Clinical Protocol

STUDY TITLE: **A**ssessment of prospective CYP2C19 genotype guided **D**osing of **A**nti-**P**latelet **T**herapy in Percutaneous Coronary Intervention (**ADAPT)**

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LIST OF ABBREVIATIONS & DEFINITIONS

CYP2C19	cytochrome P450 2C19
GCP	Good Clinical Practice
HUP	Hospital of the University of Pennsylvania
HrQOL	health related quality of life
ICER	Incremental cost effectiveness ratio
ICH	International Conference on Harmonization
LOF	loss of function
PCI	percutaneous coronary intervention
PGx	pharmacogenetics
PPMC	Penn Presbyterian Medical Center
PHI	Protected health information
QALYs	Quality adjust life years
TIA	Transient ischemic attack

SYNOPSIS

Title	**A**ssessment of prospective CYP2C19 genotype guided **D**osing of **A**nti-**P**latelet **T**herapy in Percutaneous Coronary Intervention **(ADAPT)**
Objectives	• To determine the effect of *CYP2C19* genotyping on the prescribing of antiplatelet therapies following PCI • To identify factors linked with successful implementation of clinical pharmacogenetic (PGx) testing in a large academic medical center. • To determine the rates of clinical outcomes. • To conduct a prospective pilot study to determine means and variances for cost, quality adjusted life years (QALYs), and the correlation of cost and effect.
Study Design	The study utilizes a novel genotyping device, SpartanRx™ (Spartan Bioscience, Ottawa, Canada) that provides identification of a patient's *CYP2C19* *2, *3, and *17 genotypes determined from genomic DNA from a buccal swab sample with 1 hour turnaround time. <u>PCI Patient Study</u> This is a randomized, prospective, pragmatic open label study. Patients undergoing percutaneous intervention (PCI) with stent implantation, who require anti-platelet therapy, will be randomized either to: Arm 1) genotype guided dosing of antiplatelet therapy or Arm 2) usual care. In Arm 1, a buccal swab will be obtained from subjects immediately following PCI/stent, to determine *CYP2C19* genotype with the SpartanRx system. Subject with slow metabolizer status [1 or 2 loss-of-function (LOF) mutations (*2 or *3) in *CYP2C19*] will be recommended to initiate therapy with prasugrel or ticagrelor in place of clopidogrel. Subjects with normal metabolizer status (homozygous for the *1 allele in *CYP2C19*) will be recommended to initiate therapy with clopidogrel. Antiplatelet choice is ultimately decided by physician judgment incorporating all clinical factors. In Arm 2, choice of antiplatelet therapy will be decided by treating physician as per usual care. DNA will be collected via a saliva sample to assess *CYP2C19* genotype at the conclusion of the study. Subjects in both groups will complete a baseline health related quality of life questionnaire (HrQoL) and additional clinical data pertaining to cardiac history will be collected from medical records. Subjects will be contacted every three months for medical services utilization, clinical information, and HrQoL assessments for a total of one year. Medical records will be reviewed for clinical outcomes until May 31, 2017.
Study Duration	3 years
Study Centers	Hospital of the University of Pennsylvania (HUP) Penn Presbyterian Medical Center (PPMC)
Primary Objective	To determine the effect of *CYP2C19* genotyping on the prescribing of antiplatelet therapies following PCI.
Secondary and Tertiary Objectives	1. To determine physician adherence to genotype guided recommendations. 2. To determine clinical outcomes (myocardial infarction, stroke, stent thrombosis, revascularization, death and bleeding) 3. To determine means and variances needed for economic evaluation

	including cost, QALYs, and the correlation between cost and effect. 4. To estimate the incremental cost per quality-adjusted life year (QALY) ratio 5. Assess patient and prescriber attitudes towards PGx testing.
Number of subjects	500-600
Inclusion criteria	1. Male and female subjects, ≥18 to ≤80 years at time of study 2. Status post PCI with stent implantation requiring antiplatelet therapy 3. Willingness to comply with all study-related procedures
Exclusion criteria	1. Pending imminent surgery placing patients at increased risk for bleeding with prasugrel or ticagrelor. 2. History of intracranial hemorrhage, transient ischemic attack (TIA), stroke 3. Active bleeding 4. Need for long-term anticoagulation (i.e. warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, or lovenox). 5. Current or prior (within the past four weeks) treatment with voraxapar (Zontivity). 6. Severe renal or hepatic impairment 7. Treating physician does not want subject to participate
Statistical methodology	For the primary outcome the number (proportion) of participants receiving prasugrel/ticagrelor in each randomized arm will be determined. The adherence rate will be determined as the number of participants in genotyped arm with LOF variants that received prasugrel or ticagrelor + the number of participants without these variants that received clopidogrel divided by the total number. For categorical variables, frequencies and percentages will be presented. For continuous variables, the number of subjects, mean, standard deviation, minimum, 25th percentile, median, 75^{th} percentile and maximum will be presented. Reported differences will include standard errors and 95% CI. Analyses will be based on the modified intention to treat.

1.0 ETHICS

The study will be conducted in accordance with the site's clinical research standards that meet regulations relating to Good Clinical Practice (GCP). These standards adhere to the following guidelines:

- Good Clinical Practice: ICH Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1997).
- United States (US) Code of Federal Regulations (21 CFR) dealing with human subject protection and conduct of investigational clinical studies (21 CFR parts 50, 54, 56, 312, and 314).
- Declaration of Helsinki, concerning medical research in humans ("Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects," Helsinki 1964, amend Tokyo 1975, Venice 1983, Hong Kong 1989 and revised version of Somerset West, Republic of South Africa, October, 1996).

