a Mount Sinai venture

Pain Pharmacogenetic Genotyping Panel

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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 Pain Pharmacogenetic (PGx) Genotyping panel that is intended to help physicians prescribe selected medications that can be influenced by interindividual genetic variability. The panel includes 80 variants in 8 genes. These genes and variants in the clinical Pain PGx panel inform on 38 medications used across this clinical specialty.

The Sema4 Pain PGx Genotyping Panel is intended for adults and older children. Please note that a Sema4 Pediatric Pharmacogenetic (PGx) Genotyping panel is also available for children.

Indications

The Sema4 Pain 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 interrogate copy number variants in the *CYP2B6, CYP2C19, CYP2C9,* and *CYP2D6*, genes. 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

Postnatal 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.

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.

Tubes of blood should be kept and shipped refrigerated or at room temperature (PLEASE DO NOT FREEZE).

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 (Comprehensive 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
1428 Madison Avenue, Atran 2-25
New York, NY 10029

Contact:
labgeneticcounselors@sema4genomics.com
Tel: 212-241-7518
Fax: 212-241-0139

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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Medications list

Allopurinol
Allopurinol (Zyloprim®) is a xanthine oxidase inhibitor that decreases uric acid production. Allopurinol is indicated for and the standard treatment for hyperuricemia associated with gout. It is also used in patients undergoing certain chemotherapy regimens that cause hyperuricemia. Allopurinol and its active metabolite, oxypurinol, inhibits the enzyme xanthine oxidase, blocking the conversion of the oxypurines hypoxanthine and xanthine to uric acid. Elevated concentrations of oxypurine and oxypurine inhibition of xanthine oxidase through negative feedback results in a decrease in the concentrations of uric acid in the serum and urine. Preliminary studies show that the gene ABCG2 is an allopurinol transporter and a determinant of drug response. Loss of function polymorphism predicts poor response to allopurinol in patients with gout.
References: Dailymed, PMID: 26810134, 25676789

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

Carisoprodol
Carisoprodol (Soma®) is a centrally acting skeletal muscle relaxant that does not directly relax skeletal muscles. Carisoprodol is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults. A metabolite of carisoprodol, meprobamate, has anxiolytic and sedative properties. The degree to which these properties of meprobamate contribute to the safety and efficacy of carisoprodol is unknown. The mechanism of action of carisoprodol in relieving discomfort associated with acute painful musculoskeletal conditions has not been clearly identified. The major pathway of carisoprodol metabolism is via the liver by cytochrome enzyme CYP2C19 to form meprobamate. This enzyme exhibits genetic polymorphism. The FDA label states that patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Therefore, caution should be exercised in administration of carisoprodol to these patients.
References: DailyMed FDA-approved drug label

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

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

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

Dexlansoprazole
Dexlansoprazole (Dexilant®) is a proton pump inhibitor indicated for the healing of erosive esophagitis, maintenance of healed erosive esophagitis, and symptomatic non-erosive gastroesophageal reflux disease (GERD). Dexlansoprazole decreases acid secretion in gastric parietal cells through inhibition of (H+, K+)-ATPase enzyme system, blocking the final step in gastric acid production. Metabolism of dexlansoprazole is mediated via CYP2C19 hydroxylation. CYP2C19 polymorphism is expected to affect dexlansoprazole exposure. In a study involving

Japanese men following a single dose of dexlansoprazole, Cmax and AUC were up to 2 times greater in intermediate metabolizers compared to extensive metabolizers. In addition, mean Cmax and mean AUC were up to 4 times greater and up to 12 times greater, respectively, in poor metabolizers compared to extensive metabolizers. Though such study was not conducted in Caucasians and African Americans, it is expected dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well.
References: FDA reference ID 3360126, PMID: 25303292

Diclofenac
Diclofenac (Voltaren®, Cataflam®) is a nonsteroidal anti-inflammatory drug (NSAID). Diclofenac is indicated for the acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity. Metabolism of diclofenac in human partitions between acyl glucuronidation and phenyl hydroxylation, with the former reaction catalyzed primarily by uridine 5'-diphosphoglucuronosyl transferase 2B7 while the latter is catalyzed by cytochrome P450 CYP2C9 and 3A4. Polymorphisms in the CYP2C9 show that patients with the CC genotype who are treated NSAIDs, celecoxib or diclofenac may have an increased risk of gastrointestinal bleeding as compared to patients with the AA genotype.
References: DrugBank, DailyMed FDA-Approved drug label, PMID: 14707031

