4U Health

PATIENT INFORMATION		SPECIMEN DETAILS		PROVIDER INFORMATION
NAME:	**Demo Patient**	**SPECIMEN TYPE:**		DEMO PHYSICIAN
ACC #:	DEMO	**COLLECTION DATE:**		
DOB:	1/1/1900	**RECEIVED DATE:**		
SEX:		**REPORT DATE:**	8/20/2020	

Comprehensive Pharmacogenetic Report

Risk Management

⚠ Antipsychotic-Induced Tardive Dyskinesia

Increased Risk of Antipsychotic-Induced Tardive Dyskinesia

The patient does not carry the Taq1A variant (homozygous for the A2 allele).

The genotype results predict that the patient has normal dopamine receptor DRD2 density and functioning. The patient has increased risk for tardive dyskinesia when treated with antipsychotics.

Closely monitor the patient for signs of tardive dyskinesia.

✓ Antipsychotic-Induced Hyperprolactinemia

Normal Risk of Antipsychotic-Induced Hyperprolactinemia

The patient does not carry the Taq1A variant (homozygous for the A2 allele).

The genotype results predict that the patient has normal dopamine receptor DRD2 density and functioning. The patient has normal risk of hyperprolactinemia when treated with antipsychotics.

Monitor the patients closely for any signs of hyperprolactinemia.

✓ Antipsychotic-Induced Weight Gain

Low Risk of Antipsychotic-Induced Weight Gain

The patient does not carry the Taq1A variant (homozygous for the A2 allele).

The genotype results predict that the patient has normal dopamine receptor DRD2 density and functioning. The patient has a normal risk for weight gain when treated with antipsychotics.

Monitor the 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.

✓ Platelet Hyperactivity

Normal Response to Aspirin

The patient is negative for the ITGB3 176T>C (Leu59Pro) mutation. The genotype for the integrin β3 gene is wild-type, which is the most common genotype in the general population.

The wild-type genotype results confers a "normal" platelet reactivity, and is not associated with a resistance to the antithrombotic effects of aspirin. However, because the variability in response to antiplatelet drugs is multifactorial and not caused by single gene mutations, testing for the ITGB3 mutation alone should not be used as a diagnostic tool.

✓ Hyperhomocysteinemia - Depression

No Increased Risk of Hyperhomocysteinemia

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

Patients diagnosed with depression often have low folate levels and homocysteine is a highly sensitive marker of folate status. Functional folate deficiency is indicated by elevated homocysteine. With a normal MTHFR activity, this patient can process folate normally and is unlikely to have elevated plasma levels of homocysteine.

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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.

Hyperlipidemia/Atherosclerotic Cardiovascular Disease

No increased risk of cardiovascular disease

The patient is a non carrier of the risk alleles in LPA gene for both the variants (rs3798220 and rs10455872).
The patient's genotype is associated with normal lipoprotein levels. The patient has no increased risk of atherosclerosis and cardiovascular disease as compared to the general population unless other risk factors are present.
No action is needed for this patient unless other genetic and non genetic risk factors (e.g. high blood pressure, smoking, diabetes, obesity, high blood cholesterol and excessive alcohol use) are present.

Thrombophilia

Normal Risk of Thrombosis

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

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

Hyperhomocysteinemia - Thrombosis

No Increased Risk of Hyperhomocysteinemia

The patient carries one copy of MTHFR c.1286A>C variant (heterozygous). MTHFR enzyme activity is reduced (80% of normal activity).
The patient's slightly reduced MTHFR activity is not a risk factor for hyperhomocysteinemia. Unless other risk factors are present, the patient is not expected to have an increased risk for venous thromboembolism (VTE).
The patient's MTHFR activity is slightly reduced.

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.