2.0 INTRODUCTION

Clopidogrel is a thienopyridine antiplatelet agent, which inhibits the purinergic P2Y12 receptor on platelets and prevents their aggregation. It is commonly used in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI). *CYP2C19* is one of the principal enzymes involved in the bioactivation of clopidogrel from the pro-drug to its active metabolite. The most common loss of function (LOF) allele is *2 (c.681G>A; rs4244285), with frequencies of ~15% in Caucasians and Africans and 29-35% in Asians. A large meta-analysis performed by Mega and colleagues demonstrated that CYP2C19*2 carriers treated with clopidogrel have a higher risk for major adverse cardiac events compared to noncarriers (hazard ratio (HR) of 1.55, 95%CI 1.11-2.17 for heterozygotes; HR 1.76, 95% CI 1.24-2.50) and higher risk of stent thrombosis (HR 2.67, 95% CI 1.69-4.22 for heterozygotes; HR 3.97, 95% CI 1.75-9.02 for homozygotes.)[1] Therefore, clopidogrel is less effective in patients who are CYP2C19 poor metabolizers and alternative therapy is recommended.[2]

A newer-generation thienopyridine, prasugrel, was found to be associated with a reduction in major adverse cardiac events (death, myocardial infarction, stroke) compared to clopidogrel, but with an increased risk of fatal and major bleeding events.[3]

While a body of observational literature[1] and clinical guidelines[4] suggest prescribing alternative antiplatelet therapy in carriers of *CYP2C19* LOF alleles, it is unknown whether physicians will follow genotype guided recommendations when pharmacogenetic (PGx) results are presented to them in a real world setting. To provide evidence regarding the implementation and effectiveness of PGx testing following PCI, we will examine the differences in prescribing of antiplatelet drugs when presented with genotype data. We will also evaluate physician's adherence to the genotype guided antiplatelet recommendations.

Now that clopidogrel is available in generic form, pharmacogenetic (PGx) screening could allow for individualized anti-platelet therapy in which patients with functional *CYP2C19* alleles could be prescribed clopidogrel, and the more expensive agent would be reserved for patients with poor metabolizer status. A cost-effectiveness analysis of *CYP2C19* screening for selection of antiplatelet therapy found that genotype-guided therapy would lead to more cost-effective care rather than uniform usage of either clopidogrel or prasugrel.[5] Genotyping produced 450 fewer cardiovascular events compared with treating all patients with clopidogrel. The number needed to genotype (NNG) was 23, i.e. one excess cardiovascular event was avoided for every 23 patients genotyped when compared to a clopidogrel-for-all strategy. The NNG was 30 when comparing genotype guided therapy to prasugrel-

for- all. Cost-savings were not evident when genotype-guided therapy was compared to generic clopidogrel for all patients. The analysis did not examine quality measures that are important in assessing patient outcomes.

A more recent economic evaluation determined that genotyping and prescribing ticagrelor to LOF allele carriers was the most effective strategy when compared against routine clopidogrel or prasugrel use as well as genotyping and prescribing prasugrel to LOF carriers.[6] However, these results were based on decision model of a hypothetical cohort of patients with ACS who underwent PCI and several assumptions were made regarding outcomes, cost and quality of life. True costs associated with genotype guided antiplatelet therapy are unknown. Future prospective studies evaluating the cost effectiveness of a genotype guided approach are needed. We are proposing a pilot study which will provide information necessary for planning a prospective study that will directly estimate events averted, costs, QALYs and cost per QALY ratios. Information to be obtained in this pilot includes estimates of costs and their variance, preference scores (for calculating QALYs) and their variance, the correlation of cost and effects (required for sample size estimation for cost-effectiveness ratios), event rates, and implementation metrics (to estimate likely penetration of testing in the trial). The results from this study will provide more accurate estimates of the means and variances of cost and QALYs required to plan future trials. We will also examine the cost-effectiveness of genotyping for *CYP2C19* in daily clinical practice.

3.0 OBJECTIVES

- To determine the effect of *CYP2C19* genotyping on the prescribing patterns of antiplatelet therapies following cardiac catheterization.
- To determine the rates of clinical outcomes.
- To identify factors linked with successful implementation of clinical pharmacogenetic (PGx) testing in a large academic medical center.
- To conduct a prospective pilot study to determine means and variances for cost, quality-adjust life years (QALYs), and the correlation of cost and effect.
- Assess patient and prescriber attitudes towards PGx testing.

4.0 STUDY DESIGN

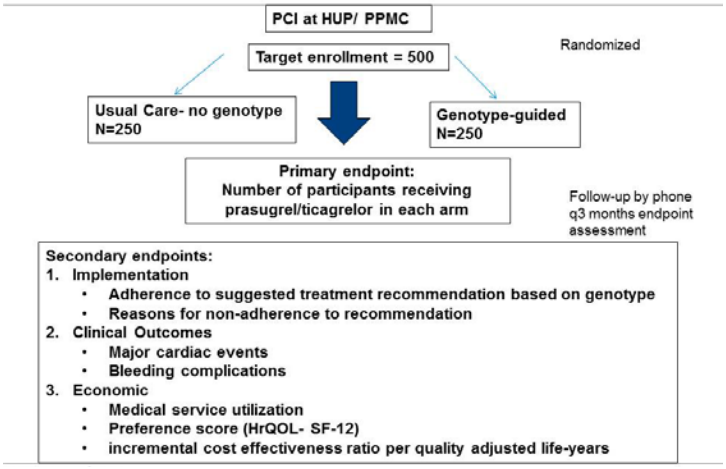
This is a randomized, prospective, pragmatic open label pilot study (Figure 1). Patients undergoing PCI with stent implantation, who require anti-platelet therapy, will be randomized to: Arm 1) genotype guided dosing of antiplatelet therapy or Arm 2) usual care. Randomization will be stratified by the occurrence of acute coronary syndrome (ACS).

