Genomics, Demographics, Epidemics, Economics and Ethics: The Complex Forces Shaping Healthcare

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First Constantin Spiegelfeld Lecture, Research Center for Molecular Medicine Austrian Academy of Sciences, Vienna
8 November 2010
Slides available @ www.casi.asu.edu
Challenges for Healthcare Delivery Systems

**Cost**
- Inefficient use of Information

**Demographics**
- Fragmented, Compartmentalized Services

**Chronic Diseases**
- Protracted Adoption of Best Practices

**Life Style Disease**
- Subsidiarity and Policy Complexity
The Healthcare Challenge

- Increasing cost of care
- Infinite demand versus finite resources
- Unmet medical needs
- Increasing cost of care and acceleration of new technologies
The Healthcare Challenge

Outcomes
clinical, economic, quality-of-life

Infinite demand versus finite resources
unmet medical needs

Innovation and Cost of Care
increasing cost of care and impact of technology acceleration

Access to Care
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities

20% of the Population Generate 80% Cost

Health Status

Value

Cost

Healthy/ Low Risk
At-Risk
High Risk

multiple co-morbidities

end-of-life care
chronic disease progression
chronic disease early stage
acute disease
Designing Delivery Systems to Sustain Health (Wellness) Versus Systems for Treating Illness

Shift from Diagnosis and Treatment of Ongoing Disease to Disease Prediction and Prevention
# The Intellectual Frontiers of Medicine

<table>
<thead>
<tr>
<th>Antiquarian</th>
<th>Medieval</th>
<th>Renaissance</th>
<th>Enlightenment</th>
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The Intellectual Frontiers of Medicine

Anesthesia | Hygiene | Sanitation | Vaccination
---|---|---|---
| | | | 

Nutrition | Surgery | Imaging | Revolutionary Rx
Systems Biology: Mapping The Design of Complex, Adaptive Networks of Increasingly Higher Structural Order

Gene Expression

Protein Structure and Function

Molecular Pathways

Cells and Tissues

Organs and Homeostasis

Whole Organism (System)
The Intellectual Frontiers of Medicine

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<tr>
<th>Biology as Information</th>
<th>Pathways, Models Networks</th>
<th>Differentiation of Multiple Cell Types</th>
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- Biology as Information
- Pathways, Models Networks
- Differentiation of Multiple Cell Types
- Systems Biology
- Analytical Technologies (Platforms)
- Integrated Analytical Technologies
- Dysregulation (disease)
- Massive Data Analysis
The Complex Inter-Relationships Shaping the Future of Healthcare

- Personalized medicine
- Population-based medicine
- Global public health
- Outcomes
- Values
The Molecular Profiling of Human Diseases:
Biomarkers, Biosignatures as the Foundation for Accurate Diagnosis and Rational Treatment Decisions
The Waste and Risk of Empirical Rx: 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 adverse events (AEs)
Disease Subtyping: Next-Generation Molecular Diagnostics (MDx) and A New Molecular Taxonomy of Disease

MDx Platforms

- massive parallelism
- miniaturization
- automation
- rapid
- POC

RIGHT Rx for RIGHT DISEASE SUBTYPE
Molecular Diagnostics (MDx)
The Convergence of Molecular Biology, Engineering and Computing

Complex Biosignature Profiling

<table>
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<tr>
<th>genomics</th>
<th>proteomics</th>
<th>immunosignatures</th>
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<td>![Genomics Image]</td>
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Signature Detection, Deconvolution and Multivariate Analysis

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Molecular Diagnostics (MDx)
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Complex Biosignature Profiling

- genomics
- proteomics
- immunosignatures

Profile

Sense

Act

Signature Detection, Deconvolution and Multivariate Analysis

- automated, high throughput multiplex assays
- novel test formats and devices for point-of-care (POC)
- new algorithms for complex signal/deconvolution
From Pharmaceuticals to Pharmasuitables: Right Rx for the Right Disease (Subtype)

ID Molecular Targets for Rx Action

Disease Profiling to Identify Subtypes (+ or - Rx Target)
K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy

- higher response in patients with K-RAS versus mutant-K-RAS
- estimated $604 million/year savings (ASCO)

clinical guidelines

- regulatory endorsement in product labeling
From Pharmaceuticals to Pharmasuitables: The Right Rx for the Right Patient