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Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Anticancer Agents	**Antifolates**	Methotrexate (Trexall®)		
Cardiovascular	**Angiotensin II Receptor Antagonists**	Azilsartan (Edarbi®, Edarbyclor®) Candesartan (Atacand®) Eprosartan (Teveten®) Irbesartan (Avapro®) Losartan (Cozaar®, Hyzaar®) Olmesartan (Benicar®) Telmisartan (Micardis®) Valsartan (Diovan®, Entresto®)		
	Antianginal Agents	Ranolazine (Ranexa®)		
	Antiarrhythmics	Amiodarone (Nexterone®, Pacerone®) Disopyramide (Norpace®) Quinidine (Quinidine®) Sotalol (Betapace®, Sorine®, Sotylize®)	Flecainide (Tambocor®) Mexiletine (Mexitil®) Propafenone (Rythmol®)	
	Anticoagulants	Apixaban (Eliquis®) Betrixaban (Bevyxxa®) Dabigatran Etexilate (Pradaxa®) Edoxaban (Savaysa®) Fondaparinux (Arixtra®) Rivaroxaban (Xarelto®) Warfarin (Coumadin®)		
	Antiplatelets	Prasugrel (Effient®) Ticagrelor (Brilinta®) Vorapaxar (Zontivity®)	Clopidogrel (Plavix®)	
	Beta Blockers	Atenolol (Tenormin®) Bisoprolol (Zebeta®) Carvedilol (Coreg®) Labetalol (Normodyne®, Trandate®) Nebivolol (Bystolic®) Propranolol (Inderal®)	Metoprolol (Lopressor®) Timolol (Timoptic®)	
	Diuretics	Torsemide (Demadex®)		
	Statins	Atorvastatin (Lipitor®) Fluvastatin (Lescol®) Lovastatin (Mevacor®, Altoprev®, Advicor®) Pitavastatin (Livalo®) Pravastatin (Pravachol®) Rosuvastatin (Crestor®) Simvastatin (Zocor®)		
	Meglitinides	Nateglinide (Starlix®) Repaglinide (Prandin®, Prandimet®)		

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Diabetes	**Sulfonylureas**	Chlorpropamide (Diabinese®) Glimepiride (Amaryl®) Glipizide (Glucotrol®) Glyburide (Micronase®) Tolbutamide (Orinase®)		
Gastrointestinal	**Antiemetics**	Aprepitant (Emend-oral®) Dolasetron (Anzemet®) Dronabinol (Marinol®) Fosaprepitant (Emend-IV®) Fosnetupitant / Palonosetron (Akynzeo-IV®) Granisetron (Sancuso®, Sustol®) Netupitant / Palonosetron (Akynzeo -oral®) Ondansetron (Zofran®, Zuplenz®) Palonosetron (Aloxi®) Rolapitant (Varubi®)	Metoclopramide (Reglan®)	
	Proton Pump Inhibitors	Esomeprazole (Nexium®) Rabeprazole (Aciphex®)	Dexlansoprazole (Dexilant®, Kapidex®) Lansoprazole (Prevacid®) Omeprazole (Prilosec®) Pantoprazole (Protonix®)	
Infections	**Antifungals**	Amphotericin B (AmBisome®, Abelcet®) Anidulafungin (Eraxis®) Caspofungin (Cancidas®) Fluconazole (Diflucan®) Isavuconazonium (Cresemba®) Itraconazole (Sporanox®) Micafungin (Mycamine®) Posaconazole (Noxafil®)		Voriconazole (Vfend®)
	Anti-HIV Agents	Dolutegravir (Tivicay®, Triumeq®) Doravirine (Pifeltro®) Etravirine (Edurant®) Raltegravir (Isentress®, Dutrebis®) Rilpivirine (Intelence®)	Efavirenz (Sustiva®)	
	Antimalarials	Proguanil (Malarone®)		
	Fibromyalgia Agents	Milnacipran (Savella®)		
	Muscle Relaxants	Cyclobenzaprine (Flexeril®, Amrix®) Metaxalone (Skelaxin®) Methocarbamol (Robaxin®)	Carisoprodol (Soma®) Tizanidine (Zanaflex®)	

