Single Nucleotide Polymorphism (SNP) genes:

ANKK1/DRD2
APO E
COMT
CYP1A2
CYP2B6
CYP2C9
CYP2C19
CYP2D6
CYP3A4/5
FACTOR II
FACTOR V
HAPTOGLOBIN
KIF6
MTHFR
OPRM1
PCSK9
SLCO1B1
VKORC1
4q25
9p21

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Changing the way people are diagnosed and treated around the world.
Clinical Utility:
Dopamine, a key neurotransmitter that controls cognition, emotion, locomotor activity and other endocrine functions, exerts its action by binding to five different receptors including the dopamine D2 receptor (DRD2). Dysregulation of dopaminergic signal transmission found in many pathological conditions such as Parkinson’s disease and schizophrenia and compounds that act as DRD2 agonists or antagonists are used to treat these conditions. Both therapeutic and adverse events of several antipsychotics result from their high affinity to antagonize DRD2.

Useful For:
- Influencing choice of antipsychotics prior to treatment, especially to ascertain if atypical antipsychotics may be used with low risk of tardive dyskinesia
- Identifying those patients receiving antipsychotics who are at increased risk of developing tardive dyskinesia. Individuals with the 25G allele should be monitored closely for signs of tardive dyskinesia if a decision is made to treat with antipsychotics.
- Testing may also be considered for individuals who will receive antipsychotic medications, if they are first-degree relatives of patients who have developed tardive dyskinesia.
- Assessing potential for effective treatment response with clozapine, olanzapine, and risperidone
- Determining efficacy of nicotine replacement therapy; The presence of the Taq1A allele (32806C>T; rs1800497) seem to be associated with nicotine dependence and the efficacy of bupropion and nicotine replacement therapy. Smokers carrying the normal DRD2 phenotype (A2/A2 genotype) using bupropion for smoking cessation are three times more likely to be abstinent at end of treatment than non-carriers of this genotype. Smokers with the Taq1A T variant allele (A1) seem to derive greater benefits from nicotine replacement therapies. Antipsychotic agents have been associated with hyperprolactinemia and tardive dyskinesia (TD). TD-positive patients taking antipsychotics have a higher A2 allele frequency while A1 allele is overrepresented among those experiencing hyperprolactinemia.

Assay Interpretation:
Within the several genetic variants of DRD2 that are relevant to disease susceptibility and therapeutic response, the Taq1A (32806C>T; rs1800497) is one of the most studied. This variant is located downstream of the DRD2 gene within the ankyrin repeat of the ANKK1 gene. The presence of the Taq1A variant defines the A1 allele that is associated with a reduced DRD2 gene expression and function. The A2 allele defines the reference allele. The frequency of the minor Taq1A allele differs among ethnic populations. It occurs in 22% of Caucasians, and 42% of Asians and Africans.

The “Stop Smoking” Gene
DRD2 is the gene that codes for dopamine D2 receptor. It is located on chromosome 11. Those who carry certain alleles of the gene DRD2 have been shown to be more prone to alcoholism, drug use, and other addictive behaviors. Recently, researchers have found that those with these alleles may be more prone to smoking as well. DRD2 is made up of two alleles, A1 and A2. Therefore you can have three different genotypes if you carry the DRD2 gene (A1/A1, A1/A2, A2/A2).
References:
5. David et al. Bupropion efficacy for smoking cessation is influenced by the DRD2 Taq1A polymorphism: analysis of pooled data from two clinical trials. Nicotine Tob Res. 2007 Dec;9(12):1251-7.
Clinical Utility:
Apolipoproteins (APO) are structural constituents of lipoprotein particles that have critical roles in blood lipid metabolism and transport. Apolipoprotein E (APOE) is a major constituent of triglyceride-rich chylomicrons, very low-density lipoproteins VLDL and some subclasses of high-density lipoproteins HDL. Defects in apolipoprotein E (APOE) can result in dyslipidemia, which is an important risk factor in the genesis of atherosclerosis and subsequent development of cardiovascular disease (CVD).

- The APOE E3/E3 genotype is considered the normal genotype and is not associated with an increased risk of atherosclerotic CVD.
- The APOE E2 allele is strongly associated with type III hyperlipoproteinemia.
- Patients with symptoms (xanthomas) and with a lipid profile consistent with type III hyperlipidemia are candidates for APOE genotype analysis. Over 90% of individuals presenting the type III hyperlipoproteinemia have the rare E2/E2 genotype. However, only 1-5% of individuals with this genotype develop type III hyperlipoproteinemia suggesting that other genetic, hormonal or environmental factors must contribute to this disease.
- The APOE E2/E3 and E2/E4 genotypes are associated with type III hyperlipoproteinemia in patients heterozygous for familial hypercholesterolemia.
- Although individuals with the APOE E2/E2 genotype are at higher risk of premature vascular disease, they may never develop the disease because this genotype is only one of the risk factors.
- In normolipidemic patients, the E2 allele is associated with lower serum cholesterol concentrations and may confer a protection against hypercholesterolemia.
- The APOE E4 allele has been linked to pure elevations of low-density lipoproteins (LDL and the E4/E4 genotype is associated with the increased serum cholesterol levels and increased risk of CVD).

Useful For:
- Determining the specific apolipoprotein E genotypes in patients with type III hyperlipoproteinemia

Assay Interpretation:
There are three common APOE alleles designated E2, E3, E4 resulting from combinations of the two genetic polymorphisms 388T>C and 526C>T. These alleles result into E2, E3, and E4 protein isoforms, respectively. The approximate allele frequencies for most populations are 8-12% for E2, 74-78% for E3, and 14-15% for E4.

CPT Code: 81401
References:

CPT Code: 81401
**Clinical Utility:**
Catechol-O-Methyltransferase (COMT) is an enzyme responsible for the metabolism of catecholamines and catechol-estrogens in both the central nervous system and other organs. Dopamine is cleared mainly by COMT in the frontal cortex and a reduced activity of this enzyme results in higher synaptic levels of dopamine, which affects prefrontal cortex cognitive response to certain drugs. A single nucleotide polymorphism of the COMT gene produces an amino acid change from valine to methionine (Val158Met) and reduces the enzyme activity by 3 to 4 fold.