In Arm 1, a buccal swab will be obtained from subjects immediately following PCI/stent, to determine *CYP2C19* genotype with the SpartanRx system. This arm provides pharmacogenetic information to help guide decision making: initiation of therapy with prasugrel or ticagrelor will be recommended for participants found to be slow metabolizers [1 or 2 loss-of-function (LOF) mutations (*2 or *3) in *CYP2C19*]; initiation of therapy with clopidogrel will be recommended for participants found to be normal metabolizers (*CYP2C19 *1/*1*). See Table 1 and Appendix A. Antiplatelet choice will ultimately be decided by the treating physician taking into account all clinical factors.

In Arm 2, the choice of antiplatelet therapy will be decided by the treating physician as per usual care. DNA will be collected by –saliva sample and CYP2C19 genotype will be determined at the completion of the study.

Subjects in both groups will complete baseline health related quality of life questionnaire (HrQoL). Subjects will be contacted every three months for clinical information, medical service utilization and HrQoL assessments. No specific recommendations will be made regarding use of vorapaxar, a recently approved anti-platelet agent for which guideline-based recommendations regarding genotyping are not available.

Figure 1. Clinical Trial Study Design and Endpoints



4.1 Primary endpoint

- Number of participants receiving prasugrel/ticagrelor in each arm.

4.2 Secondary endpoints

1. Implementation
    a. Adherence to suggested treatment recommendations based on genotype
    b. Reasons for non-adherence to recommendations Medical service utilization
2. Clinical Outcomes
    a. Major adverse cardiac event (CV related death, MI, stroke, urgent need for revascularization, stent thrombosis, all deaths).
    b. Bleeding complications (defined by the Bleeding Academic Research Consortium).[7]
    c. Clinical outcomes will be ascertained by medical records until May 31, 2017.
3. Economic- Incremental cost effectiveness ratio per quality adjusted life-year (ICER/QALYs).
    a. Medical services utilization
    b. Cost of services
    c. Preference score (SF-12 questionnaire) performed at baseline and every 3 months for one year for determination of QALYs.

4.3 Tertiary Endpoints

a. Additional implementation metrics
    a. Number of genotype results returned
    b. Average genotype test completion time
    c. Genotype assay failure rate (inconclusive test result)
    d. Number/reason for screening failure
    e. Time from test order to result in medical record
b. Patient attitudes towards PGx testing as determined by questionnaire will be completed at the 3 month phone follow-up.
c. Prescriber attitudes towards PGx testing as determined by questionnaire that will be administered at the start and end of the study.

Table 1. Treatment recommendations for antiplatelet therapy based on *CYP2C19* genotype[4]

Genotype	Phenotype	Description	Treatment[a]
CYP2C19 *1/*1	Extensive metabolizer (normal)	Two inferred normal alleles	Clopidogrel 75 mg per day
CYP2C19 *1/*17	Ultra-rapid metabolizer	One inferred normal allele One increased function allele	
CYP2C19 *17/*17		Two gain of function alleles	
CYP2C19 *1/ *2	Intermediate metabolizer	One inferred normal allele One loss of function allele	Prasugrel (Effient) 10 mg per day[b] Or Ticagrelor (Brilinta) 90 mg twice daily[c]
CYP2C19 *1/*3		One inferred normal allele One loss of function allele	
CYP2C19 *2/*17		One loss of function allele One gain of function allele	
CYP2C19 *3/*17		One loss of function allele One gain of function allele	
CYP2C19 *2/*2	Poor metabolizer	Two loss of function alleles	Prasugrel (Effient) 10 mg per day[b] Or Ticagrelor (Brilinta) 90 mg twice daily[c]
CYP2C19 *3/*3		Two loss of function alleles	
CYP2C19 *2/*3		Two loss of function alleles	

[a] Please consider all clinical contraindications before prescribing alternative antiplatelet agent. Prasugrel and ticagrelor are recommended only when not clinically contraindicated.

[b] Consider prasugrel 5 mg per day for patients <60 kg.
Individual risks/benefits of prasugrel must be carefully considered in patients over age 75.
Do not use prasugrel in patients with active bleeding or a history of transient ischemic attack or stroke.
Do not start prasugrel in patients likely to undergo **urgent** coronary bypass graft surgery (CABG).

[c] Do not use ticagrelor in patients with active bleeding or a history of transient ischemic attack or stroke.
Do not start ticagrelor in patients likely to undergo **urgent** coronary bypass graft surgery (CABG).
Do not use maintenance aspirin does above 100 mg in combination with ticagrelor.

5.0 STUDY POPULATION

All patients undergoing PCI with stent implantation at HUP or PPMC who will require clopidogrel, prasugrel or ticagrelor treatment will be considered for this protocol.

5.1 Inclusion Criteria

1. Male and female subjects, ≥18 to ≤80 years at time of study
2. Status post PCI with stent implantation requiring antiplatelet therapy
3. Willingness to comply with all study-related procedures

5.2 Exclusion criteria:

1. Pending imminent surgery placing patients at increased risk for bleeding with prasugrel or ticagrelor.
2. History of intracranial hemorrhage, TIA, and stroke
3. Active bleeding

4. Need for long-term anticoagulation (i.e. warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, or lovenox).
5. Current or prior (within the past four weeks) treatment with voraxapar (Zontivity).
6. Severe renal or hepatic impairment
7. Treating physician does not want subject to participate

6.0 STUDY PROCEDURES

6.1 Informed Consent
Subjects will be approached for enrollment 2 hours following their PCI/stent implantation in the holding area or their inpatient hospital bed by the research coordinator.

