Cytochrome P-450 2C19 Genotyping

CYP2C19 acts on 5-10 % of drugs in current clinical use. About 2-6% of individuals of European origin, 15-20% of Japanese, and 10-20% of Africans have a slow acting, poor metabolizer form of this enzyme. However there is wide variability among populations. For example, the percent of Polynesians who are poor metabolizers ranges from 38-79% depending on location. CYP2C19 is an important drug metabolizing enzyme that catalyzes the biotransformation of many other clinically useful drugs including antidepressants, barbiturates, proton pump inhibitors, antimalarial and antitumor drugs.

Genelex offers improved detection rates using an extended Cytochrome P-450 2C19 DNA test. This test identifies 8 small nucleotide variants in PCR-multiplex format, providing increased sensitivity and quality performance. This CYP2C19 detection panel is the most extensive on the market and covers seven known poor metabolizer alleles and one known rapid metabolizer allele. Analytical specificity and sensitivity for detection of these mutations are >99%.

Indication for Testing

For individuals with a personal or family history of adverse drug reactions to medications metabolized by CYP2C19. Confirm presence of genotypes that affect the metabolism of drugs such as Plavix that are metabolized by cytochrome CYP2C19.

Specimen Types

Please call Client Services at 800-523-3080 to obtain specimen kits.

- **Buccal Swabs**: 4 sterile Buccal Swabs
- **Blood:** 5-10 cc whole blood lavender-top EDTA or Yellow-top ACD-A tubes
- **Turnaround Time**: 6 days

CPT Codes

CYP2C19 Mutation DNA Analysis (provided for your guidance only)
1 X 83891, 3 X 83892, 1 X 83900, 2 X 83901, 8 X 83914, 1 X 83909

Clinical Significance

Phenotype prevalence is 2-6% PM Caucasian, 13-19% PM Asians, 10-20% PM African, 24-36% IM, ~5% URM; Drugs metabolized by this enzyme approximately 5-10%.

Cytochrome P450 2C19 (CYP2C19) is a highly polymorphic liver enzyme of the cytochrome P450 super family involved with the metabolism and elimination of many commonly prescribed drugs. Genetic polymorphisms in CYP2C19 are common and can affect therapeutic response to drugs. The enzyme activity is expressed at highly variable levels. Five phenotypes are identified: normal metabolizers (NM), poor metabolizers (PM), intermediate metabolizers (IM), rapid metabolizers (RM) and ultra rapid metabolizers (URM).

Detecting genetic variations in drug-metabolizing enzymes is useful for identifying individuals who may experience adverse drug reactions with conventional doses of certain medications. Individuals who possess CYP2C19 poor metabolizer variants may exhibit different pharmacokinetics (drug levels) than normal individuals. As a result, such individuals may require non-conventional doses of medications that require CYP2C19 activity for biotranformation. Conversely, medications that do not require CYP2C19 biotranformation may be preferentially selected for patients with potentially impaired CYP2C19 metabolic capacity to avoid adverse drug reactions.

The eight CYP2C19 allelic variants detected in this genotyping test provide greater than 98% coverage of the variant alleles found for this gene. The active allele (wild type) of the CYP2C19 gene is designated CYP2C19*1. Homozygous wild-type individuals have a normal metabolizer phenotype (NM). The most common poor metabolizer phenotypes have been identified as CYP2C19*2 and CYP2C19*3. CYP2C19*2 (G681A) and CYP2C19*3 (G636A) each differ from the active CYP2C19*1 by a single nucleotide substitution, which leads to impaired enzyme activity. The allele frequency of CYP2C19*2 has been reported to be as high as 75-85% in Asians and approximately 15% in Europeans and African Americans. The allele frequency of CYP2C19*3 has been reported to be as high as 6-10% in Asians and is rare in Europeans and African Americans. Other alleles associated with reduced metabolism include CYP2C19 *4, *5, *6, *7 and *8, but these are less frequent in the general population. CYP2C19*4 accounts for approximately 3% of Caucasian poor metabolizers. CYP2C19 *17 is found in ~40% of patients, About 5% are URMs and the remaining heterozygotes vary depending on the other allele.