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Pain	NSAIDs	Celecoxib (Celebrex®) Diclofenac (Voltaren®) Flurbiprofen (Ansaid®) Ibuprofen (Advil®, Motrin®) Indomethacin (Indocin®) Ketoprofen (Orudis®) Ketorolac (Toradol®) Meloxicam (Mobic®) Nabumetone (Relafen®) Naproxen (Aleve®) Piroxicam (Feldene®) Sulindac (Clinoril®)		
	Opioids	Alfentanil (Alfenta®) Buprenorphine (Butrans®, Buprenex®) Dihydrocodeine (Synalgos-DC®) Fentanyl (Actiq®) Hydromorphone (Dilaudid®, Exalgo®) Levorphanol (Levo Dromoran®) Meperidine (Demerol®) Oxymorphone (Opana®, Numorphan®) Sufentanil (Sufenta®) Tapentadol (Nucynta®)	Benzhydrocodone (Apadaz®) Codeine (Codeine; Fioricet® with Codeine) Hydrocodone (Vicodin®) Methadone (Dolophine®) Morphine (MS Contin®) Oxycodone (Percocet®, Oxycontin®) Tramadol (Ultram®)	
	Antiaddictives	Lofexidine (Lucemyra®)	Bupropion (Wellbutrin®, Zyban®, Aplenzin®, Contrave®) Naltrexone (Vivitrol®, Contrave®)	
	Anti-ADHD Agents	Amphetamine (Adderall®, Evekeo®) Clonidine (Kapvay®) Dexmethylphenidate (Focalin®) Dextroamphetamine (Dexedrine®) Guanfacine (Intuniv®) Lisdexamfetamine (Vyvanse®) Methylphenidate (Ritalin®, Aptensio XR®, Concerta®, Metadate ER®, Quillivant ER®)	Atomoxetine (Strattera®)	

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Psychotropic	Anticonvulsants	Brivaracetam (Briviact®) Cannabidiol (Epidiolex®) Carbamazepine (Tegretol®, Carbatrol®, Epitol®) Eslicarbazepine (Aptiom®) Ethosuximide (Zarontin®) Ezogabine (Potiga®) Felbamate (Felbatol®) Fosphenytoin (Cerebyx®) Gabapentin (Neurontin®) Lacosamide (Vimpat®) Lamotrigine (Lamictal®) Levetiracetam (Keppra®) Oxcarbazepine (Trileptal®, Oxtellar XR®) Perampanel (Fycompa®) Phenobarbital (Luminal®) Phenytoin (Dilantin®) Pregabalin (Lyrica®) Primidone (Mysoline®) Rufinamide (Banzel®) Tiagabine (Gabitril®) Topiramate (Topamax®) Valproic Acid (Depakote®, Depakene®) Vigabatrin (Sabril®) Zonisamide (Zonegran®)		
	Antidementia Agents	Donepezil (Aricept®) Galantamine (Razadyne®) Memantine (Namenda®)		
	Antidepressants	Desvenlafaxine (Pristiq®) Duloxetine (Cymbalta®) Fluoxetine (Prozac®, Sarafem®) Fluvoxamine (Luvox®) Levomilnacipran (Fetzima®) Mirtazapine (Remeron®) Nefazodone (Serzone®) Paroxetine (Paxil®, Brisdelle®) Trazodone (Oleptro®) Vilazodone (Viibryd®) Vortioxetine (Trintellix®)	Amoxapine (Amoxapine®) Desipramine (Norpramin®) Maprotiline (Ludiomil®) Nortriptyline (Pamelor®) Protriptyline (Vivactil®) Sertraline (Zoloft®)	Amitriptyline (Elavil®) Citalopram (Celexa®) Clomipramine (Anafranil®) Doxepin (Silenor®) Escitalopram (Lexapro®) Imipramine (Tofranil®) Trimipramine (Surmontil®) Venlafaxine (Effexor®)

