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

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Disclosures:

Consultant: Bristol Myer-Squibb/Sanofi-Aventis; USDS
Research funding: NIH (PGRN; U01HL105198)

SOM/UMMS Program in Personalized Medicine

Education

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 Education Initiatives:

- Medical students
- Graduate School (MD/PhD)
- CME
- Seminars/Symposia
- Web-based programs
- EMR-assisted learning

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)

JAMA®

Online article and related content current as of August 25, 2009.

Association of Cytochrome P450 2C19 Genotype With the Antiplatelet Effect and Clinical Efficacy of Clopidogrel Therapy

Alan R. Shuldiner; Jeffrey R. O'Connell; Kevin P. Bliden; et al.

JAMA. 2009;302(8):849-857 (doi:10.1001/jama.2009.1232)

http://jama.ama-assn.org/cgi/content/full/302/8/849

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)***

and

REVIEW

Reduced-Function *CYP2C19* Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated With Clopidogrel Predominantly for PCI

A Meta-analysis

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Jeffrey L. Anderson, MD
Elliott M. Antman, MD
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Content Clopidogrel, one of the most commonly prescribed medications, is a prodrug requiring CYP450 biotransformation. Data suggest its pharmacologic effect varies based on *CYP2C19* genotype, but there is uncertainty regarding the clinical risk imparted by specific genotypes.

Objective To define the risk of major adverse cardiovascular outcomes among carriers of 1 (≈26% prevalence in whites) and carriers of 2 (≈2% prevalence in whites) reduced-function *CYP2C19* genetic variants in patients treated with clopidogrel.

Data Sources and Study Selection A literature search was conducted (January 2000-August 2010) in MEDLINE, Cochrane Database of Systematic Reviews, and EMBASE. Genetic studies were included in which clopidogrel was initiated in predominantly invasively managed patients in a manner consistent with the current guideline recommendations and in which clinical outcomes were ascertained.

Data Extraction Investigators from 9 studies evaluating *CYP2C19* genotype and clinical outcomes in patients treated with clopidogrel contributed the relevant hazard ratios (HRs) and 95% confidence intervals (CIs) for specific cardiovascular outcomes by genotype.

Results Among 9685 patients (91.3% who underwent percutaneous coronary intervention and 54.5% who had an acute coronary syndrome), 863 experienced the composite end point of cardiovascular death, myocardial infarction, or stroke; and 84 patients had stent thrombosis among the 5894 evaluated for such. Overall, 71.5% were noncarriers, 26.3% had 1 reduced-function *CYP2C19* allele, and 2.2% had 2 reduced-function *CYP2C19* alleles. A significantly increased risk of the composite end point was evident in both carriers of 1 (HR, 1.55; 95% CI, 1.11-2.17; $P=.01$) and 2 (HR, 1.76; 95% CI, 1.24-2.50; $P=.002$) reduced-function *CYP2C19* alleles, as compared with noncarriers. Similarly, there was a significantly increased risk of stent thrombosis in both carriers of 1 (HR, 2.67; 95% CI, 1.69-4.22; $P<.0001$) and 2 (HR, 3.97; 95% CI, 1.75-9.02; $P=.001$) *CYP2C19* reduced-function alleles, as compared with noncarriers.

Conclusion Among patients treated with clopidogrel for percutaneous coronary intervention, carriage of even 1 reduced-function *CYP2C19* allele appears to be associated with a significantly increased risk of major adverse cardiovascular events, particularly stent thrombosis.

JAMA. 2010;304(16):1821-1830 www.jama.com

CLOPIDOGREL BLOCKS THE $P2Y_{12}$ adenosine diphosphate (ADP) receptor on platelets and has been shown to reduce cardiovascular events in patients presenting with an acute coronary syndrome (ACS), particularly in those undergoing percutaneous coronary intervention (PCI).[1,2] However, there is a large degree of interindividual variability in the pharmacodynamic response to clopidogrel.[3] One source of the variability is the metabolism of clopidogrel, which is a prodrug requiring biotransformation to generate its active metabolite. Cytochrome P450 (CYP) isoenzymes, specifically CYP2C19,[4] play a key role in clopidogrel metabolism, and carriers of reduced-function genetic variants in the *CYP2C19* gene have lower active clopidogrel metabolite levels and diminished platelet inhibition.[5]

Based in part on a pharmacokinetic and pharmacodynamic study in 40

For editorial comment see p 1839.