6.2 Genotyping
If randomized to Arm 1 (genotyping arm), the research coordinator will obtain a buccal swab for the PGx test on the Spartan Rx system. If randomized to Arm 2 (control group), a saliva sample will be obtained with the Oragene-DNA 500 kit (DNA Genotek, Ottawa, Canada) and the genotyping will be performed at the completion of the study. For Arm 2, DNA will be extracted from saliva using the QIAamp DNA mini kit (Qiagen, Valencia, CA). Samples will be genotyped using the Infinium Global Screening Array (Illumina, SanDiego, CA), a genome-wide genotyping array that also contains pharmacogenetic variants. Genotyping will be performed on Illumina's iScan System at the Center for Advanced Genomics at the Children's Hospital of Philadelphia. The *CYP2C19* SNPs of interest *2 (rs4244285), *3 (rs4986893) and *17 (rs12248560) will be extracted from the array data.

6.3 Clinical data collection
Subjects in both arms will have baseline clinical data collected from medical records and will be telephoned every 3 months for clinical endpoint collection and medical service utilization. Medical records will be reviewed for the occurrence of major cardiac events (CV- related death, myocardial infarction, stroke, urgent need for revascularization, and stent thrombosis), bleeding events and death until May 31, 2017.

6.4 Heath-related quality of life (HrQoL)
Subjects in both arms will complete a baseline SF-12 and 4 additional questionnaires by phone or on paper and returned by mail (every 3 months).

6.5 Patient attitudes towards pharmacogenetic testing
Patients will complete a paper survey at 3 months to assess their understanding and attitudes towards pharmacogenetic testing (Appendix B).

6.6 Provider attitudes towards pharmacogenetic testing
Treating physicians participating in the study will complete a survey at baseline and 1 year to assess their attitudes towards pharmacogenetic testing and needs for medical education in this area (Appendix C).

6.7 Collection of saliva for future genetic tests
An optional component of the study will be saliva collection for DNA biobanking. If the subject provides consent for this component, a saliva sample will be collected with the Oragene-DNA 500 kit (DNA Genotek. This is the same sample we are collecting in 6.2 above for the control group and not a separate sample. To avoid confusion for subjects and study personnel, a saliva sample will be collected for all participants and the purpose will be labeled (e.g. for CYP2C19 genotyping only OR for biobanking and CYP2C19 genotyping).

7.0 STATISTICAL ANALYSIS

Data collected in this study will be reported using summary tables and results will be displayed for each treatment arm. For categorical variables, frequencies and percentages will be presented. For continuous variables, the number of subjects, mean, standard deviation, minimum, 25th percentile, median, 75th percentile and maximum will be presented. Reported differences will include standard errors and 95% CI. Analyses will be based on the intention to treat. Continuous variables will be compared using Student's t-test. Categorical variables will be compared using the chi-square test or Fisher's exact test when appropriate.

7.1 Primary endpoints

1. We will tabulate the number and proportion of prasugrel/ticagrelor in each Arm. We will compare discharge antiplatelet therapy choice between the genotype and control arm using the chi-square or Fisher's exact test. The probability of receipt of antiplatelet agents will be determined by logistic regression.

7.2 Secondary endpoints

1. Implementation.
    a. We will estimate adherence to suggested treatment recommendations based on results of the *CYP2C19* genetic test. The adherence rate is defined as the number of participants in Arm 1 with LOF variants that received prasugrel or ticagrelor + the number of participants without these variants that received clopidogrel divided by the total number in Arm 1.
    b. We will tabulate reasons for non-adherence to recommendations.
2. Clinical outcomes.
    a. Frequencies of CV related death, MI, stroke urgent, need for revascularization and stent thrombosis will be reported as will frequencies of bleeding complications. We will determine time to first major cardiac event as a composite endpoint (CV related death, MI, stroke urgent need for revascularization and stent thrombosis). The incidence of first MACE and first major bleeding events between the groups will be compared by use of Kapan-Meier estimators and statistical tests will be evaluated based on log-rank tests.
    b. To determine whether MACE outcomes differ in participants with ACS, an interaction term between ACS and group assignment will be tested in a Cox proportional hazard model.
3. Medical service utilization. We will develop descriptive statistics for use of antiplatelet drugs, use of other cardiovascular medications, number of hospitalizations, number of physician visits, and use of rehabilitation services
4. Direct medical cost. We will also develop descriptive statistics for total cost, *CYP2C19* genetic testing cost, medication cost, hospitalization cost, physician visit cost, and rehabilitation cost.
5. Preference scores / QALYs. We will develop descriptive statistics for the SF-12 physical and mental scale scores, the SF-6D, a preference-based health-related quality of life score that can be derived from the SF-12,[8] and for QALYs, a composite measure of its quality (based on the SF-6D). We will also report the correlation between the difference in cost and difference in QALYs (this correlation will be used in sample size estimation for the full study that this pilot study is designed to support).
6. Incremental cost-effectiveness ratio. Based on the differences in primary outcomes total cost and QALYs, we will calculate the ratio incremental costs divided by incremental QALYs, the 95% CI for this ratio, and the cost-effectiveness acceptability curve.

7.3 Tertiary endpoints

We will also tabulate the number of genotype results returned, the average genotype test completion time, the genotype assay failure rate, the number of and reason for screening failure, time from test order to result in medical record, and patient/prescriber attitudes towards PGx test results.

