Biotechnology, Molecular Medicine and the Future Evolution of Healthcare

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Biotechnology Entrepreneur Lecture Series
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A Few Current Challenges for the US Healthcare System

- $2.3 trillion dollar expenditures (2007): 16% of GDP ($1 in every $7)
- Escalating and unsustainable fraction of GDP
- Highest per capita expenditure in OECD
- $510 billion cost of chronic disease
- 2 million annual hospital-acquired infections
- 2.5 million hospitalizations due to adverse Rx reactions
- Highly variable treatment patterns
- Slow diffusion of best practices
- No reserve capacity for disasters, epidemics or pandemics
Healthcare Costs are Unevenly Distributed

- 0.5% patients consume 25% of healthcare budget
- 1% consume 35%
- 5% consume 60%
- 10% consume 70%
- 50% consume 3%
- 75% of cost is for patients with chronic diseases

*Source: Healthcare Reform Now
G. Halvorson, Chairman and CEO
Kaiser Foundation Health Plan and Hospitals
Wiley, NY 2007 p.2
Market Distortions and Perverse Incentives in Modern Healthcare Delivery

- focus on late-stage detection and intervention
  - high cost
  - low reversibility
- multiple reimbursements for fragmented (siloed) care versus integrated management of patient needs
- illness versus wellness
- inadequate social and economic incentives for wellness
Knowing What Works (or Doesn’t)

- Pervasive Inefficiencies and Errors in Healthcare Created by Empirical Care and Lack of Robust Outcomes and Performance Data
- E7 hypertension
  - 2005: 639 million
  - 2025: 1.2 billion
- E7 diabetes
  - 2005: 140 million
  - 2025: 228 million
- accelerating impact of chronic diseases in E7
  - urbanization and pulmonary disease
  - deteriorating environmental quality and occupational exposures
  - diabesity, CVD
  - tobacco-use
- chronic diseases account for 80% of E7 mortality but earlier onset than in G7
Global Health: Understanding the Implications of Major Economic and Environmental Dislocations
The Urgent Imperative to Control the Growing Global Threat from Infectious Diseases
The Strategic Future of Healthcare

Economic Unsustainability or Reform and Rational Care

Confronting the Imbalance Between Infinite Demand and Finite Resources
The Imperative for the Courage to Address Complexity: Political Populism Versus Stark Realities and Unpalatable Choices
Most Americans are unhappy with the performance of the U.S. Congress, which has granted no favors recently to the pharmaceutical and biotech industries. Both regulation and its congressional oversight are broken with no repair in sight.

Recent polls have found congressional approval ratings in the range of 20–28%, but we continue to elect and re-elect scoundrels, liars, and the intellectually challenged. The 110th Congress might be the last chance to fix the system before the public moves on.

Henry I. Miller, M.D., a physician and fellow at Stanford University’s Hoover Institution, was an official at the NIH and FDA from 1977 to 1994. Phone: (650) 725-0185. E-mail: miller@hoover.stanford.edu.
The Three Forces Shaping the Evolution of Healthcare

- Molecular medicine and personalized medicine
- Access, cost, and quality of care
- Proficient use of information (e.health)

Demonstrating Value
“If it were not for the great variability among individuals, medicine might be a science, not an art”  
Sir William Osler (1892)

Osler Reframed

“Because of the great variability among individuals, medicine must finally become a science, not an art”
Personalized medicine: Key Drivers

Science

Policy

Cost and Outcomes
NICE (UK) and Renal Carcinoma Rx (2008)

- Clinical efficacy but not cost-effective
- QALY threshold of £30,000 or lower
  - bevacizumab £171,301
  - sorafenib tosulate £102,498
  - temsirolimus £94,385
  - sunitinib £71,462
Personalized Medicine: New Value Propositions in Healthcare