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FDA Boxed warning: Plavix (3/20/2010):

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?

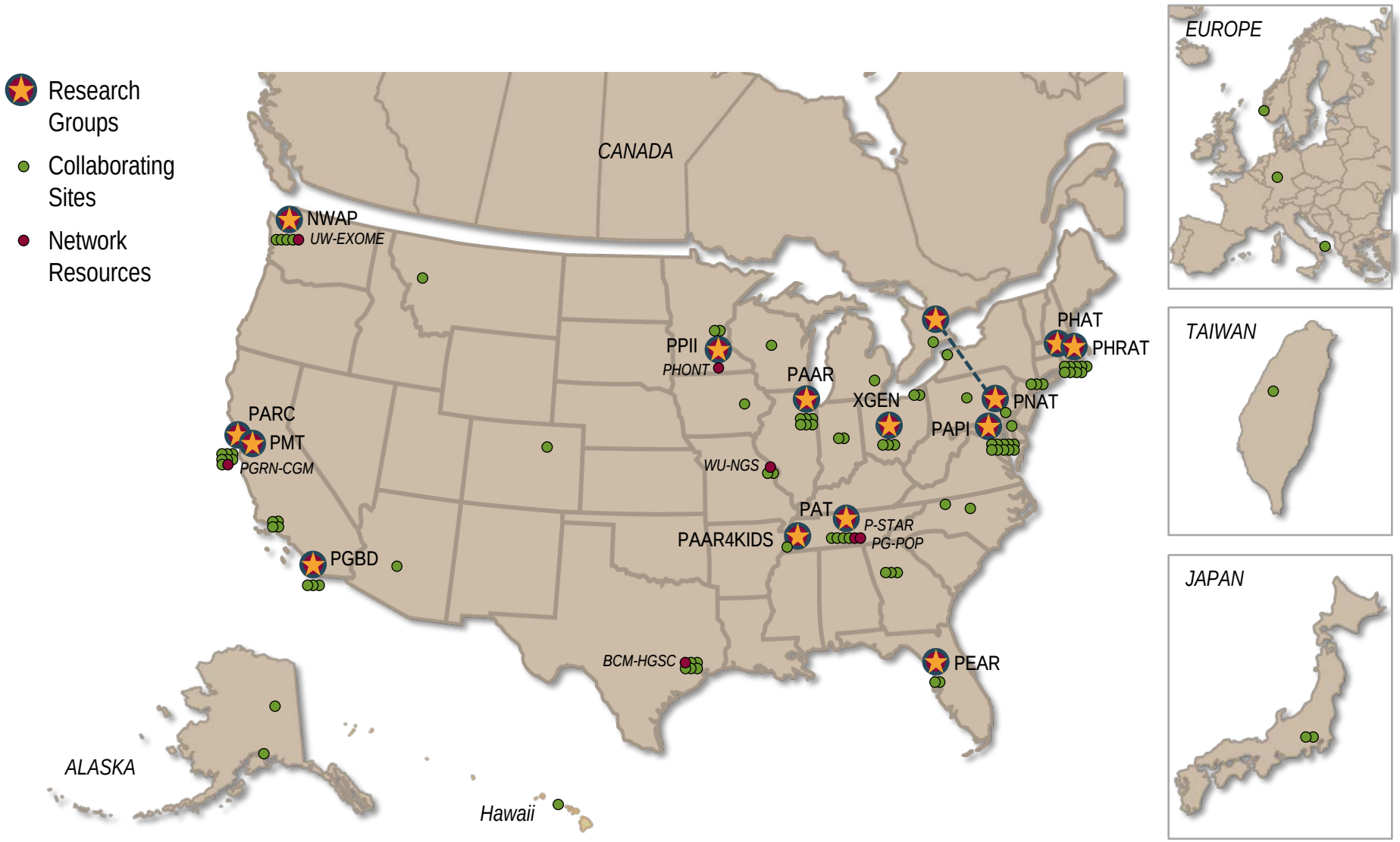
- Lack of prospective randomized clinical trials
  - Does pgx improve outcomes?
  - What is the optimal clinical algorithm for its application?
  - Is it cost effective?
  - Who will pay for a RCT?
- Health care provider education (and expectations)
- Logistics of genetic testing
  - Turnaround time, 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)



