Sustaining Healthcare Innovation in an Era of Constraint

Dr. George Poste
Director, Complex Adaptive Systems Initiative and Del E. Webb Chair in Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu
## Major Challenges in Healthcare

<table>
<thead>
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<th>Cost</th>
<th>Demographics</th>
<th>Access</th>
<th>Variation in Clinical Practice</th>
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Major Challenges in Healthcare

- Inefficient Use of Information
- Fragmented Care Versus Integrated Care
- Duplication, Defensive Medicine & Waste
- Protracted Adoption of Innovation
“If you lie down long enough, someone will scan you.”

Mike McCallister
CEO, Humana
www.forbes.com/2009/03/19
Fragmentation Versus Integration in Healthcare Delivery

**Physicians**
- specialization and fee-for-service drives volume and siloed care provision
- lack of curriculum reform and propagation of anachronistic behavior/expectations

**Payors**
- impenetrable thickets of eligibility/reimbursement criteria
- bloated administrative infrastructure to accommodate multiple payment channels

**Politicians**
- boldness or timidity in healthcare reform?

**Patients**
- confused and increasingly afraid
Reasonable Expectations for Rational Healthcare

● what works?
● why it works?
● who it works for?
● what works best?
● when should it be used optimally?

● validated evidence
● mechanism of action
● personalized medicine
● comparative effectiveness
● best practice guidelines, standard-of-care and malpractice

VALUE
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities

20% of the Population Generate 80% Cost

- multiple co-morbidities
- end-of-life care
- chronic disease progression
- chronic disease early stage
- acute disease

Health Status

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

Value

Cost
New Value Propositions in Healthcare

- social and economic value of reducing disease burden will rise
  - earlier disease detection and mitigation
  - rational Rx and guaranteed outcomes
  - integrated care management of complex chronic diseases
  - extension of working life

- progressive shift from ‘reactive’ medicine to ‘proactive’ care and ‘integrated’ delivery
  - prospering in an era of increasing constraints
  - managing the limit(s) of society’s willingness and ability to pay for innovation
Global Health: Understanding the Implications of Major Economic and Environmental Dislocations
The Three Convergent Forces Shaping the Evolution of Healthcare

- Molecular medicine and personalized medicine
- Access, cost and quality of care
- Proficient use of information (e.health)

Value
Mapping the Molecular Signatures of Disease

PROFILE
ID patterns of pathway and network dyregulation in disease
- “biosignatures’

SENSE
automated platforms for rapid detection of multiplex analytes

ACT
rapid analytics and customized data formats/visualization to guide optimum decisions by clinicians, patients and payors
Molecular Diagnostics and Miniaturized Devices: A Key Future Driver in the Healthcare Value Chain

### Complex Biosignature Profiling

<table>
<thead>
<tr>
<th>genomics</th>
<th>proteomics</th>
<th>immunosignatures</th>
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<td><img src="genomics.png" alt="Image" /></td>
<td><img src="proteomics.png" alt="Image" /></td>
<td><img src="immunosignatures.png" alt="Image" /></td>
</tr>
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</table>

### Signature Detection, Deconvolution and Multivariate Analysis

- **automated, high throughput multiplex assays**
- **novel test formats and devices (POC)**
- **new algorithms For complex signal/deconvolution**
Trends in Mapping Diagnostic Signatures of Health and Disease

- unianalyte
- simple analytical endpoint(s)
- technician dependent
- centralized laboratory
- population-based reference index

- multiplex
- complex analytical algorithms
- high throughput automation
- lab-on-a-chip
- remote fault-diagnostics/repair
- migration to POC
- wireless remote monitoring
- individualized profile and longitudinal person record as reference index
The Value of Blood-Based Diagnostic Profiling

- minimally invasive
- blood bathes all organs
- organ-specific ‘biosignatures’ detectable in blood
- facile routine tracking of disease progression and Rx responsiveness
- value of highly stable biomarkers for retrospective studies to correlate with clinical outcomes
- POC testing
Disease Subtyping: Next-Generation Molecular Diagnostics (MDx) and A New Molecular Taxonomy of Disease

MDx Platforms

- massive parallelism
- miniaturization
- automation
- rapid
- POC

RIGHT Rx for RIGHT DISEASE SUBTYPE
The Evolving Market for (Bio)Pharmaceutical Therapies

