Precision Health and Digital Health: Evolving Inter-Dependencies in the Transformation of Healthcare Delivery

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Aspirations for the U.S. Healthcare System:
National Academy of Medicine

The Triple Aim
- improved outcomes
- reduced cost
- value-based care

The Learning Healthcare System
- right information
- right decisions
- right culture
Global Healthcare Leader at the Core of Clinical Decision Making

**Diagnostic Imaging**
- We help achieve highest diagnostic quality and efficiency
  - Computed Tomography
  - Magnetic Resonance
  - Molecular Imaging
  - X-Ray Products
  - Imaging IT

**Advanced Therapies**
- We enable advanced therapeutic procedures
  - Cardiology
  - Interventional Radiology
  - Radiation Oncology
  - Surgery

**Ultrasound**
- We enable real-time access to decision critical information

**Laboratory Diagnostics**
- We enable clinical and workflow excellence in the lab
  - Chemistry, Automation & Immunoassay
  - Hemostasis, Hematology or Specialty Business
  - Business Solutions Group
  - Molecular Diagnostics

**Point of Care**
- We provide fast and accurate results to improve patient outcomes and reduce costs

**Services**
- We help achieve best institutional performance
  - Customer Services
  - Digital Health Services
  - Enterprise Services & Solutions
Aspirations for the U.S. Healthcare System: National Academy of Medicine

The Triple Aim

- improved outcomes
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VALUE

- right information
- right decisions
- right culture

The Learning Healthcare System
The Complex Ecosystem of Biomedical Research and Clinical Care: Different Perceptions of Value By Different Constituencies

VALUE

- public health and national security
- research community and public funding agencies
- translational science and development (public and private sectors)
- clinical trials and regulators
- consumers: patients
- physicians and other healthcare professionals
- payers
Biomedical Research and Healthcare Delivery: The Imperative for Major Performance Improvement

- slow translation of research for patient benefit
- ageing societies, increased chronic disease burden and unsustainable cost of care
- fragmented and uncoordinated expertise and poor continuity in patient care
- wide variation in patterns of clinical care
- error, duplication, waste and administrative bloat
- public dissatisfaction and political turmoil over care access and affordability
Biomedical Research and Healthcare Delivery

- siloed data and poor use of available information
- slow adoption of advanced IT systems relative to other sectors
- implications of advanced computing and decision support systems for medical education and professional competencies
Ageing Societies and the Chronic Disease Burden: Confronting the Largest Clinical and Economic Disruptions and Threats to Sustainable Healthcare

cancer  neurodegeneration  cardio-vascular/metabolic disease  mental illness
‘One Health’: Surveillance for Zoonotic Diseases with Pandemic Potential

- pandemic (avian) influenza
- Ebola virus
- Zika virus

what’s out there?
the global virome project
pathogen evolution
Technology Acceleration and Cross-Sector Convergence: Blurring the Boundaries of Biomedicine

Convergence of Advances in Biomedicine, Materials Science, Engineering, Telecommunications, Robotics, Advanced Computing and Data Science
The Path to Precision Medicine: From Superstitions to Symptoms to (Molecular) Signatures

“humors”, astrology, shamanism, sin and divine fate

biochemistry and organ-based pathophysiology

molecular biology and multi-omics profiling
Precision Medicine:

**(Epi)Genomics**

Causal Relationships Between Disruption of Molecular Signaling Networks and Disease

- terabytes per individual
- zettabyte – yottabyte population databases

Patient-Specific Signatures of Disease or Predisposition to Disease

Big (Messy) Data
Molecular Diagnostics and Biomarkers as the Intellectual Drivers of Precision Medicine

- disease predisposition risk
- increased accuracy of disease classification (molecular subtypes) and staging
- more rational treatment selection based on presence/absence of specific molecular targets for $R_x$ action
- pharmacogenetic profiling to avoid $R_x$ adverse events
- monitoring $R_x$ efficacy
- detection of emergence of $R_x$ resistance (microbiology; oncology)
- earlier alert of pending relapse and detection of minimal residual disease
Still Two Largely Separate Worlds