Editorial

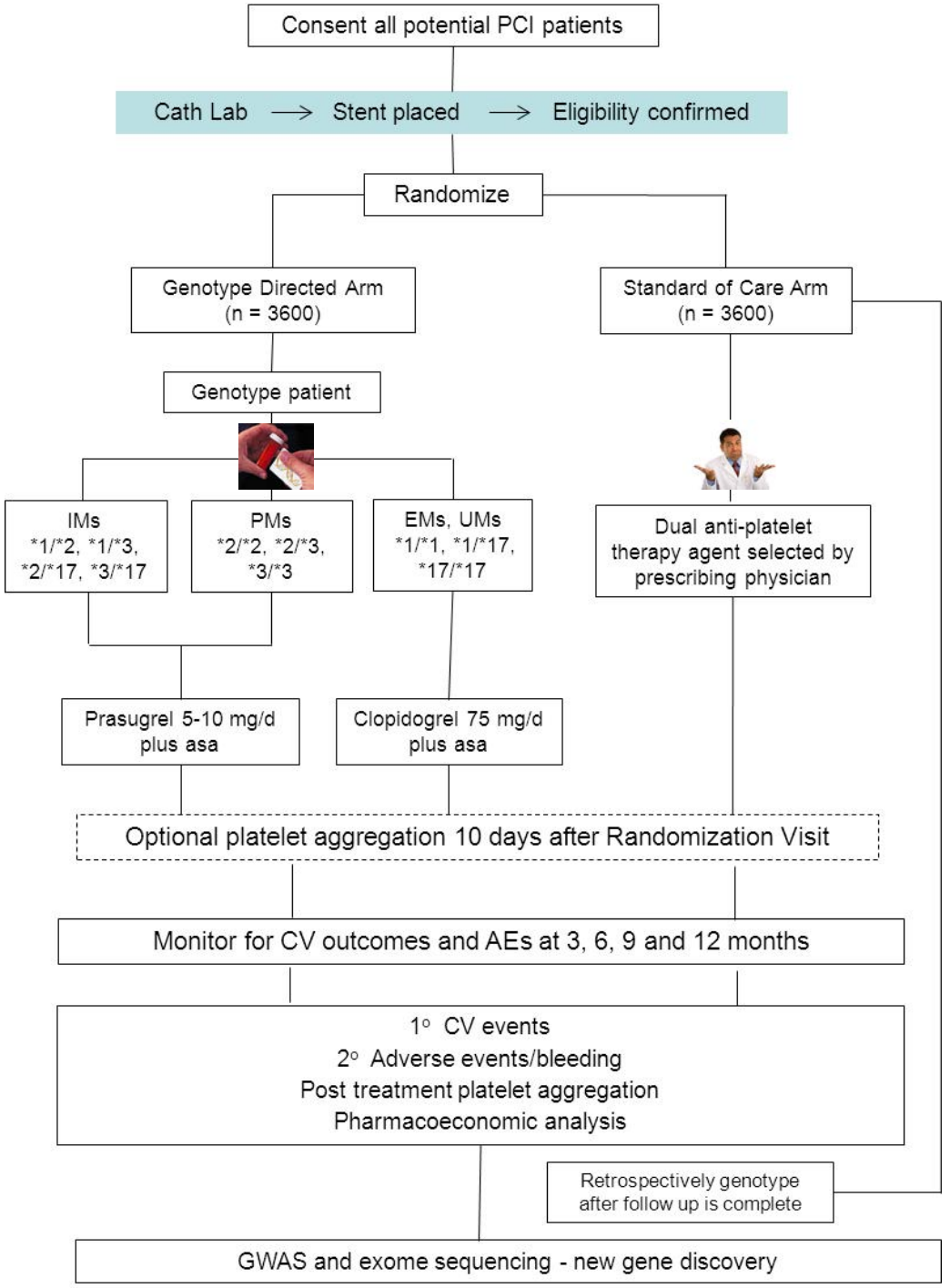
A Step toward Personalized Asthma Treatment

Jeffrey M. Drazen, M.D.