**Useful For:**
- Early identification of patients who may show cognitive improvement with treatment for schizophrenia, this is associated with the *2/*2 genotype
- Investigation of inhibitor dosing for decreasing L-DOPA metabolism
- Research use for assessing estrogen metabolism
- Several complex associations between the Val158Met variant as a risk factor for numerous diseases have been found but they all seem to have a limited predictive value.
- In the treatment of attention deficit hyperactivity disorder; The response to some psychotropic medications seems to be dependent to some extent upon the COMT status. In general, the wild-type genotype predicts a good response to methylphenidate and amphetamines
- In the treatment of pain; patients homozygous for the Met allele require lower doses of morphine to achieve analgesia.

**Assay Interpretation:**
The most well studied COMT genetic variant (rs4680; 472G>A) is the one resulting into a valine to methionine change at codon 158. The variant allele called the Met allele is found in 30-47% of Caucasians, 23% of Africans, and 27-32% of Asians. The phenotype is defined by the presence of the reduced activity Met allele (A variant). The wild-type genotype (Val/Val; GG) predicts a high/normal COMT activity; the heterozygous genotype (Val/Met; GA) predicts an intermediate COMT activity and the homozygous (Met/Met; AA) results in a low COMT activity.

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**Drugs Metabolized by COMT**
- Alpha-methyl DOPA
- Apomorphine
- Benserazide
- Bitolterol
- Dihydroxyphenylserine
- Dobutamine
- Dopamine
- Epinephrine
- 2-Hydroxyestrogens
- 4-Hydroxyestrogens
- Isoetherine
- Isoprenaline
- Isoproterenal
- Norepinephrine
- Rimiterol

**Drugs that Undergo Structural Modification but not Metabolized by COMT**
- Albuterol
- Metaproterenol
- Methoxamine
- Phenylephrine
- Perbuterol
- Terbutaline

**Drugs Known to Decrease COMT Activity**
- Entacapone
- Tolcapone
- Nitecapone

**Dietary Components Known to Decrease COMT Activity**
- Quercetin
- Tea Catechins
References:
Clinical Utility:
The cytochrome P450 1A2 (CYP1A2) accounts for 13% of total CYP in the human liver and is responsible for metabolizing 8-10% of commonly used drugs as well as natural compounds such as caffeine. A large inter-individual variability in the elimination of drugs that are metabolized by CYP1A2 has been observed, which has been ascribed to both genetic variations and environmental factors including smoking (tobacco), some drugs, and several dietary compounds (cruciferous vegetables).

Useful For:
- Identifying patients who are poor, intermediate, extensive, or ultrarapid metabolizers of drugs metabolized by CYP1A2
- Adjusting dosages for drugs that are metabolized by CYP1A2
- Clinical Utility: CYP1A2 genotype can help identify patients with high or low sensitivity to inducing agents especially those released during smoking. The clinical relevance of this sensitivity becomes important in patients who are smokers or who quit smoking. Patients with the highly inducible genotype CYP1A2*1F/*1F can experience loss of response to drug substrates while they are exposed to dietary or environmental inducers and therefore may require higher doses.

Assay Interpretation:
Primary metabolism of many drugs is performed by cytochrome P450 (CYP), a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP enzymes, CYP1A2, is wholly or partially responsible for the hydroxylation or dealkylation of many commonly prescribed drugs. The current clinical application of this test is focused on the impact of allelic variation on antidepressant and antipsychotic metabolism.

CYP1A2-mediated drug metabolism is highly variable. CYP1A2*1A is the wild type or normal allele. Some individuals have altered CYP1A2 gene sequences that result in synthesis of a defective enzyme. These individuals metabolize CYP1A2 substrates poorly. Changes in the promoter impacting gene induction of the CYP1A2 gene has been observed, which results in either an increase or decrease of overall metabolic activity. Dosing of drugs that are metabolized through CYP1A2 may require adjustment based on the individual patient's genotype. Patients who are poor metabolizers may require lower than usual doses to achieve optimal response. Patients who are ultrarapid metabolizers may benefit from increased doses. Patients with either ultrarapid or poor metabolism may also benefit by conversion to other comparable drugs that are not primarily metabolized by CYP1A2.

More than 20 different alleles have been characterized for the CYP1A2 gene and some have been shown to affect enzyme activity and its sensitivity towards inducers (inducibility). The CYP1A2*1F is the most studied allele and results into a rapid metabolizer phenotype in presence of inducers while CYP1A2*1K and *1C alleles result in enzymes that are less active and less sensitive to induction. The CYP1A2*1F allele is found in 25-50% of Caucasians, 30% of Asians, and 50% of Ethiopians. The genotype-phenotype relationship for CYP1A2 is not well established and can be expressed in terms of metabolic capacity as well as sensitivity towards induction (inducibility). Individuals are predicted to have normal, intermediate, or poor metabolic CYP1A2 capacity with high, possible, or low inducibility depending on their genotype.

Drugs & Substances that Undergo Metabolism by CYP1A2
- Acetaminophen
- Amisulpride
- Amoxycillin
- Antacids
- Aspirin
- Caffeine
- Clobazam
- Clomipramine
- Clobazam
- Cyclobenzaprine
- Estradiol
- Fluoxetine
- Haloperidol
- Imipramine
- Moxifloxacin
- Naproxen
- Olanzapine
- Ondanestron
- Phenacetin
- Propranolol
- Riluzole
- Ropivacaine
- Tacrine
- Theophylline
- Tizanidine
- Verapamil
- R-Warfarin
- Zileuton
- Zolmitriptan

Drugs & Substances Known to Increase CYP1A2 Activity
- Broccoli
- Brussel Sprouts
- Char-grilled meat
- Insulin
- Methylcholanthrene
- Modafinil
- Nafcillin
- Beta-Naptholflavone
- Omeprazole
- Tobacco

Drugs Known to Decrease CYP1A2 Activity
- Amiodarone
- Cimetidine
- Ciprofloxacin
- Fluoroquinolones
- Fluvoxamine
- Furafyllin
- Interferon
- Methoxsalen
- Mibefradil

CPT Code: 81479
References:

1: Metabolic Drug Interactions. RH Levy, KE Thummel, WF Trager. Publisher: Lippincott Williams & Wilkins (March 15, 2000).
Clinical Utility:
The Cytochrome P450 2B6 (CYP2B6) is involved in the metabolism of 4% of clinically important medications. This enzyme is highly polymorphic and to date, 37 different variants have been identified. The CYP2B6 assay identifies some common variants that are associated with variability in enzyme activity.