- precision medicine
- routine healthcare delivery and SOC

- slow and erratic adoption of technological advances

- research and early clinical adopters

- $100-125* billion (estimated)
- $3.4 trillion (19% GDP)

*includes investment in investigationalRx candidates
Large Scale Genome Sequencing Projects: The Dangers of Reductionism and Ignoring Biological Complexity
Individual Variation and Genotype-Phenotype Relationships

Junk No More: Pervasive Transcription
- alternate transcription/translation/(co)splicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- phasing
- epistasis
- imprinting
- cis-and trans regulation
- RNA universe

Cell-specific Molecular Interaction Networks

Perturbed Networks and Disease

recognition of (epi)genome organizational and regulatory complexity
Interaction Network of Genotypes and Phenotypes in Obesity

Precision Medicine and Digital Medicine: Obligate Inter-Dependencies

**Individual Data**

- Matching individuals to ‘best match’ cohorts using data on similarities of molecular profiles and treatment outcomes.

**Population Databanks**

- Integration and analysis of large scale, diverse data classes.

- $3.2$ trillion
Precision Medicine and Digital Medicine: Obligate Inter-Dependencies

Individual Data

Population Databanks

integration and analysis of large scale, diverse data classes

“digital phenotypes” and “digital siblings”
Impact of Different Factors On The Risk of Premature Death

Most Events That Affect Our Health Occur Outside of the Healthcare System And Are Not Monitored

Need for Continuity of Care Record: From Womb to Tomb

Behavior

Environment
Consortium for Exome Sequencing of 500,000 UK Biobank Samples by 2020

- announced January 2018
- integration with medical records, lab test data and psychological assessments
Healthcare Beyond the Clinic: Remote Health Status Monitoring

- smartphones, wearables, sensors and self-reported data
- telemedicine and virtual consultations
- environmental sensor networks
  - biosurveillance and EID/pandemic monitoring
  - smart homes
- POC/PON distributed diagnostic test capabilities
- IoT and IoHT
- AORTA: Always On, Real Time, Access
Wellness Apps for Fitness, Diet and Exercise
Remote Monitoring of Health Status
Limitations of Consumer-Based Wearables for Health Status Monitoring

- restricted analyte menu
- clinical value still viewed as marginal by physicians/payers
- novelty item, rapid abandonment and lack of user ‘stickiness’
- regulation as medical devices
- erratic integration into electronic PHR/HER and anomaly alerts requiring intervention
- limited adoption incentives
  - users, payers and physicians
Gray Technologies and Ageing in Place: The Rapid Expansion of Telemedicine for Remote Health Monitoring

- Rx adherence
- Cognitive stimulation
- In home support and reduced readmissions
- Reduced office visits
SIEMENS Healthineers

synge.via
Reading as it should be: simple and cinematic.
The Growth of Telehealth and Telemedicine: Expanding the Care Space

- estimated use by 60% HCI’s and 50% hospitals (NEJM 2017, 377, 1585)
- virtual consults in Kaiser Permanente exceeded in-person visits in 2016
- healthcare consumerism and Ux expectancy
- 21st Century Cures Act and efficacy evaluation projects for Medicare
Chatbots and Support Robots in Healthcare
VR/AR and Training for Complex Tasks
VR/AR and Neuromodulation

- promote behavior change via altered sensory inputs and feedback reinforcement learning
- mental illness, PTSD, physical rehabilitation, substance abuse and pain control
Computer-Based Facial and Voice Recognition and Idiosyncratic Patterns of Body Language, Gait and Behavior
“People Analytics”
Social Activities and Behavior 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

- the confessional of social media

- the blurring of private and public spaces

- complex ethical and legal issues
  - consent, privacy, security, surveillance
Digital Psychometrics in Psychiatry and Evaluation of Mental Illness

