Clarity
Max Rx™ Test

PATIENT INFORMATION		SPECIMEN DETAILS		PROVIDER INFORMATION	
NAME:	**Test**	**COLLECTION DATE:**	2/12/2022	Andrew Sakla	
ACC #:	22045000035	**RECEIVED DATE:**	2/14/2022	**SPECIMEN TYPE:**	Extracted DNA
DOB:	3/5/1992	**REPORT DATE:**	2/25/2022		
SEX:	Male				

ClarityX Pharmacogenomics Comprehensive Report: MaxRx

⊗ A medication has potentially reduced efficacy, increased toxicity or the patient has an increased risk for the indicated condition.

⚠ 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.

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.

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.

Current Patient Medications

✓ Clopidogrel
Plavix®

Normal Response to Clopidogrel (CYP2C19: Normal Metabolizer) — ACTIONABLE

Clopidogrel can be prescribed at standard label-recommended dosage.

⚠ 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).

✓ Celecoxib
Celebrex®

Normal Celecoxib Exposure (CYP2C9: Intermediate Metabolizer) — ACTIONABLE

Celecoxib therapy can be initiated at standard label-recommended dosage and administration.

Patients with other risk factors such as hepatic impairment or advanced age are more likely to experience toxicities. Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when celecoxib is administered with CYP2C9 inhibitors or inducers.

Osteoarthritis, Rheumatoid Arthritis, Ankylosing Spondylitis, Acute Pain, Primary Dysmenorrhea: Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Acute Migraine: Consider using for the fewest number of days per month, as needed.

Osteoarthritis and Hypertension (co-formulation with amlodipine): Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

⊗ 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.

⚠ Tramadol
Ultram®

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

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.

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Risk Management

⚠ 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 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 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.

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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 and carries one copy of the MTHFR c.1286A>C variant (heterozygous). MTHFR enzyme activity is reduced (80% of normal activity).
Based on results for the MTHFR c.1286A>C variant, the patient has slightly reduced MTHFR activity, which is not a risk factor for hyperhomocysteinemia. 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.
The patient's MTHFR activity is slightly reduced.

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Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Antihistamines	**Histamine (H1) Receptor Antagonists**		Meclizine (Antivert®)	
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	Clopidogrel (Plavix®) Prasugrel (Effient®) Ticagrelor (Brilinta®) Vorapaxar (Zontivity®)		
	Beta Blockers	Atenolol (Tenormin®) Bisoprolol (Zebeta®) Carvedilol (Coreg®) Labetalol (Normodyne®, Trandate®) Nebivolol (Bystolic®) Propranolol (Inderal®)	Metoprolol (Lopressor®) Timolol (Blocadren®)	
	Diuretics	Torsemide (Demadex®)		
	Statins	Atorvastatin (Lipitor®) Lovastatin (Mevacor®, Altoprev®, Advicor®) Pitavastatin (Livalo®) Pravastatin (Pravachol®) Rosuvastatin (Crestor®) Simvastatin (Zocor®)	Fluvastatin (Lescol®)	

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Diabetes	Meglitinides	Nateglinide (Starlix®) Repaglinide (Prandin®, Prandimet®)		
	Sulfonylureas	Chlorpropamide (Diabinese®) Glimepiride (Amaryl®) Glipizide (Glucotrol®) Glyburide (Micronase®) Tolbutamide (Orinase®)		
Gastrointestinal	Antiemetics	Aprepitant (Emend-oral®) Dolasetron (Anzemet®) Fosaprepitant (Emend-IV®) Fosnetupitant / Palonosetron (Akynzeo-IV®) Granisetron (Sancuso®, Sustol®) Netupitant / Palonosetron (Akynzeo -oral®) Ondansetron (Zofran®, Zuplenz®) Palonosetron (Aloxi®) Rolapitant (Varubi®)	Dronabinol (Marinol®) Metoclopramide (Reglan®)	
	Proton Pump Inhibitors	Esomeprazole (Nexium®) Rabeprazole (Aciphex®)	Dexlansoprazole (Dexilant®, Kapidex®) Lansoprazole (Prevacid®) Omeprazole (Prilosec®) Pantoprazole (Protonix®)	
Gynecology	Endometriosis Pain Agents	Elagolix (Orilissa®)		
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®) Lornoxicam (Xefo®) Meloxicam (Mobic®) Nabumetone (Relafen®) Naproxen (Aleve®) Piroxicam (Feldene®) Sulindac (Clinoril®)		

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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®) Methadone (Dolophine®) Morphine (MS Contin®) Oliceridine (Olinvyk) Oxycodone (Percocet®, Oxycontin®) Oxymorphone (Opana®, Numorphan®) Sufentanil (Sufenta®) Tapentadol (Nucynta®)	Benzhydrocodone (Apadaz®) Codeine (Codeine; Fioricet® with Codeine) Hydrocodone (Vicodin®) Tramadol (Ultram®)	
	Antiaddictives	Lofexidine (Lucemyra®)	Bupropion (Wellbutrin®, Zyban®, Aplenzin®, Contrave®) Naltrexone (Vivitrol®, Contrave®)	
	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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CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
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®) Stiripentol (Diacomit®) Tiagabine (Gabitril®) Topiramate (Topamax®) Valproic Acid (Depakene®) Vigabatrin (Sabril®) Zonisamide (Zonegran®)		
	Antidementia Agents	Donepezil (Aricept®) Galantamine (Razadyne®) Memantine (Namenda®)		
	Antidepressants	Citalopram (Celexa®) 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®) Clomipramine (Anafranil®) Desipramine (Norpramin®) Doxepin (Silenor®) Imipramine (Tofranil®) Maprotiline (Ludiomil®) Nortriptyline (Pamelor®) Protriptyline (Vivactil®) Trimipramine (Surmontil®)	Venlafaxine (Effexor®)

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CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
	Antipsychotics	Aripiprazole (Abilify®, Aristada®) Asenapine (Saphris®) Brexpiprazole (Rexulti®) Cariprazine (Vraylar®) Chlorpromazine (Thorazine®) Cyamemazine (Tercian®) Flupenthixol (Depixol®, Fluanxol®) Fluphenazine (Prolixin®) Haloperidol (Haldol®) Loxapine (Loxitane®, Adasuve®) Lurasidone (Latuda®) Paliperidone (Invega®) Periciazine (Neuleptil®, Zentiva®) Pimavanserin (Nuplazid®) Pimozide (Orap®) Quetiapine (Seroquel®) Risperidone (Risperdal®) Thiothixene (Navane®) Trifluoperazine (Stelazine®) Ziprasidone (Geodon®)	Clozapine (Clozaril®) Iloperidone (Fanapt®) Olanzapine (Zyprexa®) Perphenazine (Trilafon®) Zuclopenthixol (Clopixol®)	Thioridazine (Mellaril®)
	Benzodiazepines	Alprazolam (Xanax®) Clobazam (Onfi®) Clonazepam (Klonopin®) Diazepam (Valium®)		
	Other Neurological Agents	Deutetrabenazine (Austedo®) Dextromethorphan / Quinidine (Nuedexta®) Flibanserin (Addyi®) Valbenazine (Ingrezza®)	Tetrabenazine (Xenazine®)	
Sleep Disorder Agents	**Narcoleptic Agents**	Pitolisant (Wakix®)		

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Dosing Guidance

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; CYP2C19: Normal Metabolizer)

ACTIONABLE

The patient's reduced CYP2D6 activity 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 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 starting 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.

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.

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.

Atomoxetine

Strattera®

Possible Atomoxetine Underexposure Leading to Decreased Response (CYP2D6: Intermediate 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.

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

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.

Clomipramine

Anafranil®

Increased Clomipramine Exposure (CYP2D6: Intermediate Metabolizer; CYP2C19: Normal Metabolizer) — INFORMATIVE

The patient's reduced CYP2D6 activity 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.

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®

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

Smokers have a high 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 will 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.

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.

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.

PATIENT INFORMATION

NAME: **Test ACC #:**
22045000033 **DOB:**
3/5/1990 **SEX:**
Male

Dexlansoprazole

Dexilant®, Kapidex®

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

The patient's genotype is predictive of normal metabolism but may be associated with a slightly decreased dexlansoprazole clinical 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.

Doxepin

Silenor®

Increased Doxepin Exposure (CYP2D6: Intermediate Metabolizer; CYP2C19: Normal Metabolizer) — INFORMATIVE

The patient's reduced CYP2D6 activity 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.

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.

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.

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).

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.

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.

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.

Imipramine

Tofranil®

Increased Imipramine Exposure (CYP2D6: Intermediate Metabolizer; CYP2C19: Normal Metabolizer) — INFORMATIVE

The patient's reduced CYP2D6 activity 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.

Imipramine

Increased Imipramine Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

Tofranil®

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.

Lansoprazole

Prevacid®

Normal or Possible Slightly Decreased Exposure to Lansoprazole (CYP2C19: Normal Metabolizer) ACTIONABLE

The patient's genotype is predictive of normal metabolism but may be associated with a slightly decreased lansoprazole clinical 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.

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.

Meclizine

Antivert®

Increased Exposure to Meclizine (CYP2D6: Intermediate Metabolizer) ACTIONABLE

Genetic polymorphism of CYP2D6 could contribute to large inter-individual variability in meclizine exposure. Meclizine can be prescribed at standard label-recommended dosage and administration. Consider increased monitoring for adverse effects.

- FDA Table of Pharmacogenetic Associations
- Antivert [package insert]. East Brunswick, NJ: Casper Pharma LLC; 2019.

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.

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.

Metoprolol

Lopressor®

Increased Exposure to Metoprolol (CYP2D6: Intermediate Metabolizer) ACTIONABLE

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

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.

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.

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.

Olanzapine

Zyprexa®

Non-Response to Olanzapine (CYP1A2: Normal Metabolizer - Higher 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.

Omeprazole

Prilosec®

Normal or Possible Slightly Decreased Exposure to Omeprazole (CYP2C19: Normal Metabolizer) — ACTIONABLE

The patient's genotype is predictive of normal metabolism but may be associated with a slightly decreased omeprazole clinical 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.

Pantoprazole

Protonix®

Normal or Possible Slightly Decreased Exposure to Pantoprazole (CYP2C19: Normal Metabolizer)

ACTIONABLE

The patient's genotype is predictive of normal metabolism but may be associated with a slightly decreased pantoprazole clinical 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 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).

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.

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

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.

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.

Tizanidine

Zanaflex®

Possible Non-Response to Tizanidine (CYP1A2: Normal Metabolizer - Higher 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

Ultram®

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

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; CYP2C19: Normal Metabolizer) — **INFORMATIVE**

The patient's reduced CYP2D6 activity 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.

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

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.

Zuclopenthixol
Clopixol®

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

The patient's genotype may be associated with an increased zuclopenthixol exposure following standard dosing. Consider a 25% dose reduction or consider an alternative medication. Examples of alternative medications include flupenthixol, clozapine, olanzapine or quetiapine.

- 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).

Alfentanil
Alfenta®

Normal Response to Alfentanil — INFORMATIVE

Pharmacogenetic guidance: alfentanil is primarily metabolized by CYP3A4 and CYP3A5. Studies in healthy subjects showed that CYP3A5 genotype had no effect on the systemic or apparent oral clearances, or pharmacodynamics of alfentanil. **Polypharmacy guidance:** Alfentanil should be used with caution when prescribed to patients taking CYP3A4 inhibitors or inducers.

- Alfenta [package insert]. Lake Forest, IL: Akorn, Inc.; 2016.

Alprazolam
Xanax®

Normal Response to Alprazolam — INFORMATIVE

Pharmacogenetic guidance: Alprazolam is primarily eliminated by metabolism via CYP3A4 and CYP3A5. Genetic polymorphisms of these genes are not expected to affect the efficacy or safety profiles of this drug. **Polypharmacy guidance:** The concomitant use of alprazolam with CYP3A4 inhibitors may result in increased alprazolam levels and prolonged sedation. Impairment of motor skills are also observed with some combinations. Monitor patients for exaggerated sedative effects. If possible, alprazolam should be avoided in patients receiving strong inhibitors of CYP3A4 such as ketoconazole, itraconazole and ritonavir. Drugs that induce CYP3A enzymes may decrease alprazolam levels, which results in a loss of efficacy.

- Xanax [package insert]. New York, NY: Pfizer Inc.; 2011.

Amiodarone
Nexterone®, Pacerone®

Normal Exposure to Amiodarone — INFORMATIVE

Pharmacogenetic guidance: Amiodarone is metabolized to N-desethylamiodarone. This process is mediated primarily by CYP3A. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of amiodarone with drugs that are, a strong inducer or inhibitor of CYP3A may affect drug plasma levels. In addition, co-administration of amiodarone with drugs known to prolong QT interval can precipitate drug induced long QT syndrome.

- Nexterone [package insert]. Deerfield, IL: Baxter Healthcare Corporation; 2016.
- 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).

Amphetamine
Adderall®, Evekeo®

Normal Exposure to Amphetamine (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

Amphetamine can be prescribed at standard label-recommended dosage and administration. Individualize the dosage according to the therapeutic needs and response of the patient.

- Adderall XR [package insert]. Lexington, MA: Takeda Pharmaceutical Company Limited.; 2019.
- Adzenys ER [package insert]. Grand Prairie, TX: Neos Therapeutics, Inc.; 2017.
- Evekeo ODT [package insert]. Atlanta, GA: Arbor Pharmaceuticals, LLC; 2019.

Amphetamine
Adderall®, Evekeo®

Good Response to Amphetamine salts (COMT: Intermediate COMT Activity)

INFORMATIVE

The patient's genotype result predicts a favorable response to amphetamine stimulants. Amphetamines should be administered at the lowest effective dose, and dosage should be individually adjusted.

- Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A 2003 May;100(10):6186-91.
- Hamidovic A, Dlugos A, Palmer AA, de Wit H. Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. Psychiatr Genet 2010 Jun;20(3):85-92.

Apixaban
Eliquis®

Normal Response to Apixaban

INFORMATIVE

Pharmacogenetic guidance: Apixaban is not extensively metabolized and only ~20% of the dose is metabolized primarily by CYP3A4 and CYP3A5, with minor contributions from CYP1A2 and CYP2J2. This drug is a substrate for the efflux transport proteins P-gp (ABCB1) and BCRP (ABCG2). While these enzymes and transporters are polymorphic, genetic variations are unlikely to have a clinically significant impact on apixaban exposure, and no genotype-based dosing adjustments are recommended. **Polypharmacy guidance:** Exposure to apixaban increases by 100% when co-administered with ketoconazole, a strong CYP3A/P-gp inhibitor. This translates into an increased bleeding risk (70% increase). Hence, for patients receiving 5 mg twice daily, apixaban dose should be decreased to 2.5 mg twice daily when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, and clarithromycin). In patients already taking 2.5 mg twice daily, coadministration of apixaban with strong dual inhibitors of CYP3A4 and P-gp should be avoided. No dose adjustment is recommended when co-administered with moderate inhibitors. Co-administration with rifampin, a strong CYP3A/P-gp inducer, results in halving of exposure to apixaban. There is no clinical experience at these reduced exposures. Hence, concomitant administration of strong CYP3A/P-gp inducers should be avoided.

- Eliquis [package insert]. Princeton, NJ: Bristol-Myers Squibb Pharma Company; 2014.

Aprepitant
Emend-oral®

Normal Response to Aprepitant

ACTIONABLE

Pharmacogenetic guidance: Aprepitant undergoes extensive metabolism via N- and O-dealkylations. These pathways are primarily catalyzed by CYP3A4 with minor involvement from CYP1A2 and CYP2C19. The drug is also glucuronidated by UGT1A4 and UGT1A3. No genetically guided drug selection or dosing recommendations are available.
Polypharmacy Guidance: In presence of moderate and strong CYP3A4 inhibitors, a significantly increased exposure of aprepitant is expected which may lead to adverse reactions. These drugs should be avoided with aprepitant. Strong CYP3A4 inducers can significantly decrease aprepitant exposure resulting in a loss of efficacy. These drugs should also be avoided with aprepitant. Aprepitant is a moderate (dose-dependent) inhibitor, and an inducer of CYP3A4 and an inducer of CYP2C9. Some substrates of these enzymes are contraindicated with aprepitant while others should be closely monitored and their doing adjusted when coadministered with this antiemetic medication.

