Transformational Technologies in Biomedical R&D and Healthcare Delivery

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Hever 18, Lansdowne, VA
4 May 2013
Slides available @ http://casi.asu.edu/
The Imperative to Achieve Sustainability in Healthcare: Societal (Economic) and Individual (Wellness)

- Balancing Infinite Demand Versus Finite Resources in an Era of Economic Constraint
- More Effective Management of Chronic Disease in Aging Populations
- Shift From a “Do More, Bill More” (FFS) Delivery System To Integrated Care and Managing Individual Risk to Improve Outcomes and Control Cost
- Technology, Innovation and New Value Propositions
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
Technology Convergence and Disruption in Healthcare

- Engineering and materials science
- Biomedicine and biotechnology
- Telecommunications
- Computing and big data
"Thinking Beyond the Pill"
Leveraging Rx Value In Broadened Healthcare Domains

Integrated Solutions
Rx, Dx, Devices, HIT and ACKM
Accelerating Convergence: Conceptual, Technological, Informational and Commercial

Biomedicine, Biotechnology, Synthetic Biology

Ubiquitous Sensing/Devices & Social Networks

Advanced Computing and Modeling

Neurosciences and Human-Machine Interactions

Disruptive Technologies

"Bio-Space"

"Connected Space"

"Cyberspace" and "Simulation Space"

"Cognitive Space"

"Competition and Opportunity Space"

New Patterns of Technology Fusion, Evolution and Adoption

New Knowledge Networks

New Participants

New Markets and Business Models
Transformational Technologies and Major Challenges in Biomedical R&D and Healthcare: Understanding the Design and Control of Complex Networks

- (epi)genotype
- molecular networks and cellular specificity
- genome engineering networks
- brain networks
- digital networks

- phenotype (phenomes)
- network perturbation/dysregulation in disease
- cellular reprogramming and synthetic biology
- cognition and behavior
- brain machine interface technology
- data-intensive R&D and new knowledge networks
- new products and services
- social media and healthcare
- implications for education, scientific methods
Will Low Cost Whole Genome Sequencing Change Everything?

- 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
Genome Sequencing: The Competitive Landscape is Crowded
WGS: The Protracted Journey to Routine Clinical Utility in Major Multigenic Diseases?

- closing current ‘holes’ to get to ‘wholes’ (Heidi Rehm)
- still major technical challenges in capturing complete and accurate WGS
- actionable data
- unraveling complex epistatic and epigenetic events in late-onset multigenic diseases
- size of clinical cohorts needed to validate actionable correlations for regulatory approval
- reimbursement
- ‘the incidentalome’
<table>
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<tr>
<th>Decision</th>
<th>Single Genes</th>
<th>Gene Panels</th>
<th>WES</th>
<th>WGS</th>
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<tr>
<td>actionable variants</td>
<td>inherited and rare disorders</td>
<td>Rx targets: response/resistance</td>
<td>late onset</td>
<td>microbes</td>
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<td>carrier screening</td>
<td>PGx &amp; Rx adverse events</td>
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<td>NIPT</td>
<td>NIPT aneuploidy</td>
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<td>multi-genic diseases</td>
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<td>informative but not yet actionable</td>
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<td>GWAS</td>
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<td>unknown significance</td>
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WGS and Claims Outstripping Current Analytical Capabilities for Disease Predisposition Risk Profiling (PDx)
Understanding Genome Organization and Regulation

- topology
- role of non-coding regions and the RNA universe
- TF-binding and chromatin states in cell differentiation and disease
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
The Complex Interplay Between the Genome, Molecular Networks and Environmental Factors

- Genome
- Epigenome
- Environment
- Microbiome
- Cell, tissue and organ-specific molecular networks
Commensal Microbiomes: The “Frenemy Within”

Metagenome-wide Association Studies (MGWAS)

- Immune-Mediated GI Diseases
- Type 2 Diabetes Profile
- Aging Metabolism and Fragility
- Metabolic Activation of Carcinogens/Pollutants
Make Me......