7.4 Post-hoc analyses

Genotyped will be determined in the control group at the end of the trial. We will combine the groups and evaluate outcomes by CYP2C19 genotype and antiplatelet drugs prescribed at discharge. Participants will be grouped into the following categories: 1) Carriers of normal function alleles receiving any antiplatelet drug, 2) LOF carriers receiving clopidogrel, or 3) LOF carriers receiving prasugrel or ticagrelor. Time to MACE, major bleeding and a composite safety/efficacy endpoint consisting of MACE, major bleeding and non-cardiac mortality will be determined in the three groups. Cox proportional hazards models will be used to assess the effects of having an LOF allele and receiving clopidogrel therapy, having an LOF allele and receiving alternative therapy, and not having an LOF allele on the occurrence of first MACE, first major bleed, and first composite outcome. The Cox model will be controlled for age at entry to the study, the date of catheterization, gender, race, hospital site, and history of ACS, smoking, hypertension, diabetes, and myocardial infarction.

7.5 Sample size for Primary Outcome

The sample size calculation is based on two factors: 1) the rate of pre-study prasugrel/ticagrelor antiplatelet therapy prescribing (20%) and 2) anticipated increase in alternative antiplatelet prescribing based on the frequency *CYP2C19* LOF variants (~30-35%). We estimate a 15% difference in the use of prasugrel/ticagrelor prescriptions in the two groups (35% in the genotype group and 20% in the control group). A sample size of 138 per group (a total of 276) would provide 80% power at an alpha level of 0.05 to detect this difference. We will increase our sample size to ~250 per group to allow for subgroup comparisons (e.g. ACS vs. stable coronary disease).

7.6 Sample Size for Economic Evaluation

While there is little published guidance on sample size determination for pilot studies[9, 10], we present confidence intervals that will result for expected population means and standard deviations and a sample size of 350 per treatment arm (see Table 2). Knowing the expected mean and standard deviation of hospital cost will be important when designing the more definitive study of the cost-effectiveness of genotype guided dosing of anti-platelet therapy.

Given that hospital cost distributions typically have long heavy right tails[11], we assume that these costs are distributed log normally. There are limited data on the expected cost and expected standard deviation for a year of hospital costs after initiation of antiplatelet therapy. We have derived our "baseline" assumptions (mean = $7800; SD = $9355) from Nikolic et al., a European study that may or may not be representative of costs in the U.S.

Simulation indicates that for a sample size of 350 per group (total N = 700) if the population mean is 7800 and the average standard deviation for repeated draws of participants is 9355, then if we repeated the pilot study 1000 times, in 95% of them the observed mean would range between 6851 and 8775 and the observed standard deviation would range between 6875 and 13138 (see row 2 of Table 2). Rows 1 and 3 of the table indicate that if we are incorrect that the average standard deviation from repeated draws is 9355, the expected standard deviations in 95% of repeated experiments would range between 4942 and 7499 if average standard deviation for repeated draws of were 6000. It would range between 7853 and 19423 if the average standard deviation were 12,000.

Rows 4-6 report sensitivity analyses for cases in which we assume the population mean is 10,000; rows 7-9 report these analyses for cases in which we assume the population mean is 15,000. In the

most extreme case (population mean 15,000, average SD from repeated draws of 18000), in 95% of repeated experiments the mean would fall in the range between 13,345 and 17,044 and the standard deviation would fall in the range between 13,240 and 25,658.

Substitution of the more realistic assumption of log normality for the less realistic assumption of normality increased the magnitude of the average range of the standard deviation by more than 300%. Assuming log normality, but substitution of a sample size of 175 per group (total N=350) for the proposed 350 per group would lead to an average increase in the magnitude of the ranges of 32%.

Table 2. Expected 95% Confidence Intervals for Sample Means and Sample Standard Deviations for Hospital Cost in Dollars Given Varying Population Means and Standard Deviations, N = 350 per Treatment Group*

Population Mean	95% Confidence Interval for Mean	Population Standard Deviation	95% Confidence Interval for Standard Deviation
1. 7800	7248 to 8471	6000	4942 to 7499
2. 7800	6851 to 8775	9355	6875 to 13138
3. 7800	6633 to 9125	12,000	7853 to 19,423
4. 10,000	9300 to 10,774	7000	5771 to 8478
5. 10,000	9021 to 11,164	10,000	7732 to 13,529
6. 10,000	8715 to 11,393	13,000	9252 to 18,413
7. 15,000	13,771 to 16,249	12,000	9641 to 5203
8. 15,000	13,510 to 16,778	15,000	11,550 to 19,889
9. 15,000	13,345 to 17,044	18,000	13,240 to 25,638

* Costs assumed to be log normally distributed. Estimates derived from simulation.

8.0 DATA MANAGEMENT

We will create a shared database with common data definitions. This database will be programmed in REDCap (Research Electronic Data Capture). REDCap is a secure, web-based application with the capacity for direct export to Excel and common statistical packages (SPSS, SAS, Strata, R). REDCap has electronic CRFs, real-time data entry validation, audit trails, user authentication, data logging and encryption. It is HIPAA compliant with mechanisms in place to ensure confidentiality.

Specific forms will be used for each component of the subject's progress. The forms and data dictionary will be available online for all individuals who perform data entry. Research personnel, trained on data definitions, will enter data via web-based data forms after abstraction from the primary medical record and source documents. The multisite feature of REDCap will be used to restrict data viewing by investigators. REDCap allows double-data entry on some or all of the data elements. We will apply this feature to predefined "key" variables. In addition, logical data checks will be used to assess data quality for mis-entry. Suspect data entries will be flagged for re-review and confirmation by the investigative team at each site. When data are complete and all suspect entries addressed for a time period, the database will be "locked" for analysis. Analysis will use only this final locked version.

9.0 SUBJECT PRIVACY / PROTECTED HEALTH INFORMATION

Protected health information (PHI) collected on the case report forms and via the electronic medical records will be stored in an encrypted research database. Only designated research staff will have access to the research database unless otherwise requested to the IRB by the Principal Investigator.

