PEDIATRIC

PHARMACOGENETIC

GENOTYPING PANEL

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PEDIATRIC PHARMACOGENETIC GENOTYPING PANEL

About the Test

Pharmacogenetics is the study of genetic determinants of interindividual drug response variability, and accumulating evidence supporting clinical utility for certain pharmacogenetic variants has prompted recent genotype-directed clinical practice recommendations for selected gene/drug pairs. Sema4 has designed and validated a Pediatric Pharmacogenetic (PGx) Genotyping panel that is intended to help physicians prescribe selected medications that can be influenced by interindividual genetic variability. The panel includes 84 variants in 9 genes. These genes and variants in the clinical PGx panel inform on 41 medications that may be prescribed for children across several clinical specialties.

The Sema4 Pediatric PGx Genotyping Panel is intended for children up to 18 years of age. Please note that the Sema4 Natalis Pediatric Pharmacogenetic (PGx) Genotyping panel is also available for children, which also includes the *MT-RNR1* gene.

Indications

The Sema4 Pediatric PGx Genotyping panel is intended to provide medication recommendations and drug response information to health care providers based on pharmacogenetic results. The information provided from this panel may help physicians make more informed management decisions regarding drug administration. **Please note that any modification of therapy should only be performed as directed by a healthcare professional.**

Testing Methods, Sensitivity, and Limitations

Targeted genotyping is performed for this test using multiplex Polymerase Chain Reaction (PCR) and multiplex Single Base Extension (SBE) reaction with Agena® SpectroCHIP® II on a MassARRAY® Analyzer 4 system. In addition, Multiplex ligation-dependent probe amplification (MLPA) serves as an adjunct test to determine copy number variants in the *CYP2C19, CYP2C9, CYP2D6*, and *CYP3A5* genes. This panel also includes targeted interrogation of the *UGT1A1* promoter dinucleotide repeat variant (**28*), which is genotyped by PCR and capillary electrophoresis. Resources including the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, FDA drug label recommendations, and peer-reviewed literature are used in the interpretation of these PGx testing results.

The analytical sensitivity and specificity of this assay is estimated to be greater than 99%. Only genes and variants included in this panel will be detected and reported. This test does not detect all the known alleles that result in altered or inactive gene function. This test does not account for all genetic variants in tested individuals. Absence of a detected gene variant with this panel does not rule out the possibility that a patient will have an atypical drug response phenotype, which could be due to an untested genetic variant or other factors such as drug-drug interactions, comorbidities, and/or other clinical and environmental variables.

Turnaround Time

Results are reported to the referring physician within 7-10 business days from the receipt of the specimen.

Specimen and Shipping Requirements

blood samples: Two lavender-top (EDTA) or two yellow-top (ACD-A or ACD-B) tubes, 5-10 mL of blood from the patient are required.
Tubes of blood should be kept and shipped refrigerated or at room temperature (PLEASE DO NOT FREEZE).

Extracted DNA samples: We request 50 µL DNA (50-250 ng/µL) or at minimum require 20 µL DNA (50-250 ng/µL). Causes for rejection include impurities in the test or reference DNA samples, including NaCl or KCl (>40 mM) and other salts, phenol, ethanol, heparin, EDTA (>1.5 mM), and Fe, contaminated DNA, and low concentration of DNA (<20 ng/µL).

Saliva samples: We can accept saliva specimens upon request. Saliva samples should be collected in Oragene DNA (OG-500) kits by DNA Genotek. Please contact our laboratory to obtain saliva kits.

Customer Services and Genetic Counseling

Include the following with each sample:

- Completed and signed test requisition form and informed consent
- Billing information or payment (include copy of insurance card)
- Contact information for referring physician
- Testing to be performed (Pediatric PGx Panel)
- Indication for testing, patient's family history, ethnic background and prior relevant test results

Send same day *or overnight (check for morning delivery)* to:

Sema4
62 Southfield Avenue
Stamford, CT 06902

Contact:

gc@sema4.com
Tel: 800-298-6470
Fax: 646-859-6871

Disclaimer

This test was developed and its performance characteristics were determined by Sema4 and was considered acceptable for patient testing. It has not been cleared or approved by the FDA. The FDA has determined that such clearance or approval is not necessary. This type of mutation analysis generally provides highly accurate genotype information for single nucleotide variants and small insertion/deletion variants. Despite this level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, rare polymorphisms, or other rare genetic variants that interfere with analysis. In addition, families should understand the limitations of the testing and that rare diagnostic errors may occur for the reasons described.

