Cytochrome P450 Pain Management Panel, *CYP2D6, CYP2C9, CYP2C19* – Common Variants

Indications for Ordering

Assess genetic risk for altered cytochrome P450 (CYP) CYP2D6-, CYP2C9-, and CYP2C19-mediated drug metabolism

Test Description

- *CYP2D6* – polymerase chain reaction/primer extension
- *CYP2C9* and *CYP2C19* – polymerase chain reaction/ fluorescence monitoring

Tests to Consider

Primary test

Cytochrome P450 Pain Management Panel, *CYP2D6, CYP2C9, CYP2C19* – Common Variants 2008920

- May aid in drug selection and dose planning for drugs metabolized by CYP2D6, CYP2C9, and CYP2C19
- Single gene tests for *CYP2D6, CYP2C9,* and *CYP2C19* are available separately

Related tests

Cytochrome P450 2D6 (*CYP2D6*) 14 Variants and Gene Duplication 0051232

- May aid in drug selection and dose planning for drugs metabolized by CYP2D6

Cytochrome P450 2C9, *CYP2C9* – 2 Variants 2012766

- May aid in drug selection and dose planning for drugs metabolized by CYP2C9

Cytochrome P450 2C19, *CYP2C19* – 9 Variants 2012769

- May aid in drug selection and dose planning for drugs metabolized by CYP2C19

Disease Overview

Treatment issues

- Drug use is widespread
- Variants in genes affecting the CYP pathways may result in altered drug metabolism
- CYP2D6, CYP2C9, and CYP2C19 metabolic phenotypes may be predicted by genotype
- Combined effect of variant *CYP2D6*, *CYP2C9*, and *CYP2C19* 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
  - Pharmacodynamic factors
    - Not detected by this test
  - Nongenetic factors
    - Drug/drug or food/drug interactions
    - Age-related changes in pharmacokinetics
    - Impact of disease on pharmacokinetics
    - Body size
- Refer to P450 Drug Interaction Table (medicine.iupui.edu/clinpharm/ddis/main-table/) for drug substrates/inhibitors/inducers for CYP (Flockhart DA, Indiana University School of Medicine, 2013)
- See Table 1
- Refer to Clinical Pharmacogenetics Implementation Consortium (CPIC) Gene-Drug Pairs (www.pharmgkb.org/page/cpicGeneDrugPairs)

Genetics

Genes – *CYP2D6, CYP2C9, CYP2C19*

- Refer to Anaesthetist.com for overview of CYP genes (www.anaesthetist.com/physiol/basics/metabol/cyp/Findex.htm)
- Refer to The Human Cytochrome P450 (*CYP*) Allele Nomenclature Database (www.cypalleles.ki.se/)

Allele frequencies – see Table 2

Inheritance – autosomal codominant

Penetrance – drug dependent

Variants detected – see Table 3 for alleles tested and effect of functionality of CYP450 pathways

Test Interpretation

Sensitivity/specificity

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

Results

- Positive – one or more variant alleles detected that are associated with altered enzyme function
  - Reported metabolizer phenotypes include
    - Normal
      - Two functional alleles, or specific combinations of alleles, as defined per gene
    - 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
- Negative – no variants detected
  - Predictive of *1 functional alleles and normal enzymatic activity
    - Predicts normal metabolizer phenotype
- *CYP2D6* gene duplication detected
  - Specific allele duplicated may not be determined
  - Metabolizer phenotype may not be predicted

Limitations

- Only the targeted *CYP2D6, CYP2C9,* and *CYP2C19* variants will be detected
- Diagnostic errors can occur due to rare sequence variations
- Risk of therapeutic failure or adverse reactions with CYP2D6, CYP2C9, or CYP2C19 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

Clinical Pharmacogenetics Implementation Consortium. CPIC Genes/Drugs, PharmGKB (www.pharmgkb.org/cpic/pairs), Stanford, CA

Table 1. Cytochrome P450 Pathways for Common Analgesics (CYP2C9, CYP2C19, and CYP2D6)

Drug	CYP2C9	CYP2C19	CYP2D6
acetaminophen	-----	-----	inactivation
buprenorphine	-----	-----	-----
codeine	-----	-----	activation
fentanyl	-----	-----	inactivation
hydrocodone	-----	-----	activation
hydromorphone	-----	-----	-----
ibuprofen	inactivation	-----	-----
meperidine	-----	activation	-----
methadone	-----	inactivation	inactivation
morphine	-----	-----	-----
naproxen	inactivation	-----	-----
oxycodone	-----	-----	activation
oxymorphone	-----	-----	-----
propoxyphene	-----	-----	-----
tapentadol	inactivation	inactivation	inactivation
tramadol	-----	-----	activation

Note: Table does not reflect all analgesics. Many other drug classes are metabolized by *CYP2C9, CYP2C19* and *CYP2D6*. This information is provided as an illustration for how results may be applied clinically.

Table 2. Common Allele Frequencies

Allele	Populations
CYP2D6 Incidence of poor metabolizer phenotype	Caucasians and Hispanics 10% African Americans 2% Asians 1%
*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%

Table 3. Expected Functionality for CYP450 Pathways Based on Allelic Variants (*CYP2D6, CYP2C9,* and *CYP2C*19)				
Gene (reference sequence)	**Allele Function**			
	Nonfunctional	**Decreased Function**	**Functional**	**Increased Function**
CYP2D6 (M33388 sequence)	*3 (2549delA) *4 (c1846G>A) *5 (gene deletion) *6 (1707delT) *7 (2935A>C) *8 (1758G>T) *12 (124G>A) *14 (1758G>A)	*9 (2613-5delAGA) *10 (100C>T) *17 (1023C>T) *29 (1659G>A) *41 (2988G>A)	*2 (2850C>T) *2A (-1584C>G, 2850C>T)	Duplicated functional alleles
CYP2C9 (NM_000771)	*3 (rs1057910, c.1075A>C)	*2 (rs1799853, c.430C>T)		
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