PanOmics, Informatics, Economics, Ethics and Politics: The Five Forces Shaping the Evolution of Precision Medicine

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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DEPARTMENT OF COMPUTATIONAL MEDICINE AND BIOINFORMATICS (DCM&B)
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Challenges Facing U.S. Healthcare

1. Balancing Infinite Demand versus Finite Resources
2. From Volume-Based FFS Care to Value-Based Care
3. From Reactive, Episodic Interventions in Disease Episodes to Proactive Continuity of Care Services
4. Improving Outcomes at Lower Cost and Realizing the Wellness Premium
5. Technology, Innovation and New Value Propositions in Healthcare
Demographics and the Clinical and Economic Challenges to U.S. Healthcare

Wellness with longevity and high QOL

or

Multiple co-morbidities and low QOL
Unmet Medical Needs and Disease Burden: Confronting the Largest Economic Disruptions to Achieve Sustainable Healthcare

cancer  |  neurodegeneration  |  cardio-vascular/metabolic disease  |  infectious disease wildcard
Precision Medicine: Major New USG Funding Initiatives

Precision Medicine Initiative
January 30, 2015

The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine

Precision Medicine Initiative (PMI) Working Group Report to the Advisory Committee to the Director, NIH
September 17, 2015

July 22, 2015
Precision Medicine: Not If, But…

- what?
- when?
- how?
- who?
- value?
The Ethics of Hype and Hope
Precision Medicine

Research:
- Molecular classification of disease
- Elucidation of disease mechanisms

Healthcare Delivery:
- RWE and learning healthcare systems
Precision Medicine

research

molecular classification of disease and elucidation of disease mechanisms

subpopulation and individual phenotypes

healthcare delivery

RWE and learning healthcare systems

populations
The Virtuous Circle of Data on Population Health and Individuals in Driving Precision Medicine

- Large Scale Population Data Profiles
- Pattern Analysis to ID Subgroup/Individual Profiles
- Correlation of Subgroup/Individual Patterns with Disease Progression/Rx Outcomes
- Guidelines/Best Practices for Precision Medicine
- Continued Data Capture and Analytical Refinement
Precision Medicine and Data-Intensive Computational Medicine: Evolving Inter-Dependencies

- Molecular classification of disease and elucidation of disease mechanisms
- Large scale data aggregation, curation, and analysis
- RWE and learning healthcare systems
Precision Medicine, Digital Health and A Learning Healthcare System

qualitative, descriptive information of uncertain quality and provenance

evolving, inter-connected networks of data sources for robust decisions and improved care

complex ecosystem of largely unconnected data sources

quantitative data of known provenance and validated quality
Healthcare as a Complex Information Ecosystem

- Consumers: Patients
- Best Practices
- Big Data Analytics
- Research
- Translation and Clinical Trials
- Payers
- Regulators

VALUE
Medical Progress: From Superstitions to Symptoms to Signatures
Precision Medicine: PanOmics Profiling and Mapping the Disruption of Molecular Signaling Networks in Disease

(Ep)Genomics

Proteomics

Molecular Pathways and Networks

Network Regulatory Mechanisms

ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease
Precision Medicine: Molecular Subtypes, Endophenotypes and the Dynamic Range of Clinical Phenotypes

Disease-Based Classification

Molecular Subtypes and Prevalence

Shared Network Perturbations in Different Diseases

D_1

D_2

D_3

Oncology

CNS

Autoimmunity

CV/Metab

Oncology

early

late
Genome Variants in Related Disease Categories Cluster in Shared Gene Regulatory Networks

M. T. Maurano et al. (2012) Science 337, 1190
dbSNP

- over 150 million variants (2016)
- over 6 million coding variants
  - one variant every 5 or 6 base pairs
  - single variant may affect multiple transcripts/genes
- over 80 million variants lie outside coding exons
- over representation of NW European, East African and East Asian population groups
- challenge of variant filtering and robust taxonomy of variants of pathogenic significance
Genome Sequencing and Big Data
(Z.D., Stephens et al. (2015) PLOS Biology)

- 3.6 petabases of raw sequence data
  - c.250,000 individual human genomes
  - c.32,000 microbial genomes
  - c.5,000 plant and animal genomes

- Omics maps catalog of worldwide sequencers
  - 2500 instruments, 1000 centers in 55 countries
  - capacity of c.35 petabases/year

