Overview of Personalized Medicine

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Personalized Medicine & Molecular Diagnostics: Legal, Regulatory & Ethical Aspects

Sandra Day O'Connor, College of Law, ASU
2 March 2007
The Imperative for Major Improvements in Clinical Medicine and Healthcare Delivery

- rising costs
- cost escalation not linked to improvements in quality
- increasing restrictions on services and/or access
- highly variable treatment patterns
- slow diffusion of best practices
- high rates of preventable error
- uniform dissatisfaction: patients, physicians, providers, payors and politicians
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)

VALUE
Complex and Pervasive Problems in Healthcare with No Easy Solutions

- different ‘value’ metrics for different constituencies
  - patients, physicians, payors, politicians
- public expectations and populist politics
  - zero-cost, zero-risk = zero care
- lack of transparency in costs, billing and reimbursement
- anachronistic institutional mechanisms for national health policy debate

CHANGING MINDS AND CHANGING BEHAVIORS
The Fundamental Challenge Facing Healthcare Systems in the Early 21st Century

- the growing imbalance between infinite demand for care and finite resources

- rationed care or rational care?
“You may believe you’ve been overcharged, but, remember, you’re overmedicated.”

“Try this — I just bought a hundred shares.”
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 caused by empirical Rx
- cost of futile therapy
- medical error and AEs
“The direction that medicine is moving is actually toward more individualized therapies through an understanding of the molecular and genetic bases for diseases in individual patients.”

Dr. Mark B. McClellan
Commissioner, FDA
MX. September 2003, p. 26

“Challenges and changes for the industry even include rethinking the concept of market share and where the opportunities lie with regard to the development, not of drugs, not of biologics, not of devices but, more importantly (sic), the development of solutions”

Dr. A. von Eschenbach
Acting FDA Commissioner
Keynote Address
RPM Reports FDA-CMS Summit 2005
“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”
Molecular Medicine, Rational Therapy and Targeted Care

**Pharmacogenomics**
- identification of molecular targets for new Rx classes
- better diagnostics (Dx) and medicines (Rx) for populations
- earlier detection
  - better outcomes
- disease subtyping
  - right drug for the right disease
- better disease monitoring tools
  - Rx responsiveness, relapse

**Pharmacogenetics**
- influence of individually unique genetic status on responses to Rx, xenobiotics, diet
- targeted Rx with improved benefit/risk ratios for individuals
The Leading Edge of Personalized Medicine: Pharmacogenomics and Pharmacogenetics

- faces fewest hurdles to clinical adoption and payor acceptance
- does not impose major redesign on healthcare delivery systems

but

requires significant increase in physician/provider/payor literacy regarding applications

- potential to transform cost and clinical outcomes for major disease categories with high Rx use
  - efficacy, safety, compliance

- obligate need to demonstrate value to overcome acceptance barriers
Molecular Diagnostics and Biomarkers

The Fundamental Technology Platforms For Molecular Medicine and Vital Elements of the Future Healthcare Value Chain
In Vitro Diagnostic (IVD) Tests

- legacy of high volume, low margin, commodity tests and low commercial appeal
- nine companies hold 80% US market revenue of $11.2 billion and $28.6 billion global sales
- limited technical complexity of current tests and diffuse regulatory oversight (CLIA and ‘homebrew class)
- 5% of US hospital costs and 1.6% of Rx costs but influence
- 60-70% of healthcare decisions
- future evolution analogous to the vaccine market?
Patterns of Gene Expression in Progression of Malignant Melanoma

B1 skin, B2, melanocytes, B3, melanoma, B4 and 5 metastatic melanoma

From: C. Haqq et al. (2005) 102, 6092

- massive parallelism
- miniaturization
- automation
- rapid
- POC
Disease Biomarkers and Molecular Diagnostics

Rx Efficacy

• molecular Dx, accurate Dx and disease subtyping
  • right Rx for right disease subtype

Personalized Medicine

• DMPK pharmacogenetics
  • right Rx for right patient
  • toxicology markers
  • population-based pharmacovigilance

• predictable Rx outcomes
  • relapse/resistance markers
  • elimination of cost/risk of futile Rx
  • reduced AE risk