- social and economic value of reducing disease burden will rise
  - earlier disease detection and mitigation
  - rational Rx and guaranteed outcomes
  - integrated care management of complex chronic diseases
  - extension of working life
- progressive shift from ‘reactive’ medicine to ‘proactive’ care and ‘integrated’ delivery
  - wellness versus illness
  - predict and prevent versus detect and treat
Molecular Diagnostics and Biomarkers: The Fundamental Technology Platforms For Molecular Medicine and the Future Healthcare Value Chain
Ignoring The Obvious in Clinical Practice

- diseases are not uniform
- patients are not uniform
- a “one-size fits all” Rx approach cannot continue
- inefficiency and waste of empirical Rx
- cost of futile therapy
- medical error and AEs
The Disease-Gene Network

- nodes define specific genes and node size is proportional to # of disorders in which the indicated gene is implicated
- link lines identify genes implicated in the same disorder.
Human Oncogene-Signaling Map

326 nodes, 92 links and 12 topological ‘blocks’
Targeted Therapeutics: Identification of Subtypes of Disease with Different Molecular Pathologies

- right Rx for right disease subtype
- Dx – Rx combinations
The Emergence of Drug: Diagnostic Combinations

- **Invader® chemistry**

- 5-**Fluorouracil**

- **AMGEN**(panitumumab)
Molecular Diagnostics, Disease Subtyping and Pharmacogenomics:

- right diagnosis, the first time
- right Rx selection, the first time
- rise of Dx-Rx combination
- Rx approval and labeling only with obligate Dx

- premium pricing for predictable Rx outcomes
- pay-for-performance (P4P)
Adverse Drug Reactions: Pharmacogenomics (2007) 8 (4), 311

- CDC (2006)
  - 6.7% of all US emergency department visits in 2004/05
  - additive burden from drug abuse, suicides and medical errors
  - 6.5%
- Germany (2004)
  - 6.2%
- France (2007)
  - 7.1
Adapting to a Safety First World: RISK Trumps Benefit

“Sentinel Initiative”

“Safety First” Initiative

VIOXX® (rofecoxib, MSD)

Avandia® (rosiglitazone maleate)

VYTORIN® (ezetimibe/simvastatin) tablets

Cordarone® (amiodaronum)

ZOCOR® (simvastatin)

Byetta® (exenatide injection)

European Medicines Agency

The New York Times

The Washington Post

abc

CBS

NBC

FOX NEWS.com
From Pharmaceuticals to Pharmasuitables

Disease Subtyping:

Right Rx for Right Disease

Individual Variation and AE risk

Right Rx for Right Patient
The Evolution of Molecular Medicine and Information-Based Medicine: The Foundation for Rational Care and Personalized Medicine

new competencies in molecular medicine and biomedical informatics

molecular diagnostics

real-time information for optimum decision-making

disease management protocols, patient information

Medicine 2018
Disease-Associated Biomarkers

- literature dominated by anecdotal studies
  - academic laboratories
  - small patient cohorts
  - poor replication and confirmatory studies
- lack of standardization
- very few biomarkers subjected to rigorous validation
  - case-control studies with sufficient statistical power
  - inadequate stringency in clinical phenotyping
- widespread lack of understanding of regulatory requirements
  - complexities imposed by multiplex tests
  - new regulatory oversight (IVDMIAs)
Development of Molecular Diagnostics and Biomarkers for Personalized Medicine: The Need for End-to-End R&D Solutions

### Complex Biosignature Profiling

<table>
<thead>
<tr>
<th>genomics</th>
<th>proteomics</th>
<th>immunosignatures</th>
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</thead>
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### Signature Detection, Deconvolution and Multivariate Analysis

<table>
<thead>
<tr>
<th>multiplex assays</th>
<th>novel test devices (POC)</th>
<th>new algorithms</th>
</tr>
</thead>
</table>

![Image of genomics data](image1)
![Image of proteomics data](image2)
![Image of immunosignatures data](image3)
Genomic, Proteomic and Metabolomic Data

- useful only when correlated with additional parameters
  - clinical outcomes
  - clinical utility
  - actionable information
  - demonstrable economic value
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches

Biospecimens and Molecular Pathway Analysis

Biomarker Validation and Multiplex Assays

Instrumentation and Informatics

Clinical Impact and Patient Monitoring
Personalized Medicine: Disease Predisposition Profiling
Early Identification of a Predisposition Trait

Michael Phelps
Genome-wide association defines more than 30 distinct susceptibility loci for Crohn’s disease


Several risk factors for Crohn’s disease have been identified in recent genome-wide association studies. To advance gene discovery further, we combined data from three studies on Crohn’s disease (a total of 3,230 cases and 4,829 controls) and carried out replication in 3,664 independent cases with a mixture of population-based and family-based controls. The results strongly confirm 11 previously reported loci and provide genome-wide significant evidence for 21 additional loci, including the regions containing STAT3, JAK2, ICIOSLG, CDKAL1 and ITLN1. The expanded molecular understanding of the basis of this disease offers promise for informed therapeutic development.
Disease Predisposition Risk Profiling for Common, Multigenic Late-Onset Disorders

- slower evolution than many predict
- Genome-Wide Association Studies (GWAS)
  - high cost
  - multiple low penetrance alleles
- substantial ambiguities regarding probabilistic risk of overt diseases
  - epistasis
  - epigenetics
  - environmental confounders
  - source of poor replication of GWAS studies?
Disease Predisposition Risk Profiling for Common, Multigenic Late-Onset Disorders

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The premature quest to provide consumer genomic testing (CGx) for future risk of major diseases
“They (consumer genomics tests) are a premature integration of technology and there is no clinical validation of the information”

Dr. Muin J. Khoury
Director, National Office of Public Health Genomics

The Nations Health
May 2008 p.26
If you build it will they pay?
Misaligned Reimbursement Incentives: Rewarding Process Versus Results

“If it isn’t billable – it isn’t going to happen!”

- 9000 billing codes for care procedures, services and units of care
- not a single code for patient improvement
- no billing code for cure of chronic disease
Reimbursement for Diagnostic Tests

- inadequate US Medicare coding and payment mechanisms
  - out moded, out-dated, lacking in transparency, inconsistently applied
- no effort to link reimbursement to value
- inappropriate assignment of existing CPT codes to new tests
- engagement of third party payers who derive economic/clinical value from new Dx
  - Genomic Health Oncotype Dx
Pharmacogenetic Predisposition to Adverse Drug Reactions

- 1.5 to 3 million annual hospitalizations (US)
- 80 to 140 thousand annual deaths (US)
- est. cost of $30-50 billion
## Courses in Medical Genetics in US and Canadian Medical Schools 2004-2005

**Table 1**

**General Characteristics of Courses in Medical Genetics Taught in U.S. and Canadian Medical Schools, 2004 to 2005**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%) respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of course</strong></td>
<td></td>
</tr>
<tr>
<td>Stand-alone</td>
<td>52/112 (46)</td>
</tr>
<tr>
<td>Integrated</td>
<td>60/112 (54)</td>
</tr>
<tr>
<td><strong>Course taught with multiple instructors</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>99/112 (88)</td>
</tr>
<tr>
<td>No</td>
<td>12/112 (11)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1/112 (1)</td>
</tr>
<tr>
<td><strong>Year of curriculum in which course was taught</strong></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>85/112 (77)</td>
</tr>
<tr>
<td>Second</td>
<td>35/112 (31)</td>
</tr>
<tr>
<td>Third</td>
<td>6/112 (5)</td>
</tr>
<tr>
<td>Fourth</td>
<td>1/112 (1)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>0/112 (0)</td>
</tr>
<tr>
<td><strong>Total hours taught in course</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>20/112 (18)</td>
</tr>
<tr>
<td>20–40</td>
<td>69/112 (62)</td>
</tr>
<tr>
<td>41–60</td>
<td>15/112 (13)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>5/112 (4)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>3/112 (3)</td>
</tr>
<tr>
<td><strong>Type of sponsoring unit</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical sciences</td>
<td>55/112 (49)</td>
</tr>
<tr>
<td>Basic sciences</td>
<td>32/112 (29)</td>
</tr>
<tr>
<td>Multidisciplinary/integrated</td>
<td>19/112 (17)</td>
</tr>
<tr>
<td>Other/Unspecified</td>
<td>6/112 (5)</td>
</tr>
</tbody>
</table>