- Illumina X-Ten systems
  - c.2 petabases/year per machine

- current doubling time c.7 months

  - 1 exabase of sequence/year in 5 yrs
  - 1 zettabyte of sequence/year by 2025

  plus

  - projected 100 million to 2 billion human genomes sequenced by 2025
  - multiple sequencing: genome, transcriptome, microbiome
New Alliance for Large Scale Acquisition and Analysis of Cancer Genomics Data (8 Jan. 2017)

- machine and artificial intelligence algorithms
- BaseSpace™ Sequence Hubs
- TruSight Tumor 170 Panel
- GRAIL™
- IntelliSpace clinical informatics platform
Ignoring Biological Complexity

Genes For ....
The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective

The Over-Simplified Perspective That While Exome-and Whole Genome-Sequence-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis
The Reductionist, Simplistic Obsession With Genome Sequencing
Precision Medicine: The Complexity of Genotype-Phenotype Relationships

- Genome Sequencing Alone Will Not Suffice: The Need for Deep Phenotyping
- Understanding the Complex Interplay Between PanOmics, Environment and Behavior
- Phenome-Association Data (PheWAS): Integration of panOmics Profiling with Clinical Disease Progression and Treatment Outcomes
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
- ncRNAs
- phasing
- epistasis
- imprinting
- silencing
- miRNAs/ceRNAs/circRNAs

Cell-specific Molecular Interaction Networks

Perturbed Networks and Disease
Adoption of NCCN Guidelines and FDA Companion Diagnostics Requires panOmics Profiling for Comprehensive Oncology Treatment Selection
Precision Medicine: Mapping Biological Signaling (Information) Networks

- “health”
- homeostasis
- subclinical disease
- graded threshold states
- overt clinical disease
- diverse phenomes
Precision Medicine: Understanding Network Organization and Dynamics in Complex Adaptive Systems

- deconvolution of complex adaptive networks
  - spatial
  - temporal

- mapping the topology of molecular signaling (information) in health and disease pathways and networks
Precision Medicine: Understanding Network Organization and Dynamics in Complex Adaptive Systems

increased predictive accuracy of pending state shifts (emergence) and probabilistic most likely trajectories
Precision Medicine: Understanding Network Organization and 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
Neighbor Maps: 3-D and 4D Genomes
Mapping Genotype-Phenotype Relationships and Disease Risk:

Systematic Integration of Diverse Data for Population Health Analytics

Continuity of Care Record: From Womb to Tomb

Behavior

Environment
A map of diversity in the human microbiome

- *nutrition*
- *autoimmunity*
- *obesity*
- *neuroimmunology*
- *Rx response*
The Trajectory for Precision Medicine: Era One

A Larger Return from Analysis of Real World Data Than panOmics-Driven Innovations?

- improved outcomes, quality and resource allocations
- lower cost
Invasion of the Body Trackers: Changing The Touch Points in Healthcare Delivery

- Healthcare Beyond The Clinic
- Remote Health Status Monitoring
- Smartphones, Wearables, Devices and Digital Services
- M4: Making Medicine More Mobile
Social Spaces Become Quantifiable

- who knows why people do what they do?
  - the fact is that they do!

- these actions can now be traced and measured with unprecedented precision

- with sufficient data, the numbers reveal increasingly predictable behavior and individual risk patterns

- new ethical and legal issues
  - consent, privacy, surveillance, security
Applications of Sensors, Mobile Devices and Wearables in Improved Treatment Adherence and Risk Reduction

- engage and educate patients in personal health management
- remote tracking of health status
  - on-body: in-body, ambient environment
- improve adherence to prescribed treatment plans
- real time, longitudinal incentives for compliance and behavioral changes
- data capture
  - feedback, intervention alerts
  - aggregated, de-identified metadata for observational research
“Medical Selfies”:
The Proliferation of Mobile Devices in Healthcare
Robotics: Telemedicine and Home Healthcare
Virtual Healthcare

- subscription based service
- virtual consultants: video, voice, chat via smartphone, tablet, computer
- 100,000 US-licensed MDs
- 3,000 cities in all 50 states
- 100 cities world wide
Smart Materials for Improved Therapeutic Adherence
Implantable Devices and Wireless Monitoring (and Modulation)

next-generation miniaturized power sources

security and hacker protections
Software Security in Medical Devices
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 Personal Assistants