Reprogramming ESCs/iPSCs to Generate Specific Cell Lineages as Committed Precursors or End-Stage Differentiated Cells

(Re)Building Complex Histiotypic Structures with Full Homeostatic Controls
Make Me......

- reading and writing genomes
- stem cells and genome reprogramming
- materials science, bioengineering, bio-inductive scaffolds, 3D printing
- regenerative medicine and synthetic biology
Master Transcriptional Regulators and Reprogramming Factors in Mammalian Cell Lineages


Validation of (Epi)Genomic Fidelity for Therapeutic Uses
Analysis of Chromatin-State Landscapes for ESCs/iPSCs, Tissues In Vivo, and Primary Cell Cultures

“activation” marks

H3K4me1

Pluripotent

NPC

Neurons

Tissues

Blood

H3K27ac

“repressor” marks

H3K27me3

H3K9me3

Embryonic stem cell

Differentiated cell (in vivo)

Differentiated cell (in vitro)

From: J. Zhu et al. (2013) Cell 152, 642
Seeding of Autologous Cells Onto Biocompatible Scaffolds to Generate Implantable Organ-Mimetic Structures
Synthetic Biology: Engineering Microbial Genomes

Programmable Genomes

Metabolic Engineering

A New Industrial Ecology and Novel Biosyntheses
Advanced Manufacturing
Digital Programming of 3-D Fabrication and New Assembly Technologies
Programmable Matter:
Computer-Controlled 3D Assembly of Structures of Increasing Complexity

- digital code for automated assembly of complex multi-scale structures
- uncoupling of design from fabrication and rise of point-of-need (PON) production capabilities
- 3D printing
  - spatio-temporal assembly at nano-/Ångstrom-level scale
  - abiotic materials
  - biotic materials
  - abiotic:biotic hybrids
- 4D systems
  - dynamic behavior of constructed systems
Electroceuticals:
The Use of Electrical Impulses to Modulate Neural Circuits

From: K. Framm et al. (2013) 496, 161
Sensor World:
Biomedicine Meets Materials Science, Engineering and Telecommunications

- Materials science, self-assembling and self-repairing ‘intelligent’ materials
- Miniaturization, automation, networked sensors and devices
- Wireless technologies and biomimetic power sources
- Nano-and Å-scale fabrication and spatial molecular assemblies
Implantable Microelectrode Arrays for Different Sections of the Nervous System

From: J. Ordonez et al. (2013) MRS Bulletin 37, 590
The BRAIN Initiative (2 April 2013)
Brain Research Through Advancing Innovative Neurotechnologies
The Brain Initiative:
Mapping Neuronal Network Connectivities In Escalating Brain Complexity

150,000 neurons

1 million neurons

10 million neurons

950 neurons: reconstruction in 5 years
A Comparison of High Performance Network Computing: Cortical Simulations at Cat Scale*

147,456 CPUs 144 TB Main Memory but still 83x slower firing rate

Optogenetics
In Vivo Activation or Inhibition of Neurons Labeled with Microbial Opsin Genes

Transgenic Label Insertion

Microelectrode Label Insertion
3D Mapping of Brain Structure and CNS Network Functions

- mapping the complex topologies and excitation patterns in neuronal networks
- integration of long-distance regional connectivities and local columnar architectures
CLARITY: Lipid Clearing in Acrylamide Infused Whole Brains by SDS and 3D Mapping of Neural Networks

Karl Deisseroth

(Quote from S. R. Y. Cajal)
Optical Retinal Prostheses

- artificial stimulation of surviving nerve cells in outer-retinal degeneration of bionic vision restoration
- holographic optogenetic stimulation of patterned neuronal activity with millisecond temporal resolution at individual cell scale

Reutsky-Gefen et al. (2013) Nature Comm. 4, doi.10.1038/ncomms2500
“Brain Net”

- first brain-to-brain link via remote transfer of encoded brain pattern to decoder animal and triggering of behavioral mimicry
- build inventory of codes to elicit specific behavior in target (decoder)
  - control of animals
  - design of new control systems for robots
- legal and ethical implications of extension to elicited behavior (control, modulation) of humans
Brain: Machine Interface Technologies
Direct Cognitive Control of External Devices
Biomedical R&D and Healthcare Delivery as Increasingly Data-Intensive Disciplines

Managing the Data Deluge

The V5 Challenge of Big Data:
Volume, Variety, Velocity, Verification, Value
“The Fourth Site of Care is going to be the Internet.”

