Computational Challenges and Opportunities in Personalized Medicine

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Healthcare: An Expensive Menu Without Prices

Sustainable Health: Societal (Economic) and Individual (Wellness)

Managing the Demands of an Aging Society and Escalating Chronic Disease Burden in an Era of Economic Constraint

From a “Do More, Bill More” Healthcare System to Managing System and Individual Risks for Improved Health Outcomes and Cost Control
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities

Health Status

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

20% of the Population Generate 80% Cost

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

Value

Cost
New Value Propositions:
Risk Reduction and The Wellness Premium

Emergence of a New Health Information Ecosystem
via
Convergence of Molecular Medicine, Digital Networks and Social Media

Shift from Reactive, Incident-Centric Care
to
Proactive Engagement to Mitigate Individual Risk

From “One Size Fits All” Treatment Approaches
to Individual Molecular Profiling and Personalized Medicine
One Size Does Not Fit All: The Huge Economic Waste in Therapeutics

Percent of population for whom class of drugs do not work

- Antidepressants: 38%
- Asthma: 40%
- Diabetes: 43%
- Arthritis: 50%
- Cancer: 75%

Cost of Ineffective Rx

- 90% of drugs work in only 30-50% individuals
- 2011 global sales of $880 billion ≡ $350 million wasted
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
Personalized (Precision) Medicine

- right diagnosis
- right treatment
- right patient
- right time
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

**Disease Profiling to Identify Subtypes (+ or - Rx Target)**

**ID Molecular Targets for MDx and/or Rx Action**
Mapping the Molecular Signatures of Disease, Disease Subtyping and Targeted Therapy: Companion Diagnostics and the Right Rx for the Right Disease (Subtype)

- Her-2+ (Herceptin)
- EML4-ALK (Xalkori)
- KRAS (Erbitux) (Vectibix)
- BRAF-V600 (Yervoy) (Zelboraf)
The Journey to Integrative Personal Omics Profiling (iPOP) and Personalized Medicine

Integrated Omics (iOmics): Building the Core Technical Foundations of Molecular Medicine and Improved Healthcare Delivery
The Integrative Personal Omics Profile (iPOP)

- genomics
- epigenomics
- proteomics
- metabolomics
- ‘Omics\(^n\)

- integrated omics data
- biological network regulation (health) and dysregulation (disease)
Information-Based Services for Healthcare and Wellness

- Precision Profiling of Health Status
- Population- and Individual-Datasets
- Actionable Information
- Integrated Care and Wellness

- exposome
- genome
- behavioral and social networks
- phenomes (clinical and subclinical)

facile integration and analysis of diverse datasets

risk identification and mitigation

VALUE
Information-Based Services for Healthcare and Wellness

- **exposome**
- **lifestyle**
- **phenomes**
- **genome**

Data curation and analysis → risk identification and mitigation + decision-support

- earlier detection of disease
- rational Rx
- monitoring of health status
- predisposition risk

profile → analyze → act
The Evolution of Clinical Diagnostic Testing in ‘Omics Era and Device Technologies

Unianalyte Tests

Whole Genome Sequencing

Centralized Testing and Large Capital Instrumentation Investment

Multianalyte Tests

Portable and Point of Need

On-Body: In-Body Sensors

Increasingly Decentralized Testing
The Transformation of Biomedical Research and Clinical Care Into Information-Intensive Domains

The Big Data Challenge and Disruption of Academic Research, Clinical Care, Supply Chains and Current Business Models

New Operational Competencies and New Value Propositions
Will Low Cost Whole Genome Sequencing Change Everything?

- 1 million genomes x $1,000 = $1 billion
  "It’s not even a scary number anymore!"

The Cost of Whole Genome Sequencing (WGS) Vs.
The Cost of Computational Analysis and Storage

- the $1000 genome
- the $? analysis and interpretation cost
- the $? storage, retrieval and security costs
- turn around time (TAT) and cost for clinical use
- regulatory and reimbursement policies
What Is A Complete and Accurate Analysis of Genome Sequence, Architecture, Topology and Regulatory Networks?

