The Evolution of Personalized Medicine: Opportunities and Challenges

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Montreux, Switzerland, 10 November 2010
Slides available @ www.casi.asu.edu

Declared Interests:

- Board of Directors: Monsanto, Exelixis, Caris Life Sciences
- Scientific Advisory Board: Synthetic Genomics, Anacor
## Challenges for Healthcare Delivery Systems

<table>
<thead>
<tr>
<th>Cost</th>
<th>Demographics</th>
<th>Chronic Diseases</th>
<th>Life Style Disease</th>
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<tbody>
<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>
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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 in Healthcare

- social and economic value of reducing disease burden will rise
  - earlier disease detection and mitigation
  - rational Rx and guaranteed outcomes
  - integrated care for complex chronic diseases
  - extension of working life
  - prospering in an era of increasing constraints
  - managing the limit(s) of society’s willingness and ability to pay for innovation
The Three Convergent Forces Shaping the Evolution of Healthcare

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

VALUE
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)
Defining A New Taxonomy for the Diagnosis and Classification of Disease

- redefining pathology as the deregulation/dysregulation of specific biological pathways
- disease with similar symptoms can arise in the same cell type via different patterns of pathway dysregulation
  - different points in the same biological pathway
  - multiple points in connected biological pathways
- molecular profiling of disease subtypes as the intellectual foundation for rational drug discovery and Rx treatment selection
  - “targeted therapeutics”
  - “personalized medicine”
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
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?
The Hunt for Gene Loci Associated with Complex Human Diseases
Disease Predisposition Risk Profiling for Common, Multigenic Late-Onset Disorders

- Slower evolution than many predict
- Genome-Wide Association Studies (GWAS)
  - High cost and to date low yield in terms of clinically exploitable markers
  - Disease origins from multiple low penetrance alleles versus small set of high penetrance alleles
- Substantial ambiguities regarding probabilistic risk of overt disease
  - Epistasis
  - Epigenetics
  - Environmental confounders, including Rx
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
The Progressive Evolution of Personalized Healthcare

- **“Blockbuster” Rx**
  - empirical “one-size-fits-all”
  - population-based Rx

- **Stratified/Targeted Rx**
  - Rx targeted to patient subgroups with same molecular pathology
  - Dx-Rx combinations and Rx labeling

- **Individualized Rx**
  - individualized Rx
    - relevant disease subtype and AE risk profiling
    - identification and mitigation of disease predisposition risk(s)

- **Personalized Healthcare**
  - integrated framework of coordinated care and longitudinal care
Biomarkers, Biosignatures and Molecular Diagnostics: The Key Value Drivers for Personalized Medicine, Improved Healthcare and Maximizing Wellness
“The output (for drug discovery/biomarkers) has been as close to zero as you can come. We have achieved nothing substantial that’s the bottom line.”

Dr. Tommy Nilsson
McGill Univ.
Nature Biotechnology (2010) 28, 669

“Biomarkers have been the biggest disappointment of the decade, probably because proteomics role in their discovery was overhyped.”

Dr. John Yates
Scripps Institute
Disease-Associated Biomarkers and Validation of Novel Molecular Diagnostics

- Literature dominated by anecdotal studies
  - academic laboratories
  - small patient cohorts
  - lack of standardization
  - poor replication and confirmatory studies
- Very few biomarkers subjected to rigorous validation
  - inadequate stringency in clinical phenotyping
  - case-control studies with sufficient statistical power
- Widespread lack of understanding of regulatory requirements in academic research community
  - complexities imposed by multiplex tests
  - new regulatory oversight (IVDMIAs)
Biomarkers, Biosignatures and Molecular Profiling of Human Diseases

Agnostic

- analytes
- analytical platforms

Success Determinants

- systems-based strategies
- standards/standardization
- subjects
- specimens
- scale
- sociology
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
Molecular Diagnostics and Miniaturized Devices: A Key Future Driver in the Healthcare Value Chain

Complex Biosignature Profiling

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<th>proteomics</th>
<th>immunosignatures</th>
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<td><img src="image2.png" alt="Image" /></td>
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Signature Detection, Deconvolution and Multivariate Analysis