Rx Safety

Value
Personalized Medicine: From Pharmaceuticals to Pharmasuitables

Disease Subtyping: Right Rx for Right Disease

Reduction of Adverse Drug Reactions
Adverse Event Reports

Calendar year

- Direct (MedWatch) 15-day
- Periodic
- Nonserious periodic

Counts:
- 1995: 0
- 1996: 191,865
- 1997: 156,477
- 1999: 266,978
- 2000: 278,265
- 2001: 247,607
- 2002: 322,691
- 2003: 898,904
- 2004: 423,031
- 2005: 464,068
Cytochrome 450 Isoform Patient Profiling to Reduce ADR Risk

- slow adoption despite wide potential impact
- CYP2D6 profiling
  - relevant to 196 million prescriptions/yr (USA)
  - $13.7 billion Rx expenditures/yr (USA)
  - high fraction of heart disease and mental health Rx
  - drug interaction liabilities from polypharmacy in the aged
- limited data to evaluate ‘value’
- malpractice litigation as a catalyst for adoption?
Label Modification of Approved Drugs to Address Pharmacogenetic Risk of Adverse Reactions

- TMPT and 6MP and AZA (pharmacokinetics)
- UGT and irinotecan (pharmacokinetics)
- VKOR polymorphisms (pharmacodynamics) and CYP2C9 (pharmacokinetics) and warfarin therapy
Building An Integrated Framework for Molecular Medicine and Targeted Care

- biobanks
- biosignatures
- biomedical informatics
- outcomes analysis
- biomarker validation
- multiplex Dx
- POC testing
- disease monitoring Dx
- disease heterogeneity and Rx selection
- remote monitoring and compliance
- improved clinical trial design
- improved patient care
Biomarkers

- literature dominated by anecdotal studies
  - academic laboratories
  - small patient cohorts
  - limited 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
Linking Genotype and Phenotype

DNA Sequence

The Locus and its Alleles

DNA Sequence Variations

Proteomics and PTCM

Gene Expression Data

Clinical Phenotypes
GWAS
mapping the future of genetics
Genetic Variation in the Human Genome: The One Percent Difference

- genome assembly comparison as robust tool to ID all classes of genetic variation

  - MegaBLAST comparison of two human genome assemblies
  - Celera R27c compilation (C. Venter) and Build 35 reference sequence

- from 99.9% sequence similarity in unrelated humans to 99%: substantial unrecognized variation in the two assemblies
  - 30 million bp
  - 1.5 million SNPs
  - 24 million bp unmatched sequences
  - 3.5 million bp multi-copy sequences
  - 1 million bp inverted sequence
  - major CNV regions
Variation in Expression of 1097 Genes in 166 Individuals from European and Asian Ethnic

From: R. S. Spielman et al. (2007) Nature Genetics 39, 326
Rapid Dissection of the Genetic Risk of Age-Related Macular Degeneration: Achieving the Promise of the Genomic Era

Archives of Ophthalmology

A Prospective Study of 2 Major Age-Related Macular Degeneration Susceptibility Alleles and Interactions With Modifiable Risk Factors

Debra A. Schaumberg, ScD, OD, MPH; Susan E. Hankinson, ScD; Qun Guo, MSc; Eric Rimm, ScD; David J. Hunter, MBBS, ScD

Objectives: To delineate the magnitude of susceptibility to age-related macular degeneration (AMD) due to common variants in the gene for complement factor H (CFH) and the predicted gene LOC387715 and to determine whether these variants interact with modifiable risk factors.

Methods: We compared cases who developed AMD (n=457) with 1071 age- and sex-matched control subjects in a prospective nested case-control study within the Nurses' Health Study and the Health Professionals Follow-up Study. We determined the incidence rate ratios and 95% confidence intervals (CIs) for AMD for each genotype and examined the interactions with modifiable risk factors.

Results: Participants with 1 or 2 copies of the Y402H variant of CFH were, respectively, 1.98 (95% CI, 1.64-2.40) and 3.92 (95% CI, 2.69-5.76) times more likely to develop AMD, whereas the incident rate ratios (95% CIs) for 1 and 2 copies of LOC387715 A69S were 2.38 (1.92-2.96) and 5.66 (3.69-8.76), respectively. The fraction of AMD cases attributable to these 2 variants was 63% (95% CI, 58%-68%). Subjects homozygous for both risk alleles had a 50-fold increased risk of AMD (95% CI, 10.8-237), and cigarette smoking and obesity multiplied the risks associated with these variants.

