Big Data and the Evolution of Precision Medicine

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Challenges Facing US Healthcare

- Balancing Infinite Demand versus Finite Resources
- From Volume-Based FFS Care to Value-Based Care
- From Reactive, Episodic Interventions in Disease Episodes to Proactive Continuity of Care Services
- Improving Outcomes at Lower Cost and Realizing the Wellness Premium
- Technology, Innovation and New Value Propositions in Healthcare
Extending Life: Balancing Cost and Quality of Life
Unmet Medical Needs and Disease Burden: Confronting the Largest Economic Disruptions in Sustainable Healthcare

cancer
neurodegeneration
cardio-vascular/metabolic disease
infectious disease wildcard
Medical Progress: From Superstitions to Symptoms to Signatures
Precision Medicine: PanOmics Profiling and Mapping the Disruption of Molecular Networks in Disease

(Epi)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: Not If, But…

- when?
- what?
- how?
- who?
- value?
Precision Medicine

- panOmics profiling and a new molecular taxonomy of disease
- intellectual foundation for diagnostic accuracy and rational therapy
- mapping the diversity and dynamic range of disease-associated alterations in the architecture of molecular signaling (information) networks
- profiling individual variation in disease risk, patterns of disease progression and therapeutic responses
- understanding the topologies and dynamics of molecular signaling (information) networks
Analytical and Clinical Validation Protocols for the Utility of Molecular Profiling in Precision Medicine
Precision Medicine: Mapping The Signatures Of Biological Signaling (Information) Networks

- “health”
- homeostasis

- subclinical disease
- graded threshold states

- overt clinical disease
- diverse phenomes

Emergence(E)

E₁, E₂, ..., Eₙ

network topology

state shifts
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-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
- miRNAs/
- ceRNAs/
- circRNAs

**Cell-specific Molecular Interaction Networks**

**Perturbed Networks and Disease**
The Reductionist, Simplistic Obsession With Genome Sequencing
(Epi)Genome Sequencing and Clinical Care

- because we can?
- because it is useful?

Meeting the 'Fit-for-Purpose' Standard

The Urgent Imperative to Define Analytical and Interpretation Standards for Clinical Grade Genome Sequencing
Standards for Genome Sequencing and Pathogenic Variant Classification*

- Comparison of BRCA1 and BRCA2 variant classification across five databases
  - Breast Cancer Information Core
  - Leiden Open Variation Database 2.0
  - UMD (INSERM)
  - ClinVar
  - Human Gene Mutation Database

- 2017 variants cataloged
  - 116 identified as pathogenic in at least one database
  - consensus on only 4 variants as pathogenic in all five databases

- 34% of mutations in Myriad db not present in these public repositories

Genome Sequencing Alone Will Not Suffice: The Need for Deep Phenotyping

Phenome-Association Data (PheWAS): Integration of panOmics Profiling with Clinical Disease Progression and Treatment Outcomes

Understanding the Complex Interplay Between PanOmics, Environment and Behavior
Precision Medicine: Molecular Subtypes, Endophenotypes and the Dynamic Range of Clinical Phenotypes

Disease-Based Classification

D_1  D_2  D_3  Oncology

Molecular Subtypes and Prevalence

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Disease-Based Classification

D_1  D_2  D_3  Oncology

Molecular Subtypes and Prevalence
Precision Medicine: Molecular Subtypes, Endophenotypes and the Dynamic Range of Clinical Phenotypes

Disease-Based Classification
- \( D_1 \)
- \( D_2 \)
- \( D_3 \)
- Oncology

Molecular Subtypes and Prevalence

Shared Network Perturbations in Different Diseases
- CNS
- Autoimmunity
- CV/Metab
- Oncology

early
late
The Challenge of Translation of Burgeoning panOmics Data Into Clinically Relevant (Actionable) Knowledge

- Data
- Reliability and Robustness
- Biological Insight
- Clinical Utility
Invasion of the Body Trackers: Changing The Touch Points in Healthcare Delivery

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

Remote Health Status Monitoring

M4: Making Medicine More Mobile
Mobile Devices, Wearables, Sensors and Remote Health Status Monitoring: The Changing ‘Care Space’ and Improved Continuity in Care Provision

- from fixed, tethered, compartmentalized, provider-centric facilities
  - to
- distributed- and virtual-architectures linking multiple providers, home, work and the internet

