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.aruplab.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
  - Presence of increased functional allele(s)
  - More than two copies of a functional allele
- *CYP2D6* gene duplication detected
  - Specific allele duplicated may not be determined
  - 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
  - Therapeutic drug monitoring
  - Clinical monitoring

References

- Anaesthetist. Cytochrome P450 (www.anaesthetist.com/physiol/basics/metabol/cyp/Findex.htm). Last updated Oct 2006. Accessed Jan 2016
- Clinical Pharmacogenetics Implementation Consortium. CPIC Gene-Drug Pairs (www.pharmgkb.org/page/cpicGeneDrugPairs). PharmGKB, Stanford University, Stanford, CA. Accessed Jan 2016
- Coriell Life Sciences (www.coriell.com)
- Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). (http://medicine.iupui.edu/clinpharm/ddis/main-table) Accessed Jan 2016
- GeneDose (http://genedose.com/)
- The Human Cytochrome P450 (*CYP*) Allele Nomenclature Database (www.cypalleles.ki.se/)

Table 1. Common Allele Frequencies
Coriell Life Sciences and GeneDose

Allele	Populations
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% Caucasian 0%%

Table 2. Expected Functionality for CYP450 Pathways Based on Allelic Variants (*CYP2D6*, *CYP2C9, CYP2C*19, and *CYP3A5*)				
Gene (reference sequence)	**Allele Function**			
	No Function	**Decreased Function**	**Functional**	**Increased Function**
CYP2D6 (M33388 sequence)	*3 (rs35742686, 2549delA) *4 (rs3892097, c.1846G>A) *5 (gene deletion) *6 (rs5030655, 1707delT) *7 (rs5030867, 2935A>C) *8 (rs5030865, 1758G>T) *12 (rs5030862, 124G>A) *14 (rs5030865, 1758G>A)	*9 (rs5030656, 2613-5delAGA) *10 (rs1065852, 100C>T) *17 (rs28371706, 1023C>T) *29 (rs59421388, 1659G>A) *41 (rs28371725, 2988G>A)	*2 or *2A (rs16947, 2850C>T; rs1080985, -1584C>G, 2850C>T)	Duplicated functional alleles such as *1xN and *2xN
CYP2C9 (NM_000771)		*2 (rs1799853, c.430C>T) *3 (rs1057910, c.1075A>C)		
CYP2C19 (NM_000769)	*2 (rs4244285, c.681G>A) *3 (rs4986893, c.636G>A) *4 (rs28399504, c.1A>G) *6 (rs72552267, c.395G>A) *7 (rs72558186, c.819+2T>A) *8 (rs41291556, c.358T>C)	*9 (rs17884712, c.431G>A) *10 (rs6413438, c.680C>T)		*17 (rs12248560, c.-806C>T) Increased gene transcription
CYP3A5 (NG_000004.3)	*3 (rs776746, c.6986A>G) *6 (rs10264272, c.14690G>A)			