GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

Comprehensive Pharmacogenetic Report

PATIENT INFORMATION

NAME: Jane Doe
ACC #: GSPGX0001
DOB: 1/6/1961
SEX: female

SPECIMEN DETAILS

SPECIMEN TYPE: Buccal Swab
COLLECTION DATE: 1/18/2022
RECEIVED DATE: 1/25/2022
REPORT DATE: 1/31/2022

PROVIDER INFORMATION

Current Patient Medications

mupirocin, aspirin, docusate, doxycycline, naloxone, furosemide, gabapentin, donepezil, rosuvastatin

✓ Donepezil

Aricept®

Normal Response to Donepezil (CYP2D6: Intermediate Metabolizer) — **INFORMATIVE**

Donepezil can be prescribed at standard label-recommended dosage and administration. Careful titration is recommended until a favorable response is achieved.

- Seripa D, Bizzarro A, Pilotto A, D'onofrio G, Vecchione G, Gallo AP, Cascavilla L, Paris F, Grandone E, Mecocci P, Santini SA, Masullo C, Pilotto A. Role of cytochrome P4502D6 functional polymorphisms in the efficacy of donepezil in patients with Alzheimer's disease. Pharmacogenet Genomics 2011 Apr;21 (4):225-30.
- Varsaldi F, Miglio G, Scordo MG, Dahl ML, Villa LM, Biolcati A, Lombardi G. Impact of the CYP2D6 polymorphism on steady-state plasma concentrations and clinical outcome of donepezil in Alzheimer's disease patients. Eur J Clin Pharmacol 2006 Sep;62(9):721-6.
- Aricept [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2018.

✓ Gabapentin

Neurontin®

Normal Response to Gabapentin — **INFORMATIVE**

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: Gabapentin is eliminated primarily through renal excretion and is not metabolized by CYPs. Genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. Gabapentin can be prescribed at standard label-recommended dosage and administration.

- Neurontin [package insert]. New York, NY: Pfizer Inc.; 2015.

✓ Rosuvastatin

Crestor®

Normal Myopathy Risk (SLCO1B1 521T>C T/T; ABCG2 421C>A C/C) — **INFORMATIVE**

The patient does not carry a polymorphism in the ABCG2 gene that is associated with a higher rosuvastatin plasma exposure. The patient does not carry a polymorphism in the SLCO1B1 gene that is associated with an increased risk of myopathy. Rosuvastatin plasma concentrations are not expected to increase, and the patient's risk of rosuvastatin-induced myopathy is not elevated. However, because this test cannot find all of the inherited or circumstantial reasons for myopathy, other factors may affect this risk assessment. Examples of such factors include: uncontrolled hypothyroidism, renal impairment, diabetes, and comedications with ABCG2 or SLCO1B1 inhibitors. For patient age of 20-60 years, the maximum recommended dose range to reduce the risk of high statin exposure: 20-40 mg/day (highest dose). Start with usual doses 10-20 mg/day. It is possible to increase dose to 40 mg/day in non-Asian patients if no other risk factors are present and the patient is closely monitored for adverse events. For patient age of >60 years, the maximum recommended dose range to reduce the risk of high statin exposure: 20-40 mg/day. Start with usual doses 10-20 mg/day. It is possible to increase dose to 40 mg/day in non-Asian patients if no other risk factors are present and the patient is closely monitored for adverse events.

- Wu HF, Hristeva N, Chang J, Liang X, Li R, Frassetto L, Benet LZ. Rosuvastatin Pharmacokinetics in Asian and White Subjects Wild Type for Both OATP1B1 and BCRP Under Control and Inhibited Conditions. J Pharm Sci 2017 09;106(9):2751-2757.
- Sugiyama Y, Maeda K, Toshimoto K. Is Ethnic Variability in the Exposure to Rosuvastatin Explained Only by Genetic Polymorphisms in OATP1B1 and BCRP or Should the Contribution of Intrinsic Ethnic Differences in OATP1B1 Be Considered? J Pharm Sci 2017 09;106(9):2227-2230.
- Birmingham BK, Bujac SR, Elsby R, Azumaya CT, Wei C, Chen Y, Mosqueda-Garcia R, Ambrose HJ. Impact of ABCG2 and SLCO1B1 polymorphisms on pharmacokinetics of rosuvastatin, atorvastatin and simvastatin acid in Caucasian and Asian subjects: a class effect? Eur J Clin Pharmacol 2015 Mar;71(3):341-55.

Medications outside the scope of the report: Mupirocin, Aspirin, Docusate, Doxycycline, Naloxone, Furosemide

GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

A medication has potentially reduced efficacy, increased toxicity or the patient has an increased risk for the indicated condition.	**ACTIONABLE**	Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA, EMA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as knowledge arises.
Guidelines exist for adjusting dosage, increased vigilance or the patient has a moderate risk for the indicated condition.		
The medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.	**INFORMATIVE**	There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

Risk Management

Hyperuricemia and Gout

Normal Risk of Gout

The patient carries two copies of ABCG2 rs2231142 C allele.

The ABCG2 rs2231142 C allele is associated with normal ABCG2 activity and subsequent normal renal elimination of uric acid. The patient's genotype is associated with a normal risk of hyperuricemia and gout.

No action is needed for this patient unless other genetic or non-genetic risk factors are present.

Antipsychotic-Induced Tardive Dyskinesia

Moderate Risk of Antipsychotic-Induced Tardive Dyskinesia

The patient carries one copy of the Taq1A variant (heterozygous for the A1 allele).

The genotype results predict that the patient may have reduced dopamine receptor DRD2 density and hypodopaminergic functioning. The patient has moderate risk for tardive dyskinesia when treated with antipsychotics.

Monitor the patient for any signs of tardive dyskinesia.

Antipsychotic-Induced Hyperprolactinemia

Moderate Risk of Antipsychotic-induced Hyperprolactinemia

The patient carries one copy of the Taq1A variant (heterozygous for the A1 allele).

The genotype results predict that the patient may have reduced dopamine receptor DRD2 density and hypodopaminergic functioning. The patient has moderate risk of hyperprolactinemia when treated with antipsychotics.

Monitor patient closely for signs of hyperprolactinemia. An evaluation of the risk-benefit profile of the antipsychotic medication may be required.

Antipsychotic-Induced Weight Gain

Moderate Risk of Antipsychotic-Induced Weight Gain

The patient carries one copy of the Taq1A variant (heterozygous for the A1 allele).

The genotype results predict that the patient may have reduced dopamine receptor DRD2 density and hypodopaminergic functioning. The patient has moderate risk for weight gain when treated with antipsychotics.

Monitor patient closely for signs of weight gain.

Type III Hyperlipoproteinemia

Not Associated with Type III Hyperlipoproteinemia

The patient is positive for the APOE c.388 T>C (Cys130Arg) mutation and negative for the APOE c.526 C>T (Arg176Cys) mutation. The patient's genotype is ε3/ε4 (frequency: 15-28%).

The APOE E3 is the normal APOE. The APOE E4 confers a limitation of HDL binding to its receptor, and is associated with increased plasma cholesterol, LDL, and triglycerides. Individuals that are heterozygous for this allele may have higher total cholesterol levels and elevated LDL cholesterol levels. The APOE ε3/ε4 genotype is associated with an increased risk for developing atherosclerosis and cardiovascular disease.

Consider dietary adjustments (very low fat diet) and lipid-lowering therapy based on lipid profiles and other risk factors.

Platelet Hyperactivity

Possible Altered Response to Aspirin

The patient carries one ITGB3 176T>C (Leu59Pro) mutation.

Preliminary studies have found an association between the 176T>C mutation of the integrin β3 gene and the possible resistance to the antithrombotic effects of aspirin. However, because the variability in response to antiplatelet drugs is multifactorial and not caused by single gene mutations, testing for the ITGB3 mutation alone should not be used as a diagnostic tool.

Hyperhomocysteinemia - Depression

No Increased Risk of Hyperhomocysteinemia

The patient does not carry the MTHFR c.665C>T variant. MTHFR enzyme activity is normal.

Patients diagnosed with depression often have low folate levels and homocysteine is a highly sensitive marker of folate status. Functional folate deficiency is indicated by elevated homocysteine. With a normal MTHFR activity, this patient can process folate normally and is unlikely to have elevated plasma levels of homocysteine.
Patients diagnosed with depression: as lower folate levels are associated with poorer antidepressant response, and baseline levels of folate within the normal range predict antidepressant response, testing for homocysteine levels and serum folate levels may be informative for this patient before prescribing methylfolate as an antidepressant-augmenting agent.

✓ Thrombophilia

Normal Risk of Thrombosis

The patient does not carry the F5 c.1601G>A variant (also known as Factor V Leiden) or the F2 c.*97G>A variant (also known as Factor II 20210G>A).
The patient's risk of thrombosis is not increased (average risk of clotting is about 1 in 1000 for anyone in a year). However, because this test cannot find all of the inherited reasons for abnormal clotting, other factors may affect this risk assessment.
Assess thrombotic risk based on other genetic and/or circumstantial risk factors such as smoking, obesity, malignancy, prolonged immobilization or surgery.

Estrogen-containing contraceptive and hormone replacement therapy: unless other genetic and/or circumstantial risk factors are present, consider standard prescribing and monitoring practices.

✓ Hyperhomocysteinemia - Thrombosis

No Increased Risk of Hyperhomocysteinemia

The patient does not carry the MTHFR c.665C>T variant or MTHFR c.1286A>C variant. MTHFR enzyme activity is normal.
Based on results for the MTHFR c.665C>T and c.1286A>C variants, the patient has normal MTHFR activity and is unlikely to have elevated plasma levels of homocysteine. Hyperhomocysteinemia is associated with a risk for venous thromboembolism (VTE). Unless other risk factors are present, the patient is not expected to have an increased risk for VTE.
MTHFR enzyme activity is normal.

GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Anticancer Agents	Anti-Estrogens			Tamoxifen (Nolvadex®, Soltamox®)
	Antifolates	Methotrexate (Trexall®)		
	Aromatase Inhibitors	Anastrozole (Arimidex®) Exemestane (Aromasin®) Letrozole (Femara®)		
	Protein Kinase Inhibitors	Erdafitinib (Balversa®) Gefitinib (Iressa®)		
	Thiopurines	Azathioprine (Azasan®, Imuran®) Mercaptopurine (Purinethol®, Purixan®) Thioguanine (Tabloid®)		
Cardiovascular	Angiotensin II Receptor Antagonists	Azilsartan (Edarbi®, Edarbyclor®) Candesartan (Atacand®) Eprosartan (Teveten®) Irbesartan (Avapro®) Losartan (Cozaar®, Hyzaar®) Olmesartan (Benicar®) Telmisartan (Micardis®) Valsartan (Diovan®, Entresto®)		
	Antianginal Agents	Ranolazine (Ranexa®)		
	Antiarrhythmics	Amiodarone (Nexterone®, Pacerone®) Disopyramide (Norpace®) Quinidine (Quinidine®) Sotalol (Betapace®, Sorine®, Sotylize®)	Flecainide (Tambocor®) Mexiletine (Mexitil®) Propafenone (Rythmol®)	
	Anticoagulants	Apixaban (Eliquis®) Betrixaban (Bevyxxa®) Dabigatran Etexilate (Pradaxa®) Edoxaban (Savaysa®) Fondaparinux (Arixtra®) Rivaroxaban (Xarelto®)	Warfarin (Coumadin®)	
	Antiplatelets	Prasugrel (Effient®) Ticagrelor (Brilinta®) Vorapaxar (Zontivity®)		Clopidogrel (Plavix®)
	Beta Blockers	Atenolol (Tenormin®) Bisoprolol (Zebeta®) Labetalol (Normodyne®, Trandate®) Nebivolol (Bystolic®) Propranolol (Inderal®)	Metoprolol (Lopressor®) Timolol (Blocadren®)	
	Diuretics	Torsemide (Demadex®)		

GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
	Statins	Atorvastatin (Lipitor®) Lovastatin (Mevacor®, Altoprev®, Advicor®) Pitavastatin (Livalo®) Pravastatin (Pravachol®) Rosuvastatin (Crestor®) Simvastatin (Zocor®)	Fluvastatin (Lescol®)	
Diabetes	**Meglitinides**	Nateglinide (Starlix®) Repaglinide (Prandin®, Prandimet®)		
	Sulfonylureas	Chlorpropamide (Diabinese®) Glimepiride (Amaryl®) Glipizide (Glucotrol®) Glyburide (Micronase®) Tolbutamide (Orinase®)		
	Thiazolidinediones		Pioglitazone (Actos®, Oseni®) Rosiglitazone (Avandia®)	
Gastrointestinal	**Antiemetics**	Aprepitant (Emend-oral®) Dolasetron (Anzemet®) Fosaprepitant (Emend-IV®) Fosnetupitant / Palonosetron (Akynzeo-IV®) Netupitant / Palonosetron (Akynzeo-oral®) Palonosetron (Aloxi®) Rolapitant (Varubi®)	Dronabinol (Marinol®) Granisetron (Sancuso®, Sustol®) Metoclopramide (Reglan®) Ondansetron (Zofran®, Zuplenz®)	
	Proton Pump Inhibitors	Dexlansoprazole (Dexilant®, Kapidex®) Esomeprazole (Nexium®) Lansoprazole (Prevacid®) Omeprazole (Prilosec®) Pantoprazole (Protonix®) Rabeprazole (Aciphex®)		
Gaucher Disease	**Endocrine-Metabolic Agents**	Eliglustat (Cerdelga®) Imiglucerase (Cerezyme®) Miglustat (Zavesca®) Taliglucerase alfa (Elelyso®) Velaglucerase alfa (Vpriv®)		
Gynecology	**Endometriosis Pain Agents**	Elagolix (Orilissa®)		
Hematology	**Hemostatic Agents**	Avatrombopag (Doptelet®) Eltrombopag (Promacta®) Lusutrombopag (Mulpleta®)		

GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Infections	Antifungals	Amphotericin B (AmBisome®, Abelcet®) Anidulafungin (Eraxis®) Caspofungin (Cancidas®) Fluconazole (Diflucan®) Flucytosine (Ancobon®) Isavuconazonium (Cresemba®) Itraconazole (Sporanox®) Micafungin (Mycamine®) Posaconazole (Noxafil®) Voriconazole (Vfend®)		
	Anti-HIV Agents	Dolutegravir (Tivicay®, Triumeq®) Doravirine (Pifeltro®) Etravirine (Edurant®) Raltegravir (Isentress®, Dutrebis®) Rilpivirine (Intelence®)	Efavirenz (Sustiva®)	
	Antimalarials	Proguanil (Malarone®)		
Multiple Sclerosis	Disease-Modifying Agents	Siponimod (Mayzent®)		
Pain	Fibromyalgia Agents	Milnacipran (Savella®)		
	Muscle Relaxants	Carisoprodol (Soma®) Cyclobenzaprine (Flexeril®, Amrix®) Metaxalone (Skelaxin®) Methocarbamol (Robaxin®)	Tizanidine (Zanaflex®)	
	NSAIDs	Celecoxib (Celebrex®) Diclofenac (Voltaren®) Flurbiprofen (Ansaid®) Ibuprofen (Advil®, Motrin®) Indomethacin (Indocin®) Ketoprofen (Orudis®) Ketorolac (Toradol®) Meloxicam (Mobic®) Nabumetone (Relafen®) Naproxen (Aleve®) Piroxicam (Feldene®) Sulindac (Clinoril®)		

GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
	Opioids	Alfentanil (Alfenta®) Buprenorphine (Butrans®, Buprenex®) Dihydrocodeine (Synalgos-DC®) Fentanyl (Actiq®) Hydromorphone (Dilaudid®, Exalgo®) Levorphanol (Levo Dromoran®) Meperidine (Demerol®) Oliceridine (Olinvyk) Oxycodone (Percocet®, Oxycontin®) Oxymorphone (Opana®, Numorphan®) Sufentanil (Sufenta®) Tapentadol (Nucynta®)	Benzhydrocodone (Apadaz®) Codeine (Codeine; Fioricet® with Codeine) Hydrocodone (Vicodin®) Methadone (Dolophine®) Morphine (MS Contin®) Tramadol (Ultram®)	
	Antiaddictives	Lofexidine (Lucemyra®)	Bupropion (Wellbutrin®, Zyban®, Aplenzin®, Contrave®) Naltrexone (Vivitrol®, Contrave®)	
	Anti-ADHD Agents	Amphetamine (Adderall®, Evekeo®) Clonidine (Kapvay®) Dexmethylphenidate (Focalin®) Dextroamphetamine (Dexedrine®) Guanfacine (Intuniv®) Lisdexamfetamine (Vyvanse®) Methylphenidate (Ritalin®, Aptensio XR®, Concerta®, Metadate ER®, Quillivant ER®)	Atomoxetine (Strattera®)	
	Anticonvulsants	Brivaracetam (Briviact®) Cannabidiol (Epidiolex®) Carbamazepine (Tegretol®, Carbatrol®, Epitol®) Eslicarbazepine (Aptiom®) Ethosuximide (Zarontin®) Ezogabine (Potiga®) Felbamate (Felbatol®) Fosphenytoin (Cerebyx®) Gabapentin (Neurontin®) Lacosamide (Vimpat®) Lamotrigine (Lamictal®) Levetiracetam (Keppra®) Oxcarbazepine (Trileptal®, Oxtellar XR®) Perampanel (Fycompa®) Phenytoin (Dilantin®) Pregabalin (Lyrica®) Rufinamide (Banzel®) Tiagabine (Gabitril®) Topiramate (Topamax®) Valproic Acid (Depakene®) Vigabatrin (Sabril®)	Phenobarbital (Luminal®) Primidone (Mysoline®) Zonisamide (Zonegran®)	

GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Psychotropic	Antidementia Agents	Donepezil (Aricept®) Galantamine (Razadyne®) Memantine (Namenda®)		
	Antidepressants	Desvenlafaxine (Pristiq®) Duloxetine (Cymbalta®) Escitalopram (Lexapro®) Fluoxetine (Prozac®, Sarafem®) Fluvoxamine (Luvox®) Levomilnacipran (Fetzima®) Mirtazapine (Remeron®) Nefazodone (Serzone®) Paroxetine (Paxil®, Brisdelle®) Sertraline (Zoloft®) Trazodone (Oleptro®) Vilazodone (Viibryd®) Vortioxetine (Trintellix®)	Amitriptyline (Elavil®) Amoxapine (Amoxapine®) Citalopram (Celexa®) Clomipramine (Anafranil®) Desipramine (Norpramin®) Doxepin (Silenor®) Imipramine (Tofranil®) Maprotiline (Ludiomil®) Nortriptyline (Pamelor®) Protriptyline (Vivactil®) Trimipramine (Surmontil®)	Venlafaxine (Effexor®)
	Antipsychotics	Aripiprazole (Abilify®, Aristada®) Asenapine (Saphris®) Brexpiprazole (Rexulti®) Cariprazine (Vraylar®) Chlorpromazine (Thorazine®) Fluphenazine (Prolixin®) Haloperidol (Haldol®) Loxapine (Loxitane®, Adasuve®) Lurasidone (Latuda®) Paliperidone (Invega®) Pimavanserin (Nuplazid®) Pimozide (Orap®) Thiothixene (Navane®) Trifluoperazine (Stelazine®) Ziprasidone (Geodon®)	Clozapine (Clozaril®) Iloperidone (Fanapt®) Olanzapine (Zyprexa®) Perphenazine (Trilafon®) Risperidone (Risperdal®)	Thioridazine (Mellaril®)
	Benzodiazepines	Alprazolam (Xanax®) Clonazepam (Klonopin®) Diazepam (Valium®)	Clobazam (Onfi®) Lorazepam (Ativan®) Oxazepam (Serax®)	
	Other Neurological Agents	Deutetrabenazine (Austedo®) Dextromethorphan / Quinidine (Nuedexta®) Flibanserin (Addyi®) Valbenazine (Ingrezza®)	Tetrabenazine (Xenazine®)	
Rheumatology	Anti-Hyperuricemics and Anti-Gout Agents	Allopurinol (Zyloprim®, Lopurin®, Aloprim®) Colchicine (Mitigare®) Febuxostat (Uloric®)		
	Immunomodulators	Apremilast (Otezla®) Tofacitinib (Xeljanz®)	Leflunomide (Arava®)	
	Other Antirheumatic Agents		Sulfasalazine (Azulfidine®, Sulfazine®)	
Sjogren's Syndrome	Cholinergic Agonists	Cevimeline (Evoxac®)		
Transplantation	Immunosuppressants	Tacrolimus (Prograf®)		

GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Urologicals	5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia	Dutasteride (Avodart®) Finasteride (Proscar®)		
	Alpha-Blockers for Benign Prostatic Hyperplasia	Alfuzosin (UroXatral®) Doxazosin (Cardura®) Silodosin (Rapaflo®) Tamsulosin (Flomax®) Terazosin (Hytrin®)		
	Antispasmodics for Overactive Bladder	Darifenacin (Enablex®) Fesoterodine (Toviaz®) Mirabegron (Myrbetriq®) Oxybutynin (Ditropan®) Solifenacin (Vesicare®) Tolterodine (Detrol®) Trospium (Sanctura®)		
	Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra®) Sildenafil (Viagra®) Tadalafil (Cialis®) Vardenafil (Levitra®)		

GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

Dosing Guidance

Clopidogrel
Plavix®

Reduced Response to Clopidogrel (CYP2C19: Intermediate Metabolizer) — **ACTIONABLE**

Consider alternative therapy. Examples of alternative drugs: prasugrel (contraindicated in TIA/Stroke patients), ticagrelor, aspirin, aspirin plus dipyridamole.

- Scott SA, Sangkuhl K, Stein CM, Hulot JS, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR, . Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther 2013 Sep;94(3):317-23.

Thioridazine
Mellaril®

Increased Sensitivity to Thioridazine (CYP2D6: Intermediate Metabolizer) — **ACTIONABLE**

Reduced cytochrome CYP2D6 activity results in elevated plasma levels of thioridazine, would be expected to augment the prolongation of the QTc interval associated with thioridazine, and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes-type arrhythmias. Such an increased risk may result also from the additive effect of coadministering thioridazine with other agents that prolong the QTc interval. Therefore, thioridazine is contraindicated in patients with reduced levels of CYP2D6 activity.

- Dorado P, Peñas-LLedó EM, de la Rubia A, LLerena A. Relevance of CYP2D6 -1584C>G polymorphism for thioridazine:mesoridazine plasma concentration ratio in psychiatric patients. Pharmacogenomics 2009 Jul;10(7):1083-9.
- Berecz R, de la Rubia A, Dorado P, Fernández-Salguero P, Dahl ML, LLerena A. Thioridazine steady-state plasma concentrations are influenced by tobacco smoking and CYP2D6, but not by the CYP2C9 genotype. Eur J Clin Pharmacol 2003 May;59(1):45-50.
- LLerena A, Berecz R, de la Rubia A, Dorado P. QTc interval lengthening is related to CYP2D6 hydroxylation capacity and plasma concentration of thioridazine in patients. J Psychopharmacol 2002 Dec;16(4):361-4.

Venlafaxine
Effexor®

Increased Exposure to Venlafaxine (CYP2D6: Intermediate Metabolizer) — **ACTIONABLE**

The patient has a decreased CYP2D6 activity which may result in elevated plasma concentrations of venlafaxine at standard doses. Consider an alternative medication or consider prescribing venlafaxine at a reduced dose and be extra alert for adverse events; adjust the dose based on tolerability and therapeutic monitoring.