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	Antipsychotics	Aripiprazole (Abilify®, Aristada®) Asenapine (Saphris®) Brexpiprazole (Rexulti®) Cariprazine (Vraylar®) Chlorpromazine (Thorazine®) Fluphenazine (Prolixin®) Haloperidol (Haldol®) Loxapine (Loxitane®, Adasuve®) Lurasidone (Latuda®) Paliperidone (Invega®) Pimavanserin (Nuplazid®) Pimozide (Orap®) Quetiapine (Seroquel®) Risperidone (Risperdal®) Thiothixene (Navane®) Trifluoperazine (Stelazine®) Ziprasidone (Geodon®)	Clozapine (Clozaril®) Iloperidone (Fanapt®) Olanzapine (Zyprexa®) Perphenazine (Trilafon®)	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®)	
Rheumatology	**Anti-Hyperuricemics and Anti-Gout Agents**	Colchicine (Mitigare®) Febuxostat (Uloric®)		
	Immunomodulators	Apremilast (Otezla®) Leflunomide (Arava®) Tofacitinib (Xeljanz®)		
Transplantation	**Immunosuppressants**	Tacrolimus (Prograf®)		
Urologicals	**5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia**	Dutasteride (Avodart®) Finasteride (Proscar®)		
	Alpha-Blockers for Benign Prostatic Hyperplasia	Alfuzosin (UroXatral®) Doxazosin (Cardura®) Silodosin (Rapaflo®) Tamsulosin (Flomax®) Terazosin (Hytrin®)		
	Antispasmodics for Overactive Bladder	Darifenacin (Enablex®) Fesoterodine (Toviaz®) Mirabegron (Myrbetriq®) Oxybutynin (Ditropan®) Solifenacin (Vesicare®) Tolterodine (Detrol®) Trospium (Sanctura®)		
	Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra®) Sildenafil (Viagra®) Tadalafil (Cialis®) Vardenafil (Levitra®)		

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Dosing Guidance

Amitriptyline
Elavil®

Decreased Amitriptyline Exposure (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

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

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

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

Citalopram
Celexa®

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

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

Clomipramine
Anafranil®

Decreased Clomipramine Exposure (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

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

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

Doxepin
Silenor®

Decreased Doxepin Exposure (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

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

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

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

Escitalopram
Lexapro®

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

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

Imipramine
Tofranil®

Decreased Imipramine Exposure (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

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

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

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.

Trimipramine
Surmontil®

Decreased Trimipramine Exposure (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

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

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

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.

Voriconazole
Vfend®

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

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

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.

Atomoxetine
Strattera®

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

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

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

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).

Bupropion
Wellbutrin®, Zyban®, Aplenzin®, Contrave®

Altered Bupropion Exposure (CYP2B6: Intermediate Metabolizer) — INFORMATIVE

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

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

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

Carisoprodol
Soma®

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

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

Clopidogrel
Plavix®

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

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

Clozapine
Clozaril®

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

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

Codeine
Codeine; Fioricet® with Codeine

Possible Non-Response to Codeine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

Reduced morphine levels are anticipated, and the patient may or may not experience adequate pain relief with codeine. Codeine can be prescribed at standard label-recommended dosage and administration, with monitoring for symptoms of insufficient pain relief. Other opioids not metabolized by CYP2D6 may also be considered (i.e., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone).

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.

Dexlansoprazole
Dexilant®, Kapidex®

Insufficient Exposure to Dexlansoprazole (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

Dexlansoprazole is the R-enantiomer of lansoprazole. The patient's genotype is associated with a significantly decreased dexlansoprazole exposure following standard dosing.

- **For Helicobacter pylori eradication**: A dose increase can be considered and be alert to insufficient response.
- **For other indications**: Be alert to insufficient response and a dose increase can be considered, if needed.

Diazepam
Valium®

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

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

Efavirenz
Sustiva®

Increased Efavirenz Exposure (CYP2B6: Intermediate Metabolizer) — ACTIONABLE

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

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.

Hydrocodone
Vicodin®

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

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 hydrocodone. 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).

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.

Lansoprazole
Prevacid®

Insufficient Exposure to Lansoprazole (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

The patient's genotype is associated with a significantly decreased lansoprazole exposure following standard dosing.

- **For Helicobacter pylori eradication**: Consider prescribing a 4-fold higher dose and be alert to insufficient response.
- **For other indications**: Be alert to insufficient response and consider increasing the dose by 4-fold, if needed.

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.

Methadone
Dolophine®

Increased Methadone Exposure (CYP2B6: Intermediate Metabolizer) — INFORMATIVE

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

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

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

Metoclopramide

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

Reglan®	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.	

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).

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.

Morphine
MS Contin®

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

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

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.

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.

