Pharmacogenomics of Anti-platelet Intervention - 2 (PAPI-2) Study

Alan R. Shuldiner, M.D.
Associate Dean for Personalized Medicine
University of Maryland School of Medicine

Disclosures:
Consultant: Bristol Myer-Squibb/Sanofi-Aventis; USDS
Research funding: NIH (PGRN; U01HL105198)
SOM/UMMS Program in Personalized Medicine

**Evidence-based Medicine**

**Translation**

**Discovery**

**Clinical Research**

**Basic Research**

**PPM Translational Initiatives:**
- Expand clinical services
- Translation demonstration projects
  - Egs., CYP2C19/clopidogrel (TPP, PAPI-2), cancer, ID, transplant, diabetes
- Preemptive genotyping in EMR
  - (Biobank/Bioinformatics)
- Advance institutional culture
- Marketing/Branding of UMMS as *The PM Institution*
- Philanthropy

**PPM Discovery Initiatives:**
- CLIA-approved Translational Genomics Lab
- Biobanks: BiobankUMD
- Amish Wellness Program
- VA Million Veterans Project
- Faculty Recruitment
- Create synergies (IGS, other UM Schools, FDA)
- Leverage institutional support to garner new funding (grants/contracts/philanthropy)

**PPM Education Initiatives:**
- Medical students
- Graduate School (MD/PhD)
- CME
- Seminars/Symposia
- Web-based programs
- EMR-assisted learning
Highly consistent results for PCI patients in > 20 (retrospective) studies…

CYP2C19*2 associated with:
- Active metabolite levels (PK)
- Ex vivo platelet aggregation (PD)
- CV events (outcomes)
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)

http://www.plavix.com/plavix-videos.aspx
Why aren’t cardiologists performing genetic testing?

- Lack of prospective randomized clinical trials
  - Does pgx improve outcomes?
  - What is the optimal clinical algorithm for its application?
  - Is it cost effective?
  - Who will pay for a RCT?
- Health care provider education (and expectations)
- Logistics of genetic testing
  - Turnaround time, Point-of-care, CLIA, etc.
- Reimbursement
- Ethical and legal considerations
  - FDA
- Despite above: Patients ‘get it’ and want it!
Pharmacogenomics Research Network
National Institutes of Health
U.S. Department of Health & Human Services

PAPI-1 (U01 GM074518; 09/23/05-04/09/10)
PAPI-2 (U01HL105198; 04/10/10 – 03/31/15)

Research Groups
Collaborating Sites
Network Resources
Editorial
A Step toward Personalized Asthma Treatment
Jeffrey M. Drazen, M.D.

…the next step must be to mount clinical trials in which patients are stratified according to their biologic signature to determine whether knowledge of this information leads to better clinical outcomes. If personalized medicine is going to become a reality, we need to design and execute these critical trials.
PAPI-2 Study

Consent all potential PCI patients

Cath Lab → Stent placed → Eligibility confirmed

Randomize

Genotype Directed Arm (n = 3600)

Genotype patient

IMs
- 1/2, 1/3, 2/17, 3/17

PMs
- 2/2, 2/3, 3/3

EMs, UMs
- 1/1, 1/17, 17/17

Standard of Care Arm (n = 3600)

Dual anti-platelet therapy agent selected by prescribing physician

Optional platelet aggregation 10 days after Randomization Visit

Prasugrel 5-10 mg/d plus asa

Clopidogrel 75 mg/d plus asa

Monitor for CV outcomes and AEs at 3, 6, 9 and 12 months

1° CV events

2° Adverse events/bleeding
Post treatment platelet aggregation
Pharmacoeconomic analysis

Retrospectively genotype after follow up is complete

GWAS and exome sequencing - new gene discovery
Outcomes

• Primary Endpoint
  – Composite CV events in IM/PMs from each arm (Non-fatal MI, stroke, stent thrombosis, death due to any CV cause)

• Secondary Endpoints
  – Composite CV Events from each arm, inclusive of EMs (Non-fatal MI, stroke, stent thrombosis, death due to any CV cause)
  – Any component of the composite of all-cause death, MI, and repeat revascularization
  – Bleeding events (BARC definition)
  – Post-treatment platelet aggregation
  – Adverse events
  – Pharmacoeconomic analysis
Verigene® CYP2C19 Validation

### Table 1. Call Rate Summary

<table>
<thead>
<tr>
<th></th>
<th>Initial Testing</th>
<th>Final Testing after retesting No Calls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples Tested</td>
<td>100</td>
<td>107</td>
</tr>
<tr>
<td>Calls Made</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>No Calls</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Call Rate%</td>
<td>94%</td>
<td>99%</td>
</tr>
<tr>
<td>Accuracy*</td>
<td>100%</td>
<td>-</td>
</tr>
</tbody>
</table>