- Rx adverse events (AE) as major source of injury and death
- AEs due to genetic variation in drug transport and metabolism systems
  - fast and slow metabolizers
- AE due to drug interactions
  - action of one Rx in inhibiting metabolic capacity to handle second drug
- AE due to Rx and OTC drugs/supplements
  - latter not tracked
Mapping the Human Pan-Genome: Identification of Ethnic Differences and Implications for Rx Efficacy and Safety

From: Ruiqiang Li et al. (2010) Nature Biotech. 28, 59
We Are Not Alone:  
The Human Microbiome – A Barely Understood Factor in Human Health and Disease

- human body contains 10x more bacterial cells than human cells
- complex meta-system  
  - host, microbes, viruses, other organisms, metabolites, xenobiotics  
  - is there a core microbiome?  
  - how do perturbations affect disease and vice-versa?  
  - does the microbiome influence xenobiotic metabolism and the metabolite spectrum?
Mapping Genetic Predisposition to Disease
Hundreds of variants clustered in genomic loci and biological pathways affect human height
“Our ignorance of the laws of variation is profound”

Charles Darwin
Mapping the Complexity of Genome Organization and the Cause of Multigenic Diseases

- recognition of increasing levels of organizational and regulatory complexity
  - haplotypes
  - CNV
  - indels
  - RNA universe
  - ‘dark’ elements
  - epistasis
  - epigenetics
  - nuclear compartmentalization and trans-expression

- impact of environmental factors
- gene-RX interactions
US Regulatory Action Against Direct-to-Consumer Genetic Testing
Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes

European Society of Human Genetics*
Whole Genome Sequencing

28 October 2010

A THOUSAND GENOMES

Pilot studies prepare the way for population-scale gene sequencing. Pages 1050 & 1051

$1000 Genomes
Evolution of Molecular Profiling and Diagnostics for Improved Disease Detection, Classification and Risk Evaluation

- Adverse Event Risk
- Rx-Dx Combination for Optimum Rx Selection
- Molecular Markers for Disease Subtypes
- Low Cost WGS
- Genetic Predisposition to Disease
- Consumer Genomics
- Prevention (P-Rx)
- Tracking for Early Detection of Disease Emergence

5 yr  10 yr  15 yr
Global Population Demographics

## The Disease Burden in Europe

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Impact</th>
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<tbody>
<tr>
<td>cardiovascular</td>
<td>4.3 million deaths/yr</td>
</tr>
<tr>
<td>cancer</td>
<td>1 in 3 men, 1 in 4 women</td>
</tr>
<tr>
<td>tobacco</td>
<td>650,000 deaths/yr</td>
</tr>
<tr>
<td>obesity</td>
<td>30-80% adult population</td>
</tr>
<tr>
<td>diabetes</td>
<td>246 million cases/3.8 million deaths/yr</td>
</tr>
<tr>
<td>depression</td>
<td>23 million cases</td>
</tr>
<tr>
<td>schizophrenia</td>
<td>1.5 million cases</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>800,000 cases, 75,000 new cases/yr</td>
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Urbanization

- 2 billion increase in world’s urban population by 2030
- 90% of world’s urban population will be in DCs by 2030
- 35% of current 3 billion urban residents reside in slums (UN-HABITAT)
- accelerating deterioration of physical and social well-being
- worsening morbidity and mortality for both communicable and non-communicable diseases
- polar demographics
  - aging urban populations in G8/OECD
  - record cohort of population younger than 25 yrs in DCs
Slums of the World: The face of urban poverty in the new millennium?

Monitoring the Millennium Development Goal, Target 11: World-wide Slums Dwellers Estimation

Working Paper
The Global Public Health Challenge Posed by Rapid Urbanization in Developing Countries

- High Disease Transmission
- Lack of Safe Water
- Toxic Waste
- Major Deficits in Health Infrastructure
- Expanded Eco-niches and Increased Zoonotic Risks
Emerging Infections:
Global Transport and Trade: New Interactions of People, Animals and Product Supply Chains

The Super Vector

World Container Traffic Doubled Since 1997

Billion Cross-Border Travelers

Global Food Networks
Factors Driving the Evolution of Microbial Drug Resistance

Intensive Agriculture

Aquaculture

Empirical Rx

Poor Infection Control in Healthcare Facilities
Comfort and Complacency: The Enemies of Vigilance and Preparedness
The Growing Challenge Posed by Antimicrobial Drug Resistance (AMR)