Olanzapine
Zyprexa®

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

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

Omeprazole
Prilosec®

Insufficient Exposure to Omeprazole (CYP2C19: Ultra-Rapid Metabolizer) — ACTIONABLE

The patient's genotype is associated with a significantly decreased omeprazole exposure following standard dosing.

- **For Helicobacter pylori eradication**: Consider prescribing a 3-fold higher dose and be alert to insufficient response.
- **For other indications**: Be alert to insufficient response and consider increasing the dose by 3-fold, if needed.

Oxycodone
Percocet®, Oxycontin®

Possible Altered Response to Oxycodone (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

Decreased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 intermediate metabolizers. However, there is insufficient evidence whether these patients have decreased analgesia when taking oxycodone. 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).

Pantoprazole
Protonix®

Insufficient Exposure to Pantoprazole (CYP2C19: Ultra-Rapid Metabolizer) — ACTIONABLE

The patient's genotype is associated with a significantly decreased pantoprazole exposure following standard dosing.

- **For Helicobacter pylori eradication**: Consider prescribing a 5-fold higher dose and be alert to insufficient response.
- **For other indications**: Be alert to insufficient response and consider increasing the dose by 5-fold, if needed.

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.

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.

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.

Sertraline
Zoloft®

Possible Reduced Response to Sertraline (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

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

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.

Timolol
Timoptic®

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.

Tizanidine
Zanaflex®

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

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

⚠ **Tramadol**
Ultram®

Possible decreased exposure to Tramadol (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype may be associated with a reduced conversion of tramadol to an active metabolite with higher activity. Consider monitoring for reduced effectiveness and titrate the dose if analgesia is not achieved. If titration fails, choose an alternative not as dependent on CYP2D6 metabolism (fentanyl, morphine, hydromorphone, oxymorphone or tapentadol) or try a non-opioid analgesic such as a NSAID or a COX-2 inhibitor.

✓ **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.

✓ **Alfuzosin**
UroXatral®

Normal Response to Alfuzosin — INFORMATIVE

Pharmacogenetic guidance: No genetically-guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Alfuzosin is extensively metabolized by CYP3A4 into pharmacologically inactive metabolites. Alfuzosin is **contraindicated with strong CYP3A4 inhibitors, as the risk for QTc prolongation induced by this drug is increased at higher concentrations**. Take caution when this drug is prescribed with CYP3A4 moderate inhibitors, as drug levels may increase.

✓ **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.

✓ **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.

✓ **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.

✓ **Amphetamine**
Adderall®, Evekeo®

Good Response to Amphetamine salts (COMT: High/Normal COMT Activity) — INFORMATIVE

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

✓ **Amphotericin B**
AmBisome®, Abelcet®

Normal Response to Amphotericin B — ACTIONABLE

Pharmacogenetic guidance: Amphotericin B is excreted very slowly (over weeks to months) by the kidneys with 2 to 5% of a given dose being excreted in the biologically active form. Details of possible metabolic pathways are unknown. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Nephrotoxic medications such as aminoglycosides, cyclosporine, and pentamidine may enhance the potential for amphotericin B-induced renal toxicity, and should be used concomitantly only with great caution. Intensive monitoring of renal function is recommended in patients requiring any combination of nephrotoxic medications.

Anidulafungin
Eraxis®

Normal Response to Anidulafungin
ACTIONABLE

Pharmacogenetic guidance: Anidulafungin undergoes slow chemical degradation to a peptide that lacks antifungal activity and which is subsequently converted to peptidic degradants and eliminated. Hepatic metabolism of anidulafungin has not been observed. Anidulafungin is not a substrate, inducer, or inhibitor of cytochrome P450 enzymes. No genetically guided drug selection or dosing recommendations are available.

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.

Apremilast
Otezla®

Normal Response to Apremilast
ACTIONABLE

Pharmacogenetic guidance: Apremilast is primarily eliminated via both hydrolysis and cytochrome P450-mediated oxidative metabolism (with subsequent glucuronidation). Cytochrome P450-metabolism is mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6. Genetic polymorphisms of these enzymes are not expected to affect the efficacy or safety profiles of apremilast. **Polypharmacy guidance:** The use of metabolizing enzyme inducers (e.g. rifampin, phenobarbital, carbamazepine, phenytoin) with apremilast is not recommended.

