Cytochrome P450 Genotyping

The cytochrome P450 (CYP) isozymes 2C19, 2C8, 2C9, 2D6, and the CYP3A subfamily are involved in the metabolism of many drugs. Variants in the genes that code for these enzymes will influence pharmacokinetics of the respective medications, and may predict or explain nonstandard dose requirements, therapeutic failure, or adverse reactions.

DISEASE OVERVIEW

Treatment Issues

- Actual metabolic phenotype is subject to drug/drug interactions, clinical factors, and other nongenetic factors.
- 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).
- The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Food and Drug Administration (FDA) have published dosing guidelines involving *CYP* genotypes (https://cpicpgx.org/guidelines/), such as:
  - Clopidogrel (eg, Plavix): refer to CPIC dosing guideline
  - Codeine: refer to CPIC dosing guideline
  - Mayzent (siponimod): refer to dosage section of FDA labeling
  - Ondansetron and Tropiesetron: refer to CPIC dosing guideline
  - Phenytoin (eg, Dilantin): refer to CPIC dosing guideline
  - Selective serotonin reuptake inhibitors (eg, citalopram): refer to CPIC dosing guideline
  - Tacrolimus (eg, Prograf): refer to CPIC dosing guideline
  - Tamoxifen: refer to CPIC dosing guideline
  - Tricyclic antidepressants (eg, amitriptyline): refer to CPIC dosing guideline
  - Voriconazole: refer to CPIC dosing guideline
  - Warfarin (eg, Coumadin): refer to CPIC dosing guideline

GENETICS

Genes

CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4, CYP3A5

Inheritance

Autosomal codominant

Tests to Consider

Cytochrome P450 Genotyping Panel 3001524

Method: Polymerase Chain Reaction/Fluorescence Monitoring

- Assesses genetic variants contributing to risk of abnormal drug metabolism for drugs metabolized by enzymes coded by *CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4*, and *CYP3A5*.
- May aid in drug selection and dose planning for many drugs that are either activated or inactivated by one or more CYP450 enzymes. Recommendations may include drug avoidance or nonstandard dosing.
- Report includes comprehensive medication guidance based on the genotypes detected and access to GeneDose Live, a cloud-based medication management and risk mitigation tool.

Related Tests

CYP2C19 3001508

Method: Polymerase Chain Reaction/Fluorescence Monitoring

Assesses genetic risk of abnormal drug metabolism for CYP2C19 substrates. May aid in drug selection and dose planning.

CYP2C8 and CYP2C9 3001501

Method: Polymerase Chain Reaction/Fluorescence Monitoring

Assess genetic risk of abnormal drug metabolism for CYP2C8 and/or CYP2C9 substrates. May aid in drug selection and dose planning.

CYP2D6 3001513

Method: Polymerase Chain Reaction/Fluorescence Monitoring

Assesses genetic risk of abnormal drug metabolism for CYP2D6 substrates. Includes detection of common copy number variations and gene hybrids. May aid in drug selection and dose planning.

Variants Tested

Variants or groups of variants are classified as “star” (*) alleles, that are associated with predicted enzyme function, based on international consensus nomenclature. However, all variants are not detected and assumptions about phase are made, as shown below. More details about nomenclature, allele frequencies and phenotype predictions available at www.pharmvar.org or www.pharmgkb.org.

CYP3A4 and CYP3A5 3001518

Method: Polymerase Chain Reaction/Fluorescence Monitoring

Assesses genetic risk of abnormal drug metabolism for substrates of CYP3A4 and/or CYP3A5. May aid in drug selection and dose planning.

