Molecular Medicine and Digital Medicine:
Disruptive Technologies in the Future Evolution of Healthcare

Dr. George Poste
Chief Scientist, Complex Adaptive Systems
and Del E. Webb Chair in Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

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Healthcare: An Expensive Menu Without Prices

Managing the Demands of an Aging Society and Chronic Disease Burden in an Era of Economic Constraint

Shift From a “Do More, Bill More” Healthcare System to Managing Individual Risk for Improved Health Outcomes and Cost Control

Sustainable Health: Societal (Economic) and Individual (Wellness)
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities

Health Status

- Healthy/Low Risk
- At-Risk
- High Risk

20% of the Population Generate 80% Cost

- Multiple co-morbidities
- End-of-life care
- Chronic disease progression
- Chronic disease early stage
- Acute disease

Value

Cost
New Value Propositions

Emergence of a New Health Information Ecosystem via Convergence of Molecular Medicine, Digital Networks and Social Media

Shift from Reactive, Incident-Centric Care to Proactive Engagement and Continuity of Care to Mitigate Individual Risk

From “One Size Fits All” Treatment Approaches to Individual Molecular Profiling and Precision (Personalized) Medicine
Medical Progress: From Superstitions to Symptoms to Signatures
Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

- 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
The Integrative Personal Omics Profile (iPOP)

Population Profiling
‘Big N’

Integrative Personal Omics Profile (iPOP)
N = 1
Information-Based Services for Healthcare and Wellness

- Precision Profiling of Health Status
- Population- and Individual-Datasets
- Actionable Information
- Integrated Care and Wellness

- genome
- exposome
- behavioral and social networks
- phenomes (clinical and subclinical)

facile integration and analysis of diverse datasets
risk identification and mitigation

VALUE
The Evolution of Clinical Diagnostic Testing in The Pending ‘Omics Era and New Device Technologies

- **Unianalyte Tests**

- **Multianalyte Tests**

- **Whole Genome Sequencing**

- **New Regulatory and Reimbursement Policies**

- **On-Body: In-Body Sensors**

- **Portable and Point of Need Devices**

- **Increasingly Distributed Data Feeds and Real Time Health Monitoring**
Will Low Cost Whole Genome Sequencing Change Everything?

1 million genomes x $1,000 = $1 billion
“It’s not even a scary number anymore!”

The $1000 (or less) Whole Genome Sequence (WGS)

The $ ? Interpreted WGS

The $ ? Reimbursed WGS for Clinical Use

Techno-optimism and the Seduction of New Technologies: Omnipresent Hype and Herd Mentalities
current technical limitations dictate that “hole” exomes/genomes is a more accurate description of status today

still major challenges in capturing complete and accurate WGS
Whole Genome Sequencing and Molecular Medicine

**correlation and causality analytics**
- allele frequencies
- SNPs, haplotypes
- CNVs, indels
- rearrangements
- non-coding regions
- ancestry and ethnic diversity
- eQTL
- epistasis
- epigenetics
- Integration with other ‘omics’

**clinical decision analytics**
- Rx response/resistance
  - target(s), networks
- Rx adverse event risk
- prognosis/progression
- predisposition to disease
- environmental exposures/ lifestyle confounders

**privacy and security**
- technical standards
- regulatory requirements
- reimbursement
- clinician education
The Scale and Complexity of Human Genome Variation

- Individual genomes on average carry:
  - 3.5 - 4.0 million SNV, 1000 CNVs (>450bp)
  - 3-4 hundred indels
  - 200-500,000 private SNV
  - 20-400 loss-of-function variants
- Estimated up to 60 new inherited mutations/generation
  - Gender dependent transmission: maternal 15/paternal 25-45
  - Impact of paternal age at fertilization

Sequencing accuracy of 99.99%
=300,000 misreads per genome
Genes For ....
The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective

The Over-Simplified Perspective That Whole Exome- and Whole Genome-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis
Individual Variation, 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

**Cell-specific Molecular Interaction Networks**

**Perturbed Networks and Disease**

recognition of genome organizational and regulatory complexity
Precision Medicine: Evidentiary Standards for Dissecting the Correlation:Causality Matrix in “Omics” Profiling

Population Datasets “Big N”

ability to use N=1 (personalized) approaches requires validation using large N analyses
Mapping Human Genome Variation and Identification of Causal Variants for Disease

- both causal and protective alleles
- hypotheses
  - small number of common variants with large effects
  - large number of common variants with small effects
  - large number of rare variants with small effects

  plus

- role of environmental and epigenetic influences
The Diversity of the Human Variome*

- most human genetic variants are rare (fewer than 5 people in 1000)
- every individual carries between 25 to 30 “private” variants not shared with any one else
- major implications for gene:disease correlations
  - deep sequencing (100 x coverage) of 20,000 or more individuals to link causal variants/variant combinations to disease phenotypes