What Standards of Accuracy Will Regulatory Agencies Require For Use of Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) in Clinical-Decision-Making?
Low Cost Whole Genome Sequencing and Molecular Medicine: Dependency on Large Scale (Massive) Data Annotation and Analytics

- correlation and causality analytics
  - SNPs, haplotypes
  - CNVs, rearrangements
  - non-coding regions
  - ethnic diversity
  - epistasis
  - epigenetics
  - other ‘omics’

- decision analytics
  - Rx response/resistance - target(s), networks
  - Rx adverse event risk
  - prognosis/progression
  - predisposition to disease
  - environmental exposure/lifestyle confounders for predisposition

- privacy and security
  - technical standards
  - regulatory requirements
  - reimbursement
  - clinician education

- • technical standards
  • regulatory requirements
  • reimbursement
  • clinician education

- • technical standards
  • regulatory requirements
  • reimbursement
  • clinician education
The Human Genome (ENCODE 2012)

- protein-coding DNA = c.1.5% genome = 20,687 protein-coding genes
- pervasive genome transcription
  - 93% bases transcribed into RNA
  - 18,400 non-coding RNA genes
  - 70,000 promoter regions, 400,000 enhancer regions
  - diverse transcription and (co)splicing processing patterns
- 11,244 DNA pseudogene regions with variable transcription
- 42% DNA accessible at 3.0 million sites for interaction with regulatory elements
- complex 3-D topology
  - average 3.9 distal (long range) DNA regions link with beginning of each gene
Its the Network, Stupid!

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

Cell-specific Molecular Interaction Networks

Perturbed Networks and Disease

recognition of genome organizational and regulatory complexity
The Epigenome

Modulation of Gene Expression/Regulation by Environmental Factors, Xenobiotics and Rx (The Exposome)

Effect of Maternal Diet/Stress/Rx exposure on Germ Line Genome Imprinting (+ trans-three-generational?)

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
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

iOomics Profiling to Identify Disease Subtypes (+ or - Rx Target)

Altered Network Structure and ID of Molecular Targets for MDx and/or Rx Action

Modeling of Information Flow in Biological Networks
Initial Response (A/B) of BRAF-V600 Positive Metastatic Miliary Melanoma After 15 Weeks Therapy with Vemurafenib (Zelboraf® - Roche) Followed by Rapid Recurrence of Rx-Resistant Lesions with MEKI C1215 Mutant Allele After 23 Weeks Therapy

From: N. Wagle et al. (2011)
J. Clin. Oncol. 29, 3085
Reducing The Failure Rate of Investigational Drugs in Clinical Trials

• targeted therapies, YES!

but

• improved success requires targeting network modules, pathways and subnetworks not single molecular targets

• network pharmacology
Intratumor Genetic Heterogeneity in Multiple Regions of Primary Clear Cell Tumor and Three Metastases (Perinephric and Chest Wall) in RCC

From: M. Gerlinger et al. (2012) NEJM 366, 883
is the multiplicity of pathways dysregulated in advanced metastatic cancer and the degenerative neuropathies (Alzheimer's disease) an insurmountable technical barrier to design of poly-target (promiscuous) agent/combinations?

– highest failure rates of new Rx in any therapeutic category
The Ever Earlier Detection of Major Diseases: Different Clinical Scenarios

- **Cancer: Detection Before Metastasis**
- **Cardiovascular/Metabolic Diseases**
- **Neurodegenerative Diseases**

- **Early Diagnosis and Curative Surgery**
- **Lifestyle Changes and/or Rx to Limit Risk**
- **The Dilemma of Early Diagnosis Without Rx**
We Are Not Alone: The Scale and Diversity of Our Companion Microbiomes
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities

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multiple co-morbidities

Value

Cost
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”
Invasion of the Body Trackers

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

Remote Health Status Monitoring

M4: Making Medicine More Mobile
m.Health

Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)
Healthcare Products are Merging into Consumer Retail

Example:

Alivecor’s iPhone ECG
Technology-Enabled Independent Living

“If I’d known I was going to live this long I’d have taken better care of myself”

Eubie Blake, Musician on 100th Birthday, 1983
Consumer Health Informatics

- on-line help/support services (practice-and patient-specific unrelated to general web information)
- automation of out-of-office care
- decreased office visits
- e-pharmacy
- new tools for improved compliance and coaching
- reduced hospital readmissions
- m.health and remote health status monitoring
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
Proactive Engagement of Patient Communities in Investigational Clinical Trials and Observational Outcomes Studies
Interactive Participant-Centered Initiatives (PCI)

- social media, patient advocacy and consumer/caregiver engagement
- new opportunities to capture, share, mine and integrate data
  - research (deidentified) and clinical care (identified)
- faster recruitment for clinical trials accumulation of large sample sizes for suitable statistical power
- build new repository biobank networks of well-curated and standardized samples to support research
Data: The Fastest Growing Resource on Earth
Burgeoning Research Datasets in Biomedical Informatics
Large Scale Imaging Datasets