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<th>automated, high throughput multiplex assays</th>
<th>novel test formats and devices (POC)</th>
<th>new algorithms for complex signal deconvolution</th>
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Molecular Diagnostics (MDx)
The Convergence of Molecular Biology, Engineering and Computing

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- 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
Rigorous Selection of Specimen Donors and Specimen Collection

- Challenge of obtaining fresh tissue
- Poorly standardized tissues and erratic availability
- Variable value of legacy tissue blocks and consents

Standardized clinical phenotyping and annotated health records and outcomes
Access to Quality Biospecimens for Medical Research: A Critical ‘Choke Point’ in Biomedical Research

Ease of Acquiring the Quality of Biospecimens

- Difficult/Very difficult: 48%
- Somewhat difficult: 32%
- Somewhat easy: 13%
- Very easy/Easy: 8%

Question Their Data Because of the Quality of Biospecimens

- Never/Rarely: 40%
- Sometimes: 40%
- Often/Always: 20%

Limit Research Scope of Work Due to the Shortage of Quality Biospecimens

- Never/Rarely: 19%
- Sometimes: 36%
- Often/Always: 45%

http://biospecimens.cancer.gov/cahub/
The Formidable Challenge of Standardization of Pre-Analytical Sources of Variation in Clinical Biospecimens

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<th>Pre-Sampling</th>
<th>Post-Sampling</th>
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<tr>
<td>● pre-existing medical conditions</td>
<td>● room temperature</td>
</tr>
<tr>
<td>● Rx</td>
<td>● time at room temperature</td>
</tr>
<tr>
<td>● type and duration of anesthesia</td>
<td>● rate of freezing</td>
</tr>
<tr>
<td>● vessel clamp time and tissue anoxia</td>
<td>● fixative type and time in fixative</td>
</tr>
<tr>
<td>● blood pressure variation</td>
<td>● collection container(s)</td>
</tr>
<tr>
<td>● intra-operative blood/fluid shifts</td>
<td>● biomarker extraction methods</td>
</tr>
<tr>
<td></td>
<td>● storage conditions</td>
</tr>
<tr>
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Time Between Ligation Of Main Artery And Tumor Resection (Intrasurgical Ischemia) Affects Gene Expression In Colon Cancer (NCI-Indivumed study)

Intrasurgical Ischemia

PCA mapping: grouping of warm ischemia time points

Indivumed-NCI Study: Courtesy of Dr. C. C. Compton
“The technological capacity exists to produce low-quality data from low-quality analytes with unprecedented efficacy.”

“We now have the ability to get the wrong answers with unprecedented speed.”

Dr. Carolyn C. Compton
Director, Office of Biorepositories and Biospecimen Research
National Cancer Institute
‘IOM, July 2010’
“The study of cancer cells in two dimensions seems quaint if not archaic”


“Medline search reveals that more than 80% of cancer and molecular biologists still use two-dimensional techniques”

D.W. Hutmacher (2010) Nature Materials 9, 90
Challenging Questions

- Are the phenotypes and molecular pathways of cell lines and 2D cell cultures so unrepresentative of the situation to render them irrelevant and pose blind avenues for diagnostic/therapeutic discovery?

- Can the biology of metastasis be elucidated by analysis of non-metastatic cells?
A Global Map of Human Gene Expression

- 5372 microarray samples
- 206 different laboratories
- 163 different laboratories
- 369 cells, tissues, disease states and cell lines
- Solid tissue cell lines cluster together rather than with respective tissues of origin or neoplasms from same lineage
  - 1217 genes upregulated in all cell lines
  - Cell cycle, division and mitosis genes

http://www.ebi.ac.uk/gxa/array/U133A
LC:MS-Based Platforms for Biomarker and Biosignature Profiling

Analytes
- proteomics (and PTMs)
- metabolomics
- toxicology

Analysis
- global analysis (non-biased)
- targeted analysis (hypothesis-driven)

Applications
- candidate ID for use with more facile platform
- routine clinical use

Alternatives
- cost
- speed
- instrumentation capital cost
- regulatory/clinical issues
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**Standardized Methods, Data Reporting and Database Design**
- GLP/GMP; LIMS/CTMS; Regulatory Dossiers

**Instrumentation:** Research Use Only or Approval for Clinical Use
Sample Complexity and Dynamic Range in MS-Based Proteome Analysis

- formidable dynamic range of analyte abundance
- detection of low abundance species
- femtomol or attomol range sensitivity modulated by nature of sample (abundance, dynamic range)
- ion suppression from high abundance proteins/peptides
- 35% estimated human proteins yet to be reliably identified by MS
- under sampling
- time, cost and efficiency of pre-analytical fractionation(s)
- targeted depletion of abundant proteins and/or affinity enrichment of low abundance species
“It is time for the debate about the reproducibility of mass spectrometry to end.”

