

## ANKK1/DRD2

### 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 is 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. Therapeutic and adverse events of several antipsychotics both result from their high affinity to antagonize DRD2.

### 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 T 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 T allele differs among ethnic populations. It occurs in 22% of Caucasians, and 42% of Asians and Africans.

**The reference range for the Taq1A variant is 32806C>T CC (A2/A2) and is associated with a normal DRD2 expression.**

### Clinical Implications

The presence of the Taq 1A A1 allele (32806C>T) seems 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 the 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.

### References

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## COMT

### Clinical Utility

Catechol-O-Methyltransferase (COMT) is an enzyme responsible for the metabolism of catecholamines and catechol-estrogens in 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.

### Assay Interpretation

The most well studied COMT genetic variant (rs4680; 472G>A) is the one resulting in 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; M) results in a low COMT activity.

**The reference range for COMT metabolic status is COMT Val158Met GG (Val/Val) (wild-type), which is consistent with a high/normal COMT activity.**

### Clinical Implications

Several complex associations with the Val158Met variant as a risk factor for numerous diseases have been found, but seem to have limited predictive value. The response to some psychotropic medications seems to be dependent to some extent upon the COMT status. In general, the wild-type genotype result predicts a good response to methylphenidate and amphetamines in the treatment of attention deficit hyperactivity disorder. In the treatment of pain, patients who are homozygous for the Met allele require lower doses of morphine to achieve analgesia.

### References

1: De Gregori et al. Genetic variability at COMT but not at OPRM1 and UGT2B7 loci modulates morphine analgesic response in acute postoperative pain. *Eur J Clin Pharmacol.* 2013 May 19; 2 : Hamidovic et al. Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. *Psychiatr Genet.* 2010 Jun;20(3):85 -92. 3 : Blasi et al. Effect of catechol-O-methyltransferase val158met genotype on attentional control. *J Neurosci.* 2005 May 18;25(20):5038-45. 4 : Mattay et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci U S A.* 2003 May 13;100(10):6186-91.

## CYP1A2

### 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 genetic variations and environmental factors. CYP1A2 activity is highly inducible (increased) by environmental factors including smoking (tobacco), some drugs, and several dietary compounds (cruciferous vegetables) .

### Assay Interpretation

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 in a rapid metabolizer phenotype in the presence of inducers, while CYP1A2\*1 K 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 CYP1A2 normal, intermediate, or poor metabolic capacity, with high, possible, or low inducibility depending on their genotype.

**The reference range for CYP1A2 metabolic status is CYP1A2 \*1A/ \*1A, which is consistent with a normal metabolizer that is possibly inducible.**

### Clinical Implications

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.

The following drugs used in the management of pain and various psychiatric conditions are metabolized extensively by CYP1A2 and are sensitive to its function: clozapine (Clozaril), duloxetine (Cymbalta), olanzapine (Zyprexa), and tizanidine (Zanaflex). CYP1A2 also metabolizes other important drugs such as melatonin, ondansetron (Zofran), pomalidomide (Pomalyst), ramelteon (Rozerem), ropivacaine (Naropin), and tasimelteon (Hetlioz).

CYP1A2 metabolism is highly sensitive to inhibition and induction, and the occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, response, and safety profiles of many CYP1A2 drug substrates.

### Inhibitors

Some known **strong** CYP1A2 inhibitors include: ciprofloxacin (Cipro), enoxacin (Penetrex), fluvoxamine (Luvox), and zafirlukast (Accolate). Some known **moderate to weak** CYP1A2 inhibitors include: oral contraceptives, mexiletine (Mexitil), allopurinol (Zyloprim), peginterferon alfa- 2a (Pegasys), norfloxacin (Norflo), ticlopidine (Ticlid), vemurafenib (Zelboraf), and zileuton (Zyflo).

### Inducers

Known CYP1A2 inducers include: carbamazepine (Tegretol), montelukast (Singulair), rifampin (Rifadin), phenytoin (Dilantin), moricizine (Ethmazine), omeprazole (Prilosec), phenobarbital, and primidone (Mysoline). Some dietary and environmental compounds found in cigarette smoke, cruciferous vegetables, and charcoal-grilled food can also increase CYP1A2 activity.

### References

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## CYP2B6

### Clinical Utility

The cytochrome P450 2B6 (CYP2B6) is involved in the metabolism of 4% of clinically important medications. This enzyme is highly polymorphic: to date, 37 different variants have been identified. The CYP2B6 assay identifies some common variants that are associated with variability in enzyme activity.

### Assay Interpretation

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

The most common functionally deficient allele is CYP2B6\*6. It is found in 7-18%, 10-17%, 23%, and 33% of Caucasians, Asians, Mexican-Americans, and African-Americans, respectively. 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 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.