Gene (Transcript)	Alleles	Predicted Allele Function
CYP2C19 (NM_000769)	*CYP2C19*2*: rs4244285, c.681G>A; rs12769205, c.332-23A>G	No function
	*CYP2C19*3*: rs4986893, c.636G>A	No function
	*CYP2C19*4*: rs28399504, c.1A>G	No function
	*CYP2C19*5*: rs56337013, c.1297C>T	No function
	*CYP2C19*6*: rs72552267, c.395G>A	No function
	*CYP2C19*7*: rs72558186, c.819+2T>A	No function
	*CYP2C19*8*: rs41291556, c.358T>C	No function
	*CYP2C19*9*: rs17884712, c.431G>A	Decreased function
	*CYP2C19*10*: rs6413438, c.680C>T	Decreased function
	*CYP2C19*15*: rs17882687, c.55A>C	Functional
	*CYP2C19*17*: rs12248560, c.-806C>T	Increased function
	*CYP2C19*35*: rs12769205, c.332-23A>G	No function
CYP2C8 (NM_000770)	*CYP2C8*1C*: rs17110453, c.-370T>G	Unclassified
	*CYP2C8*2*: rs11572103, c.805A>T	Decreased function
	*CYP2C8*3*: rs10509681, c.1196A>G	Decreased function
	*CYP2C8*4*: rs1058930, c.792C>G	Probably decreased function
CYP2C9 (NM_000771)	*CYP2C9*2*: rs1799853, c.430C>T	Decreased function
	*CYP2C9*3*: rs1057910, c.1075A>C	Decreased function

	Alleles	Predicted Allele Function
	*CYP2C9*4*: rs56165452, c.1076T>C	Decreased function
	*CYP2C9*5*: rs28371686, c.1080C>G	Decreased function
	*CYP2C9*6*: rs9332131, c.818del	No function
	*CYP2C9*8*: rs7900194, c.449G>A	Decreased function
	*CYP2C9*11*: rs28371685, c.1003C>T	Decreased function
CYP2D6 **(M33388 sequence)**	*CYP2D6*2*: rs16947, g.2850C>T; rs1135840, g.4180G>C	Functional
	*CYP2D6*2A*: rs1080985, g.-1584C>G; rs16947, g.2850C>T; rs1135840, g.4180G>C	Functional
	*CYP2D6*3*: rs35743686, g.2549del	No function
	*CYP2D6*4*: rs1065852, g.100C>T; rs3892097, g.1846G>A; rs1135840, g.4180G>C	No function
	*CYP2D6*5*: gene deletion	No function
	*CYP2D6*6*: rs5030655, g.1707del; rs1135840, g.4180G>C	No function
	*CYP2D6*7*: rs5030867, g.2935A>C	No function
	*CYP2D6*8*: rs5030865, g.1758G>T; rs16947, g.2850C>T; rs1135840, g.4180G>C	No function
	*CYP2D6*9*: rs5030656, g.2615_2617del	Decreased function
	*CYP2D6*10*: rs1065852, g.100C>T; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*11*: rs1080985, g.-1584C>G; rs201377835, g.883G>C; rs16947, g.2850C>T; rs1135840, g.4180G>C	No function
	*CYP2D6*12*: rs5030862, g.124G>A; rs16947, g.2850C>T; rs1135840, g.4180G>C	No function
	*CYP2D6*13*: a CYP2D7-derived exon 1 conversion	No function
	*CYP2D6*14*: rs5030865, g.1758G>A; rs16947, g.2850C>T; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*15*: rs774671100, g.137_138insT	No function
	*CYP2D6*17*: rs28371706, g.1023C>T; rs16947, g.2850C>T; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*29*: rs16947, g.2850C>T; rs59421388, g.3183G>A; rs1135840, g.4180G>C	Decreased function

	Alleles	Predicted Allele Function
	*CYP2D6*35*: rs1080985, g.-1584C>G; rs769258, g.31G>A; rs16947, g.2850C>T; rs1135840, g.4180G>C	Functional
	*CYP2D6*36*: a CYP2D6*10 carrying a CYP2D7-derived exon 9 conversion	No function
	*CYP2D6*36-*10*: a *CYP2D6*36* and a *CYP2D6*10* in tandem	Decreased function
	*CYP2D6*41*: rs16947, g.2850C>T; rs28371725, g.2988G>A; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*45*: rs28371710, g.1716G>A; rs16947, g.2850C>T; rs1135840, g.4180G>C	Functional
	*CYP2D6*46*: rs28371696, g.77G>A; rs28371710, g1716G>A; rs16947, g.2850C>T; rs1135840, g.4180G>C	Functional
	*CYP2D6*49*: rs1065852, g.100C>T; rs1135822, g.1611T>A; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*53*: rs1135822, g.1611T>A	Functional
	*CYP2D6*69*: rs1065852, g.100C>T; rs16947, g.2850C>T; rs28371725, g.2988G>A; rs1135840, g4180G>C	No function
	*CYP2D6*114*: rs1065852, g.100C>T; rs5030865, g.1758G>A; rs16947, g.2850C>T; rs1135840, g.4180G>C	No function
	DUP. complete gene duplication	Varies based on the allele that is duplicated
CYP3A4 (NM_017460)	*CYP3A4*1B*: rs2740574, c.-392G>A	Unclassified
	*CYP3A4*15*: rs4986907, c.485G>A	Unclassified
	*CYP3A4*22*: rs35599367, c.522-191C>T	Decreased function
CYP3A5 (NM_000777)	*CYP3A5*3*: rs776746, c.219-237A>G	Severely decreased function
	*CYP3A5*6*: rs10264272, c.624G>A	Severely decreased function
	*CYP3A5*7*: rs41303343, c.1035dup	Probably severely decreased function