*Based on DNA Sequence Confirmation

### Table 2. Genotype Counts:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>36</td>
</tr>
<tr>
<td>*2 Homozygous</td>
<td>8</td>
</tr>
<tr>
<td>*2 Heterozygous</td>
<td>28</td>
</tr>
<tr>
<td>*3 Homozygous</td>
<td>0</td>
</tr>
<tr>
<td>*3 Heterozygous</td>
<td>3</td>
</tr>
<tr>
<td>*17 Homozygous</td>
<td>2</td>
</tr>
<tr>
<td>*17 Heterozygous</td>
<td>17</td>
</tr>
<tr>
<td>*2/*3</td>
<td>2</td>
</tr>
<tr>
<td>*2/*17</td>
<td>2</td>
</tr>
<tr>
<td>*3/*17</td>
<td>1</td>
</tr>
<tr>
<td>No Call</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total Valid</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
Statistical Considerations

Primary analysis: Between IMs/PMs randomized to the SOC versus genotype-directed arms:

• 1-yr cardiovascular event rates (non-fatal MI or stroke, definite/probable stent thrombosis, death 2° to any CV cause)

• With 1,000 IM/PM completers from each arm
  – 80% power at p = 0.05 to detect difference between SOC and genotype-directed arm of 7% and 4.1% in, respectively (RR 0.6)
PAPI-2 Progress Report

- IRB Approved at UMD
  - Approval at other centers in progress
- FDA exempt
- DSMB convened
  - Approval to initiate recruitment immanent
- Recruitment to begin at UMD Feb 2012
- Other sites to phase in soon thereafter
- Seeking new sites in late Spring 2012
CENTERS FOR MEDICARE & MEDICAID SERVICES
CLINICAL LABORATORY IMPROVEMENT AMENDMENTS

CERTIFICATE OF REGISTRATION

LABORATORY NAME AND ADDRESS
UNIV OF MD SCH OF MED TRANSLATIONAL GE
660 WEST REDWOOD ST HOWARD HALL RM 560-564
BALTIMORE, MD 21201

CLIA ID NUMBER
21D2027356

EFFECTIVE DATE
07/22/2011

LABORATORY DIRECTOR
RICHARD ZHAO

EXPIRATION DATE
07/21/2013

Pursuant to Section 353 of the Public Health Services Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), the above named laboratory located at the address shown hereon (and other approved locations) may accept human specimens for the purposes of performing laboratory examinations or procedures.

This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.

Judith A. Yost, Director
Division of Laboratory Services
Survey and Certification Group
Center for Medicaid and State Operations
What services will we provide?

- Specialized technologies (Verigene for CYP2C19 genotyping)
- Sanger Sequencing (p53, EGFR, CYP2C19, etc)
- Chip technologies
  - Genotyping
  - Metabolism Chips (DMET, ADME, Metabochips, etc)
  - Gene Expression
  - Cytogenetics
- Next-Gen Sequencing
  - Resequencing applications
  - Targeted sequencing
  - Exome Sequencing
  - Whole Genome Sequencing
PGRN Translational Pharmacogenomics Project (TPP): Translating CPIC Guidelines into Clinical Practice

- 6 Implementation sites (more to come on-line later)
- 3 Pilots: TPMT/thiopurines; CYP2C19/clopidogrel; CYP2C9, CYP4F2 and VKORC1/warfarin; DMET/preemptive testing; custom panels
- All testing in CLIA-approved environments
- Develop decision support software for commonly used EMRs
- Health care provider education programs
- Collect implementation data metrics (test quality, turn around time, efficiency of adoption, provider feedback surveys/focus groups)
- Disseminate knowledge

Implementation Sites

- University of Maryland (Shuldiner – PI)
- University of Florida (Johnson)
- Vanderbilt University (Roden and Peterson)
- St Jude's Children's Research Hospital (Relling)
- Ohio State University (Sadee)
- Mayo Clinic (Weinshilboum and Pereira)
TPP Progress Report

• Monthly teleconferences
  – St-Jude – Stanford working group

• PharmGKB site for sharing documents/ppts/info

• Standardizing definitions
  – E.g., diplotype → metabolizer phenotype
  – Populating tables (e.g., institution-specific suggested actions)

• Outcomes tracking
  – Standardized tools
    • Implementation process
    • Changes in prescribing practices
    • User satisfaction surveys
    • ?Focus groups

• Sharing of education materials
International Clopidogrel Pharmacogenomics Consortium (ICPC)

• Goal:
  – To contribute to the evidence base for CYP2C19 genetic testing in clinical care
    • Rare variants, indication, ethnicity, PPIs, etc.
  – To further study less well-documented candidate genes (e.g., ABCB1, PON1, P2Y12, others)
  – To perform a large GWAS to discover novel variants for clopidogrel response
ICPC Progress Report

- Coordination of ICPC through PharmGKB
- Executive committee convened
  - Phenotype definitions
  - Genotypes/validation
  - DNA availability/sample requirements
  - Data management
  - Analysis plan
- MOU being drafted
- ClinTrial.gov lists 365 clopidogrel studies
  - Invitations to join Consortium to be initiated in early 2012