The Critical Path Initiative Meets Genomics

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Philadelphia Phillies Are In 1st Place

If Citizens Bank Park were filled to capacity with fans who were going on warfarin for atrial fibrillation, 3200 of them would have a major bleeding event within 1 year. 250 would die!

Can this be prevented? Which fan is at risk?

With Choices, Comes Decisions

Physicians have basically two decisions to make when treating patients:
1. Selecting the right drug
2. Choosing the right dose

The Problem: Interpreting Inter-Individual Variability in Outcomes

“If it were not for the great variability among individuals, medicine might have well been a science and not an art”
Sir William Osler (1849 – 1919)
The Father of Modern Medicine

“One important characteristic of biology is its diversity, its variation. It’s why personalized medicine is so important”
Dr. Andy Kessler
NY Times Best Selling Author

The Challenge of Individualizing Drug Therapy: Trial and Error Medicine

Observation -> Variable Response -> Action
All patients with same diagnosis

- Non-Responders with Unacceptable Toxicity (20%)
- Non-Responders (50%)
- Responders to Average Dose of Usual Therapy (30%)

Alternative Therapies

Rational Prescribing

“Fortunately a surgeon who uses the wrong side of the scalpel cuts his or her own fingers and not the patients……

……if the same applied to drugs they would have been investigated very carefully a long time ago”
Rudolph Buchheim (1820-1879)
Founder of Translational Science

Beitrage zur Arzneimittelkunde, 1849
Clinical Problem: Can We Do Better?

Co-existing diseases
Concomitant therapies
Lifestyle issues
Financial constraints

With choices, comes decisions
With decisions, comes commitment

Fact: We Don’t Know Enough About How Drugs Work

Interpreting Variability Includes a Wide Spectrum of Sources

Fact: We Don’t Know Enough About The Risks of Drug Toxicity

Number of New Drugs Is Not Keeping Pace With Spending: High Attrition Rate

Average Response in Clinical Trials vs. Individual or Individual Group Outcomes

“…..if a clinical trial doesn’t work, they just throw the drug away, when in fact the average of the trial data may hide stuff that did work…..there’s something that makes patients different”

“A good drug wrongfully convicted means the loss of benefits goes on forever”
**Will The Human Genome and Genomics Change Your Life?**

**Government Thinks It Can and Should Lead the Way: Initiatives Including Genomics**

- Personalized Health Care Initiative of HHS Secretary Michael Leavitt (2007)
  - [http://www.hhs.gov/myhealthcare/](http://www.hhs.gov/myhealthcare/)

- Critical Path Initiative of FDA Acting Director of CDER Janet Woodcock (2005)
  - [http://www.hhs.gov/myhealthcare/](http://www.hhs.gov/myhealthcare/)

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**Role of FDA in Supporting Genomics**

**Definitions and Concepts: Personalized Medicine**

**Personalized medicine (PM)** is the science of individualizing medical intervention based on certain diagnostic tests:

1. Total patient populations are "stratified" into subgroups based on similar test results
2. Subgroups of patients follow different treatment strategies with "probabilities" for outcomes
3. Major goal is make clinical outcomes in individuals and individual subgroups more predictable and optimal

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**Personalized Medicine Doesn’t Have to Be Genomics**

**Other Definitions and Concepts**

- **Pharmacogenomics (PGx):** science of using inherited variations in genes that influence drug exposure (PK) and drug action (PD)
- **Genomic biomarkers:** measurable DNA or RNA characteristics in human, tumor or virus samples that are indicators of:
  - normal biologic processes
  - pathogenic processes
  - response to drugs

Source: Adapted from ICH E15 Guideline on Definitions and Coding, January 2008
Diagnostic tests are the linchpin of personalized medicine.