- Emend (Oral) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2015.

Aripiprazole
Abilify®, Aristada®

Normal Exposure to Aripiprazole (CYP2D6: Intermediate Metabolizer)

ACTIONABLE

The patient's genotype is associated with slightly increased aripiprazole exposure. Consider prescribing aripiprazole at standard label-recommended dosage and administration. Careful titration is recommended until a favorable response is achieved.

Daily dosing (oral): the daily maintenance and maximum recommended doses are 10-15 mg and 30 mg, respectively. Reduce dose by 50% if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered. Reduce the dose to 25% of the usual dose if both a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor are co-administered. Double the dose if a strong CYP3A4 inducer is co-administered.

Single dosing (intramuscular): consider one single injection of 675 mg of *Aristada Initio* when initiating treatment with *Aristada*. Avoid using *Aristada Initio* if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor or a strong CYP3A4 inducer is co-administered.

Monthly dosing (intramuscular): the starting and maintenance monthly recommended dose is 400 mg for *Abilify Maintena* or 441 mg, 662 mg and 882 mg for *Aristada*. For *Abilify Maintena*, reduce the monthly dose to 300 mg if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered to patients receiving aripiprazole at 400 mg, and reduce dose to 200 mg in patients receiving aripiprazole at 300 mg. For *Aristada*. reduce the dose to the next lower strength if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered for more than 14 days. For *Abilify Maintena*, reduce the dose to 200 mg if both a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor are co-administered to patients receiving aripiprazole at 400 mg, and reduce the dose to 160 mg in patients receiving aripiprazole at 300 mg. For *Aristada*. avoid use for patients at 662 mg or 882 mg dose if both a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor are co-administered. No dosage adjustment is necessary in patients taking 441 mg *Aristada*. if tolerated. If a strong CYP3A4 inducer is co-administered for more than 14 days, avoid using *Abilify Maintena*. For *Aristada*. if a strong CYP3A4 inducer is co-administered for more than 14 days, increase the 441 mg dose to 662 mg; no dose adjustment is necessary for 662 mg and 882 mg doses.

Every 6 weeks or two months dosing with *Aristada* (intramuscular): depending on individual patient's needs, treatment may be initiated with the 882 mg dose every 6 weeks or 1064 mg dose every two months. Reduce the dose to a lower strength: 441 mg every 4 weeks if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered for more than 14 days. Reduce the dose to a lower strength: 441 mg every 4 weeks if a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor are both co-administered for more than 14 days. If a strong CYP3A4 inducer is co-administered for more than 14 days, no dose adjustment is necessary for the 662 mg, 882 mg or 1064 mg doses, whereas 441 mg dose should be increased to 662 mg.

- Abilify Maintena [package insert]. Tokyo, Japan: Otsuka America Pharmaceutical, Inc.; 2017.
- Aristada [package insert]. Waltham, MA: Alkermes; 2018.
- Aristada Initio [package insert]. Waltham, MA: Alkermes; 2018.
- Abilify [package insert]. Tokyo, Japan: Otsuka America Pharmaceutical, Inc.; 2019.

✓ Asenapine

Saphris®

Normal Response to Asenapine

INFORMATIVE

Pharmacogenetic Guidance: Asenapine is extensively metabolized to more than 38 inactive metabolites. The primary metabolism route occurs via direct glucuronidation catalyzed by UGT1A4. Also important but less pronounced is the demethylation pathway as well as the oxidative reactions catalyzed by CYP1A2 with contributions from CYP3A4 and CYP2D6. There are no studies documenting the effect of genetic polymorphisms of these metabolizing enzymes on asenapine disposition and there are no available genetically guided drug selection or dosing recommendations. Asenapine should be prescribed based on the clinical response and tolerability of the individual patient. **Polypharmacy guidance:** Coadministration of asenapine with CYP1A2 inhibitors such as fluvoxamine should be approached with caution as asenapine plasma concentrations will increase resulting in more side effects. Cigarette smoking, which induces CYP1A2 activity, has a limited effect on asenapine plasma concentrations. Asenapine is a weak inhibitor of CYP2D6 and its coadministration with paroxetine (both a substrate and an inhibitor of CYP2D6) should be approached with caution. Long-term therapy with strong enzyme inducers (e.g. carbamazepine, phenytoin, rifampin) may decrease asenapine exposure and dosage adjustment may be needed.

- Saphris [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2014.

✓ Atenolol

Normal Response to Atenolol

INFORMATIVE

Tenormin®

Pharmacogenetic guidance: The bioavailability of atenolol is approximately 40–50% and renal excretion eliminates approximately 90% of the absorbed drug in its unchanged form. A negligible amount of the drug is metabolized. Atenolol is a substrate of several organic anion and cation transporters including SLC22A1, SLC22A2, SLC47A1, and SLC47A2. No genetically-guided drug selection or dosing recommendations are available.

- Tenormin [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2012.

Atorvastatin

Lipitor®

Normal Myopathy Risk (SLCO1B1: Normal Function) — ACTIONABLE

The patient's genotype is associated with normal SLCO1B1 function which results in normal atorvastatin plasma concentrations. Consider prescribing atorvastatin at standard FDA-recommended starting doses and adjust based on disease-specific guidelines.

- 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).

Atorvastatin

Lipitor®

Normal Response to Atorvastatin (CYP3A4: Normal Metabolizer) — INFORMATIVE

The genotype result indicates that the patient does not carry the CYP3A4*22 allele (this allele is associated with a decreased CYP3A4 enzyme activity). The patient is expected to achieve an optimal lipid control goal with standard atorvastatin dose requirements.

- Wang D, Guo Y, Wrighton SA, Cooke GE, Sadee W. Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. Pharmacogenomics J 2011 Aug;11(4):274-86.

Azilsartan

Edarbi®, Edarbyclor®

Normal Azilsartan Exposure (CYP2C9: Intermediate Metabolizer) — INFORMATIVE

Azilsartan medoxomil is hydrolyzed to azilsartan, its active metabolite, in the gastrointestinal tract during absorption. Azilsartan is further metabolized to inactive metabolites by CYP2C9. Consider standard label-recommended dosage and administration.

- De Caterina AR, Harper AR, Cuculi F. Critical evaluation of the efficacy and tolerability of azilsartan. Vasc Health Risk Manag 2012 ;8():299-305.

Betrixaban

Bevyxxa®

Normal Response to Betrixaban — ACTIONABLE

Pharmacogenetic guidance: The predominant metabolic pathway of betrixaban is amide hydrolysis with minor cytochrome P450 enzymes-based metabolism (less than 1% of the drug is metabolized by CYP1A1, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). The main elimination pathway of the drugs is biliary excretion followed by urinary excretion. Betrixaban is a substrate for the efflux transport protein P-gp (ABCB1) and while this transporter is polymorphic, genetic variations are unlikely to have a clinically significant impact on betrixaban exposure, and no genotype-based dosing adjustments are available. **Polypharmacy guidance:** Concomitant use with P-gp inhibitors such as amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin results in increased plasma levels of betrixaban and increased risk of bleeding. Dosing reduction and close monitoring are recommended in presence of P-gp inhibitors.

- Bevyxxa [package insert]. South San Francisco, CA: Portola Pharmaceuticals, Inc; 2017.

Bisoprolol

Zebeta®

Normal Response to Bisoprolol — INFORMATIVE

Pharmacogenetic guidance: Bisoprolol is eliminated by renal and non-renal pathways with 50% of the total dose being metabolized in the liver and 50% being excreted via the kidneys unchanged. Bisoprolol is predominantly metabolized by CYP3A4 with smaller contribution from CYP2D6. Limited studies suggest that bisoprolol plasma concentrations and its beta-adrenergic inhibition are not affected by CYP2D6 genetic variability. No genetically-guided drug selection or dosing recommendations are available.

- Zebeta [package insert]. Pomona, NY: Barr Pharmaceuticals, Inc.; 2011.

Brexpiprazole

Rexulti®

Slightly Increased Exposure to Brexpiprazole (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype may be associated with a slightly increased brexpiprazole exposure following standard dosing. Consider prescribing brexpiprazole at standard label-recommended dosage and administration. Careful titration is recommended until a favorable response is achieved.

Adjunctive Treatment of Major Depression Disorder: the recommended starting doses are 0.5 mg or 1 mg once daily. The daily maintenance doses and maximum recommended dose are 1-2 mg and 3 mg, respectively.

Schizophrenia: the recommended starting dose is 1 mg once daily. The daily maintenance doses and maximum recommended dose are 2-4 mg and 4 mg, respectively.

Dose adjustments with co-medications: reduce dose by 50% if a strong CYP2D6 inhibitor or a strong CYP3A4 inhibitor is co-administered. Administer a quarter of the usual dose if both a strong/moderate CYP2D6 inhibitor and a strong/moderate CYP3A4 inhibitor are co-administered. Double the usual dose over 1 to 2 weeks if a strong CYP3A4 inducer is co-administered.

- Rexulti [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; 2018.

✓ Brivaracetam

Briviact®

Normal Sensitivity to Brivaracetam (CYP2C19: Normal Metabolizer)

ACTIONABLE

Brivaracetam is primarily metabolized by hydrolysis and to a minor extent by hydroxylation, which is mediated by CYP2C19. Brivaracetam can be prescribed at the standard label recommended dosage.

- Stockis A, Watanabe S, Rouits E, Matsuguma K, Irie S. Brivaracetam single and multiple rising oral dose study in healthy Japanese participants: influence of CYP2C19 genotype. Drug Metab Pharmacokinet 2014 ;29(5):394-9.
- Briviact [package insert]. Smyrna, GA: UCB, Inc.; 2016.

✓ Buprenorphine

Butrans®, Buprenex®

Normal Response to Buprenorphine

INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. Buprenorphine is primarily metabolized by CYP3A4 to norbuprenorphine and by UGT enzymes (mainly UGT1A1 and 2B7). The effects of genetic variants in these enzymes on its response have not been studied. **Polypharmacy guidance:** The concomitant use of buprenorphine with all CYP3A4 inhibitors may result in an increase in the drug levels, which could increase or prolong adverse drug effects. Monitor patients receiving buprenorphine with a CYP3A4 inhibitor. CYP and UGT inducers may decrease buprenorphine levels.

- Butrans [package insert]. Stamford, CT: Purdue Pharma L.P.; 2014.

✓ Candesartan

Atacand®

Normal Sensitivity to Candesartan Cilexetil

ACTIONABLE

Pharmacogenetic guidance: Candesartan cilexetil is hydrolyzed to candesartan its active metabolite in the gastrointestinal tract during absorption. Candesartan undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. Genetic variability of the cytochrome P450 genes is not expected to affect the patient's response to candesartan cilexetil. No genotype-based dosing adjustments are available.

- Atacand [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2016.

✓ Cannabidiol

Epidiolex®

Normal Response to Cannabidiol

INFORMATIVE

Pharmacogenetic guidance: Cannabidiol is metabolized to oxidative metabolites by CYP3A4 and CYP2C19 and by direct glucuronidation. There are insufficient studies documenting the impact of genetic polymorphisms of these metabolizing enzymes on cannabidiol response. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Enzyme-inducing drugs increase cannabidiol clearance significantly, and careful titration is recommended when the drug is prescribed with enzyme-inducing-antiepileptic drugs. Coadministration of CYP3A4 inhibitors increase cannabidiol exposure by 2-fold, and a dose reduction should be considered in presence of CYP3A inhibitors.

- Jiang R, Yamaori S, Takeda S, Yamamoto I, Watanabe K. Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes. Life Sci 2011 Aug;89(5-6):165-70.
- Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc; 2018.

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

✓ Carbamazepine

Tegretol®, Carbatrol®, Epitol®

Normal Response to Carbamazepine

INFORMATIVE

Pharmacogenetic guidance: Genotype results obtained from the pharmacogenetic test performed in this patient cannot be used to identify patients at risk for severe cutaneous adverse reactions such as anticonvulsant hypersensitivity syndrome, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Carbamazepine, a drug with a narrow therapeutic window, is extensively metabolized by CYP3A4/5 to its active epoxide metabolite, which is further metabolized by epoxide hydrolase (EPHX1) to an inactive metabolite. Preliminary studies indicate that carbamazepine plasma concentrations are 30% higher in individuals with the CYP3A5*3/*3 genotype compared to those with CYP3A5*1/*1 or *1/*3 genotypes. The clinical impact of this change is poorly documented. **Polypharmacy guidance:** The dosage of carbamazepine should be decreased in patients receiving CYP3A4 inhibitors. Enzyme-inducing drugs significantly decrease carbamazepine levels, and dose adjustments are recommended when the drug is used with other inducers.

- Tegretol [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.

✓ Cariprazine

Vraylar®

Normal Response to Cariprazine

ACTIONABLE

Pharmacogenetic guidance: Cariprazine is extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6. Genetic variants of CYP2D6 do not have clinically relevant effect on pharmacokinetics of cariprazine and its metabolites. No geneticallly guided dosing recommendations are available. **Polypharmacy guidance:** CYP3A4 inhibitors or inducers may affect cariprazine plasma concentrations. Cariprazine dose may have to be reduced to half if cariprazine and a strong CYP3A4 inhibitor are used concomitantly. Concomitant use of Cariprazine and a CYP3A4 inducer has not been evaluated and is not recommended.

- Vraylar [package insert]. Parsippany, NJ: Actavis, Inc.; 2015.

✓ Carisoprodol

Soma®

Normal Sensitivity to Carisoprodol (CYP2C19: Normal Metabolizer)

INFORMATIVE

Carisoprodol can be prescribed at standard label-recommended dosage and administration.

- 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.

✓ Carvedilol

Coreg®

Normal Exposure to Carvedilol (CYP2D6: Intermediate Metabolizer)

INFORMATIVE

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

- Coreg [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2017.

✓ Celecoxib

Celebrex®

Normal Celecoxib Exposure (CYP2C9: Intermediate Metabolizer)

ACTIONABLE

Celecoxib therapy can be initiated at standard label-recommended dosage and administration.

Patients with other risk factors such as hepatic impairment or advanced age are more likely to experience toxicities. Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when celecoxib is administered with CYP2C9 inhibitors or inducers.

Osteoarthritis, Rheumatoid Arthritis, Ankylosing Spondylitis, Acute Pain, Primary Dysmenorrhea: Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Acute Migraine: Consider using for the fewest number of days per month, as needed.

Osteoarthritis and Hypertension (co-formulation with amlodipine): Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

Chlorpromazine
Thorazine®

Normal Sensitivity to Chlorpromazine (CYP2D6: Intermediate Metabolizer) — **INFORMATIVE**

Chlorpromazine is metabolized by CYP2D6, CYP3A4 and flavin-containing monooxygenases. This drug can be prescribed at standard label recommended-dosage and administration. Careful titration is recommended until a favorable response is achieved.

- 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.

Chlorpropamide
Diabinese®

Normal Exposure to Chlorpropamide — **INFORMATIVE**

Pharmacogenetic guidance: Chlorpropamide is metabolized mainly by CYP2C9 and to a lesser extent by CYP2C19. While this clearance pathway is diminished in subjects with reduced CYP2C9 activity, such a change has not been shown to be clinically significant. No genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: Co-administration of chlorpropamide with a strong CYP2C9 and/or CYP2C19 inhibitors may result in higher chlorpropamide concentrations possibly leading to hypoglycemia. Co-administration with a strong CYP2C9 and/or CYP2C19 inducers may result in lower chlorpropamide concentrations and a lack of efficacy.

- Shon JH, Yoon YR, Kim MJ, Kim KA, Lim YC, Liu KH, Shin DH, Lee CH, Cha IJ, Shin JG. Chlorpropamide 2-hydroxylation is catalysed by CYP2C9 and CYP2C19 in vitro: chlorpropamide disposition is influenced by CYP2C9, but not by CYP2C19 genetic polymorphism. Br J Clin Pharmacol 2005 May;59(5):552-63.

Citalopram
Celexa®

Normal sensitivity to Citalopram (CYP2C19: Normal Metabolizer) — **ACTIONABLE**

Citalopram can be prescribed at standard label-recommended dosage and administration.

