Cytochrome P450 2D6, CYP2D6

Indications for Ordering

- Assess genetic risk of abnormal drug metabolism for drugs metabolized by CYP2D6
- Investigate genetic causes that might contribute to a personal or family history of an adverse drug event or therapeutic failure involving a drug metabolized by CYP2D6

Test Description

Polymerase chain reaction (PCR)/fluorescence monitoring
- Gene duplication also assessed

Tests to Consider

Primary test
Cytochrome P450 2D6 (CYP2D6) 15 Variants and Gene Duplication 2014547
- May aid in drug selection and dose planning for drugs metabolized by CYP2D6

Related tests
- Many drugs can be metabolized by alternative cytochrome P450 (CYP) enzymes
- Single gene tests available separately
  - Cytochrome P450 2C9, CYP2C9 – 2 Variants 2012766
  - Cytochrome P450 2C19, CYP2C19 – 9 Variants 2012769
  - Cytochrome P450 3A5 Genotyping, CYP3A5, 2 Variants 2012740
- Panel includes a comprehensive medication guide based on the genotypes detected
  - Cytochrome P450 Genotype Panel 2013098
  - See sample Enhanced Report for panel test
- Therapeutic drug monitoring and/or metabolic ratios may be useful for evaluating the pharmacokinetics of a particular drug for a particular patient
  - See the ARUP Laboratory Test Directory
    (www.aruplab.com/) for a list of available drug-specific testing (search by test name or number)

Disease Overview

Prevalence
- Allele frequencies differ among ethnic groups
- See Table 1 for allele frequencies

Predicted Phenotypes
- Poor metabolizer
  - 2 no function alleles
  - May result in few to no drug metabolites when the parent drug is a substrate of CYP2D6; activity score prediction is 0 of 2
- Intermediate metabolizer
  - 1 no function allele and 1 decreased function allele
  - May result in lower levels of drug metabolites when the parent drug is a substrate of CYP2D6; activity score prediction is <1 of 2
  - Avoid concomitant use of CYP2D6 inhibitors to prevent conversion of intermediate metabolizer to a poor metabolizer
- Normal metabolizer
  - 2 functional alleles
  - Normal levels of drug metabolites when the parent drug is a substrate of CYP2D6
  - Activity score prediction is 1-2 of 2
  - Avoid concomitant use of CYP2D6 inhibitors to prevent conversion of normal metabolizer to an intermediate or poor metabolizer
- Ultrarapid metabolizer
  - More than 2 copies of functional alleles (gene duplication)
  - May result in higher levels of drug metabolites when the parent drug is a substrate of CYP2D6; activity score prediction is >2
Treatment issues
• CYP2D6 is an isozyme involved in the metabolism of up to 25% of all clinically used drugs, including
  o Antiestrogens (eg, tamoxifen)
  o Alpha blockers
  o Analgesics
  o Anticonvulsives
  o Antidepressants (eg, nortriptyline)
  o Antidiabetics
  o Antihypertensives
  o Antipsychotics
  o Antitussives (eg, codeine)
  o Beta blockers
  o Cardioactives
  o Norepinephrine reuptake inhibitors
  o Stimulants
• Some drugs are
  o Activated by the pathway (eg, codeine)
  o Inactivated by the pathway (eg, nortriptyline)
• Pharmacogenetic variation may lead to inappropriate concentrations of drugs and metabolites, resulting in
  o Toxicity and risk for adverse drug reactions
  o Lack of therapeutic benefit
• Actual metabolic phenotype is subject to
  o Drug/drug and drug/food interactions
  o Clinical factors
  o Other nongenetic factors

Treatment guidelines
• The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published dosing guidelines for CYP2D6 genotypes and
  o Codeine – refer to CPIC dosing guideline (www.pharmgkb.org/guideline/PA166104996)
  o Tricyclic antidepressants (eg, nortriptyline) – refer to CPIC dosing guideline (www.pharmgkb.org/guideline/PA166105006)
  o Selective serotonin reuptake inhibitors (eg, citalopram) – refer to CPIC dosing guideline (www.pharmgkb.org/guideline/PA166127638)

Genetics

Gene – CYP2D6
Inheritance – autosomal codominant
Penetrance – drug dependent
Variants detected – see Table 2
Structure/function – located on chromosome 22

Test Interpretation

Sensitivity/specificity
• Clinical sensitivity – drug dependent
• Analytical sensitivity/specificity – >99%

Results
• By report
• No variants detected (negative) – predictive of *1 functional allele and normal enzymatic activity

Limitations
• Only the targeted CYP2D6 variants will be detected
• Combination of *5 (gene deletion) and gene duplication cannot be specifically identified
  o Combination is not expected to adversely affect the prediction of activity score or phenotype
• Diagnostic errors can occur due to rare sequence variations
• Risk of therapeutic failure or adverse reactions with CYP2D6 substrates may be affected by genetic and nongenetic factors that are not detected by this test
• This result does not replace the need for therapeutic drug or clinical monitoring