Anonymous Editorial:
The Call of the Human Proteome
Nature Methods (2010) Sept. 7 (9) 661

Mass spectrometry in high-throughput proteomics: ready for the big time

Tommy Nilsson¹,², Matthias Mann³, Ruedi Aebersold⁴,⁵, John R Yates III⁶, Amos Bairoch⁷,⁸ & John J M Bergeron¹,²

Mass spectrometry has evolved and matured to a level where it is able to assess the complexity of the human proteome. We discuss some of the expected challenges ahead and promising strategies for success.
Common Problems in MS-Based Proteomics
A.W. Bell et al. (2009) Nature Methods 6, 423

- evaluation of test sample of 20 purified proteins at 5 pmole equimolar abundance
- 7/27 labs with initial correct characterization
- raw data from all sufficient to identify full 20 protein catalog and 22 derivative 1250 Da peptides
- diverse and poorly standardized databases and search engines as principal sources of erroneous reporting
  - variation in curation, annotation, comprehensiveness

- real world challenges: high complexity samples and large preanalytical (collection/storage) sample variation
- education and training to use complex technologies
- publication standards, formats and open-source dbases
Databases and Data Matching for “Shotgun” MS-Based Proteomics

- chaotic legacy of multiple nomenclature identifiers for human proteins
- urgent imperative for standardized ontologies and software search engines
- disparate databases and success rates for automatic mapping across databases rarely reaches 95%
- HUPO Proteomics Standards Initiative proposal
- neXtProt: gene-protein centric proteome annotation scheme
- ProteomeXchange consortium as parallel repository for raw MS data
The Value of Blood-Based Diagnostic Profiling

- minimally invasive
- blood bathes all organs
- organ-specific ‘biosignatures’ detectable in blood
- facile routine tracking of disease progression and Rx responsiveness
- value of highly stable biomarkers for retrospective studies to correlate with clinical outcomes
- Point-of-Care (POC) testing
- repeated testing/longitudinal profiling versus feasibility/cost/trauma of repeated biopsies
Immunosignatures:

- large scale arrays of random peptides (12-20 mers)
- consistent patterns of binding antibodies (polyclonal immunoglobulins and specific monoclonals)
- high throughput dynamic analyses of antibody profile in individual people/animals
  - autoantibodies
  - immune response to infectious diseases and vaccination
  - early pre-symptomatic disease detection

Courtesy Dr. S. Johnston, Biodesign Institute, ASU
five healthy individuals sampled across 21 days show consistent pattern

note that individuals differ from each other

this difference disappears whenever multiple persons have the same illness (e.g., influenza)

Courtesy Dr. S. Johnston, Biodesign Institute, ASU
Capture and Biosignature Profiling of Microvesicles

• released by normal and diseased cells
  – 0.03-1.0 micron diameter
• Upto x 4 greater levels in cancer patient plasma samples
• role in inter-cellular communication
  – immune responses, (stimulation and suppression)
  – epithelial-mesenchymal transition in cancer
• protein markers (membrane)
  – identification of cell of origin
  – novel disease-associated markers
• miRNA and mRNA (intravesicular cargo)
  – novel disease-associated profiles
Carisome™ Prostate MDx 1.0 Diagnostic: A Significant Performance Improvement Over PSA

Sensitivity 85%
Specificity 86%
AUC 94%
Our first project, funded in part by the Bill and Melinda Gates Foundation, is a low cost, point-of-care diagnostic device for measuring liver function – critical for monitoring the adverse side effects of the powerful drugs used to treat HIV/AIDS and TB, and for managing the effects of viral hepatitis.
Remote Health Status Monitoring

Biosignature Profiling Via Sensors and Devices
On Body: In Body Sensors/Devices:
Real Time and Remote Monitoring of Individual Health Status
m.Health

Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)
Wireless Devices for Health Status Monitoring