• high variation in clinical assessment of same patients by different psychiatrists
• major need for objective measurements of nuanced behavior
  - (micro) saccades, facial dynamics
  - motor functions, gait
  - speech prosody (rhythm, tone, volume, construct)
  - stimulus response reactions and interaction speed
• analysis of conversations with chatbots
• machine learning and AI analytics of large video banks
  - bipolar disorder, schizophrenia, depression, PTSD and suicidal ideation
• alerts to care teams when intervention is indicated
New Horizons in Diagnostic Medicine
Diagnostic Laboratory Tests and Imaging: <5% of Healthcare Expenditures But Used in c.70-80% Clinical Decisions
Faster Diagnosis Saves Lives:
POC & PON Multi-Agent ‘Stat’ Diagnostic Assays for Infectious Diseases
Faster Diagnosis Saves Lives: The Primacy of Diagnostics in Biosurveillance and Preparedness Mobilization

Profile: signatures of infectious agents

Detect: rapid automated PON/POC diagnostics

Act: real-time situation awareness, decisions

surveillance sans frontières

pathogen evolution

dual-use research and engineered biothreats
Biomarkers, Molecular ‘Multi-Omics’ Diagnostics and Mapping the Organization of Biological Signaling (Information) Networks

Fundamental Source Data for Making Precision Medicine A Reality

From Reductionist Analysis of Components to Understanding the Assembly, Dynamics and Information Architecture of Complex Biological Systems In Health and Disease
Defining Individual Uniqueness: Mapping the Organization, Dynamics and Information Architecture of Complex Systems in Health and Disease

(epi)genome

transcriptome, proteome, immunome, exposome

regulation and dynamics of molecular interaction networks
Precision Medicine: Understanding the Disruption of Molecular Information Networks in Disease

- **encoded information and expression as cell-specific signaling networks**
- **patterns of information flow in signaling networks (network topology)**
- **stable networks and information fidelity (health)**
- **dysregulated networks and altered information patterns (disease)**
Understanding System State Shifts and Emergent Perturbations in Molecular Signaling Networks in the Health to Disease Continuum

- (epi) genomic, transcriptomic and protein expression networks
- gene-gene interactions (epistasis)
- multi-omic network-environmental interactions
- context: multicellular signaling interactions across multiple levels of biological scale
Understanding System State Shifts and Emergent Perturbations in Molecular Signaling Networks In the Health to Disease Continuum
Understanding System State Shifts and Emergent Perturbations in Molecular Signaling Networks In the Health to Disease Continuum

$T_1$: health

$T_2$: subclinical disease

$T_3$: overt disease
Integrative Gene Expression Network Models and Classification of Functional Modules (Communities) That Span Multiple Chromosomes

Courtesy of Dr. J. Quackenbush, Dana Farber Cancer Center
Defining Short- and Long-Range Cis- and Trans- Regulation of Gene Networks

Chromosomal Neighborhoods: Understanding the 3-D and 4-D Genome

ChromEMT Mapping of Chromatin Ultrastructure and DNA Packing

- spatial and temporal regulation
- inter-chromosommal juxtaposition of TFs, promoters and enhancers

From: International School of Advanced Studies (SISSA) [October 26, 2016]

From: H. D. Ou et al. (2017) Science eaaag.0025
Molecular Diagnostics, Biomarkers and Understanding the Dysregulation of Molecular Information Flows in Disease

- **unianalyte biomarkers**
- **small panels** ($10^2$ to $10^3$)
- **pan-Omics multiplex biomarker profiling panels** ($10^5$ to $10^9$)
- **mapping the architecture of molecular interaction networks**
- **disease and patient-specific perturbations in network architecture**

**Traditional diagnostics**

**Emerging next-generation molecular diagnostics**

**The grand challenge for systems biology**
The V6 Data Deluge
volume, variety, velocity, veracity, visualization, VALUE

• data production, analysis and storage
  • standards, inter-operability and provenance
    • scalability, infrastructure and cost
      • new conceptual models and analytical platforms for mapping network architectures
        • deep learning and artificial intelligence
HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
Welcome to The World of Biomedical Research and Healthcare Information Systems
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 biological systems and disease processes)
“I don’t think any physician today should be practicing without artificial intelligence assisting in their practice. It’s just impossible otherwise to pick up on patterns, to pick up on trends to really monitor care.”