If therapeutic drug monitoring is utilized, the sum of venlafaxine and O-desmethylvenlafaxine (an active metabolite) plasma concentrations should be used for efficacy. While the sum of the parent and the active metabolite are informative for efficacy, a higher parent (venlafaxine) concentration may be associated with higher side effects, including QT prolongation.

- The Royal Dutch Pharmacists Association of the KNMP. (2020). Pharmacogenetic Recommendations 2020 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2020.pdf (Accessed September 8, 2020).

Amitriptyline
Elavil®

Increased Amitriptyline Exposure (CYP2D6: Intermediate Metabolizer) — **ACTIONABLE**

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of amitriptyline to less active compounds and a subsequent increase in amitriptyline exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Neuropathic Pain: Amitriptyline therapy can be prescribed according to standard recommended dosage and administration when lower doses are considered. If higher doses are warranted, consider a 25% reduction of the recommended dose and monitor patient for side effects.

- Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

Atomoxetine
Strattera®

Possible Atomoxetine Overexposure Leading to Toxicity (CYP2D6: Intermediate Metabolizer) — **ACTIONABLE**

The genotype result indicates that the patient is likely to have an increased risk of adverse events following standard dosing. Consider the following dosing strategy:

- Initiate treatment at 40 mg/day.
- If after 2 weeks, optimal clinical response is not observed and adverse events are not present, consider a dose increase to 80 mg/day.
- If after 2 weeks, optimal clinical response is not observed and adverse events are not present, consider therapeutic drug monitoring 2-4 hours post dose. If the plasma concentration is less than 200 ng/ml consider a dose increase to a target of 400 ng/ml. Doses greater than 100 mg/day may be needed to achieve a targeted therapeutic concentration. (Therapeutic range: 200-1000 ng/ml).

- Brown JT, Bishop JR, Sangkuhl K, Nurmi EL, Mueller DJ, Dinh JC, Gaedigk A, Klein TE, Caudle KE, McCracken JT, de Leon J, Leeder JS. Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther 2019 Jul;106(1):94-102.

Clobazam

Onfi®

Possible Sensitivity to Clobazam (CYP2C19: Intermediate Metabolizer) **ACTIONABLE**

In CYP2C19 intermediate metabolizers, plasma levels of the active metabolite N-desmethylclobazam were 2-fold higher than those found in CYP2C19 normal metabolizers. The dose adjustment for intermediate metabolizers is not well established, and therefore the recommendation for poor metabolizers is proposed. The starting dose should be 5 mg/day, and dose titration should proceed slowly according to weight. Patients should be titrated initially to 10 mg /day (≤30 kg body weight) or 20 mg/day (>30 kg body weight). If necessary and based upon clinical response, an additional titration to the maximum doses 20 mg/day (≤30 kg body weight) or 40 mg/day (>30 kg body weight) may be started on day 21.

- Onfi [package insert]. Deerfield, IL: Lundbeck Inc.; 2013.
- Seo T, Nagata R, Ishitsu T, Murata T, Takaishi C, Hori M, Nakagawa K. Impact of CYP2C19 polymorphisms on the efficacy of clobazam therapy. Pharmacogenomics 2008 May;9(5):527-37.
- Kosaki K, Tamura K, Sato R, Samejima H, Tanigawara Y, Takahashi T. A major influence of CYP2C19 genotype on the steady-state concentration of N-desmethylclobazam. Brain Dev 2004 Dec;26(8):530-4.

Codeine

Codeine; Fioricet® with Codeine

Decreased Exposure to Codeine Active Metabolite (CYP2D6: Intermediate Metabolizer) **ACTIONABLE**

The patient genotype is associated with decreased conversion of codeine to its active metabolite (morphine), which may result in decreased effectiveness.

Codeine can be prescribed at standard label-recommended age- or weight-based dosing. If no response and opioid use is warranted, consider a non-tramadol opioid. Alternative opioids may include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

- Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, Dunnenberger HM, Leeder JS, Callaghan JT, Samer CF, Klein TE, Haidar CE, Van Driest SL, Ruano G, Sangkuhl K, Cavallari LH, Müller DJ, Prows CA, Nagy M, Somogyi AA, Skaar TC. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther 2021 10;110(4):888-896.

Dronabinol

Marinol®

Increased Dronabinol Exposure (CYP2C9: Intermediate Metabolizer) **ACTIONABLE**

The patient's genotype predicts a reduced CYP2C9 metabolic activity. Increased drug exposure may occur in this patient leading to prolonged sedation. Consider standard label-recommended dosing and close monitoring for adverse effects.

- Sachse-Seeboth C, Pfeil J, Sehrt D, Meineke I, Tzvetkov M, Bruns E, Poser W, Vormfelde SV, Brockmöller J. Interindividual variation in the pharmacokinetics of Delta9-tetrahydrocannabinol as related to genetic polymorphisms in CYP2C9. Clin Pharmacol Ther 2009 Mar;85(3):273-6.
- Syndros [package insert]. Chandler, AZ: Insys Therapeutics, Inc.; 2016.

Efavirenz

Sustiva®

Increased Efavirenz Exposure (CYP2B6: Intermediate Metabolizer) **ACTIONABLE**

The genotype result indicates that the patient is likely to have higher dose-adjusted trough concentrations of efavirenz following standard dosing. This may result in increased risk of CNS adverse events. Consider initiating efavirenz with a decreased dose of 400 mg/day. If therapeutic drug monitoring is available and a decreased efavirenz dose is prescribed, consider obtaining steady-state plasma efavirenz concentrations to ensure concentrations are in the suggested therapeutic range (~1 to 4 µg/mL).

- Desta Z, Gammal RS, Gong L, Whirl-Carrillo M, Gaur AH, Sukasem C, Hockings J, Myers A, Swart M, Tyndale RF, Masimirembwa C, Iwuchukwu OF, Chirwa S, Lennox J, Gaedigk A, Klein TE, Haas DW. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy. Clin Pharmacol Ther 2019 Apr;():.

Flecainide

Tambocor®

Increased Exposure to Flecainide (CYP2D6: Intermediate Metabolizer) **ACTIONABLE**

The patient's genotype may be associated with an increased flecainide exposure following standard dosing. Consider prescribing a lower flecainide dose for therapeutic indications. When compared to a CYP2D6 normal metabolizer, an intermediate metabolizer may require a 25% dose reduction. Careful titration with ECG recording and monitoring of flecainide plasma concentrations are recommended until a favorable clinical response is achieved.

Dose adjustments are not required when flecainide is utilized for diagnostic uses.

- The Royal Dutch Pharmacists Association of the KNMP. (2020). Pharmacogenetic Recommendations 2020 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2020.pdf (Accessed September 8, 2020).

Iloperidone

Fanapt®

Moderate Sensitivity to Iloperidone (CYP2D6: Intermediate Metabolizer) **ACTIONABLE**

Because iloperidone is associated with QTc prolongation, caution is warranted when prescribing the drug in patients with reduced CYP2D6 activity. Iloperidone must be titrated slowly from a low starting dose to avoid orthostatic hypotension. If patients taking iloperidone experience symptoms that could indicate the occurrence of cardiac arrhythmias (e.g., dizziness, palpitations, or syncope), the prescriber should initiate further evaluation, including cardiac monitoring.

- Fanapt [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.

Metoprolol
Lopressor®

Increased Exposure to Metoprolol (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype may be associated with an increased metoprolol exposure following standard dosing. When compared to a normal metabolizer, an intermediate metabolizer may require a 50% dose reduction. If metoprolol is prescribed, be alert to adverse events (e.g., bradycardia or cold extremities).

- The Royal Dutch Pharmacists Association of the KNMP. (2020). Pharmacogenetic Recommendations 2020 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2020.pdf (Accessed September 8, 2020).

Mexiletine
Mexitil®

Increased Sensitivity to Mexiletine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

Consider prescribing a lower mexiletine dose. A slow titration with ECG recording and monitoring of mexiletine plasma concentrations are recommended until a favorable clinical response is achieved.

- MEXILETINE HYDROCHLORIDE- mexiletine hydrochloride capsule [package insert]. Sellersville, PA: Teva Pharmaceuticals USA. https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=ca648488-4f8d-4d26-be4d-6a75fbb8b62c&type=pdf&name=ca648488-4f8d-4d26-be4d-6a75fbb8b62c. Rev Apr 2012.
- Otani M, Fukuda T, Naohara M, Maune H, Senda C, Yamamoto I, Azuma J. Impact of CYP2D6*10 on mexiletine pharmacokinetics in healthy adult volunteers. Eur J Clin Pharmacol 2003 Sep;59(5-6):395-9.
- Hanioka N, Okumura Y, Saito Y, Hichiya H, Soyama A, Saito K, Ueno K, Sawada J, Narimatsu S. Catalytic roles of CYP2D6.10 and CYP2D6.36 enzymes in mexiletine metabolism: in vitro functional analysis of recombinant proteins expressed in Saccharomyces cerevisiae. Biochem Pharmacol 2006 Apr;71(9):1386-95.

Nortriptyline
Pamelor®

Increased Nortriptyline Exposure (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of nortriptyline to less active compounds and a subsequent increase in nortriptyline exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

- Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

Perphenazine
Trilafon®

Possible Sensitivity to Perphenazine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

Patients with a decreased CYP2D6 function will eliminate perphenazine more slowly, which can result in higher drug concentrations and possibly more adverse events (extrapyramidal symptoms). Consider close monitoring and dose reduction to avoid toxicity.

- Jerling M, Dahl ML, Aberg-Wistedt A, Liljenberg B, Landell NE, Bertilsson L, Sjöqvist F. The CYP2D6 genotype predicts the oral clearance of the neuroleptic agents perphenazine and zuclopenthixol. Clin Pharmacol Ther 1996 Apr;59(4):423-8.
- Dahl-Puustinen ML, Lidén A, Alm C, Nordin C, Bertilsson L. Disposition of perphenazine is related to polymorphic debrisoquin hydroxylation in human beings. Clin Pharmacol Ther 1989 Jul;46(1):78-81.
- Pollock BG, Mulsant BH, Sweet RA, Rosen J, Altieri LP, Perel JM. Prospective cytochrome P450 phenotyping for neuroleptic treatment in dementia. Psychopharmacol Bull 1995 ;31(2):327-31.
- Linnet K, Wiborg O. Steady-state serum concentrations of the neuroleptic perphenazine in relation to CYP2D6 genetic polymorphism. Clin Pharmacol Ther 1996 Jul;60(1):41-7.
- Perphenazine [package insert]. Princeton, NJ: Sandoz Inc.; 2010.

Propafenone
Rythmol®

Increased Exposure to Propafenone (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype may be associated with an increased propafenone exposure following standard dosing. There is insufficient data to allow calculation of dose adjustment. Titrate carefully and adjust the dose in response to plasma concentration and ECG monitoring. An alternative medication such as sotalol, disopyramide, quinidine or amiodarone may also be considered.

Dose adjustments with co-medications: concurrent use of propafenone along with CYP3A4 inhibitors and CYP2D6 inhibitors may significantly increase the plasma concentration of propafenone increasing the risk of proarrhythmia and other adverse events. Therefore, avoid simultaneous use of propafenone with both a CYP2D6 inhibitor and a CYP3A4 inhibitor.

- Rythmol [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2018.
- Rythmol SR [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2018.
- The Royal Dutch Pharmacists Association of the KNMP. (2020). Pharmacogenetic Recommendations 2020 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2020.pdf (Accessed September 8, 2020).