- **“Blockbuster” Rx**
  - empirical “one-size-fits-all”
  - population-based Rx

- **Stratified/Targeted Rx**
  - Rx targeted to patient subgroups with common molecular pathology
  - Dx-Rx combinations and Rx labeling

- **Individualized Rx**
  - relevant disease subtype
  - AE risk profiling
  - compliance monitoring

- **Personalized Healthcare**
  - integrated framework of coordinated care and longitudinal care
K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy

- higher response in patients with K-RAS versus mutant-K-RAS
- estimated $604 million/year savings (ASCO)
- regulatory endorsement in product labeling
- payor adoption
Molecular Medicine and Rational Therapeutics: Molecular Diagnostics and Targeted Rx

- opening era in linking disease molecular pathology to rational Rx
- increasing payor, regulatory and public pressures for reliable ID of Rx-responsive patients
- demand for Dx-Rx combinations will intensify
- Dx-Rx combination will become an obligate element of NDA/BLA submission and product labeling
- development of Dx-Rx combinations as intrinsic components of R&D programs for investigational Rx

Companion Therapeutics Selected by Precision Diagnostics
From Pharmaceuticals to Pharmasuitables

Disease Subtyping:
Right Rx for Right Disease

Individual Variation and AE risk
Right Rx for Right Patient
Molecular Diagnostics and Pharmacogenetic Profiling to Identify Individuals at Risk for Rx Adverse Events

- broader, more complex profiling platforms than MDx assays for ID of drug targets
  - number of isoforms for DMPK enzymes and scale of individual variation within populations
- ID of slow metabolizer genotypes
- unknown effects of genetic and environmental confounders in AD(M)E beyond genetic variation in drug-metabolism (I-III) repertoire
- growing recognition of importance of variation in HLA alleles as additional risk factor
- touching the third rail: race and ethnopharmacology-PC trumps rational science
The Hunt for Gene Loci Associated with Complex Human Diseases
“Our ignorance of the laws of variation is profound”

Charles Darwin
Disease Predisposition Risk Profiling for Common, Multigenic Late-Onset Disorders

- slower evolution than many predict
- Genome-Wide Association Studies (GWAS)
  - high cost and to date low yield in terms of clinically exploitable markers
  - disease origins from multiple low penetrance alleles versus small, dominant set of high penetrance alleles
- substantial ambiguities regarding probabilistic risk of overt disease
  - epistasis
  - epigenetics
  - environmental confounders

The premature quest to provide consumer genomic testing (CGx) for future risk of major diseases
Mapping the Complexity of Genome Organization

- recognition of increasing levels of organizational and regulatory complexity
  - haplotypes
  - CNV
  - indels
  - RNA universe
  - ‘dark’ elements
  - epistasis
  - epigenetics
  - nuclear compartmentalization and trans-expression
Mapping Global Pathway and Network Regulatory Perturbations in Disease

- ID deregulated pathways
- ID promoter and 3’UTR cis-regulatory elements related to deregulated pathways
- Map regulatory elements to DNA transcription sites
- ID perturbation of upstream signaling pathways that activate/deactivate key regulators
- Role of post-transcriptional regulation via miRNAs and RNA-binding proteins
miRNAs Associated with Leukemia

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>miRNA</th>
<th>Regulation</th>
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<tbody>
<tr>
<td>CLL</td>
<td>miR-15a, miR-1G-1, miR-181a, let-7a, miR30d, miH-150, miR-92</td>
<td>Downregulation</td>
</tr>
<tr>
<td>Pediatric Burkitt’s lymphoma, Hodgkin’s lymphoma, diffuse large B cell lymphoma</td>
<td>miR-155, miR-17-92</td>
<td>Upregulation</td>
</tr>
<tr>
<td>Hodgkin’s disease, Burkitt lymphoma cells</td>
<td>miR-9, let-7a</td>
<td>Upregulation</td>
</tr>
<tr>
<td>B cell malignancies</td>
<td>miR-143, miR-145</td>
<td>Downregulation</td>
</tr>
<tr>
<td>AML</td>
<td>miR-127, miR-154, miR-299, miR-323, miR-368, miR-370</td>
<td>Upregulation</td>
</tr>
<tr>
<td>AML</td>
<td>miR-221, miR-222</td>
<td>Downregulation</td>
</tr>
<tr>
<td>Hematopoietic malignancies</td>
<td>miR-203</td>
<td>Downregulation</td>
</tr>
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</table>

