Types of clopidogrel (Plavix®) metabolizers based on the CYP2C19 genotype:
• Poor metabolizer
• Intermediate metabolizer
• Extensive/Normal metabolizer
• Ultra-rapid metabolizer

Population statistics for poor metabolizers¹-³:
• 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 form².

• 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 infarction⁴.

• Ultra-rapid metabolizers (increased CYP2C19 activity) have a reduced risk of major adverse cardiac events while being treated with clopidogrel⁵, but are at an increased risk of bleeding⁶.

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.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnosis Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Hypercholesterolemia</td>
<td>272.0</td>
</tr>
<tr>
<td>Unspec. Hyperlipidemia</td>
<td>272.4</td>
</tr>
<tr>
<td>Mixed Hyperlipidemia</td>
<td>272.2</td>
</tr>
<tr>
<td>Coronary atherosclerosis of native coronary artery</td>
<td>414.01</td>
</tr>
</tbody>
</table>
Treatment Considerations

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

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype</th>
<th>Interpretation</th>
<th>Treatment Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Metabolizer</td>
<td>Two non-functional alleles (*2/*2 or *2/*3 or *3/*3)</td>
<td>Poor metabolizers do not effectively convert the drug to its active metabolite and exhibit poor anti-platelet responsiveness.</td>
<td>Consider a higher dosage of clopidogrel (Plavix®) or an alternative therapy.</td>
</tr>
<tr>
<td>Intermediate Metabolizer</td>
<td>One WT and one non-functional allele (WT/2 or WT/3)</td>
<td>Intermediate metabolizers convert the drug to an active metabolite at a slower rate than a normal metabolizer and exhibit decreased responsiveness to the drug.</td>
<td></td>
</tr>
<tr>
<td>Normal (Extensive)</td>
<td>No mutations (WT/WT)</td>
<td>Normal metabolizers effectively convert the drug to an active metabolite.</td>
<td>Consider a standard dosage of clopidogrel (Plavix®).</td>
</tr>
<tr>
<td>Ultra-Rapid Metabolizer</td>
<td>One WT and one hyperactive allele or 2 hyperactive alleles (WT/*17 or 117/*17)</td>
<td>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.</td>
<td>Consider a standard or reduced dosage of clopidogrel (Plavix®) and monitoring the patient for potential bleeding.</td>
</tr>
<tr>
<td>Unknown</td>
<td>One non-functional allele and one hyperactive allele (*2/*17 or *3/*17)</td>
<td>The metabolizer status is unknown for individuals with this genotype.</td>
<td>Consider an alternative therapy.</td>
</tr>
</tbody>
</table>

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