Kuri (Mayfield Robotics)
An Apps-Based Information Economy in Healthcare

- theoretical rationale but integration of data with EHR platforms poses numerous challenges
  - lack of developer access to high quality healthcare data to validate App platforms
  - cross-platform standardization and application programming interfaces (APIs)
  - regulation: accuracy, reliability, security and privacy regulation compliance
- FDA focus on Apps that transform phone/tablet into a regulated medical device
- renewed FTC interest on Apps making unsubstantiated claims
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?
Machine Intelligence and Facial Recognition Technologies
Computational Analysis of Facial Expressions, Voice, Social Interaction Patterns in Diagnostic Profiling of Psychiatric Disorders

- high variation in assessment of same patients by different psychiatrists
- major need for objective measurements of nuanced behavior
  - gaze
  - speech prosody (rhythm, tone, volume)
  - stimulus response reactions and interaction speed
- AI and learning from large video banks
  - bipolar disorder, schizophrenia, depression
  - suicidal ideation
  - PTSD
- signal alerts to care teams when interventions indicated
“Do you solemnly swear to have no involvement in your own care?”
Patients Are No Longer Patient for Solutions

Patient Communities and Disease Advocacy Groups

Increased Patient Engagement in Care Decisions and Disease Management
Empowered Patients: Social Networking Sites (SNS) and Their Role in Clinical Care

• logical extension of rapid rise of web/apps in mainstream culture to healthcare

• increasingly proactive and engaged consumers/patients/families

• more transparent information on treatment options, cost and provider performance

• new clinical practice tools to optimize physician: patient relationships

• improved recruitment of patients into investigational and pragmatic clinical trials

• Ux
Now Comes the Hard Part!

- Driving Precision Medicine and Large Scale Data Analytics into Routine Clinical Practice
- Integration of Rapidly Expanding and Increasingly Diverse Datasets for Longitudinal Observational Studies and Continuity in Care Delivery
- New Incentives and New Delivery Models
- New Participants and New Business Models
“If only Hewlett Packard (HP) knew what HP knows, we’d be three times more productive (profitable).”

Lew Platt
Former CEO, Hewlett Packard
The Challenge of Translation of Burgeoning Datasets Into Clinically Relevant (Actionable) Knowledge

- Data Generation
- Reliability and Robustness
- Biological Insight
- Clinical Utility
Precision Medicine and Computational Medicine: Evolving Inter-dependencies

- Molecular classification of disease and elucidation of disease mechanisms
- Large scale data aggregation, curation and analysis
- RWE and learning healthcare systems

- Unprecedented scale
- Standards and database inter-operability
- Open data and sharing
- Cloud computing
- Data science
- Machine/artificial intelligence
- Decision-support
Real World Data (RWD) and Real World Evidence (RWE)

Integration of Diverse Data Sources on Effectiveness, Cost and Utilization of Healthcare Resources
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
Real World Evidence (RWE): Data Sources

- EHRs
- Claims Data
- Pharmacy Data
- Prospective Observational Data
- Disease Registries
- Mobile Devices
- Patient Reported Data
- Social Media
Real World Evidence (RWE): Identification of Unmet Needs and Tracking Provider Performance

- Incidence and Prevalence
- Burden of Disease
- Co-morbidities
- Subpopulations
- Socio-economic Disparities
- Clinical Practice Patterns
- Outcomes
- Cost
- Trends Analysis
Drivers of Open Data Initiatives and Development of Real World Evidence and Practice

- Federal open data initiatives
  - meaningful use EHR data
  - OpenFDA, FDA Sentinel
  - access to CMS data
  - 21st Century Cures and FDA expansion of product labeling based on RWE
- expansion of clinical trial data access
  - PhRMA-EFPIA principles for trial data sharing
  - Yale YODA project
  - 21st Century Cures Bill and publication of trial data
Consortia for Multi-site Clinical Data Research

- Building Modular Pediatric Chronic Disease Registries for QI and CE Research (at Cincinnati Children’s Hospital Medical Center [CCHMC])
- Comparative Outcomes Management with Electronic Data Technologies (COMET)
- High Value Health Care Collaborative (HVHC)
- Mini-Sentinel
- Pediatric Health Information System Plus (PHIS+)
- SCAlable National Network for Effectiveness Research (SCANNER)
- Surgical Care and Outcomes Assessment Program Comparative Effectiveness Research Translation Network (SCOAP CERTAIN)
- VA Informatics and Computing Infrastructure (VINCI)
- Washington Heights Initiative Community-Based Comparative Effectiveness Research (WICER)
The Increasingly Blurred Line Between Classical Investigational Clinical Research and New Approaches to RWE Analysis

