VIKORSCIENTIFIC

KORPATH

PGX Case Review

- **Patient History:** 85-year-old – male patient with history of depression and known factor 5 variant
- **Symptoms/Disease State:** patient was not eating, became very disengaged in conversation, needed a walker for the first time for stability
- **Why Test was Ordered:** family changed primary care physician for the patient and new physician ordered the test as a starting point to identify what might be occurring?
- **Outcome:** PGx report identified anti-depressant medication was not one the patient could take. Changed medication and patient no longer needed walker and became vibrant and engaged within 2 weeks of med change.

VIKORSCIENTIFIC

PATIENT INFORMATION		SPECIMEN DETAILS		PROVIDER INFORMATION
NAME:		**SPECIMEN TYPE:**	PGx Swab	
ACC #:		**COLLECTION DATE:**	2/24/2021	
DOB:	6/9/1936	**RECEIVED DATE:**	2/26/2021	
SEX:	female	**REPORT DATE:**	3/7/2021	

Comprehensive Pharmacogenetic Report

Risk Management

✓ Type III Hyperlipoproteinemia

Not Associated with Type III Hyperlipoproteinemia

The patient is negative for both the APOE c.388 T>C (Cys130Arg) and c.526 C>T (Arg176Cys) mutations. The patient's genotype is wild-type, which is the most common genotype in the general population (frequency: >60%).
A patient with wild-type genotype does not have a defect in the apolipoprotein E (APOE), which is an integral structure of lipoprotein particles that have critical roles in blood lipid metabolism and transport. The APOE ε3/ε3 genotype is not associated with increased risk of cardiovascular disease.
No action is needed when a patient is normolipidemic.

✓ Hyperhomocysteinemia - Depression

No Increased Risk of Hyperhomocysteinemia

The patient carries one copy of the MTHFR c.665C>T variant (heterozygous). MTHFR enzyme activity is reduced (60% of normal activity).
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. The patient's small reduction in MTHFR activity is not a risk factor for hyperhomocysteinemia.
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

Increased Risk of Thrombosis

The patient carries one copy (heterozygous) of the F5 c.1601G>A variant (also known as Factor V Leiden) and does not carry the F2 c.*97G>A variant (also known as Factor II 20210G>A).
The patient's risk of thrombosis is 3 to 8 times higher than average (average risk of clotting is about 1 in 1000 for anyone in a year). Other risk factors may have additive effects on thrombotic risk, increasing it further.
Anticoagulation:
Post-VTE patients with a low or moderate bleeding risk: long-term anticoagulation may be considered with periodic reevaluation to assess risks versus benefits.
Asymptomatic individual without a history of thrombosis: a short course of prophylactic anticoagulation may be considered in high-risk settings such as surgery, pregnancy, or prolonged immobilization. Decisions regarding prophylactic anticoagulation should be based on a risk/benefit assessment.

Estrogen-containing contraceptive and hormone replacement therapy:
Women with a positive history of thrombotic events or with an additional thrombotic risk factor: consider avoiding estrogen contraception and hormone replacement therapy.
Women with no history of thrombotic events (asymptomatic): consider informing of the risk of estrogen-containing contraceptives and hormone replacement therapy use; consider alternative forms of contraception and control of menopausal symptoms. These women should avoid additional life-style risk factors (e.g., smoking or obesity, or triggering events such as surgery or travel).
Women electing to use oral contraceptives: consider avoiding third-generation formulations because of their higher thrombotic risk.
Women who require short-term hormone replacement therapy for severe menopausal symptoms: consider low-dose transdermal preparations as they may have a lower thrombotic risk.

✓ Hyperhomocysteinemia - Thrombosis

No Increased Risk of Hyperhomocysteinemia

The patient carries one copy of MTHFR c.665C>T variant (heterozygous). MTHFR enzyme activity is reduced (60% of normal activity).
The patient's small reduction in MTHFR activity is not a risk factor for hyperhomocysteinemia. Unless other risk factors are present, the patient is not expected to have an increased risk for venous thromboembolism (VTE).
The patient's MTHFR activity is slightly reduced.

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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.

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Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Anticancer Agents	Antifolates		Methotrexate (Trexall®)	
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®)	Mexiletine (Mexitil®) Propafenone (Rythmol®)	Flecainide (Tambocor®)
	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®) Carvedilol (Coreg®) Labetalol (Normodyne®, Trandate®) Nebivolol (Bystolic®) Propranolol (Inderal®) Timolol (Timoptic®)		Metoprolol (Lopressor®)
	Diuretics	Torsemide (Demadex®)		
	Statins	Atorvastatin (Lipitor®) Fluvastatin (Lescol®) Lovastatin (Mevacor®, Altoprev®, Advicor®) Pitavastatin (Livalo®) Pravastatin (Pravachol®) Rosuvastatin (Crestor®) Simvastatin (Zocor®)		
	Meglitinides	Nateglinide (Starlix®) Repaglinide (Prandin®, Prandimet®)		

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CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Diabetes	**Sulfonylureas**	Chlorpropamide (Diabinese®) Glimepiride (Amaryl®) Glipizide (Glucotrol®) Glyburide (Micronase®) Tolbutamide (Orinase®)		
Gastrointestinal	**Antiemetics**	Aprepitant (Emend-oral®) Dronabinol (Marinol®) Fosaprepitant (Emend-IV®) Granisetron (Sancuso®, Sustol®) Metoclopramide (Reglan®) Rolapitant (Varubi®)	Dolasetron (Anzemet®) Fosnetupitant / Palonosetron (Akynzeo-IV®) Netupitant / Palonosetron (Akynzeo-oral®) Palonosetron (Aloxi®)	Ondansetron (Zofran®, Zuplenz®)
	Proton Pump Inhibitors	Esomeprazole (Nexium®) Rabeprazole (Aciphex®)	Dexlansoprazole (Dexilant®, Kapidex®) Lansoprazole (Prevacid®) Omeprazole (Prilosec®) Pantoprazole (Protonix®)	
Gaucher Disease	**Endocrine-Metabolic Agents**	Imiglucerase (Cerezyme®) Miglustat (Zavesca®) Taliglucerase alfa (Elelyso®) Velaglucerase alfa (Vpriv®)		Eliglustat (Cerdelga®)
Hematology	**Hemostatic Agents**		Avatrombopag (Doptelet®) Eltrombopag (Promacta®) Lusutrombopag (Mulpleta®)	
Infections	**Antifungals**	Amphotericin B (AmBisome®, Abelcet®) Anidulafungin (Eraxis®) Caspofungin (Cancidas®) Fluconazole (Diflucan®) Isavuconazonium (Cresemba®) Itraconazole (Sporanox®) Micafungin (Mycamine®) Posaconazole (Noxafil®)		Voriconazole (Vfend®)
	Anti-HIV Agents	Dolutegravir (Tivicay®, Triumeq®) Doravirine (Pifeltro®) Efavirenz (Sustiva®) Etravirine (Edurant®) Raltegravir (Isentress®, Dutrebis®) Rilpivirine (Intelence®)		
	Antimalarials	Proguanil (Malarone®)		
	Fibromyalgia Agents	Milnacipran (Savella®)		
	Muscle Relaxants	Cyclobenzaprine (Flexeril®, Amrix®) Metaxalone (Skelaxin®) Methocarbamol (Robaxin®) Tizanidine (Zanaflex®)	Carisoprodol (Soma®)	