Results

- Genetic variant(s) detected: alleles detected are reported. The combination of alleles detected is used to predict metabolizer phenotype, and in the case of *CYP2D6*, the activity score. Phenotype predictions are subject to change as the scientific and clinical evidence evolves.
- No variants detected is predictive of **1* functional alleles.

TEST DESCRIPTION

- Polymerase chain reaction (PCR) and fluorescence monitoring
- Clinical sensitivity is drug dependent.
- Analytical sensitivity/specificity is greater than 99%.

Limitations

- Only the targeted *CYP2C19*, *CYP2C8*, *CYP2C9*, *CYP2D6*, *CYP3A4*, and *CYP3A5* variants will be detected by this this panel. Assumptions about phase and content are made to assign alleles.
- Diagnostic errors can occur due to rare sequence variations.
- A combination of the *CYP2D6*5* (gene deletion) and a *CYP2D6* gene duplication cannot be specifically identified; however, this combination is not expected to adversely affect the phenotype prediction.
- Risk of therapeutic failure or adverse reactions with gene substrates may be affected by genetic and nongenetic factors that are not detected by this test. The test result does not replace the need for therapeutic drug or clinical monitoring.

Additional Resources

Clinical Pharmacogenetics Implementation Consortium. CPIC guideline for clopidogrel and CYP2C19. [Updated: Mar 2017; Accessed: Jun 2020]

Clinical Pharmacogenetics Implementation Consortium. CPIC guideline for codeine and CYP2D6. [Updated: Oct 2019; Accessed: Jun 2020]

Clinical Pharmacogenetics Implementation Consortium. CPIC Guideline for ondansetron and tropisetron based on CYP2D6 genotype. [Last modified: Jan 2018; Accessed: Feb 2019]

Clinical Pharmacogenetics Implementation Consortium. CPIC guideline for pharmacogenetics-guided warfarin dosing. [Last modified: Apr 2019; Accessed: Apr 2019]

Clinical Pharmacogenetics Implementation Consortium. CPIC guideline for phenytoin and CYP2C9 and HLA-B. [Published: Nov 2014; Accessed: Jun 2020]

Clinical Pharmacogenetics Implementation Consortium. CPIC guideline for selective serotonin reuptake inhibitors and CYP2D6 and CYP2C19. [Updated: Oct 2019; Accessed: Jun 2020]

Clinical Pharmacogenetics Implementation Consortium. CPIC Guideline for tacrolimus and CYP3A5. [Last modified: Nov 2018; Accessed: Feb 2019]

Clinical Pharmacogenetics Implementation Consortium. CPIC Guideline for tamoxifen based on CYP2D6 genotype. [Last modified: Feb 2019; Accessed: Feb 2019]

Clinical Pharmacogenetics Implementation Consortium. CPIC guideline for tricyclic antidepressants and CYP2D6 and CYP2C19. [Updated: Oct 2019; Accessed: Jun 2020]

Clinical Pharmacogenetics Implementation Consortium. CPIC Guideline for voriconazole and CYP2C19. [Last modified: Feb 2019; Accessed: Feb 2019]

Clinical Pharmacogenetics Implementation Consortium. CPIC Guidelines. [Last modified: Nov 2018; Accessed: Feb 2019]

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