- historical role of clinical trials as highly controlled, regulated system largely separate from medical practice
- precision medicine and new clinical trial designs
  - disease subtyping and patient segmentation on basis of distinct molecular phenotypes
- rise of pragmatic trials, registries and observational trials for RWE capture and analysis
  - new questions about consent, identification, risks and benefits
  - who is the research subject: patients, clinicians or both?
The Problem With Real World Data is the Real World
HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo

WELCOME TO
BIOMEDICAL RESEARCH
AND PATIENT
MEDICAL RECORDS
Data Tombs: The Current Status of Too Much Biomedical Research and Clinical Data

- unstructured (semantic chaos)
- hoarded (limited sharing)
- siloed (poor integration)
- incompatible (data formats, db interoperabilities)
- variable quality (lack of standardization and the reproducibility problem)
- immobile (inadequate infrastructure for large scale data transfer)
- static (episodic snap shots of dynamic disease processes)
Large Scale Analytics

Structured Data

- predefined EMR fields
- diagnostic codes
- medical and pharmacy chains data
- m.health

“Unstructured Data”

- EMR open text fields
- m.health
- PRO
- social media
- support groups
- published literature
The Diversity of High Value Data Sources in Healthcare: The Integration Challenge

Building the “Data Commons” Infrastructure

• how will access to comprehensive data sources and multiple databases needed for population health analytics be implemented?

• how can proprietary databases be integrated into an open infrastructure?

• compulsory access schemes versus incentives for sharing?
Precision Medicine and Computational Medicine: Evolving Inter-dependencies

The Big Data Challenge

V6: volume, variety, velocity, veracity, virtualization, value
D3: distributed, dynamic, decision support
I3: infrastructure, investment, intelligent systems
The Unavoidable Data-Intensive Evolution of Healthcare: Major Challenges Ahead

PB and TB Data Streams

Ontologies and Formats for Data Integration

Longitudinal Data Migration and Inter-operable Dbases

New Data Analytics, Machine Learning, NLP Methods

Infrastructure, Storage and Privacy

Data Science and Data Scientists
Security of Health Data in the Cloud
Protection and Privacy Provisions for Personal Healthcare Data

- Informed consent
- Legal provisions/penalties for breach
- Voluntary or involuntary capture

Identifiable individual data

Aggregated de-identified databanks and metadata

Personal digital dust in non-healthcare settings

- Social media ‘firehose’
- Purchasing food preferences travel, political learnings

‘Exposome’ profiling and escalating prospect of individual match

Variable levels of consent
Probabilistic, multi-parameter individual ‘match’
Why Anonymous Data Isn’t (or Won’t Soon Be!)
Data Deluge

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

Cognitive Bandwidth Limits

Automated Analytics and Decision Support

Facile Formats for Actionable Decisions
The Quest for Robust Evidence
When Drinking from the Fire Hose

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The Pending Era of Cognitive Computing and Decision-Support Systems: Overcoming the “Bandwidth” Limits of Human Individuals

- limits to individual expertise
- limits to our multi-dimensionality
- limits to our sensory systems
- limits to our experiences and perceptions
- limits to our objective decision-making
The Emergence of Big Data Changes the Questions That Can Be Asked

- Isolated Data
- Complex Networked Data
- Complex Computational Data
Artificial Intelligence Reaches The Marketplace

**GOOGLE HOME**
This voice-controlled speaker is powered by the Google Assistant, which helps users manage their calendars, perform Google searches, or translate speech.

**AMAZON ECHO**
The company's Alexa software enables users to chat with its internet-connected speaker, asking it to read news and weather reports or even order a taxi.

**SPHERO BB-8**
The smartphone-controlled Star Wars toy is smart enough to remember its surroundings so it can adapt accordingly as it moves around.

**NEST CAM OUTDOOR**
The security camera's software can distinguish between people and other subjects, like animals, to reduce false alarms.

**MICROSOFT HOLOLENS**
Microsoft's intelligent eyewear can see, map, and understand its wearer's physical surroundings, allowing them to view augmented images as 3-D holographs.

**ASUS ZENBO**
This robot aims to be a more lifelike version of Echo and Home, maneuvering around the house as it answers questions and expressing "emotions" via a virtual face.

**FETCH ROBOTICS**
These bots help warehouse workers as they pick items from shelves, then help them carry inventory to reduce physical strain.

**ANKI COZMO**
This camera-equipped robotic toy can recognize and react to its owner's face, and even say his or her name.

**AETHON TUG**
This bot, which is now in use, moves through hospital hallways to deliver medicines, supplies, and lab specimens, giving doctors and nurses more time to focus on patient care.