Enterococcus faecium

Staphylococcus aureus

Klebsiella Pneumoniae

Acinetobacter baumannii

Pseudomonas aeruginosa

Enterobacter species

NO ESKAPE
New US-EU Task Force (2 Nov. 2009)

- encourage R&D on new antimicrobial drugs
- yet to be defined strategy/funding

The 10 X ’20 Initiative (20 Nov. 2009)

- grand challenge to develop 10 new antibiotics by 2020

Multi-Country Program on AMR (12 Jan. 2010)

- € 12.4 million
Maintaining Global Preparedness for a High Virulence Pandemic

- **H1N1**: high transmissibility - low virulence/mortality
- **H5N1**: low transmissibility – high virulence/mortality
- **H5N1 x (H1N1) or (X)**: potential for devastating pandemic
Epidemics

- New Zoonotic Threats
- Drug-Resistance
- Sustainable Resources
  - food production
  - food safety
  - water resources
- Instability and Conflicts

PROTECTING HEALTH FROM CLIMATE CHANGE
Global research priorities
How Much New Technology Can We Afford?
NICE Gets Nasty (or Rational?)
The Infocosm: Emerging Networks of Global Connectivity

Life's a game
Manipulating society has traditionally been the preserve of politicians and the gods. Does the current boom in virtual worlds give social scientists and economists an opportunity to join them? Jim Giles investigates.
Assembly, Integration and Analysis of Massive Data

- better diagnosis and treatment decisions (individuals)
- population data and evidence-based guidelines for best practices (health professionals)
- improved allocation of scarce/expensive resources (society)
- global health surveillance and risk reduction (global)
- acceleration of research discoveries and translation for improved care (academia, industry)
Sensor Networks for Remote Health Status Monitoring via Wireless Integrated Data Systems

- geolocation data (where)
- temporal information (when)
- contextual information (what)
On Body: In Body Sensors/Devices
For Real Time and Remote Monitoring of Individual Health Status
Remote Health Monitoring and Chronic Disease Management

Information for Proactive Health Awareness (Wellness)

Lifestyle and Fitness

m.Health
Wireless Devices for Health Status Monitoring

Zio™ Patch
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)
Intelligent Medicine Dispensers for Enhanced Rx Compliance

Gaming for Health:
Social Networks and Consumer: Patient Empowerment

Source: R&D Directions May 2010
In-Home Health Connection: Engaging the Elderly
A New Healthcare Ecosystem Arising From Technology and Market Convergence

MDx/Devices

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

Rx

HLx
Virtual Medicine Networks: Increasingly Integrated Care and Continuity of Care

- rapid, real time access to expertise
- broader range of clinical specialties
- integrated health records
- availability of lab and Rx lab data
- drug interactions risk
- electronic Rx prescribing

OTC

- optimum use of ‘wellness’ products and
- databases on OTC product performance to accelerate Rx to OTC conversion for products that regulators would otherwise be reluctant to grant full OTC approval
e. Health, m. Health and Patient Empowerment

- greater access to information on treatment options
- generation-dependent ease and expectations for shared role in decisions
- new doctor-patient relationships
- new ‘cultural’ skills for healthcare professionals
  - less paternalism
  - patient education
- major gaps in professional familiarity and competencies in molecular medicine
Genetic education and the challenge of genomic medicine: development of core competences to support preparation of health professionals in Europe

Heather Skirton, Celine Lewis, Alastair Kent and Domenico A Coviello
Global Disease Surveillance

EMERGEncy ID NET

World Health Organization

Public Health Department's Surveillance

U.S. Influenza Sentinel Provider Surveillance Network

Quarantine Activity Reporting System (QARS).

GeoSentinel
The Global Surveillance Network of the ISTM and CDC
Geodemographic Information Systems (GIS): Real-Time, Front Line, Ground Zero Data from Field Sampling and Sentinels
Geo-demographic Information Systems: Mapping Disease Patterns and Modeling Trends

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Satellite Surveillance and Predictive Modeling of Disease Trends
Wireless Sensors and Systems for Improved Agricultural Productivity
Data: The Fastest Growing Resource on Earth
“Managing Mega-Data”: (Who Knows Wins)

volume
global networks

scale

heterogeneity

integration
Standards for ‘Omics’ Data Cross-Domain Integration, Open-Source Data Sharing and Computational Analysis
OBO Foundry Ontologies
Nature Biotechnology 25, 1251 - 1255 (2009)