**The reference range for CYP2B6 metabolic status is CYP2B6 \*1/ \*1, which is consistent with a normal metabolizer.**

### Clinical Implications

CYP2B6 plays a role in the metabolism of the following drugs: artemisinin, bupropion (Wellbutrin), cyclophosphamide (Cytoxan), efavirenz (Sustiva), ketamine (Ketalar), meperidine (Demerol), methadone (Dolophine), nevirapine (Viramune), propofol (Diprivan), and selegiline (Eldepryl).

The impact of CYP2B6 polymorphism on the pharmacokinetics and the clinical response have been studied in patients taking methadone, bupropion, and efavirenz. Limited evidence exists regarding the clinical impact of other polymorphisms.

Inhibitors or inducers of the CYP2B6 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2B6 inhibitors or inducers.

### Inhibitors

Some known CYP2B6 inhibitors include: clopidogrel, darunavir, prasugrel, ticlopidine, voriconazole, ritonavir, and thiotepa.

### Inducers

Some CYP2B6 inducers include: artemether, carbamazepine, dabrafenib, efavirenz, metamizole, nevirapine, phenobarbital, phenytoin, rifampin, ritonavir, and St. John's wort.

### References

1: CYP2B6 Allele Nomenclature: [www.cypallele.ki.se/cyp2b6.htm](http://www.cypallele.ki.se/cyp2b6.htm) 2: Li et al. Worldwide variation in human drug-metabolism enzyme genes CYP2B6 and UGT2B7: implications for HIV/AIDS treatment. *Pharmacogenomics*. 2012 Apr ;13(5):555-70. 3: Li et al. The CYP2B6\*6 Allele Significantly Alters the N-Demethylation of Ketamine Enantiomers In Vitro. *Drug Metab Dispos*. 2013 Jun;41(6):1264-72. 4: Zanger and Klein. Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance. *Front Genet*. 2013;4:24. 5: Zanger et al. Polymorphic CYP2B6: molecular mechanisms and emerging clinical significance. *Pharmacogenomics*. 2007 Jul;8 (7):743-59. 6: Zhu et al. CYP2B6 and bupropion's smoking-cessation pharmacology: the role of hydroxybupropion. *Clin Pharmacol Ther*. 2012 Dec;92(6):771-7. 7: Benowitz et al. Influence of CYP2B6 genetic variants on plasma and urine concentrations of bupropion and metabolites at steady state. *Pharmacogenet Genomics*. 2013 Mar;23(3):135-41.

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## CYP2C9

### Clinical Utility

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

### Assay Interpretation

CYP2C9 enzyme activity defines a normal or 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 fully active, partially active, or inactive. The CYP2C9\*1 allele is considered wild-type and encodes a functionally active enzyme (normal). The alleles \*2, \*3, \*4, \*5, and \*11 encode a partially 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 allele's activity. 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.

**The reference range for CYP2C9 metabolic status is CYP2C9 \*1r1, which is consistent with a normal metabolizer.**

### Clinical Implications

Abnormal CYP2C9 activity affects the therapeutic outcome of a variety of drugs used to treat cardiovascular and other conditions. Following the administration of drug substrates, the clinical manifestation in a poor or an intermediate metabolizer depends on the characteristics of the drug (i.e., the amount of drug/metabolites that is cleared by the enzyme), and the safety and pharmacological profiles of the drug and its metabolites. Within the medications used to treat cardiovascular conditions, there is compelling evidence that the response to certain angiotensin II inhibitors, statins, and anticoagulants is altered in individuals exhibiting abnormal CYP2C9 activity.

CYP2C9 plays a role in the metabolism of the following psychotropic drugs: fluoxetine (Prozac), phenytoin (Dilantin), and primidone (Mysoline). Several NSAIDs and Cox-2 inhibitors are substrates of CYP2C9, and patients with reduced CYP2C9 activity may have higher plasma levels of celecoxib (Celebrex), flurbiprofen (Ocufen), piroxicam (Feldene), or meloxicam (Mabie). CYP2C9 plays a minor role in the elimination of diclofenac (Voltaren), sulindac (Clinoril), and naproxen (Aleve).

Cardiovascular medications that are metabolized by CYP2C9 include warfarin (Coumadin), fluvastatin (Lescol), losartan (Cozaar), and irbesartan (Avapro).

Other important drugs metabolized by CYP2C9 include antidiabetics such as tolbutamide, glibenclamide (Micronase), glipizide (Glucotrol), and nateglinide (Starlix).

Inhibitors or inducers of the CYP2C9 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2C9 inhibitors or inducers.

