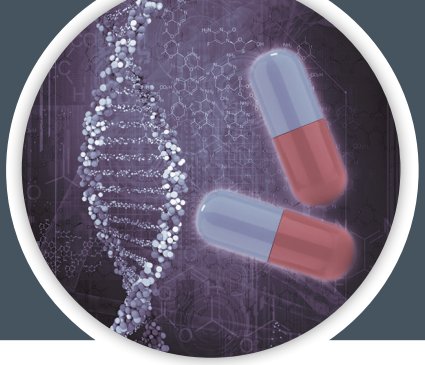
CYP2C19

CPT Code 81225
Sample Type EDTA Whole Blood

Order Code C603
Tube Type Lavender Top



genetics

Types of clopidogrel (Plavix®) metabolizers based on the CYP2C19 genotype:

- Poor metabolizer
- Intermediate metabolizer
- Extensive/Normal metabolizer
- Ultra-rapid metabolizer

Population statistics for poor metabolizers[1-3]:

- Asians (14-20%)
- African American (4%)
- Caucasian (2-4%)

Description

CYP2C19 is a member of the cytochrome P450 family of enzymes involved in the metabolism and bioactivation of drugs. In particular, CYP2C19 is integral for the generation of the active form of clopidogrel (Plavix®), which is prescribed in a prodrug form. This prodrug is converted by CYP2C19 to the active form in the liver. Several variants of CYP2C19 have been identified which have an impact on its ability to metabolize drugs. The main CYP2C19 alleles include the non-functional alleles *2 and *3, as well as the hyperactive *17 allele.

Clinical Use

CYP2C19 testing may be performed on individuals who are candidates for or are currently taking clopidogrel (Plavix®), or those who have a family history of clopidogrel (Plavix®) inefficacy.

Clinical Significance

- In 2010, the FDA announced a boxed warning for clopidogrel (Plavix®) to alert patients and physicians to the drug's inefficacy in individuals who cannot metabolize the drug to its active form[2].
- Poor metabolizers (loss of CYP2C19 activity) have 2X the risk of having a subsequent adverse cardiac event while receiving treatment with clopidogrel after a myocardial infarction[4].
- Ultra-rapid metabolizers (increased CYP2C19 activity) have a reduced risk of major adverse cardiac events while being treated with clopidogrel[5], but are at an increased risk of bleeding[6].

Sample Type

The CYP2C19 test requires **one** EDTA whole blood sample. If performing other tests that require an EDTA whole blood sample, they should be collected in a separate lavender top tube.

Testing Frequency

The CYP2C19 test should only be performed **once** on an individual as it is a genetic test.

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have been established or posted by CMS (Medicare & Medicaid). Limited information has been posted by the majority of the larger Carriers (Aetna, United HealthCare, Cigna, Blues). Medical necessity and specificity of diagnosis should be provided when ordering this test.

Understanding Medical Necessity

The following ICD-9 codes for CYP2C19 are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test and provide the 4th and 5th ICD-9 digit as appropriate.

Diagnosis	Diagnosis Code
Pure Hypercholesterolemia	272.0
Unspec. Hyperlipidemia	272.4
Mixed Hyperlipidemia	272.2
Coronary atherosclerosis of native coronary artery	414.01

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Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

Phenotype	Genotype	Interpretation	Treatment Consideration
Poor Metabolizer	Two non-functional alleles (*2/*2 or *2/*3 or *3/*3)	Poor metabolizers do not effectively convert the drug to its active metabolite and exhibit poor anti-platelet responsiveness.	Consider a higher dosage of clopidogrel (Plavix®) or an alternative therapy.
Intermediate Metabolizer	One WT and one non-functional allele (WT/*2 or WT/*3)	Intermediate metabolizers convert the drug to an active metabolite at a slower rate than a normal metabolizer and exhibit decreased responsiveness to the drug.	
Normal (Extensive) Metabolizer	No mutations (WT/WT)	Normal metabolizers effectively convert the drug to an active metabolite.	Consider a standard dosage of clopidogrel (Plavix®).
Ultra-Rapid Metabolizer	One WT and one hyperactive allele or 2 hyperactive alleles (WT/*17 or *17/*17)	Ultra-rapid metabolizers convert a higher percentage of the drug to an active metabolite, and have a greater therapeutic response to the drug compared to normal metabolizers. Ultra-rapid metabolizers may produce an adequate platelet response even when lower than normal doses of the drug are used, and are at increased risk of bleeding.	Consider a standard or reduced dosage of clopidogrel (Plavix®) and monitoring the patient for potential bleeding.
Unknown	One non-functional allele and one hyperactive allele (*2/*17 or *3/*17)	The metabolizer status is uknown for individuals with this genotype.	Consider an alternative therapy.

The Cleveland HeartLab assay identifies the non-functional alleles *2 and *3, and the ultra-rapid allele *17 of the CYP2C19 gene.
The presence of less common alleles can not be ruled out by this test.

References

1. Desta Z et al. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet.* 2002; 41: 913-958.
2. Product Information for Plavix (Sanofi/Aventis US). Label Information, approved Feb 2011. www.accessdata.fda.gov/drugsatfda_docs/label/2011/020839s052lbl.pdf. Accessed June 27, 2013.
3. Shuldiner AR et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*. 2009; 302: 849-857.
4. Mega JL et al. Cytochrome P-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009; 360: 354-362.
5. Li Y et al. The gain-of-function variant allele CYP2C19*17: A double-edged sword between thrombosis and bleeding in clopidogrel-treated patients. *J Thromb Haemost*. 2012; 10: 199-206.
6. Sibbing D et al. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation*. 2010; 121: 512-518.

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