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MEDICATION LIST

Amitriptyline
Amitriptyline (Elavil®) is a tricyclic antidepressant (TCA) used in the treatment of Depression and is commonly prescribed for a host of other conditions "off-label" including: Chronic pain management, diabetic neuropathy, fibromyalgia, insomnia, migraine prophylaxis, and others. The mechanism of action is that it Increases the synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane pump. There is substantial evidence linking CYP2D6 and CYP2C19 genotypes to phenotypic variability in tricyclic side-effect and pharmacokinetic profiles. Modifying pharmacotherapy for patients who have CYP2D6 or CYP2C19 genomic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment.
References: PMID: 27997040

Amphetamine
Amphetamine sulfate (Adzenys®) is a central nervous system stimulant. Adzenys is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. Amphetamines are noncatecholamine sympathomimetic amines that promote release of catecholamines (primarily dopamine and norepinephrine) from their storage sites in the presynaptic nerve terminals. A less significant mechanism may include their ability to block the reuptake of catecholamines by competitive inhibition. The appetite suppressing effect is probably secondary to the CNS-stimulating effect; the site of action is probably the hypothalamic feeding center. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.
References: DrugBank, DailyMed FDA-approved drug label

Aripiprazole
Aripiprazole (Abilify®) is an atypical antipsychotic indicated for the treatment of schizophrenia, acute and maintenance treatment of manic or mixed episodes associated with bipolar I disorder, adjunctive treatment of major depressive disorder, and treatment of irritability associated with autistic disorder. Aripiprazole's antipsychotic activity is likely due to a combination of antagonism at D2 receptors in the mesolimbic pathway and 5HT2A receptors in the frontal cortex. Antagonism at D2 receptors relieves positive symptoms while antagonism at 5HT2A receptors relieves negative symptoms of schizophrenia. Aripiprazole is metabolized extensively in the liver primarily by CYP3A4 and CYP2D6. Dosing recommendation in patients who are classified as CYP2D6 poor metabolizers (PM): The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose and then adjusted to achieve a favorable clinical response.
References: FDA reference ID 3348855, PMID: 21412232

Atazanavir
Atazanavir (Reyataz®) is an antiretroviral agent belonging to the class of medications known as Protease Inhibitors and is indicated for the treatment of HIV-1 infection. Atazanavir Binds to the site of HIV-1 protease activity and inhibits cleavage of viral Gag-Pol polyprotein precursors into individual functional proteins required for infectious HIV. This results in the formation of immature, noninfectious viral particles. Atazanavir also inhibits hepatic uridine diphosphate glucuronosyltransferase (UGT) 1A1, thereby preventing the glucuronidation and elimination of bilirubin. Resultant indirect hyperbilirubinemia with jaundice can cause premature discontinuation of atazanavir. Risk for bilirubin-related discontinuation is highest among individuals who carry two UGT1A1 decreased function alleles (UGT1A1*28 or *37). It is recommended to consider an alternative agent particularly where jaundice would be of concern to the patient.
References: PMID: 26417955

Atomoxetine
Atomoxetine (Strattera®) is a selective norepinephrine reuptake inhibitor indicated for the treatment of Attention-deficit/hyperactivity disorder (ADHD). Atomoxetine selectively inhibits the reuptake of norepinephrine with little to no activity at the other neuronal reuptake pumps or receptor sites. Atomoxetine is primarily metabolized through the CYP2D6 pathway. CYP2D6 poor metabolizers (PM) have atomoxetine AUCs that are ~10-fold higher and peak concentrations that are ~fivefold greater than normal metabolizers (NM). Individuals who are PM phenotypes have a statistically significant higher incidence of adverse reactions when compared to NM phenotypes. These adverse reactions include (not a comprehensive list); increased heart rate, blurred vision, dry mouth, feeling jittery, tremor, insomnia, decreased appetite, hyperhidrosis, and peripheral coldness. Dose adjustment is recommended in individuals who are known to be PM.
References: See FDA reference ID 3352061, PMID: 25919121

Azathioprine
Azathioprine (Imuran®) is classified as an immunosuppressant agent indicated for the treatment of renal transplantation, rheumatoid arthritis and a number of "off-label" uses (Crohn's disease, Multiple Sclerosis, Psoriasis, Ulcerative Colitis). Azathioprine is an imidazolyl derivative of mercaptopurine; metabolites are incorporated into replicating DNA and halt replication; also block the pathway for purine synthesis. The 6-thioguanine nucleotide metabolites appear to mediate the majority of azathioprine's immunosuppressive and toxic effects. TPMT is an enzyme that is involved in the metabolism of azathioprine to its inactive metabolites. Patients with intermediate thiopurine S-methyl transferase (TPMT) activity may be at an increased risk of myelotoxicity if receiving conventional doses of IMURAN. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of IMURAN. TPMT genotyping or phenotyping can help identify patients who are at an increased risk for developing IMURAN toxicity. Reduced dosing (30-70%) in those individuals who have intermediate activity is recommended. Those who have low or deficient TPMT activity are recommended to use alternative agents, or drastically reduce dose (10-fold reduction with thrice weekly dosing instead of daily).
References: PMID: 18253145, 21270794, 23422873