- 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.

Clobazam
Onfi®

Normal Sensitivity to Clobazam (CYP2C19: Normal Metabolizer) — **ACTIONABLE**

Clobazam can be prescribed at standard label-recommended dosage and administration. Individualize dosing within each body weight group, based on clinical efficacy and tolerability. Do not proceed with dose escalation more rapidly than weekly, because serum concentrations of clobazam and its active metabolite require 5 and 9 days, respectively, to reach steady state. Recommended daily dosing: ≤30 kg body weight: starting dose 5 mg; day 7: 10 mg and day 14: 20 mg; >30 kg body weight: starting dose 10 mg, day 7: 20 mg and day 14: 40 mg.

- 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.

Clonazepam
Klonopin®

Normal Response to Clonazepam — **INFORMATIVE**

Pharmacogenetic guidance: No genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: clonazepam is extensively metabolized by CYP3A4 to an amino metabolite that is further acetylated by N-acetyltransferases. This drug should be used with caution when prescribed with CYP3A4 inhibitors or inducers.

- Klonopin [package insert]. San Francisco, CA: Genentech USA, Inc.; 2016.

Clonidine
Kapvay®

Normal Exposure to Clonidine — **INFORMATIVE**

Pharmacogenetic guidance: Clonidine is metabolized by CYP2D6 along with CYP3A4 and CYP1A2. About 40-60% of the dose is excreted in urine as unchanged drug. Preliminary studies indicate that individuals lacking CYP2D6 activity, have increased clonidine exposure compared to subjects with normal CYP2D6 activity. The clinical relevance of this changed is not well understood and there is insufficient data to calculate dose adjustments. Other preliminary studies indicate that individuals with high CYP2D6 activity (pregnant women), have decreased clonidine exposure and may require higher doses to reach target therapeutic plasma concentrations and respond to therapy. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of clonidine with inhibitors of CYP2D6 or CYP3A4 may cause an increase in clonidine plasma concentrations while the co-administration with CYP3A4 inducers may cause a decrease in clonidine plasma concentrations. Caution should be used when co-administering drugs that can affect renal function.

- Claessens AJ, Risler LJ, Eyal S, Shen DD, Easterling TR, Hebert MF. CYP2D6 mediates 4-hydroxylation of clonidine in vitro: implication for pregnancy-induced changes in clonidine clearance. Drug Metab Dispos 2010 Sep;38(9):1393-6.
- Buchanan ML, Easterling TR, Carr DB, Shen DD, Risler LJ, Nelson WL, Mattison DR, Hebert MF. Clonidine pharmacokinetics in pregnancy. Drug Metab Dispos 2009 Apr;37(4):702-5.
- 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).

Clopidogrel

Plavix®

Normal Response to Clopidogrel (CYP2C19: Normal Metabolizer)

ACTIONABLE

Clopidogrel can be prescribed at standard label-recommended dosage.

- 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.

Cyamemazine

Tercian®

Normal Response to Cyamemazine

INFORMATIVE

Pharmacogenetic guidance: Cyamemazine undergoes extensive hepatic metabolism. The main routes of biotransformation are N-mono-demethylation which is catalyzed by CYP1A2, CYP3A4 and CYP2C8 and mono-oxidation by CYP1A2 and CYP2C9. The involvement of several CYP enzymes in the metabolism of this drug suggest that it is unlikely that genetic polymorphisms in these enzymes will affect its exposure. There are no genotype-based dosing recommendations. **Polypharmacy guidance:** Cyamemazine should not be used with dopaminergics or with QT-prolongating medications.

- Arbus C, Benyamina A, Llorca PM, Baylé F, Bromet N, Massiere F, Garay RP, Hameg A. Characterization of human cytochrome P450 enzymes involved in the metabolism of cyamemazine. Eur J Pharm Sci 2007 Dec;32(4-5):357-66.
- Vandel S, Bertschy G, Baumann P, Bouquet S, Bonin B, Francois T, Sechter D, Bizouard P. Fluvoxamine and fluoxetine: interaction studies with amitriptyline, clomipramine and neuroleptics in phenotyped patients. Pharmacol Res 1995 Jun;31(6):347-53.

Cyclobenzaprine

Flexeril®, Amrix®

Normal Response to Cyclobenzaprine

INFORMATIVE

Pharmacogenetic guidance: No genetically guided drug selection or dosing recommendations are available. Cyclobenzaprine is excreted primarily as a glucuronide via the kidneys, and as an N-demethylated metabolite by CYP3A4, CYP1A2, and to a lesser extent CYP2D6. Due to the minor involvement of CYP2D6 in the metabolism of cyclobenzaprine, the polymorphism of this enzyme is not of concern in its the clinical use.

- Flexeril [package insert]. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceutical, Inc.; 2013.

Dabigatran Etexilate

Pradaxa®

Normal Response to Dabigatran

INFORMATIVE

Pharmacogenetic guidance: Dabigatran is eliminated primarily unchanged by the kidneys. After oral administration, dabigatran etexilate is converted to its active form dabigatran by esterases. A small portion (20%) of dabigatran dose is also conjugated to form pharmacologically active acyl glucuronides. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran etexilate is a substrate of the efflux transporter P-gp (ABCB1). Common genetic polymorphism of the ABCB1 gene (2677G>T/A and 3435 C>T) do not appear to affect dabigatran exposure.
Polypharmacy guidance: *1-Reduction in Risk of Stroke and Systemic Embolism in Non-valvular AF*: In patients with moderate renal impairment (CrCl 30-50 mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole can be expected to produce dabigatran exposure similar to that observed in severe renal impairment. Consider reducing the dose of dabigatran to 75 mg twice daily. Dose adjustment is not necessary when coadministered with other P-gp inhibitors. In patients with CrCl<30 mL/min, avoid use of concomitant P-gp inhibitors with dabigatran. *2-Treatment of DVT and PE Reduction in the Risk of Recurrence of DVT and PE*: Avoid use of concomitant P-gp inhibitors with dabigatran in patients with CrCl <50 mL/min.

- Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2014.

Desvenlafaxine
Pristiq®

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

Desvenlafaxine can be prescribed at standard label-recommended dosage and administration.

- Pristiq [package insert]. New York, NY: Pfizer Inc.; 2013.

Deutetrabenazine
Austedo®

Normal Sensitivity to Deutetrabenazine (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 6 mg once daily followed by a slow titration at weekly intervals by 6 mg per day based on tolerability and up to a maximum recommended daily dosage of 48 mg (24 mg twice daily).

- Austedo [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2017.

Dextroamphetamine
Dexedrine®

Normal Exposure to Dextroamphetamine (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

Dextroamphetamine can be prescribed at standard label-recommended dosage and administration. Individualize the dosage according to the therapeutic needs and response of the patient.

- Bach MV, Coutts RT, Baker GB. Involvement of CYP2D6 in the in vitro metabolism of amphetamine, two N-alkylamphetamines and their 4-methoxylated derivatives. Xenobiotica 1999 Jul;29(7):719-32.

Dextroamphetamine
Dexedrine®

Good Response to Dextroamphetamine (COMT: Intermediate COMT Activity) — INFORMATIVE

The patient's genotype result predicts a favorable response to amphetamine stimulants. Dextroamphetamine should be administered at the lowest effective dose, and dosage should be individually adjusted.

- Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A 2003 May;100(10):6186-91.

Dextromethorphan / Quinidine
Nuedexta®

Normal Sensitivity to Dextromethorphan-Quinidine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

Patients with Pseudobulbar Affect: quinidine is a specific inhibitor of CYP2D6-dependent oxidative metabolism used in the dextromethorphan-quinidine combination to increase the systemic bioavailability of dextromethorphan. Dextromethorphan-quinidine can be prescribed according to standard label-recommended dosage and administration.

- Nuedexta [package insert]. Aliso Viejo, CA: Avanir Pharmaceuticals, Inc.; 2015.

Diazepam
Valium®

Normal Sensitivity to Diazepam (CYP2C19: Normal Metabolizer) — INFORMATIVE

Diazepam can be prescribed at standard label-recommended dosage and administration.

- 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.

Diclofenac

Voltaren®

Normal Diclofenac Exposure

INFORMATIVE

Pharmacogenetic guidance: Diclofenac is extensively metabolized by hydroxylation and direct glucuronidation. About 50% of diclofenac is eliminated as a 4-hydroxymetabolite, a reaction mediated by CYP2C9. Other CYP enzymes including CYP2C8, CYP2C19 and CYP3A4 are also involved in the formation of a 5-hydroxymetabolite. A substantial portion of the drug is also directly glucuronidated by UGT2B7 and UGT2B4. Genetic polymorphisms of CYP2C9 have not been found to affect the response to diclofenac. No dosing recommendations or genetically guided drug selection are recommended. **Polypharmacy guidance**: Co-administration of diclofenac with CYP2C9 inhibitors may enhance the drug exposure and toxicity of whereas co-administration with CYP2C9 inducers may lead to compromised efficacy of diclofenac. A dosage adjustment may be warranted when diclofenac is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.
- Voltaren [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.

Dihydrocodeine

Synalgos-DC®

Normal Response to Dihydrocodeine (CYP2D6: Intermediate Metabolizer)

INFORMATIVE

Decreased conversion of dihydrocodeine to the more active metabolite dihydromorphine is possible in CYP2D6 intermediate metabolizers. However, there is insufficient evidence whether these patients have decreased analgesia when taking dihydrocodeine. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms.

- 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.

Disopyramide

Norpace®

Normal Exposure to Disopyramide

INFORMATIVE

Pharmacogenetic guidance: Disopyramide is metabolized mainly by CYP3A4 and to a lesser extent by CYP2D6. About 50% of the dose is excreted in urine as unchanged disopyramide and 30% as metabolites. Genetic polymorphisms of CYP2D6 have not been found to affect patient response to disopyramide. No genetically guided drug selection or dosing adjustments are recommended. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of disopyramide with inhibitors of CYP3A4 may cause an increase in disopyramide plasma concentrations, which could result in a fatal interaction. Co-administration with CYP3A4 inducers may cause a decrease in disopyramide plasma concentrations. Caution should be used when co-administering drugs that can affect renal function.

- DISOPYRAMIDE PHOSPHATE- disopyramide phosphate capsule [package insert]. Parsippany, NJ: Actavis Pharma, Inc. https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=355411. Rev Oct 2015.
- 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).

Dolasetron

Anzemet®

Normal Response to Dolasetron (CYP2D6: Intermediate Metabolizer)

INFORMATIVE

Dolasetron can be prescribed at standard label-recommended dosage and administration.

- 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®

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.

Duloxetine
Cymbalta®

Normal Exposure to Duloxetine

ACTIONABLE

Pharmacogenetic guidance: Duloxetine is primarily metabolized by CYP1A2 and to a lesser extent by CYP2D6. While these clearance pathways are diminished in subjects with reduced enzyme activity, these changes have not been shown to be clinically significant. No genetically guided drug selection or dosing recommendations are recommended.
Polypharmacy guidance: Co-administration of duloxetine with a CYP1A2 inhibitor should be avoided. Co-administration of duloxetine with CYP2D6 inhibitors may result in higher duloxetine concentrations. Duloxetine is a moderate inhibitor of CYP2D6.

- Cymbalta [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.
- Drizalma Sprinkle [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2019.
- 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).

Edoxaban
Savaysa®

Normal Response to Edoxaban

INFORMATIVE

Pharmacogenetic guidance: Edoxaban is eliminated primarily as unchanged drug in urine. There is minimal metabolism via hydrolysis (mediated by carboxylesterase 1; CES1), conjugation, and oxidation by CYP3A4. Edoxaban is a substrate of the efflux transporter P-gp and its active metabolite (formed by CES1) is a substrate of the uptake transporter SLCO1B1. Studies indicate that the two common variants SLCO1B1 rs4149056 and ABCB1 rs1045642 do not affect the exposure to edoxaban or its active metabolite. There are no genotype-based dosing recommendations.
Polypharmacy guidance: Avoid the concomitant use of edoxaban with rifampin. No dose reduction is recommended for concomitant P-gp inhibitor use.

- Savaysa [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc.; 2015.

Elagolix
Orilissa®

Normal Elagolix Exposure (SLCO1B1: Normal Function)

ACTIONABLE

Elagolix can be prescribed at standard label-recommended dosage and administration.

- Orilissa [package insert]. North Chicago, IL: AbbVie Inc.; 2019.

Eprosartan
Teveten®

Normal Sensitivity to Eprosartan

ACTIONABLE

Pharmacogenetic guidance: Eprosartan is eliminated by biliary and renal excretion, primarily as unchanged compound. Eprosartan is not metabolized by the cytochrome P450 enzymes. Genetic variability of the cytochrome P450 genes is not expected to affect the patient's response to eprosartan. No genotype-based dosing adjustments are available.

- Teveten [package insert]. North Chicago, IL: AbbVie Inc.; 2014.

Escitalopram
Lexapro®

Normal Sensitivity to Escitalopram (CYP2C19: Normal Metabolizer)

ACTIONABLE

Escitalopram can be prescribed at standard label-recommended dosage and administration.

- 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.

Eslicarbazepine
Aptiom®

Normal Response to Eslicarbazepine

INFORMATIVE

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

Pharmacogenetic guidance: Genotype results obtained from the pharmacogenetic test performed in this patient cannot be used to identify patients at risk for severe cutaneous adverse reactions such as anticonvulsant hypersensitivity syndrome, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Eslicarbazepine acetate (prodrug) is converted by a reductase to its active metabolite, eslicarbazepine. Eslicarbazepine is eliminated primarily by renal excretion unchanged and as a glucuronide conjugate. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** In the presence of enzyme-inducing drugs, eslicarbazepine plasma levels are significantly decreased, and higher doses of the drug may be needed.

- Aptiom [package insert]. Marlborough, MA: Sunovion Pharmaceuticals Inc.; 2015.
- Zebinix [EPAR Product Information]. Mamede do Coronado, Portugal: BIAL - Portela & Ca, S.A.; First Published 2009.

Esomeprazole
Nexium®

Normal Exposure to Esomeprazole (CYP2C19: Normal Metabolizer) — INFORMATIVE

The patient's genotype may be associated with a normal esomeprazole exposure following standard dosing. Consider prescribing esomeprazole at standard label-recommended dosage and administration.

- 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.

Ethosuximide
Zarontin®

Normal Response to Ethosuximide — INFORMATIVE

Pharmacogenetic guidance: No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** ethosuximide is extensively metabolized by CYP3A4, and therefore this drug should be used with caution when prescribed with CYP3A4 inhibitors. Inducers of CYP3A4 increase ethosuximide clearance, and higher doses may be needed when the drug is coadministered with enzyme-inducing drugs.

- Zarontin [package insert]. New York, NY: Pfizer Inc.; 2012.

Ezogabine
Potiga®

Normal Response to Ezogabine — INFORMATIVE

Pharmacogenetic guidance: although NAT2 rapid acetylators have a 30% increase in the exposure of ezogabine active metabolite, no dose adjustment is necessary in these individuals. **Polypharmacy guidance:** Ezogabine is extensively metabolized primarily via glucuronidation (by UGT1A4 and UGT1A1) and acetylation (by NAT2). There is no evidence of oxidative metabolism of ezogabine by cytochrome P450 enzymes, and genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. Enzyme-inducing drugs such as carbamazepine and phenytoin increase ezogabine clearance by 30%, and dose increase should be considered when this drug is coadministered with enzyme-inducing antiepileptic drugs.

- Potiga [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2016.

Felbamate
Felbatol®

Normal Response to Felbamate — INFORMATIVE

Pharmacogenetic guidance: No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** About 40-50% of absorbed felbamate dose appears unchanged in urine, and an additional 50% is present as metabolites and conjugates. Felbamate is a substrate of CYP3A4 and CYP2E1, but these pathways are minor for drug elimination when the drug is given as a monotherapy. This pathway is enhanced by concomitant use of enzyme-inducing antiepileptic drugs, which results in a 30-50% decrease in felbamate plasma concentrations. Felbamate should be titrated slowly, and dose adjustment must be considered in presence of inducers.

- Felbatol [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc.; 2012.