10.0 RISK/BENEFIT ASSESSMENT

10.1 Potential Study Risks

The primary risk is the loss of privacy and breach of confidentiality. There will be ongoing assessment of the security of the data systems to ensure that subject's PHI is protected.

10.2 Potential Benefits

The potential benefit to study subjects is having their antiplatelet medication selected based on genotype. This may result in improved clinical outcomes. The potential benefits to the health system include: improved clinical outcomes for subjects and decreased cost in care. Our ultimate goal is to translate our molecular work into clinical practice. In particular, we believe that genotype in part predicts clinical outcome, and that identification of the genetic factors will assist in clinical management in the future.

10.3 Alternatives to Participation

The patient has the option to not participate and not sign the informed consent. If a patient declines to participate, there is no effect on the patient's regular, ongoing clinical care.

10.4 Data and Safety Monitoring

The Principal Investigator and Co-Investigators will be ultimately responsible for assuring the security of all computer systems to minimize risk to participants. Safety data such as major bleeding events and major cardiovascular events will be assessed six months after enrollment begins.

References

1. Mega, J.L. *et al.* Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* **304**, 1821-30 (2010).
2. Scott, S.A. *et al.* Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. *Clin Pharmacol Ther* **90**, 328-32 (2011).
3. Wiviott, S.D. *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* **357**, 2001-15 (2007).
4. Scott, S.A. *et al.* Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update. *Clin Pharmacol Ther* **94**, 317-23 (2013).
5. Reese, E.S., Daniel Mullins, C., Beitelshees, A.L. & Onukwugha, E. Cost-effectiveness of cytochrome P450 2C19 genotype screening for selection of antiplatelet therapy with clopidogrel or prasugrel. *Pharmacotherapy* **32**, 323-32 (2012).
6. Kazi, D.S. *et al.* Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. *Ann Intern Med* **160**, 221-32 (2014).
7. Mehran, R. *et al.* Standardized Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report From the Bleeding Academic Research Consortium. *Circulation* **123**, 2736-47 (2011).
8. Brazier, J.E. & Roberts, J. The estimation of a preference-based measure of health from the SF-12. *Med Care* **42**, 851-9 (2004).
9. Hertzog, M.A. Considerations in determining sample size for pilot studies. *Res Nurs Health* **31**, 180-91 (2008).
10. Thabane, L. *et al.* A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* **10**, 1 (2010).
11. Glick, H., Doshi, J., Sonnad, S. & Polsky, D. Economic Evaluation in Clinical Trials. (Oxford University Press, Oxford, 2007).

Appendix A. Treatment recommendations handout for interventional cardiologist

Table 1. Treatment recommendations for antiplatelet therapy based on *CYP2C19* genotype[4]

Genotype	Phenotype	Description	Treatment[a]
CYP2C19 *1/*1	Extensive metabolizer (normal)	Two inferred normal alleles	Clopidogrel (Plavix) 75 mg per day
CYP2C19 *1/*17	Ultra-rapid metabolizer	One inferred normal allele One increased function allele	
CYP2C19 *17/*17		Two gain of function alleles	
CYP2C19 *1/ *2	Intermediate metabolizer	One inferred normal allele One loss of function allele	Prasugrel (Effient) 10 mg per day[b] Or Ticagrelor (Brilinta) 90 mg twice daily[c]
CYP2C19 *1/*3		One inferred normal allele One loss of function allele	
CYP2C19 *2/*17		One loss of function allele One gain of function allele	
CYP2C19 *3/*17		One loss of function allele One gain of function allele	
CYP2C19 *2/*2	Poor metabolizer	Two loss of function alleles	Prasugrel (Effient) 10 mg per day[b] Or Ticagrelor (Brilinta) 90 mg twice daily[c]
CYP2C19 *3/*3		Two loss of function alleles	
CYP2C19 *2/*3		Two loss of function alleles	

Table 2. Switching recommendations based on *CYP2C19* genotype

Genotype CYP2C19	Initial loading dose	Reload	Maintenance [a]
*1/*2, *1/*3, *2/*2, *3/*3, *2/*17, *3/*17	Clopidogrel 600 mg	Prasugrel 60 mg	Prasugrel 10 mg [b]
		Ticagrelor 180 mg	Ticagrelor 90 mg [c]
*1/*1, *1/*17, *17/*17	Prasugrel 60 mg	Not needed	Clopidogrel 75 mg
	Ticagrelor 180mg	Clopidogrel 300 mg	Clopidogrel 75mg

[a] Please consider all clinical contraindications before prescribing alternative antiplatelet agent. Prasugrel and ticagrelor are recommended only when not clinically contraindicated. See table 3 below

Table 3. Clinical Contraindications to Prasugrel or Ticagrelor

Prasugrel [b]	Ticagrelor [c]
1. Do not use prasugrel in patients with active bleeding or a history of transient ischemic attack or stroke. 2. Individual risks/benefits of prasugrel must be carefully considered in patients over age 75. 3. Do not start prasugrel in patients likely to undergo **urgent** coronary bypas graft surgery (CABG). 4. Consider prasugrel 5 mg per day for patients <60 kg.	1. Do not use ticagrelor in patients with active bleeding or a history of transient ischemic attack or stroke. 2. Do not start ticagrelor in patients likely to undergo **urgent** coronary bypass graft surgery (CABG). 3. Do not use maintenance aspirin dose above 100 mg in combination with ticagrelor. 4. Avoid with strong CYP3A inhibitors or inducers.

1. Scott, S.A. *et al.* Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update. *Clin Pharmacol Ther* **94**, 317-23 (2013).