**Genomic Biomarker Are the Basis for Diagnostic Tests**

**Collection of the DNA Biospecimen Is Key to Understanding Variability**

**BIOLOGY OF DISEASE**
Changes in biology caused by gene mutations and environment

**GENETICS OF PATIENT**
Changes in systemic drug exposure and response of drug target

**INDIVIDUALIZED TREATMENT PLAN**

**New Paradigm of Medicine: Personalized Medicine**

**Linking Diagnostic Tests to Drug Choice and Dose Selection**

Breaking The Cycle of Trial and Error Medicine

**DNA-Based Biomarkers Are Ready: PhRMA Industry Survey**

- DNA collection
  - 80-90% of companies in phase I studies; PK, DD etc as a study requirement
  - 40-50% of companies in phase II – phase III studies; POC, D/R and pivotal RCT as an optional activity
- 70% of companies use ADME genotype as inclusion or exclusion analysis

**How Will PGx and Diagnostic Tests Enable Personalized Medicine?**

**Drugs Where Genome-Based Diagnostic Tests Have Been Recommended**

<table>
<thead>
<tr>
<th>EFFICACY</th>
<th>SAFETY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Test</strong></td>
</tr>
<tr>
<td>Hercepin</td>
<td>HER2</td>
</tr>
<tr>
<td>Gleevec</td>
<td>BCR-ABL</td>
</tr>
<tr>
<td>Rituxan</td>
<td>CD20</td>
</tr>
<tr>
<td>Donepezil</td>
<td>ApoE4</td>
</tr>
<tr>
<td>Eribux</td>
<td>EGFR</td>
</tr>
<tr>
<td>Saliuran</td>
<td>Trisom</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Test</strong></td>
</tr>
<tr>
<td>6-MP</td>
<td>TPMT</td>
</tr>
<tr>
<td>Compoasor</td>
<td>UGT1A1</td>
</tr>
<tr>
<td>Wartolec</td>
<td>SCS, VKORC1</td>
</tr>
<tr>
<td>Ziagen</td>
<td>HLA-B5701</td>
</tr>
<tr>
<td>Zelnico</td>
<td>HLA-B1502</td>
</tr>
<tr>
<td>CBE</td>
<td>2D6</td>
</tr>
</tbody>
</table>

Success Example # 1

Efficacy – Responsive Patient Subset

Example of HIV-AIDS: Provides an Alluring Target for PGx and PM – Why?

- HIV-AIDS has many disease subtypes
- Rapid disease progression and high mortality
- Drugs that target cellular disease pathways
- Many viral biomarkers and gene mutations
- Relatively low efficacy rate over time
- Potentially frequent and serious adverse events
- Patient stratification using resistance testing
- Physician familiarity with diagnostic tests

Examples: PhenoSense GT assay for complete picture of viral resistance and susceptibility to guide drug selection; HIV viral load (viral RNA) in blood to monitor response

Selzentry® (Maraviroc): Drug-Test Combination Approved in August 2007

- Selzentry® antagonizes CCR5 co-receptor and not effective in dual or mixed CXCR4 HIV-1
- Trofile® test stratifies HIV strains based on which receptor virus uses to enter CD4-positive T cells
- RCT could not have been conducted in patients without first identifying CCR5-tropic patients
- Selzentry® reduces viral load and increases CD4-positive T cell counts by blocking CCR5-tropic virus
- Approval based on 24 week data from phase IIB-III clinical trial in treatment-experienced HIV patients

Selzentry® (Maraviroc) Label and Success Factors

- Selzentry® label requires use of tropism assay before prescribing to identify likely responders
- Tropism assay also identifies non-responders and lack of response was confirmed
- Generally well-tolerated although label has warning of hepatotoxicity

Guiding Principles
- Knowledge of disease pathology and drug target
- Ability to identify disease subsets to increase efficacy signal
- Validation of test clinical utility during pivotal drug efficacy trials