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.

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.

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.

Atenolol
Tenormin®

Normal Response to Atenolol
INFORMATIVE

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.

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.

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.

Avanafil
Stendra®

Normal Response to Avanafil — INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Avanafil is extensively metabolized by CYP3A4, therefore **Avanafil should not be used with strong CYP3A4 inhibitors** such as ketoconazole, itraconazole, voriconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, and telithromycin. If taking a moderate CYP3A4 inhibitor, such as erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, or verapamil, the dose should be no more than 50 mg in a 24-hour period. Inducers of CYP3A4 may decrease the concentrations of avanafil.

Azilsartan
Edarbi®, Edarbyclor®

Normal Azilsartan Exposure (CYP2C9: Normal 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.

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.

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.

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.

Brivaracetam
Briviact®

Normal Sensitivity to Brivaracetam (CYP2C19: Ultra-Rapid 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.

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.

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.

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.

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.

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.

Carvedilol
Coreg®

Normal Exposure to Carvedilol — ACTIONABLE

Pharmacogenetic guidance: Carvedilol is metabolized to active metabolites primarily by CYP2D6 and CYP2C9 with lesser contribution from other CYP enzymes (including CYP3A4, CYP2C19, CYP1A2, and CYP2E1). Studies have shown that CYP2D6 poor metabolizers may experience dizziness during up-titration. No genetically guided drug selection or dosing recommendations are recommended. **Polypharmacy guidance**: Carvedilol is a racemic mixture of R(+) and S(-)-carvedilol. Strong CYP2D6 inhibitors may result in increased plasma concentrations of R(+)-carvedilol. It is postulated that this increase in R(+)-carvedilol could be responsible for the dizziness seen during up-titration in these patients.

Caspofungin
Cancidas®

Normal Response to Caspofungin
ACTIONABLE

Pharmacogenetic guidance: Caspofungin is cleared slowly and is metabolized by hydrolysis and N-acetylation. The drug undergoes also spontaneous chemical degradation. Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Co-administration of caspofungin with metabolizing enzyme inducers (e.g., rifampin, efavirenz, nevirapine, phenytoin, or carbamazepine) may result in clinically meaningful reductions in caspofungin concentrations which may require dosing adjustment.

Celecoxib
Celebrex®

Normal Celecoxib Exposure (CYP2C9: Normal Metabolizer)
ACTIONABLE

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

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.

Chlorpromazine
Thorazine®

Normal Response 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.

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.

Clobazam
Onfi®

Normal Sensitivity to Clobazam (CYP2C19: Ultra-Rapid Metabolizer)
ACTIONABLE

The genotype result predicts a rapid or an ultra-rapid metabolizer phenotype, which translates to an increased CYP2C19 function. Rapid and ultra-rapid metabolizers have a higher capacity to metabolize N-desmethylclobazam, the active metabolite of clobazam. However, there is insufficient data to allow calculation of dose adjustment when clobazam is prescribed. Therefore, the dosing recommendation for normal metabolizers is proposed. 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.

Clonazepam

Normal Response to Clonazepam
INFORMATIVE

Klonopin®

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.

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.

Colchicine
Mitigare®

Normal Response to Colchicine
INFORMATIVE

Pharmacogenetic guidance: Colchicine in eliminated both by renal excretion and metabolism. While 50% of the absorbed dose in eliminated unchanged in urine, less than 20% is metabolized by CYP3A4. Glucuronidation is also a metabolic pathway for colchicine. Colchicine is a substrate of P-glycoprotein (encoded by ABCB1 gene) and its efflux by this transporter is important in its disposition. Colchicine has a narrow therapeutic index. Preliminary and limited studies indicate a lack of an effect of CYP3A4 or ABCB1 genetic polymorphisms on clinical response to colchicine in individuals with familial Mediterranean fever (FMF). There are no available genetically-guided drug selection or dosing recommendations. **Polypharmacy guidance:** Because colchicine is a substrate for both the CYP3A4 metabolizing enzyme and the P-glycoprotein efflux transporter, inhibition of either of these pathways may lead to colchicine-related toxicity. Inhibition of both CYP3A4 and P-gp by dual inhibitors such as clarithromycin has been reported to produce life-threatening or fatal colchicine toxicity due to significant increases in systemic colchicine levels. Therefore, concomitant use of colchicine and inhibitors of CYP3A4 or P-glycoprotein should be avoided.

