The Evolution of Personalized Medicine: Opportunities and Challenges

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The Healthcare Challenge

Innovation and Defining Value

Access to Care

Outcomes
clinical, economic, quality-of-life

increasing cost of care and acceleration of new technologies

unmet medical needs

infinite demand versus finite resources
Economic Distortions and Perversions in the Healthcare “Market”

- “a menu without prices” (A. Garber)
- potential terminal illness for governments, business and patients/consumers
- supply creates its own demand
- caregivers make more money by providing more care and typically ignore cost in treatment options
- patients have entitlement mentality and don’t select treatment choice
- payors don’t apply comparative effectiveness metrics
- neither consumers nor caregivers evaluate cost or benefit and drift to “maximum” care
Demographics:
Ageing, Chronic Diseases and Cost

- by 2030 number of people over 65 will:
  - increase 140% in developing world
  - increase 51% in developed world
  - outnumber children under 5

- by 2020 account for 75% of global deaths

- US cost of chronic disease will increase 2.5X by 2023
- China loss of income due to chronic disease will increase 8X from 2005-2015
# US Cancer Prevalence Estimates 2010 and 2020

<table>
<thead>
<tr>
<th>Site</th>
<th># People (thousands)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>3461</td>
<td>4538</td>
</tr>
<tr>
<td>Prostate</td>
<td>2311</td>
<td>3265</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1216</td>
<td>1517</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1225</td>
<td>1714</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>639</td>
<td>812</td>
</tr>
<tr>
<td>Uterus</td>
<td>588</td>
<td>672</td>
</tr>
<tr>
<td>Bladder</td>
<td>514</td>
<td>629</td>
</tr>
<tr>
<td>Lung</td>
<td>374</td>
<td>457</td>
</tr>
<tr>
<td>Kidney</td>
<td>308</td>
<td>426</td>
</tr>
<tr>
<td>Leukemia</td>
<td>263</td>
<td>240</td>
</tr>
<tr>
<td>All Sites</td>
<td>13,772</td>
<td>18,071</td>
</tr>
</tbody>
</table>

Challenges for Sustained Innovation in Biomedical R&D

• inefficient translation of research (valley of death)

• macroeconomic uncertainties
  – reduced Federal funding, VC retreat and R&D reductions in bigPharma/biotech
  – budget gap closure actions and industry fees/concessions
  – off shore investment

• complexity of chronic diseases and no immediate prospect of enhancing asset success rate and/or truncation of R&D cycle time

• regulatory uncertainties and increasing hurdles
  – larger trials, zero-risk and REMs
  – inadequate budgets, staffing and science
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
Reasonable Expectations for Rational Healthcare

- what works?
- why it works?
- who it works for?
- what works best?
- when should it be used optimally?

- validated evidence
- mechanism of action
- personalized medicine
- comparative effectiveness
- best practice guidelines and standard-of-care

VALUE
The Innovation Ecosystem for Biomedical R&D and Healthcare Delivery
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
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
Disease Subtyping and Targeted Therapy: The Right Rx for the Right Disease Subtype

- improved clinical outcomes
- cost-effectiveness in eliminating futile Rx
- reducing high failure rate of new drugs in R&D clinical trials by testing only on relevant patients
  - faster and cheaper trials
  - improved efficacy, clear regulatory endpoints and faster approval
  - premium pricing for guaranteed outcomes (P4P)
K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy

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

regulatory endorsement in product labeling

payor adoption
Disease Subtyping and Targeted Therapy: The Right Rx for the Right Disease Subtype

- improved clinical outcomes
- cost-effectiveness in eliminating futile Rx
- reducing high failure rate of new drugs in R&D clinical trials by testing only on relevant patients
  - faster and cheaper trials
  - greater regulatory clarity
  - premium pricing for guaranteed outcomes (P4P)

**downside implications for ineligible patients with no therapeutic alternative(s)**
Mapping the Genetics of Drug Metabolism:
Profiling Patient Risk to Adverse Drug Reactions

Right Rx for the Right Patient

- 1.5 to 3 million annual hospitalizations (US)
- 80 to 140 thousand annual deaths (US)
- est. cost of $30-50 billion
We Are Not Alone: Variation in the Human Microbiome as a Potential Factor in Health and Disease
Genetic Profiling to Identify Risk of Predisposition to Disease
● the much publicized (hyped) $1000 genome
● $1000 genome but big bucks to interpret the results plus myriad ambiguities
  – defining probabilistic risk(s) with greater certainty
  – current unknown rules of gene-gene interactions or lifestyle/environmental factors in increasing or reducing risk(s)
  – ethical issues: privacy, disclosure, discrimination
Disruptive Innovation in Healthcare: Redefining the Value Equation in Healthcare

