A perspective on pharmacogenetics and dealing with emergent data to develop stratified medicines

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Agenda

- Scenarios
- Examples
- Evolving field to deliver personalized medicines
Development of personalized medicines during drug development optimal situation

- Drug target expressed in a sub-population or histology,
- Test directly inked to MOA/target
- Clinical development strategy requires patient stratification to demonstrate efficacy
- Rationale for parallel development of drug and test is obvious
  - Use of approved drug is linked to Dx - Physician use drug and test from start

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
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Development of personalized medicines during drug development

Emergent data: Clinical studies, External

- Emergent data may come from Phase 3 studies or studies external to Sponsor post approval
- More challenging to adopt use of genetic information
  - Strength of association and validation in independent study
  - Phenotypes: Disease being treated, safety, or efficacy
  - Utility of potential genetic marker
  - Time from approval
  - Education how scientific data is communicated and used by Stakeholders (Labels, guidelines, etc)
Post approval - GWAS Identified Response Markers: Interferon-Alfa and IL-28b

- HCV infection and response to interferon-alpha
  - IL-28b C/C allele is associated with a higher percentage of sustained virological response

- Post approval - discovery on clinical data sets and validated by other studies
- Data included in label for Interferon therapies

Warfarin is the most widely prescribed anticoagulant

Inaccurate dosing can result in major clinical consequences

Clinicians estimate the starting therapeutic dose in patients

Estimates are based on clinical factors and where available genotypes:
  - CYP2C9
  - VKORC1

Use of PGx algorithm provided the greatest benefit to those requiring weekly doses of warfarin <21mg or >49 mg


Clopidogrel – CYP2C19, ABCB1

In 2009, 3 studies demonstrated a significant association between variants of CYP2C19, the use of the anti-platelet agent Clopidogrel and outcomes in the treatment of cardiovascular diseases.

CYP2C19*2 variant accounts for 12 percent of the platelet response to the drug.

~30% of the general population in the United States have the CYP2C19*2 variant

Individuals with this variant appear to less efficiently convert clopidogrel into its active form.
Platelet aggregation response to clopidogrel was highly heritable ($h^2=0.73$; $P<.001$).

13 SNPs on chromosome 10q24 within the CYP2C19 locus were significantly associated ($P=1.5E−13$ for rs12777823, additive model) with diminished clopidogrel response. No detected signal around ABCB1 or PON1 in this Amish population.

CYP2C19*2 accounted for 12% of the variation in platelet aggregation to ADP ($P=4.3E−11$).

Replication was achieved in clopidogrel-treated patients undergoing coronary intervention ($P=.02$)
To compare prasugrel, a new thienopyridine, with clopidogrel, we randomly assigned 13,608 patients.

The primary efficacy end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The key safety end point was major bleeding. N Engl J Med 2007;357:2001-15.
TRITON TIMI Study Genetic Association Data to Clopidogrel Treated Patients

- PD - platelet inhibition in
- PK - active drug metabolite
- Primary endpoint Cardiovascular outcomes

Prasugrel Label excerpts:

“both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties.....”

“pharmacokinetics of prasugrel’s active metabolite are not known to be affected by genetic variations......”

“pharmacokinetics of clopidogrel’s active metabolite are affected by CYP2C19 genotype”

“metabolizer status and use of proton pump inhibitors may diminish clopidogrel’s activity in a fraction of the population, and may have contributed to prasugrel’s greater treatment effect and greater bleeding rate in TRITON-TIMI 38.”
Clopidogrel Black Box Label

**WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS**

- See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)

- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)

- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)

- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)
Now what to do?

“Many doctors are scrambling to figure out which heart patients should continue to take the top-selling drug Plavix after the Food and Drug Administration warned recently that the blood thinner may not work for everyone.”

"There is more than enough data now to guide an individual patient" on Plavix use, says Eric Topol, chief academic officer at Scripps and a proponent of genetic medicine. "This is how our patients should be cared for today." Dr. Topol is leading a study to test the safety and effectiveness of doubling the dosage of Plavix.

At Duke University Medical Center, patients can get the genetic test if they ask for it, but "we've not adopted a strategy of testing people," says Sunil Rao, a Duke cardiologist and director of the catheterization lab at Veterans Affairs Medical Center, Durham, N.C. "The clinical community doesn't have enough information about what to do about genetic tests," he says.

Doctors say insurance plans often don't cover the cost of a genetic test for Plavix patients. (Quest, whose test sells for $415, says it offers assistance to patients whose insurers don’t cover the test.)