Useful For:
• Monitoring of methadone treatment for analgesia or drug rehabilitation

Assay Interpretation:
CYP2B6 enzyme activity defines either a normal or an abnormal (intermediate and poor) metabolizer status for a given individual. Several variant alleles have been identified and result into different CYP2B6 isoforms that functionally are fully active, partially active, inactive or with increased activity. The CYP2B6*1 allele is considered the wild type and encodes a functionally active enzyme (normal). The alleles *6, *7, *9, *11, *16, *18, and *36 encodes a decreased activity enzyme. The allele *22 represents a gain-of-function allele. The functional impact of variants that define the CYP2B6 *4 and *5 alleles are drug dependent.

The most common functionally deficient allele is CYP2B6*6. It is found in 7-18% of Caucasians, 10-17% of Asians, 23% of Mexican Americans, and 33% of African Americans. CYP2B6*18 is found only in individuals of African descent with a frequency of 4-7%.

The genotype-phenotype relationship is not well established and there is a lack of consistency regarding the clinical impact of certain allelic variants. The following provisional genotype to phenotype assignment can be used: individuals with two fully active alleles are considered normal (extensive) metabolizers. Individuals with one fully active allele with either a partially active or an inactive allele are considered intermediate metabolizers. Individuals with two partially active alleles or with two inactive alleles are considered poor metabolizers. Individuals carrying two increased function alleles or one active allele with a gain-of-function allele are classified as normal/rapid metabolizers.

Drugs Metabolized by CYP2B6
- Artemisinin
- Bupropion
- Carbamazepine
- Cyclophosphamide
- Efavirenz
- Ketamine
- Meperidine
- Methadone
- Nevirapine
- Propofol
- Selegiline

Drugs Known to Increase CYP2B6 Activity
- Artemether
- Carbamazepine
- Dabrafenib
- Efavirenz
- Metamizole
- Nevirapine
- Phenobarbital
- Phenytoin
- Rifampin
- Ritonavir
- St John’s Wort

Drugs Known to Decrease CYP2B6 Activity
- Clopidogrel
- Darunavir
- Prasugrel
- Piclopidine
- Voriconazole
- Ritonavir
- Thiotepa

CPT Code: 81479
References:
1: CYP2B6 Allele Nomenclature: cypallele.com/ki.se

CPT Code: 81479
Clinical Utility:
The cytochrome P450 2C9 (CYP2C9) is involved in the metabolism of 15% of clinically important medications. This enzyme is highly polymorphic and to date, 30 different variants have been identified. The CYP2C9 assay identifies some common variants that are associated with variability in CYP2C9 enzyme activity, which is important pharmacological and toxicological implications for anticonvulsants, anticoagulants, and certain antidiabetics.

Useful For:
- Predicting dose when initiating warfarin therapy. Algorithms exist which combine CYP2C9 and VKORC1 status to define best path to initiate warfarin
- Predicting metabolism status for drugs that are modified by CYP2C9
- Evaluating patients for adverse drug reactions involving fluoxetine
- Aiding in altering dosing of antiepileptic drugs such as phenytoin

Assay Interpretation:
Primary metabolism of many drugs is performed by cytochrome P450(CYP450), a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP450 enzymes, CYP2C9, metabolizes a wide variety of drugs including warfarin and many nonsteroidal anti-inflammatory drugs. It is also partially responsible for metabolizing other drugs such as fluoxetine, fluvastatin, oral hypoglycemic drugs, and phenytoin.

CYP2C9-mediated drug metabolism is variable. Some individuals have altered CYP2C9 gene sequences that result in synthesis of enzyme devoid of catalytic activity or in enzyme with catalytic activity. These individuals may metabolize various drugs at a slower rate than normal and may require dosing adjustments to prevent adverse drug reactions. A number of specific polymorphisms have been found in the CYP2C9 gene that results in enzymatic deficiencies.

CYP2C9 enzyme activity defines either a normal or an abnormal (intermediate and poor) metabolizer status for a given individual. Several variant alleles have been identified and result in different CYP2C9 isoforms that functionally are either fully active, partially active, or inactive. The CYP2C9*1 allele is considered the wild type and encodes a functionally active enzyme. The allele *6 is a null (inactive) allele corresponding to a whole gene deletion.

The genotype-phenotype relationship is established based on the alleles activity. Individuals with two partially active alleles or with two inactive alleles are considered poor metabolizers.

Drugs Metabolized by CYP2C9
- Angiotensin II blockers: Irbesartan, Losartan
- Anticoagulants: S-Warfarin
- Antidepressants: Amitriptyline, Fluoxetine
- NSAIDS: Celecoxib, Diclofenac, Ibuprofen
- Oral Hypoglycemic agents: Glipizide, Glimepiride, Glyburide, Glibenclamide, Nateglinide, Tolbutamide
- Miscellaneous Drugs: Fluvastatin, Phenytoin, Rosuvastatin, Sulfamethoxazole, Tamoxifen, Torsemide

CPT Code: 81227
References:
Clinical Utility:
The Cytochrome P450 2C19 (CYP2C19) is involved in the metabolism of 10% of clinically important medications. This enzyme is highly polymorphic and more than 30 different variant alleles have been identified. The CYP2C19 assay identifies some common variants that are associated with variability in CYP2C19 enzyme activity, which has important pharmacological and toxicological implications for antidepressants, benzodiazepines, antiplatelets, and proton-pump inhibitors.

Useful For:
• Identifying patients who may be at risk for altered metabolism of drugs that are modified by CYP2C19
• Predicting anticoagulation response to clopidogrel (Plavix)

Assay Interpretation:
Primary metabolism of many drugs is performed by cytochrome P450 (CYP450) enzymes, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. CYP2C19 drug metabolism is variable among individuals. Some individuals have CYP2C19 genetic variants that result in enzyme with severely diminished or absent catalytic activity (i.e., poor metabolizers). The frequency of these variants (polymorphisms) depends on ethnicity. CYP2C19 polymorphisms that produce poor metabolizers are found with frequencies of 2-5% in Caucasians, 4% in African Americans, 13-23% in Asians, and 38-79% in Polynesians and Micronesians.

CYP2C19 enzyme activity defines either a normal or an abnormal (intermediate, poor, and rapid) metabolizer status for a given individual. Several variant alleles have been identified and result into different isoforms of the CYP2C19 enzyme that functionally are fully active, partially active, inactive, or with increased activity. The CYP2C19*1 is considered the wild type and encodes a functionally active enzyme (normal). The alleles *2, *3, *4, *5, *6 and *8 encodes and inactive enzyme and are referred to as loss-of-function alleles. Individuals with a *17 allele have an increased CYP2C19 activity.