Cell Ontology (CL)
Gene Ontology (GO)
Foundational Model of Anatomy
ZFIN
Zebralsh Anatomical Ontology
Chemical Entities of Biological Interest (ChEBI)
Disease Ontology (DO)
Plant Ontology (PO)
Sequence Ontology (SO)
Ontology for Clinical Investigations (OCI)
The Open Biomedical Ontologies
Common Anatomy Reference Ontology
Environment Ontology
Ontology for Biomedical Investigations
The Open Biomedical Ontologies
Protein Ontology (PRO)
OBO Relation Ontology
Phenotypic Quality Ontology (PATO)
RNA Ontology (RnaO)

OBO Relation Ontology
Privacy and Health 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,...
Enhancing Human Capabilities to Use the Increased Volume, Diversity and Complexity of Information Flows
Cognitive Biology, Customized Data Formats and Visualization for Improved Decision-Making
Transcending Boundaries: Emergent Domains Arising from Technology Convergence

- Systems and Synthetic Biology
- Targeted Rx
- Regenerative Medicine
- HPO
- Genetic Identity
- Bio-Enhancement
- Bionic-Enhancement
- Cognitive Enhancement
- Cogint
- Brain-Machine Interactions
Mapping Biological Control Circuits and the Expanded Dimension of the Chem-Bio (CB) Challenge

- thinking beyond ‘bio’ as just infectious agents (bugs)

- systems biology
  - targeted disruption of ANY body function
  - novel CB threats

- synthetic biology
  - exploring biospace: designing new life forms
  - designer organisms to attack materials/infrastructure
The Accelerating Convergence of Neurobiology with Advances in Engineering and Computing

- “Brains on Target”: Bio-Info-Cognitive (BIC) technologies
- “Borg Drift”: On-Body/In-Body (OBIB) devices and brain: computer interface technologies
New Strategic Technology ‘Spaces’ Created by Technology Acceleration and Convergence

Systems and Synthetic Biology

Ubiquitous Sensing

Infocosm and the Metaverse

Dual-Use Technologies

Education and Research

“Bio-Space”

“Monitored Space”

“Networked Space”

“Controlled Space”

“Aspirational Space”
New Strategic Technology ‘Spaces’ Created by Technology Acceleration and Convergence

- **Systems and Synthetic Biology**
- **Ubiquitous Sensing**
- **Infocosm and the Metaverse**
- **Dual-Use Technologies**
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**“Bio-Space”**
**“Monitored Space”**
**“Networked Space”**
**“Controlled Space”**
**“Aspirational Space”**

Rapidly Changing and Evolving Multi-dimensional Matrices of Knowledge Ecologies

Innovation Systems

Organization of Research
Dangerous Assumptions

- the future will be similar to the recent past
- policy makers understand the forces that are driving ever-faster disruptive changes
- national governance institutions, laws and regulations are adapting to the accelerating pace of discovery and globalization of technology
The Complex Inter-Relationships Shaping the Future of Healthcare

- 'Omics
  - mechanisms of disease
  - molecular diagnostics
  - rational Rx

- Demographics
  - aging
  - remote health monitoring

- Epidemics
  - urbanization
  - Rx resistance
  - food/water resources
  - instability and conflict

- Economics
  - cost/quality of care
  - better outcomes
  - R&D investment incentives

- Ethics
  - access to care
  - affordability
  - personal accountability for risk mitigation
  - privacy in a monitored networked world
  - dual-use technologies

- personalized medicine
- mHealth
- Global Public Health
- outcomes
- values
The Complex Inter-Relationships Shaping the Future of Healthcare

- ‘Omics
- Demographics
- Epidemics
- Economics
- Ethics

- wellness: predict and prevent disease versus diagnose and treat
- sustainable health: wellness + economic thresholds for acceptable ‘outcomes’
- reducing risk: remote health monitoring + personal accountability
- knowledge networks: distributed information systems for smarter decisions and better use of scarce/expensive resources
The Future of Academic Biomedical Research: Adaptive Agility or Denialism and Decline?

- myriad inefficiencies arising from the organization and performance of academy and its funders
- single discipline specialization creates isolated silos
- hubris of dangerous belief in perceived competency in an era of dramatic change
- reward systems (internal promotion, external funding) weighted to individual versus team performance
- scale, cost and logistical complexity of multidimensional multidisciplinary projects and funding policies
- proficient translation of academic discoveries to productive use requires expanded academy-industry interactions
- imperative for new cross-disciplinary curricula and training