Success Example # 2

Dosing – Optimizing Benefit/Risk Ratio

Warfarin As An Anticoagulant: Taking the Guesswork Out of Dosing

- Risks of warfarin over-anticoagulation not in doubt: one of top 3 drugs for ER visits and AE reports
- Bleeding is serious, sometimes fatal, and results in poor long-term compliance
- INR used as biomarkers to monitor rate and extent of anticoagulation; target range of 2-3
- Greatest risk occurs in initial dosing phase of 4-6 weeks until INR and dosing stabilizes
- Problem is NTI and large inter-individual variability in maintenance doses due to PK and PD differences
Warfarin Genetic Variants That Influence Dosing – Especially Induction Doses

Genetic (55%) and Clinical Factors (25%) Determine Induction Dose of Warfarin

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variable</th>
<th>Effect on Dose</th>
<th>R²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VKOR-1639/3673</td>
<td>-28%</td>
<td>0.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>BSA, per 0.25 m²</td>
<td>-11%</td>
<td>0.34</td>
<td>&lt;0.0001</td>
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<tr>
<td>3</td>
<td>CYP2C9*3</td>
<td>-33%</td>
<td>0.40</td>
<td>&lt;0.0001</td>
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<tr>
<td>4</td>
<td>Age, per decade</td>
<td>-5</td>
<td>0.45</td>
<td>&lt;0.0001</td>
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<tr>
<td>5</td>
<td>CYP2C9*2</td>
<td>-19%</td>
<td>0.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6</td>
<td>Target INR</td>
<td>-11%</td>
<td>0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>7</td>
<td>Amiodarone</td>
<td>-22%</td>
<td>0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>8</td>
<td>Smokes</td>
<td>10%</td>
<td>0.52</td>
<td>0.0022</td>
</tr>
<tr>
<td>9</td>
<td>AA race</td>
<td>-9%</td>
<td>0.53</td>
<td>0.0023</td>
</tr>
<tr>
<td>10</td>
<td>Prior DVT or PE</td>
<td>7%</td>
<td>0.55</td>
<td>0.0135</td>
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INR After 3rd Dose 80%

New Warfarin Label Containing Recommendation for Genetic Testing

Adoption of Warfarin Gene Tests: It’s Not Only About the Science

- Scientific issues
  - Debate over evidence; surrogate (INR) vs clinical endpoints (bleeding) and absence of RCT
  - No specific genetically-based dosing recommendation in revised warfarin label
  - Lack of agreement on 2C9, VKORC1 and other genes that addresses needs of all ethnic or racial groups

- Other issues
  - Perception that INR-stabilized patients don’t need test
  - Assumption that current INR monitoring system works
  - Concern that PGx tests will not eliminate need for INR
  - Cost of gene tests ($500) not paid by insurance
  - Surveys show < 10% of physicians have heard of tests

Factors Influence the Timeline for Personalized Medicine

Opportunity

Fear And Acceptance

Value

- Reduce market share
- Added costs with no return
- Inhibit practice of medicine
- Denied insurance or jobs
- Poor reimbursement of tests
- Healthcare provider education
- Clear and favorable regulation
- Standards for clinical utility
- Appropriate reimbursement
- Value and impact on outcomes

What Will Accelerate the Personalized Medicine Timeline?

1. Focus on real problems in drug development and clinical practice; find effective solutions
2. Translation of GWAS and SNP analysis to clinical utility; understand disease biology
3. Weight and strength of evidence that documents usefulness of PGx: clinical utility
4. Cost structure for reimbursement of genetic testing; support sustainable business model
5. Changes in medical infrastructure to accelerate adoption; physician education, electronic records
If Citizens Bank Park were filled to capacity with fans who were going on warfarin for atrial fibrillation, 320 of them would have a major bleeding event within 1 year. 25 would die!

Can this be prevented? Which fan is at risk?

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<th>Take Home Message</th>
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<td>PM and PGx are not “hype” but are here now. Simply the next step in applying science to understanding disease biology and drug response. Driving forces are: - technology not available 10 years ago - advances in bioinformatics and EPR - decreased productivity in drug development, - consumer interest in genomics and health care - societal expectations for safe and effective drugs</td>
</tr>
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