The genotype-phenotype relationship is established based on the alleles activity. Individuals with two fully functional alleles are considered normal (extensive) metabolizers. Individuals with one or two loss-of-function alleles are considered intermediate and poor metabolizers. Individuals with one or two increased activity alleles are considered rapid (ultra-rapid) metabolizers. Because of limited evidence, an individual with one increased activity allele and one loss-of-function allele is provisionally classified as an intermediate metabolizer.

Drugs Metabolized by CYP2C19

Anticoagulants:
- Clopidogrel (Plavix®)

Anticonvulsants:
- Mephénytoïn, Phénytoïne, Primidone

Antidepressants:
- Amitriptyline, Citalopram, S-Citalopram, Clomipramine, Imipramine

Antineoplastic Drugs:
- Cyclophosphamide, Teniposide

Antiretrovirals:
- Nelfinavir

Proton Pump Inhibitors:
- Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole

Miscellaneous Drugs:
- Diazepam, Hexobarbital, Indomethacin, Progesterone, Proguanil, Propranolol, R-Warfarin

Drugs Known to Increase CYP2C19 Activity

- Carbamazepine
- Norethindrone
- Prednisone
- Rifampin

Drugs Known to Decrease CYP2C19 Activity

- Chloramphenicol
- Cimetidine
- Esomeprazole
- Felbamate
- Fluoxetine
- Fluvoxamine
- Indomethacin
- Ketoconazole
- Lansoprazole
- Modafinil
- Omeprazole
- Oxcarbazepine
- Pantoprazole
- Probiclidine
- Rabeprazole
- Ticlopidine
- Topiramate

CPT Code: 81225
References:

CPT Code: 81225
Clinical Utility:
The Cytochrome P450 2D6 (CYP2D6) is involved in the metabolism of 25% of clinically important medications. This enzyme is highly polymorphic and more than 100 different variants have been identified. The CYP2D6 assay identifies common variants that are associated with variability in CYP2D6 enzyme activity, which has important pharmacological and toxicological implications for antidepressants, antipsychotics, opioids, beta-blockers and antiarrhythmics.

Useful For:
- Providing information relevant to Tamoxifen, psychotropic medications (such as fluoxetine, nortriptyline, paroxetine, and pimozide), codeine, and tramadol, as well as other medications metabolized by CYP2D6
- Determining the exact genotype when other methods fail to generate this information or if genotype-phenotype discord is encountered clinically
- Identifying exact genotyping when required (e.g., drug trials, research protocols)
- Identifying novel mutations that may interfere with drug metabolism

Assay Interpretation:
Primary metabolism of many drugs is performed by the cytochrome P450 (CYP) family of enzymes. This is a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP enzymes, CYP2D6, is wholly or partially responsible for the hydroxylation or dealkylation (inactivation) of many commonly prescribed drugs such as some analgesics, anticonvulsants, antidepressants, antipsychotics, antiemetics, antihypertensives, antiestrogens, antineoplastics, antiretrovirals, antitussives, beta-blockers, cardioactive drugs, H-2 blockers, stimulants, and sympathomimetics.

Some individuals have altered 2D6 gene sequences that result in synthesis of enzyme devoid of catalytic activity, or an enzyme with diminished catalytic activity. These individuals may process CYP2D6-metabolized medications more slowly depending upon the gene variant found on each chromosome. Duplications and multiplications of the CYP2D6 gene may result in ultrarapid metabolism of CYP2D6-metabolized drugs. CYP2D6 genotype results are used to predict ultrarapid, extensive (normal), intermediate, and poor metabolizer phenotypes.

Dosing drugs that are metabolized through CYP2D6 may require adjustment based on the individual patient's genotype. Patients who are poor metabolizers may require lower than standard drug doses to achieve optimal response when drugs that inactivate the CYP2D6 enzyme are co-administered and a higher than standard dose in the case of co-administered drugs that activate the CYP2D6 enzyme. Alternatively, patients who are ultrarapid metabolizers may benefit from increased doses in the case of drugs that inactivate CYP2D6 enzyme and lower doses in the case of drugs that activate the CYP2D6 enzyme.

In the absence of clear guidance from FDA on dosing for various metabolizer phenotypes, patients with either ultrarapid or poor metabolism may benefit by switching to another comparable drug that is not primarily metabolized by CYP2D6 or by therapeutic drug monitoring where applicable.

Drugs Metabolized by CYP2D6
- **Beta Blockers:** Carvedilol, S-metoprolol
- **Antidepressants:** Amitriptyline, Clomipramine, Desipramine, Duloxetine, Fluoxetine, Imipramine, Paroxetine
- **Antipsychotics:** Haloperidol, Risperidone, Thoridazine
- **Miscellaneous Drugs:** Aripiprazole, Atomoxetine, Codeine Dextromethorphan, Doxepin, Flecaainide, Mexiletine, Ondansetron, Oxycodeone, Risperidone, Tamoxifen, Tramadol, Venlafaxine

Drugs Known to Increase CYP2D6 Activity
- Dexamethasone
- Rifampin

Drugs Known to Decrease CYP2D6 Activity
- Aripiprazole, Diphenhydramine
- Bupropion, Chlorpheniramine
- Fluoxetine, Clomipramine
- Paroxetine, Doxepin
- Quinidine, Haloperidol
- Duloxetine, Methadone
- Amiodarone, Ritonavir
- Cimetidine, Terbinafine

CPT Code: 81226
References:
Clinical Utility:
The cytochrome P450 3A4 and 3A5 (CYP3A4 and CYP3A5) account for 40-80% of total CYP in human liver and intestine, respectively. Most importantly, CYP3A enzymes metabolize 50% of commonly used drugs. CYP3A4 and CYP3A5 enzymes have overlapping substrate specificity and the contribution of CYP3A5 in the overall metabolism is smaller than the one for CYP3A4. The overall CYP3A metabolism status is expected to affect drugs that have a narrow therapeutic index.

Useful For:
- Identifying patients with high or low overall CYP3A activity. Although these two enzymes metabolize many drugs, the response of only a few (like narrow therapeutic index drugs) is expected to change significantly by genetic polymorphisms.
- Patients taking multiple drugs (CYP3A metabolism is highly sensitive to inhibition and induction when a patient is taking multiple drugs). The occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, the response, and safety profiles of many CYP3A drug substrates.

Assay Interpretation:
A limited number of variants identified within the CYP3A4 and CYP3A5 genes have been associated with significant alterations in enzyme activity and subsequent variability in therapeutic response. For CYP3A5, individuals with the less prevalent “normal metabolizer phenotype” may metabolize drugs faster than those with the more common “poor metabolizer phenotype”. This may result in increased toxicity or loss of efficacy.

