Lab Dept:	**Anatomic Pathology**
Test Name:	**CYTOCHROME P450 2C19 GENOTYPE SEQUENCING**

General Information

Lab Order Codes:	2C19S
Synonyms:	P450 Genotyping
CPT Codes:	81225 – CYP2C19 gene analysis, common variants
Test Includes:	An interpretive report detailing the patient's 2C19 phenotype and ability to metabolize drugs affected by CYP2C19.

Logistics

Test Indications:

Primary metabolism of many drugs is performed by cytochrome P450, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP450 enzymes, CYP2C19, metabolizes a wide variety of drugs including antiulcer drugs such as omeprazole, antiseizure drugs such as mephenytoin, the antimalarial proguanil, and the anziolytic diazepam. It is also partially responsible for metabolizing other drugs such as the beta-blocker proranolol and the antidepressants fluvoxamine and fluoxetine. It is also involved in the activation of the anticoagulant clopidogrel.

CYP2C19 drug metabolism is variable. Some individuals have altered CYP2C19 gene sequences that result in synthesis of enzyme devoid of catalytic activity or in enzyme with diminished catalytic activity. These individuals metabolize clopidogrel, mephenytoin, omeprazole, diazepam, projuanil, and propanolol poorly. A number of specific polymorphisms have been found in the CYP2C19 gene that results in enzymatic deficiencies. The frequency of these polymorphisms varies within the major ethnic groups. CYP2C19 polymorphisms that produce poor metabolizers are found with frequencies of 2% to 5% in Caucasions, 4% in African Americans, 13 to 23% in Asians, and 38% to 79% in Polynesians and Micronesians.

CYP2C19 drug metabolism is dependent on the specific genotype detected, and also on the number and type of drugs administered to the patient. The following is a partial listing of drugs metabolized by CYP2C19 and/or known to affect CYP2C19 activity:

Drugs that undergo metabolism by CYP2C19:
•Anticoagulants: clopidogrel (Plavix)
•Anticonvulsants: mephenytoin, phenobarbitone, phenytoin, primidone
•Antidepressants: amitriptyline, citalopram, S-citalopram, clomipramine, imipramine

	•Antineoplastics: cyclophosphamide, teniposide •Antiretrovirals: nelfinavir •Proton pump inhibitors: lansoprazole, omeprazole, pantoprazole, rabeprazole •Miscellaneous drugs: diazepam, hexobarbital, indomethacin, progesterone, proguanil, propraolol, R-warfarin (less active isomer) Coadministration of these drugs may decrease the rate of elimination of other drugs metabolized by CYP2C19. Drugs know to increase CYP2C19 activity: •Carbamazepine, norethindrone, prednisone, rifampin Coadministration of these drugs increases synthesis of CYP2C19 and may increase the rate of elimination of drugs metabolized by CYP2C19 Drugs known to decrease CYP2C19 activity: •Chloramphenicol, cimetidine, esomeprazole, felbamate, fluoxetine, fluvoxamine, indomethacin, ketonconazole, lansoprazole, modafinil, omeprazole, oxcarbazepine, pantoprazole, probenecid, rabeprazole, ticlopidine, topiramate Coadministration of hese drugs may decrease the rate of metabolism of CYP2C19 metabolized drugs, increasing the possibility of toxicity, particularly in heterozygous individuals.
Lab Testing Section:	Anatomic Pathology - Sendouts
Referred to:	Mayo Medical Laboratories (MML Test: 2C19B)
Phone Numbers:	MIN Lab: 612-813-6280 STP Lab: 651-220-6550
Test Availability:	Daily, 24 hours
Turnaround Time:	5 - 10 days
Special Instructions:	N/A

Specimen

Specimen Type:	Whole blood
Container:	Lavender top tube
Draw Volume:	3 mL (minimum: 0.3 mL) blood
Processed Volume:	Same as Draw Volume
Collection:	Routine venipuncture
Special Processing:	Lab Staff: **Do Not** centrifuge. **Do Not** freeze. Submit specimen in original collection container. Store and ship at room temperature.

Patient Preparation:	Transfusions will interfere with testing. Wait 4-6 weeks post-transfusion to draw. Bone marrow and liver transplants will also interfere with testing.
Sample Rejection:	Mislabeled or unlabeled specimens

Interpretive

Reference Range:

An interpretive report will be provided.

CYP2C19 genotypes that lead to inactive or decreased activity alleles include *2, *3, *4, *5, *6, *7, *8, *9, *10. If 1 of the listed variants is not identified, the genotype is designated as *1/*1, and the individual ismost likely an exensive (normal) metabolizer. If an individual is homozygous or compound heterozygous for an allele(s) with no activity, the individual is predicted to be an intermediate metabolizer. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified.

Individuals with the CYP12C19*17 allele (in the absence of any inactive or decreased activity alleles and the *17 polymorphism are detected together, a range of potential phenotypes may be given.

Drug-drug interactions and drug/metabolite inhibition must be considered when dealing with heterozyqous individuals. Drug/metabolite inhibition can occur, resulting in inhibition of residual functional CYP2C19 catalytic activity.

Patients may also develop toxicity problems if liver and kidney functions are impaired.

Limitations:

Patients who received a heterologous blood transfusion within the preceding 6 weeks, or who have received an allogeneic blood or marrow transplant, can have inaccurate genetic test results due to presence of donor DNA.

CYP2C19 genetic test results in patients who have undergone live transplantation may not accurately reflect the patient’s CYP2C19 status.

Direct DNA testing will not detect all known mutations that result in decreased 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 detects only the specified polymorphisms. Additional findings, such as small insertions and deletions or novel mutations, will be reported if found. Other polymorphisms in the primer binding regions can affect the testing, and, ultimately, the genotyping assessment made.

Methodology:

Polymerase Chain Reaction (PCR) followed by DNA Sequence Analysis

References: Mayo Medical Laboratories September 2014