Preclinical

Digital Pathology

Clinical Imaging

Tele-surgery
A Learning Healthcare System

Proliferation of Clinical Computational Systems

HITECH Mandates

Incentives

EHR and Smart Cards

Informed Consumers/Patients
“Mega-Data” in Biomedicine

volume, variety, velocity  computational scale  global networks

bench to bedside: multiscale heterogeneity  integration
“silos” of research/clinical activities
opinion-rich, information content-poor
proliferation of poorly standardized and fragmented data, semantic anarchy and incompatible databases
unacceptable levels of inaccurate diagnoses, fragmented care provision and flawed clinical decisions
  – highly variable treatment practices and erratic clinical outcomes
extravagant waste and risk
Biomedical R&D and Clinical Medicine: An Unavoidable Yet Essential Transition to Date-and Computation-Intensive Processes

Pending Era

- Massive data (big data)
  - V3: volume, velocity, variety
  - Automated, massively parallel ‘omics’ profiling (research and clinical)

- Cross-sector convergence and integration
  - Biomedicine, engineering, computing, telecommunications, social media

- New machine-based analytics for management of mega-data, customized distribution and decision-support
The Imminent Collapse of the Genome Informatics Ecosystem?

- Moore’s Law
  - # transistors/circuit board doubles c.18 months
- Kryder’s Law
  - hard disk capacity doubles c.12 months
- Butter’s Law
  - cost of sending a bit of information over optical network halves every 9 months
- Next Generation Genome Sequencing
  - sequence data doubles every 6 months (other ’omics to follow)
The Tianhe-BGI Bioinformatics & Computing Laboratory

- 14,336 Xeon X5670 Processors
- 7,168 Nvidia Tesla M2050 general purpose GPUs
- 2,048 FeiTeng 1000 SPARC-based processors
- 2.57 petaflops per second performance
• difficulty and expense of gaining access to “Big Data” will produce a restricted academic research culture

• automating research and decision-making will dramatically alter knowledge concepts and the nature of learning

• data-intensive research and clinical services will change the dominant intellectual skills and competencies in biomedicine
  – new organizational frameworks
  – looming talent gap
  – new educational curricula and training needs
The Challenge of Data-Intensive Scientific Computing

- majority of traditional systems neither scalable nor sustainable for emerging data-intensive scientific computing requirements
  - computation infrastructure/architectures
  - storage shortage and analytics deficits
  - organizational and intellectual silos
- urgent imperative for strategic vision and national leadership (USG, academia, industry)
Cross-Domain Convergence, Complexity and Increasing Dependency on Data-Intensive Methods and New Knowledge Networks

- systems-focused
- team science
- big data sets
- mining and analytics
- reductionist
- individual investigator-centric
- datasets
- and hypotheses
Silos Subvert Solutions: The Slow Response of Biomedicine to Technology Convergence and Cross-Disciplinary Requirements

- predominance of investigator-centric, reductionist approaches
- limited linkage between experiment and theory and iterative refinement of models and simulations
- anachronistic curricula
- institutional sclerosis and career barriers
- inadequate cyberinfrastructure
- domain silos
- funding policies
- qualitative data
- poor standardization and reproducibility
New Conceptual, Methodological and Organizational Frameworks for Data-Intensive Biomedical R&D

- increasing dependency on systems-based, data-intensive analytics and new knowledge networks
- agile knowledge networks
- new curricula and career rewards
- intelligent systems
- integration and analytics for large scale datasets
- technology and cross-domain convergence
- large scale team-based projects
- increased automation
- quantitative data
- ontologies and semantics and facile data sharing and interoperabilities
- integration and analytics for large scale datasets
Science Portals: collaboration and problem
Web Services and Application building services

Grid Services: secure and uniform access and management for distributed resources

- Supercomputing and Large-Scale Storage
- Experiment
- Simulation
- Theory
- ESnet: High Speed Networking
- Computing and Storage of Scientific Groups
- Advanced Chemistry
- High Energy Physics
- Advanced Engine Design
- Macromolecular Crystallography
- Advanced Photon Source
- Spallation Neutron Source
Cyberinfrastructure Ecosystem (CIF21)

Organizations
- Universities, schools
- Government labs, agencies
- Research and Medical Centers
- Libraries, Museums
- Virtual Organizations
- Communities

Scientific Instruments
- Large Facilities, MRFECs, telescopes
- Colliders, shake Tables
- Sensor Arrays
  - Ocean, environment, weather, buildings, climate, etc