Conclusion: Age-related macular degeneration has emerged as a paradigmatic example of a common disease caused by the interplay of genetic predisposition and exposure to modifiable risk factors.

Arch Ophthalmol. 2007;125:55-62
"Supposing is good, but finding out is better."

~Mark Twain
Predictive Gene Lists (PGLs) of Altered Gene Expression in Cancer as Diagnostic and Prognostic Tests

- wide variation in PGLs reported in different publications for claimed similar patients
  - minimal overlap between studies
- discriminatory power of classifiers not reproducible when tested on published cross-sets of samples
- unacceptable abrogation of systematic implementation of assay standards and data analysis
The Imperative for Rigorous Clinical Sampling Protocols in Biomarker Profiling and Validation of IVD Tests

- statistical powering
- rigorous case-control studies
  - retrospective
  - prospective (piggy back on clinical trials)
- prospectively defined endpoints
  - diagnostic marker(s)
  - Rx responsiveness and resistance markers
  - staging, stratification, progression markers
- regulatory validation of software algorithms for multiplex tests
Access to High Quality Biospecimens

- #1 obstacle to ID and validation of novel biomarkers
- inappropriate ‘turf’ battles over legacy specimens
  - public versus private funding
- unknown or variable quality of legacy biorepositories and limited linkage to clinical records
- lack of national-level biorepository standards and management principles
- lack of information on available specimens
- lack of mechanisms for systematic classification, coordination or distribution (priorities)
Setting Regulatory Standards for Multiplex IVDs

**FDA**

- MicroArray Quarterly Control (MAQC) Project
  - generation of RNA standards for transcriptomic assays

- Statement for Reporting Studies of Diagnostic Accuracy (STARD)

- FDA Data Template

- In Vitro Diagnostics Multivariate Index Assays (IVDMIAs)

**NIST**

- External RNA Controls Consortium (ERCC)
  - ‘spike’ panel of RNAs for transcriptomic assays
<table>
<thead>
<tr>
<th>PERSONALIZED MEDICINE</th>
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<td><strong>A Realistic Strategy for the Delivery of Rational Healthcare?</strong></td>
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<td><strong>An Erstwhile Intellectual Pursuit Doomed to be Dashed on the Rocks of Commercial Myopia and Clinical Philistinism?</strong></td>
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“Pharmacogenomics is unlikely to revolutionize or personalize medical practice in the immediate future”

Personalised medicines: hopes and realities
Pharmacogenomics and Pharmaceutical Markets

● market segmentation
  - unchanged R&D cost
  versus
  - significant R&D cost reduction

● payor acceptance and premium pricing
  - “guaranteed” Rx outcomes
  - extent of Rx cost reduction (direct cost)
  - reduction in AE/medical error (indirect cost)
  - improved patient compliance (indirect cost)

● patent protection
  - reduced competition in Dx market
  - Dx/PDx asset as leverage for Rx promotion
Barriers to Integration of Pharmacogenomics in Clinical Practice:
Secretary’s Advisory Committee on Genetics, Health and Society (SACGHS)*

- lack of evidence relevant to clinical practice (outcomes?)
- cultures of medical specialties
- lack of awareness of both providers and the public
- lack of coordination between regulators and industry
- lack of guidance on use in FDA Rx review process and labeling indications
- lack of coverage and reimbursement

* www.g2reports.com July 2006
Pricing barriers to Adoption of Molecular Diagnostics for Personalized Medicine: Oncology

- 1.4 million cancer diagnoses per year (USA)
- Lung, breast, prostate, and colon account for 55% of all cases
  - 155-234,000 cases for each malignancy
  - All other cancers = < 65,000 cases per year
  - Pediatric malignancies (0-15 years) = 9000 cases
  - Adoption/pricing for recovery of $100 million R&D costs
    - $100 test = 142,000 pts; $500 test = 28,000 pts
  - Cumulative cost of molecular Dx tests with other diagnostic modalities
Reimbursement for Diagnostic Tests

- inadequate US Medicare coding and payment mechanisms
  - fixed, 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
- screening tests not covered unless Congress authorizes
  - Congressional Acts to cover mammograms and prostate cancer screening
- engagement of third party payers who derive economic/clinical value from new Dx
  - Genomic Health Oncotype Dx
## Application of Dx-Rx Combinations Applications

