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 (eg, clopidogrel)
  - Inactivated by the pathway (eg, 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 (eg, Plavix) – refer to CPIC dosing guideline (https://www.pharmgkb.org/guideline/PA166104948)
  - Tricyclic antidepressants (eg, amitriptyline) – refer to CPIC dosing guideline (https://www.pharmgkb.org/guideline/PA166105006)
  - Selective serotonin reuptake inhibitors (eg, 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

- Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. www.pharmgkb.org. Accessed Aug 2017
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake. www.pharmgkb.org. Accessed Aug 2017
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic. www.pharmgkb.org. Accessed Aug 2017
- The Human Cytochrome P450 (CYP) allele Nomenclature Database. http://www.pharmvar.org/htdocs/archive/index_original.htm. Accessed Nov 2017

Variants Detected				
Allele Designation	**Nucleotide Change (NM_000769)**	**Reference Sequence Identifier**	**Variant Effect**	**Predicted Enzyme Activity**
**2*	c.681G>A	rs4244285	Splicing defect	Nonfunctional
**3*	c.636G>A	rs4986893	Creates stop codon	Nonfunctional
**4*	c.1A>G	rs28399504	Loss of initiation codon	Nonfunctional
**6*	c.395G>A	rs72552267	R132Q	Nonfunctional
**7*	c.819+2T>A	rs72558186	Splicing defect	Nonfunctional
**8*	c.358T>C	rs41291556	W120R	Nonfunctional
**9*	c.431G>A	rs17884712	R114H	Decreased function
**10*	c.680C>T	rs6413438	P227L	Decreased function
**17*	c.-806C>T	rs12248560	Increased gene transcription	Increased function