- from reactive, incident-centric, poorly coordinated and sequential referrals and inefficient post-incident follow-up(s)
  - to
- pervasive, persistent monitoring of health status for pre-emptive risk mitigation, improved compliance and personal stewardship of health

improved continuity of care and data integration

expanded ‘points-of-touch’ with the health systems
m.Health

Real Time Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)
“Medical Selfies”:
The Proliferation of Mobile Devices in Healthcare

Siri, does this look malignant?
Gray Technologies and Aging in Place: Independent But Monitored Living for Aging Populations

- **Rx compliance**
- **cognitive stimulation**
- in home support and reduced readmissions
- reduced office visits
Implantable Devices and Wireless Monitoring (and Modulation)

next-generation miniaturized power sources

security and hacker protections
THE INTERNET OF THINGS
An Apps-Based Information Economy in Healthcare

- wearables and continuous sensors (individual, environmental)
- 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
  - reimbursement
- FDA focus on apps that transform phone/tablet into a regulated medical device
- renewed FTC interest on apps making unsubstantiated claims
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
  - 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
The Virtuous Circle of Data on Population Health and Individuals in Driving Precision Medicine

Large Scale Population Data Profiles

Guidelines/Best Practices for Precision Medicine

Correlation of Subgroup/Individual Patterns with Disease Progression/Rx Outcomes

Pattern Analysis to ID Subgroup/Individual Profiles

Continued Data Capture and Analytical Refinement
Integration of Large Scale Genomic and Clinical Information (PheWAS)

- 4 April 2016
- BioVu data base
  - de-identified DNA database of 215K genetic samples and 2.5 million clinical records

- 6 April 2016
- Million Veterans Program
- Hybrid Cloud for Genotype-Phenotype Graph Analysis Engine
Precision Medicine

- Germline and somatic (epi)genetic variation: intrinsic and acquired
- “Health”
- Homeostasis
- Subclinical disease
- Clinical disease
- Lifestyle/environmental factors/prior Rx (exposome)
The Evolution of a Data-Driven Health Ecosystem: Systematic Integration of Diverse Data Sets for Population Health Analytics

Continuity of Care Record: From Womb to Tomb

Behavior

Environment
Mobile Apps, Wearables, Sensors and Continuous Monitoring

- who sets the standards?
- who integrates and interprets the data?
- who pays?
- who consents?
- who owns the data?
“Do you solemnly swear to have no involvement in your own care?”
The Wellness Premium

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

“Patient-Centric Healthcare” Without Patient Engagement Is An Illusion
The Principal Forces Shaping The Evolution of Precision Medicine

- wearables
- sensors
- smart implants
- remote health monitoring
- telemedicine
- robotics
- panOmics profiling
- analysis of disruption in biological networks
- m.health/e.health
- data- and evidence-based decisions and Rx selection

BIG DATA
- outcomes-based healthcare and sustainable health
- new value propositions, new business models and services
Now Comes the Hard Part!

- Driving Precision Medicine and Data Analytics Capabilities into Routine Clinical Practice
- Integration of Rapidly Expanding and Increasingly Diverse Datasets for Longitudinal Observational Profiling and Continuity in Care Delivery
- New Incentives and New Delivery Models
- New Participants and New Business Models
HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo
The Worst Supply Chain in Society: The Health Information Supply Chain

- no area of the economy (15-20% GDP) generates as much information as the health sector yet uses it so poorly
- fragmented, disconnected data
- incompatible data formats as barrier to data integration
- incomplete and inaccurate data
- slow transition from paper to electronic systems
- inadequate information on behavioral and environmental influences
- legislative barriers to data transfer based on well-intentioned privacy protections
The Pending Zettabyte Era
1,000,000,000,000,000,000,000,000

Managing Big Data in Biomedicine is Not a Simple Extrapolation from Current Practices

Current Institutional Structures and Competencies Are Ill-Prepared for Pending Disruptive Change
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 Databases
- New Data Analytics, Machine Learning, NLP Methods
- Infrastructure, Storage and Privacy
- Data Science and Data Scientists
Data Privacy, Security and Ownership

- HIPAA provisions insufficient in an era of massive electronic connectivity
- ID of disease burden and potential future risk by peoples’ movements and purchasing practices via location-based services
- health data in the cloud
  - increasing need/value for shared data
  - big data collaboratories and meta-analytics
  - provenance validation, access control
  - global server networks and routine data movement beyond sovereign boundaries
Data Brokers