Tetrabenazine

Xenazine®

Normal Sensitivity to Tetrabenazine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

For treating chorea associated with Huntington's disease: Individualization of dose with careful weekly titration is required. The first week's starting dose is 12.5 mg daily; second week, 25 mg (12.5 mg twice daily); then slowly titrate at weekly intervals by 12.5 mg to a tolerated dose. **The maximum daily dose in CYP2D6 intermediate metabolizers of CYP2D6 is 100 mg with a maximum single dose of 37.5 mg**. If serious adverse events occur, titration should be stopped and the dose of tetrabenazine should be reduced. If the adverse event(s) do not resolve, consider withdrawal of tetrabenazine.

- Xenazine [package insert]. Deerfield, IL: Lundbeck Inc.; 2017.

Warfarin

Coumadin®

Dosing Adjustments are Expected (CYP2C9 *1/*2; VKORC1 -1639G>A G/A; CYP4F2 c.1297G>A G/G; CYP2C g.96405502G>A G/A) — ACTIONABLE

When initiating warfarin treatment for indications with a target INR of 2-3, consider one of the following methods to estimate dosing requirements:

FDA Label: CYP2C9 and VKORC1 genotype results indicate an expected therapeutic dose of 3-4 mg/day

Pharmacogenomics algorithms/calculators available at www.warfarindosing.org:

Caucasians and Asians: Use the patient's demographics and other clinical factors along with CYP2C9 and VKORC1 genotypes to calculate the expected therapeutic dose.

Africans (NOT African Americans): Use the patient's demographics and other clinical factors along with CYP2C9 and VKORC1 genotypes to calculate the expected therapeutic dose.

African Americans: Use the patient's demographics and other clinical factors along with CYP2C9 and VKORC1 genotypes to calculate the expected therapeutic dose. Consider an additional 10-25% decrease to the calculated dose.

The provided recommendations in Africans and African Americans apply only when all the following CYP2C9 alleles are tested: *5, *6, *8, *11.

- Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA, Lee MT, Gage BF, Kimmel SE, Perera MA, Anderson JL, Pirmohamed M, Klein TE, Limdi NA, Cavallari LH, Wadelius M. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther 2017 Sep;102(3):397-404.

Amoxapine

Amoxapine®

Possible Increased Amoxapine Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

Like other tricyclic and tetracyclic antidepressants, amoxapine is metabolized by CYP2D6. However, the overall contribution of this enzyme in the metabolism of this drug is not well documented. Decreased CYP2D6 activity may result in higher amoxapine concentrations potentially leading to higher adverse events. There are no established dosing adjustments for patients with decreased CYP2D6 function; therapy must be initiated cautiously and adjusted according to the patient's response.

- AMOXAPINE- amoxapine tablet [package insert]. Parsippany, NJ: Watson Pharma, Inc. https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=151241. Rev Jun 2014.

Benzhydrocodone

Apadaz®

Possible Altered Response to Benzhydrocodone (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

Benzhydrocodone is a prodrug of hydrocodone and is converted to active hydrocodone by intestinal enzymes. Decreased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 intermediate metabolizers. However, there is insufficient evidence whether these patients have decreased analgesia when taking benzhydrocodone. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 may also be considered (i.e., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone).

- Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC, . Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther 2014 Apr;95(4):376-82.
- Apadaz [package insert]. Coralville, IA: KemPharm Inc.; 2018.

Bupropion

Altered Bupropion Exposure (CYP2B6: Intermediate Metabolizer) — INFORMATIVE

Wellbutrin®, Zyban®, Aplenzin®, Contrave®

The genotype result indicates that the patient is likely to have increased bupropion exposure, but decreased exposure to the active metabolite (hydroxybupropion). This metabolite contributes to the therapeutic effects of bupropion when used as a smoking cessation agent or as an antidepressant. This decrease in exposure of hydroxybupropion may result in decreased therapeutic efficacy.

Smoking Cessation: There is insufficient data to allow calculation of dose adjustment. Consider standard prescribing and closer monitoring.

Major Depressive Disorder and Prevention of Seasonal Affective Disorder: There is insufficient data to allow calculation of dose adjustment. Therapeutic monitoring of bupropion-hydroxybupropion levels may be considered to guide dosing adjustments.

- Zhu AZ, Cox LS, Nollen N, Faseru B, Okuyemi KS, Ahluwalia JS, Benowitz NL, Tyndale RF. CYP2B6 and bupropion's smoking-cessation pharmacology: the role of hydroxybupropion. Clin Pharmacol Ther 2012 Dec;92(6):771-7.
- Høiseth G, Haslemo T, Uthus LH, Molden E. Effect of CYP2B6*6 on Steady-State Serum Concentrations of Bupropion and Hydroxybupropion in Psychiatric Patients: A Study Based on Therapeutic Drug Monitoring Data. Ther Drug Monit 2015 Oct;37(5):589-93.
- Laib AK, Brünen S, Pfeifer P, Vincent P, Hiemke C. Serum concentrations of hydroxybupropion for dose optimization of depressed patients treated with bupropion. Ther Drug Monit 2014 Aug;36(4):473-9.

Bupropion

Wellbutrin®, Zyban®, Aplenzin®, Contrave®

Decreased Response to Bupropion for Smoking Cessation (ANKK1: Altered DRD2 function) — INFORMATIVE

Smoking Cessation: The patient's genotype result is associated with a positive response to nicotine replacement therapy and a lesser response to bupropion treatment.

- David SP, Strong DR, Munafò MR, Brown RA, Lloyd-Richardson EE, Wileyto PE, Evins AE, Shields PG, Lerman C, Niaura R. Bupropion efficacy for smoking cessation is influenced by the DRD2 Taq1A polymorphism: analysis of pooled data from two clinical trials. Nicotine Tob Res 2007 12;9(12):1251-7.

Citalopram

Celexa®

Reduced Response to Citalopram (HTR2A: Homozygous for G allele (rs7997012)) — INFORMATIVE

The patient is homozygous for G allele in HTR2A variant rs7997012. Preliminary studies report that this genotype may be associated with an unfavorable response to citalopram.

- Niitsu T, Fabbri C, Bentini F, Serretti A. Pharmacogenetics in major depression: a comprehensive meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2013 Aug;45():183-94.

Citalopram

Celexa®

Reduced Response to Citalopram (GRIK4: Reduced Response to Citalopram) — INFORMATIVE

The patient's genotype indicates the absence of the GRIK4 favorable allele. The patient may not benefit from citalopram treatment.

- Kawaguchi DM, Glatt SJ. GRIK4 polymorphism and its association with antidepressant response in depressed patients: a meta-analysis. Pharmacogenomics 2014 Aug;15(11):1451-9.

Clomipramine

Anafranil®

Increased Clomipramine Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of clomipramine to less active compounds and a subsequent increase in clomipramine exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

- Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

Clozapine

Clozaril®

Possible Non-Response to Clozapine (CYP1A2: Normal Metabolizer- Possible Inducibility) — INFORMATIVE

Smokers may be at risk for non-response at standard doses and may require higher doses. There is an association between high clozapine doses and the risk of seizures, and therefore careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels, leading to adverse events. Therefore, therapeutic drug monitoring accompanied by dose reduction is recommended in patients who have quit smoking.

- Bolla E, Bortolaso P, Ferrari M, Poloni N, Callegari C, Marino F, Lecchini S, Vender S, Cosentino M. Are CYP1A2*1F and *1C associated with clozapine tolerability?: a preliminary investigation. Psychiatry Res 2011 Oct;189(3):483.
- Ferrari M, Bolla E, Bortolaso P, Callegari C, Poloni N, Lecchini S, Vender S, Marino F, Cosentino M. Association between CYP1A2 polymorphisms and clozapine -induced adverse reactions in patients with schizophrenia. Psychiatry Res 2012 Dec;200(2-3):1014-7.
- Ozdemir V, Kalow W, Okey AB, Lam MS, Albers LJ, Reist C, Fourie J, Posner P, Collins EJ, Roy R. Treatment-resistance to clozapine in association with ultrarapid CYP1A2 activity and the C-->A polymorphism in intron 1 of the CYP1A2 gene: effect of grapefruit juice and low-dose fluvoxamine. J Clin Psychopharmacol 2001 Dec;21(6):603-7.
- Koonrungsesomboon N, Khatsri R, Wongchompoo P, Teekachunhatean S. The impact of genetic polymorphisms on CYP1A2 activity in humans: a systematic review and meta-analysis. Pharmacogenomics J 2018 12;18(6):760-768.

Clozapine
Clozaril®

Unfavorable Response to Clozapine (HTR2A: Homozygous for the C allele (rs6311)) — **INFORMATIVE**

The patient does not carry the HTR2A variant rs6311. Preliminary studies suggest that this genotype may be associated with an unfavorable response to clozapine in patients with European ancestry.

- Arranz MJ, Munro J, Sham P, Kirov G, Murray RM, Collier DA, Kerwin RW. Meta-analysis of studies on genetic variation in 5-HT2A receptors and clozapine response. Schizophr Res 1998 Jul;32(2):93-9.
- Melkersson KI, Gunes A, Dahl ML. Impact of serotonin receptor 2A gene haplotypes on C-peptide levels in clozapine- and olanzapine-treated patients. Hum Psychopharmacol ;25(4):347-52.

Clozapine
Clozaril®

Risk of Metabolic Syndrome with Clozapine (HTR2C: Homozygous for the C allele (rs1414334)) — **INFORMATIVE**

Genetic variation in the Serotonin 2C Receptor (HTR2C) gene is known to be partially involved in the adverse effects to atypical antipsychotic medications. The patient is homozygous for C allele of HTR2C variant rs1414334. The patient may have an increased risk of developing metabolic syndrome when treated with clozapine.

- Risselada AJ, Vehof J, Bruggeman R, Wilffert B, Cohen D, Al Hadithy AF, Arends J, Mulder H. Association between HTR2C gene polymorphisms and the metabolic syndrome in patients using antipsychotics: a replication study. Pharmacogenomics J 2012 Feb;12(1):62-7.
- Mulder H, Franke B, van der-Beek van der AA, Arends J, Wilmink FW, Scheffer H, Egberts AC. The association between HTR2C gene polymorphisms and the metabolic syndrome in patients with schizophrenia. J Clin Psychopharmacol 2007 Aug;27(4):338-43.

Desipramine
Norpramin®

Increased Desipramine Exposure (CYP2D6: Intermediate Metabolizer) — **INFORMATIVE**

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of desipramine to less active compounds and a subsequent increase in desipramine exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

- Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

Doxepin
Silenor®

Increased Doxepin Exposure (CYP2D6: Intermediate Metabolizer) — **INFORMATIVE**

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of doxepin to less active compounds and a subsequent increase in doxepin exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Insomnia: Doxepin can be prescribed according to the standard recommended dosage and administration.

- Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

Fluvastatin
Lescol®

Possible Increased Fluvastatin Exposure (CYP2C9: Intermediate Metabolizer) — **INFORMATIVE**

Increased fluvastatin plasma concentrations due to reduced CYP2C9 activity may occur, resulting in myopathy/hepatotoxicity. Consider monitoring the patient for treatment-related adverse effects, and adjust dose based on tolerability and response. Other adverse events and predisposing factors include advanced age (65 and older), diabetes, hypothyroidism, renal or hepatic impairments, high statin dose, CYP2C9 inhibitors, ABCG2 inhibitors, and female sex.