**BOSTON DYNAMICS SPOTMINI**
This robotic pup (developed for research purposes) uses sensors and cameras to move with lifelike precision. It can even handle delicate objects like wineglasses.

**DJ Mavic Pro**
The foldable drone can see and avoid midflight obstacles like trees and buildings. It can also track and follow subjects, like a downhilling skier.

**TESLA MODEL S**
Thanks to a combination of cameras and sensors, the electric sedan knows how to stay in a highway lane, match its speed to that of surrounding traffic, and even park itself.

**IROBOT ROOMBA 960/980**
The sensors in these models enable them to "see" floors as they clean, which helps them do a more thorough job.

**CLOCKWISE FROM TOP CENTER:** SOFTBANK ROBOTICS; NEST; MICROSOFT; ASUS; OTTO; IROBOT; TESLA; LUCAS ZABEWSKI FOR TIME; BOSTON DYNAMICS; AETHON; SPHERO; FETCH ROBOTICS; ANKI; AMAZON; GOOGLE
Automated Learning Systems: The Future of ‘Search’ and Decision Support

- Deeper understanding of content and context
  - Structured text plus natural language processing of unstructured inputs

- Search all things
  - Integration of traditional document semantic sources with video, objects, speech

- Why should you have to ask first?
  - Smart machines and understanding where/what the user is doing

- Why wait for the slow brain to catch up to the fast machine (S. Redmore, Lexalytics)
Deep Learning and Image Recognition for Biomedical Diagnosis and Disease Staging

- digital pathology
- radiology
- ophthalmology
- cardiovascular architecture
Human-Smart Machine Interactions

If you found out your dog was an android, would you still love it?

If you found out your boss was a robot, would you obey its directives?
Deep Learning, Machine Learning and Artificial Intelligence in Data Analytics and Decision Support

“I Can’t Let You Do That Dave”

Automated Decision Support Tools and “Gated Autonomy” in the Management of Complex Systems
Living in a World Where the Data Analytics and Interpretation Algorithms Are Obscure to the End User

- Ceding decision authority to computerized support systems
- Culturally alien to professionals in their claimed expertise domain but they accept in all other aspects of their lives
- Who will have the responsibility for validation and oversight of critical assumptions used in decision tree analytics for big data?
  - Regulatory agencies and professional societies?
  - Humans?
  - Machines?
Digital Health, Automation and the Future Work Force

- Low and mid-skilled workers at risk of replacement
- Digitization of tasks and/or analyses
- Value-added human involvement will prosper leaving others redundant
- Lessons from the 19th-20th century industrial era
  - 100 years for government to establish requisite worker education and literacy levels
- 21st century
  - Need for a faster redesign of education
New Ethical and Legal Complexities in the Application of Machine Learning and Artificial Intelligence for Large Scale Data Analysis

- privacy and surveillance
- discrimination
- unemployment
- persuasion-coercion
- addiction
- manipulation of perceived reality(ies)
- us and them: seamless integration or conflict
- existential risk(s)
Deep Learning, Smart Machines and Ethical, Legal and Socio-Cultural Complexities
Precision Genomic Modifications
New Therapeutic Strategies Plus Complex Ethical and Legal Issues
A Pending Transition in Scientific Research?

hypothesis-driven data mining

hypothesis-driven data mining

hypothesis-driven → data mining
Major Transitions in Medical Education and Healthcare

1910-present
(science-centric)

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

2010 - ?

network topologies and dynamics in complex adaptive systems (network-centric)
education, R&D and care delivery
"The Callroom of Earthly Delights"
R.M. Golub and K. Bucher: JAMA 316, 2171
CHANGE is good you go first
DNR

- Denial
- Negativity
- Resistance
Precision Medicine

The Intellectual Foundation for a New Era in Clinical Medicine and Public Health

the Rise of
Data-Intensive Medicine and Digital Healthcare

Profound Economic, Organizational, Cultural Ethical Implications for Future Healthcare Delivery Channels and Professional Competencies
The Need for Systems-Based Planning to Integrate New Competencies Across the Entire Continuum from Discovery to Clinical Care
Convergence

technology

life sciences and medicine

computing and automation

sensors, robotics

BIG DATA

• Population Health
• Precision Medicine
• Data Science
• AI

connectivity, continuity and consumerism

social media

patient engagement

life style metrics

analytics for improved decisions and clinical outcomes (value)

the expanded care space (individuals)

services integration (systems)
Slides available @ http://casi.asu.edu/