* Column total exceeds 100% because some respondents reported teaching medical genetics in more than one year.
Legal pressures and incentives for personalized medicine

Gary E Marchant¹, Robert J Milligan & Brian Wilhelmi

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Tel.: +1 480 965 3246;

Legal liability has the potential to be a powerful driver pushing implementation of personalized medicine. Individuals injured by adverse drug effects are increasingly likely to bring lawsuits alleging that they have a polymorphism or biomarker conferring susceptibility to the drug that should have been identified and used to alter their drug treatment. Likely targets of such lawsuits include drug manufacturers, third party payors, physicians and pharmacists, of which physicians are most at risk of substantial liability.

Personalized Medicine (2006) 3 (4) 391-397
Wellness……..Or Else!

“The public has no idea how big the problem is. The $43 trillion in unfunded Social Security, Medicare and other retirements benefits will drive the government into insolvency by 2040 unless Congress moves quickly.”

David M. Walker
Chief, General Accounting Office
US Government 2007
Promotion of Wellness

- increased consumer responsibility for wellness
- remote monitoring of individual health status
- crucial role of healthcare information systems
  - integrated Rx care for complex chronic conditions
  - outcomes and comparative effectiveness
  - earlier detection of disease episodes and risk mitigation
  - wellness versus illness
On Body: In Body Sensors/Devices:
For Real Time and Remote Monitoring of Individual Health Status
On Body: In Body Sensors and Devices

**Healthcare**

**Objective**
- remote monitoring of health status

**Applications**
- multi-feature monitoring and broadband wireless networks
  - ubiquitous sensing
- enhanced autonomy for in-home aged
- proactive alerting and intervention to mitigate health incidents
- monitoring of patient compliance
- coupled linkage to remote Rx dispensing for efficient disease management
The Costs of Non-Compliance with Rx Regimens

- $177 billion projected cost
- 20 million workdays/year lost (IHPM)
- 40% of nursing home admissions
- Projected 45-75% non-compliance (WHO)
- 50-60% depressed patients (IHPM)
- 50% chronic care Rx (WHO)
Managing the Economic and Clinical Impact of Aging Demographics and Complex, Chronic Conditions
Challenges in the Management of Complex Chronic Conditions and Co-Morbidities

- Multiple conditions
- Multiple providers
- Multiple treatments
- Multiple coding and reimbursement policies
- Multiple medications
Personalized Medicine: Progressive Evolution
Based on Increasingly Comprehensive Profiling of
Disease Risk and Health Status

- Targeted Care
  - rational Rx based on profiling of underlying molecular pathology
  - MDx and disease subtyping

- Personalized Care
  - rational Rx based on comprehensive molecular profiling of individuals
    - disease subtypes and optimum Rx
    - Rx AE risk
    - disease predisposition risk and mitigation

- Individualized Care
  - integrated framework of longitudinal data on individual health status
  - real time remote health status monitoring
  - transition to disease prediction and preemption
Assessment of New Technology and Outcomes

- $2.3 trillion healthcare economy
- $110 billion R&D investment
- $0.9 billion on technology assessment
Information-Based Medicine

HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
Paper-Based Medical Records: Fragmented Care, Unacceptable Errors and a Major Hurdle to Performance Analysis
The Unacceptable Cost of Unconnected Healthcare

- cultural, fiscal and legal barriers to transformational electronic connectivity achieved by other sectors
- major obstacle to safe and efficient healthcare delivery
  - extravagant waste via excessive duplication of tests/procedures
  - error via lack of crucial data
  - lack of data capture for outcomes analysis and individual physician performance
- failure to capture population-based disease parameters
  - sentinel public health/national security
  - meta-analysis of outcomes
  - drug and device safety and recall
“Until the person receiving the product is responsible in some fashion for the costs, there will be no incentive to spend responsibly”