### Inhibitors

Some known CYP2C9 inhibitors include: amiodarone (Cordarone), 5-fluorouracil (Aducil), chloramphenicol, cimetidine (Tagamet), danazol (Danocrine), disulfiram (Antabuse), fluconazole (Diflucan), fluoxetine (Prozac), fluvoxamine (Luvox), miconazole (Oravig), oxandrolone (Oxandrin), capecitabine (Xeloda), co-trimoxazole (Septra), delavirdine (Rescriptor), etravirine (Intelence), fluvastatin (Lescol), efavirenz (Sustiva), gemfibrozil (Lipid), lomitapide (Juxtapid), metronidazole (Flagyl), phenytoin (Dilantin), sulfamethoxazole (Bactrim), sulfapyrazone (Anturane), tamoxifen (Nolvadex), toremifene (Fareston), tigecycline (Tygacil), voriconazole (Vfend), and zafirlukast (Accolate).

### Inducers

Some known CYP2C9 inducers include: carbamazepine (Tegretol), rifampin (Rifadin, Rimactane), rifapentine (Priftin), St. John's wort, enzalutamide (Xtandi), aprepitant (Emend), bosentan (Tracleer), dabrafenib (Tafinlar), phenobarbital, primidone (Mysoline), phenytoin (Dilantin), and ritonavir (Norvir).

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## CYP2C19

### Clinical Utility

The cytochrome P450 2C19 (CYP2C19) is involved in the metabolism of 10% of clinically important medications. This enzyme is highly polymorphic: 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.

### Assay Interpretation

CYP2C19 enzyme activity defines a normal or abnormal (intermediate, poor, or rapid) metabolizer status for a given individual. Several variant alleles have been identified and result in different isoforms of the CYP2C19 enzyme that functionally are fully active, partially active, inactive, or with increased activity. The CYP2C19\*1 allele is considered wild-type and encodes a functionally active enzyme (normal). The alleles \*2, \*3, \*4, \*5, \*6, and \*8 encode an 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 allele's activity. Individuals with two fully functional alleles are considered normal (extensive) metabolizers. Individuals with one or two loss-of-function alleles are considered intermediate or poor metabolizers, respectively. Individuals with one or two increased function alleles are considered rapid or ultra-rapid metabolizers, respectively. Because of limited evidence, an individual with one increased function allele and one loss-of-function allele is provisionally classified as an intermediate metabolizer.

**The reference range for CYP2C19 metabolic status is CYP2C19 \*1/ \*1, which is consistent with a normal metabolizer.**

### Clinical Implications

There is substantial evidence linking the CYP2C19 polymorphisms to variability in the pharmacological and safety profiles of the following therapies used in psychiatric conditions and pain management: amitriptyline (Elavil), sertraline (Zoloft), clobazam (Onfi), citalopram (Celexa), escitalopram (Lexapro), diazepam (Valium), imipramine (Tofranil), and carisoprodol (Soma). CYP2C19 plays a minor role in the elimination of methadone (Dolophine).

Cardiovascular medications that are metabolized by CYP2C19 include the prodrug clopidogrel (Plavix), propranolol (Inderal), and cilostazol (Pletal). Proton-pump inhibitors such as omeprazole (Prilosec), esomeprazole (Nexium), lansoprazole (Prevacid), dexlansoprazole (Dexilant), and pantoprazole (Protonix) are major substrates of CYP2C19.

Brivaracetam is primarily metabolized by hydrolysis and by hydroxylation. The hydrolysis reaction is mediated by amidase and the hydroxylation pathway is mediated by CYP2C19. In patients carrying genetic variations in CYP2C19 the blood level of brivaracetam is increased by 22% or 42%, in CYP2C19 intermediate and poor metabolizers, respectively. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may therefore require dose reduction to avoid concentration-dependent toxicity.

Inhibitors or inducers of CYP2C19 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2C19 inhibitors or inducers.

### Inhibitors

Some known CYP2C19 inhibitors include: fluconazole (Diflucan), fluvoxamine (Luvox), fluoxetine (Prozac), felbamate (Felbatol), ticlopidine (Ticlid), omeprazole (Prilosec), esomeprazole (Nexium), voriconazole (Vfend), armodafinil (Nuvigil), delavirdine (Rescriptor), modafinil (Provigil), oxcarbazepine (Trileptal), etravirine (Intelence), topiramate (Topamax), and moclobemide (Manerix).

### Inducers

Some known CYP2C19 inducers include: artemether (Coartem), carbamazepine (Tegretol), efavirenz (Sustiva), enzalutamide (Xtandi), fosphenytoin (Cerebyx), primidone (Mysoline), phenobarbital, phenytoin (Dilantin), rifampin (Rifadin), and St. John's wort.

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## CYP2D6

### Clinical Utility

The cytochrome P450 2D6 (CYP2D6) is involved in the metabolism of 25% of clinically important medications. This enzyme is highly polymorphic: 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.