The CYP3A4 *1B variant is the most studied and results in an enzyme with moderately decreased activity. It occurs in 50% of African Americans, 3-5% of Caucasians and <1% of Asians. The CYP3A4 *2, *3, *12 and *17 are also considered decreased activity alleles. Recently, the CYP3A4 *22 allele has been characterized as a decreased function allele that can be clinically relevant and is associated with a decreased clearance of substrates. The genotype phenotype relationship for CYP3A4 is not well established and individuals are predicted to have either a CYP3A4 normal or intermediate metabolic capacity.

The CYP3A5 *3 variant results in an enzyme with no activity and is the most common variant in the general population. The CYP3A5 *3B and *6 are also null alleles resulting in no enzyme activity. The CYP3A5 alleles *2, *8 and *9 result in a partially active enzyme. The CYP3A5 *1 allele produces an active enzyme and is found in 5% of Caucasians, 20% of Asians and 15-50% of Africans. Individuals with two CYP3A5 inactive alleles are classified as poor metabolizers. Individuals carrying at least one copy of a CYP3A5 active allele are either normal or intermediate metabolizers. CYP3A5 poor metabolizers represent 50% of Asians and 90% of Caucasians.

Drugs Metabolized by CYP3A

- Pain Management/Psychiatry: Fentanyl, Oxycodone, Buprenorphine, Carbamazepine, Quetiapine, Ziprasidone, Alprazolam, Midazolam, Triazolam, Nefazodone, Trazodone, Vilazodone, Zaleplon, Zolpidem
- Cardiovascular: Atorvastatin, Simvastatin, Lovastatin, Nifedipine, Verapamil, Nicardipine, Felodipine, Nisoldipine, Clopidogrel, Prasugrel, Ticagrelor, Cilostazol, Amiodarone, Quinidine, Disopyramide, Losartan, Rivaroxaban, Apixaban

Drugs Known to Increase CYP3A Activity

- Ketoconazole
- Itraconazole
- Posaconazole
- Voriconazole
- Clarithromycin
- Telithromycin
- Troleandomycin
- Conivaptan
- Nefazodone
- Ritonavir
- Lopinavir
- Nelfinavir
- Tipranavir
- Boceprevir
- Grapefruit Juice

Drugs Known to Decrease CYP3A Activity

- Carbamazepine
- Enzalutamide
- Fosphenytoin
- Phenyo tin
- Pheno barbital
- Primidone
- Rifampin
- Rifabutin
- Rifapentine
- St. John’s Wort
- Artemether
- Bosentan
- Nafcillin
- Nevirapine
- Fosamprenavir
- Aprepitant
- Clobazam
- Echinacea
- Piroglutazone
- Dabrafenib
- Efavirenz
- Etravirine
- Modafinil

Drugs Metabolized by CYP3A

- Pain Management/Psychiatry: Fentanyl, Oxycodone, Buprenorphine, Carbamazepine, Quetiapine, Ziprasidone, Alprazolam, Midazolam, Triazolam, Nefazodone, Trazodone, Vilazodone, Zaleplon, Zolpidem
- Cardiovascular: Atorvastatin, Simvastatin, Lovastatin, Nifedipine, Verapamil, Nicardipine, Felodipine, Nisoldipine, Clopidogrel, Prasugrel, Ticagrelor, Cilostazol, Amiodarone, Quinidine, Disopyramide, Losartan, Rivaroxaban, Apixaban

Drugs Known to Increase CYP3A Activity

- Ketoconazole
- Itraconazole
- Posaconazole
- Voriconazole
- Clarithromycin
- Telithromycin
- Troleandomycin
- Conivaptan
- Nefazodone
- Ritonavir
- Lopinavir
- Nelfinavir
- Tipranavir
- Boceprevir
- Grapefruit Juice

Drugs Known to Decrease CYP3A Activity

- Carbamazepine
- Enzalutamide
- Fosphenytoin
- Phenyo tin
- Pheno barbital
- Primidone
- Rifampin
- Rifabutin
- Rifapentine
- St. John’s Wort
- Artemether
- Bosentan
- Nafcillin
- Nevirapine
- Fosamprenavir
- Aprepitant
- Clobazam
- Echinacea
- Piroglutazone
- Dabrafenib
- Efavirenz
- Etravirine
- Modafinil

CPT Code: 81401
References:
Clinical Utility:
Clotting Factor II, or prothrombin, is a vitamin K dependent proenzyme that functions in the blood coagulation cascade. It is a precursor to thrombin, which converts fibrinogen into fibrin, which in turn strengthens a protective clot.

The prothrombin 20210G >A mutation in the Factor II gene, results in increased levels of plasma prothrombin and a concurrent increased risk for thrombosis. Prothrombin-related thrombophilia is characterized by venous thromboembolism (VTE). This risk of thrombosis is also increased when mutations exist for other coagulation factors such as Factor V Leiden or in presence of non-genetic risk factors such as obesity, injury, smoking, pregnancy, use of estrogen-containing contraceptive or replacement therapy. The clinical expression of Factor II thrombophilia is variable and many individuals may never develop thrombosis while others may experience venous thrombotic events or pregnancy complications.

The Factor II 20210G>A mutation is associated with an elevation of plasma prothrombin levels to about 30% above normal in heterozygotes and to 70% above normal in homozygotes. Heterozygotes are at a 2-to 5-fold increased risk of an initial VTE. The risk for VTE in Factor II 20210G>A homozygotes is not well defined, but presumed to be higher than in 20210G>A heterozygotes. Factor II 20210G>A homozygotes tend to develop thrombosis more frequently and at a younger age. Individuals who are doubly heterozygotes for Factor V Leiden and Factor II 20210G>A have an estimated 20-fold increased risk when compared to individuals without either mutation, suggesting a multiplicative elevation in risk. Certain circumstantial factors can increase the risk of thrombosis and include: travel, central venous catheter use, pregnancy, oral contraceptive use, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), organ transplantation, injury, age, and surgery.

Useful For:
• Finding the cause of too much bleeding (decreased blood clotting). This decreased clotting may be caused by abnormally low levels of factor II.