- Better Care at Lower Cost
- Earlier Disease Detection and Response to RX
- Treatment Personalized to the Patient

- Molecular taxonomy of disease
- Managing risk, cost and quality
- Health status monitoring
- Optimized decisions
- Precision Diagnosis
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
The Poor Performance Record of Biomarker Discovery and Validation

- ‘publish and vanish’
  - over 120,000 claimed biomarkers or biomarker combinations (biosignatures)
  - less than 100 molecular diagnostics in clinical use or advanced validation trials
- literature dominated by anecdotal studies
  - academic laboratories
  - lack of standardization: biospecimens to analytical platforms
  - small patient cohorts and insufficient statistical power
  - poor replication and confirmatory studies
- widespread lack of understanding of regulatory requirements in academic research community
  - GLP, GMP, Records, RUO instruments versus Clinical Use
  - technical complexities of multiplex assays
  - new regulatory oversight (IVDMIAs)
Building Large Scale, Standardized Resources for Biomedical Research

- rigorously phenotyped/matched/consented disease and normal specimens

- biobanking: leadership and national policies to create a vital research resource

- standardization of pre-analytical and analytical methods

- standardized data ontologies and formats for large scale datasets/federated databanks
Large Scale Profiling of Cancer Patients to Identify Cohorts Expressing Rx Target(s) for Phase II Trials

<table>
<thead>
<tr>
<th>Target</th>
<th># Patients Screened</th>
<th># Eligible Patients</th>
<th># Centers</th>
<th># Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML4 ALK*: lung cancer*</td>
<td>1500</td>
<td>82</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>HER2*: gastric cancer**</td>
<td>3803</td>
<td>549</td>
<td>122</td>
<td>24</td>
</tr>
</tbody>
</table>

* E.L. Kwak et al. (2010) NEJM 363, 1693
** Y. Bang et al. (2010) Lancet 376, 687
Individual Variation, Genome Complexity and the Challenge of Genotype-Phenotype Prediction

Junk No More!
- pervasive transcription
- alternate transcription/translation
- SNPs, CNVs
- indels, SVs
- ncRNAs
- phasing
- epistasis
- imprinting

recognition of increasing organizational and regulatory complexity

Molecular Interaction Networks

Disease Perturbations
Mapping Modules, Pathways and Subnetworks in Biological Systems: The TCGA Glioblastoma Multiform Dataset and Protein Interaction Networks

From: C. J. Vaske et al. (2011) Bioinformatics 26, i237
Network Pharmacology

- analysis of Rx action in context of network topologies and dynamics
- same drug: interaction with multiple targets
- same target: interaction with multiple drugs
- mapping structural chemotypes to specific pathways and subnetworks for targeted (poly)pharmacology

From: M. J. Keiser et al. (2011) Nature 462, 180
Mapping the Molecular Signatures of Disease, Disease Subtyping and Targeted Therapy: The Right Rx for the Right Disease (Subtype)

Her-2+ (Herceptin)  
EML4-ALK (Xalkori)  
KRAS (Erbitux) (Vectibix)  
BRAF-V600 (Yervoy) (Zelboraf)
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
Rethinking Approaches to Rx Discovery for Advanced Chronic Diseases

Is There a Fundamental Imbalance in Investment in Diagnostics Versus Therapeutics?
Opportunities and Challenges Posed by Ever Earlier Detection of Major Diseases

<table>
<thead>
<tr>
<th>Cancer Detection Before Metastasis</th>
<th>Cardiovascular/ Metabolic Diseases</th>
<th>Neurodegenerative Diseases</th>
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</thead>
<tbody>
<tr>
<td>Early Diagnosis and Curative Surgery</td>
<td>Lifestyle Changes and/or Rx to Limit Risk</td>
<td>The Dilemma of Early Diagnosis Without Rx</td>
</tr>
</tbody>
</table>

Diabetes + Obesity = DIABESITY

TheAnariestPharmacist.com
How Much New Technology Can We Afford?
# Phase III Studies Comparing Chemotherapy With or Without Bevacizumab as First-Line Therapy for Advanced Epithelial Cancers