From: M. Galasso et al. (2010) Genome Medicine 2, 12
The Race for Low Cost ($<1000) Whole Human Genome Sequencing
Translation of the Major Potential of Molecular Medicine into Routine Clinical Practice

A Complex Multi-Dimensional Challenge
Knowledge and Evidence Doesn’t Translate Easily into New (or Rational) Behaviors

- science (impact is too often unknown or abstract)
- industry (incremental timidity driven by short-term focus on markets and stock valuation)
- payors (cost control)
- physicians and healthcare professionals (status, revenue and recognition)
- patients (unaware and uninvolved in healthcare decisions)
- politicians (populism and short-term fixes)

The Trajectories for Molecular Medicine

- Data: exponential growth in research data
- Time:
  - Translational medicine and clinical validation
  - Regulatory standards
  - Clinical utility
  - Routine clinical adoption

- Exponential growth in research data
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches

- Biospecimens and Molecular Pathway Analysis
- Biomarker Validation and Multiplex Assays
- Instrumentation and Informatics
- Clinical Impact and Patient Monitoring
Data: The Fastest Growing Resource on Earth
Standards for ‘Omics’ Data
Cross-Domain Integration,
Open-Source Data Sharing
and
Computational Analysis
OBO Foundry Ontologies

Nature Biotechnology 25, 1251 - 1255 (2009)

- Cell Ontology (CL)
- Gene Ontology (GO)
- ZFIN
  - Zebrafish Anatomical Ontology
- Plant Ontology (PO)
- Common Anatomy Reference Ontology
- Environment Ontology
- Phenotypic Quality Ontology (PATO)
- Protein Ontology (PRO)
- RNA Ontology (RnaO)
- Chemical Entities of Biological Interest (ChEBI)
- Disease Ontology (DO)
- Sequence Ontology (SO)
- Ontology for Clinical Investigations (OCI)
- Ontology for Biomedical Investigations
- OBO Relation Ontology

http://www.nature.com/nbt/journal/v25/n11/fig_tab/nbt1346_T2.html
The Rise of Open-Source Networks and Consortia

NCBI
Entrez, The Life Sciences Search Engine®
ToPaz®
caBIG™
cancer Biomedical Informatics Grid™
International HapMap Project
PLoS one
ALLEN INSTITUTE for BRAIN SCIENCE | Allen Brain Atlas
W3C® WORLD WIDE WEB CONSORTIUM
PubMed
FDA/Severe Adverse Events (SAE) Consortium
The Cancer Genome Atlas
Welcome to HuGENet™
The Neurocommons
BROAD INSTITUTE
Diabetes Genetics Initiative
CRITICAL PATH INSTITUTE
Improving the Path for Innovative Therapies
PGRN
The biomarkers CONSORTIUM
NATIONAL INSTITUTES OF HEALTH
Genes, Environment and Health Initiative (GEI)
Determining Genetic and Environmental Roots of Common Diseases
Creative Commons
Clinical Semantics Group
Managing “Mega-Data” (Who Knows Wins)

- Volume
- Scale
- Global networks

- Heterogeneity
- Integration
Misaligned Reimbursement Incentives: Rewarding Process Versus Results

“If it isn’t billable – it isn’t going to happen!”

“You have a (healthcare) system that traps us into bad performance because it’s the only way you can bill”

Hon. Newt Gingrich
Medical Device Daily (2009) 27 Jan. p8
Genes and Intellectual Property

14 March 2000

5 February 2010 Report

29 March 2010 SDNY Court Decision

16 April 2010 WSJ Editorial
How Much New Technology Can We Afford?
UK National Institute for Health and Clinical Excellence (NICE)
Nice Gets Nasty (or Rational?)
Who Defines Best Practices?