Assay Interpretation:
The Factor II thrombophilia is the second most common inherited risk factor for thrombosis. The Factor II 20210G>A mutation is associated with a hypercoagulable state. In the United States, the prevalence of this mutation is 1.1% in Caucasians and Hispanics, and 0.3% in African Americans. The prevalence of heterozygosity is 2%-5% in whites and 0%-0.3% in African Americans. The prevalence of homozygosity is approximately one in 10,000.
References:
Clinical Utility:
The Factor V gene encodes the coagulation Factor V. In normal conditions, Factor V is inactivated during the clotting process by the activated protein C (APC). In subjects with Factor V Leiden thrombophilia, a mutation in the gene produces a Factor V that cannot be inactivated normally by APC and as a result, the clotting process remains active longer than usual leading to more thrombin generation. This hypercoagulable state is also increased when other mutations exist on other coagulation factors such as Factor II or in presence of non genetic risk factors such as obesity, injury, surgery, smoking, pregnancy, use of estrogen-containing contraceptive or replacement therapy. The clinical expression of Factor V Leiden thrombophilia is variable. Many individuals may never develop thrombosis while others may experience venous thrombotic events or pregnancy complications. Certain circumstantial factors can increase the risk of thrombosis and include: travel, central venous catheter use, pregnancy, oral contraceptive use, hormone replacement therapy (HRT), selective estrogen receptor modulators, (SERMs), organ transplantation, injury, age, and surgery. These factors are associated with the first thrombotic episode in at least 50% of individuals with a Factor V Leiden mutation.

While the Factor V Leiden mutation is present in only 15-20% of individuals with a first VTE, it is found in 50% of individuals with recurrent VTE or estrogen related thrombosis. The risk for VTE is increased 3- to 8-fold in factor V Leiden heterozygotes and 9- to 80-fold in homozygotes. This risk is increased further if other genetic or circumstantial factors are present. A heterozygote individual for both the Factor V Leiden and the Factor II (compound heterozygote) has an even greater risk of VTE (20-fold) than the individual with a mutation in only one factor. This illustrates the multiplicative effect of these two factors on overall thrombotic risk.

Useful For:
- Factor V Leiden mutation testing should be reserved for patients with clinically suspected thrombophilia and:
  - APC-resistance proven or suspected by low or borderline APC-resistance ration
  - A family history of Factor V Leiden

Assay Interpretation:
Factor V Leiden is the most common known inherited risk factor for thrombosis. Factor V Leiden refers to a base change (from G to A at position 1691) in the gene. As a result, Factor V is inactivated to a lesser extent and persists for a longer period in the circulation, leading to hypercoagulability. In the US, the frequency of the Factor V Leiden mutation varies by ethnicity with about 5% of Caucasians, 2% of Hispanics, and 1% of African Americans having one mutation. Only 1 in 5000 individuals have two Factor V Leiden mutations.
References

Clinical Utility:
Haptoglobin genotype is a screening for diabetic patients at risk for cardiovascular disease (CVD). Haptoglobin (Hp) is an acute phase protein that binds to freely circulating hemoglobin to prevent iron-mediated oxidative damage to blood vessels. Haptoglobin exists as two distinct forms, Hp1 and Hp2. The longer Hp2 form has been associated with cardiovascular (CVD) events and mortality in individuals with type 2 diabetes (T2DM). Haptoglobin allele frequency in European populations is 40% for Hp1 and 60% for Hp2.

Useful For:
- Identification of diabetic patients who are most at risk for cardiovascular disease for risk stratification purposes
- Identification of those diabetic patients who may benefit from Vitamin E therapy to prevent oxidative vascular damage
- May aid in the evaluation of new therapies to prevent CVD in the diabetic patient

Assay Interpretation:
In patients with diabetes, the antioxidant capacity of Hp for glycosylated hemoglobin is reduced. Hp1 has a smaller molecular weight that allows Hp to enter the extravascular space. The increased size of Hp2 prevents its entrance into the extravascular space and prolongs clearance of free hemoglobin from the circulation. The Hp2 genotype predicts the highest risk for CVD in diabetes, Hp1-2 predicts intermediate risk and Hp1-1 predicts the lowest risk. The genotype of Hp does not predict CVD risk in the general population. Hp2-2 has been associated with a 2–3 fold increased incidence of atherothrombosis in individuals with diabetes (DM) in 10 longitudinal studies compared to DM individuals not homozygous for this duplication (Hp1-1/1-2).

Haptoglobin genotype is a predictor of CVD in the diabetic population but not in the general population. Diabetic patients with the Hp2-2 are 5x more likely to have a CVD than patients with Hp1-1. Patients with an Hp1-1 genotype are at decreased risk for retinopathy, nephropathy and microvascular complications. Consider the implementation of 400U of vitamin E (daily) for diabetic patients with Hp2-2 genotype to provide additional antioxidant coverage for prevention of CVD, as demonstrated in the ICARE study.

Risk Levels by Genotype
- **Hp2-2** genotype—predicts highest risk for CVD in diabetics.
- **Hp1-2** genotype—predicts intermediate risk for CVD in diabetics.
- **Hp1-1** genotype—predicts lowest risk for CVD in diabetics.

CPT Code: 81479
References:

CPT Code: 81479
**Clinical Utility:**
Kinesin-like family 6 (KIF6) gene has been reported as a potential risk factor for coronary artery disease (CAD), as well as a predictor of response to statin therapy.

**Useful For:**
Determining who are KIF6 carriers
- KIF6 carriers may have higher lifetime risk of cardiovascular disease
  - Any statin may be beneficial
  - Maintain active disease prevention
- KIF6 non-carriers may still be at risk for cardiovascular disease
  - Monitor for signs of disease
  - May wish to avoid atorvastatin and pravastatin

**Assay Interpretation:**
Analysis of prospective observational studies of cardiovascular health and of the placebo arm of randomized controlled trials (RCTs) of statin intervention in at-risk populations has suggested a significant association between the Trp719Arg single nucleotide polymorphism (SNP; rs20455 A>G) in kinesin-like protein 6 (KIF6) and the development of clinical CAD. In both CARE and WOSCOPS, carriers of the 719Arg risk allele received substantial and significant benefit from pravastatin therapy. Carriers of the 719Arg allele also received risk reduction from high dose atorvastatin in PROVE IT. Approximately 60% of the population carries the putative KIF6 high-risk 719Arg allele. These results support the use of KIF6 Trp710Arg genotyping test as a predictor of CAD risk and the likely effectiveness of statin therapy.