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Pain	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®)		
	Opioids	Alfentanil (Alfenta®) Buprenorphine (Butrans®, Buprenex®) Fentanyl (Actiq®) Hydromorphone (Dilaudid®, Exalgo®) Levorphanol (Levo Dromoran®) Meperidine (Demerol®) Methadone (Dolophine®) Morphine (MS Contin®) Oxymorphone (Opana®, Numorphan®) Sufentanil (Sufenta®) Tapentadol (Nucynta®)	Benzhydrocodone (Apadaz®) Dihydrocodeine (Synalgos-DC®) Hydrocodone (Vicodin®) Oxycodone (Percocet®, Oxycontin®)	Codeine (Codeine; Fioricet® with Codeine) Tramadol (Ultram®)
	Antiaddictives	Bupropion (Wellbutrin®, Zyban®, Aplenzin®, Contrave®) Lofexidine (Lucemyra®)		
	Anti-ADHD Agents	Amphetamine (Adderall®, Evekeo®) Clonidine (Kapvay®) Dextroamphetamine (Dexedrine®) Guanfacine (Intuniv®) Lisdexamfetamine (Vyvanse®)	Atomoxetine (Strattera®) Dexmethylphenidate (Focalin®) Methylphenidate (Ritalin®, Aptensio XR®, Concerta®, Metadate ER®, Quillivant ER®)	

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Psychotropic	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®) Phenobarbital (Luminal®) Phenytoin (Dilantin®) Pregabalin (Lyrica®) Primidone (Mysoline®) Rufinamide (Banzel®) Tiagabine (Gabitril®) Topiramate (Topamax®) Valproic Acid (Depakene®) Vigabatrin (Sabril®) Zonisamide (Zonegran®)		
	Antidementia Agents	Galantamine (Razadyne®) Memantine (Namenda®)	Donepezil (Aricept®)	
	Antidepressants	Desvenlafaxine (Pristiq®) Duloxetine (Cymbalta®) Fluoxetine (Prozac®, Sarafem®) Levomilnacipran (Fetzima®) Mirtazapine (Remeron®) Nefazodone (Serzone®) Trazodone (Oleptro®) Vilazodone (Viibryd®) Vortioxetine (Trintellix®)	Amoxapine (Amoxapine®) Fluvoxamine (Luvox®) Maprotiline (Ludiomil®) Protriptyline (Vivactil®) Sertraline (Zoloft®)	Amitriptyline (Elavil®) Citalopram (Celexa®) Clomipramine (Anafranil®) Desipramine (Norpramin®) Doxepin (Silenor®) Escitalopram (Lexapro®) Imipramine (Tofranil®) Nortriptyline (Pamelor®) Paroxetine (Paxil®, Brisdelle®) Trimipramine (Surmontil®) Venlafaxine (Effexor®)

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	Antipsychotics	Aripiprazole (Abilify®, Aristada®) Asenapine (Saphris®) Brexpiprazole (Rexulti®) Cariprazine (Vraylar®) Clozapine (Clozaril®) Fluphenazine (Prolixin®) Iloperidone (Fanapt®) Loxapine (Loxitane®, Adasuve®) Lurasidone (Latuda®) Olanzapine (Zyprexa®) Paliperidone (Invega®) Pimavanserin (Nuplazid®) Pimozide (Orap®) Quetiapine (Seroquel®) Thioridazine (Mellaril®) Thiothixene (Navane®) Trifluoperazine (Stelazine®) Ziprasidone (Geodon®)	Chlorpromazine (Thorazine®) Perphenazine (Trilafon®)	Haloperidol (Haldol®) Risperidone (Risperdal®)
	Benzodiazepines	Alprazolam (Xanax®) Clobazam (Onfi®) Clonazepam (Klonopin®)	Diazepam (Valium®)	
	Other Neurological Agents	Deutetrabenazine (Austedo®) Dextromethorphan / Quinidine (Nuedexta®) Flibanserin (Addyi®) Valbenazine (Ingrezza®)	Tetrabenazine (Xenazine®)	
Rheumatology	Anti-Hyperuricemics and Anti-Gout Agents	Colchicine (Mitigare®) Febuxostat (Uloric®)		
	Immunomodulators	Apremilast (Otezla®) Leflunomide (Arava®) Tofacitinib (Xeljanz®)		
Sjogren's Syndrome	Cholinergic Agonists	Cevimeline (Evoxac®)		
Transplantation	Immunosuppressants	Tacrolimus (Prograf®)		
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®)		

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CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
	Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra®) Sildenafil (Viagra®) Tadalafil (Cialis®) Vardenafil (Levitra®)		

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Dosing Guidance

Amitriptyline
Elavil®

Decreased Amitriptyline Exposure (CYP2D6: Ultra-Rapid Metabolizer) — **ACTIONABLE**

The patient is predicted to be a CYP2D6 ultra-rapid metabolizer which is likely to result in a significantly increased metabolism of amitriptyline to less active compounds and a subsequent decrease in amitriptyline exposure leading to therapy failure.