*Science (2012) e. 1219240, 1217876
Implications of Role of Rare/Private Variants in Disease for Identification and Validation Studies

- renewed focus on clan:pedigree cohorts to identify “recent” disease causal variants not yet purged by negative selection
- very large sample sizes (logistics, cost)
- replication of findings across different populations (ethnicity, geographic history) will be limited
- large scale profiling of random cohorts may be less productive
Assessment of the Clinical Significance of Genome Sequence Variation

- availability of ever larger WGS databanks will allow greater precision in linking specific variants to disease risk, disease progression and Rx response
- evidentiary standards and who defines?
- logistics and cost of constant updating of newly identified risk(s) by databanks
- duty to inform individuals of new risk(s)?
American College of Medical Genetics
Guidelines on Incidental Findings

- approved March 2013 AGM
- 56 genes with certain variants for which individuals should be informed, irrespective of individual preference
High disease frequency

- Monogenic, high-penetrance alleles
- Oligogenic, high or intermediate penetrance alleles
- Complex epistatic interaction of multiple low penetrance alleles

High Rx safety adverse events
- HLA transplant immunotyping
- Monogenic rare diseases/inborn errors of metabolism
- Prenatal fetal aneuploidy

Autoimmunity
- Mental illness/neurodevelopmental
- Late-onset multigenic diseases
  - Cancer
  - Neurodegeneration
  - Diabesity
  - Aging

Low actionable data
WGS and Claims Outstripping Current Analytical Capabilities

Disease Predisposition Risk Profiling (PDx)
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

Disease Profiling to Identify Subtypes (+ or - Rx Target)

ID Molecular Targets for MDx and/or Rx Action
Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics – the Right Rx for the Right Disease (Subtype)

- Her-2+ (Herceptin) (Perjeta)
- EML4-ALK (Xalkori)
- KRAS (Erbitux) (Vectibix)
- BRAF-V600 (Zelboraf)
- CFTR-G551 (Kalydeco)
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly
Targeted Therapeutics and Cancer

Molecular Subtyping and ID of RX Targets

Initial Rx-Response to Targeted Rx

Rx-Resistance via Redundant Molecular Pathways

B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)
targeted therapies, YES!

but

improved success requires targeting network modules, pathways and subnetworks not single molecular targets

network pharmacology
“malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations

disturbing implications for development of new Rx
is the multiplicity of pathways dysregulated in advanced metastatic cancer and the degenerative neuropathies (Alzheimer's disease) an insurmountable technical barrier to design of poly-target (promiscuous) agent/combinations?

- highest failure rates of new Rx in all therapeutic categories
Three Different Scenarios for the Use (Value) of New Diagnostic Technologies for Early Detection of Disease and/or Disease Predisposition

- **Cancer Detection Before Metastasis**
- **Cardiovascular/Metabolic Diseases**
- **Neurodegenerative Diseases**

- **Early Diagnosis and Curative Surgery**
- **Lifestyle Changes and/or Rx to Limit Risk**
- **The Dilemma of Early Diagnosis Without Rx**

- Diabetes + Obesity = DIABESITY

TheAnariestPharmacist.com
The Epigenome

Effect of Maternal Diet/Stress/Rx exposure on Germ Line Genome (+ trans-three-generational?)

Modulation of Gene Expression/Regulation by Environmental Factors, Xenobiotics and Rx (The Exposome)

International Human Epigenome Consortium

- 1000 reference genomes by 2020

Project blueprint
- Launch September 2011 with €30-million
- Map epigenome in 60 human blood cell classes and neoplastic counterparts
We Are Not Alone: The “Frenemy Within” Variation in the Human Microbiome as a Potential Factor in Health and Disease
Signaling Between Mammalian Microbiota and Organ Systems

From: M. McFall-Ngai et al. (2013) PNAS 110, 3229
Commensal Microbiomes: The “Frenemy Within”
An Additional Dimension to Biomarker Profiling

Metagenome-wide Association Studies (MGWAS)

- Immune-Mediated GI Diseases
- Type 2 Diabetes Profile
- Aging Metabolism and Fragility
- Metabolic Activation of Carcinogens/Pollutants
The Complex Interplay Between the Genome, Molecular Networks and Environmental Factors
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities

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Cost
Greater Engagement and Incentivization of Consumers/Patients in Care Decisions and Sustaining Wellness

“Patient-Centric Healthcare Without Patient Engagement Is An Illusion”
Miniaturation of Analytical Technologies

“Lab-on-a-Chip”

“Lab-on-a-Tip”

“Lab-Always On” and “Lab-On-Me”
Invasion of the Body Trackers

Individual Biosignature Profiling Via On Body: In Body (OBIB) Sensors and Devices