Bernard J. Tyson
CEO, Kaiser Permanente
Cited in Forbes: The Future of Work
1 March 2017
90+ Startup AI Companies in Healthcare
Major Investments in Digital Health by Major Corporations Within and Outside of Traditional Healthcare
400 patents and patent applications in machine learning

75 patent applications in deep learning

more than 30 AI-enriched offerings on the market
Early Entrants Into The Use of Blockchain for Secure Contract Transactions in Healthcare

![Blockchain in Healthcare](image-url)
Breaching Anonymity in “De-identified” Healthcare Data

“Mishandling of patient information shows how governments and companies must become more worthy of trust.”

Nature(2017) 547, 259

The Dark Web and Healthcare Data Theft and Fraud
The Emergence of Big Data Changes the Questions That Can Be Asked

- Isolated Data
- Complex Networked Data
- Complex Computational Data
A Pending Transition in Scientific Research?

hypothesis-driven → data mining → hypothesis-driven
Data-Driven Knowledge Generation and Decision Support Systems

● 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 and decision-support systems

● changing the cognitive and intellectual competencies for knowledge-intensive expertise in multiple domains

● changing education, training and research
The Co-evolution of Augmented Humans, Robotics and Human-Machine Interactions
Robotics, Autonomous Systems, Machine Learning and Artificial Intelligence

4-D Jobs – Dull, Dirty, Dangerous, Digital

Speed of Progressive Redundancy and Replacement of Human Skills?
“Explainable AI”

- need to better characterize the evolution of decision algorithms
  - keeping humans in the loop
- deconvolution of how and why machine learning algorithms reach flawed conclusions
- broad national security issues related to data integrity
- concern over AI-directed manipulation of social networks, advertising and personal data
- corruption of critical military and civilian systems and decision tools
Technology Acceleration and Convergence:
The Escalating Challenge for Professional Competency, Decision-Support
and Future Medical Education

Data Deluge

Cognitive Bandwidth Limits

Automated Analytics and Decision Support

Facile Formats for Actionable Decisions
Machine Learning and Image Analysis in Clinical Medicine

- large scale training sets and classification parameters
- standardized, reproducible and scalable
- 260 million images/day for $1000 GPU
Artificial Intelligence (AI) and Healthcare

- how will AI algorithms/decision analytics be validated/regulated?
- how will AI be integrated into current work flow or will radical reorganization/re-training be required?
- how will AI platforms alter payment schemes?
- which clinical specialties/processes will be at risk of replacement by AI and when?
- how will professional competencies in using AI decision-support tools be evaluated?
  - MD curriculum, CME
- what new malpractice liabilities will emerge by failure to use/interpret AI platforms
The Future of Healthcare: Precision Medicine and Digital Medicine

- New technology platforms
  - Multiplex profiling of molecular network topologies
  - Automation and advanced computing
  - Sensors, robotics
- Molecular classification of disease

- The expanded care space
  - Wearables, sensors, telemedicine
  - Social media and life style metrics
  - Patient engagement
  - Remote monitoring of health status
The Future of Healthcare: Precision Medicine and Digital Medicine

- new technology platforms
- the expanded care space
- Big Data
  - PHR/EHR
  - population health
  - precision medicine
  - digital medicine
  - AI
- molecular classification of disease
- analytics for improved decisions and clinical outcomes at lower cost (value)
- remote monitoring of health status

- sensors, robotics
- automation and advanced computing
- multiplex profiling of molecular network topologies
- wearables, sensors, telemedicine
- social media and life style metrics
- patient engagement
A Long History of Transformational Innovations
The Evolution of Data-Intensive Precision Medicine

- Technology Convergence and Acceleration
- Mapping Geno-Phenotype Complexity
- Topology of Biological Information Networks
- V6 Big Data
- Data Security and Privacy
- Robotics and Human Machine Interactions
- Artificial Intelligence and Decision Support
- Identity, Ethics, Risk and Regulation
The Evolution of Data-Intensive Precision Medicine

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