Psychiatric Conditions: Consider an alternative medication. If Amitriptyline is warranted, consider increasing the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Neuropathic Pain: Consider an alternative medication. If amitriptyline is warranted titrate dose according to the patient's clinical response and tolerability.

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.

Amitriptyline
Elavil®

Decreased Amitriptyline Exposure (CYP2C19: Rapid Metabolizer) — **INFORMATIVE**

The patient's high CYP2C19 activity is likely to result in a significantly increased metabolism of amitriptyline to nortriptyline and a subsequent decrease in amitriptyline exposure leading to therapy failure or increased side effects.

Psychiatric Conditions: Consider an alternative medication. If amitriptyline is warranted, consider therapeutic drug monitoring to guide dose adjustments.

Neuropathic Pain: Consider an alternative medication. If amitriptyline is warranted titrate dose according to the patient's clinical response and tolerability.

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.

Citalopram
Celexa®

Insufficient Response to Citalopram (CYP2C19: Rapid Metabolizer) — **ACTIONABLE**

At standard label-recommended dosage, citalopram plasma concentrations levels are expected to be low which may result in a loss of efficacy. Consider an alternative medication. If citalopram is warranted, consider increasing the dose to a maximum of 150% and titrate based on the clinical response and tolerability.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-34.

Clomipramine
Anafranil®

Decreased Clomipramine Exposure (CYP2D6: Ultra-Rapid Metabolizer) — **INFORMATIVE**

The patient is predicted to be a CYP2D6 ultra-rapid metabolizer which is is likely to result in a significantly increased metabolism of clomipramine to less active compounds and a subsequent decrease in clomipramine exposure leading to therapy failure.

Psychiatric Conditions: Consider an alternative medication. If clomipramine is warranted, consider increasing 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.

Clomipramine
Anafranil®

Decreased Clomipramine Exposure (CYP2C19: Rapid Metabolizer) — **INFORMATIVE**

The patient's high CYP2C19 activity is likely to result in a significantly increased metabolism of clomipramine to desmethyl clomipramine and a subsequent decrease in clomipramine exposure leading to therapy failure or increased side effects.

Psychiatric Conditions: Consider an alternative medication. If clomipramine is warranted, consider 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.

Codeine

Increased Response to Codeine (CYP2D6: Ultra-Rapid Metabolizer) — **ACTIONABLE**

Codeine; Fioricet® with Codeine

Codeine is converted into its active metabolite morphine by CYP2D6. Since this patient is a ultra-rapid metabolizer, greatly increased morphine levels are expected, and the patient is at high risk of toxicity when taking codeine. The ultra-rapid conversion of codeine to morphine in breast feeding mothers can result in high and unsafe levels of morphine in the breast milk potentially causing life threatening respiratory depression in the breastfed infant. Avoid prescribing codeine, and consider an alternative opioid or a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

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.

Desipramine

Norpramin®

Decreased Desipramine Exposure (CYP2D6: Ultra-Rapid Metabolizer) — INFORMATIVE

The patient is predicted to be a CYP2D6 ultra-rapid metabolizer which is likely to result in a significantly increased metabolism of desipramine to less active compounds and a subsequent decrease in desipramine exposure leading to therapy failure.

Psychiatric Conditions: Consider an alternative medication. If desipramine is warranted, consider increasing 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®

Decreased Doxepin Exposure (CYP2D6: Ultra-Rapid Metabolizer) — INFORMATIVE

The patient is predicted to be a CYP2D6 ultra-rapid metabolizer which is likely to result in a significantly increased metabolism of doxepin to less active compounds and a subsequent decrease in doxepin exposure leading to therapy failure.

Psychiatric Conditions: Consider an alternative medication. If doxepin is warranted, consider increasing 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. Monitor patient closely for decreased efficacy.

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®

Decreased Doxepin Exposure (CYP2C19: Rapid Metabolizer) — INFORMATIVE

The patient's high CYP2C19 activity is likely to result in a significantly increased metabolism of doxepin to desmethyl doxepin and a subsequent decrease in doxepin exposure leading to therapy failure or increased side effects.

Psychiatric Conditions: Consider an alternative medication. If doxepin is warranted, consider 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.

Eliglustat

Cerdelga®

Decreased Exposure to Eliglustat (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

The genotype result indicates that the patient is likely to have significantly reduced eliglustat exposure. The patient may not reach adequate concentrations of eliglustat to achieve a therapeutic effect. Consider an alternative medication.

Cerdelga [package insert]. Waterford, Ireland: Genzyme Ireland, Ltd.; 2018.

Escitalopram

Lexapro®

Insufficient Response to Escitalopram (CYP2C19: Rapid Metabolizer) — ACTIONABLE

At standard label-recommended dosage, escitalopram plasma concentrations levels are expected to be low which may result in a loss of efficacy. Consider an alternative medication. If escitalopram is warranted, consider increasing the dose to a maximum of 150% and titrate based on the clinical response and tolerability.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-34.

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Flecainide
Tambocor®

Decreased Exposure to Flecainide (CYP2D6: Ultra-Rapid Metabolizer) — INFORMATIVE

The patient's genotype may be associated with a decreased flecainide exposure following standard dosing. For therapeutic indications, consider titrating carefully and consider adjusting 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 are not required when flecainide is utilized for diagnostic uses.

The Royal Dutch Pharmacists Association of the KNMP. (2019). Pharmacogenetic Recommendations 2019 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf (Accessed August 21, 2019).

Haloperidol
Haldol®

Decreased Exposure to Haloperidol (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

The patient's genotype may be associated with a decreased haloperidol exposure following standard dosing. Consider an alternative medication or prescribe haloperidol at the standard dose and adjust dosage to achieve a favorable clinical response. Be alert to decreased haloperidol exposure.

The Royal Dutch Pharmacists Association of the KNMP. (2019). Pharmacogenetic Recommendations 2019 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf (Accessed August 21, 2019).

Imipramine
Tofranil®

Decreased Imipramine Exposure (CYP2D6: Ultra-Rapid Metabolizer) — INFORMATIVE

The patient is predicted to be a CYP2D6 ultra-rapid metabolizer which is is likely to result in a significantly increased metabolism of imipramine to less active compounds and a subsequent decrease in imipramine exposure leading to therapy failure.

Psychiatric Conditions: Consider an alternative medication. If imipramine is warranted, consider increasing 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.