Remote Health Status Monitoring

M4: Making Medicine More Mobile
Evidentiary Standards and Liabilities for Biomedical Apps

Siri, does this look malignant?
Consumer Health Informatics

- on-line help/support services (practice-and patient-specific unrelated to general web information)
- automation of out-of-office care
- decreased office visits
- e-pharmacy
- new tools for improved compliance and coaching
- reduced hospital readmissions
- m.health and remote health status monitoring
Mobile Devices, Wireless Technologies, Big Data and Increasingly Patient-Centric Delivery Channels

- extend reach and continuity in care
- each individual becomes their own control
- better real time patient-specific data and decision-support tools
- new patterns (touch points) of patient engagement with the health system
  - AORTA: Always-On-Real Time Access
  - new delivery channels and services
  - the changing ‘care space’
  - targeted care and ability to monitor larger number of patients
Interactive Participant-Centered Initiatives (PCI)

- Social media, patient advocacy and consumer/caregiver engagement
- New opportunities to capture, share, mine and integrate data
  - Research (deidentified) and clinical care (identified)
- Faster recruitment for clinical trials accumulation of large sample sizes for suitable statistical power
- Build new repository biobank networks of well curated and standardized samples to support research
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 individual risk patterns
- new business opportunities in multiple sectors including healthcare
- new ethical and legal issues regarding privacy and data security
Data-Intensive Computing, Big Data and New Knowledge Networks in Biomedical R&D and Healthcare Delivery
Silos Subvert Solutions

HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
The Design of Facile, Seamless Cross-Domain Data Exchange Formats for Large Scale Biomedical Data

- research and discovery
- translation and clinical trials
- m.health
- healthcare delivery
- payors
- outcomes analytics/best practices
- proliferation of decision support tools
- patients
- consumers
Biomedical R&D and Clinical Medicine: An Unavoidable Transition to Data-and Computation-Intensive Methods

Current Era

- “silos” of research/clinical activities
- opinion-rich, information content-poor
- proliferation of poorly standardized and fragmented data, semantic anarchy and incompatible databases
- unacceptable levels of inaccurate diagnoses, fragmented care provision and flawed clinical decisions
  - highly variable treatment practices and erratic clinical outcomes
- extravagant waste and risk
Burgeoning Research Datasets in Biomedical Informatics

- **Genomics**
- **Proteomics**
- **Molecular Pathways**
- **Molecular Interactions**
- **Medicinal Chemistry SAR**
- **Cell Content Imaging**
Large Scale Imaging Datasets

Preclinical

Digital Pathology

Clinical Imaging

Tele-surgery
Data-Intensive Biomedical R&D and ‘The Data Deluge’

Patient Stratification For Clinical Trials  | Pharmacogenomics  | m.Health  | Monitoring Networks

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Microbial Diagnostics  | Biosurveillance and Public Health  | Computing Infrastructure  | Health IT and EMRs
A Learning Healthcare System

Proliferation of Clinical Computational Systems

HITECH Mandates
Incentives
EHR and Smart Cards
Informed Consumers/Patients
Biomedical R&D and Clinical Medicine: An Unavoidable Yet Essential Transition to Date- and Computation-Intensive Processes

- **massive data (big data)**
  - V5: volume, velocity, variety, veracity, value
  - automated, massively parallel ‘omics’ profiling (research and clinical)

- **cross-sector convergence and integration**
  - biomedicine, engineering, computing, telecommunications, social media

- **new machine-based analytics for management of mega-data, customized distribution and decision-support**
Design of Facile Exchange Formats for Data Assembly, Curation and Use Across the Continuum from Discovery to Healthcare Delivery
• today EHRs not designed to support secondary use of data to inform research/translational medicine

• HITECH funding for health IT promotes largely e-replication of paper records

• lack of harmonized data standards in different disciplines/delivery systems as handicap to data meta-analytics outside of original capture institution

• urgent need for new integration models for diverse data
Biomedical Data in the Cloud

- research data (deidentified/anonymized)
- vs.
- clinical trials and healthcare data (confidentiality, privacy and security)
- informed consent for transfer of personal data to, and use in, cloud-based services?
What Is?
The Evolution of Computation Capabilities for Natural Language Q&A in Large Unstructured Datasets

- IBM’s Watson
  - 2880 CPUs
  - natural language questions
- prelude to Q&A systems for biomedicine beyond keyword IR searches

Jeopardy 16 February 2011
The Cost, Logistics and Infrastructure for Analysis and Management of Large Population WGS and ‘omics’ Data and Integration Into Clinical Records

- big data
- big knowledge gaps
- big pipes
- big storage
- big bucks
- big payoffs?
The Omics Data Storage Challenge
(J. Starren et al. 2013 JAMA 309, 1237)

- typical EHR
  - 375 KB/patient
- radiologic picture archiving and communication system (PACS)
  - 104 MB/patient
  - x277 > EHR
- WGS
  - 3-10 million variants/individual
  - 5-10 GB/individual
  - x50 > imaging
Large Scale WGS, Big Data and Cyberinfrastructure:

- 1 million cancer patient WGS = 100 petabytes (after compression)
- Not feasible to move such datasets
- Not feasible to ‘add on’ to existing databases
- ‘digital Darwinism’: the prospect of stark separation between data-rich and data-poor enterprises
Managing Big Data in Biomedicine is Not a Simple Extrapolation from Current Practices

Radical and Disruptive Changes Await!!!