- controversy over US Preventive Task Force (USPTF) recommendations on mammograms for women age 40-49
- endorsed by ACP
- opposed by ASCO and NCCN
- USPTF did not address cost but it dominated public debate
- “should policy makers set a price on saving a life?”
Wellness:

The Most Broad and Most Valuable Definition of Successful Healthcare

Consumers at the Center
After a Short Stay in America, Michelangelo's David Returned to Europe
Consumer Behavior and Healthcare Costs

“diabesity” $200 billion

smoking $190 billion
alcohol $20 billion
Engaging Consumers and Patients for Wellness and Greater Responsibility for Mitigation of Health Risk(s)

- entitlement mentality
- lack of accountability
- lack of transparency in pricing and evidence-based performance to guide choice
- cost-shifting
  - a negative but blunt economic driver
- economic incentives
  - positive drivers for wellness
  - employers, payors, taxation policies
- providing tools and information to support informed choices and improved outcomes tracking
On Body: In Body Sensors/Devices
For Real Time and Remote Monitoring of Individual Health Status
23% Medicare beneficiaries have 5 or more conditions
polypharmacy and AEs
poor patient compliance
multiple physician/venue encounters
poor communication/coordination between siloed healthcare services
procedure-based reimbursement versus care continuum integrated
The Costs of Non-Compliance with Rx Regimens

- $177 billion projected cost
- 20 million workdays/year lost (IHPM)
- 40% of nursing home admissions
- projected 45-75% non-compliance (WHO)
- 50-60% depressed patients (IHPM)
- 50% chronic care Rx (WHO)
The Infocosm: Emerging Networks of Global Connectivity

Life's a game
Manipulating society has traditionally been the preserve of politicians and the gods. Does the current boom in virtual worlds give social scientists and economists an opportunity to join them? Jim Giles investigates.
Information-Based Medicine

HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
EHR Incentive Programs Funded by ARRA 2009 “Meaningful Use”

- proposed rule and fact sheet comment deadline 2/28/10
- www.cms.hhs.gov/recovery/11-healthit.asp

- interim final rule: comment deadline 2/28/10
- http://healthit.hhs.gov/standardsandcertification
Wireless Technologies: Consumer and Clinical Markets Converge
Wireless Integrated Data Systems

- geolocation data (where)
- temporal information (when)
- contextual information (what)
Virtual Medicine Networks: Increasingly Integrated Care and Continuity of Care

- rapid, real time access
- clinical specialties
- health records
- lab data
- drug interactions
- electronic Rx prescribing
The Dominant Future Element in Primary Healthcare Delivery???
The Expanding Universe of Health Information Resources

- diversified information sources
- dramatic expansion of social-media networks
- new brokers for validation of information authenticity
- shift in trust from traditional medical establishment to other institutions
“Real personalized medicine should begin long before we’re faced with pharmacology”

“Our health information is too important to leave to an archaic, insular system.

If there’s no longer a need to rely solely on a doctor’s advice for treatment and care, why should we be expected to artificially limit our options.”

Thomas Goetz
Deputy Editor of Wired
In-Home Health Connection: Engaging the Elderly
A New Healthcare Ecosystem Arising From Technology and Market Convergence

- Passive/active data collection
- Analytics and network architecture
- EMR/PMR
- Performance and outcomes analysis

MDx/Devices

HLx

Rx

Integrated Technology Platforms

Data Mining and Integration Services

Patients

Consumers

Increasingly Targeted Care and Efficient Use of Finite Resources

Services for integrated care
Technology Acceleration and Convergence in Healthcare Delivery
The Coming Convergence in Healthcare Delivery

**Technologies**
- biotechnology, medicine, engineering, computing, telecommunications and social media

**Clinical Practice**
- molecular medicine and increasingly customized care
- diagnostic, drug and device combinations
- POC testing and remote monitoring
- reduced error and improved compliance
- improved outcomes

**Realigned Incentives**
- integrated care for complex chronic diseases
- earlier disease detection and risk reduction
- wellness versus illness
- remote health status monitoring
The Coming Convergence in Healthcare Delivery

**Consumers**
- increased personal responsibility for health
- new incentives for wellness/compliance
- remote health status monitoring

**Connectivity**
- integrated care networks for chronic disease
- social media networks and informed consumers
- new supplier networks of specialized turnkey expertise
- value added ‘content’ services for clinical data mining
- clinical decision-support systems