Appendix B

Participant Survey- Pharmacogenetic testing

Demographics

1. Name: _____
2. Age:_____
3. Sex:

   ☐ Male
   ☐ Female

4. Race (check all that apply):

   ☐ White
   ☐ Black/African-American
   ☐ Asian
   ☐ American Indian/ Alaska Native
   ☐ Native Hawaiian/ Pacific Islander
   ☐ Other

5. Ethnicity:

   ☐ Hispanic
   ☐ Non-Hispanic

6. Educational level:

   ☐ Less than high school
   ☐ High school graduate (or GED)
   ☐ Some college/ university
   ☐ College/university graduate
   ☐ Post college/ university degree
   ☐ Not provided

7. What is your current occupational status? (circle)
   - ☐ Employed
   - ☐ Unemployed
   - ☐ Homemaker
   - ☐ Student
   - ☐ Retired
   - ☐ Disabled
   - ☐ Other, please specific_____

8. What is your marital status? (circle)
   - ☐ Married
   - ☐ Living as married
   - ☐ Divorced
   - ☐ Widowed
   - ☐ Separated
   - ☐ Single, never been married

9. What is your combined annual income (total pre-tax income from all sources earned in the past year)?
   - ☐ $0-$9,999
   - ☐ $10,000-$14,999
   - ☐ $15,000-$19,999
   - ☐ $20,000-$34,999
   - ☐ $35,000-$49,999
   - ☐ $50,000-$74,999
   - ☐ $75,000-$99,999
   - ☐ $100,000-$199,999
   - ☐ $200,000 or more
   - ☐ Choose not to respond

10. How would you rate your current health
    - ☐ Excellent
    - ☐ Good
    - ☐ Fair
    - ☐ Poor

11. Have you ever experienced side effects due to your medications?
    - ☐ No
    - ☐ Yes, mild

☐ Yes, severe

12. How confident are you in filling out forms in a doctor's office by yourself?

☐ Extremely
☐ Quite a bit
☐ Somewhat
☐ A little bit
☐ Not at all

The following section includes questions about the role of genetics in health and disease. When we refer to a variant, we are referring to a change in a gene which may or may not be harmful.

Please circle one number to indicate how much you agree or disagree with each statement.

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
13. A health care provider can always tell a person their exact chance of developing a disease based on the results from genetic testing.	1	2	3	4	5
14. Even if a person has a variant in a gene that affects their risk of a disease, they may not develop that disease.	1	2	3	4	5
15. Genetic testing may find variants in a person's genes that may determine how they respond to certain medicines.	1	2	3	4	5
16. A person's health habit, like diet and exercise, can affect whether or not their genes can cause disease.	1	2	3	4	5
17. Genetic variants in a gene can change over a person's lifetime.	1	2	3	4	5

18. **On a scale of 1 to 5 (1 being "Not at all important" and 5 being "very important"),** how important is it to you to learn more about how your genes affect your chance of experiencing a side effect from a medication?

Not At All Important				Very Important
1	2	3	4	5

19. **On a scale of 1 to 5 (1 being "Not at all important" and 5 being "very important"),** how important is it to you to learn more about how your genes may help in predicting which medications will work for you?

Not At All Important				Very Important
1	2	3	4	5

20. Before participating in this study how aware were you about the use of genetic testing to predict whether certain medications will work for you?

☐ Aware

☐ Not aware

21. Did you receive genetic test result regarding CYP2C19 genotyping?

☐ Yes

☐ No

☐ Unsure

22. If yes in 21. **On a scale of 1 to 5 (1 being "not at all clear" and 5 being "very clear"),** how clearly did you understand the PGx test results as it related to your antiplatelet medication?

Not At All Clearly				Very Clearly
1	2	3	4	5

23. If applicable, what did you find unclear about your CYP2C19 test result?

_____

_____

Reminder, a pharmacogenetic test is a type of genetic test that could allow doctors to choose the right drug that will work for a patient while avoiding using certain drugs that may cause side effects.

To what extent do you agree or disagree with the following statements?

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
24. I feel comfortable about the pharmacogenetic tests that might be offered to me, if they could predict if a medication would work for my condition.	1	2	3	4	5
25. I feel comfortable about the pharmacogenetic tests that might be offered to me, if they could predict the correct dose of the medication that I needed.	1	2	3	4	5
26. I feel comfortable about the pharmacogenetic tests that might be offered to me, if they could predict a mild side effect.	1	2	3	4	5
27. I feel comfortable about the pharmacogenetic tests that might be offered to me, if they could predict a serious side effect.	1	2	3	4	5
28. I feel comfortable about the pharmacogenetic tests that might be offered to me, if they could explain a family history of medication side effect or nonresponse.	1	2	3	4	5
29. It is important that my health care provider tells me about these pharmacogenetic tests, before any of them are done.	1	2	3	4	5
30. If these pharmacogenetic tests were part of my usual blood work it is important that my health care provider seek separate approval from me, specifically for the pharmacogenetic tests.	1	2	3	4	5

31. If I had to pay for the pharmacogenetic tests myself, financial costs would be one of my concerns about taking these tests.	1	2	3	4	5
32. If I took the test, I would be concerned that insurance companies may use the pharmacogenetic test results to deny healthcare coverage.	1	2	3	4	5
33. If I took the test, I would be concerned about the effect of the pharmacogenetic test results on my employment opportunities.	1	2	3	4	5

Appendix C

Provider Survey- Pharmacogenetic testing

Demographics

1. Sex:

   ☐ Male
   ☐ Female

2. Race (check all that apply):

   ☐ White
   ☐ Black/African-American
   ☐ Asian
   ☐ American Indian/ Alaska Native
   ☐ Native Hawaiian/ Pacific Islander
   ☐ Other

3. Ethnicity:

   ☐ Hispanic
   ☐ Non-Hispanic

4. Year of gradation from medical school: _____

5. Medical Specialty:

   ☐ Internal medicine / family medicine/ general practice

   ☐ Cardiology

   ☐ Gastroenterology

   ☐ Genetics

   ☐ Oncology

   ☐ Surgery

   ☐ Other: _____

6. Where do you primarily practice?

   ☐ HUP
   ☐ PPMC
   ☐ PAH
   ☐ VA hospital
   ☐ Other: _____

Pharmacogenetic (PGx) testing: Testing to predict likelihood of drug toxicity or therapeutic efficacy. Testing identifies genetic variants in genes that may affect drug disposition (e.g., metabolism) or drug target resulting in increased risk for an adverse drug reaction or low likelihood of responding to a drug, respectively.

