Psychiatry Pharmacogenetics Expanded Panel

Disorder: Cytochrome P450 2D6 and 2C19 Genotyping.

Indications: Cytochrome P450 is a group of oxidative/dealkylating enzymes found mostly in liver but may also occur in intestinal tissues. Two enzymes within the cytochrome P450 superfamily are CYP2C19 and CYP2D6. CYP2C19 metabolizes approximately 15% of all prescribed drugs including antidepressants, barbiturates, proton pump inhibitors, antimalarial and antitumor drugs. CYP2D6 acts on approximately 25% of all prescribed drugs, including serotonin reuptake inhibitors (SSRI), analgesics, anticonvulsants, antidepressants, antiemetics, antihypertensives, antiestrogens, antineoplastics, antipsychotics, antiretrovirals, antitussives, beta-blockers, cardioactive drugs, H-2 blockers, stimulants, and sympathomimetics. The activity of these enzymes is expressed at highly variable levels. Detecting genetic variations in drug-metabolizing enzymes is useful to identify individuals who may experience adverse drug reactions due to their differences in metabolic rates.

There are four metabolic phenotypes: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), and ultra-rapid metabolizer (UM). Individuals can be classified into the phenotypic groups based on the alterations which are found in their CYP2C19 and CYP2D6 alleles. Individuals who are poor metabolizers (PM) have no active alleles and therefore lack functional enzyme activity. Intermediate metabolizers (IM) can have either one active and one inactive allele (in the case of CYP2C19) or one inactive and one partially active allele (CYP2D6). Individuals with an extensive metabolizer phenotype have normal enzyme activity with either two active alleles or one active and one partially active allele or two partially active alleles. Ultra-rapid metabolizers (UM) have duplicate or multiple copies of active CYP2D6 alleles or at least one copy of the CYP2C19*17 allele.

Individuals with homozygous *CYP2C19*1* (wildtype) alleles have an extensive metabolizer phenotype (EM). Approximately 74% of Caucasians have an EM phenotype, compared to 66% of Africans and 38% of Chinese. For *CYP2C19*, the prevalence of poor metabolizers is 2-6% of Europeans, 15-20% of Japanese, and 10-20% of Africans; however there is wide variability among populations. The most common poor metabolizer phenotypes are *CYP2C19*2* and *CYP2C19*3*. Other alleles associated with reduced metabolism include *CYP2C19*4, *5, *6, *7,*8,* which are seen less frequently in the general population.

Individuals who are homozygous for CYP2D6*1 (wildtype) have normal enzyme activity and are classified as extensive metabolizers (EM). Between 77-92% of all patients are extensive metabolizers. Approximately 5-10% of Caucasians are poor metabolizers based on CYP2D6 genotype. Alleles which are associated with decreased CYP2D6 activity include *9, *10, *17, and *41. Alleles associated with no enzyme activity include *3, *4, *5, *6, *7, *8, *11,*14, *15, *18, *19, *20, *40, *42 and *44. Duplication of functional CYP2D6 alleles are associated with increased metabolic activity.

Testing is appropriate for any patient that has a lack of therapeutic effect or has difficulties with side effects from any of the drugs metabolized by CYP2C19 or CYP2D6. Any drug that is primarily metabolized by CYP2C19 or CYP2D6 and ingested by a PM may have a delayed metabolism. PMs usually require lower doses of a drug to achieve desired effects, or may require an alternative medication. Conversely, UMs may need higher doses of medications as drugs are metabolized faster than normal. Both UMs and PMs are susceptible to drug-induced side effects.

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Common Alleles	Enzyme Activity	Allele Frequency		
		Caucasian	African American	Asian
*CYP2C19*2*	poor	15%	15%	29%
*CYP2C19*3*	poor	rare	rare	8.9%
*CYP2C19*17*	ultra	21%	16%	2.7%
*CYP2D6*3*	none	1.3%	rare	rare
*CYP2D6*4*	none	18.3%	6%	rare
*CYP2D6*5*	none	2.7%	5.9%	5.7%

Common drugs metabolized by *CYP2C19*

Amitriptyline	Carisoprodol	Citalopram*	Clomipramine
Clopidogrel	Cyclophosphamide	Diazepam	Escitalopram
Esomeprazole	Fluoxetine	Imipramine	Lansoprazole
Malarone	Mephenytoin	Moclobemide	Nelfinavir
Omeprazole	Pantoprazole	Phenytoin	Propranolol
R-warfarin	Sertraline	Trimipramine	Voriconazole

Common drugs metabolized by *CYP2D6*

Amitriptyline	Cimetidine	Cyclobenzaprine	Diphenhydramine
Fexofenadine	Fluoxetine	Haloperidol	Hydrocodone
Loratidine	Metoprolol*	Paroxetine	Propafenone*
Sertraline	Tamoxifen		

*Currently, the FDA incorporates *CYP2C19* or *CYP2D6* genotype into drug information for these drugs.

Specimen: At least 2ml whole blood in purple top (EDTA) tube or two cytobrushes. Label tube/brushes with patient's name, birth date, and date of collection. Phlebotomist must initial tube to verify patient's identity. Please call for free cytobrush collection kit, if desired.

Testing Methodology: DNA is isolated from peripheral blood or buccal samples. Genotypes are determined using the TaqMan allelic discrimination system on a low density microarray and long range PCR assays.

Sensitivity: This test detects 29 different alleles in *CYP2D6* (*2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *40, *41, *42, *44 and duplication) and *CYP2C19* (*2, *3, *4, *5, *6, *7, *8, *17), which account for 93-98% of *CYP2D6* and *CYP2C19* genotypes that are associated with null, deficient, or ultra-rapid enzyme activity. NOTE: *1 genotypes are inferred from the absence of the above alleles.

Turn-Around Times: Two days.

Costs: Please call 1-866-450-4198 with any billing inquiries.

CPT Codes: 81225, 81226

Shipping Instructions:

Please enclose **test requisition** with sample.
All information must be completed before sample can be processed.

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

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