### Dx for Approved Rx

- market expansion
- or
- market fragmentation
- value-dependent on regulator/payor responses

### Dx-Rx Co-development

- optimized Rx trial design
- restricted label but predictable Rx outcome
- market creation, penetration and payor receptivity

### Biomarker Profiling

- ID of novel Rx target(s)
- Dx test
  - Rx response (PD)
  - ADR risk (PK)

### Product Rescue/Protection

- toxicogenomics
  - eliminate future failure
- post-marketing risk management
- new targets/new indications
Applications of Dx-Rx Combinations

Dx for Approved Rx

Integrated Dx-Rx Co-Development

Biosignatures

Product Rescue
Evolution of Molecular Diagnostic Profiling to Support Rational Rx Utilization

Subtyping of Existing Diseases and Rx Selection

Pharmacogenetic Profiling for ADR Risk

Technology maturation (---), Clinical adoption (-----)

Dx tests

Availability of Subtype-Specific Rx

Adoption dynamics parallel new Rx introductions

Routine co-development of Dx-Rx combination

Years
Adoption of Molecular Diagnostic for Disease Classification and Pharmacogenetic ADR Risk Profiling

- position as integral element of treatment
  - personalized medicine/targeted therapy versus
  - ‘genetic testing’
"In 2010, if all goes the way we expect, it will be possible for all of us to find out what we are at (genetic) risk for."

Francis Collins,
Director, NHGRI
Bio-IT World April 2003
Ethical and Legal Issues Associated with the Evolution of Disease Predisposition Testing

- evidentiary standards for regulation of tests for probabilistic risk(s)
- data protection
- anti-discrimination legislative protections
- testing without counselling
- testing without availability of Rx
- procreative liberty
- abortion
- behavioral genetics
Projected Trajectory of Availability and Adoption of Disease Predisposition Diagnostic Tests for Multigenic, Late-Onset Diseases

Technology maturation (——–)
Clinical adoption (——–)

robust probabilistic risk profile tests
availability of PRx
viable non-Rx modifier options
no PRx available

5 10 15
Public Health at Risk: Failures in Oversight of Genetic Testing Laboratories
### Maintenance of Health and Wellness: A Critical Economic and Clinical Dimension to Healthcare Delivery

#### The Principle Intentions of Physick
Thomas Curteis (1704)

#### Key Needs

- earlier detection of disease (pre-symptomatic) or disease progression
- remote monitoring of “wellness”
- instant access to patient information
  - anytime, any place, any patient
- increased personal responsibilities for wellness and disease management
Smart Pills and Smart Containers: Improving Patient Compliance

- high definition logos and bar codes
- electronic ID
- covert chemical taggants
- pearlescent coatings
- RFID tags
Information-Based Medicine

HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
Pervasive Inefficiencies and Errors in Healthcare Created by Empirical Care and Lack of Robust Outcomes Data
Translating Evidence into Clinical Practice

- protracted adoption curve
  - 10 to 25 years
  - insidious legacy of practitioner’s ‘era’ of medical education
  - disproportionate role of unvalidated views of medical ‘opinion-leaders’
- consensus guidelines widely ignored
  - clinical medicine as ‘art’
- patients have only 50:50 chance of receiving appropriate care
- 5-10% probability of preventable and or predictable adverse event/error
- skepticism of healthcare professionals, providers and payors due to shortcomings of historical outcomes analyses
Barriers to the Evolution of Personalized Medicine

**Cultural**
- conservatism of medical profession
- uncertain clinical utility
- activism and portrayal of discrimination risks

**Public Policy**
- lack of integrated approach for improved disease detection, diagnosis and classification and patient risk profiling
- role of drug regulators
  - facilitate innovation (carrot)
  - strengthen regulation (stick)
- drivers of the evidence base
  - NIH, CDC, CMS
  - payors
The Evolution of Large-Scale Biology, Molecular Medicine and Information-Based Personalized Medicine

- Genome sequencing
- Comparative genomics
- Proteomics
- Functional genomics
- Structural genomics
- Genetic circuits
- Biological order
- Complex systems
- SNPs, haplotypes, CNVs
- And global gene-disease association studies
- Large-scale population
- And statistical genetics
- Robust geno-phenotype
- Correlations
- Individual genotyping
- And disease risk profiling