Dihydrocodeine
Dihydrocodeine is an opioid analgesic used as an alternative or adjunct to codeine to treat moderate to severe pain, severe dyspnea, and cough. Possible opioid related side effects include, but are not limited to, drowsiness, nausea, headache, dry mouth, constipation, difficulty passing urine, and mild euphoria. Dihydrocodeine is metabolized to dihydromorphine -- a highly active metabolite with a high affinity for mu opioid receptors. Metabolized in the liver by CYP2D6 into an active metabolite, dihydromorphine, and by CYP3A4 into secondary primary metabolite, nordihydrocodeine. A third primary metabolite is dihydrocodeine-6-glucuronide. Since Dihydrocodeine is structurally similar to codeine and since both are metabolized by CYP2D6 to substances that have a higher affinity to the mu opiate receptors, it would stand to reason that the same pharmacogenetic guidelines for CYP2D6 and codeine would apply to dihydrocodeine, however published evidence is lacking in this area. Codeine CPIC guidelines state that if an individual is a CYP2D6 poor metabolizer or and CYP2D6 ultra-rapid metabolizer that codeine should be avoided.
References: DailyMed FDA label, DrugBank, UpToDate, PMID: 22205192

Duloxetine
Duloxetine (Cymbalta®) is a selective SNRI (selective serotonin-norepinephrine reuptake inhibitor). It is indicated for the acute and maintenance treatment of major depressive disorder (MDD), as well as acute management of generalized anxiety disorder. Also used for the management of neuropathic pain associated with diabetic peripheral neuropathy, and fibromyalgia. The antidepressant and pain inhibitory actions of duloxetine are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism. The FDA label states that concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax.
References: DailyMed FDA-approved drug label, DrugBank, PMID: 21412232

Esomeprazole
Esomeprazole (Nexium®) belongs to a class of medications known as the Proton Pump Inhibitors (PPI). It is indicated for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. Esomeprazole suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity. Esomeprazole is completely metabolized by the cytochrome P450 system via CYP2C19 and CYP3A4. Current guidelines suggest increasing the dose by 50-100% in the population of persons with a CYP2C19 ultra-rapid metabolizer phenotype.
References: DrugBank, DailyMed FDA drug label, PMID: 21412232

Fentanyl

Fentanyl (Duragesic®, Subsys®, Abstral®) is an opioid agonist. It is indicated for the management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. It is also used as a narcotic analgesic supplement in general or regional anesthesia. Fentanyl may increase the patient's tolerance for pain and decrease the perception of suffering, although the presence of the pain itself may still be recognized. In addition to analgesia, alterations in mood, euphoria and dysphoria, and drowsiness commonly occur. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system. Individuals with polymorphisms in the OPRM1 gene have been shown to have varying response to fentanyl postoperatively.
References: DailyMed FDA-approved drug label, DrugBank, PMID: 25615449, 23909491

Flurbiprofen
Flurbiprofen (Ocufen®) is a member of the phenylalkanoic acid derivative group of nonsteroidal anti-inflammatory drugs (NSAID). Flurbiprofen exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Flurbiprofen, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. In vitro studies have demonstrated that cytochrome P450 2C9 plays an important role in the metabolism of flurbiprofen to its major metabolite. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) should be administered flurbiprofen with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.
References: FDA labeling on Dailymed

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

Ibuprofen
Ibuprofen (Advil®, Motrin®) is a non-steroidal anti-inflammatory drug (NSAID). It is indicated for symptomatic treatment of rheumatoid arthritis, juvenile rheumatoid arthritis and osteoarthritis. Ibuprofen may be used to treat mild to moderate pain and for the management of dysmenorrhea. Ibuprofen is also used to reduce fever. The exact mechanism of action of ibuprofen is unknown. Ibuprofen is a non-selective inhibitor of cyclooxygenase, an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. Its pharmacological effects are believed to be due to inhibition cylooxygenase-2 (COX-2) which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever and swelling. Cytochrome P450 2C9 is the major catalyst in the formation of oxidative metabolites. Polymorphisms in CYP2C9, specifically CYP2C9*3 had a 45% reduction of clearance of ibuprofen with respect to CYP2C9*1.
References: DailyMed FDA-approved drug label, PMID: 18694831

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

Indomethacin
Indomethacin (Indocin®) is a non-steroidal anti-inflammatory drug (NSAID). It is indicated for moderate to severe rheumatoid arthritis including acute flares of chronic disease, ankylosing spondylitis, osteoarthritis, acute painful shoulder (bursitis and/or tendinitis) and acute gouty arthritis. Indomethacin is more selective for COX-1 than COX-2, which accounts for its increased adverse gastric effects relative to other NSAIDs. COX-1 is required for maintaining the protective gastric mucosal layer. The analgesic, antipyretic and anti-inflammatory effects of indomethacin occur as a result of decreased prostaglandin synthesis. Indomethacin appears to be O-demethylated exclusively by CYP2C9 in humans. Individuals who are of the poor metabolizer phenotype are expected to have higher plasma concentrations of indomethacin increasing risk of adverse events.
References: DailyMed FDA-approved drug label, DailyMed, PMID: 9492390