Data
- Databases, Data repositories
- Collections and Libraries
- Data Access, storage, navigation, management, mining tools, curation, privacy

Networking
- Campus, national, international networks
- Research and experimental networks
- End-to-end throughput
- Cybersecurity

Software
- Applications, middleware
- Software development and support
- Cybersecurity: access, authorization, authentication

Computational Resources
- Supercomputers
- Clouds, Grids, Clusters
- Visualization
- Compute services
- Data Centers

Expertise
- Research and Scholarship
- Education
- Learning and Workforce Development
- Interoperability and operations
- Cyberscience

Discovery, Collaboration, Education

Maintainability, sustainability, and extensibility
The Design of Facile, Seamless Cross-Domain Data Exchange Formats for Large Scale Biomedical Data

- research and discovery
- translation and clinical trials
- m.health
- healthcare delivery
- payors
- outcomes analytics/best practices
- proliferation of decision support tools
- patients
- consumers

- regulations
Silos Subvert Solutions

HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
Rich Data Will Drive Clinical Profiling to ‘Interpreted Phenotypes’

- clinical annotation
- EHR data mining

**Observed Phenotype**

**Interpreted Phenotype and Phenomes**

- clinical annotation
- iPOPs
  - large scale data analytics for “robustness of match” of observed clinical phenotype + iPOP profile + curated literature as a multi-dimensional matrix
The Design Challenge for Next Generation HIT Systems

- today EHRs not designed to support secondary use of data to inform research/translational medicine
- lack of harmonized data standards in different disciplines/delivery systems as handicap to data meta-analytics outside of original capture institution
- urgent need for new integration models for diverse data
Lessons from the UK
Whither public HIEs?

BY MIKE MILIARD, Managing Editor

LONDON – Some sobering news came from across the pond this past year. On September 22, England’s Department of Health announced it would finally scrap the country’s decade-long, problem-plagued health information technology initiative, the National Programme for IT (NPfIT).

Its government-led approach, by hand-picking vendors and following a one-size-fits-all nationwide strategy – and especially by giving short shrift to the needs and feedback of physicians – NPfIT, however well-intentioned, was bound to fail.

“Labour’s IT programme let down the NHS and wasted taxpayers’ money by imposing a top-down IT system on the local NHS, which didn’t fit their needs,” said Andrew Lansley,

Some have predicted that the U.K.’s problems with top-down information exchange will soon be echoed here in the U.S.

• 22 September 2011 announcement by NHS to terminate decade long HIT initiative with sunk cost of £6.5 billion of planned £11 billion
• challenge of top-down, one size-fits-all approach
● proliferation of over 700 EMR vendors with 1750 distinct certified products

● the vendor trap (K. D Mandl, I.S. Kohane, NEJM (2012) 336, 2240)
  – major barriers to use of common open-source systems for sharing population-level data and analytics

● import large scale web-based platforms and secure cloud-based storage from other industries
  – process automation and quality metrics
  – care coordination, patient engagement and reporting

● aggregated EMR data and longitudinal tracking of individuals as rich substrate to inform research/translational trials on outcomes
urgent need for new integration models for diverse data

- iPOPs
- current and planned clinical trials
- observational data from primary care provider and patient self-reported data
- SEER (surveillance, epidemiology and end results) data
- m.health/sensor net remote data monitoring
- payor data and outcomes
The Growing Education and Knowledge Gaps in Comprehension of Molecular Medicine Concepts Among Healthcare Professionals
Overcoming Gaps in Physician Knowledge of Molecular Medicine and a Paper-Centric Healthcare System

- 90% of Americans lack confidence in their clinicians’ ability to understand and use genetic information. 
- professional cultural vulnerability/reluctance to acknowledge
- refuge in outdated SOC/guidelines that fail to integrate much new molecular profiling data
- protracted deliberations by professional societies/boards
- less than 4% of 8967 ACGME programs relate to genetic expertise (JAMA 2011 306, 1015)
- MD curriculum/CME challenges
- generational gap in IT use/facilenes and resistance to computerized decision-support tools
Integration of iOmics Data Into Electronic Health Records and Clinical Decisions
What Is?
The Evolution of Computation Capabilities for Natural Language Q&A in Large Unstructured Datasets