- Zhou Q, Ruan ZR, Yuan H, Zeng S. CYP2C9*3(1075A>C), MDR1 G2677T/A and MDR1 C3435T are determinants of inter-subject variability in fluvastatin pharmacokinetics in healthy Chinese volunteers. Arzneimittelforschung 2012 Nov;62(11):519-24.
- Miroševic Skvrce N, Božina N, Zibar L, Barišic I, Pejnovic L, Macolic Šarinic V. CYP2C9 and ABCG2 polymorphisms as risk factors for developing adverse drug reactions in renal transplant patients taking fluvastatin: a case-control study. Pharmacogenomics 2013 Sep;14(12):1419-31.
- Kirchheiner J, Kudlicz D, Meisel C, Bauer S, Meineke I, Roots I, Brockmöller J. Influence of CYP2C9 polymorphisms on the pharmacokinetics and cholesterol-lowering activity of (-)-3S,5R-fluvastatin and (+)-3R,5S-fluvastatin in healthy volunteers. Clin Pharmacol Ther 2003 Aug;74(2):186-94.

Granisetron
Sancuso®, Sustol®

Unfavorable Response to Standard Granisetron Dosing (ABCB1: Heterozygous-Variant Allele Present) — **INFORMATIVE**

The genotype result predicts that the patient has decreased ABCB1 transporter expression. Patients with this genotype may experience decreased efficacy. No dose adjustments are recommended.

- Babaoglu MO, Bayar B, Aynacioglu AS, Kerb R, Abali H, Celik I, Bozkurt A. Association of the ABCB1 3435C>T polymorphism with antiemetic efficacy of 5-hydroxytryptamine type 3 antagonists. Clin Pharmacol Ther 2005 Dec;78(6):619-26.

Hydrocodone

Vicodin®

Possible Decreased Exposure to Hydrocodone Active Metabolite (CYP2D6: Intermediate Metabolizer) **INFORMATIVE**

The patient genotype may be associated with a reduced conversion of hydrocodone to an active metabolite (hydromorphone), which may result in decreased effectiveness.

Hydrocodone can be prescribed at standard label-recommended age- or weight-based dosing. If no response and opioid use is warranted, consider a non-codeine or non-tramadol opioid. Alternative opioids may include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

- Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, Dunnenberger HM, Leeder JS, Callaghan JT, Samer CF, Klein TE, Haidar CE, Van Driest SL, Ruano G, Sangkuhl K, Cavallari LH, Müller DJ, Prows CA, Nagy M, Somogyi AA, Skaar TC. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther 2021 10;110(4):888-896.

Imipramine

Tofranil®

Increased Imipramine Exposure (CYP2D6: Intermediate Metabolizer) **INFORMATIVE**

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of imipramine to less active compounds and a subsequent increase in imipramine exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

- Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

Leflunomide

Arava®

Increased Exposure to Leflunomide (CYP2C19: Intermediate Metabolizer) **INFORMATIVE**

Leflunomide is metabolized by CYP2C19 and CYP1A2 to its active metabolite teriflunomide. Preliminary studies indicate that patients with decreased CYP2C19 activity have a higher risk of developing gastrointestinal side effects and hepatotoxicity. There is insufficient data to calculate dose adjustment. If leflunomide is prescribed at standard dosing, monitor closely the patient's response and be alert to increased side effects.

Full blood cell count (CBC) and liver function parameters should be checked no more than 6 months before beginning treatment, and every month for the initial 6 months of therapy. Blood pressure should be checked before beginning treatment and periodically thereafter.

- Wiese MD, Schnabl M, O'Doherty C, Spargo LD, Sorich MJ, Cleland LG, Proudman SM. Polymorphisms in cytochrome P450 2C19 enzyme and cessation of leflunomide in patients with rheumatoid arthritis. Arthritis Res Ther 2012 Jul;14(4):R163.
- Bohanec Grabar P, Grabnar I, Rozman B, Logar D, Tomsic M, Suput D, Trdan T, Peterlin Masic L, Mrhar A, Dolzan V. Investigation of the influence of CYP1A2 and CYP2C19 genetic polymorphism on 2-Cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-2-butenamide (A77 1726) pharmacokinetics in leflunomide-treated patients with rheumatoid arthritis. Drug Metab Dispos 2009 Oct;37(10):2061-8.

Lorazepam

Ativan®

Possible Altered Response to Lorazepam (UGT2B15: Intermediate Metabolizer) **INFORMATIVE**

Lorazepam clearance may be reduced in this patient. However, there is insufficient evidence whether this change results in a significant clinical effect. Consider monitoring the patient for increased sedation and adjust dosing accordingly.

- Chung JY, Cho JY, Yu KS, Kim JR, Jung HR, Lim KS, Jang IJ, Shin SG. Effect of the UGT2B15 genotype on the pharmacokinetics, pharmacodynamics, and drug interactions of intravenous lorazepam in healthy volunteers. Clin Pharmacol Ther 2005 Jun;77(6):486-94.

Maprotiline

Ludiomil®

Possible Increased Maprotiline Exposure (CYP2D6: Intermediate Metabolizer) **INFORMATIVE**

Like other tricyclic and tetracyclic antidepressants, maprotiline is metabolized by CYP2D6 as well as CYP1A2. Decreased CYP2D6 activity results in higher maprotiline concentrations potentially leading to higher adverse events. There are no established dosing adjustments for patients with decreased CYP2D6 function therefore, therapy must be initiated at a low dosage and gradually adjusted according to the patient's response. The lowest effective dosage should always be considered during maintenance therapy.

- Firkusny L, Gleiter CH. Maprotiline metabolism appears to co-segregate with the genetically-determined CYP2D6 polymorphic hydroxylation of debrisoquine. Br J Clin Pharmacol 1994 Apr;37(4):383-8.
- Maprotyline Hydrochloride [package insert]. Morgantown, WV: Mylan Pharmaceuticals Inc.; 2014.

Methadone

Dolophine®

Increased Methadone Exposure (CYP2B6: Intermediate Metabolizer) **INFORMATIVE**

The patient's genotype may be associated with an increased methadone exposure following standard dosing.

For Addiction Treatment: There is limited evidence indicating that intermediate metabolizers require lower doses, therefore, a dose adjustment cannot be calculated.

For Pain Management: There are no studies documenting the effect of CYP2B6 genetic variations on methadone exposure when this drug is used as an analgesic. Consider standard prescribing and monitoring practices.

- Dennis BB, Bawor M, Thabane L, Sohani Z, Samaan Z. Impact of ABCB1 and CYP2B6 genetic polymorphisms on methadone metabolism, dose and treatment response in patients with opioid addiction: a systematic review and meta-analysis. PLoS One 2014 ;9(1):e86114.
- Kharasch ED. Current Concepts in Methadone Metabolism and Transport. Clin Pharmacol Drug Dev 2017 Mar;6(2):125-134.
- Ahmad T, Valentovic MA, Rankin GO. Effects of cytochrome P450 single nucleotide polymorphisms on methadone metabolism and pharmacodynamics. Biochem Pharmacol 2018 07;153():196-204.

Metoclopramide

Reglan®

Possible Sensitivity to Metoclopramide (CYP2D6: Intermediate Metabolizer) **INFORMATIVE**

There is no data documenting the changes in plasma concentrations of metoclopramide in CYP2D6 intermediate metabolizers. Metoclopramide can be prescribed at standard label-recommended dosage and administration with careful monitoring for possible increase of side effects.

- Reglan [package insert]. Baudette, MN: ANI Pharmaceuticals, Inc.; 2017.

Morphine

MS Contin®

Altered Response to Morphine (COMT: High/Normal COMT Activity) **INFORMATIVE**

The patient does not carry the COMT Val158Met variant. The patient may require higher doses of morphine for adequate pain control. The dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

- Rakvåg TT, Ross JR, Sato H, Skorpen F, Kaasa S, Klepstad P. Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. Mol Pain 2008 Dec;4():64.
- Rakvåg TT, Klepstad P, Baar C, Kvam TM, Dale O, Kaasa S, Krokan HE, Skorpen F. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain 2005 Jul;116(1-2):73-8.
- Matic M, Simons SH, van Lingen RA, van Rosmalen J, Elens L, de Wildt SN, Tibboel D, van Schaik RH. Rescue morphine in mechanically ventilated newborns associated with combined OPRM1 and COMT genotype. Pharmacogenomics 2014 Jul;15(10):1287-95.

Naltrexone

Vivitrol®, Contrave®

Altered Response to Naltrexone (OPRM1: Normal OPRM1 Function) **INFORMATIVE**

Treatment of alcohol dependence: the patient has the OPRM1 118AA wild-type genotype that is associated with a poorer outcome with naltrexone therapy. Naltrexone-treated patients not carrying the OPRM1 118A>G G allele are less likely to respond to this drug, and may have higher relapse rates than those who are carriers of this allele. This association has not been reported consistently across studies.

- Kranzler HR, Armeli S, Covault J, Tennen H. Variation in OPRM1 moderates the effect of desire to drink on subsequent drinking and its attenuation by naltrexone treatment. Addict Biol 2013 Jan;18(1):193-201.
- Chamorro AJ, Marcos M, Mirón-Canelo JA, Pastor I, González-Sarmiento R, Laso FJ. Association of µ-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis. Addict Biol 2012 May;17(3):505-12.
- Coller JK, Cahill S, Edmonds C, Farquharson AL, Longo M, Minniti R, Sullivan T, Somogyi AA, White JM. OPRM1 A118G genotype fails to predict the effectiveness of naltrexone treatment for alcohol dependence. Pharmacogenet Genomics 2011 Dec;21(12):902-5.

Olanzapine

Zyprexa®

Possible Non-Response to Olanzapine (CYP1A2: Normal Metabolizer- Possible Inducibility) **INFORMATIVE**

There is little evidence regarding the impact of CYP1A2 genetic variants on olanzapine response. Smokers may be at risk for non-response at standard doses. Careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels, leading to adverse events. Therefore, therapeutic drug monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

- Perera V, Gross AS, Polasek TM, Qin Y, Rao G, Forrest A, Xu J, McLachlan AJ. Considering CYP1A2 phenotype and genotype for optimizing the dose of olanzapine in the management of schizophrenia. Expert Opin Drug Metab Toxicol 2013 Sep;9(9):1115-37.
- Laika B, Leucht S, Heres S, Schneider H, Steimer W. Pharmacogenetics and olanzapine treatment: CYP1A2*1F and serotonergic polymorphisms influence therapeutic outcome. Pharmacogenomics J 2010 Feb;10(1):20-9.
- Koonrungsesomboon N, Khatsri R, Wongchompoo P, Teekachunhatean S. The impact of genetic polymorphisms on CYP1A2 activity in humans: a systematic review and meta-analysis. Pharmacogenomics J 2018 12;18(6):760-768.

Olanzapine

Zyprexa®

Increased Risk of Weight Gain with Olanzapine (HTR2C: Homozygous for the C allele (rs3813929)) **INFORMATIVE**

Genetic variations in the Serotonin 2C Receptor (HTR2C) gene in known to be partially involved in the adverse effects associated with atypical antipsychotic medications. The patient is homozygous for C allele of HTR2C variant rs3813929. Patients with this genotype may have an increased risk of weight gain when treated with olanzapine.

- Godlewska BR, Olajossy-Hilkesberger L, Ciwoniuk M, Olajossy M, Marmurowska-Michałowska H, Limon J, Landowski J. Olanzapine-induced weight gain is associated with the -759C/T and -697G/C polymorphisms of the HTR2C gene. Pharmacogenomics J 2009 Aug;9(4):234-41.
- Ellingrod VL, Perry PJ, Ringold JC, Lund BC, Bever-Stille K, Fleming F, Holman TL, Miller D. Weight gain associated with the -759C/T polymorphism of the 5HT2C receptor and olanzapine. Am J Med Genet B Neuropsychiatr Genet 2005 Apr;134B(1):76-8.
- Daray FM, Rodante D, Carosella LG, Silva ME, Martínez M, Fernández Busch MV, Faccone DF, Rothlin RP, Maffía PC. -759C>T Polymorphism of the HTR2C Gene is Associated with Second Generation Antipsychotic-Induced Weight Gain in Female Patients with Schizophrenia. Pharmacopsychiatry 2017 Jan;50(1):14-18.

