Cytochrome P450 2C19, CYP2C19

Indications for Ordering

- Assess genetic risk of abnormal drug metabolism for drugs metabolized by CYP2C19
- 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 CYP2C19

Test Description

Polymerase chain reaction (PCR)/fluorescence monitoring
- Variant alleles detected – *2 to *4, *6 to *10, *17

Tests to Consider

Primary test
**Cytochrome P450 2C19, CYP2C19 – 9 Variants 2012769**
- May aid in drug selection and dose planning for drugs metabolized by CYP2C19

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 2D6 (CYP2D6) 15 Variants and Gene Duplication 2014547**
  - **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
- Most common nonfunctional alleles are *2 and *3
  - **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%
- Increased function allele
  - **CYP2C19*17** – Caucasian 21.5%, African American 19.4%, South Asian 16.5%, Oceanian 2.5%

Predicted Phenotypes

- Poor metabolizer phenotype
  - 2 no function alleles
  - May result in few to no drug metabolites when the parent drug is a substrate of CYP2C19

- Intermediate metabolizer phenotype
  - 1 no function allele with a functional or *17 allele
  - May result in lower levels of drug metabolites when the parent drug is a substrate of CYP2C19

- Normal metabolizer
  - 2 functional alleles
  - Normal levels of drug metabolites when the parent drug is a substrate of CYP2C19

- Rapid metabolizer
  - One CYP2C19*17 with a functional allele
  - May result in moderately higher levels of drug metabolites when the parent drug is a substrate of CYP2C19

- Ultrarapid metabolizer
  - 2 *17 alleles
  - May result in much higher levels of drug metabolites when the parent drug is a substrate of CYP2C19

Treatment issues

- CYP2C19 is an isoenzyme involved in the metabolism of many clinically used drugs, including
  - Antidepressants
  - Antimalarials
  - Clopidogrel
  - Diazepam
  - Phenytoin
  - Proton pump inhibitors
  - R-warfarin
  - Selective serotonin reuptake inhibitors
  - Tamoxifen
Some drugs are
- Activated by the pathway (e.g., clopidogrel)
- Inactivated by the pathway (e.g., citalopram)
Pharmacogenetic variation may lead to inappropriate concentrations of drugs and metabolites, resulting in
- Toxicity and risk of adverse drug reactions
- Lack of therapeutic benefit
Actual metabolic phenotype is subject to
- Drug/drug interactions
- Clinical factors
- Other nongenetic factors

Treatment guidelines
- The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published dosing guidelines for CYP2C19 genotypes and
- Clopidogrel (e.g., Plavix) – refer to CPIC dosing guideline (https://www.pharmgkb.org/guideline/PA166104948)
- Tricyclic antidepressants (e.g., amitriptyline) – refer to CPIC dosing guideline (https://www.pharmgkb.org/guideline/PA166105006)
- Selective serotonin reuptake inhibitors (e.g., citalopram) – refer to CPIC dosing guideline (https://www.pharmgkb.org/guideline/PA166127638)

Genetics
Gene – CYP2C19
Inheritance – autosomal codominant
Penetrance – drug dependent
Variants detected – see table
Structure/function – located on chromosome 10

Test Interpretation

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

Results
- By report

Limitations
- Only the targeted CYP2C19 variants will be detected
- Diagnostic errors can occur due to rare sequence variations
- Risk of therapeutic failure or adverse reactions with CYP2C19 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>
<thead>
<tr>
<th>Variants Detected</th>
<th>Nucleotide Change (NM_000769)</th>
<th>Reference Sequence Identifier</th>
<th>Variant Effect</th>
<th>Predicted Enzyme Activity</th>
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<td>c.681G&gt;A</td>
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