Capecitabine

Capecitabine (Xeloda®) is an antineoplastic agent known as a Pyrimidine analog. It is used in the treatment of metastatic breast cancer, colorectal cancer and as adjuvant therapy in Dukes' C colon cancer. Capecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle. Detoxifying metabolism of fluoropyrimidines (capecitabine) requires dihydropyrimidine dehydrogenase (DPD, encoded by the DPYD gene), and reduced or absent activity of this enzyme can result in severe, and sometimes fatal toxicity. Current guidelines state that those individuals who are found to be heterozygous variant or having intermediate DPD activity it is recommended to start with at least a 50% reduction in starting dose. Individuals who are homozygous variant with complete DPD deficiency it is recommended to use an alternate drug.

References: PMID: 23988873, 18253145

Celecoxib

Celecoxib (Celebrex®), a selective cyclooxygenase-2 (COX-2) inhibitor, is classified as a nonsteroidal anti-inflammatory drug (NSAID). Celecoxib is indicated to treat rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis (JRA), acute pain, primary dysmenorrhea and ankylosing spondylitis. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis. Unlike most NSAIDs, which inhibit both types of cyclooxygenases (COX-1 and COX-2), celecoxib is a selective noncompetitive inhibitor of cyclooxygenase-2 (COX-2) enzyme. Celecoxib metabolism is primarily mediated via CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. Patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers (i.e., CYP2C9*3/*3). Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers.

References: FDA-approved drug label

Citalopram

Citalopram (Celexa®) is one in a class of antidepressants known as selective serotonin reuptake inhibitors (SSRI). It is indicated for the treatment of depression. Citalopram's mechanism of action is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Citalopram blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on 5HT ~1A~ autoreceptors. In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram. In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. Celexa 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation. In other guidelines CYP2C19 ultra-rapid metabolizers are recommended to use an alternative drug, one not predominantly metabolized by CYP2C19.

References: FDA-approved drug label, PMID: 21412232, 25974703

Clomipramine

Clomipramine (Anafranil®) is a tricyclic antidepressant and may be used to treat obsessive-compulsive disorder and disorders with an obsessive-compulsive component (e.g. depression, schizophrenia, Tourette's disorder). Unlabeled indications include: depression, panic disorder, chronic pain (e.g. central pain, idiopathic pain disorder, tension headache, diabetic peripheral neuropathy, neuropathic pain), cataplexy and associated narcolepsy (limited evidence), autistic disorder (limited evidence), trichotillomania (limited evidence), onchophagia (limited evidence), stuttering (limited evidence), premature ejaculation, and premenstrual syndrome. Clomipramine is a strong, but not completely selective serotonin reuptake inhibitor (SRI), as the active main metabolite desmethyclomipramine acts preferably as an inhibitor of noradrenaline reuptake. α1-receptor blockage and β-down-regulation have been noted and most likely play a role in the short-term effects of clomipramine. A blockade of sodium-channels and NDMA-receptors might, as with other tricyclics, account for its effect in chronic pain, in particular the neuropathic type. There is substantial evidence linking *CYP2D6* and *CYP2C19* genotypes to phenotypic variability in tricyclic side-effect and pharmacokinetic profiles. Modifying pharmacotherapy for patients who have *CYP2D6* or *CYP2C19* genomic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment.
References: DailyMed drug label, DrugBank, PMID 27997040

Clonidine

Clonidine (Catapres®) is an imidazoline-derivative hypotensive agent is a centrally-acting α2-adrenergic agonist. Clonidine may be used as an adjunct in the treatment of hypertension, as an epidural infusion as an adjunct treatment in the management of severe cancer pain that is not relieved by opiate analgesics alone, for differential diagnosis of pheochromocytoma in hypertensive patients, prophylaxis of vascular migraine headaches, treatment of severe dysmenorrhea, management of vasomotor symptoms associated with menopause, rapid detoxification in the management of opiate withdrawal, treatment of alcohol withdrawal used in conjunction with benzodiazepines, management of nicotine dependence, topical use to reduce intraocular pressure in the treatment of open-angle and secondary glaucoma and hemorrhagic glaucoma associated with hypertension, and in the treatment of attention-deficit hyperactivity disorder (ADHD). Clonidine is an α-adrenergic agent that acts specifically on α2-receptors. α2-receptors regulate a number of signaling pathways mediated by multiple Gi proteins, Gαi1, Gαi2, and G&alphai3. The α2A- and α2C-receptors are located presynaptically and inhibit the released of noradrenaline from sympathetic nerves. Stimulation of these receptors decreases sympathetic tone, resulting in decreases in blood pressure and heart rate. It has been shown that the CYP2D6 enzyme has a role in the metabolism of clonidine. Individuals with a variant in the CYP2D6 gene either increasing or decreasing function can have a subtherapeutic response or increased risk for adverse reactions, respectively.
References: DailyMed FDA-approved drug label, DrugBank, PMID: 20570945