INFORMATICS
Thinking Ahead

- R&D databases
  - scale
  - standards
  - architecture
- advanced computing
  - inter-operability
  - hyperlinking
  - network infrastructure

- platform design
- platform applications

- patient profiles and clinical care
  - privacy
  - confidentiality
  - security
- healthcare delivery network
  - scale
  - access
  - operational efficiency

Thinking Ahead
Legal pressures and incentives for personalized medicine

Gary E Marchant1,
Robert J Milligan &
Brian Wilhelmi

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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.
### Assembly of Data on CYP2D6 Metabolism for Commonly Prescribed Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prescribing Information (MD Consult)**</th>
<th>PharmGKB (academic research website)**</th>
<th>Literature review**</th>
<th>Drug response</th>
<th>Prescribing Information (MD Consult)**</th>
<th>PharmGKB (academic research website)**</th>
<th>P450 Drug Interaction (academic website)**</th>
<th>Clinical outcomes</th>
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*Y: yes; ---: no data given.

Ethical and Legal Issues in Personalized Medicine

Clinical Practices

- introduction of Dx, PGx, PDx without adequate validation
  - IVDMIAs
- testing without consent
- withholding Rx from patients who refuse Dx test
- harm created by lack of professional/payor knowledge
  - suboptimal Rx, ADRs
- malpractice liabilities
  - physicians, pharmacists, insurers and third party payors
- duty to disclose risk to biologically-related individuals
- psychosocial harm conveyed by PGx, PDx
- discriminatory data abuses by third parties
Emerging Perspectives and Guidelines and Anticipated Shift in Standard-of-Care Provision for Malpractice

- National Academy of Clinical Biochemistry

- FDA
  http://www.fda.gov/cder/genomics

- Evaluation of Genomic Applications in Practice and Prevention
  http://www.cdc.gov/genomics/gtesting/EGAPP/group.htm

- Secretary’s Advisory Committee on Genetics, Health and Society (SACGHS)
  http://www.od.nih.gov/oba/SACGHS
The Analysis and Comprehension of Biological Systems

descriptive ignorance

complexity

defined rule sets

initial mechanistic insights

burgeoning, bewildering complexity

• elucidation of patterns
• defining rule sets

• elegant simplicity revealed
• predictive biology

• disease heterogeneity
• patient heterogeneity
• disease predisposition

• right Rx : right disease
• right Rx : right patient
• from reactive treatment to proactive prevention
Drivers for the Increased Use of Molecular Diagnostics for Accurate Diagnosis and Improved Rx Selection

**Efficacy/Cost/Value**
- significant Rx non-responsiveness for highly prescribed drugs
- escalating Rx cost
  - volume
  - next-generation targeted therapies (oncology)
- scientific and regulatory trends

**Safety**
- societal, political and regulatory focus (zero-risk)
- preclinical toxicogenomics
- retrofitting ADR risks to drug labels
- post-approval pharmacovigilance
- patient compliance

**Policy**
- economic implications of wasteful, empirical Rx
- crucial future role of CMS
- media and public expectations
Personalized Medicine: Obstacles to Implementation

- expedient convenience of sustained status quo versus radical redesign of clinical practice standards and healthcare delivery patterns
- demonstration of ‘value’
  - value versus cost
  - clinical benefits, healthcare costs, societal gains
- literacy
  - lack of familiarity in professionals, payors and patients/consumers
- incentives
Key Issues in the Evolution of Molecular Medicine and Personalized Medicine

- enhance understanding of the role of Dx, PGx and biomarkers in patient care and outcomes
  - trial design, regulation, education
- establish proactive approaches for evaluation of clinical, economic and non-economic benefits
- establish transparent, streamlined regulatory policies
- anachronistic cost-based reimbursement for Dx sector with value-based pricing
- promote Dx/PGx-Rx co-development models by Rx industry
PERSONALIZED MEDICINE & MOLECULAR DIAGNOSTICS

DATE:  Friday, March 2, 2007
   8:30 a.m. - 5:30 p.m.

AT:    SANDRA D'CONNOR
       COLLEGE OF LAW
       ARIZONA STATE UNIVERSITY

This prescription is personalized.