**Predicting patient response is possible:**

**CYP2C19 genotyping**

Know your patient’s response to clopidogrel before prescribing

**Clopidogrel decreases the likelihood of future atherothrombotic events**

Clopidogrel is an anti-platelet medication that requires activation by the isoenzyme Cytochrome P450 2C19. Roughly 40 million patients worldwide are treated with Clopidogrel to avert future atherothrombotic events.

Clopidogrel is prescribed for patients who have experienced a recent heart attack, heart related chest pain, percutaneous coronary intervention, or were diagnosed with peripheral arterial disease.

Clopidogrel (Plavix) blocks the platelet P2Y12 adenosine diphosphate (ADP) receptor, inhibition of which has been shown to reduce cardiovascular events in patients with acute coronary syndrome and in patients undergoing percutaneous coronary intervention, with stent implantation. The response to Clopidogrel is highly variable among patients and inter-individual differences in Clopidogrel metabolism are a source of the variable response to the antiplatelet therapy. Clopidogrel is a pro-drug that undergoes biotransformation to form an active metabolite.

CYP2C19 is a hepatic microsomal enzyme involved in the metabolism and elimination of many commonly prescribed drugs including anticoagulants, antidepressants, anti-epileptics, antineoplastics, antiretrovirals, barbiturates, and proton pump inhibitors.

The CYP2C19 gene maps to chromosome 10q24.1-q24.3 and encodes a 490 amino acid protein. The CYP2C19*2 allele (a substitution in exon 5, position 681G>A) and CYP2C19*3 allele (point mutation in exon 4 leading to a premature stop codon, position 636G>A) are non-functional and result in poor metabolizers (PM) phenotypes. CYP2C19 *2 and *3 account for the majority of PM phenotypes in Caucasians (85 percent) and Asian (99 percent). Other alleles associated with absent or reduced metabolism are less frequent and include (but are not limited to) *4, *5, *6, *7, *8, *9, *10, and *13. Frequencies of poor metabolizer genotypes vary in different ethnic groups: approximately 2 percent in Caucasians, 4 percent in African-Americans and 14 percent in Asians.

**Variants of the CYP2C19 gene are associated with decreased efficiency of Clopidogrel therapy:**

Frequency of poor metabolizer genotypes varies with ethnicity: 2 percent in Caucasians, 4 percent in African-Americans, and 14 percent in Asians.

See reverse side for individualized therapy options.
CYP2C19 genotyping allows individualized therapy for clopidogrel.

Patients may be classified as extensive, intermediate, poor, or ultra-rapid metabolizers of Clopidogrel.

- **Poor or intermediate metabolizers** of Clopidogrel exhibit resistance to the drug and will either require higher dose levels or alternative therapies.

- **Ultra-Rapid metabolizers** have an enhanced response to Clopidogrel and thus experience an increased risk of bleeding.

- **Extensive (normal) metabolizers** will obtain the maximum benefits of standard Clopidogrel therapy.

### Allele Mutation Enzyme Activity

<table>
<thead>
<tr>
<th>Allele</th>
<th>Mutation</th>
<th>Enzyme Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>*2</td>
<td>681 G&gt;A</td>
<td>Non-functional</td>
</tr>
<tr>
<td>*3</td>
<td>636 G&gt;A</td>
<td>Non-functional</td>
</tr>
<tr>
<td>*4</td>
<td>1 A&gt;T</td>
<td>Non-functional</td>
</tr>
<tr>
<td>*5</td>
<td>1297 C&gt;T</td>
<td>Non-functional</td>
</tr>
<tr>
<td>*6</td>
<td>395 G&gt;A</td>
<td>Non-functional</td>
</tr>
<tr>
<td>*7</td>
<td>19294 T&gt;A</td>
<td>Non-functional</td>
</tr>
<tr>
<td>*8</td>
<td>358 T&gt;C</td>
<td>Non-functional</td>
</tr>
<tr>
<td>*9</td>
<td>431 G&gt;A</td>
<td>Decreased</td>
</tr>
<tr>
<td>*10</td>
<td>680 C&gt;T</td>
<td>Decreased</td>
</tr>
<tr>
<td>*13</td>
<td>1228 C&gt;T</td>
<td>Decreased</td>
</tr>
<tr>
<td>*17</td>
<td>-806 C&gt;T</td>
<td>Increased Expression</td>
</tr>
</tbody>
</table>

**Allele Mutation Enzyme Activity**

- *1 Normal
- *2 681 G>A Non-functional
- *3 636 G>A Non-functional
- *4 1 A>T Non-functional
- *5 1297 C>T Non-functional
- *6 395 G>A Non-functional
- *7 19294 T>A Non-functional
- *8 358 T>C Non-functional
- *9 431 G>A Decreased
- *10 680 C>T Decreased
- *13 1228 C>T Decreased
- *17 -806 C>T Increased Expression

**FDA’s march 2010 black box warning:**

- “Effectiveness of PLAVIX depends on activation to active metabolite by cytochrome P450 (CYP) system, principally CYP2C19
- Poor metabolizers treated with PLAVIX at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function
- Tests are available to identify a patient’s CYP2C19 genotype and can be used as an aid in determining therapeutic strategy
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers”


**For more information or questions on CYP2C19 Genotyping please call Domnita Crisan, M.D., Ph.D. at 248-551-7261 or a Customer Service Agent at 800-551-0488.**