“We Are Staring at a black box warning” Brigam And Womens Dr Cannon says, “Are we obligated to test everyone to make sure they are not a poor metabolizer” He adds “There are lots of issues, none of which have any answers.”

Quotes from Ron Winslow  article Wall st Journal March 2010
Problem Statement: Personalized Medicine

- Pharmaceutical Industry is under pressure from multiple stakeholders to produce medicines with an improved benefit: risk profile
  - Patients, Practitioners, Payers, Regulators
  - Personalized medicine offers one approach to improving benefit:risk

<table>
<thead>
<tr>
<th>Whole Population</th>
<th>Targeted Medicine</th>
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</thead>
<tbody>
<tr>
<td>100% Population</td>
<td>30% Responders 300,000</td>
</tr>
<tr>
<td>1,000,000</td>
<td>10% Sub-responder Type A 100,000</td>
</tr>
<tr>
<td></td>
<td>15% Sub-responder Type B 150,000</td>
</tr>
<tr>
<td></td>
<td>25% Sub-responder Type A&amp;B 250,000</td>
</tr>
<tr>
<td></td>
<td>20% Non-responders 200,000</td>
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Why Develop Drugs for Subpopulations?

<table>
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<tr>
<th>Opportunities</th>
<th>Concerns/Barriers</th>
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<tbody>
<tr>
<td>● Identify those patients with greatest unmet medical need</td>
<td>● Substantial investment in disease understanding and biomarkers</td>
</tr>
<tr>
<td>● Improve success in development by better target selection and enriched trial design</td>
<td>● More complex patient screening algorithms lengthen study cycle times and increase costs</td>
</tr>
<tr>
<td>● Optimize product benefit to risk ratio by:</td>
<td>● Clinical validation of tests will require co-development partner and more complex regulatory program</td>
</tr>
<tr>
<td>- Identifying responders and those at risk of adverse experiences</td>
<td>● Concerns over limiting market size</td>
</tr>
<tr>
<td>● Improve compliance</td>
<td>● Expensive tests will limit access to new medicines</td>
</tr>
<tr>
<td>● Improve cost effectiveness</td>
<td>● Critical to choose the right opportunities for investment</td>
</tr>
<tr>
<td>● Differentiate from competitors</td>
<td></td>
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</table>
Opportunity: Enablers and Drivers

- Genomic Technology
- Health Information Technology
- Regulation
- Providers/Payors
- Personalized Medcos
- Pharmas
Genomic technologies are robust, multiple platforms and vendors are available
- Speed to generate data rapidly improving (Ion torrent, Pac Bio etc)
- Post production analysis is additional cost and time consuming

Sequencing is being rapidly adopted, based on falling cost and an understanding that rare variants may play an important role in complex diseases and drug response
PGt Data are Already Impacting an Increasing Number of Drug Labels

<table>
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<tr>
<th>Drug</th>
<th>Label</th>
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<tr>
<td>Erbitux, Vectibix</td>
<td>Yes</td>
<td>K-Ras mutations</td>
<td>Colon cancer: identify non responders</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chemotherapies</td>
<td>Yes</td>
<td>Expression profile</td>
<td>Recurrence risk: value of chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Ziagen</td>
<td>Yes</td>
<td>HLAB5701</td>
<td>HIV/AIDS: severe allergic responses</td>
<td></td>
</tr>
<tr>
<td>Camptosar</td>
<td>?</td>
<td>UGT1A1</td>
<td>Colon cancer: risk of diarrhea, neutropenia</td>
<td></td>
</tr>
<tr>
<td>PEGInt Alpha – 2b</td>
<td>Yes</td>
<td>IL28</td>
<td>Hepatitis C ID responders</td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Yes</td>
<td>CCR5 tropic HIV-1</td>
<td>HIV Therapy responders</td>
<td></td>
</tr>
<tr>
<td>Tegretol</td>
<td>yes</td>
<td>HLAB1502</td>
<td>Epilepsy: severe allergic responses,</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Yes/?</td>
<td>CYP2C9/VKORC1</td>
<td>Antithrombotic: establish target dose level</td>
<td></td>
</tr>
<tr>
<td>Celebrex</td>
<td>?</td>
<td>CYP2C9</td>
<td>Analgesic: target dose level</td>
<td></td>
</tr>
<tr>
<td>Plavix</td>
<td>Yes/?</td>
<td>CYP2C19</td>
<td>Antithrombotic: identify non responders</td>
<td></td>
</tr>
<tr>
<td>Iressa</td>
<td>Yes</td>
<td>EGFR mutations</td>
<td>Lung cancer: identify responders</td>
<td></td>
</tr>
<tr>
<td>Isentress</td>
<td>No</td>
<td>UGT1A1</td>
<td>No clinically meaningful alteration on PK</td>
<td></td>
</tr>
<tr>
<td>Prozac</td>
<td>?</td>
<td>CYP2D6</td>
<td>Depression: optimize risk:benefit</td>
<td></td>
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</table>

