CYP2C19 SEQUENCE VARIANTS ASSOCIATED WITH RESISTANCE TO CLOPIDOGREL (PLAVIX)

The UNC Molecular Genetics Laboratory performs molecular testing to detect *cytochrome P450 2C19 (CYP2C19)* sequence variants associated with resistance to clopidogrel (Plavix) anti-platelet therapy and increased cardiovascular morbidity and mortality.

Background: Clopidogrel (Plavix) is an anti-platelet agent used to treat coronary artery disease, peripheral vascular disease and cerebrovascular disease. A significant proportion of patients is at risk for myocardial infarction, stent thrombosis, or stroke due to insufficient clopidogrel-induced platelet inhibition. Clopidogrel is metabolized by CYP2C19 and other liver enzymes to an active form. Genetic variants of *CYP2C19* associated with altered CYP2C19 activity have been identified and are relatively common in most populations. Individuals with loss of function variants CYP2C19*2 or CYP2C19*3 (~15% of the population) are at increased risk for thrombotic cardiovascular events due to decreased drug efficacy. In contrast, the fast (ultra)-metabolizing variant CYP2C19*17 (in ~20% of the population) is associated with increased drug activation and increased risk of bleeding. The US FDA has recently recommended considering a higher dose of clopidogrel or use of alternative therapy such as Prasugrel in CYP2C19 poor metabolizers who are homozygous for loss of function alleles.

Clinical Indications for *CYP2C19* polymorphism testing: Testing is recommended in patients who are being considered for clopidogrel antiplatelet therapy or who are already on this medication.

Laboratory Testing for *CYP2C19* polymorphisms: The preferred sample is 2mL of EDTA anticoagulated blood (lavender-top), which may be refrigerated up to 48 hours before analysis. Genomic DNA is extracted and CYP2C19 *2, *3 and *17 targets are PCR amplified and detected by TaqMan probes using an ABI real-time PCR instrument. Allelic discrimination is facilitated by software analysis of the fluorescence data. Homozygous or heterozygous presence of three common *CYP2C19* genotype variants (*2, *3, *17) is reported. A pathologist interprets the clinical significance of variants associated with clopidogrel response.

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