Laboratory Test Interpretation

Genelex offers improved detection rates using an extended Cytochrome P-450 2C19 DNA mutation panel. This test identifies 8 small nucleotide variants in PCR-multiplex format, providing increased sensitivity and quality performance.

Cytochrome P-450 2C19 Mutations Detected

CYP2C19 allele	Nucleotide change	Effect on Enzyme Metabolism
*1	None (wildtype)	Normal
*2	681G>A	Inactive
*3	636G>A	Inactive
*4	1A>G	Inactive
*5	1297C>T	Inactive
*6	395G>A	Inactive
*7	19294T>A	Inactive
*8	358T>C	Inactive*
*17	-806C>T	Increased

For additional information see the CYP2C19 allele nomenclature database at
http://www.cypalleles.ki.se/cyp2c19.htm
* Severely deceased activity 70-90%

Phenotype Categories and Dosage Recommendations

Testing places individuals in one of the following phenotype categories:

- ✔ CYP2C19 Normal Metabolizers are the common phenotype for CYP2C19 enzyme activity. In general, they can be administered CYP2C19 metabolized drugs following standard dosing practices.
  NM genotypes consist of two active CYP2C19 alleles.
- ⚠ CYP2C19 Intermediate Metabolizers exhibit approximately half-normal enzyme activity and may require less than standard dosage to prevent overdose toxicity, drug interactions and for optimal

therapeutic response to CYP2C19 inactivated drugs. For prodrugs, such as clopidogrel, requiring activation by CYP2C19, consider increased dosage or alternative treatment.
IM genotypes consist of one active and one inactive CYP2C19 allele.
Clopidogrel (Plavix): Consult label for dosing guidance.

⚠ CYP2C19 Normal/Intermediate Metabolizers are likely intermediate in metabolic activity between normal and intermediate metabolizers. In general, they may be administered CYP2C19 drugs following standard dosing practices with increased vigilance.
N/IM genotypes consist of one inactive and one rapid (*17) CYP2C19 alleles.

CYP2C19 Poor Metabolizers have greatly decreased enzyme activity and may require alternative treatments or less than standard dosage to prevent overdose toxicity, drug interactions and for optimal therapeutic response to CYP2C19 inactivated drugs. For prodrugs, such as clopidogrel requiring activation by CYP2C19, consider alternative treatment or increased dosage.
PM genotypes consist of two inactive CYP2C19 alleles.
Clopidogrel (Plavix): Consult label for dosing guidance.

⚠ CYP2C19 Rapid Metabolizers have elevated levels of enzyme activity and may require more than standard dosage to prevent treatment failure with drugs inactivated by CYP2C19. For prodrugs, like clopidogrel, rapid metabolizers may be at increased risk of elevated exposure to active drug metabolites requiring lower than standard dosage.
RM Genotypes consist of one increased and one normal activity CYP2C19 alleles.
Clopidogrel (Plavix): Bleeding risk increased. Consult label for dosing guidance.

CYP2C19 Ultra Rapid Metabolizers have markedly elevated levels of enzyme activity and may require more than standard dosage to prevent treatment failure with drugs inactivated by CYP2C19. For prodrugs, like clopidogrel, rapid metabolizers may be at increased risk of elevated exposure to active drug metabolites requiring lower than standard dosage.
URM Genotypes consist of two increased activity CYP2C19 alleles.
Clopidogrel (Plavix): Bleeding risk increased. Consult label for dosing guidance.

Co-administration of other drugs. Genotype results should be interpreted in context of the individual clinical situation. In all cases monitor for co-administration of CYP2C19 inhibitors which may convert patients to poor metabolizer status. Potential adverse outcomes included overdose toxicity or treatment failure particularly for prodrugs. For more information see GeneMedRx drug-drug and drug-gene interaction software and Cytochrome P450 Metabolism Inhibitor/Inducer Tables. Access GeneMedRx via the patient lab number at www.GeneMedRx.com/DNAlogin.