Imipramine
Tofranil®

Decreased Imipramine Exposure (CYP2C19: Rapid Metabolizer) — INFORMATIVE

The patient's high CYP2C19 activity is likely to result in a significantly increased metabolism of imipramine to desipramine and a subsequent decrease in imipramine exposure leading to therapy failure or increased side effects.

Psychiatric Conditions: Consider an alternative medication. If imipramine is warranted, consider 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.

Metoprolol
Lopressor®

Possible Decreased Exposure to Metoprolol (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

The patient's genotype may be associated with a decreased metoprolol exposure following standard dosing.Consider an alternative beta-blocker such as bisoprolol or carvedilol. If use of metoprolol is warranted, use the maximum dose for the prescribed indication. If response is still not adequate, increase the dose to 250% of the standard dose.

The Royal Dutch Pharmacists Association of the KNMP. (2019). Pharmacogenetic Recommendations 2019 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf (Accessed August 21, 2019).

Nortriptyline
Pamelor®

Decreased Nortriptyline Exposure (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

The patient is predicted to be a CYP2D6 ultra-rapid metabolizer which is likely to result in a significantly increased metabolism of nortriptyline to less active compounds and a subsequent decrease in nortriptyline exposure leading to therapy failure.

Psychiatric Conditions: Consider an alternative medication. If nortriptyline is warranted, consider increasing 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.

Ondansetron
Zofran®, Zuplenz®

Non-Response to Ondansetron (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

A substantially decreased antiemetic effect has been reported in CYP2D6 ultra-rapid metabolizers when taking standard doses of this medication. Consider prescribing an alternative drug not metabolized by CYP2D6 such as granisetron.

Bell GC, Caudle KE, Whirl-Carrillo M, Gordon RJ, Hikino K, Prows CA, Gaedigk A, Agundez J, Sadhasivam S, Klein TE, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther 2017 08;102(2):213-218.

Paroxetine
Paxil®, Brisdelle®

Reduced Response to Paroxetine (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

There is a risk for decreased efficacy at standard dosage. If a standard dose is prescribed to a CYP2D6 ultra-rapid metabolizer, suboptimal plasma concentrations of the drug are likely. Consider an alternative medication.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-34.

Risperidone
Risperdal®

Reduced Exposure to Risperidone (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

The patient's genotype is associated with a decreased risperidone exposure and increased active metabolite (paliperidone) exposure following standard dosing. Consider an alternative medication.

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).

Tramadol
Ultram®

Increased Exposure to Tramadol (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

The patient's genotype may be associated with an increased conversion of tramadol to an active metabolite with higher activity. If an alternative is not available, consider reducing the dose by 60% and monitor for opioid side effects (such as drowsiness, confusion, constipation, nausea and vomiting, respiratory depression or urine retention). Alternatively, try an analgesic not as dependent on CYP2D6 metabolism (fentanyl, morphine, hydromorphone, oxymorphone or tapentadol) or try a non-opioid analgesic such as a NSAID or a COX-2 inhibitor.

Warning: Breastfeeding is not recommended when taking tramadol due to the risk of serious adverse reactions in breastfed infants.

The Royal Dutch Pharmacists Association of the KNMP. (2019). Pharmacogenetic Recommendations 2019 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf (Accessed August 21, 2019).

Trimipramine
Surmontil®

Decreased Trimipramine Exposure (CYP2D6: Ultra-Rapid Metabolizer) — INFORMATIVE

The patient is predicted to be a CYP2D6 ultra-rapid metabolizer which is likely to result in a significantly increased metabolism of trimipramine to less active compounds and a subsequent decrease in trimipramine exposure leading to therapy failure.

Psychiatric Conditions: Consider an alternative medication. If trimipramine is warranted, consider increasing 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.

Trimipramine
Surmontil®

Decreased Trimipramine Exposure (CYP2C19: Rapid Metabolizer) — INFORMATIVE

The patient's high CYP2C19 activity is likely to result in a significantly increased metabolism of trimipramine to desmethyl trimipramine and a subsequent decrease in trimipramine exposure leading to therapy failure or increased side effects.

Psychiatric Conditions: Consider an alternative medication. If trimipramine is warranted, consider 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.

Venlafaxine
Effexor®

Decreased Exposure to Venlafaxine (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

The patient is unlikely to achieve adequate serum levels of venlafaxine and O-desmethylvenlafaxine when taking standard doses of venlafaxine.Consider an alternative medication or consider increasing the venlafaxine dose to a maximum of 150% of the normal dose and adjust the dose based on clinical response 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. (2019). Pharmacogenetic Recommendations 2019 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf (Accessed August 21, 2019).

Voriconazole
Vfend®

Non-Response to Voriconazole (CYP2C19: Rapid Metabolizer) — ACTIONABLE

Voriconazole plasma concentrations are expected to be low if a standard dose is used, increasing the risk of loss of response and effectiveness and subsequent disease progression. Consider an alternative medication that is not dependent on CYP2C19 metabolism, such as isavuconazole, liposomal amphotericin B or posaconazole.

Moriyama B, Obeng AO, Barbarino J, Penzak SR, Henning SA, Scott SA, Agúndez J, Wingard JR, McLeod HL, Klein TE, Cross SJ, Caudle KE, Walsh TJ. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. Clin Pharmacol Ther 2017 07;102(1):45-51.

Amoxapine
Amoxapine®

Possible Decreased Amoxapine Exposure (CYP2D6: Ultra-Rapid 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. Patients with increased CYP2D6 function may metabolize amoxapine more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations. There are no established dosing adjustments for patients with increased 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.

Atomoxetine
Strattera®

Possible Atomoxetine Underexposure Leading to Decreased Response (CYP2D6: Ultra-Rapid Metabolizer) — ACTIONABLE

The genotype result indicates that the patient is likely to have an insufficient response due to inadequate drug exposure following standard dosing. Consider the following dosing strategy:

- Initiate treatment at 40 mg/day, increase to 80 mg/day after 3 days and maintain dose.
- If after 2 weeks, optimal clinical response is not observed and adverse events are not present, consider a dose increase to 100 mg/day.
- If after 2 weeks, optimal clinical response is not observed and adverse events are not present, consider therapeutic drug monitoring 1-2 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.