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Study</th>
<th>Bevacizumab Effect</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PFS (months)</td>
</tr>
<tr>
<td>Breast</td>
<td>ECOG E2100</td>
<td>+5.9*</td>
</tr>
<tr>
<td></td>
<td>AVADO</td>
<td>+0.8*</td>
</tr>
<tr>
<td></td>
<td>RIBBON-1</td>
<td>+2.9*</td>
</tr>
<tr>
<td>Ovarian</td>
<td>GOG 0218</td>
<td>+0.9</td>
</tr>
<tr>
<td>Lung</td>
<td>ECOG E4599</td>
<td>+1.7*</td>
</tr>
<tr>
<td>Gastric</td>
<td>AVAGAST</td>
<td>+1.4*</td>
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<tr>
<td>Pancreas</td>
<td>CALGB 80303</td>
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</tr>
<tr>
<td>CRC</td>
<td>Hurwitz</td>
<td>+4.4*</td>
</tr>
<tr>
<td></td>
<td>Saltz</td>
<td>+1.4</td>
</tr>
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</table>

*Statistically significant

Categories of Care and Cost: Today

- Categories:
  - Acute Care
  - Complex Chronic Care (oncology, neurodegeneration)
  - End-of-life (EOL) Interventions/Care
  - 1°/2° Chronic Care
  - Integrated Care
  - Wellness
Recalibrating Categories of Care and Cost:
Bending the Cost and Quality Curves

- acute care
- complex chronic
- stable chronic
- EOL* (end-of-life care)
- wellness

*EOL = end-of-life care
The Rise of m.(mobile)Health and e.Health

Individual Biosignature Profiling Via Sensors and Devices

Remote Health Status Monitoring
Wireless Devices and Remote Monitoring of Health Status and Rx Compliance
Wireless Devices for Health Status Monitoring
Increasing Engagement of Informed Consumers/Patients in Healthcare Decisions: Increased Personal Responsibility for Maintaining Health (Wellness)

**Information Resources**
- disease specific advocacy groups
- mass media
- web resources and social media
- mobile apps
- healthcare providers/professionals

**Optimizing Wellness and Risk Reduction**
- “my profile”
- “my biorepository”
- “my health today”
- early alerts and risk mitigation
- virtual expertise network
- expertise locaters and clinical trial enrollment
The Changing Roles of Consumers (well)/Patients (ill)

**past**
- passive role and medical paternalism
- reliance on physicians to maintain health records
- reliance on physicians as primary source of trusted medical information
- isolated illness episodes and annual check-up

**future**
- increasingly active managers of personal health
- increasing knowledge of genetic risks, Rx actions
- access to own digital health records
- extensive use of internet, social networks for medical information
- real time, remote monitoring of health and wellness with digital devices
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
Data: The Fastest Growing Resource on Earth
Managing “Mega-Data” in Biomedicine

volume

computational scale

global networks

bench to bedside: multiscale heterogeneity

integration
Managing Massive Data

Standards for Data Reporting and Database Design

Interoperability of Databases Across The Continuum from Discovery to Patient Care

New Analytics and High Performance Computing
The Only Valuable Data is Validated, Actionable Data
New Visualization Tools, Interactive Interfaces and Rapid Customization Formats
New Value Propositions in Healthcare: Improved Quality and Outcomes at Lower Cost

- Improved outcomes at lower cost
- Disease subtyping and rational Rx selection
- Molecular profiling/precision Dx
- EHR/PHR
- OBIB sensor networks
- Data-centric health systems
- Meta-analytics for outcomes/performance/compliance
- Integrated care
- Decision support systems and patient-centric algorithms
- Proactive risk mitigation
- Remote health monitoring
- Team-based delivery
- Patient empowerment/engagement
- Remote health monitoring
- Team-based delivery
- Patient empowerment/engagement
Building Knowledge Networks to Improve Individual Health and Sustainable Healthcare Delivery

ACKM and superior decisions: improved care, lower cost, better outcomes

- on-body, in-body sensors/devices
- molecular profiling of patients (personalized medicine) and global disease surveillance (public health)
- mapping the dysregulation of biological networks in disease
- e. Health: mining large scale population databases
- m. Health and remote health status monitoring

molecular profiling of patients (personalized medicine) and global disease surveillance (public health)
The Innovation Ecosystem for Biomedical R&D and Healthcare Delivery

- molecular medicine
  - precision Dx and rational Rx
  - regenerative medicine
- engineering-based medicine
  - sensors and remote health status monitoring
- information-based medicine
  - meta-analysis of massive data
  - new decision support algorithms
- networked medicine
  - expertise networks and integrated care
- consumer/patient engagement
  - increased personal responsibility for wellness
- realignment of role of MD in healthcare
  - matching skills to needs
  - education curricula
Disruptive Innovation Demands Boldness!

- the failures of timid incrementalism and the retreat from complexity

“It’s not because things are difficult that we dare not venture. It’s because we dare not venture that they are difficult.” Seneca