Lacosamide
Lacosamide (Vimpat®) is an Anticonvulsant agent prescribed for adjunctive therapy for partial onset seizures in patients with epilepsy over 17 years old. Lacosamide stabilizes hyperexcitable neuronal membranes and inhibits repetitive neuronal firing by enhancing the slow inactivation of sodium channels. Plasma concentrations of the lacosamide O-desmethyl metabolite were reduced by approximately 70% in CYP2C19 poor metabolizers (PMs) as compared to normal metabolizers (NMs). However, there are no clinically relevant differences in lacosamide pharmacokinetics between PMs and NMs.
References: FDA approved drug label

Lansoprazole
Lansoprazole (Prevacid®) belongs to a class of medications known as the Proton Pump Inhibitors (PPI). It is indicated for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. Lansoprazole suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Lansoprazole blocks the final step in acid production, thus reducing gastric acidity. Lansoprazole is completely metabolized by the cytochrome P450 system via CYP2C19 and CYP3A4. Current guidelines suggest increasing the dose by 50-100% in the population of persons with a CYP2C19 ultra-rapid metabolizer phenotype.
References: DrugBank, DailyMed FDA drug label, PMID: 21412232

Lesinurad
Lesinurad (Zurampic®) is and antigout medication known as a uric acid transporter 1 (URAT1) inhibitor. It is indicated for the treatment of hyperuricemia associated with gout (in combination with a xanthine oxidase inhibitor) in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone. Lesinurad inhibits the function of transporter proteins involved in renal uric acid reabsorption (uric acid transporter 1 [URAT1] and organic anion transporter 4 [OAT4]) and lowers serum uric acid levels and increases renal clearance and fractional excretion of uric acid in patients with gout. Lesinurad is primarily metabolized by the enzyme CYP2C9 and the FDA-approved label states; Lesinurad exposure is increased when ZURAMPIC is co-administered with inhibitors of CYP2C9, and in CYP2C9 poor metabolizers. ZURAMPIC should be used with caution in patients taking moderate inhibitors of CYP2C9 (eg, fluconazole, amiodarone), and in CYP2C9 poor metabolizers.
References: FDA reference ID 3864748

Meloxicam
Meloxicam (multiple brand names) is an Anti-inflammatory agent prescribed for symptomatic treatment of arthritis and osteoarthritis. Meloxicam reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors. CYP2C9 poor metabolizers have increased risk of developing acute gastrointestinal bleeding.
References: PMID: 19422321

Methadone
Methadone (multiple brand names) is an analgesic opioid agent prescribed for the treatment of dry cough, drug withdrawal syndrome, opioid type drug dependence, and pain. Methadone binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression. Methadone is partially metabolized by CYP2B6. Variants in this gene are associated with decreased clearance and dosage. In addition, methadone is an opioid receptor delta 1 agonist and TT genotype for the rs678849 in this gene is associated with a higher risk of failure of treatment.

References: PMID: 25456329, 21902500, 23612435

Metoclopramide
Metoclopramide (multiple brand names) is an antiemetic agent prescribed for the treatment of gastroesophageal reflux disease (GERD). It is also used in treating nausea and vomiting, and to increase gastric emptying. Metoclopramide blocks dopamine receptors and (when given in higher doses) also blocks serotonin receptors in chemoreceptor trigger zone of the CNS; enhances the response to acetylcholine of tissue in upper GI tract causing enhanced motility and accelerated gastric emptying without stimulating gastric, biliary, or pancreatic secretions; increases lower esophageal sphincter tone. It is partially metabolized by CYP2D6 and poor metabolizers for the enzyme have higher risk to show side effects.
References: PMID: 22688145

Morphine
Morphine (multiple brand names) is an analgesic opioid agent prescribed for the relief and treatment of severe pain. Morphine binds to opioid receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression. Morphine is an opioid receptor mu 1 (OPRM1) agonist and variants in this gene are associated with decreased efficacy of the drug. In addition, genetic variation in the catechol-o-methyltransferase (COMT) may also indirect influence the clinical efficacy of morphine.
References: PMID: 17898703, 28084056

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

Omeprazole
Omeprazole (Prilosec®) belongs to a class of medications known as the Proton Pump Inhibitors (PPI). It is indicated for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. Omeprazole suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Omeprazole blocks the final step in acid production, thus reducing gastric acidity. Omeprazole is completely metabolized by the cytochrome P450 system via CYP2C19 and CYP3A4. Current guidelines suggest increasing the dose by 50-100% in the population of persons with a CYP2C19 ultra-rapid metabolizer phenotype.
References: DrugBank, DailyMed FDA drug label, PMID: 21412232