A complicating factor in correlating CYP2C19 genotype with phenotype is that most drugs may reduce CYP2C19 catalytic activity but prodrugs increase CYP2C19 activity. It is important to interpret the results of testing in the context of other co-administered drugs.

CYP2C19 activity also is dependent upon hepatic and renal function status, as well as age. Patients also may develop toxicity if hepatic or renal function is decreased. Consider the results of testing and dose adjustments in the context of renal and hepatic function and age.

Therapeutic drug monitoring in PM, URM, RM and IM subjects is highly recommended. Again use standard measures of efficacy. For specific dosages see charts and tables are adapted from Julia Kirchheiner, et al Molecular Psychiatry Feature Review, 9 442-473 (2004), "Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response," a meta analysis of published research from 1970-2003 on the relevance of pharmacogenetic effects of CYP2D6 and CYP2C19 on 36 antidepressants and 38 antipsychotics.

Test Methodology and Limitations

DNA extraction / Polymerase Chain Reaction (PCR) / Mutation detection with hybridization probes.

This assay detects all common and many rare cytochrome P 450 2C19 (CYP2C19) variants with known clinical significance. Laboratory specimens were analyzed using PCR based technologies that detect 8 nucleotide variants. The performance of this assay was validated by Genelex Corporation. As with all laboratory testing there is a possibility of error. Genelex Corporation is certified by the Clinical Laboratory Improvement Amendments (CLIA No. 50D0980559) and as Washington State Medical Test Site No. MTS-3919, qualified to perform high complexity clinical testing.

DNA testing will not detect all the known mutations that result in decreased, increased, or inactive CYP2C19. Absence of a detectable gene mutation or polymorphism does not rule out the possibility that a patient has an intermediate or poor metabolizer phenotype. This test does not detect polymorphisms other than those listed. Other polymorphisms in the primer binding regions can affect the testing, and ultimately, the genotyping assessments made. Rare diagnostic errors may occur due to primer site mutations. Mutations in other genes associated with drug metabolism will not be detected. Drug metabolism may be affected by non-genetic factors. DNA testing does not replace the need for clinical and therapeutic drug monitoring.

Drug Metabolism Guide

This list is not all inclusive and is for your guidance only.

Substrates Metabolized through Cytochrome P-450 2C19

Substrates refers to drugs that are either activated or deactivated by the pathway.
Note=italics indicated minor pathway

amitriptyline	{esomeprazole}	nelfinavir	sertraline
carisoprodol	{fluoxetine}	omeprazole	Soma
citalopram	flunitrazapam	{pantoprazole}	trimipramine
clomipramine	imipramine	phenytoin	*Vfend*
clopidogrel	lansoprazole	Plavix	voriconazole
cyclophosphophamide (p)	*Malarone*	proguanil (p)	
diazepam	mephenytoin	Propranolol	
escitalopram	moclobemide	R-warfarin	

Inhibitors of Cytochrome P-450 2C19

Inhibitors refers to drugs that reduce the ability of the pathway to process drugs.
Co-administration will decrease the rate of metabolism of drugs through the metabolic pathway listed, increasing the possibility of toxicity.

chloramphenicol	fluoxetine	omeprazole	ticlopidine
delavirdine	fluvoxamine	oral contraceptives	topiramate
efavirenz	isoniazid	oxcarbazepine	voriconazole
felbamate	lansoprazole	Prilosec	
fluconazole	modafinil	Provigil	

Inducers of Cytochrome P-450 2C19

Inducers refers to drugs that increase the activity of a pathway.
Co-administration increases the rate of excretion for drugs metabolized through the pathway indicated, reducing the drug's effectiveness.

ginko biloba	rifampin	St John's Wort

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For immediate consultation Call 800-523-3080
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