- Zio™ Patch
- CARDIONET
- cardiograms
- PHILIPS
- BIOTRONIK
- excellence for life
- OMRON
- QUALCOMM
- AMD
- CHEALCOMM
- vitaPhone
- Telemedicine
- corventis
- Sotera Wireless
- myca
- card Guard
- GE
- AIRSTRIP Technologies
- SIEMENS
- LG
- TELCOMED
- BIOWATCH
- MEDICAL
- INTouch HEALTH
- Medic4all
- Vitalograph
- LifeCOMM
- at&t
- NOKIA
- Google
innovation in science and technology alone is necessary but not sufficient

adoption requires overcoming multiple barriers
  – existing competition/standard of care
  – cultural conservatism
  – reimbursement and other financial obstacles
  – regulatory hurdles

wide variation in adoption speed by different sectors
  – healthcare (10-30 years)
  – computing (1-2 years)
  – engineering (1-10 years)
Payor Perspectives and Reimbursement for Molecular Diagnostics

- **#1** will test alter patient management?
  - reduce cost of care
  - improve outcomes

- **#2** what additional resources/services/training are affected by test adoption?

- **#3** mindset of ‘lab data’ as low cost (<1% total cost) despite role in most treatment decisions (>85%)
  - unianalyte versus multiplex tests
  - outdated US reimbursement codes
Payor Perspectives and Reimbursement for Molecular Diagnostics

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- #3 mindset of ‘lab data’ as low cost (<1% total healthcare cost) despite role in most treatment decisions (>85%)
  - transition form unianalyte versus multiplex tests
  - higher regulatory hurdles

SHIFT FROM COST-BASED TO VALUE-BASED REIMBURSEMENT
The High Information Content (Complexity) of Biological Datasets
Validation of Disease Associated Biomarkers

- Disease related differences are small compared to biological variability.
- Many variables behave as QTLs with graded continuum rather than binary normal: disease separation.
- The high dimensionality small sample size (HDSS) problem:
  - High number of variables (2000-10000) and low sample size (10-100).
  - Increased risk of selection of variables due to chance (overfitting).
- Standardization and statistical powering of validation studies:
- New regulatory complexities for multiplex ‘signatures’.
Regulatory Oversight of Molecular Diagnostics
“Specific Intended Use” and “Fit-for-Purpose”

- unianalyte versus multianalyte tests
- profiling existing disease/Rx selection versus claims for probabilistic risks for disease predisposition
- IVDMIAs and validation of algorithms/software
  - “non-transparent derivation that cannot be independently derived or verified by the end user”
- probabilistic versus absolute endpoints
- is the ‘kit’/‘assay’ or the ‘information content’ the product?
Standards for ‘Omics’ Data:
Annotation and Curation
Cross-Domain Integration,
Open-Source Data Sharing
and
Managing Massive Data
“Managing Mega-Data”

- **Volume**
- **Infrastructure**
- **Global Networks**

**Multiscale Heterogeneity**

**Database Interoperabilities**
Leveraging the Potential of Molecular Medicine

Sustainable Health: A Complex Multi-Dimensional Challenge
Sustainable Health: Societal and Individual

- Current systems for healthcare delivery are economically unsustainable.
- Earlier disease detection, rational treatment selection and pre-emptive mitigation of disease risk are fundamental to controlling cost, enhancing clinical outcomes and maximizing individual health (wellness).
- Biosignature-centric molecular diagnostics provide the intellectual and practical foundations for achieving these objectives.
- Productive translation of these opportunities requires large scale projects and sophisticated integration of diverse scientific, clinical, industrial and regulatory capabilities.
Successful Development of Precision Diagnostic Technologies for Personalized Medicine Requires a Systems-Based Approach

- silos are the enemy
- academia, industry and funding agencies must build new training and research networks for biomarker discovery and validation
- urgent imperative for faster progress in adoption of standards
  - multi-domain: from discovery to health records
  - multiple constituencies
- industry engagement drives adoption of standards
- standards drive industry engagement
• the potential economic and health benefits from biosignature diagnostic profiling transcend any other current category of healthcare innovation

• realization of this potential will depend less on technological advances, albeit crucial, than the circumvention of entrenched economic, cultural and institutional interests in sustaining the status quo
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