Clopidogrel

Clopidogrel (Plavix®) is an antiplatelet agent prescribed for prevention of ischemic events resulting from acute coronary syndromes (ACS), ischemic stroke, and symptomatic peripheral artery disease (PAD). Clopidogrel is biotransformed in the liver to an active

metabolite that binds specifically and irreversibly to the platelet P2Y12 receptor, inhibiting ADP-mediated platelet activation and aggregation. Interindividual variability in platelet aggregation is common during clopidogrel therapy and individuals who carry variant CYP2C19 alleles have increased risks for reduced active clopidogrel metabolites, higher on-treatment platelet aggregation, and major adverse cardiovascular events. Current guidelines recommend alternative antiplatelet agents for ACS patients undergoing percutaneous coronary intervention (PCI) who carry decreased function CYP2C19 alleles.
References: PMID: 23698643, 21412232

Codeine
Codeine (multiple brand names) is one of a class of medications known as opiates. It is indicated for the management of mild to moderate pain. It is also used in the treatment of a cough. Codeine is a prodrug, itself inactive, but demethylated to the active morphine by the liver enzyme CYP2D6. Current guidelines state that if an individual is a CYP2D6 poor metabolizer, there is greatly reduced morphine formation following codeine administration, leading to insufficient pain relief. Also, if an individual is a CYP2D6 ultra-rapid metabolizer there will be increased formation of morphine following codeine administration, leading to higher risk of toxicity. Alternative medications should be used in these individuals.
References: FDA reference ID 4028523, PMID: 18253145, 22205192

Desipramine
Desipramine (NORPRAMIN®) is an antidepressant drug belonging to the tricyclic antidepressants class. Desipramine is indicated for the treatment of depression. While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Desipramine is extensively metabolized in the liver by CYP2D6. Current guidelines recommend if an individual is a CYP2D6 poor metabolizer, avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose. If an individual is a CYP2D6 ultra-rapid metabolizer, avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments
References: PMID: 23486447

Dextroamphetamine
Dextroamphetamine (Dexedrine®) is a central nervous system stimulant. Dextroamphetamine is the dextrorotary stereoisomer of the amphetamine molecule, which can take two different forms. Used to treat attention deficit hyperactivity disorder (ADHD) and Narcolepsy. The exact mechanism of action is not known. Dextroamphetamine stimulates the release of norepinephrine from central adrenergic receptors. At higher dosages, it causes release of dopamine from the mesocorticolimbic system and the nigrostriatal dopamine systems by reversal of the monoamine transporters. Dextroamphetamine may also act as a direct agonist on central 5-HT receptors and may inhibit monoamine oxidase. The concomitant use of DEXEDRINE and

CYP2D6 inhibitors may increase the exposure of DEXEDRINE compared to the use of the drug alone and increase the risk of serotonin syndrome.
References: FDA-approved drug label, DrugBank

Doxepin

Doxepin (Silenor®, Sinequan®) is a tricyclic antidepressant (TCA). Doxepin is used for the treatment of depression and/or anxiety. It can also be used for chronic urticaria and in the management of pain. The mechanism of action of doxepin is not completely understood. It is thought that like amitriptyline, doxepin enhances the actions of norepinephrine and serotonin by blocking their reuptake at the neuronal membrane. However, doxepin weakly inhibits the reuptake of dopamine. Doxepin may also act on histamine H1-receptors, resulting in sedative effects, and β-adrenergic receptors. Doxepin is metabolized primarily by the CYP enzymes, CYP2D6 (major), CYP2C19, CYP1A2 and CYP3A4 (minor). Current guidelines are in place for individuals being initiated on Doxepin recommending either lower doses in the case of poor metabolizers or alternative medications for rapid metabolizers.
References: DrugBank, UpToDate, PMID: 23486447, 18253145