Avatrombopag
Doptelet®

Increased Risk of Avatrombopag-Induced Thrombosis (F2 rs1799963 GG; F5 rs6025 CT) — ACTIONABLE

The patient carries one copy (heterozygous) of the F5 c.1601G>A variant (also known as Factor V Leiden), which is a known risk factor for thromboembolism. Consider potential increased risk of thrombosis when administering this drug and monitor the patient closely for any signs of thrombosis or thromboembolism.

Dopletet [package insert]. Durham, NC: Dova Pharmaceuticals, Inc.; 2018.

Benzhydrocodone
Apadaz®

Possible Altered Response to Benzhydrocodone (CYP2D6: Ultra-Rapid Metabolizer) — INFORMATIVE

Benzhydrocodone is a prodrug of hydrocodone and is converted to active hydrocodone by intestinal enzymes. Increased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 ultrarapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower doses. Other opioids not metabolized by CYP2D6 (e.g., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if excessive side effects are reported.

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.

Carisoprodol
Soma®

Altered Sensitivity to Carisoprodol (CYP2C19: Rapid Metabolizer) — INFORMATIVE

There is insufficient data to allow calculation of dose adjustment. If carisoprodol is prescribed, it is recommended to use a lower dose, and to carefully monitor the patient for side effects.

Bramness JG, Skurtveit S, Fauske L, Grung M, Molven A, Mørland J, Steen VM. Association between blood carisoprodol:meprobamate concentration ratios and CYP2C19 genotype in carisoprodol-drugged drivers: decreased metabolic capacity in heterozygous CYP2C19*1/CYP2C19*2 subjects? Pharmacogenetics 2003 Jul;13(7):383-8.

Chlorpromazine
Thorazine®

Possible Non-Response to Chlorpromazine (CYP2D6: Ultra-Rapid Metabolizer) — INFORMATIVE

Chlorpromazine is metabolized by CYP2D6, CYP3A4 and flavin-containing monooxygenases. Subjects with increased CYP2D6 function will metabolize chlorpromazine more rapidly which can result in sub-therapeutic drug concentrations. Consider a standard dose and adjust dosage according to the patient's tolerability and response. Higher doses may be necessary to achieve efficacy.

de Leon J, Barnhill J, Rogers T, Boyle J, Chou WH, Wedlund PJ. Pilot study of the cytochrome P450-2D6 genotype in a psychiatric state hospital. Am J Psychiatry 1998 Sep;155(9):1278-80.
Kobylecki CJ, Jakobsen KD, Hansen T, Jakobsen IV, Rasmussen HB, Werge T. CYP2D6 genotype predicts antipsychotic side effects in schizophrenia inpatients: a retrospective matched case-control study. Neuropsychobiology 2009 ;59(4):222-6.

Clopidogrel
Plavix®

Increased Response to Clopidogrel (CYP2C19: Rapid Metabolizer) — ACTIONABLE

Clopidogrel can be prescribed at standard label-recommended dosage. Individuals with the *17 allele may have an increased risk of bleeding while taking clopidogrel.

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.

Dexlansoprazole
Dexilant®, Kapidex®

Slightly Decreased to Normal Exposure to Dexlansoprazole (CYP2C19: Rapid Metabolizer) — INFORMATIVE

The patient's genotype may be associated with a slightly decreased dexlansoprazole exposure following standard dosing. Be alert for insufficient response, consider prescribing dexlansoprazole at standard label-recommended dosage and administration. May consider increasing the recommended dose for certain indications by 50-100% to optimize therapeutic efficacy.

Lima JJ, Thomas CD, Barbarino J, Desta Z, Van Driest SL, El Rouby N, Johnson JA, Cavallari LH, Shakhnovich V, Thacker DL, Scott SA, Schwab M, Uppugunduri CRS, Formea CM, Franciosi JP, Sangkuhl K, Gaedigk A, Klein TE, Gammal RS, Furuta T. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. Clin Pharmacol Ther. 2020 Aug 8.

Dexmethylphenidate
Focalin®

Decreased Response to Dexmethylphenidate (COMT: Intermediate COMT Activity) — INFORMATIVE

The patient's genotype result predicts a less optimal response to dexmethylphenidate. Dosage should be individualized according to the needs and response of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

Cheon KA, Jun JY, Cho DY. Association of the catechol-O-methyltransferase polymorphism with methylphenidate response in a classroom setting in children with attention-deficit hyperactivity disorder. Int Clin Psychopharmacol 2008 Sep;23(5):291-8.
Kereszturi E, Tarnok Z, Bognar E, Lakatos K, Farkas L, Gadoros J, Sasvari-Szekely M, Nemoda Z. Catechol-O-methyltransferase Val158Met polymorphism is associated with methylphenidate response in ADHD children. Am J Med Genet B Neuropsychiatr Genet 2008 Dec;147B(8):1431-5.

Diazepam
Valium®

Possible Altered Sensitivity to Diazepam (CYP2C19: Rapid Metabolizer) — INFORMATIVE

CYP2C19 rapid and ultra-rapid metabolizers metabolize diazepam and nordiazepam more rapidly than normal metabolizers. However, there is insufficient data to allow calculation of dose adjustment when diazepam is prescribed. Monitor the patient's response and adjust the dose accordingly.

Inomata S, Nagashima A, Itagaki F, Homma M, Nishimura M, Osaka Y, Okuyama K, Tanaka E, Nakamura T, Kohda Y, Naito S, Miyabe M, Toyooka H. CYP2C19 genotype affects diazepam pharmacokinetics and emergence from general anesthesia. Clin Pharmacol Ther 2005 Dec;78(6):647-55.
Wan J, Xia H, He N, Lu YQ, Zhou HH. The elimination of diazepam in Chinese subjects is dependent on the mephenytoin oxidation phenotype. Br J Clin Pharmacol 1996 Oct;42(4):471-4.

Dihydrocodeine
Synalgos-DC®

Possible Altered Response to Dihydrocodeine (CYP2D6: Ultra-Rapid Metabolizer) — INFORMATIVE

Increased conversion of dihydrocodeine to the more active metabolite dihydromorphine is expected in CYP2D6 ultra-rapid metabolizers. This may result in an exaggerated response. Adequate pain relief can be achieved by decreasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 (i.e., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if signs of overdose (excessive sleepiness, confusion, or shallow breathing) are reported.