### Assay Interpretation

CYP2D6 enzyme activity defines a normal or abnormal (intermediate, poor, or rapid) metabolizer status for a given individual. Commonly tested CYP2D6 variant alleles are classified into functional groups: Full or normal function (e.g., CYP2D6 \*1, \*2 and \*35), reduced function (e.g., CYP2D6\*9, \*10, \*14B, \*17, \*29, and \*41) and no function (e.g., CYP2D6 \*3, \*4, \*5, \*6, \*7, \*8, \*11, \*12, \*14A, \*15, \*36 and \*56). Increased CYP2D6 activity is found in individuals carrying multiple copies of functional alleles. CYP2D6 is subject to gene duplications, and these are denoted "XN", where N represents the number of CYP2D6 gene copies when available.

The genotype-phenotype relationship is established using a scoring system that assigns an activity value to every CYP2D6 allele, in order to assign a predicted phenotype. For a given genotype, the activity values of the constituent alleles are added together to calculate the CYP2D6 activity score. This activity score (AS) is then used to assign a predicted phenotype as follows: AS of 0 predicts a poor metabolizer, AS ranging between 1 and 2 predicts a normal (extensive) metabolizer, AS=0.5 predicts an intermediate metabolizer, and AS greater than 2 predicts a rapid (ultra-rapid) metabolizer. Fully functional alleles are assigned an activity value of 1, reduced function alleles have an activity value of 0.5, while non-functional alleles are assigned an activity value of 0.

**The reference range for CYP2D6 metabolic status is a CYP2D6 \*1/ \*1 genotype, which is consistent with a normal metabolizer.**

### Clinical Implications

There is substantial evidence linking the CYP2D6 polymorphisms to variability in the pharmacological and safety profiles of the following psychotropics: desipramine (Norpramin), imipramine (Tofranil), amitriptyline (Elavil), nortriptyline (Pamelor), haloperidol (Haldol), trimipramine (Surmontil), venlafaxine (Effexor), doxepin (Silenor), aripiprazole (Abilify), atomoxetine (Strattera), duloxetine (Cymbalta), risperidone (Risperdal), clomipramine (Anafranil), and pimozide (Orap).

CYP2D6 polymorphisms have been shown to affect the pharmacological and safety profiles of the following analgesics: codeine, tramadol (Ultram), and hydrocodone (Vicodin). Codeine and tramadol are prodrugs that need to be activated by CYP2D6. Poor metabolizers are at high risk of therapy failure when given codeine or tramadol. On the other hand, rapid metabolizers may experience increased toxicity when given standard dosage of codeine or tramadol. Because CYP3A4 is also involved in the metabolism of oxycodone, patients with abnormal CYP2D6 activity may still experience adequate analgesia when taking this drug. CYP2D6 polymorphism has been shown to affect dihydrocodeine (Synalgos-DC) pharmacokinetics and can potentially alter the response to this drug.

Morphine, oxycodone (Opana), hydromorphone (Dilaudid), buprenorphine (Butrans), methadone (Dolophine), morphine (Avinza), and tapentadol (Nucynta) are not substrates of CYP2D6, and the patient's response to these drugs is not expected to be affected by polymorphisms in this enzyme.

Several important cardiovascular medications are metabolized by CYP2D6, and include: metoprolol (Lopressor), carvedilol (Coreg), flecainide (Tambocor), and propafenone (Rythmol).

Eliglustat (Cerdelga) is a glucosylceramide synthase inhibitor used for the long-term treatment of adult patients with Gaucher disease type 1. Both the FDA-approved drug label and the EMA Summary of Product Characteristics for this drug state that CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of eliglustat to achieve a therapeutic effect. Therefore this drug should not be used in these individuals. Patients who are CYP2D6 intermediate and normal metabolizers have a recommended dose of 84 mg twice daily, while poor metabolizers have a recommended dose of 84 mg once daily.

Cevimeline (Evoxac) is a muscarinic agonist indicated for the treatment of symptoms of dry mouth in patients with Sjogrens Syndrome. Both CYP2D6 and CYP3A are responsible for the metabolism of cevimeline, and this drug should be used with caution in individuals who are CYP2D6 poor metabolizers, as they may be at a higher risk of adverse events.

Inhibitors of the CYP2D6 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2D6 inhibitors. Although there are no known clinical inducers of CYP2D6, the pharmacokinetics of a drug substrate can be affected by inducers of other enzymes (such as CYP3A) that are involved in the metabolism of that drug.

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### Inhibitors

Some known **strong and moderate** CYP2D6 inhibitors include: abiraterone (Zytiga), bupropion (wellbutrin), cobicistat (Stribild), fluoxetine (Prozac), quinidine (Quinidex), paroxetine (Paxil), cinacalcet (Sensipar), duloxetine (Cymbalta), terbinafine (Lamisil), tipranavir/ritonavir (Aptivus), mirabegron (Myrbetriq), peginterferon alfa-2b (Sylatron) and ecstasy.