N Engl J Med 2011; 365:1245-1246

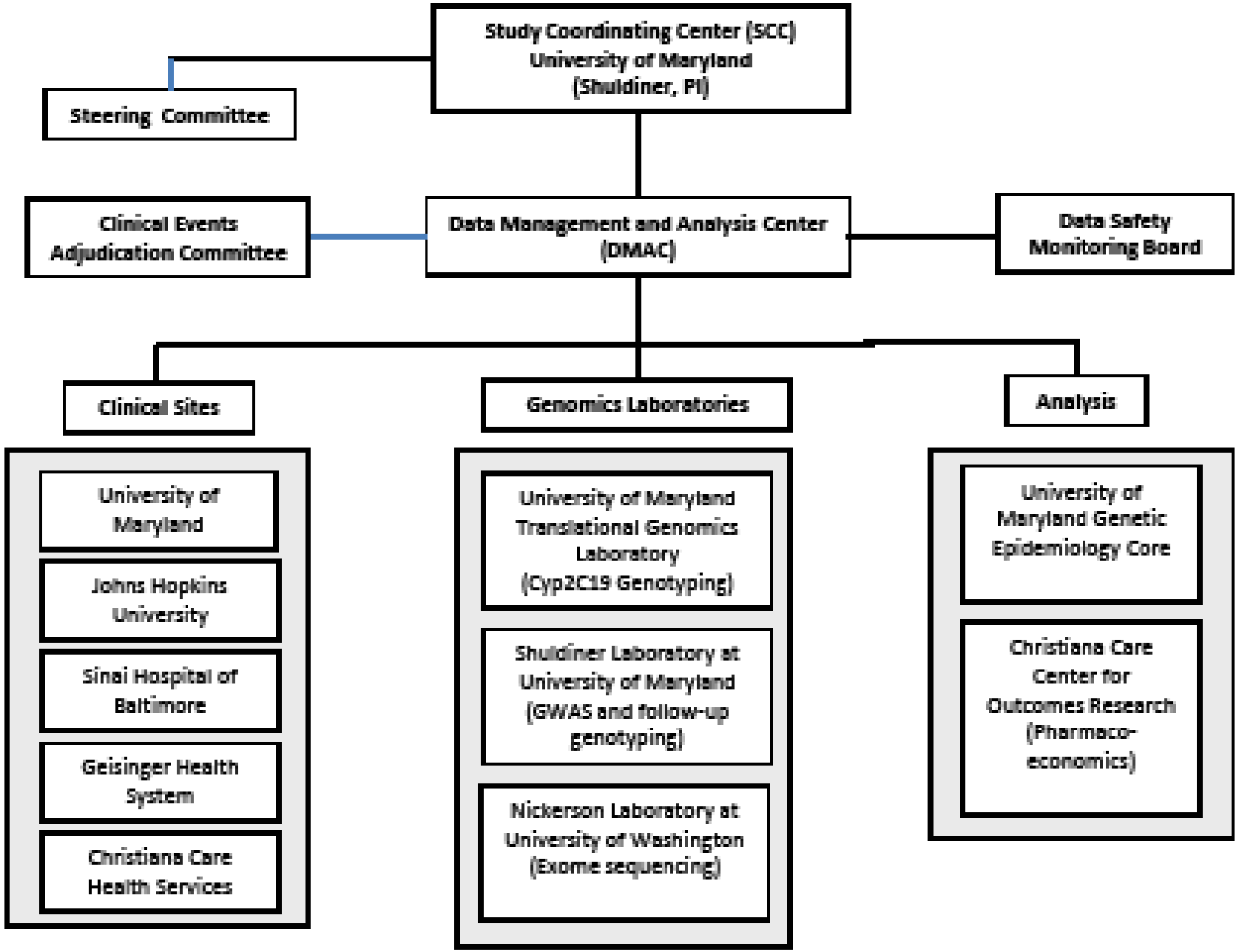
…the next step must be to mount clinical trials in which patients are stratified according to their biologic signature to determine whether knowledge of this information leads to better clinical outcomes. If personalized medicine is going to become a reality, we need to design and execute these critical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