George Halvorson
CEO, Kaiser Permanente
Statement at ONC 2012 Annual Meeting
134 digital health companies each raised $2M+ in 2012
Real Time Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

m.Health
The Proliferation of Mobile Devices in Healthcare
Mobile Devices and Telemedicine
The Quest for Minimally Invasive Monitoring of Multiple Health Status Markers
“The Walk and Die Syndrome:”
On Site Monitoring of TBI and Cerebral Hematoma

- Undetected TBI problem in Iraq/Afghanistan theaters
- 30% wounded combatants suffered head injury, 40% of which have brain hematomas

- OD of hematoma on IR scan differs from normal brain
- Handheld unit
- Disposable AA batteries

Infrascanner
200 ADS Medical
Geodemographic Information Systems (GIS): Real-Time, Front Line, Ground Zero Data from Field Sampling and Sentinels
Maintaining Global Preparedness for a High Virulence Pandemic

April 2013 announcement will now first release new epidemiological data (eg. H7N9) via Twitter
Miniaturization of Analytical Technologies

“Lab-on-a-Chip”

“Lab-on-a-Tip”

“Lab-Always On” and “Lab-On-Me”
The Measured (Quantified) Self: Real Time Biometrics of Health Status

Every Individual Becomes Their Own Control
Health eHeart: Framingham Meets e.World

- Recruitment of 1 million participants
- From profiling every two years (Framingham) to daily monitoring
- Longitudinal observational monitoring with every individual acting as own control
- Large sample size and avoidance of selection bias
- 1.5% cohort = entire Framingham study (15,000 participants)
Gray Technologies: Independent But Monitored Living for Aging Populations

- Compliance
- Cognitive stimulation
- Early alert of deterioration
- Use of home appliances and lifestyle

- Fujitsu's 'smart walking stick'
Robotics: Telemedicine and Home Healthcare

RP-VITA Remote Presence Robot: (iRobot Corp) FDA 501(k) clearance 1/24/13
For Trevor Jones: Your Next Acquisition?
The Robotic Coach to Improve Your Golf Swing
Mobile Devices, 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
Retail Healthcare: New Services and Value-Based Shopping for Healthcare
Forging a New Relationship With Patients

- diabetes self-management program using digital coaching and wireless glucose meter to transmit data to clinical monitors
- improve patient outcomes through interactive web application for patients and doctors
- initial focus on patients at risk for diabetes and cardiovascular disease
- pharmacy-based service in the UK to provide health screenings to prevent heart attack and stroke
Patient-Driven Data: Registries, Clinical Trial Enrollment and Observational Outcomes Studies

From: The Scientist March 2013, p. 36
Social Behavior Becomes 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
Web-Based Health Information and Research Uses: The Blurring of Informed Consent in Cyberspace

- Information supplied by the user
  - Medical history, genomic data, web posts
- Personal information harvested in interaction with web sites
  - IP and e.mail addresses, searches, location data
- Content that users provide becomes trading capital for web services providers
- Do browsewrap disclosure agreements (click “I agree”) represent affirmative consent?
Data-Intensive Computing, Big Data and New Knowledge Networks in Biomedical R&D and Healthcare Delivery
HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
The Need for Facile, Seamless Data Exchange Formats for Large Scale Biomedical Data Systems
Healthcare Data and EMR/EHRs Not Designed for Facile Mining or the Integration of New Data Classes (Omics)
Design of Agile EHR/EMR Formats for New Data Classes and Large Scale Data Mining

