Background
Anti-platelet therapy with clopidogrel (Plavix) and aspirin is the standard of care for secondary prevention of myocardial infarction. Despite its widespread use, 4 - 32% of individuals are not responsive to clopidogrel. Research has shown that variability in clopidogrel response is due in part to variants in the CYP2C19 gene. CYP2C19 encodes a cytochrome P450 (CYP) enzyme that catalyzes the biotransformation of the clopidogrel prodrug into its active metabolite. Individuals harboring loss-of-function variants in CYP2C19 convert less clopidogrel into its active form, resulting in decreased antiplatelet response and increased rates of cardiovascular events. In patients undergoing percutaneous coronary interventions, patients harboring the *2 allele (~30% of the population) are at approximately 1.5-2.4-fold higher risk of having an ischemic cardiac event or death and a 2.5-4-fold increased risk of stent thrombosis. In response to these findings, the FDA issued a boxed warning on clopidogrel that it may have reduced effectiveness in people who carry two loss-of-function variants. Based on Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations, alternate therapies should also be considered in intermediate metabolizers (those with one loss-of-function variant).

Clinical Use
Results of CYP2C19 genotyping can be considered when selecting antiplatelet agents for patients with acute coronary syndrome undergoing percutaneous coronary intervention.

Methodology
CYP2C19 SNP genotyping is performed using the TaqMan genotyping platform. This test’s performance characteristics were determined by the University of Maryland School of Medicine Translational Genomics Laboratory (TGL); it has not been cleared by the FDA. The TGL is accredited by the College of American Pathology (CAP) and is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing. This test is used for clinical purposes. It should not be regarded as investigational or research.

Interpretation & Reporting
The TGL test analyzes six allelic variants of CYP2C19 (NM_000769.2). The normal *1 (“star 1”) allele is inferred based on the absence of any of the six targeted allelic variants. Variants other than those listed below will not be detected by this assay; however, other known allele variants are very rare in the general population. Mutations in other genes associated with drug response will not be detected. Bone marrow or liver transplantation may interfere with genotype testing.

### Allele | Variant | Variant Effect | Predicted Enzyme Activity
--- | --- | --- | ---
*1 | None | Inferred normal allele | Normal
*2 | c.681G>A | Splicing defect | Loss of function
*3 | c.636G>A, p.Trp212Ter | Premature termination | Loss of function
*4 | c.1A>G, p.Met1Val | Initiation defect | Loss of function
*6 | c.395G>A, p.Arg132Gln | No catalytic activity | Loss of function
*8 | c.358T>C, p.Trp120Arg | No catalytic activity | Loss of function
*17 | c.-806C>T | Increased transcription | Gain of function

Clinical Recommendations
The following therapeutic recommendations for clopidogrel use for individuals with ACS who have undergone PCI were established by the Clinical Pharmacogenetics Implementation Consortium (CPIC). Of note, CYP2C19 genotype may also influence choice and/or dosing of other medications, including some tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, trimipramine), selective serotonin reuptake inhibitors (sertraline, citalopram, escitalopram), and voriconazole. Recommendations will vary depending on the drug.

NOTE: CYP2C19 genotype is one of many factors that influence clopidogrel efficacy. It is unclear if alternative antiplatelet agents are appropriate in CYP2C19 poor metabolizers who have other indications for antiplatelet therapy (i.e. not ACS or PCI).

**Diploptypes:** *1/*17 (RM) or *17/*17 (UM)

**Rapid or Ultrarapid metabolizer** (Increased enzyme activity)
- Normal or increased platelet inhibition; normal or decreased residual platelet aggregation; possible increased risk of bleeding
- If no other contraindications, standard therapy with clopidogrel: 600mg loading dose followed by 75mg daily

**Diploptyle: *1/*1**

**Normal metabolizer** (formerly called extensive metabolizer, EM) (Normal enzyme activity)
- Normal platelet inhibition; normal residual aggregation
- If no other contraindications, standard therapy with clopidogrel: 600mg loading dose followed by 75mg daily

**Diploptypes: *1/*2(*3,*4,*6,*8), *17/*2(*3,*4,*6,*8)**

**Intermediate metabolizer, IM** (Intermediate enzyme activity)
- Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events
- Consider ALTERNATE THERAPIES: ticagrelor 180mg loading dose followed by 90mg twice daily OR prasugrel 60mg loading dose followed by 10mg daily OR if neither of these is appropriate consider increased dose of clopidogrel to 225mg daily
Diplotype: *2(*3,*4,*6,*8)/*2(*3,*4,*6,*8)

Poor metabolizer, PM  
(Low or no enzyme activity)

- Significantly reduced platelet inhibition;  
  increased residual platelet aggregation; increased  
  risk for adverse cardiovascular events
- Consider ALTERNATE THERAPIES:  
  ticagrelor (Brilinta) 180mg loading dose  
  followed by 90mg twice daily OR prasugrel  
  (Effient) 60mg loading dose followed by 10mg  
  daily

Testing Schedule
Test is performed Monday-Friday. Turnaround  
time is less than 24 hours (except on weekends).  
Samples received by 2 pm M-F will be run the  
same day. Samples submitted after 2 pm or during  
the weekend will be reported the following work  
day before noon.

CPT Codes
81225

Specimen Requirements
Please send 3-5 mL whole blood in EDTA (purple  
top tube). Ship at room temperature.

Shipping Information
University of Maryland School of Medicine  
Translational Genomics Laboratory  
655 W. Baltimore St  
Bressler Research Building 7-037  
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References
   functional characterization of new potentially  
   defective alleles of human CYP2C19.  
   Pharmacogenetics. 12(9):703-711.
   polymorphism and risk of adverse clinical events  
   in clopidogrel-treated patients: a meta-analysis  
   based on 23,035 patients. Archives of  
   Cardiovascular Diseases. 106(10): 517-527.
   polymorphisms and response to clopidogrel. N.  
   CYP2C19 genotype and risk of adverse clinical  
   outcomes among patients treated with  
   clopidogrel predominantly for PCI: a meta-  
   Pharmacogenetics Implementation Consortium  
   Guidelines for Cytochrome P450-2C19  
   (CYP2C19) Genotype and Clopidogrel Therapy.  
   Clinical Pharmacology & Therapeutics. 90:  
   328–332.
   Pharmacogenetics Implementation Consortium  
   Guidelines for Cytochrome P450-2C19  
   (CYP2C19) Genotype and Clopidogrel Therapy:  
   2013 Update. Clinical Pharmacology &  
   Therapeutics. 94(3): 317–323.
7. University of Maryland Medical Center  
   Pharmacy and Therapeutics Committee,  
   Baltimore, MD.