Cytochrome P450 2D6/2C19

<table>
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<tr>
<th>TESTS</th>
<th>RESULT</th>
<th>FLAG</th>
<th>UNITS</th>
<th>REFERENCE INTERVAL</th>
<th>LAB</th>
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<td>2D6 Genotype:</td>
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<td>2C19 Metabolic Activity:</td>
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Interpretation:

Ultrarapid metabolizers (UM) have elevated enzyme activity. For drugs that are active when administered, ultrarapid metabolizers may not reach therapeutic levels due to rapid clearance. For drugs that require activation, ultrarapid metabolizers may be at increased risk for adverse reactions due to higher than expected concentrations of active metabolite.

Normal (extensive) metabolizers (EM) are anticipated to have normal enzyme activity. For CYP2D6, there is a range of enzyme activity within this category. The distinction between normal and intermediate metabolizer differs between publications and may differ depending on the drug in question.

Intermediate to normal metabolizers (IM-EM) are anticipated to have a range of reduced to normal enzyme activity.

Intermediate metabolizers (IM) have reduced enzyme activity, and may experience some, or none, of the consequences similar to poor metabolizers.

Poor metabolizers (PM) have significantly reduced or absent enzyme activity. Drugs are metabolized slowly or not at all. For drugs that are active when administered, poor metabolizers may have increased concentrations of active drug with potential for serious side effects. For drugs that require activation, poor metabolizers may have lower than expected concentrations of active metabolite and limited effect of the therapy.
The metabolism of drugs is also influenced by ethnicity, diet, and other drugs. All factors should be considered prior to initiating new therapy. This testing does not rule out the possibility of variant alleles in other drug metabolism pathways.

Common drugs metabolized by 2D6 include, but are not limited to:

**OPIOIDS:** Codeine, dihydrocodeine, hydrocodone, oxycodone, tramadol

**BETA-BLOCKERS:** Carvedilol, S-metoprolol, Propafenone, Propranolol, Timolol

**CARDIOREACTIVE DRUGS:** Encainide, Flecaïnide, Lidocaine, Mexiletine, Phexilin

**ANTIDEPRESSANTS:** Amitriptyline, Clomipramine, Desipramine, Doxepin (E-isomers), Fluoxetine, Fluvoxamine, Imipramine, Maprotiline, Nortriptyline, Paroxetine, Venlafaxine

**ANTIPSYCHOTICS:** Haloperidol, Perphenazine, Risperidone, Thioridazine, Zuclopenthixol

**OTHERS:** Tamoxifen, Ondansetron, Phenformin

Common drugs metabolized by 2C19 include, but are not limited to:

**PLATELET AGGREGATION INHIBITOR:** CLOPIDOGREL

Poor metabolizers (PM) and intermediate metabolizers (IM) are at risk for recurrence of cardiovascular atherosclerotic disease. Alternative antiplatelet agents are recommended for PM patients and may be considered for IM patients, if not clinically contraindicated. Ultrarapid metabolizers (UM) may have an enhanced response to clopidogrel, and may be at increased risk of bleeding. Standard dosing may be considered for UM patients. Co-administration of clopidogrel alongside CYP2C19 inhibitors can reduce clopidogrel's platelet inhibition.

**TRI-CYCLIC ANTIDEPRESSANTS (TCA):** AMITRIPTYLINE, NORTRIPTYLINE

Important Interactions: Studies suggest that PMs may benefit from a lower starting dose.

**SELECT SEROTONIN REUPTAKE INHIBITOR (SSRI):** CITALOPRAM, SERTRALINE

Important Interactions: Mean clearance rates may be decreased in PMs as compared with EMs. Studies suggest that PMs may be at risk for SSRI related cardiotoxicity.
### TESTS

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<th>PROTON PUMP INHIBITORS: OMEPRAZOLE</th>
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<td>Important Interactions: Data suggests improved cure rates for EM and PM with double or triple therapy.</td>
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<th>ANTI-EPILEPTICS: DIAZEPAM, PHENYTOIN</th>
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<td>Important Interactions: Diazepam half-life is significantly prolonged in 2C19 PM and may cause prolonged sedation, particularly if administered with inhibitors of 2C19.</td>
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This is not intended to be comprehensive lists of drugs metabolized by CYP2D6 and/or CYP2C19. Healthcare providers are encouraged to consult the current literature, the package insert of any medication considered, or contact the drug manufacturer for specific drug information.

### CYP2D6/2C19 Information:

Cytochrome P450 enzymes (including 2D6 and 2C19) are involved in the hepatic metabolism of a large percentage of clinically relevant drugs. Of all drugs, 25-30% are metabolized by CYP2D6.

The 2C19 phenotype assigned is based on an FDA-cleared algorithm introduced in 2005 using the highest functioning allele to predict the enzyme activity for that individual. Emerging data suggests that, at least for some drugs such as clopidogrel, gene dosage drug response differences can be clinically significant.

Methodology:

DNA analysis of the Cytochrome P450 2D6 gene (OMIM 124030) and Cytochrome P450 2C19 gene (OMIM 124020, 10q24.1-10q24.3) is performed using primer extension chemistry. Multiplex PCR amplifies DNA fragments containing the variants below. Primer extension then generates a biotin-labeled product to permit flow-sorted detection of both normal and variant sequences. Molecular-based testing is highly accurate, but as in any laboratory test, rare diagnostic errors may occur.

### Alleles Detected for CYP2D6:

*1,*2,*3,*4,*5,*6,*7,*8,*9,*10,*11,*15,*29,*35,*41, and gene duplications.

Variant *5 is a gene deletion. Copy number of duplicated alleles is not determined. Duplications are often functional (whole gene) but may be nonfunctional (partial gene). It is not always possible to determine which allele is duplicated.

### Alleles Detected for CYP2C19:

*1,*2,*3,*17

*1 represents detection of the normal sequence for the
variant sites tested. This assay does not detect other variants in the CYP2D6 or CYP2C19 genes that may affect metabolic activity.

Buccal cells for CYP2D6 and 2C19: This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.

References:
7. LabCorp Pharmacogenetic Testing flyer (L14582). Available upon request.

Director Review:
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ABNORMAL, 511905

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Description of Predicted Metabolic Activity Types:

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