Ondansetron

Zofran®, Zuplenz®

Unfavorable Response to Standard Ondansetron Dosing (ABCB1: Heterozygous-Variant Allele Present) — **INFORMATIVE**

The genotype result predicts that the patient has decreased ABCB1 transporter expression. Patients with this genotype may experience decreased efficacy. No dose adjustments are recommended.

- Perwitasari DA, Wessels JA, van der Straaten RJ, Baak-Pablo RF, Mustofa M, Hakimi M, Nortier JW, Gelderblom H, Guchelaar HJ. Association of ABCB1, 5-HT3B receptor and CYP2D6 genetic polymorphisms with ondansetron and metoclopramide antiemetic response in Indonesian cancer patients treated with highly emetogenic chemotherapy. Jpn J Clin Oncol 2011 Oct;41(10):1168-76.
- Babaoglu MO, Bayar B, Aynacioglu AS, Kerb R, Abali H, Celik I, Bozkurt A. Association of the ABCB1 3435C>T polymorphism with antiemetic efficacy of 5-hydroxytryptamine type 3 antagonists. Clin Pharmacol Ther 2005 Dec;78(6):619-26.

Oxazepam

Serax®

Possible Altered Response to Oxazepam (UGT2B15: Intermediate Metabolizer) — **INFORMATIVE**

Oxazepam clearance may be reduced in this patient. However, there is insufficient evidence whether this change results in a significant clinical effect. Consider monitoring the patient for increased sedation and adjust dosing accordingly.

- He X, Hesse LM, Hazarika S, Masse G, Harmatz JS, Greenblatt DJ, Court MH. Evidence for oxazepam as an in vivo probe of UGT2B15: oxazepam clearance is reduced by UGT2B15 D85Y polymorphism but unaffected by UGT2B17 deletion. Br J Clin Pharmacol 2009 Nov;68(5):721-30.
- Court MH, Hao Q, Krishnaswamy S, Bekaii-Saab T, Al-Rohaimi A, von Moltke LL, Greenblatt DJ. UDP-glucuronosyltransferase (UGT) 2B15 pharmacogenetics: UGT2B15 D85Y genotype and gender are major determinants of oxazepam glucuronidation by human liver. J Pharmacol Exp Ther 2004 Aug;310(2):656-65.
- Court MH, Duan SX, Guillemette C, Journault K, Krishnaswamy S, Von Moltke LL, Greenblatt DJ. Stereoselective conjugation of oxazepam by human UDP-glucuronosyltransferases (UGTs): S-oxazepam is glucuronidated by UGT2B15, while R-oxazepam is glucuronidated by UGT2B7 and UGT1A9. Drug Metab Dispos 2002 Nov;30(11):1257-65.

Phenobarbital

Luminal®

Possible Sensitivity to Phenobarbital (CYP2C19: Intermediate Metabolizer) — **INFORMATIVE**

CYP2C19 is partly involved in the metabolism of phenobarbital, and although CYP2C19 intermediate metabolizers have a lower clearance of phenobarbital than normal metabolizers, no significant changes in clinical outcome has been reported with this antiepileptic drug. Therefore, phenobarbital can be prescribed at standard label-recommended dosage and administration with a closer monitoring for adverse events.

- Lee SM, Chung JY, Lee YM, Park MS, Namgung R, Park KI, Lee C. Effects of cytochrome P450 (CYP)2C19 polymorphisms on pharmacokinetics of phenobarbital in neonates and infants with seizures. Arch Dis Child 2012 Jun;97(6):569-72.
- Mamiya K, Hadama A, Yukawa E, Ieiri I, Otsubo K, Ninomiya H, Tashiro N, Higuchi S. CYP2C19 polymorphism effect on phenobarbitone. Pharmacokinetics in Japanese patients with epilepsy: analysis by population pharmacokinetics. Eur J Clin Pharmacol ;55(11-12):821-5.
- Yukawa E, Mamiya K. Effect of CYP2C19 genetic polymorphism on pharmacokinetics of phenytoin and phenobarbital in Japanese epileptic patients using Non -linear Mixed Effects Model approach. J Clin Pharm Ther 2006 Jun;31(3):275-82.
- Anderson, Gail D. "Chemisry, Biotransformation, and Pharmacokinetics." Antiepileptic Drugs. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002. 496-03. Print.

Pioglitazone

Actos®, Oseni®

Possible Reduced Exposure to Pioglitazone (CYP2C8: Intermediate Metabolizer) — **INFORMATIVE**

The patient carries one copy of the CYP2C8 *3 allele. The patient may have an increased pioglitazone clearance and a decreased pioglitazone plasma exposure. Pioglitazone should be used with caution, and dosing adjustment may be needed for this patient.

- Kaspera R, Naraharisetti SB, Evangelista EA, Marciante KD, Psaty BM, Totah RA. Drug metabolism by CYP2C8.3 is determined by substrate dependent interactions with cytochrome P450 reductase and cytochrome b5. Biochem Pharmacol 2011 Sep;82(6):681-91.
- Aquilante CL, Wempe MF, Spencer SH, Kosmiski LA, Predhomme JA, Sidhom MS. Influence of CYP2C8*2 on the pharmacokinetics of pioglitazone in healthy African-American volunteers. Pharmacotherapy 2013 Sep;33(9):1000-7.
- Kadam R, Bourne D, Kompella U, Aquilante C. Effect of Cytochrome P450 2C8*3 on the Population Pharmacokinetics of Pioglitazone in Healthy Caucasian Volunteers. Biol Pharm Bull 2013 ;36(2):245-51.

Primidone

Mysoline®

Possible Sensitivity to Primidone (CYP2C19: Intermediate Metabolizer) — **INFORMATIVE**

CYP2C19 is partly involved in the metabolism of primidone, and although CYP2C19 intermediate metabolizers have a lower clearance of phenobarbital (active metabolite) than normal metabolizers, no significant changes in clinical outcome has been reported with this antiepileptic drug. Therefore, primidone can be prescribed at standard label-recommended dosage and administration with a closer monitoring for adverse events.

- Fincham, Richard W., and Dorothy D. Schottelius. "Primidone." Antiepileptic Drugs. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002. 621-36. Print.

Protriptyline

Vivactil®

Possible Increased Protriptyline Exposure (CYP2D6: Intermediate Metabolizer) — **INFORMATIVE**

Like other tricyclic and tetracyclic antidepressants, protriptyline is metabolized by CYP2D6. Decreased CYP2D6 activity results in higher protriptyline concentrations potentially leading to higher adverse events. There are no established dosing adjustments for patients with decreased CYP2D6 function. Therefore, therapy must be initiated at a low dosage and gradually adjusted according to the patient's response. The lowest effective dosage should always be considered during maintenance therapy.

- Vivactil [package insert]. Horsham, PA: Teva Pharmaceuticals USA, Inc.; 2014.

Risperidone

Risperdal®

Risk of Metabolic Syndrome with Risperidone (HTR2C: Homozygous for the C allele (rs1414334)) — **INFORMATIVE**

Genetic variations in the Serotonin 2C Receptor (HTR2C) gene in known to be partially involved in the adverse effects associated with atypical antipsychotic medications. The patient is homozygous for C allele of HTR2C variant rs1414334. The patient may have an increased risk of developing metabolic syndrome when treated with risperidone.

- Risselada AJ, Vehof J, Bruggeman R, Wilffert B, Cohen D, Al Hadithy AF, Arends J, Mulder H. Association between HTR2C gene polymorphisms and the metabolic syndrome in patients using antipsychotics: a replication study. Pharmacogenomics J 2012 Feb;12(1):62-7.

Rosiglitazone

Avandia®

Possible Reduced Exposure to Rosiglitazone (CYP2C8: Intermediate Metabolizer) — **INFORMATIVE**

The patient carries one copy of the CYP2C8 *3 allele. The patient is likely to have an increased rosiglitazone oral clearance and reduced therapeutic response. The patient may also have a lower risk of developing edema during treatment with rosiglitazone. Carefully monitor the patient's responsiveness during rosiglitazone therapy.

- Stage TB, Christensen MM, Feddersen S, Beck-Nielsen H, Brøsen K. The role of genetic variants in CYP2C8, LPIN1, PPARGC1A and PPARγ on the trough steady-state plasma concentrations of rosiglitazone and on glycosylated haemoglobin A1c in type 2 diabetes. Pharmacogenet Genomics 2013 Apr;23(4):219-27.
- Aquilante CL, Bushman LR, Knutsen SD, Burt LE, Rome LC, Kosmiski LA. Influence of SLCO1B1 and CYP2C8 gene polymorphisms on rosiglitazone pharmacokinetics in healthy volunteers. Hum Genomics 2008 Sep;3(1):7-16.
- Kirchheiner J, Thomas S, Bauer S, Tomalik-Scharte D, Hering U, Doroshyenko O, Jetter A, Stehle S, Tsahuridu M, Meineke I, Brockmöller J, Fuhr U. Pharmacokinetics and pharmacodynamics of rosiglitazone in relation to CYP2C8 genotype. Clin Pharmacol Ther 2006 Dec;80(6):657-67.

Sulfasalazine

Azulfidine®, Sulfazine®

Decreased Response to Sulfasalazine For the Treatment of Rheumatoid Arthritis (ABCG2: Normal Function) — **INFORMATIVE**

Rheumatoid Arthritis: The patient carries two copies of ABCG2 rs2231142 C allele. Preliminary data suggests that this genotype may be associated with decreased plasma levels of sulfasalazine which may decrease the likelihood of response to this drug.

- Wiese MD, Alotaibi N, O'Doherty C, Sorich MJ, Suppiah V, Cleland LG, Proudman SM. Pharmacogenomics of NAT2 and ABCG2 influence the toxicity and efficacy of sulphasalazine containing DMARD regimens in early rheumatoid arthritis. Pharmacogenomics J 2014 Aug;14(4):350-5.
- Gotanda K, Tokumoto T, Hirota T, Fukae M, Ieiri I. Sulfasalazine disposition in a subject with 376C>T (nonsense mutation) and 421C>A variants in the ABCG2 gene. Br J Clin Pharmacol 2015 Nov;80(5):1236-7.

Timolol

Blocadren®

Possible Sensitivity to Timolol (CYP2D6: Intermediate Metabolizer) — **INFORMATIVE**

Potentiated systemic beta-blockade (e.g., bradycardia) has been reported during timolol treatment by patients with decreased CYP2D6 activity. Monitor patient for treatment-related adverse effects.

- Yuan H, Yu M, Yang Y, Wu K, Lin X, Li J. Association of CYP2D6 single-nucleotide polymorphism with response to ophthalmic timolol in primary open-angle Glaucoma--a pilot study. J Ocul Pharmacol Ther 2010 Oct;26(5):497-501.
- Canpolat U, Gürses KM, Aytemir K, Oto A. Severe bradycardia and syncope due to topical ophthalmic timolol. Herz 2013 Aug;38(5):556-7.
- Mäenpää J, Pelkonen O. Cardiac safety of ophthalmic timolol. Expert Opin Drug Saf 2016 Nov;15(11):1549-1561.

Tizanidine

Zanaflex®

Possible Non-Response to Tizanidine (CYP1A2: Normal Metabolizer- Possible Inducibility) — **INFORMATIVE**

There is little evidence regarding the impact of CYP1A2 genetic variants on tizanidine response. Smokers may be at risk for non-response and may require higher doses. There is an association between high tizanidine plasma concentrations and the risk of hypotension and excessive sedation. Therefore, careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels, leading to excessive hypotension and sedation. Careful monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

- Backman JT, Schröder MT, Neuvonen PJ. Effects of gender and moderate smoking on the pharmacokinetics and effects of the CYP1A2 substrate tizanidine. Eur J Clin Pharmacol 2008 Jan;64(1):17-24.
- Granfors MT, Backman JT, Neuvonen M, Ahonen J, Neuvonen PJ. Fluvoxamine drastically increases concentrations and effects of tizanidine: a potentially hazardous interaction. Clin Pharmacol Ther 2004 Apr;75(4):331-41.
- Al-Ghazawi M, Alzoubi M, Faidi B. Pharmacokinetic comparison of two 4 mg tablet formulations of tizanidine. Int J Clin Pharmacol Ther 2013 Mar;51(3):255-62.
- Koonrungsesomboon N, Khatsri R, Wongchompoo P, Teekachunhatean S. The impact of genetic polymorphisms on CYP1A2 activity in humans: a systematic review and meta-analysis. Pharmacogenomics J 2018 12;18(6):760-768.