7. I feel well-informed about the role of PGx testing in therapeutic decision-making.
   - ☐ Strongly agree
   - ☐ Somewhat agree
   - ☐ Neutral
   - ☐ Somewhat disagree
   - ☐ Strongly disagree
   - ☐ Prefer not to answer

8. I believe that PGx testing is or will soon become a valuable tool to predict risk of adverse events or likelihood of effectiveness.
   - ☐ Strongly agree
   - ☐ Somewhat agree
   - ☐ Neutral
   - ☐ Somewhat disagree
   - ☐ Strongly disagree
   - ☐ Prefer not to answer

9. Had you heard of pharmacogenetic (PGx) testing before this survey?
   - ☐ Yes
   - ☐ No

10. Are you aware that the Food and Drug Administration (FDA) has revised drug labels to include information about pharmacogenetics?
    - ☐ Yes
    - ☐ No

11. Please indicate where and/or how you have learned about pharmacogenetics. *(Please check all that apply.)*

- ☐ Genetics training in medical school
- ☐ Genetics training in residency
- ☐ Continuing medical education (CME) meeting, in-person course, grand rounds
- ☐ CME distance learning (mail or web-based)
- ☐ Journals
- ☐ Colleagues
- ☐ Other *(Please specify.)* _____
- ☐ I have not had any education about pharmacogenetics.

12. In your opinion, what is the **BEST** way to educate physicians about PGx testing? ***(Please select only one response.)***

- ☐ Genetics training in medical school
- ☐ Genetics training in residency
- ☐ Continuing medical education (CME) meeting, in-person course, or grand rounds
- ☐ CME distance learning (mail or web-based)
- ☐ Journals
- ☐ Grand rounds or other types of in-house seminars
- ☐ Other *(Please specify.)* _____
- ☐ Genetics education is not necessary

13. How often do you order PGx tests?

- ☐ Never
- ☐ 1-2 times per year
- ☐ 3-10 times per year
- ☐ 11-25 times per year
- ☐ More than 25 times per year
- ☐ Unsure

14. In general, how likely are you to order a PGx test that predicts the **efficacy** of a drug for an individual patient?

- ☐ Very likely
- ☐ Somewhat likely
- ☐ Neutral
- ☐ Somewhat unlikely

- ☐ Very unlikely

15. In general, how likely are you to order a PGx test that predicts the **safety** of a drug for an individual patient?

    - ☐ Very likely
    - ☐ Somewhat likely
    - ☐ Neutral
    - ☐ Somewhat unlikely
    - ☐ Very unlikely

16. In your opinion, when deciding whether or not to order a pharmacogenetic test to **determine a potential adverse drug reaction** for an individual patient, how important are the following considerations?

	Very important	Somewhat important	Neutral	Somewhat unimportant	Not at all important
a. Severity of the potential drug reaction.	○	○	○	○	○
b. Prevalence of the potential drug reaction.	○	○	○	○	○
c. Predictive value of the test.	○	○	○	○	○
d. Availability of other clinical testing to monitor drug toxicity.	○	○	○	○	○
e. Severity of the condition being treated.	○	○	○	○	○
f. Prevalence of genetic variant (positive test result).	○	○	○	○	○
g. Inclusion of information about the test on the drug label/package insert.	○	○	○	○	○
h. Availability of practice guidelines for test use and interpretation.	○	○	○	○	○
i. Insurance reimbursement of test.	○	○	○	○	○
j. Cost of the test.	○	○	○	○	○
k. Turnaround time for the test results to be returned.	○	○	○	○	○
l. Cost of the drug for which test is ordered.	○	○	○	○	○
m. Availability of an alternative drug.	○	○	○	○	○

17.

18. In your opinion, when determining the value of a PGx test to identify a patient who is **unlikely to respond to a drug (efficacy),** how important are the following considerations

	Very important	Somewhat important	Neutral	Somewhat unimportant	Not at all important
a. Likelihood of non-response to the drug.	○	○	○	○	○
b. Predictive value of the test.	○	○	○	○	○
c. Availability of other clinical testing to monitor drug response.	○	○	○	○	○
d. Urgency of treatment.	○	○	○	○	○
e. Severity of the condition being treated.	○	○	○	○	○
f. Likelihood of genetic variant (positive test result).	○	○	○	○	○
g. Inclusion of information about the test on the drug label.	○	○	○	○	○
h. Availability of practice guidelines for test use and interpretation.	○	○	○	○	○
i. Insurance reimbursement of the test.	○	○	○	○	○
j. Cost of the test.	○	○	○	○	○
k. Turnaround time for the test results to be returned.	○	○	○	○	○
l. Cost of the drug for which test is ordered..	○	○	○	○	○
m. Availability of an alternative drug.	○	○	○	○	○

19. Please indicate which professional or group should have **PRIMARY** responsibility to discuss PGx test result with the patient.

☐ Physician ordering the test

☐ Primary care provider

☐ Geneticist / Genetic Counselor

- [ ] Pharmacist
- [ ] Genetic testing lab
- [ ] Don’t know