Fromm MF, Hofmann U, Griese EU, Mikus G. Dihydrocodeine: a new opioid substrate for the polymorphic CYP2D6 in humans. Clin Pharmacol Ther 1995 Oct;58 (4):374-82.
Kirkwood LC, Nation RL, Somogyi AA. Characterization of the human cytochrome P450 enzymes involved in the metabolism of dihydrocodeine. Br J Clin Pharmacol 1997 Dec;44(6):549-55.

Dolasetron
Anzemet®

Possible Altered Response to Dolasetron (CYP2D6: Ultra-Rapid Metabolizer) — INFORMATIVE

The reduction of dolasetron to its active metabolite hydrodolasetron is mediated by a carbonyl reductase. Hydrodolasetron is further eliminated by multiple routes, including renal excretion and by glucuronidation or hydroxylation by CYP2D6. Compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower hydroxydolasetron plasma concentrations at standard dosing. However, the clinical significance of this change remains unclear. Dolasetron can be prescribed at standard label-recommended dosage and administration. Monitor the patient for possible decreased efficacy.

Bell GC, Caudle KE, Whirl-Carrillo M, Gordon RJ, Hikino K, Prows CA, Gaedigk A, Agundez J, Sadhasivam S, Klein TE, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther 2017 08;102(2):213-218.
Janicki PK, Schuler HG, Jarzembowski TM, Rossi M. Prevention of postoperative nausea and vomiting with granisetron and dolasetron in relation to CYP2D6 genotype. Anesth Analg 2006 Apr;102(4):1127-33.

Donepezil
Aricept®

Possible Altered Exposure to Donepezil (CYP2D6: Ultra-Rapid Metabolizer) — **INFORMATIVE**

When compared to a normal metabolizer, a ultra-rapid metabolizers has a 24% increase in donepezil clearance. The clinical significance of this increase is not well documented. Consider using a standard dosing regimen and adjust dosage in response to clinical response and tolerability.

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.

Eltrombopag
Promacta®

Increased Risk of Eltrombopag-Induced Thrombosis (F5: Moderate Thrombosis Risk) — **ACTIONABLE**

Venous and arterial thromboses have been reported in adult patients being treated with eltrombopag, more frequently in patients with hepatitis C and chronic liver disease. Other risk factors that can potentially increase the risk of thrombosis include but are not limited to splenectomy, immobilization, surgery, anti-phospholipid antibody syndrome and use of estrogen-containing contraceptives. The presence of the F5 c.1601G>A variant (also known as Factor V Leiden) in this patient represents an additional risk factor for thrombosis. Eltrombopag should be used with caution in this patient with closer monitoring of platelet count.

Wong RS, Bakshi K, Brainsky A. Thrombophilia in patients with chronic immune thrombocytopenia. Scand J Clin Lab Invest 2015 Jan;75(1):13-7.
Promacta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017.

Fluvoxamine
Luvox®

Possible Reduced Response to Fluvoxamine (CYP2D6: Ultra-Rapid Metabolizer) — **INFORMATIVE**

There is insufficient data documenting fluvoxamine exposure for this phenotype. If a standard dose is prescribed to a CYP2D6 ultra-rapid metabolizer, suboptimal plasma concentrations of the drug may occur. An alternative medication not metabolized by CYP2D6 may also be considered.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-34.

Fosnetupitant / Palonosetron
Akynzeo-IV®

Possible Altered Response to Fosnetupitant-Palonosetron (CYP2D6: Ultra-Rapid Metabolizer) — **INFORMATIVE**

Fosnetupitant: Fosnetupitant is converted to netupitant via metabolic hydrolysis. Netupitant is extensively metabolized to three major metabolites (desmethyl, N-oxide and a hydroxy-methyl derivatives). Metabolism is mediated primarily by CYP3A4 and to a lesser extent by CYP2C9 and CYP2D6. No genetically guided drug selection or dosing recommendations are available for this drug. Fosnetupitant can be prescribed at standard label-recommended dosage and administration.

Palonosetron: Palonosetron is eliminated by multiple routes including metabolism. While CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in its metabolism to two inactive metabolites. Compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower palonosetron plasma concentrations at standard dosing. However, the clinical significance of this change remains unclear. Palonosetron can be prescribed at standard label-recommended dosage and administration. Monitor the patient for possible decreased efficacy.

Ho KY, Gan TJ. Pharmacology, pharmacogenetics, and clinical efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. Curr Opin Anaesthesiol 2006 Dec;19(6):606-11.
Bell GC, Caudle KE, Whirl-Carrillo M, Gordon RJ, Hikino K, Prows CA, Gaedigk A, Agundez J, Sadhasivam S, Klein TE, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther 2017 08;102(2):213-218.

Hydrocodone
Vicodin®

Possible Altered Response to Hydrocodone (CYP2D6: Ultra-Rapid Metabolizer) — **INFORMATIVE**

Increased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 ultra-rapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower hydrocodone doses. Other opioids not metabolized by CYP2D6 (e.g., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if excessive side effects are reported.

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.

Lansoprazole

Prevacid®

Slightly Decreased to Normal Exposure to Lansoprazole (CYP2C19: Rapid Metabolizer)

ACTIONABLE

The patient's genotype may be associated with a slightly decreased lansoprazole exposure following standard dosing. Be alert for insufficient response, consider prescribing lansoprazole at standard label-recommended dosage and administration. May consider increasing the recommended dose for certain indications by 50-100% to optimize therapeutic efficacy.

Lima JJ, Thomas CD, Barbarino J, Desta Z, Van Driest SL, El Rouby N, Johnson JA, Cavallari LH, Shakhnovich V, Thacker DL, Scott SA, Schwab M, Uppugunduri CRS, Formea CM, Franciosi JP, Sangkuhl K, Gaedigk A, Klein TE, Gammal RS, Furuta T. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. Clin Pharmacol Ther. 2020 Aug 8.

Lusutrombopag

Mulpleta®

Increased Risk of Lusutrombopag-Induced Thrombosis (F2 rs1799963 GG; F5 rs6025 CT)

ACTIONABLE

The patient carries one copy (heterozygous) of the F5 c.1601G>A variant (also known as Factor V Leiden), which is a known risk factor for thromboembolism. Consider potential increased risk of thrombosis when administering this drug and monitor the patient closely for any signs of thrombosis or thromboembolism.