Fentanyl
Actiq®

Good Response to Fentanyl (OPRM1: Normal OPRM1 Function) — INFORMATIVE

The patient does not carry the OPRM1 118A>G variant. Acute postoperative and cancer pain: the patient is expected to experience good analgesia at standard fentanyl doses. Because fentanyl has a narrow therapeutic window, it is advised to carefully titrate this drug to a tolerable dose that provides adequate analgesia with minimal side effects.

- Zhang F, Liao Q, Li L, Wang SY, Hu R, Tang YZ, Ouyang W. The correlation between post-operative fentanyl requirements and μ-opioid receptor gene A118G polymorphism in patients undergoing radical gastrectomy. Exp Ther Med 2013 Apr;5(4):1147-1152.
- Landau R, Liu SK, Blouin JL, Carvalho B. The effect of OPRM1 and COMT genotypes on the analgesic response to intravenous fentanyl labor analgesia. Anesth Analg 2013 Feb;116(2):386-91.
- Khalil H, Sereika SM, Dai F, Alexander S, Conley Y, Gruen G, Meng L, Siska P, Tarkin I, Henker R. OPRM1 and COMT Gene-Gene Interaction Is Associated With Postoperative Pain and Opioid Consumption After Orthopedic Trauma. Biol Res Nurs 2017 03;19(2):170-179.
- Hwang IC, Park JY, Myung SK, Ahn HY, Fukuda K, Liao Q. OPRM1 A118G gene variant and postoperative opioid requirement: a systematic review and meta-analysis. Anesthesiology 2014 Oct;121(4):825-34.

Flibanserin

Addyi®

Normal Exposure to Flibanserin (CYP2C19: Normal Metabolizer)

ACTIONABLE

For treating premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD): Flibanserin is primarily metabolized by CYP3A4 and, to a lesser extent, by CYP2C19. The genotype results predict that the patient is expected to have a normal clearance and a typical exposure to flibanserin. Use label-recommended dosage and follow standard precautions.

- Addyi [package insert]. Raleigh, NC: Sprout Pharmaceuticals, Inc.; 2019.

Fluoxetine

Prozac®, Sarafem®

Normal Sensitivity to Fluoxetine (CYP2D6: Intermediate Metabolizer)

INFORMATIVE

Fluoxetine is metabolized to its active metabolite norfluoxetine and to other metabolites by multiple enzymes including CYP2D6, CYP2C19, CYP2C9, and CYP3A4. Fluoxetine can be prescribed at standard label-recommended dosage and administration.

- 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.

Flupenthixol

Depixol®, Fluanxol®

Normal Response to Flupenthixol

ACTIONABLE

Pharmacogenetic guidance: Flupenthixol is metabolized via sulphoxidation, N-dealkylation and glucuronic acid conjugation. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy Guidance:** Flupenthixol may increase QT interval and therefore co-administration of other drugs known to significantly increase the QT interval should be avoided.

- Fluanxol Tablets [Summary of Product Characteristics]. St. Albans, England: Lundbeck Limited; First Published 1982.

Fluphenazine

Prolixin®

Normal Exposure to Fluphenazine

INFORMATIVE

Pharmacogenetic guidance: Fluphenazine is metabolized by CYP2D6, CYP2C19, CYP3A4 and other enzymes. Genetic polymorphisms of CYP2D6 have not been found to affect patient response to fluphenazine. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of fluphenazine with inhibitors of CYP3A4 may cause an increase in fluphenazine plasma concentrations while the co-administration with CYP3A4 inducers may cause a decrease in fluphenazine plasma concentrations. The co-administration of fluphenazine with a potent inhibitor of CYP2D6 (e.g. fluoxetine) did not increase fluphenazine exposure to a clinically relevant extent.

- Fluphenazine Decanoate [package insert]. Schaumburg, IL: APP Pharmaceuticals LLC; 2010.
- 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).

Flurbiprofen

Ansaid®

Normal Flurbiprofen Exposure (CYP2C9: Intermediate Metabolizer)

ACTIONABLE

Rheumatoid Arthritis and Osteoarthritis: Flurbiprofen therapy can be initiated at standard label-recommended dosage and administration. Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when flurbiprofen is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.

PATIENT INFORMATION

NAME: **Test ACC #:**
22045000033 **DOB:**
3/5/1990 **SEX:**
Male

Fluvoxamine
Luvox®

Normal Sensitivity to Fluvoxamine (CYP2D6: Intermediate Metabolizer) — **ACTIONABLE**

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

- 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.

Fondaparinux
Arixtra®

Normal Response to Fondaparinux — **INFORMATIVE**

Pharmacogenetic guidance: Fondaparinux is eliminated unchanged through renal excretion and is not metabolized by CYPs, and therefore genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** The concomitant use of fondaparinux with aspirin or NSAIDS may enhance the risk of hemorrhage. Discontinue agents that may enhance the risk of hemorrhage prior to initiation of therapy with fondaparinux unless essential. If co-administration is necessary, monitor patients closely for hemorrhage.

- Arixtra [package insert]. Notre Dame de Bondeville, France: Aspen NDB; 2014.

Fosaprepitant
Emend-IV®

Normal Response to Fosaprepitant — **ACTIONABLE**

Pharmacogenetic guidance: Fosaprepitant is a prodrug of aprepitant which is rapidly converted to aprepitant following intravenous administration. Its antiemetic effects are attributable to aprepitant. Aprepitant undergoes extensive metabolism via N- and O-dealkylations. These pathways are primarily catalyzed by CYP3A4 with minor involvement from CYP1A2 and CYP2C19. The drug is also glucuronidated by UGT1A4 and UGT1A3. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy Guidance:** In presence of moderate and strong CYP3A4 inhibitors, a significantly increased exposure of aprepitant is expected which may lead to adverse reactions. These drugs should be avoided with fosaprepitant. Strong CYP3A4 inducers can significantly decrease aprepitant exposure resulting in a loss of efficacy. These drugs should also be avoided with fosaprepitant. Aprepitant is a moderate (dose-dependent) inhibitor, and an inducer of CYP3A4 and an inducer of CYP2C9. Some substrates of these enzymes are contraindicated with fosaprepitant while others should be closely monitored and their doing adjusted when coadministered with this antiemetic medication.

- Emend (I.V.) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2016.

Fosnetupitant / Palonosetron
Akynzeo-IV®

Normal Response to Fosnetupitant-Palonosetron (CYP2D6: Intermediate 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 can be prescribed at standard label-recommended dosage and administration.

- 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.

Fosphenytoin
Cerebyx®

Normal Phenytoin (Fosphenytoin Active Metabolite) Exposure (CYP2C9: Intermediate Metabolizer) — **ACTIONABLE**

Fosphenytoin is a prodrug of phenytoin. The genotype results indicate that the patient is expected to have a slightly reduced CYP2C9 enzyme activity. Fosphenytoin can be prescribed at a standard loading dose and a standard maintenance dose. Consider therapeutic drug monitoring and evaluate the patient's response to optimize the maintenance dosage.

- Karnes JH, Rettie AE, Somogyi AA, Huddart R, Fohner AE, Formea CM, Ta Michael Lee M, Llerena A, Whirl-Carrillo M, Klein TE, Phillips EJ, Mintzer S, Gaedigk A, Caudle KE, Callaghan JT. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. Clin Pharmacol Ther 2021 Feb;109(2):302-309.

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

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.

Galantamine
Razadyne®

Normal Sensitivity to Galantamine (CYP2D6: Intermediate Metabolizer)
INFORMATIVE

Galantamine can be prescribed at standard label-recommended dosage and administration. Individualization of dose with weekly titration is recommended.

- Noetzli M, Guidi M, Ebbing K, Eyer S, Zumbach S, Giannakopoulos P, von Gunten A, Csajka C, Eap CB. Relationship of CYP2D6, CYP3A, POR, and ABCB1 genotypes with galantamine plasma concentrations. Ther Drug Monit 2013 Apr;35(2):270-5.
- Clarke JA, Cutler M, Gong I, Schwarz UI, Freeman D, Dasgupta M. Cytochrome P450 2D6 phenotyping in an elderly population with dementia and response to galantamine in dementia: a pilot study. Am J Geriatr Pharmacother 2011 Aug;9(4):224-33.
- Razadyne [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2020.

Glimepiride
Amaryl®

Normal Exposure to Glimepiride
ACTIONABLE

Pharmacogenetic guidance: Glimepiride is metabolized by CYP2C9. While this clearance pathway is diminished in subjects with reduced CYP2C9 activity, such a change has not been shown to be clinically significant. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of glimepiride with a strong CYP2C9 inhibitor may result in higher glimepiride concentrations possibly leading to hypoglycemia. Co-administration with a strong CYP2C9 inducer may result in lower glimepiride concentrations and a lack of efficacy.

- 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).

Glipizide
Glucotrol®

Normal Exposure to Glipizide
INFORMATIVE

Pharmacogenetic guidance: Glipizide is metabolized by CYP2C9. While this clearance pathway is diminished in subjects with reduced CYP2C9 activity, such a change has not been shown to be clinically significant. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: Co-administration of glipizide with a strong CYP2C9 inhibitor may result in higher glipizide concentrations possibly leading to hypoglycemia. Co-administration with a strong CYP2C9 inducer may result in lower glipizide concentrations and a lack of efficacy.

- Klen J, Dolžan V, Janež A. CYP2C9, KCNJ11 and ABCC8 polymorphisms and the response to sulphonylurea treatment in type 2 diabetes patients. Eur J Clin Pharmacol 2014 Apr;70(4):421-8.
- Zhou K, Donnelly L, Burch L, Tavendale R, Doney AS, Leese G, Hattersley AT, McCarthy MI, Morris AD, Lang CC, Palmer CN, Pearson ER. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther 2010 Jan;87(1):52-6.

Glyburide
Micronase®

Normal Exposure to Glyburide
ACTIONABLE

Pharmacogenetic guidance: Glyburide is partially metabolized by CYP2C9 and to a lesser extent by CYP3A4. While these clearance pathways are diminished in subjects with reduced enzyme activity, these changes have not been shown to be clinically significant. No genetically guided drug selection or dosing recommendations are recommended. **Polypharmacy guidance**: Co-administration of glyburide with strong CYP2C9 and/or CYP3A4 inhibitors may result in higher glyburide concentrations, leading to possible hypoglycemia. Co-administration with strong CYP2C9 and/or CYP3A4 inducers may result in lower glyburide concentrations and a lack of efficacy.

- Swen JJ, Wessels JA, Krabben A, Assendelft WJ, Guchelaar HJ. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010 Nov;11(11):1517-23.
- Glynase [package insert]. New York, NY: Pfizer Inc.; 2017.
- 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).

Granisetron
INFORMATIVE

Sancuso®, Sustol®

Favorable Response to Standard Granisetron Dosing (ABCB1: Homozygous Mutant - Variant Allele Present)

The genotype result predicts that the patient has markedly decreased ABCB1 transporter expression. A high response rate in controlling nausea and vomiting has been reported when patients with this genotype are treated with granisetron. Granisetron can be prescribed at standard label-recommended dosage and administration.

- 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.

✓ Guanfacine

Intuniv®

Normal Response to Guanfacine

INFORMATIVE

Pharmacogenetic guidance: Guanfacine is predominantly metabolized by CYP3A4. No genetically guided drug selection or dosing recommendations are available and guanfacine extended-release should be titrated based on the clinical response and tolerability of the individual patient. **Polypharmacy guidance**: The dose of guanfacine extended-release should be reduced to **one half of the standard dose** when co-medicated with a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, indinavir, ritonavir, nefazodone). When the strong CYP3A4 inhibitor is discontinued, the dose should be increased to the standard recommended dose. Guanfacine dose should be increased up to double the recommended dose when used in combination with a strong CYP3A4 inducer (e.g., phenytoin, carbamazepine, rifampin, St. John's wort etc.). When the CYP3A4 inducer is discontinued, the dose should be reduced to the standard recommended dose within 7-14 days.

- Intuniv [package insert]. Wayne, PA: Shire LLC; 2015.

✓ Haloperidol

Haldol®

Normal Exposure to Haloperidol (CYP2D6: Intermediate Metabolizer)

ACTIONABLE

The patient's genotype may be associated with a normal haloperidol exposure following standard dosing. Consider prescribing haloperidol at standard label-recommended dosage and administration. Careful titration is recommended until a favorable response is achieved.

- 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).

✓ Hydromorphone

Dilaudid®, Exalgo®

Normal Response to Hydromorphone

INFORMATIVE

No genetically guided drug selection or dosing recommendations are available. Hydromorphone is not metabolized by CYPs, and genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. Hydromorphone can be prescribed at standard label-recommended dosage and administration.

- Dilaudid [package insert]. Stamford, CT: Purdue Pharma L.P.; 2011.
- Exalgo [package insert]. Hazelwood, MO: Mallinckrodt Inc.; 2015.

✓ Ibuprofen

Advil®, Motrin®

Normal Ibuprofen Exposure (CYP2C9: Intermediate Metabolizer)

ACTIONABLE

Pain, Dysmenorrhea, Rheumatoid Arthritis, Osteoarthritis, Fever and Other Anti-Inflammatory Uses: Ibuprofen therapy can be initiated at standard label-recommended dosage and administration. Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when ibuprofen is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.

✓ Indomethacin

Indocin®

Normal Indomethacin Exposure

INFORMATIVE

Pharmacogenetic guidance: Indomethacin is metabolized mainly by O-demethylation to its inactive metabolite O-desmethyl indomethacin, a reaction catalyzed by CYP2C9. Genetic polymorphisms of CYP2C9 have not been found to affect the response to indomethacin. No genetically guided drug selection or dosing recommendations are available.

- Tivorbrex [package insert]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; 2019.
- Indocin [package insert]. Philadelphia, PA: Iroko Pharmaceuticals, LLC; 2019.

PATIENT INFORMATION

NAME: **Test ACC #:**
22045000033 **DOB:**
3/5/1990 **SEX:**
Male

Irbesartan
Avapro®

Normal Irbesartan Exposure (CYP2C9: Intermediate Metabolizer) — **INFORMATIVE**

The plasma concentrations of irbesartan may be higher than expected and preliminary findings indicate a larger diastolic blood pressure reduction in individuals with this genotype. Consider standard label-recommended dosage and administration.

- Hong X, Zhang S, Mao G, Jiang S, Zhang Y, Yu Y, Tang G, Xing H, Xu X. CYP2C9*3 allelic variant is associated with metabolism of irbesartan in Chinese population. Eur J Clin Pharmacol 2005 Oct;61(9):627-34.
- Hallberg P, Karlsson J, Kurland L, Lind L, Kahan T, Malmqvist K, Ohman KP, Nyström F, Melhus H. The CYP2C9 genotype predicts the blood pressure response to irbesartan: results from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation vs Atenolol (SILVHIA) trial. J Hypertens 2002 Oct;20 (10):2089-93.

Ketoprofen
Orudis®

Normal Response to Ketoprofen — **INFORMATIVE**

Pharmacogenetic guidance: Ketoprofen is primarily eliminated by glucuronidation (by UGT1A3, UGT1A9 and UGT2B7) and no major implication of CYP2C9 in the metabolism of this drug has been demonstrated. No genetically guided drug selection or dosing recommendations are available.

- Oruvail [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; 2007.

Ketorolac
Toradol®

Normal Response to Ketorolac — **INFORMATIVE**

Pharmacogenetic guidance: Ketorolac is metabolized by glucuronidation (UGT enzymes) and oxidation but the enzymes catalyzing the oxidation are not well characterized. No genetically guided drug selection or dosing recommendations are available.

- Sprix [package insert]. Wayne, PA: Egalet US Inc; 2018.

Labetalol
Normodyne®, Trandate®

Normal Response to Labetalol — **INFORMATIVE**

Pharmacogenetic guidance: Labetalol is extensively metabolized by UGT2B7, UGT1A1, and CYP2C19 to inactive metabolites. Preliminary studies indicate that following a single 200-mg oral dose, labetalol plasma concentrations are 2.9-fold higher in Chinese individuals with the CYP2C19 *2/*2 genotype than those with the CYP2C19 *1/*1 genotype. The clinical impact of this change is unknown. **Polypharmacy guidance:** Cimetidine increases the bioavailability of labetalol, and clinical monitoring is advised when both drugs are coadministered.