PAPI-2 Study

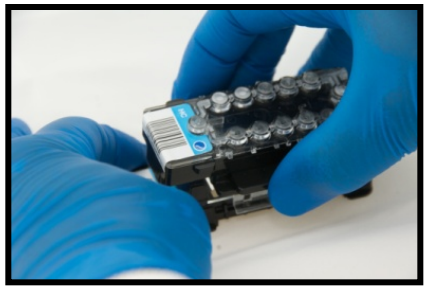

Consent all potential PCI patients
Cath Lab → Stent placed → Eligibility confirmed
Randomize
Genotype Directed Arm (n = 3600)
Standard of Care Arm (n = 3600)
Genotype patient
IMs *1/*2, *1/*3, *2/*17, *3/*17
PMs *2/*2, *2/*3, *3/*3
EMs, UMs *1/*1, *1/*17, *17/*17
Dual anti-platelet therapy agent selected by prescribing physician
Prasugrel 5-10 mg/d plus asa
Clopidogrel 75 mg/d plus asa
Optional platelet aggregation 10 days after Randomization Visit
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

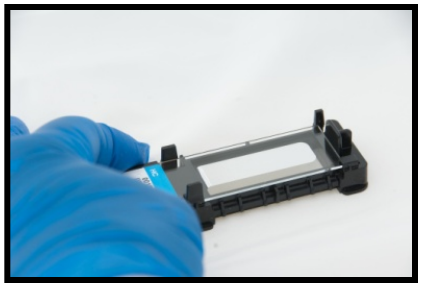
Outcomes

- 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


Study Coordinating Center (SCC)
University of Maryland
(Shuldiner, PI)
Steering Committee
Clinical Events Adjudication Committee
Data Management and Analysis Center (DMAC)
Data Safety Monitoring Board
Clinical Sites
University of Maryland
Johns Hopkins University
Sinai Hospital of Baltimore
Geisinger Health System
Christiana Care Health Services
Genomics Laboratories
University of Maryland Translational Genomics Laboratory (Cyp2C19 Genotyping)
Shuldiner Laboratory at University of Maryland (GWAS and follow-up genotyping)
Nickerson Laboratory at University of Washington (Exome sequencing)
Analysis
University of Maryland Genetic Epidemiology Core
Christiana Care Center for Outcomes Research (Pharmaco-economics)

Verigene® CYP2C19 Validation





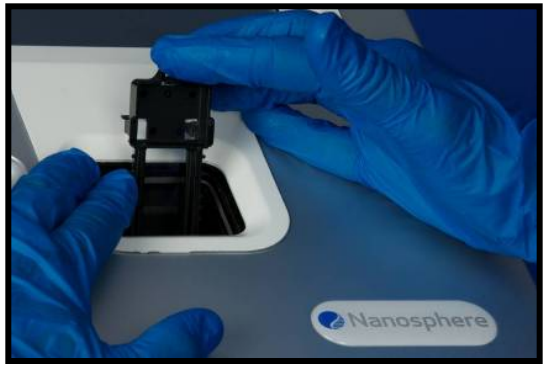


Table 1. Call Rate Summary

	Initial Testing	Final Testing after retesting No Calls
Samples Tested	100	107
Calls Made	94	99
No Calls	6	1
Call Rate%	94%	99%
Accuracy*	100%	-

*Based on DNA Sequence Confirmation

Table 2. Genotype Counts:

WT	36
*2 Homozygous	8
*2 Heterozygous	28
*3 Homozygous	0
*3 Heterozygous	3
*17 Homozygous	2
*17 Heterozygous	17
*2/*3	2
*2/*17	2
*3/*17	1
No Call	1
Total Valid	**100**

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.