Some known **weak** CYP2D6 inhibitors include: amiodarone (Cordarone), celecoxib (Celebrex), clobazam (Onfi), desvenlafaxine (Pristiq), diltiazem (Cardiazem), diphenhydramine (Benadryl), escitalopram (Lexapro), febusostat (Uloric), gefitinib (Iressa), hydralazine (Apresoline), hydroxychloroquine (Plaquenil), imatinib (Gleevec), methadone (Dolophine), perphenazine (Trilafon), propafenone (Rythmol), ranitidine (Zantac), ritonavir (Norvir), sertraline (Zoloft), telithromycin (Ketek), verapamil (Isoptin, Cevera-HS), venlafaxine (Effexor), and Echinacea.

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## CYP3A4

### 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.

### 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\*1 B variant is the most studied, and results in an enzyme with a 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 (associated with a decreased clearance of certain substrates). The genotype-phenotype relationship for CYP3A4 is not well established, and individuals are predicted to have a CYP3A4 normal or intermediate metabolic capacity.

**The reference range for CYP3A4 metabolic status is CYP3A4 \*1/ \*1, which is consistent with a normal metabolizer.**

The CYP3A5\*3 variant results in an enzyme with no activity, and is the most common variant in the general population. The CYP3A5\*3B, \*6 and \*7 are also null alleles resulting in no enzyme activity. The functional effects of the CYP3A5 alleles \*2, \*4, \*5, \*8, and \*9 are not well established. 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 normal or intermediate metabolizers. CYP3A5 poor metabolizers represent 50% of Asians and 90% of Caucasians.

The reference range for CYP3A5 metabolic status is CYP3A5 \*1/ \*1, which is consistent with a normal metabolizer. This genotype is the least prevalent in Caucasians and Asians.

### Clinical Implications

CYP3A4 and CYP3A5 genotypes can help identify patients with high or low overall CYP3A activity. Although these two enzymes metabolize many drugs, the response of only a few (such as narrow therapeutic index drugs) is expected to change significantly by genetic polymorphisms. Fentanyl (Duragesic) is a narrow therapeutic drug that is mainly metabolized by CYP3A. There is limited evidence suggesting that the response to this drug is altered in individuals with abnormal CYP3A activity.

The following drugs used in pain management and various psychiatric conditions are metabolized extensively by CYP3A: fentanyl (Duragesic), oxycodone (Oxycontin), buprenorphine (Suboxone), carbamazepine (Tegretol), quetiapine (Seroquel), ziprasidone (Geodon), alprazolam (Xanax), midazolam (Versed), triazolam (Halcion), nefazodone (Serzone), trazodone (Oleptro), vilazodone (Vibryd), zaleplon (Sonata), and zolpidem (Ambien). CYP3A contributes to a small extent in the elimination of methadone (Dolophine).

Within the major therapeutic classes used in cardiovascular conditions, the following drugs are substantially metabolized by CYP3A: atorvastatin (Lipitor), simvastatin (Zocor), lovastatin (Mevacor), nifedipine (Procardia), verapamil (Verelan), nicardipine (Cardena), felodipine (Plendil), nisoldipine (Sular), clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), cilostazol (Pletal), amiodarone (Cordarone), quinidine (Quaaluaquin), disopyramide (Norpace), losartan (Cozaar), rivaroxaban (Xarelto), and apixaban (Eliquis).

CYP3A metabolism is highly sensitive to inhibition and induction when a patient is taking multiple drugs. In this case, occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, as well as the responses and safety profiles of many CYP3A drug substrates.

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### Inhibitors

Some known strong CYP3A inhibitors include: ketoconazole (Nizoral), itraconazole (Sporanox), posaconazole (Noxatil), voriconazole (Vfend), clarithromycin (Biaxin), telithromycin (Ketek), troleandomycin (TAO), conivaptan (Vaprisol), nefazodone (Serzone), ritonavir (Norvir), saquinavir (Invirase), lopinavir, (Kaletra), nelfinavir (viracept), tipranavir (aptivus), boceprevir (Victrelis), telaprevir (Incivek), grapefruit juice (high dose) and idelalisib (Zydelig).

Some known moderate CYP3A inhibitors include: amprenavir (agenerase), aprepitant (Emend), atazanavir (Reyataz), darunavir (Prezista), fosamprenavir (Lexiva), erythromycin (Eryc), ciprofloxacin (Cipro), diltiazem (cardizem), verapamil (Isoptin, Covera-HS), fluconazole (Diflucan), imatinib (Gleevec), quinupristin/dalfopristin (Synercid), and grapefruit juice (low dose).

Some known weak CYP3A inhibitors include: amiodarone (Cordarone), amlodipine (Norvasc), atorvastatin (Lipitor), bicalutamide (Casodex), cilostazol (Pletal), fluvoxamine (Luvox), fluoxetine (Prozac), sertraline, cimetidine, ranitidine (Zantac), ranolazine (Ranexa), and ticagrelor (Brilinta).