- Chan SW, Hu M, Ko SS, Tam CW, Fok BS, Yin OQ, Chow MS, Tomlinson B. CYP2C19 genotype has a major influence on labetalol pharmacokinetics in healthy male Chinese subjects. Eur J Clin Pharmacol 2013 Apr;69(4):799-806.
- Trandate [package insert]. San Diego, CA: Prometheus Laboratories Inc.; 2010.

Lacosamide
Vimpat®

Normal Exposure to Lacosamide — **ACTIONABLE**

Pharmacogenetic guidance: Lacosamide is primarily cleared by renal excretion and metabolized by CYP3A4, CYP2C9 and CYP2C19. While these clearance pathways are diminished in subjects with reduced enzyme activity, these changes have not been shown to be clinically significant. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of lacosamide, in patients with reduced renal function, with strong CYP2C9 and/or CYP3A4 inhibitors may result in higher lacosamide concentrations.

- Vimpat [package insert]. Smyrna, GA: UCB, Inc.; 2019.

Lamotrigine
Lamictal®

Normal Response to Lamotrigine — **INFORMATIVE**

Pharmacogenetic guidance: Genotype results obtained from the pharmacogenetic test performed in this patient cannot be used to identify patients at risk for severe cutaneous adverse reactions such as anticonvulsant hypersensitivity syndrome, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Lamotrigine is metabolized by glucuronidation, which is mediated primarily by UGT1A4 with some contribution from UGT1A1 and UGBT2B7. There are insufficient studies documenting the impact of genetic polymorphisms of these metabolizing enzymes on lamotrigine response. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Enzyme-inducing drugs increase lamotrigine clearance significantly, and higher doses of this drug are required to maintain therapeutic concentrations. Coadministration of valproic acid, an inhibitor of UGT enzymes, increases lamotrigine levels and may result in serious lamotrigine adverse effects (neurological and cutaneous). A low starting dose with a slow titration schedule is recommended when lamotrigine is added to existing valproic acid treatment.

- Lamictal [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2015.

Levetiracetam
Keppra®

Normal Response to Levetiracetam — INFORMATIVE

Pharmacogenetic guidance: No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Levetiracetam is minimally metabolized by non-CYP enzymes (esterases) and is primarily excreted unchanged in urine. Coadministration of enzyme-inducing antiepileptic drugs produce modest decreases in levetiracetam plasma levels.

- Keppra [package insert]. Smyrna, GA: UCB, Inc.; 2015.

Levomilnacipran
Fetzima®

Normal Response to Levomilnacipran — INFORMATIVE

Pharmacogenetic guidance: Levomilnacipran is moderately metabolized by desethylation, which is catalyzed primarily by CYP3A4, with minor contributions by CYP2C8, CYP2C19, CYP2D6, and CYP2J2. More than 58% of the dose is excreted in urine as unchanged levomilnacipran, and 18% as N-desethyl levomilnacipran. Genetic polymorphisms of CYPs are not expected to have a significant impact on levomilnacipran exposure. no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: the daily levomilnacipran dose should not exceed 80 mg when coadministered with strong CYP3A4 inhibitors, such as ketoconazole, itrazonazole, and ritonavir.

- Fetzima [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2014.

Levorphanol
Levo Dromoran®

Normal Response to Levorphanol — INFORMATIVE

Pharmacogenetic guidance: Levorphanol is metabolized by glucuronidation which is mediated by UGT2B7. There are no studies documenting the impact of genetic polymorphisms of this metabolizing enzyme on levorphanol response. And no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Enzyme inducing drugs are expected to increase levorphanol clearance significantly.

- LEVORPHANOL TARTRATE- levorphanol tartrate tablet [package insert]. Solana Beach, CA: Sentynl Therapeutics, Inc. https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=242855. Rev Dec 2016.

Lisdexamfetamine
Vyvanse®

Normal Exposure to Lisdexamfetamine (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

Lisdexamfetamine can be prescribed at standard label-recommended dosage and administration. Individualize the dosage according to the therapeutic needs and response of the patient.

- Bach MV, Coutts RT, Baker GB. Involvement of CYP2D6 in the in vitro metabolism of amphetamine, two N-alkylamphetamines and their 4-methoxylated derivatives. Xenobiotica 1999 Jul;29(7):719-32.

Lisdexamfetamine
Vyvanse®

Good Response to Lisdexamfetamine (COMT: Intermediate COMT Activity) — INFORMATIVE

The patient's genotype result predicts a favorable response to amphetamine stimulants. Lisdexamfetamine should be administered at the lowest effective dose, and dosage should be individually adjusted.

- Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A 2003 May;100(10):6186-91.
- Hamidovic A, Dlugos A, Palmer AA, de Wit H. Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. Psychiatr Genet 2010 Jun;20(3):85-92.

Lofexidine
Lucemyra®

Normal Exposure to Lofexidine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

Lofexidine is metabolized by CYP2D6 with contributions from CYP2C19 and CYP1A2. The genotype results predict that the patient is expected to have a normal clearance and a typical exposure to this drug. Use label-recommended dosage and follow standard precautions.

- Lucemyra [package insert]. Louisville, KY: US WorldMeds, LLC; 2018.

Lornoxicam
Xefo®

Normal Lornoxicam Exposure (CYP2C9: Intermediate Metabolizer) — ACTIONABLE

Pain, Rheumatoid Arthritis and Osteoarthritis: Lornoxicam therapy can be initiated at standard label-recommended dosage and administration. Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when lornoxicam is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.

Losartan

Cozaar®, Hyzaar®

Possible Decreased Response to Losartan (CYP2C9: Intermediate Metabolizer) — INFORMATIVE

Losartan is metabolized to its active metabolite by CYP2C9 and CYP3A4. The patient's genotype predicts a non-clinically significant change in losartan's active metabolite exposure. Losartan can be prescribed at label-recommended dosage and administration with additional monitoring of the patient's response.

- Dorado P, Beltrán LJ, Machín E, Peñas-Lledó EM, Terán E, Llerena A, . Losartan hydroxylation phenotype in an Ecuadorian population: influence of CYP2C9 genetic polymorphism, habits and gender. Pharmacogenomics 2012 Nov;13(15):1711-7.
- Joy MS, Dornbrook-Lavender K, Blaisdell J, Hilliard T, Boyette T, Hu Y, Hogan SL, Candiani C, Falk RJ, Goldstein JA. CYP2C9 genotype and pharmacodynamic responses to losartan in patients with primary and secondary kidney diseases. Eur J Clin Pharmacol 2009 Sep;65(9):947-53.
- Li Z, Wang G, Wang LS, Zhang W, Tan ZR, Fan L, Chen BL, Li Q, Liu J, Tu JH, Hu DL, Liu ZQ, Zhou HH. Effects of the CYP2C9*13 allele on the pharmacokinetics of losartan in healthy male subjects. Xenobiotica 2009 Oct;39(10):788-93.
- Bae JW, Choi CI, Lee HI, Lee YJ, Jang CG, Lee SY. Effects of CYP2C9*1/*3 and *1/*13 on the pharmacokinetics of losartan and its active metabolite E-3174. Int J Clin Pharmacol Ther 2012 Sep;50(9):683-9.

Lovastatin

Mevacor®, Altoprev®, Advicor®

Normal Myopathy Risk (SLCO1B1: Normal Function) — INFORMATIVE

Lovastatin acid plasma concentration is not expected to be elevated. Unless other genetic or circumstantial risk factors are present, lovastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. Other myopathy predisposing factors include advanced age (65 and older), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female sex.

- Tornio A, Vakkilainen J, Neuvonen M, Backman JT, Neuvonen PJ, Niemi M. SLCO1B1 polymorphism markedly affects the pharmacokinetics of lovastatin acid. Pharmacogenet Genomics 2015 Aug;25(8):382-7.
- Zhao G, Liu M, Wu X, Li G, Qiu F, Gu J, Zhao L. Effect of polymorphisms in CYP3A4, PPARA, NR1I2, NFKB1, ABCG2 and SLCO1B1 on the pharmacokinetics of lovastatin in healthy Chinese volunteers. Pharmacogenomics 2017 Jan;18(1):65-75.

Lovastatin

Mevacor®, Altoprev®, Advicor®

Normal Response to Lovastatin (CYP3A4: Normal Metabolizer) — INFORMATIVE

The genotype result indicates that the patient does not carry the CYP3A4*22 allele (this allele is associated with a decreased CYP3A4 enzyme activity). The patient is expected to achieve an optimal lipid control goal with standard lovastatin dose requirements.

- Okubo M, Murayama N, Shimizu M, Shimada T, Guengerich FP, Yamazaki H. CYP3A4 intron 6 C>T polymorphism (CYP3A4*22) is associated with reduced CYP3A4 protein level and function in human liver microsomes. J Toxicol Sci 2013 ;38(3):349-54.
- Kitzmiller JP, Sullivan DM, Phelps MA, Wang D, Sadee W. CYP3A4/5 combined genotype analysis for predicting statin dose requirement for optimal lipid control. Drug Metabol Drug Interact 2013 ;28(1):59-63.

Loxapine

Loxitane®, Adasuve®

Normal Response to Loxapine — INFORMATIVE

Pharmacogenetic guidance: Loxapine is metabolized extensively in the liver following oral administration, with multiple metabolites formed. Loxapine metabolism occurs via hydroxylation and oxidation catalyzed by CYP1A2 along with contributions from CYP3A4, CYP2D6 and FMO. There are no studies documenting the effect of genetic polymorphisms of these metabolizing enzymes on Loxapine disposition and there are no available genetically-guided drug selection or dosing recommendations. **Polypharmacy guidance:** Loxapine is a central nervous system (CNS) depressant. The concurrent use of Loxapine with other CNS depressants (*e.g.*, alcohol, opioid analgesics, benzodiazepines, tricyclic antidepressants, general anesthetics, phenothiazines, sedative/hypnotics, muscle relaxants, and/or illicit CNS depressants) can increase the risk of respiratory depression, hypotension, profound sedation, and syncope. Therefore, consider dose reduction/modification of CNS depressants if used concomitantly with Loxapine. Loxapine has anticholinergic activity and concomitant use with other anticholinergic drugs can increase the risk of adverse reactions, including exacerbation of glaucoma and urinary retention.

- Adasuve [package insert]. Mountain View, CAL: Alexza Pharmaceuticals, Inc.; 2012.

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

Lurasidone
Latuda®

Normal Response to Lurasidone
ACTIONABLE

Pharmacogenetic guidance: Lurasidone is metabolized by CYP3A4. No genotype-based dosing adjustments are available. **Polypharmacy guidance:** The concomitant use of lurasidone with all CYP3A4 inhibitors may result in an increase in lurasidone plasma concentrations, which could increase or prolong adverse drug effects. **Lurasidone should not be administered with strong CYP3A4 inhibitors**. Lurasidone dose should not exceed 40 mg when administered with moderate CYP3A4 inhibitors. Monitor patients receiving lurasidone and any CYP3A4 inhibitor. **Rifampin or other strong inducers of CYP3A should not be administered with lurasidone.** If lurasidone is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase lurasidone dose after chronic treatment (7 days or more) with the CYP3A4 inducer.

- Latuda [package insert]. Marlborough, MA: Sunovion Pharmaceuticals Inc.; 2013.

Meloxicam
Mobic®

Normal Meloxicam Exposure (CYP2C9: Intermediate Metabolizer)
ACTIONABLE

Pain, Rheumatoid Arthritis and Osteoarthritis: Meloxicam therapy can be initiated at standard label-recommended dosage and administration. Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when meloxicam is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.

Memantine
Namenda®

Normal Response to Memantine
INFORMATIVE

Pharmacogenetic Guidance: Memantine is excreted predominantly unchanged in the urine. This drug undergoes partial hepatic metabolism to three inactive metabolites (N-glucuronide, 6--hydroxy metabolite, and 1-nitroso-deaminated metabolite). CYP450 enzymes do not play a significant role in the metabolism of memantine. There are no studies documenting the effects of genetic variability in metabolizing enzymes or organic cationic transporters on memantine response. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy Guidance:** Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to interact with memantine. Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide, triamterene, metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents.

- Namenda XR [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2014.

Meperidine
Demerol®

Normal Response to Meperidine
INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. Meperidine is metabolized to normeperidine by multiple CYPs, including CYP2B6, CYP3A4, and CYP2C19. The effects of genetic variants in these enzymes have not been studied. **Polypharmacy guidance:** In patients taking **strong CYP inducers**, meperidine metabolism is increased resulting in higher levels of its neurotoxic metabolite normeperidine. In presence of ritonavir, meperidine's exposure is significantly reduced while normeperidine concentrations are increased. Based on these findings, the risk of narcotic-related adverse effects from this combination appears to be minimal. However, increased concentrations of normeperidine suggest a potential for toxicity with increased dosages or long-term therapy. This combination should be avoided is possible.

- Ramírez J, Innocenti F, Schuetz EG, Flockhart DA, Relling MV, Santucci R, Ratain MJ. CYP2B6, CYP3A4, and CYP2C19 are responsible for the in vitro N-demethylation of meperidine in human liver microsomes. Drug Metab Dispos 2004 Sep;32(9):930-6.

Metaxalone
Skelaxin®

Normal Response to Metaxalone
INFORMATIVE

Pharmacogenetic guidance: Metaxalone is extensively metabolized by multiple CYP enzymes, including CYP1A2, CYP2D6, CYP2E1, and CYP3A4. Genetic polymorphisms of these enzymes are unlikely to affect its exposure to a significant extent. no genetically guided drug selection or dosing recommendations are available.

- Skelaxin [package insert]. Brisol, TN: King Pharmaceuticals, Inc.; 2008.

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

Methadone
Dolophine®

Normal Methadone Exposure (CYP2B6: Normal Metabolizer) — INFORMATIVE

The patient's genotype is associated with a normal methadone exposure following standard dosing.

For Addiction Treatment: Consider standard prescribing and monitoring practices.

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.

Methocarbamol
Robaxin®

Normal Response to Methocarbamol — INFORMATIVE

Pharmacogenetic guidance: Methocarbamol is metabolized via dealkylation and hydroxylation. The enzymes responsible for the metabolism of this drug have not been characterized. No genetically guided drug selection or dosing recommendations are available.

- Robaxin [package insert]. Milwaukee, WI: Schwarz Pharma, Inc.; 2003.

Milnacipran
Savella®

Normal Response to Milnacipran — INFORMATIVE

Pharmacogenetic guidance: milnacipran is minimally metabolized by UGT enzymes and primarily excreted unchanged in urine. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** coadministration of drugs that inhibit or induce CYP or UGT enzymes are unlikely to affect the exposure of milnacipran.

- Savella [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2013.

Mirtazapine
Remeron®

Normal Exposure to Mirtazapine — ACTIONABLE

Pharmacogenetic guidance: Mirtazapine is metabolized by CYP2D6 as well as CYP1A2 and CYP3A4. While these clearance pathways are diminished in subjects with reduced enzyme activity, these changes have not been shown to be clinically significant. No genetically guided drug selection or dosing recommendations are recommended.
Polypharmacy guidance: Co-administration of mirtazapine with CYP inhibitors did not result in clinically relevant pharmacokinetics changes. While co-administration with strong CYP inducers (ex. phenytoin, carbamazepine, rifampicin) may result in lower mirtazapine concentrations and a lack of efficacy.

- Remeron [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2016.
- 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).

Morphine
MS Contin®

Good Response to Morphine (OPRM1: Normal OPRM1 Function) — INFORMATIVE

The patient does not carry the OPRM1 118A>G variant. Acute postoperative and cancer pain: the patient is expected to experience good analgesia at standard morphine doses. The dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

- Sia AT, Lim Y, Lim EC, Goh RW, Law HY, Landau R, Teo YY, Tan EC. A118G single nucleotide polymorphism of human mu-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. Anesthesiology 2008 Sep;109 (3):520-6.
- Klepstad P, Rakvåg TT, Kaasa S, Holthe M, Dale O, Borchgrevink PC, Baar C, Vikan T, Krokan HE, Skorpen F. The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 2004 Nov;48(10):1232-9.
- 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.