**Trials and Studies**
- **WOSCOP**
  - West of Scotland Coronary Prevention Study
- **CARE**
  - Cholesterol and Recurrent Events

CPT Code: 81479
References:
**Clinical Utility:**
Methylenetetrahydrofolate reductase (MTHFR) is involved in folate metabolism and is involved in folate metabolism and is essential for the remethylation of homocysteine. Two common mutations in the MTHFR gene: 677C>T and 1298A>C result in an enzyme with decreased activity, which is linked to increased plasma homocysteine levels (i.e. hyperhomocysteinemia). Mild to moderate hyperhomocysteinemia has been identified as a risk factor for venous thromboembolism and other cardiovascular diseases such as coronary heart disease and stroke. Other conditions in which hyperhomocysteinemia is found include recurrent pregnancy loss, placental infarction, and birth defects. However, the casual role of MTHFR mutations in these conditions is not well established.

Homozygosity for the MTHFR 677C>T mutation (individual with MTHFR 677 TT genotype) predisposes for hyperhomocysteinemia (especially during times of folate insufficiency) and an increase in premature cardiovascular disease. Measurement of total plasma homocysteine is informative in this case.

Compound heterozygosity (individual with both MTHFR 677 CT and MTHFR 1298AC genotypes) is associated with increased in plasma homocysteine level and an increase in premature cardiovascular disease. Measurement of total plasma homocysteine is informative in this case.

Homozygosity or heterozygosity for the MTHFR 1298A>C mutation alone (individual with MTHFR 1298AC or MTHFR 1298CC genotypes) does not increase homocysteine levels. Similarly, heterozygosity for the MTHFR 677C>T mutation alone (individuals with MTHFR 677 CT genotype) does not increase homocysteine levels.

The response to methotrexate, a drug used in cancer and autoimmune diseases is affected by the presence of MTHFR genetic mutations. Methotrexate intolerance is expected to be increased in individuals that are compound heterozygous for both the MTHFR 677C>T and MTHFR 1298A>C mutations as well as in individuals that are homozygous for the MTHFR 677C>T mutation.

**Useful For:**
- Patients with coronary artery disease, acute myocardial infarction, peripheral vascular artery disease, stroke, or venous thromboembolism who have increased basal homocysteine levels or an abnormal methionine-load test
- Providing information about potential causes of elevated homocysteine and approaches for addressing it

**Assay Interpretation:**
The approximate minor allele frequencies for most populations are 30-50% for the MTHFR 1298 A variant and 18-30% for the MTHFR 677 T variant. Heterozygotes and homozygotes for the MTHFR 677P>T mutation have 60% and 30% of normal MTHFR activity, respectively.

Hyperhomocysteinemia related to MTHFR genetic mutations has been associated with neural tube defects, stillbirths, and recurrent pregnancy loss. However, because hyperhomocysteinemia is multifactorial, involving a combination of other genetic, physiologic and environmental factors, the presence of MTHFR mutations in an individual should not be used alone to predict the risk of these conditions.

CPT Code: 81291
References:
**Clinical Utility:**

“Mu” opioid receptors are the most important site of action of opioid drugs. Single polymorphisms in the human mu-opioid receptor (OPRM1) have been investigated for their role in human nociception, opiate efficacy, and addiction.

**Useful For:**
- Identifying individuals with a higher probability of successful treatment for alcoholism with naltrexone

**Assay Interpretation:**

OPRM1 is the primary binding site of action for many opioid drugs and for binding of beta-endorphins. One of the effects of opiate and alcohol use is to increase release of beta-endorphins, which subsequently increases release of dopamine and stimulates cravings. Naltrexone is an opioid antagonist used to treat abuse of opiates, alcohol, and other substances. Naltrexone binds to OPRM1, preventing beta-endorphin binding and subsequently reducing the craving for substances of abuse.

The variant mostly studied is a single substitution at position 118, from an adenine to a guanine (A118G). This variant reduces the OPRM1 receptor signaling efficiency induced by exogenous opioids. Reduced OPRM1 mRNA expression levels were observed in carriers of the G variant. The variant allele (G) is present in 7-15% of Caucasians, 1.5% of African Americans, and up to 48.5% of Asians. The major interest of this particular SNP is due to its pharmacological and physiological consequences; however, the exact mechanism by which the altered receptor influences opioid analgesia is still unresolved. The presence of the G allele seems to reduce the effect of exogenous agonists, but increase the effects of exogenous antagonists.

The presence of the G allele (A118G) seems to be associated with pain sensitivity as well as opioid dosage requirements. But only weak evidence of these associations is available to date. It is suggested that patients carrying the G allele report higher intensity pain. In terms of drug response patients with the G allele have a favorable response to the anti-addictive drug naltrexone. Several studies conducted in post surgical setting or in cancer analgesia, showed that G allele carriers require slightly higher doses of morphine or fentanyl. This association still needs to be confirmed in larger studies and does not hold in other situations such as labor pains.

CPT Code: 81479
References:
Clinical Utility:
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) mediates the degradation of LDLR by interacting with the extracellular domain and targeting the receptor for degradation. Polymorphisms in PCSK9 are known to contribute to the development of familial hypercholesterolemia (FH). FH is characterized by severely elevated LDL-C levels.

Increased PCSK9 activity leads to anywhere from 5 to 25x higher affinity for LDLR. High PCSK9 plasma levels are associated with increased inflammation and hypercholesterolemia. Patients with PCSK9 Gain of Function mutations have elevated LDL-C levels and are at risk of premature cardiovascular disease. For patients with PCSK9 Gain of Function variants, consideration should be given to additional testing for variation in LDLR, ApoE and ApoB genes to rule out familial hypercholesterolemia (FH). FH develops as a result of mutations in three genes. Mutations in LDLR can be evidenced in 67% of FH patients, ApoB mutations in 14%, and PCSK9 mutations in 2.3% of patients with FH. The remaining 16% arises from other genes such as ApoE. Patients with PCSK9 Gain of Function may benefit from treatment with PCSK9 inhibitor therapy.

Useful For:
• Screening patients at risk for hypercholesterolemia

Assay Interpretation:
Variants in PCSK9 can result in two phenotypes that affect the LDL levels in the bloodstream. PCSK9 gain of function mutations result in the reduction of cell surface LDLR and increasing concentrations of LDL-C in the bloodstream. Conversely, PCSK9 loss of function mutations result in higher cell surface LDLR concentrations and very low levels of circulating LDL-C.
References:

CPT Code: 81479
Clinical Utility:
The SLCO1B1 gene encodes a liver-specific transporter involved in the removal of endogenous compounds (bile acids, bilirubin) and drugs such as statins from the blood to the liver. Some variants of the SLCO1B1 gene result in a low-functioning protein, which impairs statin clearance and may lead to an increased risk of muscle pain, tenderness or weakness called myopathy. Certain medications can potentially inhibit SLCO1B1 causing clinically significant drug reactions.

