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).

Diplotypes: ***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

Diplotype: ***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

Diplotypes: ***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

Diplotypes: ***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
Baltimore, MD 21201

Contacts

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References

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2. Mao, L., et al. (2013) Cytochrome CYP2C19 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.
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4. Mega, J.L.., et al. (2010) Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA. 304(16): 1821-1830.
5. Scott, S.A., et al. (2011) Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy. Clinical Pharmacology & Therapeutics. 90: 328–332.
6. Scott, S.A., et al. (2013) Clinical 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.

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CYP2C19 Genotyping

Provider Information