Morphine
MS Contin®

Average Response to Morphine (COMT: Intermediate COMT Activity) — INFORMATIVE

The patient carries one COMT Val158Met variant, which translates to a reduced COMT function. The patient may require average to low 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.

Nabumetone
Relafen®

Normal Response to Nabumetone — INFORMATIVE

Pharmacogenetic guidance: Nabumetone is a prodrug, which is converted by CYP1A2 to an active metabolite (6-MNA) that is further metabolized by CYP2C9 to an inactive metabolite. Theoretically, individuals with reduced CYP2C9 activity (i.e CYP2C9 poor metabolizers) may have higher levels of the active metabolite, but it is unknown whether this results in altered drug response. No genetically guided drug selection or dosing recommendations are available.
Polypharmacy Guidance: CYP1A2 inhibitors may inhibit the activation of nabumetone to its active metabolite resulting in a reduction in the therapeutic effects of this drug. On the other hand, CYP1A2 inducers (i.e smoking) may result in higher levels of nabumetone active metabolite, which may affect the response to this drug.

- Ralafen [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2011.

Naproxen
Aleve®

Normal Sensitivity to Naproxen — INFORMATIVE

Pharmacogenetic guidance: UGT2B7 is responsible for hepatic naproxen acyl glucuronidation, which is the primary elimination pathway for this drug (60% of total clearance). CYP2C9 and CYP1A2 are responsible for the formation of O-desmethylnaproxen but this pathway is not the primary pathway for the elimination for naproxen. Genetic polymorphism of CYP2C9 has not been found to affect the response to naproxen. No genetically guided drug selection or dosing recommendations are available.

- Naprosyn [package insert]. Alpharetta, GA: Canton Laboratories, LLC; 2017.

Nateglinide
Starlix®

Normal Sensitivity to Nateglinide (SLCO1B1: Normal Function) — INFORMATIVE

The patient does not carry the SLCO1B1 521T>C variant, which is associated with normal transporter function. Nateglinide can be prescribed at label-recommended standard dosage and administration.

- Cheng Y, Wang G, Zhang W, Fan L, Chen Y, Zhou HH. Effect of CYP2C9 and SLCO1B1 polymorphisms on the pharmacokinetics and pharmacodynamics of nateglinide in healthy Chinese male volunteers. Eur J Clin Pharmacol 2013 Mar;69(3):407-13.
- Zhang W, He YJ, Han CT, Liu ZQ, Li Q, Fan L, Tan ZR, Zhang WX, Yu BN, Wang D, Hu DL, Zhou HH. Effect of SLCO1B1 genetic polymorphism on the pharmacokinetics of nateglinide. Br J Clin Pharmacol 2006 Nov;62(5):567-72.

Nateglinide
Starlix®

Normal Nateglinide Exposure (CYP2C9: Intermediate Metabolizer) — INFORMATIVE

The patient's genotype predicts a normal exposure to nateglinide, and this drug can be prescribed at label-recommended dosage and administration.

- Cheng Y, Wang G, Zhang W, Fan L, Chen Y, Zhou HH. Effect of CYP2C9 and SLCO1B1 polymorphisms on the pharmacokinetics and pharmacodynamics of nateglinide in healthy Chinese male volunteers. Eur J Clin Pharmacol 2013 Mar;69(3):407-13.
- Holstein A, Plaschke A, Ptak M, Egberts EH, El-Din J, Brockmöller J, Kirchheiner J. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005 Jul;60(1):103-6.

Nebivolol
Bystolic®

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

Nebivolol can be prescribed at standard label-recommended dosage and administration. Caution is recommended during up-titration until a favorable response is achieved.

- Briciu C, Neag M, Muntean D, Vlase L, Bocsan C, Buzoianu A, Gheldiu AM, Achim M, Popa A. A pharmacokinetic drug interaction study between nebivolol and paroxetine in healthy volunteers. J Clin Pharm Ther 2014 Oct;39(5):535-40.
- Bystolic [package insert]. Irvine, CA: Allergan USA, Inc.; 2017.

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

Nefazodone
Serzone®

Normal Sensitivity to Nefazodone (CYP2D6: Intermediate Metabolizer) — **INFORMATIVE**

Nefazodone is metabolized by CYP3A4 to its active metabolite m-chlorophenylpiperazine and other metabolites. The m-chlorophenylpiperazine metabolite which may contribute to adverse events, is further metabolized by CYP2D6. Nefazodone can be prescribed standard label recommended-dosage and administration.

- Rotzinger S, Fang J, Coutts RT, Baker GB. Human CYP2D6 and metabolism of m-chlorophenylpiperazine. Biol Psychiatry 1998 Dec;44(11):1185-91.
- Barbhaiya RH, Buch AB, Greene DS. Single and multiple dose pharmacokinetics of nefazodone in subjects classified as extensive and poor metabolizers of dextromethorphan. Br J Clin Pharmacol 1996 Nov;42(5):573-81.

Netupitant / Palonosetron
Akynzeo-oral®

Normal Response to Netupitant-Palonosetron (CYP2D6: Intermediate 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 can be prescribed at standard label-recommended dosage and administration.

- 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.

Oliceridine
Olinvyk

Normal Exposure to Oliceridine (CYP2D6: Intermediate Metabolizer) — **INFORMATIVE**

Oliceridine can be prescribed at standard label-recommended dosage and administration

- Olinvyk [package insert]. Chesterbrook, PA; Trevena, Inc.; 2020.

Olmesartan
Benicar®

Normal Sensitivity to Olmesartan Medoxomil — **ACTIONABLE**

Pharmacogenetic guidance: Olmesartan medoxomil is hydrolyzed to olmesartan its active metabolite in the gastrointestinal tract during absorption. There is virtually no further metabolism of olmesartan. Genetic variability of the cytochrome P450 genes is not expected to affect the patient's response to olmesartan medoxomil. No genotype-based dosing adjustments are available.

- Benicar [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc.; 2014.

Ondansetron
Zofran®, Zuplenz®

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

Ondansetron can be prescribed at standard label-recommended dosage and administration.

- 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.

Ondansetron
Zofran®, Zuplenz®

Favorable Response to Standard Ondansetron Dosing (ABCB1: Homozygous Mutant - Variant Allele Present) — **INFORMATIVE**

The genotype result predicts that the patient has markedly decreased ABCB1 transporter expression. A high response rate in controlling nausea and vomiting has been reported when patients with this genotype are treated with ondansetron. Ondansetron can be prescribed at standard label-recommended dosage and administration.

- 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.

Oxcarbazepine

Normal Response to Oxcarbazepine — **INFORMATIVE**

Trileptal®, Oxtellar XR®

Pharmacogenetic guidance: Genotype results obtained from the pharmacogenetic test performed in this patient cannot be used to identify patients at risk for severe cutaneous adverse reactions such as anticonvulsant hypersensitivity syndrome, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Oxcarbazepine (prodrug) in converted by a reductase to its active monohydroxylated active metabolite: 10-hydroxycarbazepine (MHD). This active metabolite is eliminated by direct renal excretion, glucuronidation, and hydroxylation (minimal). No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** In the presence of enzyme-inducing drugs, the plasma levels of the active metabolite (MHD) are decreased by 30%.

- Trileptal [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2014.

Oxycodone

Percocet®, Oxycontin®

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

The patient genotype may be associated with the reduced conversion of oxycodone to an active metabolite (oxymorphone), but this does not appear to translate into decreased analgesia or side effects.

Oxycodone can be prescribed at standard label-recommended age- or weight-based dosing and monitoring.

- 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.

Oxymorphone

Opana®, Numorphan®

Normal Response to Oxymorphone — **INFORMATIVE**

No genetically guided drug selection or dosing recommendations are available. Oxymorphone is not metabolized by CYPs, and genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. Oxymorphone can be prescribed at standard label-recommended dosage and administration.

- Opana [package insert]. Chadds Ford, PA: Endo Pharmaceuticals Inc.; 2006.

Paliperidone

Invega®

Normal Sensitivity to Paliperidone (CYP2D6: Intermediate Metabolizer) — **ACTIONABLE**

Paliperidone can be prescribed at standard label-recommended dosage and administration.

- Invega [package insert]. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceutical, Inc.; 2011.

Palonosetron

Aloxi®

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

Palonosetron can be prescribed at standard label-recommended dosage and administration.

- 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.

Paroxetine

Paxil®, Brisdelle®

Normal Sensitivity to Paroxetine (CYP2D6: Intermediate Metabolizer) — **ACTIONABLE**

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

- 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.

Perampanel

Fycompa®

Normal Response to Perampanel — **INFORMATIVE**

Pharmacogenetic guidance: Perampanel is eliminated either unchanged or following oxidative metabolism by CYP3A4 and CYP3A5. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Enzyme-inducing drugs decrease perampanel plasma concentrations by 50-60%, and the initial dosage of the drug should be increased when it is added to a stable therapy regimen containing enzyme-inducing antiepileptic drugs. Coadministration with strong enzyme-inducers others than antiepileptic drugs (e.g., rifampin) should be avoided. Coadministration with perampanel with strong CYP3A4 inhibitors such as ketoconazole increases perampanel exposure by 20%.

- Fycompa [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2015.

Periciazine

Neuleptil®, Zentiva®

Normal Response to Periciazine

INFORMATIVE

Pharmacogenetic guidance: Periciazine undergoes extensive first pass metabolism in the gut and/or liver. Although, the drug is metabolized to a 7-hydroxy metabolite and a sulfoxide metabolite, the enzymes responsible for the formation of these metabolites are unknown. There are no genotype-based dosing recommendations. **Polypharmacy guidance**: Periciazine should not be used with dopaminergics or with QT-prolongating medications.

- Cai HL, Deng Y, Fang PF, Cao S, Hou ZY, Wu YQ, Chen XJ, Yan M, Zhang B. A sensitive LC-MS/MS method for analysis of pericyazine in presence of 7-hydroxypericyazine and pericyazine sulphoxide in human plasma and its application to a comparative bioequivalence study in Chinese healthy volunteers. J Pharm Biomed Anal 2017 Feb;135():67-74.
- Neulactil [package insert]. Auckland, New Zealand: Sanofi-Aventis New Zealand Limited; 2013.

Phenobarbital

Luminal®

Normal Sensitivity to Phenobarbital (CYP2C19: Normal Metabolizer)

INFORMATIVE

CYP2C19 is partly involved in the metabolism of phenobarbital, and this drug can be prescribed at standard label-recommended dosage and administration.

- 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.

Phenytoin

Dilantin®

Normal Phenytoin Exposure (CYP2C9: Intermediate Metabolizer)

ACTIONABLE

The genotype results indicate that the patient is expected to have a slightly reduced CYP2C9 enzyme activity. Phenytoin can be prescribed at a standard loading dose and a standard maintenance dose. Consider therapeutic drug monitoring and evaluate the patient's response to optimize the maintenance dosage.

- Karnes JH, Rettie AE, Somogyi AA, Huddart R, Fohner AE, Formea CM, Ta Michael Lee M, Llerena A, Whirl-Carrillo M, Klein TE, Phillips EJ, Mintzer S, Gaedigk A, Caudle KE, Callaghan JT. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. Clin Pharmacol Ther 2021 Feb;109(2):302-309.

Pimavanserin

Nuplazid®

Normal Response to Pimavanserin

INFORMATIVE

Pharmacogenetic guidance: Pimavanserin is predominantly metabolized by CYP3A4 and CYP3A5 and to a lesser extent by CYP2J2, CYP2D6, and other CYP and FMO enzymes. CYP3A4 is the major enzyme responsible for the formation of its major active metabolite (AC-279). There are no available genetically-guided drug selection or dosing recommendations. **Polypharmacy guidance:** Pimavanserin prolongs the QT interval and its use should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin). Concomitant use of pimavanserin with CYP3A4 inhibitor increases pimavanserin exposure and a dose reduction of 50% is needed when this drug is coadministered with strong CYP3A inhibitors. Coadministration of pimavanserin with strong CYP3A inducers may result in reduced efficacy and a dose increase may be needed.

- Nuplazid [package insert]. San Diego, CA: ACADIA Pharmaceuticals Inc.; 2016.

Pimozide

Normal Exposure to Pimozide (CYP2D6: Intermediate Metabolizer)

ACTIONABLE

Orap®

Consider prescribing pimozide at standard label-recommended dosage and administration. Standard starting dose: 1 to 2 mg/day. Doses may be increased to a maximum of 10 mg/day.

Concomitant use of pimozide with strong CYP2D6 or strong CYP3A inhibitors is contraindicated. Cautions should be taken when pimozide is administered with other drugs that prolong QT.

- Orap [package insert]. Sellersville, PA: Gate Pharmaceuticals; 2011.
- Rogers HL, Bhattaram A, Zineh I, Gobburu J, Mathis M, Laughren TP, Pacanowski M. CYP2D6 genotype information to guide pimozide treatment in adult and pediatric patients: basis for the U.S. Food and Drug Administration's new dosing recommendations. J Clin Psychiatry 2012 Sep;73(9):1187-90.

Piroxicam

Feldene®

Normal Piroxicam Exposure (CYP2C9: Intermediate Metabolizer)

ACTIONABLE

Rheumatoid Arthritis and Osteoarthritis: Piroxicam therapy can be initiated at standard label-recommended dosage and administration. Consider using the lowest effective dosage for the shortest duration consistent with the patient treatment goals.

Consider initiating treatment at the lowest end of the dosing range in geriatric patients. A dosage adjustment may be warranted when piroxicam is administered with CYP2C9 inhibitors or inducers.

- Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther 2020 Mar;():.

Pitavastatin

Livalo®

Normal Myopathy Risk (SLCO1B1: Normal Function)

INFORMATIVE

Pitavastatin plasma concentrations are not expected to increase, and unless other genetic or circumstantial risk factors are present, pitavastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. The myopathy risk increases with use of the 4 mg daily dose. Other myopathy predisposing factors include advanced age (65 and older), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female sex.

- Niemi M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther 2010 Jan;87(1):130-3.
- Talameh JA, Kitzmiller JP. Pharmacogenetics of Statin-Induced Myopathy: A Focused Review of the Clinical Translation of Pharmacokinetic Genetic Variants. J Pharmacogenomics Pharmacoproteomics 2014 Apr;5(2):.

Pitolisant

Wakix®

Normal Exposure to Pitolisant (CYP2D6: Intermediate Metabolizer)

ACTIONABLE

The patients's genotype is associated with a normal pitolisant exposure. Consider the following standard daily dosing regimen:

- Initiation and up-titration: 8.9 mg once daily; increase dose to 17.8 mg once daily after one week.
- Maintenance: may adjust dose up to the maximum dose of 35.6 mg once daily on week 3 based on tolerability.

Consider decreasing maximum daily dose to 17.8 mg once daily if co-administered with a strong CYP2D6 inhibitor.

Consider increasing to double the current maintenance dose over 7 days if co-administered with a strong CYP3A4 inducer.

- Wakix [package insert]. Plymouth Meeting, PA: Bioproject Pharma; 2019.

Prasugrel

Effient®

Normal Response to Prasugrel

ACTIONABLE

Pharmacogenetic guidance: Prasugrel is a prodrug that is hydrolyzed in the intestine to a thiolactone, which is then converted to the active metabolite primarily by CYP3A4 and CYP2B6, and to a lesser extent by CYP2C9 and CYP2C19. Prasugrel active metabolite exposure and platelet reactivity are not affected by CYP2C19 genetic variants. Prasugrel efficacy or safety profile are also unaffected by CYP2B6, CYP3A5, and CYP2C9 genetic variants. No genetically-guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: Prasugrel can be administered with drugs that are inducers or inhibitors of cytochrome P450 enzymes.

Pravastatin

Normal Myopathy Risk (SLCO1B1: Normal Function)

INFORMATIVE

Pravachol®

Pravastatin plasma concentrations are not expected to increase, and unless other genetic or circumstantial risk factors are present, pravastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease -specific guidelines. Other myopathy predisposing factors include advanced age (65 and older), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female sex.