Eliglustat
Eliglustat (Cerdelga®) is a Glucosylceramide Synthase Inhibitor indicated for the treatment of Gaucher disease. Eliglustat inhibits the enzyme needed to produce glycosphingolipids and decreases the rate of glycosphingolipid glucosylceramide formation. Glucosylceramide accumulates in type 1 Gaucher disease, causing complications specific to this disease. Systemic exposure depends upon the patient's CYP2D6 phenotype; systemic exposure is up to 9-fold higher in poor metabolizers (PMs). CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect. According to the FDA approved label testing for a patient's CYP2D6 metabolizer status is a requirement prior to initiating treatment.
Reference: See FDA-approved drug label
https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205494Orig1s000lbl.pdf

Escitalopram
Escitalopram (Lexapro®) is an antidepressant agent prescribed for major depressive disorder (MDD) and generalized anxiety disorder (GAD). Escitalopram selectively inhibits the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on 5HT1A autoreceptors. It is extensively metabolized by CYP2C19 and variations in the enzyme activity may result in altered drug exposure. Current guidelines recommend, for CYP2C19 poor metabolizers, to consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.
References: PMID: 25974703

Fluorouracil
Fluorouracil (Adrucil®, Efudex®) is a widely used antineoplastic agent (pyrimidine analog) indicated for the treatment of a number of different cancers, including breast, colorectal,

gastric and pancreatic. As a topical agent fluorouracil is indicated for actinic or solar keratosis, and also for superficial basal cell carcinoma. Fluorouracil inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle. Detoxifying metabolism of fluoropyrimidines requires dihydropyrimidine dehydrogenase (DPD, encoded by the DPYD gene), and reduced or absent activity of this enzyme can result in severe, and sometimes fatal toxicity. Current guidelines state that those individuals who are found to be heterozygous variant or having intermediate DPD activity it is recommended to start with at least a 50% reduction in starting dose. Individuals who are homozygous variant with complete DPD deficiency it is recommended to use an alternate drug.
References: PMID: 21412232, 23988873

Fluoxetine
Fluoxetine (Prozac®) an antidepressant agent belonging to the selective serotonin reuptake inhibitors (SSRIs), is used to treat depression, bulimia nervosa, premenstrual dysphoric disorder, panic disorder and post-traumatic stress. Fluoxetine's effects are thought to be associated with the inhibition of 5HT receptor, which leads to an increase of serotonin level. A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-norfluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) also contribute to the metabolism of fluoxetine.
References: DailyMed FDA-approved drug label, DrugBank, PMID: 11386497

Fluvoxamine
Fluvoxamine (Luvox®) is one in a class of antidepressants known as selective serotonin reuptake inhibitors (SSRI). Fluvoxamine is indicated for the treatment of obsessive-compulsive disorder, and a number of "off-label" uses (bulimia nervosa, panic disorder, post-traumatic stress disorder, social anxiety disorder). The exact mechanism of action of fluvoxamine has not been fully determined, but appears to be linked to its inhibition of CNS neuronal uptake of serotonin. Fluvoxamine blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on 5HT ~1A~ autoreceptors. Current guidelines state that if an individual is a CYP2D6 poor metabolizer that the provider considers a 25-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6.
References:PMID: 25974703

Fosphenytoin
Fosphenytoin (Cerebyx®) is an anticonvulsant agent prescribed for the control of generalized convulsive status epilepticus and prevention and treatment of seizures. Fosphenytoin is a prodrug of phenytoin and accordingly, its anticonvulsant effects

are attributable to phenytoin. Phenytoin acts on sodium channels on the neuronal cell membrane, limiting the spread of seizure activity and reducing seizure propagation. By promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses. Loss of post-tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference. Besides that, there is an association between the presence of the HLA-B*15:02 allele and development of Stevens–Johnson syndrome and toxic epidermal necrolysis. Current guidelines state that phenytoin is contraindicated in individuals with the HLA-B*15:02 variant allele ("HLA-B*15:02-positive") due to significantly increased risk of phenytoin-induced cutaneous adverse reactions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Additionally, patients with the CYP2C9 poor metabolizer phenotype may require reduced doses of phenytoin.
References: PMID: 25099164, 21412232 (phenytoin references)

Hydrocodone
Hydrocodone (multiple brand names) is an opioid agonist indicated for the relief of moderate to moderately severe pain. Also used for the symptomatic relief of nonproductive cough, alone or in combination with other antitussives or expectorants. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. Hydrocodone is metabolized to hydromorphone (active metabolite) by the CYP2D6 enzyme system. Poor metabolizer and ultrarapid metabolizer phenotypes of CYP2D6 have been shown to experience either poor pain control or adverse symptoms related to this drug. It has also been shown that patients with the GG allele on rs1799971 of the OPRM1 gene are more likely to experience adverse effects when compared to patients carrying the AA or AG allele.
References: DailyMed FDA approved drug label, PMID: 23703421, 28769582

