets and classification parameters
- Standardized, reproducible and scalable
- 260 million images/day for $1000 GPU
“I don’t think any physician today should be practicing without artificial intelligence assisting in their practice. It’s just impossible (otherwise) to pick up on patterns, to pick up on trends, to really monitor care.”

Bernard J. Tyson
CEO, Kaiser Permanente
Cited in Forbes: The Future of Work
1 March 2017
Recent AI Investments in Drug Discovery
Biology and Medicine Meets Blockchain

- Security of patient data
- Improve efficiency of clinical trials
- User validation, proof of work, smart contracts
- Supply chain tracking and anti-counterfeiting
Cognitive Computing and Decision-Support Systems: Overcoming the “Bandwidth” Limits of Human Individuals

- limits to experiences and perceptions
- limits to objective decision-making
  - escalating (paralyzing?) complexity
  - shorter time-to-act
- limits to individual expertise
- limits to sensory and cognitive capacities
Complex Autonomous Systems and Automated Computational Decision Support Systems

Creative Disruption
Technology, Strategy and the Future of the Global Defense Industry
By Ben FitzGerald and Kelley Sayler
Forward by the Honorable William J. Lynn III and ADM James Stavridis, USN (Ret.)

Deep Learning, Machine Intelligence, AI and Decision Control

“I Can’t Let You Do That Dave”
• ceding decision authority to computerized support systems

• culturally alien to professionals in their claimed expertise domain but they accept in all other aspects of their lives

• who will have the responsibility for validation and oversight of algorithms used in decision tree analytics for big data?

  - regulatory agencies and professional societies?

  - humans?

  - machines?
“Explainable AI”

- need to better characterize the evolution of decision algorithms
  - keeping humans in the loop
- deconvolution of how and why machine learning algorithms reach flawed conclusions
- concern over AI-directed manipulation of financial and social networks, advertising and personal data
  - implant bias and distrust
  - crime
  - broad national security issues related to data integrity and national cyber-vulnerabilities
Creative Destruction
Schumpeterian Creative Destruction

- comfort and complacency erode capabilities and competitiveness
- failure to see/adapt to disruptive forces and threats to the status quo
- technology as the most potent catalyst for industrial transformation and market disruption
Technology Innovation and Creative Destruction

**emergence at margin of an existing domain**

- big Pharma amnesia and evolution of biotechnology in 1980’s

**emergence by convergence of previously separate domains**

- multi-omics and precision medicine
- big data, machine learning and AI
CHANGE is good you go first
DNR: Is the Current Healthcare System Terminal?

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

- slow translation of research for patient benefit
- unsustainable cost of care
- fragmented, uncoordinated duplication, waste and administrative bloat
- poor use of available information
- slow adoption of advanced IT systems relative to other sectors
- public dissatisfaction and political turmoil over care access and affordability
The Co-Evolution of Precision Medicine and Learning Healthcare Information Systems

**Convergent Technologies**
- Biomedical research and clinical medicine
- Computing and automation
- MDx, sensors, robotics

**Big Data**
- Population databases
- Individuals
- EHRs
- Data science
- AI

**The Expanded Care Space**
- Social media
- Patient engagement
- Life style metrics
- Population databases
- Individuals
- EHRs
- Data science
- AI

**Mapping the Complexity of Geno-phenotypic Relationships and Individual Risks**

**Analytics for Improved Decisions and Clinical Outcomes (Value)**

**Longitudinal Monitoring of Individual Health Status**
Slides available @ http://casi.asu.edu/