- Niemi M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther 2010 Jan;87(1):130-3.
- Talameh JA, Kitzmiller JP. Pharmacogenetics of Statin-Induced Myopathy: A Focused Review of the Clinical Translation of Pharmacokinetic Genetic Variants. J Pharmacogenomics Pharmacoproteomics 2014 Apr;5(2):.

✓ Pregabalin

Lyrica®

Normal Response to Pregabalin — INFORMATIVE

Pharmacogenetic guidance: No genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: Pregabalin 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. Pregabalin can be prescribed at standard label-recommended dosage and administration.

- Lyrica [package insert]. New York, NY: Pfizer Inc.; 2016.

✓ Primidone

Mysoline®

Normal Sensitivity to Primidone (CYP2C19: Normal Metabolizer) — INFORMATIVE

CYP2C19 is partly involved in the metabolism of phenobarbital, the active metabolite of primidone, and this drug can be prescribed at standard label-recommended dosage and administration.

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

✓ Propranolol

Inderal®

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

Propranolol can be prescribed at standard label-recommended dosage and administration with careful titration and monitoring until a favorable response is achieved.

- Sowinski KM, Burlew BS. Impact of CYP2D6 poor metabolizer phenotype on propranolol pharmacokinetics and response. Pharmacotherapy ;17(6):1305-10.

✓ Quetiapine

Seroquel®

Normal Response to Quetiapine — INFORMATIVE

Pharmacogenetic guidance: Quetiapine is predominantly metabolized to several metabolites by CYP3A4. CYP3A5 and CYP2D6 are also responsible for quetiapine metabolism but their role in the overall metabolism of this drug is minor compared to CYP3A4. N-desalkylquetiapine, a pharmacologically active metabolite (responsible of the antidepressant effect) is further metabolized by CYP2D6 and CYP3A4. Preliminary studies have shown that genetic polymorphisms of CYP3A4, CYP2D6 and CYP3A5 enzymes may be responsible in variable exposures to quetiapine and to its active metabolite N-desalkylquetiapine. However, the clinical significance of these changes is not established yet and no genetically guided drug selection or dosing recommendations are available. Quetiapine dose should be titrated based on the clinical response and tolerability of the individual patient. **Polypharmacy guidance**: Quetiapine dose should be reduced to **one sixth of original dose** when co-medicated with a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, indinavir, ritonavir, nefazodone). When the CYP3A4 inhibitor is discontinued, the dose should be increased by 6 fold. Quetiapine dose should be increased up to 5 fold of the original dose when used in combination with a chronic treatment (e.g. > 7-14 days) of a potent CYP3A4 inducer (e.g., phenytoin, carbamazepine, rifampin, St. John's wort etc.). When the CYP3A4 inducer is discontinued, the dose should be reduced to the original level within 7-14 days.

- Seroquel [package insert]. Wilmington, DE: AstraZeneca; 2013.
- van der Weide K, van der Weide J. The influence of the CYP3A4*22 polymorphism on serum concentration of quetiapine in psychiatric patients. J Clin Psychopharmacol 2014 Apr;34(2):256-60.

✓ Quinidine

Quinidine®

Normal Exposure to Quinidine — INFORMATIVE

Pharmacogenetic guidance: In vitro studies using human liver microsomes have shown CYP3A as the primary metabolizing enzyme for quinidine. No genetically guided drug selection or dosing adjustments are recommended.
Polypharmacy guidance: Co-administration of drugs/herbs that are known to induce or inhibit CYP3A can change plasma concentrations of quinidine. This may result in adverse events or sub-or supra-therapeutic drug concentration modulating the risk of QT prolongation.

PATIENT INFORMATION

NAME: **Test ACC #:**
22045000033 **DOB:**
3/5/1990 **SEX:**
Male

- Quinidine Gluconate [package insert]. Philadelphia, PA: Mutual Pharmaceutical Company, Inc.; 2010.
- 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).

Rabeprazole
Aciphex®

Normal Exposure to Rabeprazole (CYP2C19: Normal Metabolizer)

INFORMATIVE

The patient's genotype may be associated with a normal rabeprazole exposure following standard dosing. Consider prescribing rabeprazole at standard label-recommended dosage and administration.

- 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.

Ranolazine
Ranexa®

Normal Sensitivity to Ranolazine (CYP2D6: Intermediate Metabolizer)

ACTIONABLE

Ranolazine is metabolized mainly by CYP3A4, and to a lesser extent by CYP2D6. This drug can be prescribed at standard label-recommended dosage and administration. The recommended initial dose is 375 mg twice daily. After 2–4 weeks, the dose should be titrated to 500 mg twice daily, and according to the patient's response, further titrated to a recommended maximum dose of 1000 mg twice daily.

If patient experiences treatment-related adverse events (e.g. dizziness, nausea, vomiting, or syncope), Down titration of ranolazine to 500 mg or 375 mg twice daily may be required. If symptoms do not resolve after dose reduction, treatment should be discontinued.

Ranolazine is a QTc prolonging drug. Caution should be observed when treating: 1- patients with a history of congenital or a family history of long QT syndrome, 2- patients with known acquired QT interval prolongation, and 3- patients treated with drugs affecting the QTc interval. Administration of CYP3A4 inhibitors increases the exposure of ranolazine significantly. As a consequence, the QTc prolongation by ranolazine in the presence of potent CYP3A inhibitors is significantly elevated relative to when the drug is administered alone.

- Ranexa [EPAR Product Information]. Luxembourg, Luxembourg: Menarini International Operations Luxembourg S.A.; First Published 2009.

Repaglinide
Prandin®, Prandimet®

Normal Sensitivity to Repaglinide (SLCO1B1: Normal Function)

INFORMATIVE

The patient does not carry the SLCO1B1 521T>C variant. This genotype is associated with normal transporter function. Repaglinide can be prescribed at label-recommended standard dosage and administration.

- Kalliokoski A, Neuvonen M, Neuvonen PJ, Niemi M. The effect of SLCO1B1 polymorphism on repaglinide pharmacokinetics persists over a wide dose range. Br J Clin Pharmacol 2008 Dec;66(6):818-25.
- Kalliokoski A, Neuvonen M, Neuvonen PJ, Niemi M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. J Clin Pharmacol 2008 Mar;48(3):311-21.

Risperidone
Risperdal®

Slightly Increased Exposure to Risperidone (CYP2D6: Intermediate Metabolizer)

ACTIONABLE

The patient's genotype may be associated with a slightly increased risperidone exposure and decreased active metabolite (paliperidone) exposure following standard dosing. Consider prescribing risperidone according to standard label-recommended dosing and administration. Dosing is individualized based on the patient's tolerability and clinical response.

- 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).

Rivaroxaban
Xarelto®

Normal Response to Rivaroxaban

INFORMATIVE

Pharmacogenetic guidance: Rivaroxaban is metabolized by CYP3A4, CYP3A5, and CYP2J2. It is also a substrate for P-gp (ABCB1) and BCRP (ABCG2) transporters. Genetic polymorphisms of these genes are not expected to affect the efficacy or safety profiles of rivaroxaban. **Polypharmacy guidance:** Avoid concomitant use of rivaroxaban with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan). Avoid concomitant use of rivaroxaban with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's wort). Patients with renal impairment coadministered rivaroxaban with drugs classified as combined P-gp and moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, dronedarone, and erythromycin) have increased exposure compared with patients with normal renal function and no inhibitor use. Significant increases in rivaroxaban exposure may increase bleeding risk.

- Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2014.

Rolapitant
Varubi®

Normal Response to Rolapitant — ACTIONABLE

Pharmacogenetic guidance: Rolapitant is metabolized primarily by CYP3A4 to a major active metabolite, (C4pyrrolidine-hydroxylated rolapitant). Rolapitant is eliminated primarily through the hepatic/biliary route. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy Guidance:** Strong CYP3A4 inducers can significantly decrease rolapitant exposure resulting in a loss of efficacy. These drugs should be avoided with rolapitant. Rolapitant is a moderate CYP2D6 inhibitor and some CYP2D6 substrates (e.g. thioridazine, pimozide) are contraindicated with rolapitant while others should be closely monitored and their doing adjusted when coadministered with this antiemetic medication. Rolapitant is an inhibitor two major drug efflux transporters: breast-cancer-resistance protein (BCRP) and P-glycoprotein (P-gp). Increased plasma concentrations of BCRP or P-gp substrates may result in potential adverse reactions when coadministered with rolapitant.

- Varubi [package insert]. Waltham, MA: TESARO, Inc.; 2015.

Rosuvastatin
Crestor®

Normal Myopathy Risk (SLCO1B1 521T>C T/T) — INFORMATIVE

Rosuvastatin plasma concentrations are not expected to increase, and unless other genetic or circumstantial risk factors are present, rosuvastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. The myopathy risk increases with use of the 40 mg dose. Other myopathy predisposing factors include advanced age (65 and older), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female sex.

- Niemi M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther 2010 Jan;87(1):130-3.

Rufinamide
Banzel®

Normal Response to Rufinamide — INFORMATIVE

Pharmacogenetic guidance: No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Rufinamide is extensively metabolized by carboxylesterases. Cytochrome P450 enzymes are not involved in its metabolism. Therefore, genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. Coadministration of enzyme-inducing antiepileptic drugs produce modest decreases in rufinamide plasma levels, while coadministration of valproate increases the drug levels and requires dose adjustment. Patients stabilized on rufinamide should begin valproate therapy at a low dose, and titrate to a clinically effective dose. Similarly, patients on valproate should begin rufinamide at a lower dose.

- Banzel [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2015.

Sertraline
Zoloft®

Normal Sensitivity to Sertraline (CYP2C19: Normal Metabolizer) — ACTIONABLE

Sertraline can be prescribed at standard label-recommended dosage and administration.

- 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.

Simvastatin
Zocor®

Normal Myopathy Risk (SLCO1B1: Normal Function) — ACTIONABLE

Simvastatin plasma concentrations are not expected to be elevated, and unless other genetic or circumstantial risk factors are present, simvastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. **The FDA recommends against the use of the 80 mg daily dose unless the patient had already tolerated this dose for 12 months without evidence of myopathy.** Other myopathy predisposing factors include advanced age (65 and older), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female sex.

- Wilke RA, Ramsey LB, Johnson SG, Maxwell WD, McLeod HL, Voora D, Krauss RM, Roden DM, Feng Q, Cooper-Dehoff RM, Gong L, Klein TE, Wadelius M, Niemi M, . The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. Clin Pharmacol Ther 2012 Jul;92(1):112-7.

✓ Simvastatin

Zocor®

Normal Response to Simvastatin (CYP3A4: Normal Metabolizer)

INFORMATIVE

The genotype result indicates that the patient does not carry the CYP3A4*22 allele (this allele is associated with a decreased CYP3A4 enzyme activity). The patient is expected to achieve an optimal lipid control goal with standard simvastatin dose requirements.

- Okubo M, Murayama N, Shimizu M, Shimada T, Guengerich FP, Yamazaki H. CYP3A4 intron 6 C>T polymorphism (CYP3A4*22) is associated with reduced CYP3A4 protein level and function in human liver microsomes. J Toxicol Sci 2013 ;38(3):349-54.
- Elens L, Becker ML, Haufroid V, Hofman A, Visser LE, Uitterlinden AG, Stricker BCh, van Schaik RH. Novel CYP3A4 intron 6 single nucleotide polymorphism is associated with simvastatin-mediated cholesterol reduction in the Rotterdam Study. Pharmacogenet Genomics 2011 Dec;21(12):861-6.
- Wang D, Guo Y, Wrighton SA, Cooke GE, Sadee W. Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. Pharmacogenomics J 2011 Aug;11(4):274-86.
- Luzum JA, Theusch E, Taylor KD, Wang A, Sadee W, Binkley PF, Krauss RM, Medina MW, Kitzmiller JP. Individual and Combined Associations of Genetic Variants in CYP3A4, CYP3A5, and SLCO1B1 With Simvastatin and Simvastatin Acid Plasma Concentrations. J Cardiovasc Pharmacol 2015 Jul;66(1):80-5.

✓ Siponimod

Mayzent®

Normal Exposure to Siponimod (CYP2C9: Intermediate Metabolizer)

ACTIONABLE

The patient's genotype is associated with a normal siponimod clearance. Consider the following standard daily dosing regimen:

- Initiation and up-titration: days 1-2: 0.25 mg - day 3: 0.50 mg - day 4: 0.75 mg - day 5: 1.25 mg
- Maintenance dose starting day 6 and after: 2 mg

Concomitant use of CYP2C9/3A4 dual inhibitor (e.g. fluconazole) or moderate CYP2C9 inhibitor concomitantly with a strong or moderate CYP3A4 inhibitor are not recommended. Caution should be exercised for concomitant use of moderate CYP2C9 inhibitors.

Concomitant use of strong CYP3A4/moderate CYP2C9 inducers (e.g. rifampicin or carbamazepine) is not recommended.

- Mayzent [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2019.

✓ Sotalol

Betapace®, Sorine®, Sotylize®

Normal Exposure to Sotalol

INFORMATIVE

Pharmacogenetic guidance: Excretion of sotalol is predominantly via the kidney in the unchanged form, and therefore lower doses are necessary in conditions of renal impairment. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of sotalol with drugs that can prolong the QT interval can increase the patient's risk for developing drug induced long QT syndrome.

- Betapace [package insert]. Zug, Switzerland: Covis Pharma; 2016.
- Sotylize [package insert]. Atlanta, GA: Arbor Pharmaceuticals, LLC; 2014.
- 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).

✓ Stiripentol

Diacomit®

Normal Sensitivity to Stiripentol

INFORMATIVE

Pharmacogenetic guidance: CYP2C19 is partly involved in the metabolism of stiripentol along with CYP3A4 and CYP1A2. This drug can be prescribed at standard recommended dosage and administration regardless of the CYP2C19 phenotype status. **Polypharmacy guidance:** Inducers of cytochrome P450 enzymes increase stiripentol clearance by 3-fold, and the initial dosage of the drug should be considered carefully when added to a stable therapy regimen containing enzyme-inducing antiepileptic drugs.

- Levy, René H., Mattson, Richard H., Meldrum, Brian S., Perucca, Emilio. Antiepileptic Drugs. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002. Print.
- Perucca, Emilio, and Harvey J. Kupferberg. "Drugs in Early Clinical Development." Antiepileptic Drugs. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002. 922. Print.

Sufentanil
Sufenta®

Normal Response to Sufentanil
INFORMATIVE

Pharmacogenetic guidance: No genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: Sufentanil is primarily metabolized by CYP3A4 and so should be used with caution when prescribed with CYP3A4 inhibitors or inducers.

- SUFENTANIL CITRATE- sufentanil citrate injection, solution [package insert]. Lake Forest, IL: Hospira, Inc. https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=283510. Rev Oct 2017.

Sulindac
Clinoril®

Normal Response to Sulindac
INFORMATIVE

Pharmacogenetic guidance: Sulindac is primarily eliminated by glucuronidation which is catalyzed by several isoforms including UGT1A3, UGT1A9 and UGT2B7. The role of CYP2C9 in sulindac metabolism is of minor relevance. No genetically guided drug selection or dosing recommendations are available.

- Clinoril [package insert]. South Granville, NSW, Australia: Merck Sharp & Dohme Pty., Ltd; 2010.

Tapentadol
Nucynta®

Normal Response to Tapentadol
INFORMATIVE

No genetically guided drug selection or dosing recommendations are available. Tapentadol is not metabolized by CYPs, and genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. Tapentadol can be prescribed at standard label-recommended dosage and administration.

- Nucynta [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013.

Telmisartan
Micardis®

Normal Sensitivity to Telmisartan
ACTIONABLE

Pharmacogenetic guidance: Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide. Telmisartan is not metabolized by the cytochrome P450 isoenzymes. Genetic variability of the cytochrome P450 genes is not expected to affect the patient's response to telmisartan. No genotype-based dosing adjustments are available.

- Micardis [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2014.

Thiothixene
Navane®

Normal Response to Thiothixene
INFORMATIVE

Pharmacogenetic guidance: Thiothixene is metabolized by UGTs and by cytochrome P450 enzymes (CYP1A2 and CYP3A4). No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** It is likely that strong enzyme inducers may lead to substantial decreases in thiothixene plasma concentrations with the potential for reduced effectiveness. Consider increasing the dose of thiothixene when concomitantly used with strong CYP3A4 inducers (e.g., carbamazepine).