Iloperidone
Iloperidone (FANAPT®) is an atypical antipsychotic agent indicated for the treatment of schizophrenia in adults. The mechanism of action of iloperidone, as with other drugs having efficacy in schizophrenia, is unknown. However it is proposed that the efficacy of iloperidone is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT2) antagonisms. Iloperidone dose should be reduced by one-half for poor metabolizers of CYP2D6 according to the FDA approved drug label.
References: FDA-approved drug label

Imipramine
Imipramine (Tofranil®) is a tricyclic antidepressant indicated for the relief of symptoms of depression and as temporary adjunctive therapy in reducing enuresis in children aged 6 years and older. May also be used to manage panic disorders, with or without agoraphobia, as a second line agent in ADHD, management of eating disorders, for short-term management of acute depressive episodes in bipolar disorder and schizophrenia, and for symptomatic treatment of postherpetic neuralgia. Imipramine works by inhibiting the

neuronal reuptake of the neurotransmitters norepinephrine and serotonin. There is substantial evidence linking *CYP2D6* and *CYP2C19* genotypes to phenotypic variability in tricyclic side-effect and pharmacokinetic profiles. Modifying pharmacotherapy for patients who have *CYP2D6* or *CYP2C19* genomic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment.
References: DailyMed Drug Labels, DrugBank, PMID 27997040

Lisdexamfetamine
Lisdexamfetamine (Vyvanse®) is a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and Moderate to Severe Binge Eating Disorder in adults. Lisdexamfetamine is a pro-drug of dextroamphetamine. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Norepinephrine and dopamine contribute to maintaining alertness, increasing focus, and sustaining thought, effort, and motivation. However, the exact therapeutic action in ADHD is not known. CYP2D6 is known to be involved in the metabolism of amphetamines. Individuals with certain polymorphisms in the CYP2D6 gene can have a potential for variation in amphetamine metabolism. The FDA label states that when given concomitantly with CYP2D6 inhibitors can increase exposure to amphetamine, increasing the risk of serotonin syndrome.
References: DailyMed FDA-approved drug label, DrugBank

Mercaptopurine
Mercaptopurine (Purinethol®) is an antimetabolite (purine analog) and immunosuppressant agent. Mercaptopurine is indicated for the treatment acute lymphoblastic leukemia (ALL), and "off-label" for Crohn's disease, and Ulcerative Colitis. Mercaptopurine is a purine antagonist which inhibits DNA and RNA synthesis; acts as false metabolite and is incorporated into DNA and RNA, eventually inhibiting their synthesis; specific for the S phase of the cell cycle. Thiopurine S-methyltransferase (TPMT) inactivates mercaptopurine, leaving less parent drug available to form thioguanine nucleotides TGNs, the major active metabolite. Guidelines suggest that those individuals who are heterozygote (intermediate activity), having one functional allele and one nonfunctional allele, starting doses be reduced by 30-70% of full dose. In those individuals who are homozygous variant, having low or deficient TPMT activity, starting doses of mercaptopurine should be drastically reduced by 10-fold and given only 3 times a week as opposed to daily. Doses should be adjusted according to myelosuppression and disease specific guidelines.
References: PMID: 28520348, 23422873, 21412232

Nortriptyline
Nortriptyline (Pamelor®) is a tricyclic antidepressant (secondary amine) indicated for the relief of depression, along with several "off-label" uses; including, chronic pain, diabetic neuropathy, orofacial pain, postherpetic neuralgia and smoking cessation. It is believed that nortriptyline either inhibits the reuptake of the neurotransmitter serotonin at the neuronal membrane or acts at beta-adrenergic receptors. The major pathway of metabolism of nortriptyline is subject to genetic polymorphism in the *CYP2D6* gene. Guidelines exist that recommend the consideration of alternative therapy for those individuals expressing the phenotype "ultrarapid metabolizer". Dosing

recommendations are available for those individuals who are known "intermediate metabolizer", or "poor metabolizers", to reduce the risk of known side-effects.
References: DrugBank, FDA Drug label, PMID: 27997040

Ondansetron
Ondansetron (multiple brand names) is an antiemetic agent prescribed for treatment of nausea and vomiting caused by cytotoxic chemotherapy drugs. Ondansetron is a selective 5-HT3-receptor antagonist, blocking serotonin, both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone. It is a substrate for CYP2D6, among other CYP enzymes. Variants in the CYP2D6 gene can alter the effect of the drug. Current guidelines recommend selecting an alternate drug for CYP2D6 ultrarapid metabolizers. It is recommended that the alternate drug not be predominantly metabolized by CYP2D6 (eg. granisetron).
References: PMID: 28002639