### Inducers

Some known strong CYP3A inducers include: carbamazepine (Tegretol), enzalutamide (Xtandi), fosphenytoin (Cerebyx), phenytoin (Dilantin), phenobarbital, primidone (Mysoline), rifampin (Rifadin), rifapentine (Priftin), and St. John's wort.

Some known moderate CYP3A inducers include: artemether (Coartem), bosentan (Tracleer), dabrafenib (Tatinlar), efavirenz (Sustiva), etravirine (Intence), modafinil (Provigil), nafcillin (Unipen), rifabutin (Mycobutin), and nevirapine (Viramune).

Some known weak CYP3A inducers include: fosamprenavir (Lexiva), aprepitant (Emend), clobazam (Onti), Echinacea, pioglitazone (Actos), dexamethasone (Decadron), oxcarbazepine (Trileptal), methylprednisolone (Medrol), and rutinamide (Banzel).

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## FACTOR II

### 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, surgery, smoking, pregnancy, use of estrogen-containing contraceptives 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.

### 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.

**The reference range for Factor II 20210G>A mutation is Factor II 20210GG.**

### Clinical Implications

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 is 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.

### Management Guidelines

Decisions regarding prophylactic anticoagulation should be based on a risk/benefit assessment. The first acute thrombosis should be treated according to standard guidelines. Following a first acute thrombotic event, long-term anticoagulation can be considered in homozygotes or in individuals with multiple thrombophilic disorders. In the absence of a history of thrombosis, anticoagulation is not routinely recommended for asymptomatic individuals who are heterozygotes. In asymptomatic individuals with a history of thrombosis and with one or two Factor II 20210G>A mutation(s), a short course of prophylactic anticoagulation may be considered in high-risk settings such as surgery, pregnancy, or prolonged immobilization. 2- Estrogen-containing contraceptives and replacement therapies: Heterozygote or homozygous women for Factor II 20210G>A mutation and with a history of VTE should avoid estrogen contraception and replacement therapy. Asymptomatic women who are heterozygote for Factor II 20210G>A mutation should be counseled on the risks of estrogen contraception and replacement therapy. Asymptomatic heterozygote women electing to use oral contraceptives should avoid third-generation formulations because of their higher thrombotic risk. Women homozygous for the Factor II 20210G>A mutation with or without prior VTE should avoid estrogen contraception and replacement therapy.

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## FACTOR V LEIDEN

### 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. 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 in other coagulation factors such as Factor II, or in the presence of non-genetic risk factors such as obesity, injury, surgery, smoking, pregnancy, or use of estrogen-containing contraceptive or estrogen containing 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.

### 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 longer 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.

**The reference range for Factor V Leiden mutation is Factor V 1691 GG.**

### Clinical Implications

About 1 in 1000 people in the U.S. experience a first venous thromboembolism (VTE) each year. VTE is caused by inherited and environmental factors, and 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 an individual with a mutation in only one factor. This illustrates the multiplicative effect of these two factors on overall thrombotic risk.

### Management Guidelines

Decisions regarding prophylactic anticoagulation should be based on a risk/benefit assessment. The first acute thrombosis should be treated according to standard guidelines. Following a first acute thrombotic event, long-term anticoagulation can be considered in individuals homozygous for the Factor V Leiden mutation or with multiple thrombophilic disorders. In the absence of a history of thrombosis, anticoagulation is not routinely recommended for asymptomatic individuals who are heterozygote for the Factor V Leiden allele, because the 1- 3%/year risk for major bleeding from anticoagulation is greater than the estimated < 1%/year risk for thrombosis. In heterozygote individuals, a short course of prophylactic anticoagulation during exposure to hemostatic stresses may be considered. These situations include: surgery, pregnancy, and prolonged immobilization. 2- Estrogen-containing contraceptives and replacement therapies: women with one or two Factor V Leiden mutations and a history of VTE should avoid estrogen contraception and replacement therapy. Asymptomatic women who are heterozygote for Factor V Leiden should be counseled on the risks of estrogen contraception and replacement therapy. Asymptomatic women electing to use oral contraceptives should avoid third-generation formulations because of their higher thrombotic risk. Homozygote women with or without prior VTE should avoid estrogen contraception and replacement therapy.

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## HTR2A

### Clinical Utility

5-hydroxytryptamine (serotonin) receptor 2A (HTR2A) is a G protein-coupled receptor that encodes one of the receptors for serotonin. Serotonin is a neurotransmitter with many roles, including regulating mood, anxiety, feeding, and other behaviors, as well as dopamine and norepinephrine release in certain areas of the brain. HTR2A receptors are extensively distributed throughout the brain with high localization in the frontal and temporal regions. Preliminary studies indicate that some genetic variations in this gene are associated with susceptibility to schizophrenia and obsessive-compulsive disorder. They may also modulate the response to the antidepressant citalopram in patients with major depressive disorder (MDD).