- Navane [package insert]. New York, NY: Pfizer Inc.; 2010.

Tiagabine
Gabitril®

Normal Response to Tiagabine
INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: Tiagabine is extensively metabolized by CYP3A4, and therefore this drug should be used with caution when prescribed with CYP3A4 inhibitors. Inducers of CYP3A4 increase tiagabine clearance by 2-fold, and the initial dosage of the drug should be considered carefully when added to a stable therapy regimen containing enzyme-inducing antiepileptic drugs.

- Gabitril [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2015.

Ticagrelor
Brilinta®

Normal Response to Ticagrelor
INFORMATIVE

Pharmacogenetic guidance: Ticagrelor is extensively metabolized by CYP3A4 and CYP3A5 to both active and inactive metabolites, and this drug does not require bioactivation to achieve its antiplatelet effect. The drug is also a substrate of P-glycoprotein, encoded by the ABCB1 gene. Studies have shown that the efficacy and safety profile of ticagrelor do not depend on CYP2C19 or CYP3A5 metabolizer statuses. Moreover, preliminary studies indicate that relevant genetic variants within the ABCB1, SLCO1B1, CYP3A4 and UGT2B7 genes do not affect ticagrelor exposure, efficacy or safety profiles. No genetically-guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** In presence of strong CYP3A4 inhibitors, significantly increased exposure to ticagrelor is expected which may lead to adverse reactions such as dyspnea or bleeding. These drugs should be avoided with ticagrelor. Strong CYP3A4 inducers can significantly decrease ticagrelor exposure (resulting in a loss of efficacy) and these drugs should also be avoided. Ticagrelor is a weak inhibitor of CYP3A4 and P-glycoprotein and some substrates of these proteins should be closely monitored and their dosing adjusted when coadministered with this medication.

- Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, Husted S, Katus H, Steg PG, Shah SH, Becker RC, . Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010 Oct;376(9749):1320-8.
- Brilinta [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2016.

✓ Tolbutamide

Orinase®

Normal Exposure to Tolbutamide — ACTIONABLE

Pharmacogenetic guidance: Tolbutamide is extensively metabolized by CYP2C9. While this clearance pathway is diminished in subjects with reduced CYP2C9 activity, such a change has not been shown to be clinically significant. No genetically guided drug selection or dosing adjustments are recommended. **Polypharmacy guidance**: Co-administration of tolbutamide with a strong CYP2C9 inhibitor may result in higher tolbutamide concentrations possibly leading to hypoglycemia. Co-administration with a strong CYP2C9 inducer may result in lower tolbutamide concentrations and a lack of efficacy.

- Swen JJ, Wessels JA, Krabben A, Assendelft WJ, Guchelaar HJ. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010 Nov;11(11):1517-23.
- 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).

✓ Topiramate

Topamax®

Normal Response to Topiramate — INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** About 50% of absorbed topiramate dose appears unchanged in urine, and an additional 50% is present as metabolites and conjugates. Topiramate metabolism by cytochrome P450 enzymes is minor for its elimination when the drug is given as a monotherapy. However, this pathway is enhanced by concomitant use of enzyme-inducing antiepileptic drugs, and may result in reduced topiramate plasma concentrations. Thus, this drug should be titrated slowly, and dose adjustment must be considered in presence of inducers. Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy.

- Topamax [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2014.

✓ Torsemide

Demadex®

Normal Torsemide Exposure (CYP2C9: Intermediate Metabolizer) — INFORMATIVE

The patient's genotype predicts a normal exposure to torsemide and this drug can be prescribed at label-recommended dosage and administration.

- Vormfelde SV, Engelhardt S, Zirk A, Meineke I, Tuchen F, Kirchheiner J, Brockmöller J. CYP2C9 polymorphisms and the interindividual variability in pharmacokinetics and pharmacodynamics of the loop diuretic drug torsemide. Clin Pharmacol Ther 2004 Dec;76(6):557-66.
- Miners JO, Rees DL, Valente L, Veronese ME, Birkett DJ. Human hepatic cytochrome P450 2C9 catalyzes the rate-limiting pathway of torsemide metabolism. J Pharmacol Exp Ther 1995 Mar;272(3):1076-81.

✓ Trazodone

Oleptro®

Normal Response to Trazodone — INFORMATIVE

Pharmacogenetic guidance: Trazodone is metabolized to its active metabolite m-chlorophenylpiperazine by CYP3A4. This metabolite which may contribute to adverse events, is further metabolized by CYP2D6. The impact of genetic polymorphisms of this enzyme on the clinical response to trazodone is not well documented. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: It is likely that CYP3A4 inhibitors may lead to substantial increases in trazodone plasma concentrations with the potential for adverse effects. If trazodone is used with a potent CYP3A4 inhibitor, the risk of cardiac arrhythmia may be increased. Therefore coadministration of trazodone with drugs that are inhibit CYP3A4 should be approached with caution.

- Oleptro [package insert]. Gaithersburg, MD: Angelini Pharma Inc.; 2014.

Trifluoperazine
Stelazine®

Normal Response to Trifluoperazine — INFORMATIVE

Pharmacogenetic guidance: Thrifluoperazine extensively metabolized by oxidation, sulfoxidation, hydroxylation and direct glucuronidation catalyzed by UGT1A4. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** It is likely that strong enzyme inducers may lead to substantial decreases in trifluoperazine plasma concentrations with the potential for reduced effectiveness.

- TRIFLUOPERAZINE HYDROCHLORIDE- trifluoperazine hydrochloride tablet [package insert]. Princeton, NJ: Sandoz Inc. https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=244262. Rev Jan 2017.

Valbenazine
Ingrezza®

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

Valbenazine can be prescribed at standard label-recommended dosage and administration. The initial dose is 40 mg once daily which can be increased after a week of therapy to the recommended dose of 80 mg once daily.

Dose adjustments with comedications: reduce the daily recommended dose to 40 mg if a strong CYP3A4 inhibitor is coadministered. In presence of a CYP2D6 inhibitor, the daily recommended dose may be reduced based on tolerability. Concomitant use with CYP3A4 inducers should be avoided.

- Ingrezza [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.; 2017.

Valproic Acid
Depakene®

Normal Response to Valproic acid — INFORMATIVE

Pharmacogenetic guidance: Genotype results obtained from the pharmacogenetic test performed in this patient cannot be used to identify patients carrying mutations in mitochondrial DNA polymerase γ (POLG). Valproic acid is contraindicated in patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; e.g., Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder.

Valproic acid is extensively metabolized in the liver, which occurs primarily by glucuronidation with probable contributions of UGT1A6, UGT1A9, and UGT2B7. This drug is also metabolized by a minor CYP–dependent oxidation pathway, which includes multiple enzymes such as CYP2A6, CYP2C9, and CYP2C19. There are insufficient studies documenting the impact of genetic polymorphisms of these metabolizing enzymes on valproic acid response, and no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** enzyme-inducing drugs increase valproic acid clearance 2-fold, and higher doses of this drug are required to maintain therapeutic concentrations when added to a therapy regimen containing enzyme-inducing antiepileptic drugs.

- Depakene [package insert]. North Chicago, IL: AbbVie Inc.; 2016.

Valsartan
Diovan®, Entresto®

Normal Sensitivity to Valsartan — ACTIONABLE

Pharmacogenetic guidance: Valsartan is excreted largely as unchanged compound. CYP2C9 is responsible for the formation of a minor metabolite, valeryl 4-hydroxy valsartan, which accounts for about 9% of a dose. Given the limited contribution of CYP2C9 in the overall disposition of valsartan, genetic variability of the CYP2C9 gene is not expected to affect the patient's response to valsartan. No genotype-based dosing adjustments are available.

- Diovan [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.

Vigabatrin
Sabril®

Normal Response to Vigabatrin — INFORMATIVE

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

- Sabril [package insert]. Deerfield, IL: Lundbeck Inc.; 2015.

Vilazodone
Viibryd®

Normal Response to Vilazodone — INFORMATIVE

Pharmacogenetic guidance: Vilazodone is predominantly metabolized by CYP3A4. CYP2C19, CYP2D6, and CYP2E1 play a minor role in the biotransformation of this drug. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** It is likely that CYP3A4 inhibitors may lead to substantial increases in vilazodone plasma concentrations with the potential for adverse effects. Vilazodone should be reduced to 20 mg if co-administered with a strong inhibitor of CYP3A4 (e.g., ketoconazole). During coadministration with moderate inhibitors of CYP3A4 (e.g., erythromycin), the dose should be reduced to 20 mg for patients with intolerable adverse events. The dose can be readjusted to the original level when the CYP3A4 inhibitor is discontinued. Consider increasing the dose of vilazodone up to 2-fold when concomitantly used with strong CYP3A4 inducers (e.g., carbamazepine). The maximum daily dose should not exceed 80 mg. If CYP3A4 inducers are discontinued, reduce vilazodone dose to the original level.

- Viibryd [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2014.

Vorapaxar
Zontivity®

Normal Response to Vorapaxar — ACTIONABLE

Pharmacogenetic guidance: vorapaxar is metabolized primarily by CYP3A4, with contribution from CYP2J2. Genetic polymorphisms of these genes are not expected to affect the efficacy or safety profiles of this drug. Vorapaxar is contraindicated in people who have had a stroke, transient ischemic attack (TIA), or intracranial hemorrhage, (ICH) because of the increased bleeding risk. **Polypharmacy guidance:** Avoid concomitant use of vorapaxar with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan). Significant increases in vorapaxar exposure may increase bleeding risk. Avoid concomitant use with drugs that are strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's wort).

- Zontivity [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2014.

Vortioxetine
Trintellix®

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

Vortioxetine can be prescribed at standard label-recommended dosage and administration. The recommended starting dose is 10 mg/day, which can then be increased to 20 mg/day, as tolerated.

- Trintellix [package insert]. Deerfield, IL: Takeda Pharmaceuticals America Inc.; 2019.

Warfarin
Coumadin®

Average Dosing Requirements are Expected (CYP2C9 *1/*2; VKORC1 -1639G>A G/G) — 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 5-7 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 and African Americans: Use the patient's demographics and other clinical factors along with CYP2C9 and VKORC1 genotypes to calculate the expected therapeutic dose.

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

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

- 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.

✓ Ziprasidone

Geodon®

Normal Response to Ziprasidone

INFORMATIVE

Pharmacogenetic guidance: Ziprasidone is primarily cleared following extensive metabolism. CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone with minor involvement from CYP1A2. Less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction involving glutathione as well as aldehyde oxidase. No genetically guided drug selection or dosing recommendations are available. Individualization of ziprasidone dose with careful weekly titration is required. Dosage adjustments should generally occur at intervals of no less than 2 days, as steady-state plasma concentrations are achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, patients should ordinarily be observed for improvement for several weeks before upward dosage adjustment. When deciding among the alternative treatments available, the prescriber should consider the finding of **ziprasidone's greater capacity to prolong the QT/QTc interval** compared to several other antipsychotic drugs. **Polypharmacy guidance:** Although coadministration of strong CYP3A4 inhibitors are expected to result in modest increases in ziprasidone plasma concentrations, a closer monitoring of the patient's response and a dose reduction may be considered. Ziprasidone dose may need to be increased when used in combination with a chronic treatment of a potent CYP3A4 inducer (e.g., phenytoin, carbamazepine, rifampin, St. John's wort etc.).

- Geodon [package insert]. New York, NY: Pfizer Inc.; 2014.

✓ Zonisamide

Zonegran®

Normal Sensitivity to Zonisamide (CYP2C19: Normal Metabolizer)

INFORMATIVE

CYP2C19 is partly involved in the metabolism of zonisamide, and this drug can be prescribed at standard label-recommended dosage and administration.

- 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.

Clarity
Max Rx™ Test

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

Test Details

Gene	Genotype	Phenotype	Alleles Tested
ABCB1	3435C>T T/T	Homozygous Mutant - Variant Allele Present	3435C>T
ANKK1/DRD2	DRD2:Taq1A A/G	Altered DRD2 function	DRD2:Taq1A
APOE	ε3/ε3	Normal APOE function	ε2, ε4, (ε3 is reference)
COMT	Val158Met A/G	Intermediate COMT Activity	Val158Met
CYP1A2	*1A/*1F	Normal Metabolizer - Higher Inducibility	*1C, *1F, *1K, *1L, *7, *11
CYP2B6	*1/*1	Normal Metabolizer	*6, *9, *18, *18.002
CYP2C19	*1/*1	Normal Metabolizer	*2, *3, *4A, *4B, *5, *6, *7, *8, *17
CYP2C9	*1/*2	Intermediate Metabolizer	*2, *3, *4, *5, *6, *8, *11, *12, *13, *15, *25
CYP2D6	*1/*4	Intermediate Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *18, *19, *20, *29, *41, *114, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1/*1	Normal Metabolizer	*2, *17, *22
CYP3A5	*1/*1	Normal Metabolizer	*2, *3, *6, *7
F2 F5	rs1799963 GG rs6025 CC	Normal Risk of Thrombosis	rs1799963, rs6025
GLP1R	c.510-1135T>G T/T	Homozygous for T allele	c.780A>C, c.510-1135T>G, c.502G>A, c.502G>C
MTHFR	c.665C>T CC	Normal MTHFR Activity	c.1286A>C, c.665C>T
MTHFR	c.1286A>C AC c.665C>T CC	No Increased Risk of Hyperhomocysteinemia	c.1286A>C, c.665C>T
OPRM1	A118G A/A	Normal OPRM1 Function	A118G
PNPLA5	c.608-169G>A C/C	Homozygous for G allele	c.608-169G>A
SLCO1B1	521T>C T/T	Normal Function	521T>C
SULT4A1	c.743-374A>G T/T	Homozygous for A allele	c.743-374A>G
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity	-1639G>A

Variant Results

CACNA1S

rsID	HGVS Name	Genotype

RYR1

rsID	HGVS Name	Genotype

Clarity
Max Rx™ Test

PATIENT INFORMATION

NAME: **Test ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

ATTENTION: The report that has been generated is based on a test whose specimen data was gathered by Clarity, but the test itself performed by Helix Diagnostics - located at: 6620 Highland Road Waterford Twp, MI 48327

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: *ARK LABORATORY, LLC dba Helix Diagnostics developed the Genotype test. The performance characteristics of this test were determined by ARK LABOATORIY, LLC dba Helix Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration.*

Lab Accreditation: *COLA ID 26145; CLIA 23D1104676*

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 Amro Almradi, M.D.

Clarity Max Rx™ Test

PATIENT INFORMATION

NAME: **Test** **ACC #:** 22045000033 **DOB:** 3/5/1990 **SEX:** Male

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.

Clarity Max Rx™ Test

REPORT DETAILS

Name: Test
DOB: 3/5/1990
ACC #: 22045000033

Pharmacogenetic Test Summary

ABCB1	3435C>T T/T	Homozygous Mutant - Variant Allele Present
ANKK1/DRD2	DRD2:Taq1A A/G	Altered DRD2 function
APOE	ε3/ε3	Normal APOE function
COMT	Val158Met A/G	Intermediate COMT Activity
CYP1A2	*1A/*1F	Normal Metabolizer - Higher Inducibility
CYP2B6	*1/*1	Normal Metabolizer
CYP2C19	*1/*1	Normal Metabolizer
CYP2C9	*1/*2	Intermediate Metabolizer
CYP2D6	*1/*4	Intermediate Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*1/*1	Normal Metabolizer
F2	rs1799963 GG	Normal Thrombosis Risk
F5	rs6025 CC	Normal Thrombosis Risk
GLP1R	c.510-1135T>G T/T	Homozygous for T allele
MTHFR	c.1286A>C AC	Reduced MTHFR Activity
MTHFR	c.665C>T CC	Normal MTHFR Activity
OPRM1	A118G A/A	Normal OPRM1 Function
PNPLA5	c.608-169G>A C/C	Homozygous for G allele
SLCO1B1	521T>C T/T	Normal Function
SULT4A1	c.743-374A>G T/T	Homozygous for A allele
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity

For a complete report contact ClarityX
www.clarityxdna.com

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