Scott Serota
CEO, BCBS Association of Chicago
Chief Executive Magazine, March 2007 p. 50
After a Short Stay in America, Michelangelo's David Returned to Europe
The shape of things to come

Diabetes
POP 20,870,000
Annual Excess Healthcare Costs Related to Consumer Behavior

Conditions related to obesity and overweight: $200 billion

Smoking: $191 billion

Non-adherence to drug regimens: $177 billion

Alcohol abuse: $2 billion

Personal Medical Records (PMRs)

Google Health, a first look

Promoting Wellness
The Infocosm: Emerging Networks of Global Connectivity
The Information Age: Proliferating Information as a Constant

“It is a shame that the telegraph has been invented. Now suddenly anyone can get the news”

“One already has too much to think about when bathing, which is not good”

James Rothschild (1852)
Telecommunications and Media Industry Convergence: Implications for Healthcare
The Changing Nature of Social Interaction

Herd Behavior: 1.3 Million Bathers, Coney Island 1951

Herd Behavior: 2008 Social Networks and Virtual Communities
Consumer-Directed Healthcare

- leveraging social- and peer-networks
- increased role of fitness industry and entertainment in healthcare
  - “success via distraction”
- “virtual touch”
  - web-based medical consultation and diagnostic algorithms
  - generational gap in need for physical interaction with physician
Healthcare Information Networks: AORTA: Always On Real Time Access

- end-to-end continuity in use of internet and wireless technologies
- from routine remote monitoring of health status to advanced critical care

- comprehensive connectivity
  plus
- collapsing time
  plus
- global networks
The Growing Internet

Web 1.0
- access to information, products and services
- back-end infrastructure and navigation

Web 2.0
- access to other people (social networks)
- front-end user friendly interface

Web 3.0
- access to intelligence
- back-end focus on complex intelligence and context
- “the semantic web”
- “a seamless Web of all the data in your life” (Tim Berners-Lee)
- “go where users go”
The Evolution of Molecular Medicine and Information-Based Medicine: The Foundation for Rational Care and Personalized Medicine
A New Healthcare Ecosystem Arising From Technology Convergence

- **Dx/Devices**
- **Rx**
- **Hlx**

**Integrated Technology Platforms**

**Data Mining and Integration Services**

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

**Increasingly Targeted Care and Efficient Use of Finite Resources**

**patients**

**consumers**

**services for integrated care**
Privacy and Information

- 2010: 15 Petabits ($10^{16}$) / $250,000
- Human Genome: 10 Gigabits ($10^{11}$)

For a few million dollars, one could store the complete genome of every American and European

...for several more, could add credit card records, telephone logs, travel history,...
The Coming Convergence in Healthcare Delivery
The Coming Convergence in Healthcare Delivery

**Technologies**
- biotechnology, medicine, engineering, computing

**Clinical Practice**
- molecular medicine and increasingly customized care
- diagnostic, drug and device combinations
- POC testing and remote monitoring
- reduced error and improved compliance
- improved outcomes

**Realigned Incentives**
- integrated care for complex chronic diseases
- earlier disease detection and risk reduction
- wellness versus illness
- health status monitoring
The Coming Convergence in Healthcare Delivery

Consumers

• increased personal responsibility for health
• new incentives for wellness/compliance
• health status monitoring

Connectivity

• integrated care networks for chronic disease
• improved outcomes and effectiveness
• social networks and informed consumers
• new supplier networks of specialized turnkey expertise
• value added ‘content’ services for clinical data mining
Building The Strategic Platforms for Integrated Healthcare Delivery

- Earlier detection and prevention of disease episodes
- Coordination of care for complex chronic diseases.

Rational Therapeutics and Personalized Medicine

Optimum Use of Costly Resources

Wellness versus Illness

molecular profiling of patients and their diseases
proficient use of information: anytime, anywhere