Cytochrome P450 Genotype Panel

Indications for Ordering

• Assess genetic risk of abnormal drug metabolism for drugs metabolized by CYP2D6, CYP2C9, CYP2C19, and CYP3A5
• Predicts extremes of metabolism leading to excess parent drug (poor metabolizers) or excess metabolite (ultra-rapid metabolizers)
• May aid in drug selection and dose planning for many drugs

Test Description

Polymerase chain reaction/fluorescence monitoring

Tests to Consider

Primary test
Cytochrome P450 Genotype Panel 2013098

• Includes a comprehensive medication recommendation report based on the genotypes detected

Related tests

• Many drugs can be metabolized by alternative cytochrome P450 (CYP) enzymes
• Single gene tests available separately
  ○ Cytochrome P450 2D6 (CYP2D6) 14 Variants and Gene Duplication 0051232
  ○ Cytochrome P450 2C9, CYP2C9 – 2 Variants 2012766
  ○ Cytochrome P450 2C19, CYP2C19 – 9 Variants 2012769
  ○ Cytochrome P450 3A5 Genotyping, CYP3A5, 2 Variants 2012740
• 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.arulab.com) for a list of available drug-specific testing

Disease Overview

Treatment issues

• Drug use is widespread
• Variants in genes affecting the CYP pathways may result in altered drug metabolism
• CYP2D6, CYP2C9, CYP2C19, and CYP3A5 metabolic phenotypes may be predicted by genotype
• Combined effect of variant CYP2D6, CYP2C9, CYP2C19, and CYP3A5 genotypes on phenotype is not well understood
• Predicted phenotype may be helpful clinically for drug and dose selection decisions
  ○ Based on whether a drug is activated or inactivated by the respective CYP enzyme
• When drugs metabolized by the CYP enzymes are administered, variant genotypes are associated with
  ○ Increased potential for adverse drug reactions
  ○ Therapeutic failure
  ○ Increased risk of drug/drug interactions
• Other factors also impact drug metabolism
  ▪ Drug/drug or food/drug interactions
  ▪ Age-related changes in pharmacokinetics
  ▪ Impact of disease on pharmacokinetics
  ▪ Body size

• Refer to P450 Drug Interaction Table for drug substrates/inhibitors/inducers for CYP
• Refer to CPIC Gene-Drug Pairs

Genes – CYP2D6, CYP2C9, CYP2C19, CYP3A5

• Refer to Anaesthetist.com for an overview of cytochrome P450
• Refer to The Human Cytochrome P450 (CYP) Allele Nomenclature Database

Allele frequencies – see Table 1

Inheritance – autosomal codominant

Penetrance – drug dependent

Variants detected – see Table 2 for alleles tested and effect of functionality of CYP450 pathways

Test Interpretation

Sensitivity/specificity

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

Results

Refer to the ARUP Cytochrome P450 Genotype Panel report

Reported metabolizer phenotypes include

• Normal
  ○ Two functional alleles, or specific combinations of alleles, as defined per gene
  ○ When no variants are detected; consistent with *1 alleles
• Poor
  ○ Two nonfunctional alleles
• Intermediate (metabolizing at a rate between poor and normal)
  ○ Gene dependent
• Rapid or ultra-rapid
  o Presence of increased functional allele(s)
  o More than two copies of a functional allele
• CYP2D6 gene duplication detected
  o Specific allele duplicated may not be determined
  o Metabolizer phenotype may not be predicted

Limitations
• Only the targeted CYP2D6, CYP2C9, CYP2C19, and CYP3A5 variants will be detected
• Diagnostic errors can occur due to rare sequence variations
• Risk of therapeutic failure or adverse reactions with CYP2D6, CYP2C9, CYP2C19, or CYP3A5 substrates may be affected by genetic and nongenetic factors that are not detected by this test
• Variant detection does not replace
  o Therapeutic drug monitoring
  o Clinical monitoring

References
• Coriell Life Sciences (www.coriell.com)
• GeneDose (http://genedose.com/)
• The Human Cytochrome P450 (CYP) Allele Nomenclature Database (www.cypalleles.ki.se/)

<table>
<thead>
<tr>
<th>Allele</th>
<th>Populations</th>
</tr>
</thead>
</table>
| CYP2D6 Incidence of phenotypes | Poor metabolizer
  • Caucasians and Hispanics 10%
  • African Americans 2%
  • Asians 1%
  Intermediate metabolizer
  • 2-11% of most populations
  Ultra-rapid metabolizer
  • 1-2% of most populations |
| CYP2C9*2  | Caucasians 13%
           | African Americans 3%
           | Asians <1% |
| CYP2C9*3  | Caucasians 7%
           | Asians 4%
           | African Americans 2% |
| CYP2C19*2 | Oceanian 54.9%
           | South Asian 34.4%
           | African American 18.3%
           | Caucasian 14.6%
           | Middle Eastern 13.2% |
| CYP2C19*3 | Oceanian 13.9%
           | East Asian 8.5%
           | Middle Eastern 2.6%
           | Caucasian 0.6%
           | African American 0.3% |
| CYP2C19*17| Caucasian 21.5%
           | African American 19.4%
           | South Asian 16.5%
           | Oceanian 2.5% |
| CYP3A5*3  | Caucasian 92.1%
           | Middle Eastern 88.1%
           | Latin American 76.5%
           | Asian 74.2%
           | African 29.8% |
| CYP3A5*6  | African 17.2%
           | Latin American 3.7%
           | Middle Eastern 1.9%
           | Asian 0.1%
           | Caucasian 0.1% |
| CYP3A5*7  | African 7.7%
           | Latin American 2.5%
           | Middle Eastern 0.2%
           | Asian 0%
<pre><code>       | Caucasian 0% |
</code></pre>
<table>
<thead>
<tr>
<th>Gene (reference sequence)</th>
<th>Allele Function</th>
<th>No Function</th>
<th>Decreased Function</th>
<th>Functional</th>
<th>Increased Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP2D6</strong> (M33388 sequence)</td>
<td>*3 (rs35742686, 2549delA)</td>
<td>*4 (rs3892097, c.1846G&gt;A)</td>
<td>*5 (gene deletion)</td>
<td>*7 (rs5030867, 2935A&gt;C)</td>
<td>*8 (rs5030865, 1758G&gt;T)</td>
</tr>
<tr>
<td><strong>CYP2C9</strong> (NM_000771)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CYP2C19</strong> (NM_000769)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CYP3A5</strong> (NG_000004.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>