- EMR/EHR as e.replicant of paper records
- the vendor trap and incompatible formats
- rigid design formats and limited agility to integrate/mine new data classes (e.g. omics, social media)
- privacy and security protections as barriers to large scale mining and analytics, and of observational data
Formation of the CommonWell Health Alliance (March 2013)  
A Major Step in the Interoperability in Health IT

- 100 million claims records
- 5 million clinical records
Natural Language Processing, ‘Trained Systems’ and Big Data Analytics
Rich Data Will Drive Clinical Profiling to ‘Interpreted Phenotypes’

- Genotype
- Phenotype

- Epigenome
- Genome
- Social .net

Observed Phenotype
- clinical annotation
- EHR data mining

Interpreted Phenotype and Phenomes Via Multi-Parameter Integration
- large scale data analytics for “robustness of match”
- reported clinical phenotype
- integrated personal Omics profile
- population EMR data mining
- curated literature
- automated decision-support
Data Changes the Questions That Can Be Asked

- Isolated Data
- Complex Networked Data
- Complex Computational Data
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
“If the scientific community can justify billions of dollars, 100MW of power and thousands of staff in order to fire tiny particles that most people have never heard of around a big ring of magnets for a fairly narrow science purpose that most people will never understand…..

…..then how come we can’t make the case for facilities needing half the resources that can do wonders for a whole range of science problems and industrial applications?”

Andrew Jones
Vice-President, Numerical Algorithms Group
HPC Wire 29 August 2011
21st Century Knowledge Networks versus 20th Century Organizations
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
Data Customization and Visualization for EMRs
Pervasive Computing: The Next Major Transition?
A Leap Forward: 3D Gestural Interfaces

Project RED
virtual discharge advocate

Simulation Training in Surgery
Does Anyone Read Printed Journals Anymore?
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
From Bench to Keyboard
For Second Opinion, Consult a Computer?
BioIT World 2011 - by Sorena Nadaf, M.S. M.MI
Director - Translational Informatics, CIO

change
is good
you go first
“Outside In” Data and Processes Will Intensify as Drivers of Disruptive Change in Healthcare Delivery

- from Rx product sales to optimizing Rx value in health outcomes/cost control
- patient engagement and loyalty
- integration with MDx, devices, m.health and real time remote health status monitoring
- health data aggregation and mining of large scale observational studies of real world use
Building New Knowledge Networks: Who Knows Wins!


Building New Rx Value Propositions: Who Integrates Rx With Other Healthcare Services More Proficiently Wins!
## Transformational Technologies and New Value Propositions in Healthcare

<table>
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<tr>
<th>Technology</th>
<th>Value Drivers</th>
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<td>- understanding information patterns in complex systems</td>
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<tr>
<td>- biological networks</td>
<td>- creating value outside the Rx product</td>
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<tr>
<td>- care delivery networks</td>
<td>- health outcomes, cost control</td>
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<td>- intelligent data networks</td>
<td>- consumer: patient engagement and loyalty</td>
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<tr>
<td>- integration of RX, MDx, sensors, devices and HIT</td>
<td>- the wellness premium</td>
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<td>- increasing power of patients and payors</td>
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The Principal Forces Shaping Biomedical R&D and Healthcare Delivery

- **Device-based medicine**
  - MDx, sensors
  - remote health monitoring
  - telemedicine

- **Molecular (precision) medicine**
  - integrated analytics of biological networks

- **Information-based healthcare**
  - m.health/e.health
  - data- and evidence-based decisions and Rx selection

- **Outcomes-based healthcare and sustainable health**

- **New value propositions, new business models and services**
Precision Medicine:
Understanding Network Biology as the Intellectual Foundation for the Evolution of Robust Biological Knowledge and Rational Medicine

"Scienta potentia est" (Knowledge is power)

"Nullius in verba" (Take nobody’s word for it)

"Omnis serta est" (Everything is connected)

0011010100110…. (Code is power)

Experimental Design
Standards and Reproducibility
Mapping Network Dynamics
Precision Medicine
“Oh, God help us! We’re in the hands of engineers.”

Dr. Ian Malcolm
‘Chaotician’: Jurassic Park
Slides Available: http://casi.asu.edu/