SLCO1B1 encodes the organic anion-transporting polypeptide 1B1 (OATP1B1) influx transporter located on the basolateral membrane of hepatocytes. OATP1B1 facilitates the hepatic uptake of statins as well as other endogenous compounds (e.g. bilirubin). Changes in the activity of this transporter (e.g., through genetic variations or drug-drug interactions) can increase the severity of statin-associated myopathy (i.e. statin intolerance).

The SLCO1B1 *5 (c.521T>C, p.V174A; rs4149056) allele interferes with localization of the transporter to the plasma membrane, and can lead to increased systemic statin concentrations. All statins are substrates of OATP1B1, but the association with SLCO1B1 *5 and statin intolerance varies depending on statin and dose, and is most pronounced with higher doses of simvastatin therapy. A case-control study of simvastatin-induced myopathy observed an odds ratio (OR) for myopathy of 4.5 per copy of the *5 allele in patients receiving high-dose (80 mg/day) simvastatin therapy (the OR was 16.9 in *5 homozygotes compared to individuals who did not carry *5). Also demonstrated was a dose relationship in a replication cohort of patients taking 40 mg/day simvastatin with a relative risk of 2.6 per copy of the *5 allele. While the SLCO1B1 genotype has been shown to affect systemic exposure of other statins (e.g., atorvastatin, pravastatin, rosuvastatin), in addition to simvastatin, there is less evidence demonstrating a clinical association between SLCO1B1 genotype and myopathy with statins other than simvastatin.

Useful For:
• Aiding prediction of risk for statin-associated myopathy for patients beginning statin therapy, especially simvastatin therapy
• Determining a potential genetic effect related to statin intolerance in patients with statin-associated myopathy, especially related to simvastatin

Assay Interpretation:
There are several variants of SLCO1B1 that define over 15 alleles. One relatively common variant 521T>C results in a decreased SLCO1B1 function, which affects the transport of drug substrates such as statins. This variant is present alone on the *5 allele and in presence with another variant (388A>G) on the *15 allele. Both alleles are low-activity alleles (reduced hepatic uptake) and have a combined frequency of 1-20% in Caucasians, 10-15% in Asians, and 2% in sub-Saharan Africans and African Americans.
References:

CPT Code: 81479
**Clinical Utility:**
The vitamin K epoxide reductase complex, subunit 1 (VKORC1) is the target of anticoagulants. This enzyme is the rate-limiting step in the vitamin K cycle. Mutations in the VKORC1 gene results in variable expression levels of the VKORC1 enzyme and altered sensitivities towards anticoagulants. VKORC1 genotype defines three levels of clinical phenotype: high, moderate, and low sensitivity phenotypes towards warfarin (a widely used anticoagulant). Therefore, VKORC1 variant testing is usually used in conjunction with CYP2C9 variant testing to optimize warfarin dosing and minimize the risks of bleeding or thrombotic complications.

The -1639G>A is the common variant seen in Caucasians, and is believed to be the causative agent for the low-dose warfarin requirement phenotype. The G>A mutation results in a decreased expression of VKORC1. The 358>T (found in 21% of African-Americans) and 3730G>A variants are associated with high warfarin dose requirements.

The FDA changed the warfarin label to help clinicians offer genotype-guided therapy for their patients.

**Useful For:**
- Patients prescribed an anticoagulant

**Assay Interpretation:**
The clinically relevant variants in the VKORC1 gene are in strong linkage disequilibrium, meaning that some allele combinations occur more frequently than others. These combinations are referred to as haplotypes. The eight variants analyzed by the VKORC1 assay are used to define three haplotypes that are associated with different warfarin sensitivities.

When CYP2C9 and VKORC1 genotypes are combined with the following factors, they account for 50% of warfarin dose variation between individuals:

- **Demographic**
  - Age
  - Weight
  - Height

- **Clinical**
  - Disease
  - Co-Medications

- **Environmental**
  - Smoking

CPT Code: 81355
References:

Clinical Utility:
Variants on 4q25 chromosomal region are associated with atrial fibrillation risk. This locus on 4q25 is also known as atrial fibrillation familial 5 (ATFB5). A genome wide association study replicated in several populations found a strong association between 4q25 variant rs2200733 and atrial fibrillation. No specific gene was identified in the 4q25 region to be associated with atrial fibrillation. However, the variant rs2200733 is located adjacent to gene PITX2.

Useful For:
• To determine increased risk of atrial fibrillation

Assay Interpretation:
Variant rs2200733 at the 4q25 region is associated with increased risk of atrial fibrillation. The risk allele in rs2200733 variant is found in 30% of the Caucasian population and 70% of the Chinese population. The risk of atrial fibrillation increases by 1.7 times per copy of the risk allele in variant rs2200733 at 4q25 location. A critical point to be noted is that even if a patient is carrying a risk allele in variant rs2200733 does not mean that the patient will suffer from atrial fibrillation.

CPT Code: 81479

“A-Fib Risk”
Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, affecting more than 2 million Americans, with an overall prevalence of 0.89%. The most dreaded complication is thromboembolic stroke.
References:
Clinical Utility:
9p21 is an independent marker of cardiovascular risk. The 9p21 locus is also called coronary heart disease susceptibility 8 (CHDS8). Genetic polymorphism at 9p21 locus were amongst the first markers of increased cardiovascular disease and have been subsequently confirmed in different ethnic populations of European, Chinese, Japanese, and Indian ancestry. However, the use of 9p21 has not been substantiated in the African population.

Useful For:
Determining carriers of 9p21 polymorphisms
• Non carriers do not predict an increased risk of coronary artery disease
• Heterozygous mutations of 9p21 variant rs1333049 is associated with a 50% increased risk for coronary artery disease
• Heterozygous mutations in rs10757278 are associated with a 40% increased risk, whereas the homozygous mutations are associated with 70% increased risk for abdominal aortic aneurysm
• For coronary heart disease, the risk is increased by 30% in heterozygous carriers, and 60% in homozygous carriers

Assay Interpretation:
The two most common polymorphisms at 9p21 locus are rs13333049 (G>C) and rs10757278 (A>G). There are six different alleles resulting from combination of the two genetic polymorphisms. Population frequency for non-carriers is 27%, 50% for heterozygous carriers, and 23% for homozygous carriers.
References:
2. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007 Jun 7;447(7145):661-78.