See also:  www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
Networks information technology will enable PGt studies to be performed rapidly

- **Examples**
  - Geisinger
  - Kaiser
  - Vanderbilt

- **Current**
  - Larger networks being established (EMERGE)
  - Validate PGt data findings
  - Discovered new markers for response

- **Consequence**
  - Rapid generation of PGt data sets outside randomized clinical trials with large numbers of patients
  - Decision making algorithms for patient care based on individuals genetics
iSAEC Focused on discovering genetic markers for Safety

International DILI Consortium (iDILIC)

Key IDILIC Objectives:
1. To identify additional genetic factors determining susceptibility to DILI relative to specific causative agents
2. To investigate the possibility of the existence of common risk alleles associated with DILI, caused by different drugs
3. To investigate the role of ethnic variability in the genetics of DILI, associated with specific, high volume drugs
4. Enroll 400+ cases by ye 2012
Providers Use PGt to ensure Novel Branded Medicines Demonstrate Value

- Medco’s Personalized Medicine Division
  - Genetics for Generics™
  - Generic Defense Maximize generic (or soon to be generic) market in the face of market erosion due to imminent new drug approval
  - Genomic Blockbuster Exploit genomics to determine generic drug utilization to improve overall efficacy within an indication to “better than class”
  - Comparative effectiveness trials MEDIC value of different mechanisms to treat Diabetes DEBAIT Tamoxifen vs AI’s

- Impact
  - Branded compounds will need to demonstrate significant value to patients

- Pharma needs to be at the table
  - Strategic partnering provides opportunities for CE research and defining unmet medical need
### Perspective: Impact of PGt is becoming more important to deliver effective therapies to patients

<table>
<thead>
<tr>
<th>Driver</th>
<th>2-5 Year Perspective</th>
<th>5-10 Year Perspective</th>
</tr>
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<tbody>
<tr>
<td>Genomic Technology</td>
<td>Sequencing is technology of choice - $1000 genome. Identification of rare DNA variants and epigenetic variation</td>
<td>Rare variants are catalogued and used as PGx markers. Some patients have whole genome sequenced</td>
</tr>
<tr>
<td>Health IT</td>
<td>EMRs implemented in major healthcare systems. Informatics solutions for data extraction in place. Academics identifying PGt.</td>
<td>EMRs and data extraction combined with genomic data to identify markers of response and adverse experiences</td>
</tr>
<tr>
<td>Regulation</td>
<td>Increasing number of PGt markers in drug labels with recommendations for testing' Data requirement on known ADME variants Sentinel network active by 2012?</td>
<td>Universal DNA collection and testing for critical variants in trials. Multiple IVDs approved and in use. Sentinel network includes genomic data</td>
</tr>
<tr>
<td>Providers Payors</td>
<td>Adoption of ‘NICE’ approach in multiple countries drives more scrutiny of value. Physician and patient education remains a major barrier to personalized medicine Restricted Formularies</td>
<td>Comparative effectiveness trials to confirm or refute ‘value’ of medicines Reimbursement of IVDs that support value proposition. Shift in medical practice Further formulary restrictions using genetics</td>
</tr>
<tr>
<td>PMC</td>
<td>Will form alliances with providers and employers to provide tools for understanding genetic information.</td>
<td>If PMC business models succeeds could be at the heart of personalized medicine by providing tools and genetic data.</td>
</tr>
<tr>
<td>Pharma</td>
<td>Multiple oncology approvals with IVDs Genotyping and sequencing in regular use for exploratory PGt.</td>
<td>PGt hypotheses regularly incorporated into clinical trials for non-oncology indications. Data submitted as part of filing (non voluntary)</td>
</tr>
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Take Home Messages

- Personalized medicine approaches have arrived and are impacting other non oncology therapeutic areas

- Other stakeholders will have tools to perform PGt approaches rapidly on approved drugs – Pharma need to understand any scientific data or evidence that point to a good clinical/commercial strategy for developing a segmentation strategy prior to approval

- Integration and critical thinking across different functions and divisions will be required to be successful at developing personalized medicines

- Future for generating robust PGt data, rapidly, is advancing rapidly
Acknowledgements

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