### Assay Interpretation

HTR2A variants have been studied with a primary objective of predicting response of the patients to anti-depressant therapy. Some of the most commonly tested variants of HTR2A are rs6311, rs6313 and rs7997012. Variants rs6311, also referred to as -1438G/A, is a guanine to adenine change and is located in the HTR2A promoter region. HTR2A with the adenine allele (A allele) is shown to have a greater expression when compared to the guanine allele (G allele). The other variant, rs6313 (102T/C), is a thymine to cytosine change. In samples of European ancestry, rs6311 is found to be in strong to complete linkage disequilibrium with the variant rs6313.

HTR2A rs7997012 is the other variant that is commonly tested. This variant is associated with a guanine to adenine change in intron 2 and is not in linkage disequilibrium with rs6311 or rs6313.

### Clinical Implications

HTR2A genotyping assay may be used to determine the response to antidepressants. HTR2A rs6311 with the adenine allele (A allele) is shown to have greater expression when compared to the guanine allele (G allele). It has been reported that in patients with European ancestry, presence of the A allele of rs6311 (-1438G/A) and T allele of rs6313 (102C/T) is associated with a favorable response to clozapine. However, this association may not be consistent across patients with non-European ancestry.

HTR2A variant rs7997012 is associated with a differential response to citalopram. Patients who are homozygous for the A allele of rs7997012 respond better to citalopram when compared to the patients who are homozygous for the G allele.

These HTR2A variants have not yet been unequivocally validated as predictors of drug response. Additional studies are needed to establish their clinical impact.

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## HTR2C

### Clinical Utility

HTR2C gene encodes a receptor that responds to the endogenous neurotransmitter serotonin. This serotonin receptor is a G protein-coupled receptor with wide distribution across the central and peripheral nervous systems in humans. It mediates excitatory neurotransmission via serotonin. Serotonin signaling regulates mood, anxiety, feeding, and many other behaviors, as well as dopamine and norepinephrine release in certain areas of the brain. Genetic variation in the HTR2C gene is known to be partially involved in pathogenesis of some psychiatric disorders and adverse effects of antipsychotic medications. The HTR2C assay identifies mutations that are associated with altered serotonin receptor expression and function, which has important pharmacological and toxicological implications for the use of antipsychotic medications, such as olanzapine, clozapine and risperidone.

### Assay Interpretation

Many human polymorphisms in the HTR2C gene have been identified, of which a single nucleotide polymorphism (SNP rs3813929) is most significantly associated with a protective effect against the side effect of weight gain in patients taking olanzapine. HTR2C gene is located on the X chromosome in humans and SNP rs3813929 represents a C > T mutation in the regulatory region of this gene. As males have one copy of the HTR2C gene and in females one of the two copies of the gene is repressed, polymorphisms at this receptor can affect the two sexes to differing extent. Because of limited evidence, males with one copy of the C allele and females with one or two copies of the C allele are provisionally considered to have normal regulation of HTR2C expression and function. Males with one copy of the T allele and females with two copies of the T allele are provisionally considered to have altered regulation of HTR2C expression and function. The frequency of the minor T allele occurs in about 1% of European Caucasian and Asian populations, but is very rare in African populations.

Another single nucleotide polymorphism (SNP rs1414334) in the HTR2C gene is most significantly associated with a protective effect against the side effect of metabolic syndrome in patients taking clozapine or risperidone. SNP rs1414334 represents a C > G mutation in an intron region. Because of limited evidence, males with one copy of the C allele and females with one or two copies of the C allele are provisionally considered to have normal regulation of HTR2C expression and function. Males with one copy of the G allele and females with two copies of the G allele are provisionally considered to have altered regulation of HTR2C expression and function. The frequency of the G allele varies in different ethnic populations, and is often higher than the reference C allele. G allele occurs in about 45-65% of African populations, 80-90% of European Caucasian, and more than 90% of Asian populations.

### Clinical Implications

The HTR2C assay identifies mutations that lead to functional variability in serotonin receptor, which is associated with clinical response to antipsychotics. In particular, genotype of SNP rs3813929 is significantly associated with the side effect of weight gain in patients who are taking olanzapine for psychiatric disorders including schizophrenia. Patients who have the rs3813929 TT genotype (female) or T genotype (male) may have a favorable response to olanzapine and a decreased risk of weight gain when compared to patients who have the rs3813929 CC genotype (female) or C genotype (male). Other genetic and clinical factors may also influence a patient's response to olanzapine.

Genotype of SNP rs1414334 is significantly associated with the side effect of metabolic syndrome in patients taking clozapine or risperidone. Patients who have the rs1414334 GG genotype (female) or G genotype (male) may have a favorable response to clozapine or risperidone, and a decreased risk of developing metabolic syndrome when compared to patients who have the rs1414334 CC genotype (female) or C genotype (male). Other genetic and clinical factors may also influence a patient's response to clozapine and risperidone.