Current Institutional Structures and Competencies Are Ill-Prepared for Pending Disruptive Change
by 2018 the US will need 160,000 more individuals with expertise in statistical methods and data analytics

R.N. Rodriguez
President-Elect, American Statistical Association
Non-Clinical Biostatistics Conference, Boston 19 Oct. 2011
The Pending Era of Cognitive Systems: Overcoming the “Bandwidth” Limits of Human Individuals

- limits to our expertise
- limits to our multi-dimensionality
- limits to our sensory systems
- limits to our experiences and perceptions
- limits to our objective decision-making
Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula

Data Deluge

Cognitive Bandwidth Limits

Automated Analytics and Decision Support

Facile Formats for Actionable Decisions
21st Century Knowledge Networks versus 20th Century Organizations
The Need for New Conceptual, Methodological and Organizational Frameworks for Data-Intensive Biomedical R&D and Healthcare Delivery

- burgeoning datasets and dimensionality of hypotheses spaces transcend human cognitive capabilities
- tractable solutions to urgent clinical and economic challenges will depend increasingly on mastery of massive data and complexity
- successful development of requisite data-intensive systems and computational sophistication will require new cross-domain capabilities and design of new knowledge networks
- current institutional structures and research funding policies are ill-prepared to undertake this critical transition
• biomedicine lags other fields of science and technology
  – engineering, materials science, computing, physics, astronomy, ecology, climate modeling
• big science antithetical to traditional organizational structures and career rewards in academic life sciences
• slow adaptation of public funding agencies to shift from individual-investigator to team-based science and enforce standards demanded by translational research
• ‘3M’ projects: multi-investigator, multi-institution, multi-million
Changing Minds and Changing Cultures: The Barriers of Entrenched Behaviors and Current Reward Structures

- re-engineering a complex ecosystem approaching 20% of GDP
- perverse incentives
  - academic research: silos, inefficient translation and lack of accountability
  - clinical: “do more, bill more”; “one-size-fits-all”
  - industry: short termism and timid incrementalism
- current institutions and their financial revenue base cannot be expected “to vote themselves off the island” absent new incentives/disruptions
What is required?
What is sustainable?

- rethink  
- recalibrate  
- design
The Changing ‘Care Space’ in Healthcare Delivery

- from fixed, tethered, compartmentalized, provider-centric facilities
  to
- distributed- and virtual-architectures connecting multiple providers, home, work and the internet
- from reactive, incident-centric, poorly coordinated and sequential referrals and inefficient post-incident monitoring
  to
- pervasive, persistent monitoring of health status for pre-emptive risk mitigation and improved compliance/personal stewardship of health
A New Healthcare Ecosystem Arising From Technology and Market Convergence

Integrated Technology Platforms for Comprehensive Profiling and Remote, Real Time Monitoring

Data Mining and Integration Services

Increasingly Targeted Care and Efficient Use of Finite Resources

passive/active data collection

analytics and network architecture

EMR/PMR

performance and outcomes analysis

patients

services for integrated care

consumers

MDx/Devices m-Health

HIx

Rx
Charting a New Ecology for Healthcare

Wellness and Risk Reduction

Mapping the Dysregulation of Molecular Networks in Disease

Digital Medicine: The Healthcare Infocosm

Molecular Medicine: Precision Dx, Personalized Rx and Risk Profiling
New Competencies for Mastery of Data-Intensive Biomedicine

mHealth and remote health status monitoring

eHealth: mining large scale population databases

on-body, in-body sensors/devices

molecular profiling of patients (personalized medicine) and global disease surveillance (public health)

mapping the dysregulation of biological networks in disease
The Principal Forces Shaping Biomedical R&D and Healthcare Delivery

- Sensors and m.health
- Remote health status monitoring
- Device-based medicine
- Molecular medicine
- Information-based healthcare
- Outcomes-based healthcare ad sustaining health
- New value propositions, new business models and services

- iOomics
- Risk profiling
- Accurate Dx/Rx
- New analytics for big data
- Continuity and integration of care
- M.health/e.health
Slides Available: http://casi.asu.edu/