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

- Multiplex disease biomarkers and molecular variants
- Massive data: volume, velocity, variety, veracity
- Evidentiary standards for regulatory qualification
- Clinical outcomes, value and reimbursement
- Clinical utility and adoption
Precision Medicine: Mapping The Signatures Of Biological Signaling (Information) Networks

- "health"
- homeostasis

- subclinical disease
- graded threshold states

- overt clinical disease
- diverse phenomes

Emergence(E)

network topology

state shifts

E_1, E_2, ..., E_n
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

recognition of (epi)genome organizational and regulatory complexity
The Reductionist, Simplistic Obsession With Genome Sequencing

Revealing Pathology With Genome Sequencing

Science

MUTATION AND HUMAN DISEASE

Revealing Pathology 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

Precision Medicine: The Complexity of Genotype-Phenotype Relationships

- 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

- D₁
- D₂
- D₃
- Oncology

Molecular Subtypes and Prevalence

- Red
- Purple
- Green
Precision Medicine:
Molecular Subtypes, Endophenotypes and the Dynamic Range of Clinical Phenotypes

Disease-Based Classification

D1

D2

D3

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
Robotics: Telemedicine and Home Healthcare
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
- 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
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

- engineering and device-based medicine
  - wearables
  - sensors
  - smart implants
  - remote health monitoring
  - telemedicine
  - robotics

- molecular (precision) medicine
  - panOmics profiling
  - analysis of disruption in biological networks

- information-based healthcare
  - 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

WELCOME TO BIOMEDICAL RESEARCH AND PATIENT MEDICAL RECORDS
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

| Isolated Data | Complex Networked Data | Complex Computational Data |
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

Data Deluge

Cognitive Bandwidth Limits

Automated Analytics and Decision Support

Facile Formats for Actionable Decisions
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

technology

life sciences and medicine

computing and automation

sensors, robotics

BIG DATA

• Population Data
• Precision Medicine
• Data Science

connectivity, continuity and consumerism

social media

patient engagement

life style metrics

analytics for actionable Information and improved outcomes (value)

the expanded care space (individuals)

services integration (systems)
“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

Yes

versus

No

Squeezing Savings from Outmoded Processes and Business Models
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

- **Precision Medicine**
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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/