- IBM’s Watson
  - 2880 CPUs
  - natural language questions

- prelude to Q&A systems for biomedicine beyond keyword IR searches

Jeopardy 16 February 2011
• don’t know future value of current data
• what can we ignore or discard?
• important dots yet to be identified can’t be connected
• data provenance, authenticity and durability
• dynamic curation and ID of meaningful dots and connections
• traditional models of collect, winnow and dissemble are ill-suited for dynamic analysis of big data
Context: Data Finding Data

Feature Extraction and Classification

Context Analysis

Persistent Context

• Relevance Detection
• Situational Awareness
• Intelligence

Rapid, Informed Decisions
21st Century Knowledge Networks versus 20th Century Organizations
Change is good. You go first.
Changing Minds and Changing Cultures:
The Barriers of Entrenched Behaviors and Current Reward Structures

- re-engineering a complex ecosystem approaching 20% of GDP
- perverse incentives
  - academic research: lack of accountability and poor/slow translation
  - clinical: do more, bill more
  - industry: the tyranny of Wall Street short termism
- current institutions, leadership and financial interests can’t be expected “to vote themselves off the island”
“We’re ready to begin the next phase of keeping things exactly the way they are.”
Rethink, recalibrate, design

What is required?
What is sustainable?
<table>
<thead>
<tr>
<th>Reactive, episodic care</th>
<th>Continuous care</th>
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<tr>
<td>Reactive, symptoms-based care</td>
<td>Proactive pre-emptive risk detection and mitigation</td>
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<tr>
<td>Erratic and poor compliance</td>
<td>Monitored compliance</td>
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<td>Centralized delivery locations</td>
<td>Increasingly distributed PON systems</td>
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<td>Professional paternalism, high initial misdiagnosis and error</td>
<td>Access and democratization of relevant information by consumers and engagement in care decisions</td>
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<tr>
<td>Fragmented and uncoordinated practice data</td>
<td>Integrated datasets and analytics to optimize risk ID/mitigation and best practice guidelines</td>
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New Locations and New Services in Primary Healthcare

What Was

Will Be

From: S. Burrill
The Changing ‘Care Space’ in Healthcare Delivery

- from fixed, tethered, compartmentalized, provider-centric facilities
  to
- distributed- and virtual-architectures connecting multiple providers, home, work and the internet
- from reactive, incident-centric, poorly coordinated and sequential referrals and inefficient post-incident monitoring
  to
- pervasive, persistent monitoring of health status for pre-emptive risk mitigation and improved compliance/personal stewardship of health
A New Healthcare Ecosystem Arising From Technology and Market Convergence

- MDx/Devices
- m-Health
- HIx
- Rx

passive/active data collection
analytics and network architecture
EMR/PMR
performance and outcomes analysis

Data Mining and Integration Services

patients
services for integrated care
consumers

Increasingly Targeted Care and Efficient Use of Finite Resources

Integrated Technology Platforms for Comprehensive Profiling and Remote, Real Time Monitoring
The Rise of Digital Healthcare

- Device-based medicine
  - Sensors and m.health

- Information-based healthcare
  - M.health/e.health
  - Data integration and analytics
  - Decision-support tools

- Molecular medicine
  - Iomics
  - IPoPs

- Outcomes-based healthcare and sustaining health

New value propositions, new business models and services
Disruptive Technologies and Creative Destruction

- arise at margins of existing fields or convergence/fusion interstices of previously separate technical domains/markets
- importance typically denied by KOLs and market leaders with often fatal consequences
Disruptive Innovation in Healthcare

**Convergence**
- biomedicine, engineering, materials
- computing, telecommunications, social media

**Consumerism**
- engagement in health decisions
- responsibility for risk reduction and compliance
- remote health monitoring
- wellness premium

**Cost Control**
- precision diagnostics, rational Rx
- risk ID and mitigation
- data and evidence driven practice
Disruptive Innovation in Healthcare

**Computational biomedicine**
- big data analytics: discovery to care delivery
- m.health and e.health
- human: machine interactions

**Competencies**
- trans-disciplinary: cross-domain
- education and training

**Competition**
- new integrated services and business models
- reverse innovation (BRIC) countries
- new cross-domain coalitions and consortia
Disruptive Innovation in Healthcare

- convergence
- cost control
- competencies
- consumerism
- computational biomedicine
- competition

NEW VALUE PROPOSITIONS
Disruptive Innovation and Evolution of a New Ecosystems for Sustainable Health

Sustainable Health:
Risk Reduction and Wellness

Mastery of Data-Intensive Biomedicine

Digital Medicine:
The Infocosm of Healthcare

Molecular Medicine:
Precision Dx and Personalized Rx