Oxycodone
Oxycodone (multiple brand names) is a narcotic analgesic agent prescribed for management of pain, restless leg and Tourette syndromes. Oxycodone is as a weak agonist at mu, kappa, and delta opioid receptors within the central nervous system. It is metabolized by CYP2D6 and variations in the enzyme activity can alter the drug effect. Current guidelines recommend using an alternate drug rather than oxycodone (not codeine or tramadol) for CYP2D6 poor and intermediate metabolizer patients, or be alert to insufficient pain relief. For CYP2D6 ultra metabolizer patients, use an alternate drug rather than oxycodone (not codeine or tramadol), or be alert to adverse drug events.
References: PMID: 21412232

Paroxetine
Paroxetine (multiple brand names) is a psychotropic agent prescribed for major depressive disorder, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder. Paroxetine acts through the potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). The metabolism of paroxetine is accomplished in part by cytochrome CYP2D6. Variants in the CYP2D6 gene can alter the effect of the drug. Current guidelines recommend an alternative drug not predominantly metabolized by CYP2D6 for CYP2D6 ultrarapid metabolizers and for CYP2D6 poor metabolizers. For CYP2D6 poor metabolizers, if paroxetine use is warranted, consider a 50% reduction of recommended starting dose and titrate to response.
References: PMID: 25974703, 21412232

Phenytoin
Phenytoin (multiple brand names) is an antiepileptic agent prescribed for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery. Phenytoin acts possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. There may be

wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be hypermetabolizers of phenytoin. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference. Besides that, there is an association between the presence of the HLA-B*15:02 allele and development of Stevens–Johnson syndrome and toxic epidermal necrolysis. Current guidelines state that phenytoin is contraindicated in individuals with the HLA-B*15:02 variant allele ("HLA-B*15:02-positive") due to significantly increased risk of phenytoin-induced cutaneous adverse reactions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Additionally, patients with the CYP2C9 poor metabolizer phenotype may require reduced doses of phenytoin.
References: PMID: 25099164, 21412232, FDA-approved drug label https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008762s057s058lbl.pdf

Pimozide
Pimozide (Orap®) is an antipsychotic agent prescribed for the suppression of motor and phonic tics in patients with Tourette's Disorder. Pimozide blocks dopaminergic receptors on neurons in the central nervous system. Individuals with genetic variations resulting in poor CYP2D6 metabolism exhibit higher pimozide concentrations than extensive CYP2D6 metabolizers. Current guidelines recommend CYP2D6 genotyping should be performed at doses above 0.05mg/kg/day in children or above 4 mg/day in adults. In poor CYP2D6 metabolizers, pimozide doses should not exceed 0.05mg/kg/day in children or 4 mg/day in adults and doses should not be increased earlier than 14 days.
References: FDA-approved drug label
https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017473s041lbl.pdf

Sertraline
Sertraline (Zoloft®) is a selective serotonin-reuptake inhibitor (SSRI) antidepressant agent prescribed for major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, social anxiety disorder. Sertraline increases serotonergic activity by decreasing presynaptic serotonin reuptake. It is extensively metabolized by CYP2C19 and variations in the enzyme activity may result in altered drug exposure. Current guidelines recommend considering a 50% reduction of recommended starting dose and titrating to response or selecting alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 poor metabolizers.
References: PMID: 25974703, 21412232

Simvastatin
Simvastatin (Zocor®) is an antilipemic agent prescribed for treatment of hypercholesterolemia and for the reduction in the risk of cardiac heart disease mortality and cardiovascular events. Simvastatin acts through inhibition of HMG-CoA reductase. In patients with variants in SLCO1B1 gene, there are modest increases in myopathy risk even at lower simvastatin doses (40 mg daily). Current guidelines recommend prescribing a lower dose or considering an alternative statin for patients who have variants in SLCO1B1 gene.
References: PMID: 22617227, 24918167

Tacrolimus
Tacrolimus (multiple brand names) is an immunosuppressive agent whose main use is after organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. It is also used in a topical preparation in the treatment of severe atopic dermatitis, severe refractory uveitis after bone marrow transplants, and the skin condition vitiligo. Blood concentrations of tacrolimus are strongly influenced by CYP3A5 genotype, with substantial evidence linking CYP3A5 genotype with phenotypic variability in kidney, heart and lung transplant patients. Current guidelines recommend increasing the starting dose by 1.5 to 2 times the recommended starting dose in patients who are CYP3A5 intermediate or extensive metabolizers, though total starting dose should not exceed 0.3 mg/kg/day. Therapeutic drug monitoring should also be used to guide dose adjustments.
References: PMID: 25801146, 21412232