Mulpleta [package insert]. Florham Park, NJ: Shionogi, Inc.; 2018.

Maprotiline

Ludiomil®

Possible Decreased Maprotiline Exposure (CYP2D6: Ultra-Rapid Metabolizer)

INFORMATIVE

Like other tricyclic and tetracyclic antidepressants, maprotiline is metabolized by CYP2D6 as well as CYP1A2. Patients with increased CYP2D6 function may metabolize maprotiline more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations. **There are no established dosing adjustments for patients with increased CYP2D6 function. Seizures have been associated with the use of maprotiline especially at high doses. Therefore, therapy must be initiated at a standard dose and gradually increased in small increments according to the patient's response.**

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.

Methotrexate

Trexall®

Increased Risk for Methotrexate Toxicity (MTHFR: Reduced MTHFR Activity)

INFORMATIVE

The patient carries one copy of the MTHFR c.665C>T variant resulting in a reduced MTHFR activity. **Malignancy:** Leukemia or lymphoma patients who are treated with methotrexate standard regimens might have an increased likelihood of treatment interruptions due to methotrexate toxicity. Monitor the patient closely for increased side effects and adjust the dose accordingly. Other genetic and clinical factors may also influence the patient's risk for toxicity and response to methotrexate treatment. **Nonmalignant conditions:** a limited number of studies found an association between individuals carrying the MTHFR c.665C>T variant and methotrexate-induced toxicity in rheumatoid arthritis patients. However, there is insufficient data to calculate dose adjustment. Monitor patient closely for increased side effects and adjust the dose accordingly. Other genetic and clinical factors may also influence the patient's risk for toxicity and response to methotrexate treatment.

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.

Methylphenidate

Ritalin®, Aptensio XR®, Concerta®, Metadate ER®, Quillivant ER®

Decreased Response to Methylphenidate (COMT: Intermediate COMT Activity)

INFORMATIVE

The patient's genotype result predicts a less optimal response to methylphenidate. Dosage should be individualized according to the needs and response of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

Cheon KA, Jun JY, Cho DY. Association of the catechol-O-methyltransferase polymorphism with methylphenidate response in a classroom setting in children with attention-deficit hyperactivity disorder. Int Clin Psychopharmacol 2008 Sep;23(5):291-8.

Mexiletine

Altered Response to Mexiletine (CYP2D6: Ultra-Rapid Metabolizer)

INFORMATIVE

Mexitil®

Because mexiletine plasma concentrations may be decreased, consider adjusting dose in response to mexiletine plasma concentration and ECG monitoring, until a favorable response in 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.

Netupitant / Palonosetron

Akynzeo-oral®

Possible Altered Response to Netupitant-Palonosetron (CYP2D6: Ultra-Rapid Metabolizer) — **INFORMATIVE**

Netupitant: Netupitant is extensively metabolized to three major metabolites (desmethyl, N-oxide and a hydroxy-methyl derivatives). Metabolism is mediated primarily by CYP3A4 and to a lesser extent by CYP2C9 and CYP2D6. No genetically guided drug selection or dosing recommendations are available for this drug. Netupitant can be prescribed at standard label-recommended dosage and administration.
Palonosetron: Palonosetron is eliminated by multiple routes including metabolism. While CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in its metabolism to two inactive metabolites. Compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower palonosetron plasma concentrations at standard dosing. However, the clinical significance of this change remains unclear. Palonosetron can be prescribed at standard label-recommended dosage and administration. Monitor the patient for possible decreased efficacy.

Ho KY, Gan TJ. Pharmacology, pharmacogenetics, and clinical efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. Curr Opin Anaesthesiol 2006 Dec;19(6):606-11.

Bell GC, Caudle KE, Whirl-Carrillo M, Gordon RJ, Hikino K, Prows CA, Gaedigk A, Agundez J, Sadhasivam S, Klein TE, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther 2017 08;102(2):213-218.

Omeprazole

Prilosec®

Slightly Decreased to Normal Exposure to Omeprazole (CYP2C19: Rapid Metabolizer) — **ACTIONABLE**

The patient's genotype may be associated with a slightly decreased omeprazole exposure following standard dosing. Be alert for insufficient response, consider prescribing omeprazole at standard label-recommended dosage and administration. May consider increasing the recommended dose for certain indications by 50-100% to optimize therapeutic efficacy.

Lima JJ, Thomas CD, Barbarino J, Desta Z, Van Driest SL, El Rouby N, Johnson JA, Cavallari LH, Shakhnovich V, Thacker DL, Scott SA, Schwab M, Uppugunduri CRS, Formea CM, Franciosi JP, Sangkuhl K, Gaedigk A, Klein TE, Gammal RS, Furuta T. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. Clin Pharmacol Ther. 2020 Aug 8.

Oxycodone

Percocet®, Oxycontin®

Possible Altered Response to Oxycodone (CYP2D6: Ultra-Rapid Metabolizer) — **ACTIONABLE**

Increased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 ultra-rapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower oxycodone doses. Other opioids not metabolized by CYP2D6 (e.g., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if excessive side effects are reported.

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.

Palonosetron

Aloxi®

Possible Altered Response to Palonosetron (CYP2D6: Ultra-Rapid Metabolizer) — **INFORMATIVE**

Palonosetron is eliminated by multiple routes including metabolism. While CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in its metabolism to two inactive metabolites. Compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower palonosetron plasma concentrations at standard dosing. However, the clinical significance of this change remains unclear. Palonosetron can be prescribed at standard label-recommended dosage and administration. Monitor the patient for possible decreased efficacy.

Ho KY, Gan TJ. Pharmacology, pharmacogenetics, and clinical efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. Curr Opin Anaesthesiol 2006 Dec;19(6):606-11.

Bell GC, Caudle KE, Whirl-Carrillo M, Gordon RJ, Hikino K, Prows CA, Gaedigk A, Agundez J, Sadhasivam S, Klein TE, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther 2017 08;102(2):213-218.