References
### Table 1. Allele Frequencies

<table>
<thead>
<tr>
<th>Allele</th>
<th>African</th>
<th>Asian</th>
<th>Caucasian</th>
<th>Middle Eastern</th>
<th>Oceanian</th>
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<tbody>
<tr>
<td>CYP2D6<em>2 or CYP2D6</em>2A</td>
<td>17.6%</td>
<td>21.2%</td>
<td>27.6%</td>
<td>21.7%</td>
<td>1.2%</td>
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<tr>
<td>CYP2D6*3</td>
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<td>0%</td>
<td>1.3%</td>
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<tr>
<td>CYP2D6*4</td>
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<td>4.6%</td>
<td>18.2%</td>
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<td>CYP2D6*5</td>
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<td>4.3%</td>
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<td>2.3%</td>
<td>4.3%</td>
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<td>CYP2D6*6</td>
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<td>CYP2D6*7</td>
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<td>0%</td>
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<td>0%</td>
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<td>CYP2D6*8</td>
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<td>0%</td>
<td>0%</td>
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<td>CYP2D6*9</td>
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<td>0.5%</td>
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<td>CYP2D6*10</td>
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<td>CYP2D6*14</td>
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<td>0.4%</td>
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<td>0%</td>
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<td>CYP2D6*17</td>
<td>19.0%</td>
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<td>0.4%</td>
<td>1.6%</td>
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<td>CYP2D6*29</td>
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<td>0.8%</td>
<td>0%</td>
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<tr>
<td>CYP2D6*36</td>
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<td>0%</td>
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<td>0%</td>
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<tr>
<td>CYP2D6*41</td>
<td>9.2%</td>
<td>4.9%</td>
<td>7.9%</td>
<td>19.9%</td>
<td>0.9%</td>
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<tr>
<td>CYP2D6xN (gene duplication)</td>
<td>4.7%</td>
<td>1.6%</td>
<td>2.6%</td>
<td>7.1%</td>
<td>11.8%</td>
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</tbody>
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### Table 2. Variants Detected

<table>
<thead>
<tr>
<th>Allele Designation</th>
<th>Nucleotide Change (Numbered According to M33388 sequence)</th>
<th>Reference Sequence Identifier</th>
<th>Predicted Enzyme Activity</th>
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<tbody>
<tr>
<td>*2</td>
<td>2850C&gt;T</td>
<td>rs16947</td>
<td>Functional (normal)</td>
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<tr>
<td>*2A</td>
<td>-1584C&gt;G; 2850C&gt;T</td>
<td>rs1080985, rs16947</td>
<td>Functional (normal)</td>
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<tr>
<td>*3</td>
<td>2549delA</td>
<td>rs35742686</td>
<td>Nonfunctional</td>
</tr>
<tr>
<td>*4</td>
<td>100C&gt;T; 1846G&gt;A</td>
<td>rs3892097</td>
<td>Nonfunctional</td>
</tr>
<tr>
<td>*5</td>
<td>Gene deletion</td>
<td></td>
<td>Nonfunctional</td>
</tr>
<tr>
<td>*6</td>
<td>1707delT</td>
<td>rs5030655</td>
<td>Nonfunctional</td>
</tr>
<tr>
<td>*7</td>
<td>2935A&gt;C</td>
<td>rs5030867</td>
<td>Nonfunctional</td>
</tr>
<tr>
<td>*8</td>
<td>1758G&gt;T; 2850C&gt;T</td>
<td>rs5030865</td>
<td>Nonfunctional</td>
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<tr>
<td>*9</td>
<td>2613-5delAGA</td>
<td>rs5030656</td>
<td>Decreased function</td>
</tr>
<tr>
<td>*10</td>
<td>100C&gt;T</td>
<td>rs1065852</td>
<td>Decreased function</td>
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<td>*12</td>
<td>124G&gt;A; 2850C&gt;T</td>
<td>rs5030862</td>
<td>Nonfunctional</td>
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<td>*14</td>
<td>1758G&gt;A; 2850C&gt;T</td>
<td>rs5030865</td>
<td>Nonfunctional</td>
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<tr>
<td>*17</td>
<td>1023C&gt;T; 2850C&gt;T</td>
<td>rs28371706</td>
<td>Decreased function</td>
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<tr>
<td>*29</td>
<td>1659G&gt;A; 2850C&gt;T</td>
<td>rs59421388</td>
<td>Decreased function</td>
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<tr>
<td>*36</td>
<td>*10 carrying a CYP2D7-derived exon 9 conversion</td>
<td></td>
<td>Nonfunctional</td>
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<td>*41</td>
<td>2988G&gt;A; 2850C&gt;T</td>
<td>rs28371725</td>
<td>Decreased function</td>
</tr>
</tbody>
</table>

Duplication of functional alleles | Increased function |