Tramadol

Decreased Exposure to Tramadol Active Metabolite (CYP2D6: Intermediate Metabolizer) — **INFORMATIVE**

Ultram®

The patient genotype is associated with decreased conversion of tramadol to its active metabolite (O-desmethyltramadol), which may result in decreased effectiveness.

Tramadol can be prescribed at standard label-recommended age- or weight-based dosing and monitoring. If no response and opioid use is warranted, consider a non-codeine opioid. Alternative opioids may include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

- Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, Dunnenberger HM, Leeder JS, Callaghan JT, Samer CF, Klein TE, Haidar CE, Van Driest SL, Ruano G, Sangkuhl K, Cavallari LH, Müller DJ, Prows CA, Nagy M, Somogyi AA, Skaar TC. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther 2021 10;110(4):888-896.

Trimipramine

Surmontil®

Increased Trimipramine Exposure (CYP2D6: Intermediate Metabolizer) **INFORMATIVE**

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of trimipramine to less active compounds and a subsequent increase in trimipramine exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

- Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017 07;102(1):37-44.

Zonisamide

Zonegran®

Possible Sensitivity to Zonisamide (CYP2C19: Intermediate Metabolizer) **INFORMATIVE**

CYP2C19 is partly involved in the metabolism of zonisamide, and although preliminary studies show that CYP2C19 intermediate metabolizers have a slightly lower (15%) zonisamide clearance than normal metabolizers, no significant change in the clinical outcome has been reported with this antiepileptic drug. Therefore, zonisamide can be prescribed at standard label-recommended dosage and administration with a closer monitoring for adverse events.

- Okada Y, Seo T, Ishitsu T, Wanibuchi A, Hashimoto N, Higa Y, Nakagawa K. Population estimation regarding the effects of cytochrome P450 2C19 and 3A5 polymorphisms on zonisamide clearance. Ther Drug Monit 2008 Aug;30(4):540-3.

Anti-Cancer Dosing Guidance

Tamoxifen

Nolvadex®, Soltamox®

Decreased Response to Tamoxifen (CYP2D6: Intermediate Metabolizer) **ACTIONABLE**

Adjuvant treatment of estrogen receptor-positive breast cancer: based on the CYP2D6 genotype results, this patient is **expected** to have low endoxifen (active metabolite of tamoxifen) concentrations. This is associated with a reduced response to this drug and poor treatment outcomes.

Consider alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or an aromatase inhibitor along with ovarian function suppression in premenopausal women.

If aromatase inhibitors are contraindicated, a higher FDA approved dose of tamoxifen (40 mg/day) can be considered, although a higher dose increases but does not normalize endoxifen concentrations. Consider avoiding the co-administration of this drug with strong, moderate or weak CYP2D6 inhibitors. An increased risk of thromboembolic events is associated with tamoxifen therapy. The risks and benefits of this drug should be carefully considered in women with a history of thromboembolic events or with other coexisting risk factors for thrombosis.

- Goetz MP, Sangkuhl K, Guchelaar HJ, Schwab M, Province M, Whirl-Carrillo M, Symmans WF, McLeod HL, Ratain MJ, Zembutsu H, Gaedigk A, van Schaik RH, Ingle JN, Caudle KE, Klein TE. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and Tamoxifen Therapy. Clin Pharmacol Ther 2018 05;103(5):770-777.

Erdafitinib

Balversa®

Normal Exposure to Erdafitinib (CYP2C9: Intermediate Metabolizer) **ACTIONABLE**

The patient's genotype is associated with a normal erdafitinib clearance. Consider prescribing this drug according to standard label-recommended dosage and administration (initiate at 8 mg/day and increase to 9 mg/day based on serum phosphate levels and tolerability at 14 to 21 days). Dosing is individualized based on the patient's tolerability and serum phosphate levels; in case of adverse events, consider dose modifications according to protocol available from the approved-prescribing label (stepwise dose reduction and/or interruption).

Consider alternative agents or monitor closely for adverse reactions when erdafitinib is coadministered with strong CYP2C9 inhibitors or strong CYP3A inhibitors.

Concomitant use of strong CYP3A4 / CYP2C9 inducers is not recommended.

Consider a dose increase up to 9 mg when erdafitinib is coadministered with moderate or weak CYP2C9 / CYP3A inducers.

- Balversa [package insert]. Horsham, PA: Janssen Products, LP; 2019.

Gefitinib

Iressa®

Possible Increased Exposure to Gefitinib (CYP2D6: Intermediate Metabolizer) **ACTIONABLE**

The patient's genotype may be associated with a non-clinically relevant increased gefitinib exposure following standard dosing. Consider prescribing gefitinib at standard label-recommended dosage and administration.

- Iressa [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018.
- The Royal Dutch Pharmacists Association of the KNMP. (2020). Pharmacogenetic Recommendations 2020 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2020.pdf (Accessed September 8, 2020).

Mercaptopurine

Purinethol®, Purixan®

Normal Risk of Myelotoxicity (TPMT: Normal Metabolizer; NUDT15: Normal Metabolizer) **ACTIONABLE**

The genotype results predict that the patient does not have an increased risk of leukopenia, neutropenia or myelosuppression with standard doses of mercaptopurine.

Nonmalignant indications

Therapy initiation: unless other risk factors are present, consider a normal starting dose and adjust dosing based on disease-specific guidelines and/or myelosuppression, as needed. Allow 2 weeks to reach steady state after each dose adjustment.

Malignant indications

Therapy initiation: unless other risk factors are present, consider a normal starting dose and adjust dosing based on disease-specific guidelines and myelosuppression. Allow 2 weeks to reach steady state after each dose adjustment.

These genotype results cannot be used to assess the patient's risk of thiopurine-related pancreatitis or hepatotoxicity.

- Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther 2019 May;105(5):1095-1105.

Thioguanine

Tabloid®

Normal Risk of Myelotoxicity (TPMT: Normal Metabolizer; NUDT15: Normal Metabolizer) — **ACTIONABLE**

The genotype results predict that the patient does not have an increased risk of leukopenia, neutropenia or myelosuppression with standard doses of thioguanine.

Nonmalignant indications

Therapy initiation: unless other risk factors are present, consider a normal starting dose and adjust dosing based on disease-specific guidelines and/or myelosuppression, as needed. Allow 2 weeks to reach steady state after each dose adjustment.

Malignant indications

Therapy initiation: unless other risk factors are present, consider a normal starting dose and adjust dosing based on disease-specific guidelines and myelosuppression. Allow 2 weeks to reach steady state after each dose adjustment.

These genotype results cannot be used to assess the patient's risk of thiopurine-related pancreatitis or hepatotoxicity.

- Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther 2019 May;105(5):1095-1105.

Azathioprine

Azasan®, Imuran®

Normal Risk of Myelotoxicity (TPMT: Normal Metabolizer; NUDT15: Normal Metabolizer) — **ACTIONABLE**

The genotype results predict that the patient does not have an increased risk of leukopenia, neutropenia or myelosuppression with standard doses of azathioprine.

Nonmalignant indications

Therapy initiation: unless other risk factors are present, consider a normal starting dose and adjust dosing based on disease-specific guidelines and/or myelosuppression, as needed. Allow 2 weeks to reach steady state after each dose adjustment.

Malignant indications

Therapy initiation: unless other risk factors are present, consider a normal starting dose and adjust dosing based on disease-specific guidelines and myelosuppression. Allow 2 weeks to reach steady state after each dose adjustment.

These genotype results cannot be used to assess the patient's risk of thiopurine-related pancreatitis or hepatotoxicity.

- Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther 2019 May;105(5):1095-1105.

Letrozole

Femara®

Normal Response to Letrozole — **INFORMATIVE**

Pharmacogenetic guidance: Letrozole is metabolized via CYP3A4 and CYP2A6 to a pharmacologically-inactive carbinol metabolite which is renally excreted after glucuronidation. Although, few studies reported higher letrozole exposure in patients carrying CYP2A6 reduced-function or no-function variants, the clinical impact of this variation on the drug efficacy and toxicity profiles in breast cancer patients remains unclear. No genotype based dosing recommendations are available. While letrozole is indicated in hormone receptor (estrogen receptor and progesterone receptor) positive breast cancer patients, testing for hormone receptor status is beyond the scope of this report. **Polypharmacy guidance:** No clinically significant effect on letrozole pharmacokinetics has been reported with concomitant medications.

- Desta Z, Kreutz Y, Nguyen AT, Li L, Skaar T, Kamdem LK, Henry NL, Hayes DF, Storniolo AM, Stearns V, Hoffmann E, Tyndale RF, Flockhart DA. Plasma letrozole concentrations in postmenopausal women with breast cancer are associated with CYP2A6 genetic variants, body mass index, and age. Clin Pharmacol Ther 2011 Nov;90(5):693-700.
- Tanii H, Shitara Y, Horie T. Population pharmacokinetic analysis of letrozole in Japanese postmenopausal women. Eur J Clin Pharmacol 2011 Oct;67(10):1017-25.

Methotrexate
Trexall®

Normal Risk for Methotrexate Toxicity (MTHFR: Normal MTHFR Activity) **INFORMATIVE**

The patient does not carry the MTHFR c.665C>T variant, and unless other risk factors are present, the patient is not expected to have an increased risk for methotrexate toxicity. Consider using label-recommended dosage and administration.

- De Mattia E, Toffoli G. C677T and A1298C MTHFR polymorphisms, a challenge for antifolate and fluoropyrimidine-based therapy personalisation. Eur J Cancer 2009 May;45(8):1333-51.
- Choi YJ, Park H, Lee JS, Lee JY, Kim S, Kim TW, Park JS, Kim JE, Yoon DH, Suh C. Methotrexate elimination and toxicity: MTHFR 677C>T polymorphism in patients with primary CNS lymphoma treated with high-dose methotrexate. Hematol Oncol 2017 Dec;35(4):504-509.
- Zhao M, Liang L, Ji L, Chen D, Zhang Y, Zhu Y, Ongaro A. MTHFR gene polymorphisms and methotrexate toxicity in adult patients with hematological malignancies: a meta-analysis. Pharmacogenomics 2016 06;17(9):1005-17.

Exemestane
Aromasin®

Normal Response to Exemestane **INFORMATIVE**

Pharmacogenetic guidance: Exemestane is extensively metabolized to active 17-beta-dihydroexemestane by cytosolic keto steroid reductases AKR1Cs and CBR1, and to a smaller extent via CYP4A11, CYP1A1 and CYP1A2. UGT2B17 plays a major role in glucoronidation of 17-beta-dihydroexemestane. Exemestane is also oxidized to 6-hydroxymethylexemestane via CYP3A4. Exemestane and its major active metabolite are substrates of the OATP1B1 transporter. A few studies have reported that genetic variants within the aromatase-encoding gene, CYP19A1, may alter the efficacy of aromatase inhibitors in breast cancer patients. However, more evidence is needed to guide exemestane prescription based on CYP19A1 genotype status. Preliminary studies have reported modest increase in exposure to exemestane and its active metabolite in patients carrying CYP3A4*22 or UGT2B17 deletion. The impact of these changes on exemestane efficacy or adverse events remain unknown. Additionally, the indications for use of exemestane in breast cancer patients may depend upon the status of estrogen receptor (ER) or progersterone receptor (PGR) expression. However, testing and reporting for ER and PGR status is beyond the scope of this report. No genotype based dosing guidance is available. **Polypharmacy guidance:** Concomitant use of strong CYP3A4 inducers decreases exemestane exposure. For patients receiving exemestane with a strong CYP3A4 inducer such as rifampicin or phenytoin, the recommended dose of exemestane may have to be increased to 50 mg once daily after a meal. Concomitant use of estrogen containing products may diminish activity of exemestane.