Pantoprazole

Protonix®

Slightly Decreased to Normal Exposure to Pantoprazole (CYP2C19: Rapid Metabolizer) — **ACTIONABLE**

The patient's genotype may be associated with a slightly decreased pantoprazole exposure following standard dosing. Be alert for insufficient response, consider prescribing pantoprazole at standard label-recommended dosage and administration. May consider increasing the recommended dose for certain indications by 50-100% to optimize therapeutic efficacy.

Lima JJ, Thomas CD, Barbarino J, Desta Z, Van Driest SL, El Rouby N, Johnson JA, Cavallari LH, Shakhnovich V, Thacker DL, Scott SA, Schwab M, Uppugunduri CRS, Formea CM, Franciosi JP, Sangkuhl K, Gaedigk A, Klein TE, Gammal RS, Furuta T. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. Clin Pharmacol Ther. 2020 Aug 8.

Perphenazine
Trilafon®

Possible Non-Response to Perphenazine (CYP2D6: Ultra-Rapid Metabolizer)

INFORMATIVE

Subjects with increased CYP2D6 function will metabolize perphenazine more rapidly, which can result in sub-therapeutic drug concentrations. Consider a dose increase with close monitoring until a favorable response is achieved.

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®

Decreased Exposure to Propafenone (CYP2D6: Ultra-Rapid Metabolizer)

ACTIONABLE

The patient's genotype may be associated with a decreased 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.

The Royal Dutch Pharmacists Association of the KNMP. (2019). Pharmacogenetic Recommendations 2019 [PDF file]. Retrieved from https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2019.pdf (Accessed August 21, 2019).
Rythmol [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2018.
Rythmol SR [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2018.

Protriptyline
Vivactil®

Possible Decreased Protriptyline Exposure (CYP2D6: Ultra-Rapid Metabolizer)

INFORMATIVE

Like other tricyclic and tetracyclic antidepressants, protriptyline is metabolized by CYP2D6. Patients with increased CYP2D6 function may metabolize protriptyline more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations. There are no established dosing adjustments for patients with increased CYP2D6 function. Therefore, therapy must be initiated at a standard dose and gradually increased in small increments according to the patient's response.

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

Sertraline
Zoloft®

Possible Reduced Response to Sertraline (CYP2C19: Rapid Metabolizer)

INFORMATIVE

Sertraline can be prescribed at standard label-recommended dosage and administration. If patient does not respond to recommended maintenance dosing, consider an alternative medication.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, . Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015 Aug;98(2):127-34.

Tetrabenazine
Xenazine®

Unknown Sensitivity to Tetrabenazine (CYP2D6: Ultra-Rapid Metabolizer)

ACTIONABLE

For treating chorea associated with Huntington's disease: There is insufficient data to calculate dose adjustment, and if tetrabenazine is prescribed, 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 ultra-rapid metabolizers is not defined. The maximum daily dose in normal metabolizers 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.

VIKORSCIENTIFIC

PATIENT INFORMATION

NAME:
ACC #:
DOB: 6/9/1936
SEX: female

Test Details

Gene	Genotype	Phenotype	Alleles Tested
Apolipoprotein E	ε3/ε3	**Normal APOE function**	ε2, ε4, (ε3 is reference)
COMT	Val158Met A/G	**Intermediate COMT Activity**	Val158Met
CYP1A2	*1A/*1A	**Normal Metabolizer- Possible Inducibility**	*1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W
CYP2B6	*1/*1	**Normal Metabolizer**	*5, *7, *16, *18, *22
CYP2C19	*1/*17	**Rapid Metabolizer**	*2, *3, *4A, *4B, *5, *6, *7, *8, *9, *10, *17
CYP2C9	*1/*1	**Normal Metabolizer**	*2, *3, *4, *5, *6, *11
CYP2D6	*1/*2 XN	**Ultra-Rapid Metabolizer**	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *114, *14, *17, *29, *41, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1/*1	**Normal Metabolizer**	*2, *3, *12, *17, *22
CYP3A5	*3/*3	**Poor Metabolizer**	*2, *3, *6, *7, *8, *9
F2 **F5**	rs1799963 GG rs6025 CT	**Increased Risk of Thrombosis**	rs1799963, rs6025
MTHFR	c.665C>T GA	**Reduced MTHFR Activity**	c.1286A>C, c.665C>T
MTHFR	c.1286A>C TT c.665C>T GA	**No Increased Risk of Hyperhomocysteinemia**	c.1286A>C, c.665C>T
SLCO1B1	521T>C T/T	**Normal Function**	521T>C
VKORC1	-1639G>A G/G	**Low 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.

This CYP2B6 laboratory developed test does not interrogate the high-frequency 516G>T variant (rs3745274), which is known to confer a loss of enzyme function and is widely considered the most clinically-relevant variant. Therefore, the predictive value is considered low for this test and results for CYP2B6 are not suitable for clinical implementation.

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: Vikor Scientific, LLC developed the Genotype test. The performance characteristics of this test were determined by Vikor Scientific, LLC. 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.

Approved by John Kevin Day, Ph.D., HCLD(ABB)

Electronically Signed By: Varsha Meghnani on 3/7/2021 10:30:46 PM GMT

VIKORSCIENTIFIC

PATIENT INFORMATION

NAME:
ACC #:
DOB: 6/9/1936
SEX: female

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.

VIKORSCIENTIFIC

REPORT DETAILS

Name:
DOB: 6/9/1936
ACC #: P2215

Pharmacogenetic Test Summary

Apolipoprotein E	ε3/ε3	Normal APOE function
COMT	Val158Met A/G	Intermediate COMT Activity
CYP1A2	*1A/*1A	Normal Metabolizer- Possible Inducibility
CYP2B6	*1/*1	Normal Metabolizer
CYP2C19	*1/*17	Rapid Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*1/*2 XN	Ultra-Rapid Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
Factor II	rs1799963 GG	Normal Thrombosis Risk
Factor V Leiden	rs6025 CT	Moderate Thrombosis Risk
MTHFR	c.665C>T GA	Reduced MTHFR Activity
MTHFR	c.1286A>C TT	Normal MTHFR Activity
SLCO1B1	521T>C T/T	Normal Function
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity

For a complete report contact Vikor Scientific
www.vikorscientific.com

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This report, associated with order #, has been approved by the following reviewers:

Report Reviewer:

Electronically signed and dated on 03-08-2021 10:07
Hans Kershaw