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

Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative and Professor of Health Innovation, Arizona State University
george.poste@asu.edu
www.casi.asu.edu

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

<table>
<thead>
<tr>
<th>Cost</th>
<th>Demographics</th>
<th>Chronic Diseases</th>
<th>Life Style Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
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<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>Inefficient use of Information</td>
<td>Fragmented, Compartmentalized Services</td>
<td>Protracted Adoption of Best Practices</td>
<td>Subsidiarity and Policy Complexity</td>
</tr>
</tbody>
</table>
The Healthcare Challenge

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

Outcomes
clinical, economic, quality-of-life

Infinite demand versus finite resources
unmet medical needs

Increasing cost of care and impact of technology acceleration

Innovation and Cost of Care

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

Health Status

20% of the Population Generate 80% Cost

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

- Multiple co-morbidities
- End-of-life care
- Chronic disease progression
- Chronic disease early stage
- Acute disease

Value

Cost
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>
</tr>
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<tr>
<td><strong>Microbial Pathogens</strong></td>
<td><strong>Cellular Pathology</strong></td>
<td><strong>Molecular Mechanisms</strong></td>
<td><strong>Mechanism Based Rx</strong></td>
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In the **Antiquarian** era, the foundations of medicine were laid with the works of Galen, Avicenna, and Hippocrates. During the **Medieval** period, the plague doctors and the use of leeches were common practices. The **Renaissance** period brought advancements in anatomy and pathology, with figures like Andreas Vesalius and William Harvey. Finally, in the **Enlightenment**, the focus shifted to understanding molecular mechanisms and the development of evidence-based medicine.
# The Intellectual Frontiers of Medicine

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- **Anesthesia**
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- **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

- Biology as Information
- Pathways, Models, Networks
- Differentiation of Multiple Cell Types
- Systems Biology

- Analytical Technologies (Platforms)
- Integrated Analytical Technologies
- Dysregulation (disease)
- Massive Data Analysis
GENOMFORSCHUNG IN ÖSTERREICH

FÖRDERN

AKTUELL
21.10.2010
PhD Award

Das Österreichische Genomforschungsprogramm

Das Programm
→ Programmmanagement
→ Förderungen
→ Technologietransfer
→ International
→ Timeline

FORSCHEN

AKTUELL
08.10.2010
Call For Entries - Science, Art & Film Festival zur Synthetischen Biologie

Die Projekte
→ Aktuelle Projekte
→ Abgeschlossene Projekte
→ Institutionen
→ Personen
→ Publikationen

Geförderte Projekte 2001-2006

GEN-AU III

Dritte Phase von GEN-AU gestartet
Den Startschuss gaben Minister Hahn, Henrietta Egerth (FFG) und Giulio Superti-Furga (CeMM) bei einem Pressegespräch.

PORTRÄTSPROJEKTE

Wie bitte? Auch Pflanzen haben Stress?
Ein Interview mit GEN-AU Projektleiter und Pflanzenforscher Wolfram Weckwerth

Vakzinologie ist kein Penny-Markt
Die Impfstoffforscherin Eszter Nagy im Gespräch mit Bert Eghartner

Was ist GEN-AU?
Genomforschung ist eine Schlüsseltechnologie. GEN-AU fördert und vernetzt Forschung für Gesundheit in Österreich

http://www.gen-au.at/index.jsp?lang=de
The Complex Inter-Relationships Shaping the Future of Healthcare

- ‘Omics
  - personalized medicine

- Demographics
  - population-based medicine

- Epidemics
  - global public health

- Economics
  - outcomes

- Ethics
  - 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

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### 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**
### Molecular Diagnostics (MDx)

The Convergence of Molecular Biology, Engineering and Computing

#### Complex Biosignature Profiling

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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)
- regulatory endorsement in product labeling

clinical guidelines
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

Consumer Genetics | DNAdirect
CyGene | GeneLink
Genelex | GENECARE
INTERLEUKIN GENETICS | MediChecks.com
ScientificMatch.com | SURACELL
23andMe | Navigenics
NeuroMark | Knome
POLICY

Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes

European Society of Human Genetics
Whole Genome Sequencing

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**

Timeline:
- 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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<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
Urbanization: A Bipolar World but Shared Risks

Slums of the World:
The face of urban poverty in the new millennium?
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)

**NO ESKAPE**

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella Pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter species*
New US-EU Task Force (2 Nov. 2009)
- encourage R&D on new antimicrobial drugs
- yet to be defined strategy/funding

The I0 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
How Much New Technology Can We Afford?
NICE Gets Nasty (or Rational?)
The Infocosm: Emerging Networks of Global Connectivity
• 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
Wireless Devices for Health Status Monitoring
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
A New Healthcare Ecosystem Arising From Technology and Market Convergence

Integrated Technology Platforms

Data Mining and Integration Services

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

Increasingly Targeted Care and Efficient Use of Finite Resources

MDx/ Devices

Rx

Hlx

patients

services for integrated care

consumers
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

- optimum use of ‘wellness’ products

- 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

Infectious Diseases Society of America

ProMED-mail

GPHIN

biocaster

HealthMap

Global Disease Alert Map

U.S. Influenza Sentinel Provider Surveillance Network

DoD-GEISWeb

Global Emerging Infections System

Quarantine Activity Reporting System (QARS).

BioPortal

GIDEON

TropNet Europ

Empres Watch

RABNET

Human and Animal Rabies

EUNiD

European Network of Infectious Diseases

CDC

Centers for Disease Control and Prevention

GeoSentinel

The Global Surveillance Network of the ISTM and CDC

A worldwide communications & data collection network of travel/tropical medicine clinics

google.org

ARGUS

Research Operations Center
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

Anomaly Detection and Early Alert

Disease Progression

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

scale

global networks

heterogeneity

integration
Standards for ‘Omics’ Data Cross-Domain Integration, Open-Source Data Sharing and Computational Analysis
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

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<tr>
<th>Systems and Synthetic Biology</th>
<th>Targeted Rx</th>
<th>Regenerative Medicine</th>
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<td>Bio-Enhancement</td>
<td>Bionic-Enhancement</td>
<td>Cognitive Enhancement</td>
<td>Cogint</td>
<td>Brain-Machine Interactions</td>
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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

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"Bio-Space"

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"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
- m. Health
- Global Public Health
- outcomes
- values
The Complex Inter-Relationships Shaping the Future of Healthcare

- ‘Omnics
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- 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