Thiopurine (Thioguanine)
Thioguanine (Tabloid®) is a thiopurine antineoplastic agent prescribed for acute nonlymphocytic leukemias. Thioguanine has multiple metabolic effects. Its tumor inhibitory properties may be due to one or more of its effects on (a) feedback inhibition of de novo purine synthesis; (b) inhibition of purine nucleotide interconversions; or (c) incorporation into the DNA and the RNA. The net consequence of its actions is a sequential blockade of the synthesis and utilization of the purine nucleotides. There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effects of thioguanine and prone to developing rapid bone marrow suppression following the initiation of treatment. Current guidelines recommend to start with reduced doses of thioguanine for patients with one nonfunctional TPMT allele, or drastically reduced doses for patients with malignancy and two nonfunctional alleles; adjust dose based on degree of myelosuppression and disease-specific guidelines. Consider alternative nonthiopurine immunosuppressant therapy for patients with nonmalignant conditions and two nonfunctional alleles.
References: PMID: 23422873, 21412232

Tramadol
Tramadol (multiple brand names) is an opioid analgesic agent prescribed for management of pain in adults. Tramadol acts through both binding to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. The formation of the active metabolite is mediated by CYP2D6, a polymorphic enzyme. Current guidelines recommend for CYP2D6 poor metabolizers (PM), to select an alternative to tramadol (not oxycodone or codeine) and be alert for symptoms of insufficient pain relief. For CYP2D6 intermediate metabolizers (IM), be alert for symptoms of insufficient pain relief, and consider dose increase or select an alternative to tramadol (not oxycodone or codeine). For CYP2D6 ultrarapid metabolizers, use a 30% decreased dose and be alert for ADEs, or use an alternative to tramadol (not oxycodone or codeine).
References: PMID: 21412232, FDA Reference ID: 4028136

Trimipramine
Trimipramine (Surmontil®) is a tricyclic antidepressant (TCA) used in the treatment to relieve the symptoms of depression. The mode of action that trimipramine has on the

central nervous system is not known, however, it is thought that tricyclic antidepressants work by inhibiting the re-uptake of the neurotransmitters norepinephrine and serotonin by nerve cells. There is evidence linking *CYP2D6* and *CYP2C19* genotypes to phenotypic variability in tricyclic side-effect and pharmacokinetic profiles. Guidelines exist for dosing or recommending alternative medications for patients who have *CYP2D6* or *CYP2C19* genomic variants that affect drug efficacy and safety, which could potentially improve clinical outcomes and reduce the failure rate of initial treatment.
References: UpToDate drug reference, DrugBank, FDA Drug label, PMID: 27997040

Voriconazole
Voriconazole (Vfend®) is a triazole antifungal agent prescribed for infections caused by fungus. Its mechanism of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole. *In vivo* studies indicated that CYP2C19 is significantly involved in the metabolism of the drug. This enzyme exhibits genetic polymorphism and subjects who carry variants in this gene can present lack of efficacy or adverse events. Current guidelines recommend selecting an alternative agent that is not dependent on CYP2C19 metabolism in adults who are CYP2C19 ultrarapid metabolizers, rapid metabolizers or poor metabolizers. In pediatric patients, an alternative agent should be used in patients who are ultrarapid metabolizers or poor metabolizers. In pediatric rapid metabolizers, therapy should be initiated at recommended standard case dosing, then therapeutic dosing monitoring should be used to titrate dose to therapeutic trough concentrations.
References: PMID: 27981572, FDA reference ID: 3045001

Warfarin
Warfarin (Coumadin®) is an anticoagulant used for the treatment of retinal vascular occlusion, pulmonary embolism, cardiomyopathy, atrial fibrillation and flutter, cerebral embolism, transient cerebral ischemia, arterial embolism and thrombosis. Warfarin acts by inhibiting the synthesis of vitamin K-dependent clotting factors, which include Factors II, VII, IX, and X, and the anticoagulant proteins C and S. A number of CYP450 isozymes are involved in the metabolism of warfarin. CYP2C9, a polymorphic enzyme, is likely to be the principal form of human liver CYP450 that modulates the *in vivo* anticoagulant activity of warfarin. Patients with one or more variant CYP2C9 alleles have decreased S-warfarin clearance. Also, VKORC1, the target enzyme for warfarin, is known to have several single nucleotide polymorphisms which are associated with warfarin dosing.
References: DailyMed FDA drug label, PMID 22010099