CMS
CENTERS for MEDICARE & MEDICAID SERVICES

Judith A. Yost, Director
Division of Laboratory Services
Survey and Certification Group
Center for Medicaid and State Operations

291 certs1_082011

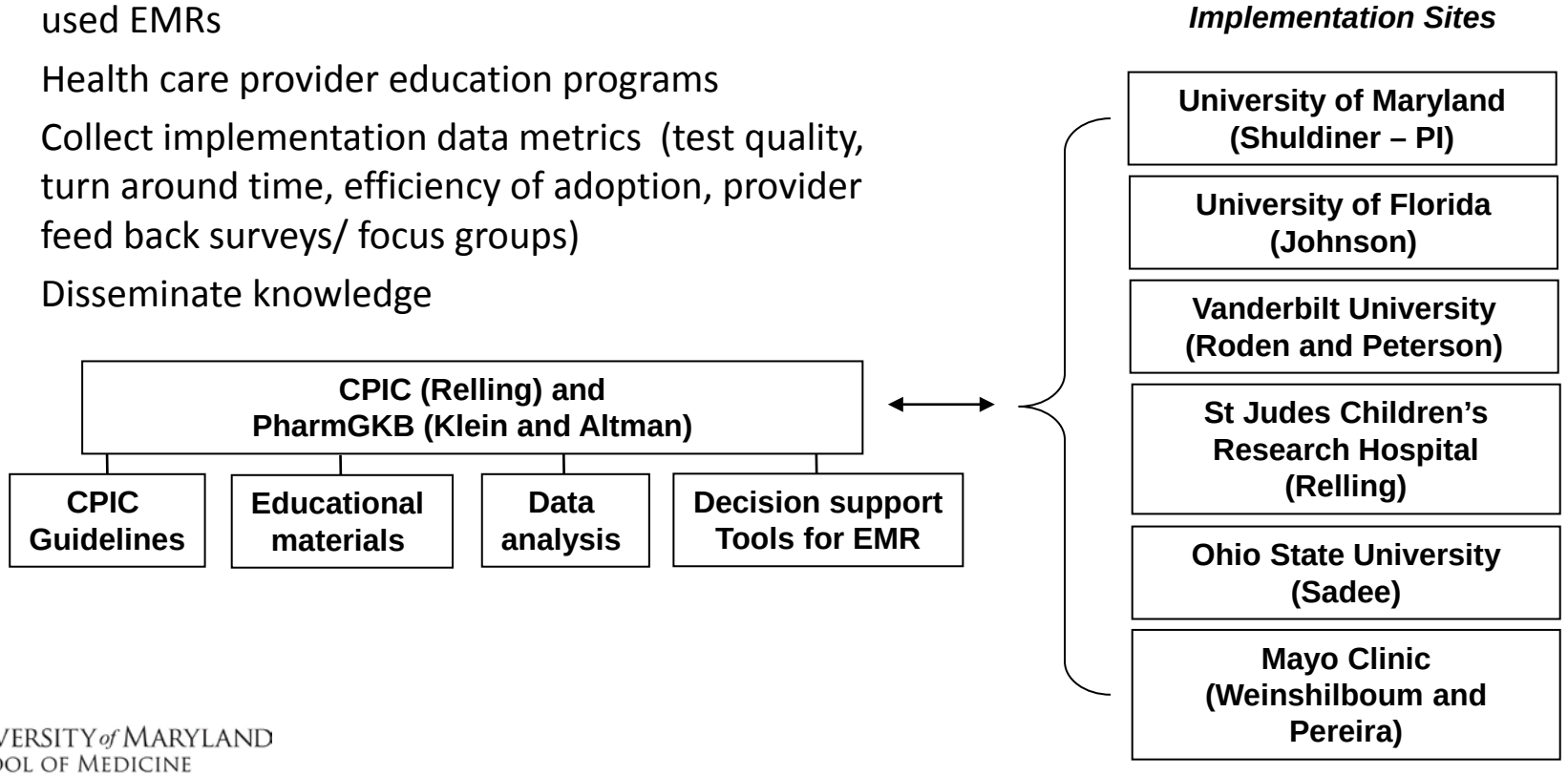
UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

Translational Genomics Laboratory

- 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 feed back surveys/ focus groups)
- Disseminate knowledge



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