- HIPAA applies only to information shared with healthcare providers, medical facilities, pharmacies and insurers.
- Information revealed to third parties outside of healthcare has no HIPAA protection.
- Over 1400 companies sell consumer data.
- Corporations spent over $7 billion in 2012 for access.
Expanding the Concept of Consent in an Era of Molecular Profiling and Digital Health

- Individual right to control use and reuse of personal information
- Primacy of use of data for individual’s care
- Simultaneous data generation for mining for multiple purposes for research and improved care for larger populations
The Emergence of Big Data Changes the Questions That Can Be Asked

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<tr>
<th>Isolated Data</th>
<th>Complex Networked Data</th>
<th>Complex Computational Data</th>
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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
Advanced Computing and Artificial Intelligence: The Rise of ‘Learning Machines’ in the Analysis of Massive Datasets and Decision Algorithms
Automated Context: Data Finding Data
“Intelligence at Ingestion”

- Feature Extraction and Classification
- Context Analysis
- Persistent Context

• Relevance Detection
• Situational Awareness
• Intelligence

Rapid, Informed Decisions
Computational Rationality

- convergence of analytics for ‘intelligence’ in brains, minds and machines
- representation and procedures for large scale probabilistic inference
- identification of decisions with maximum expected utility (MUE)
- inferential processes for learning, reasoning and predicting under uncertainty and incomplete data
Data-Driven Knowledge, Intelligence and Actionable Decisions

- changing the nature of discovery
  - hypothesis-driven versus unbiased analytics of large datasets (patterns, rules)
- changing the cultural process of knowledge acquisition
  - large scale collaboration networks, open systems versus individual investigators and siloed data
- changing knowledge application
  - increased quantification, big data analytics and decision-support systems
- changing the cognitive and intellectual competencies for knowledge-intensive competitiveness in multiple domains
- changing education, training, research and care delivery
Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Medical Education Curricula
Precision Medicine:
Implications for Future Medical Education, CME
and New Skills for Healthcare Professionals

- molecular medicine and deep phenotyping (panOmics)
- engineering-based medicine (sensors, robotics)
- data-intensive healthcare (data science)
- automated big data analytics (machine intelligence, decision science)
- consumer-engaged healthcare (UX)
Precision Medicine: 
Implications for Future Medical Education, CME 
and New Skills for Healthcare Professionals

- recalibration of the primacy of MD-centric decisions in many facets of care delivery
- integrated team based care delivery
- advanced diagnostics (panOmics) and computational decision support systems
“I Can’t Let You Do That Dave”
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 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?
Convergence

- BIG DATA
  - Population Data
  - Precision Medicine
  - Data Science

- technology
- computing and automation
- life sciences and medicine
- sensors, robotics

- connectivity, continuity and consumerism
- social media
- patient engagement
- life style metrics

- services integration (systems)

- analytics for actionable Information and improved outcomes (value)

- the expanded care space (individuals)
“DNR”

- Denial
- Negativity
- Resistance
Enduring Themes in the History of Science and Technology: The Poverty of Imagination

- the recurrent myopia of individuals and institutions in recognizing new disruptive technologies
  - arrogance, complacency, denial
  - risk avoidance, investor timidity
  - indecisive, sclerotic hierarchies/cultures

- disruptive technologies
  - created disproportionately by individuals/enterprises operating at the mainstream margins or at the convergent interstices of previously separate disciplines/domains
Incrementalism versus Disruptive Innovation:

- Incrementalism: Squeezing Savings from Outmoded Processes and Business Models

- Disruptive Innovation: Yes
  - RESET
  - easy

- No
Defining the Future Role of Clinical Pathology and Laboratory Medicine

- the changing analytical and data ‘spaces’ for clinical pathology and laboratory services
- role as knowledge integrators in making precision medicine a reality? or
- Darwinian (Schumpeterian) eclipse by new entrants and new service/business models?
“Strategic Spaces” in Biomedical R.D and Healthcare Delivery

- Precision Medicine
- Population Demographics and Disease Burden
- IoT: Ubiquitous Sensing and Sensor Networks
- Big Data Analytics, Machine Learning
- Escalating Complexity
“Strategic Spaces” in Biomedical R.D and Healthcare Delivery

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- Escalating Complexity

New Patterns of Technology Convergence, Evolution and Adoption

- New Knowledge Networks
- New Participants
- New Organizational Models

Opportunity Space
Slides available @ http://casi.asu.edu/