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

Pantoprazole
Pantoprazole (Protonix®) belongs to a class of medications known as the Proton Pump Inhibitors (PPI). It is indicated for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. Pantoprazole suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Pantoprazole blocks the final step in acid production, thus reducing gastric acidity. Pantoprazole is completely metabolized by the cytochrome

P450 system via CYP2C19 and CYP3A4. Current guidelines suggest increasing the dose by 50-100% in the population of persons with a CYP2C19 ultra-rapid metabolizer phenotype.
References: DrugBank, DailyMed FDA drug label, PMID: 21412232

Pegloticase
Pegloticase (Krystexxa®) is a PEGylated uric acid specific enzyme prescribed for the treatment of chronic gout in adult patients refractory to conventional therapy. Pegloticase acts catalyzing the oxidation of uric acid to allantoin, thereby lowering serum uric acid. Patients deficient in G6PD have reduced ability to reduce the hydrogen peroxide formed as a major byproduct of the pegloticase-catalyzed oxidation of uric acid to allantoin which is associated with development of hemolysis and methemoglobinemia. Current guidelines state that patients at risk for G6PD deficiency should be screened prior to starting treatment, and that the drug should not be administered to patients with G6PD deficiency.
References: FDA Reference ID: 3983578

Piroxicam
Piroxicam (Feldene®) is a nonsteroidal anti-inflammatory agent prescribed for treatment of osteoarthritis and rheumatoid arthritis. Piroxicam reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors. It is metabolized predominantly by CYP2C9. Intermediate and poor metabolizers for this enzyme show higher systemic levels of piroxicam as compared to normal metabolizers. FDA recommends considering a dose reduction in these patients.
References: FDA Reference ID: 3928087
Probenecid
Probenecid (multiple brand names) is a prototypical uricosuric agent prescribed for chronic gouty arthritis. Probenecid inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid and decreasing serum urate levels. An association between probenecid-induced hemolytic anemia and G6PD deficiency is highlighted in the Adverse Reactions section of the probenecid label.
References: FDA-approved drug label

Propofol
Propofol (Diprivan®) is an intravenous anesthetic agent used for induction and maintenance of general anesthesia. IV administration of propofol is used to induce unconsciousness after which anesthesia may be maintained using a combination of medications. The action of propofol involves a positive modulation of the inhibitory function of the neurotransmitter gamma-aminobutyric acid (GABA) through GABAA receptors. Hepatically metabolized mainly by glucuronidation at the C1-hydroxyl. Hydroxylation of the benzene ring to 4-hydroxypropofol may also occur via CYP2B6 and 2C9 with subsequent conjugation to sulfuric and/or glucuronic acid. Hydroxypropofol has approximately 1/3 of hypnotic activity of propofol. Polymorphisms in the CYP2B6 gene have been shown to affect the pharmacokinetic profile of propofol and could help explain some of the large inter-individual variability between patients.
References: DailyMed FDA-approved drug label, DrugBank, PMID: 27826892, 21869535, 28154789

Protriptyline
Protriptyline (Vivactil®) is indicated for the treatment of symptoms of mental depression in patients who are under close medical supervision. Its activating properties make it particularly suitable for withdrawn and anergic patients. It belongs to the class of antidepressants know as Tricyclics or TCAs. Protriptyline acts by decreasing the reuptake of norepinephrine and serotonin (5-HT). 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 FDA-approved drug label, DrugBank, PMID: 27997040

Rabeprazole
Rabeprazole (Aciphex®) belongs to a class of medications known as the Proton Pump Inhibitors (PPI). It is indicated for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. Rabeprazole suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, rabeprazole blocks the final step in acid production, thus reducing gastric acidity. Rabeprazole is completely metabolized by the cytochrome P450

system via CYP2C19 and CYP3A4. The FDA annotation states that gastric acid suppression was higher in individuals who are known CYP2C19 poor metabolizers. There are no dosing adjustments recommended at this time for those persons either having a poor metabolizer phenotype, or ultra-rapid metabolizer phenotype.

References: DrugBank, DailyMed FDA drug label, PMID: 21412232

Ranolazine
Ranolazine (Ranexa®) is an antianginal agent prescribed for the treatment of chronic angina. Ranolazine inhibits the late phase of the inward sodium channel in ischemic cardiac myocytes during cardiac repolarization reducing intracellular sodium concentrations and thereby reducing calcium influx via Na^{+}-Ca^{2+} exchange. The risk for increased exposure leading to adverse events is higher in patients lacking CYP2D6 activity (poor metabolizers, PM) than subjects with CYP2D6 metabolizing capacity (extensive metabolizers, EM). Current guidelines state that there is a lower need for precautions in patients who are CYP2D6 normal metabolizers.
References: EMA-approved drug label
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000805/WC500045937.pdf

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