- Glubb DM, O'Mara TA, Shamsani J, Spurdle AB. The Association of CYP19A1 Variation with Circulating Estradiol and Aromatase Inhibitor Outcome: Can CYP19A1 Variants Be Used to Predict Treatment Efficacy? Front Pharmacol 2017 ;8():218.
- Luo S, Chen G, Truica C, Baird CC, Leitzel K, Lazarus P. Role of the UGT2B17 deletion in exemestane pharmacogenetics. Pharmacogenomics J 2018 04;18 (2):295-300.
- Hertz DL, Kidwell KM, Seewald NJ, Gersch CL, Desta Z, Flockhart DA, Storniolo AM, Stearns V, Skaar TC, Hayes DF, Henry NL, Rae JM. Polymorphisms in drug-metabolizing enzymes and steady-state exemestane concentration in postmenopausal patients with breast cancer. Pharmacogenomics J 2017 12;17(6):521-527.
- Aromasin [package insert]. New York, NY: Pfizer Inc.; 2018.

Anastrozole
Arimidex®

Normal Response to Anastrozole **INFORMATIVE**

Pharmacogenetic guidance: Anastrozole is oxidized to hydroxyanastrozole mainly by CYP3A4 (with minor contribution from CYP2C8 and CYP3A5) and glucuronidated to anastrozole glucuronide by UGT1A4. Hydroxyanastrozole glucuronide and hydroxyanastrozole are the major metabolites of anastrozole in plasma of breast cancer patients. While CYP3A4, CYP3A5, CYP2C8 and UGT1A4 enzymes are polymorphic, genetic variations are unlikely to have a clinically significant impact on anastrozole exposure, and no genotype-based dosing adjustments are recommended. Additionally, the indications for use of anastrozole in breast cancer patients may depend upon the status of estrogen receptor (ER) or progersterone receptor (PGR) expression. However, testing and reporting for ER and PGR status is beyond the scope of this report. **Polypharmacy guidance:** Concomitant use of estrogen containing products may diminish activity of anastrozole.

- Kamdem LK, Liu Y, Stearns V, Kadlubar SA, Ramirez J, Jeter S, Shahverdi K, Ward BA, Ogburn E, Ratain MJ, Flockhart DA, Desta Z. In vitro and in vivo oxidative metabolism and glucuronidation of anastrozole. Br J Clin Pharmacol 2010 Dec;70(6):854-69.
- Arimidex [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2014.

GeneStreet Laboratories

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

Test Details

Gene	Genotype	Phenotype	Alleles Tested
ABCB1	2677G>A G/G	**Variant Allele Not Present**	3435C>T, 1236T>C, 2677G>A, 2677G>T
ABCB1	3435C>T C/T	**Heterozygous- Variant Allele Present**	3435C>T, 1236T>C, 2677G>A, 2677G>T
ABCB1	1236T>C C/C	**Homozygous Mutant - Variant Allele Present**	3435C>T, 1236T>C, 2677G>A, 2677G>T
ABCB1	2677G>T G/G	**Variant Allele Not Present**	3435C>T, 1236T>C, 2677G>A, 2677G>T
ABCG2	421C>A C/C	**Normal Function**	421C>A
ANKK1/DRD2	DRD2:Taq1A A/G	**Altered DRD2 function**	DRD2:Taq1A
APOE	ε3/ε4	**Altered APOE function**	ε2, ε4, (ε3 is reference)
ATM/C11orf65	rs11212617 C/A	**Heterozygous for the A allele (rs11212617)**	rs11212617
COMT	Val158Met G/G	**High/Normal COMT Activity**	Val158Met
CYP1A2	*1C/*1D	**Normal Metabolizer- Possible Inducibility**	*1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W
CYP2B6	*1/*6	**Intermediate Metabolizer**	*4, *5, *6, *7, *9, *18, *18.002, *22
CYP2C	g.96405502G>A G/A	**High Sensitivity**	g.96405502G>A
CYP2C19	*1/*2	**Intermediate Metabolizer**	*2, *3, *4A, *4B, *5, *6, *7, *8, *9, *10, *17, *35
CYP2C8	*1A/*3	**Intermediate Metabolizer**	*2, *3, *4
CYP2C9	*1/*2	**Intermediate Metabolizer**	*2, *3, *4, *5, *6, *8, *11, *13, *27
CYP2D6	*4/*17	**Intermediate Metabolizer**	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *29, *31, *35, *40, *41, *42, *49, *59, *114, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1/*1	**Normal Metabolizer**	*2, *3, *12, *17, *22
CYP3A5	*7/*7	**Poor Metabolizer**	*2, *3, *6, *7, *8, *9
CYP4F2	c.1297G>A G/G	**Normal Activity**	c.1297G>A
DPYD	Activity Score: 2	**Normal Metabolizer**	1905+1G>A, 1679T>G, 2846A>T, 557A>G, 1236G>A
DRD2	g.113425552A>G A/G	**Heterozygous for the G allele (rs1079598)**	-241A>G, g.113411054A>C, g.113475530dup, g.113425552A>G
DRD2	-241A>G T/T	**Homozygous for rs1799978 T allele**	-241A>G, g.113411054A>C, g.113475530dup, g.113425552A>G
F2 **F5**	rs1799963 GG rs6025 CC	**Normal Risk of Thrombosis**	rs1799963, rs6025
GRIK4	83-10039T>C T/T	**Reduced Response to Citalopram**	83-10039T>C
HTR2A	-1438G>A C/C	**Homozygous for the C allele (rs6311)**	-1438G>A, rs7997012
HTR2A	rs7997012 G/G	**Homozygous for G allele (rs7997012)**	-1438G>A, rs7997012
HTR2C	114138144C>G C/C	**Homozygous for the C allele (rs1414334)**	-759C>T, 114138144C>G

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

HTR2C	-759C>T C/C	**Homozygous for the C allele (rs3813929)**	-759C>T, 114138144C>G
ITGB3	176T>C T/C	**Increased Platelet Reactivity**	176T>C
MTHFR	c.665C>T GG	**Normal MTHFR Activity**	c.1286A>C, c.665C>T
MTHFR	c.1286A>C TT c.665C>T GG	**No Increased Risk of Hyperhomocysteinemia**	c.1286A>C, c.665C>T
NUDT15	*1/*1	**Normal Metabolizer**	*2, *3, *4, *5
OPRM1	A118G A/A	**Normal OPRM1 Function**	A118G
SLCO1B1	521T>C T/T	**Normal Function**	521T>C, 388A>G
TPMT	*1/*1	**Normal Metabolizer**	*2, *3A, *3B, *3C, *4
UGT2B15	*1/*2	**Intermediate Metabolizer**	*2
VKORC1	-1639G>A G/A	**Intermediate Warfarin Sensitivity**	-1639G>A

Limitation: This test will not detect all the known alleles that result in altered or inactive tested genes. This test does not account for all individual variations in the individual tested. Absence of a detectable gene mutation does not rule out the possibility that a patient has different phenotypes due to the presence of an undetected polymorphism or due to other factors such as drug-drug interactions, comorbidities and lifestyle habits.

Methodology: Array based assays detect listed alleles, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%.

Lab Disclaimer: Gene Street Laboratories developed the Genotype test. The performance characteristics of this test were determined by Gene Street Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration.

Translational Software Disclaimer: The information presented on this report is provided as general educational health information. The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Only a physician, pharmacist or other healthcare professional should advise a patient on the use of the medications prescribed.

The pharmacogenetic assay involves use of reporting software and genotype-phenotype associations performed by Translational Software (www.translationalsoftware.com). The software has not been evaluated by the Food and Drug Administration. The software, and the report generated by the software, is not intended to diagnose, treat, cure, or prevent any disease. A qualified designee within the lab uses Translational Software to generate and subsequently review the report. The pharmacogenetic report is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to dose guidelines does not necessarily assure a successful medical outcome.

MTHFR, CYP2D6, and CYP2C9 genotype and phenotype results are used to aid dose optimization and to reduce side effects but not to predict clinical outcomes to anticancer drugs. Hence they should not be used as predictive or prognostic biomarkers for anticancer drugs responses.

Approved by Douglas H. Posey, MD

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

Patient Information Card

This is a summary genetic report for your patient to share with other healthcare providers. The card can be cut out along the dashed line and carried with the patient.

GeneStreet Laboratories

REPORT DETAILS
Name: Jane Doe
DOB: 1/6/1961
ACC #: GSPGX0001

Pharmacogenetic Test Summary

ABCB1	1236T>C C/C	Homozygous Mutant - Variant Allele Present
ABCB1	3435C>T C/T	Heterozygous- Variant Allele Present
ABCB1	2677G>A G/G	Variant Allele Not Present
ABCB1	2677G>T G/G	Variant Allele Not Present
ABCG2	421C>A C/C	Normal Function
ANKK1/DRD2	DRD2:Taq1A A/G	Altered DRD2 function
APOE	ε3/ε4	Altered APOE function
ATM/C11orf65	rs11212617 C/A	Heterozygous for the A allele (rs11212617)
COMT	Val158Met G/G	High/Normal COMT Activity
CYP1A2	*1C/*1D	Normal Metabolizer- Possible Inducibility
CYP2B6	*1/*6	Intermediate Metabolizer
CYP2C	g.96405502G>A G/A	High Sensitivity
CYP2C19	*1/*2	Intermediate Metabolizer
CYP2C8	*1A/*3	Intermediate Metabolizer
CYP2C9	*1/*2	Intermediate Metabolizer
CYP2D6	*4/*17	Intermediate Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*7/*7	Poor Metabolizer
CYP4F2	c.1297G>A G/G	Normal Activity
DPYD	Activity Score: 2	Normal Metabolizer
DRD2	g.113425552A>G A/G	Heterozygous for the G allele (rs1079598)
DRD2	-241A>G T/T	Homozygous for rs1799978 T allele
F2	rs1799963 GG	Normal Thrombosis Risk
F5	rs6025 CC	Normal Thrombosis Risk
GRIK4	83-10039T>C T/T	Reduced Response to Citalopram
HTR2A	-1438G>A C/C	Homozygous for the C allele (rs6311)
HTR2A	rs7997012 G/G	Homozygous for G allele (rs7997012)
HTR2C	114138144C>G C/C	Homozygous for the C allele (rs1414334)

Lab Director: Douglas H. Posey, MD
CLIA: 45D2176552 | COLA: 29895
11455 Fallbrook Drive, Suite 102, Houston TX 77065
T: 866-230-0848 | F: 713-903-7916
support@genestreet.com | www.genestreet.com

HTR2C	-759C>T C/C	Homozygous for the C allele (rs3813929)
ITGB3	176T>C T/C	Increased Platelet Reactivity
MTHFR	c.665C>T GG	Normal MTHFR Activity
MTHFR	c.1286A>C TT	Normal MTHFR Activity
NUDT15	*1/*1	Normal Metabolizer
OPRM1	A118G A/A	Normal OPRM1 Function
SLCO1B1	521T>C T/T	Normal Function
TPMT	*1/*1	Normal Metabolizer
UGT2B15	*1/*2	Intermediate Metabolizer
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity

For a complete report contact Gene Street LLC
www.genestreet.com