In addition, HTR2C SNPs rs3813929 and rs1414334 may have other clinical implications in the treatment of psychiatric disorders such as depression, obsessive-compulsive disorder and anxiety-related conditions.

Both these HTR2C variants have not yet been unequivocally validated as predictors of drug response. Additional studies are needed to establish their clinical impact.

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## MTHFR

### Clinical Utility

Methylenetetrahydrofolate reductase (MTHFR) is involved in folate metabolism and is essential for the remethylation of homocysteine. Two common mutations in the MTHFR gene: 677C>T and 1298A> 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 causal role of MTHFR mutations in these conditions is not well established.

### 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 677C>T mutation have 60% and 30% of normal MTHFR activity, respectively. Heterozygotes and homozygotes for the MTHFR 1298A>C mutation have 80% and 60% of normal MTHFR activity, respectively.

**The reference ranges for both mutations of MTHFR are 677CC and 1298AA. This is consistent with a normal MTHFR activity.**

### Clinical Implications

The MTHFR assay provides information about potential causes of elevated homocysteine, and approaches for addressing it.

- 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 MTHFR 677 CT and MTHFR 1298AC genotypes) is not associated with an increase in plasma homocysteine level. 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.
- 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.
- MTHFR in depression: Low MTHFR activity may exacerbate folate deficiency in patients with depression and may increase the risk of depressive relapse or delay the response to antidepressants. Testing for homocysteine levels and serum folate levels are recommended in patients with depression. Methylfolate may substantially benefit patients with hyperhomocysteinemia and depression when used as an adjuvant to antidepressant medication.
- The response to methotrexate, a drug used in cancer and autoimmune diseases, is affected by the presence of MTHFR genetic mutations. Methotrexate intolerance is observed in individuals that are heterozygous or homozygous for the MTHFR 677C>T mutation.

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## OPRM1

### 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.

### Assay Interpretation

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 reference range for the A118G SNP is A118G AA, and is associated with a normal OPRM1 receptor signaling efficiency.**

### Clinical Implications

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 settings 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 pain.

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## SLC0181

### Clinical Utility

The SLC0181 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 SLC0181 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 SLC0181, causing clinically significant drug interactions.

### Assay Interpretation

There are several variants of the SLC0181 that define over 15 alleles. One relatively common variant 521T>C (rs4149056) results in a decreased SLC0181 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; rs2306283) on the \*15 allele. Both alleles are low-activity alleles (reduced hepatic uptake), and have a combined frequency of 15-20% in Caucasians, 10-15% in Asians, and 2% in sub-Saharan Africans and African-Americans.

**The reference range for the 521T>C mutation of SLC0181 is 521 TT. This is consistent with a normal SLC0181 transport function.**

### Clinical Implications

All statins are substrates of SLC0181, but the effects of SLC0181 genetic polymorphism differ between individual statins. The effect is the largest on simvastatin, and individuals with the 521T>C variant have increased levels of the active simvastatin form. The variant is strongly associated with simvastatin-induced myopathy (with or without CK elevation), especially with high-dose simvastatin therapy. More than 60% of the myopathy cases could be attributed to its presence. The clinical spectrum of statin-induced myopathy ranges from a mild and common myalgia to a life-threatening and rare rhabdomyolysis. Other known risk factors for statin-induced myopathy include a high-statin dose, interacting drugs that raise statin levels, age, hypothyroidism, and certain inherited muscle disorders.

At therapeutic doses, the apparent sensitivity levels of the five statins to the presence of the 521T>C variant are simvastatin>pitavastatin>atorvastatin>pravastatin>rosuvastatin. Carriers of the 521 T>C variant should avoid high-dose simvastatin therapy. These patients can take other statins, such as atorvastatin, pitavastatin, rosuvastatin, or pravastatin, but at reduced doses. Fluvastatin is not affected by the 521 T>C variant and could therefore be considered a suitable alternative.

Other drugs that are substrates of SLC0181 transporter include enalapril, olmesartan, valsartan, atrasentan, repaglinide, nateglinide, methotrexate, and bosentan. However, there is insufficient evidence documenting the impact of the 521 T>C variant on the systemic exposure and safety profile of these drugs.

### Inhibitors

Inhibitors of SLC0181 transporter may alter its activity and result in increased levels of drug substrates. These include gemfibrozil, cyclosporine, clarithromycin, protease inhibitors, simeprevir, teriflunomide, boceprevir, telaprevir, and eltrombopag.

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## VKORC1

### 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.

### 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, as shown in the following table.

### Clinical Implications

The -1639G>A is the common variant seen in the Caucasian populations, 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 358C>T (found in 21% of African-Americans) and 3730G>A variants are associated with high warfarin dose requirements.

When CYP2C9 and VKORC1 genotypes are combined with other demographic (age, weight, height), clinical (disease, co-medications), and environmental (smoking) factors, they account for 50% of warfarin dose variation between individuals.

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

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