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.

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.

Darifenacin
Enablex®

Normal Response to Darifenacin (CYP2D6: Intermediate Metabolizer)
ACTIONABLE

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

Desvenlafaxine
Pristiq®

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

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

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).

Dexmethylphenidate
Focalin®

Good Response to Dexmethylphenidate (COMT: High/Normal COMT Activity) — INFORMATIVE

The patient's genotype result predicts a higher likelihood of 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.

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.

Dextroamphetamine
Dexedrine®

Good Response to Dextroamphetamine (COMT: High/Normal COMT Activity) — INFORMATIVE

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

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.

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.

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.

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.

Dolasetron
Anzemet®

Normal Response to Dolasetron (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

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

Dolutegravir
Tivicay®, Triumeq®

Normal Response to Dolutegravir — ACTIONABLE

Pharmacogenetic guidance: Dolutegravir is eliminated mainly through metabolism by UGT1A1 and a minor contribution from CYP3A. Although UGT1A1 poor metabolizers or patients taking inhibitors of UGT1A1 activity have increased plasma levels of dolutegravir, these changes are not clinically significant. No dosing adjustments are required for dolutegravir due to genetic variations in UGT1A1. **Polypharmacy guidance**: Coadministration of dolutegravir with drugs that are strong enzyme inducers, such as rifampin, may result in reduced plasma concentrations of this drug.

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.

Doravirine
Pifeltro®

Normal Exposure to Doravirine — ACTIONABLE

Pharmacogenetic guidance: Doravirine is primarily metabolized by CYP3A. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: Doravirine is contraindicated when co-administered with drugs that are strong CYP3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of doravirine. Co-administration of doravirine with drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

Doxazosin
Cardura®

Normal Response to Doxazosin — INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** doxazosin is metabolized by multiple enzymes. There is limited data on the effects of drugs known to influence the metabolism of doxazosin.

Dronabinol
Marinol®

Normal Dronabinol Exposure (CYP2C9: Normal Metabolizer) — ACTIONABLE

The patient's genotype predicts a normal CYP2C9 metabolic activity. Dronabinol can be prescribed at standard label-recommended dosage and administration.

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.

Dutasteride

Normal Response to Dutasteride — INFORMATIVE

Avodart®

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Dutasteride is extensively metabolized in humans by CYP3A4 and CYP3A5. The effect of potent CYP3A4 inhibitors on dutasteride has not been studied. Because of the potential for drug-drug interactions, use caution when prescribing this drug to patients taking potent, chronic CYP3A4 enzyme inhibitors.

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.

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.

Eslicarbazepine
Aptiom®

Normal Response to Eslicarbazepine — 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). 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.

Esomeprazole
Nexium®

Decreased Exposure to Esomeprazole (CYP2C19: Ultra-Rapid Metabolizer) — ACTIONABLE

The patient's genotype is associated with a decreased esomeprazole exposure following standard dosing. There is not enough data to determine the effect of this patient's genotype on efficacy or adverse events for esomeprazole. Consider prescribing esomeprazole at standard label-recommended dosage and administration.

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.

Etravirine
Edurant®

Normal Exposure to Etravirine — ACTIONABLE

Pharmacogenetic guidance: Etravirine is primarily eliminated by metabolism via CYP3A4, CYP2C9 and CYP2C19. The metabolites are subsequently glucuronidated by uridine diphosphate glucuronosyltransferase. Renal elimination of etravirine is negligible. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: Co-administration of etravirine with drugs that inhibit or induce CYP3A4, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse reaction profile of etravirine. Etravirine is an inducer of CYP3A and a weak inhibitor of CYP2C9, CYP2C19 and P-glycoprotein.

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.

Febuxostat
Uloric®

Normal Response to Febuxostat
INFORMATIVE

Pharmacogenetic guidance: Febuxostat is eliminated by both hepatic metabolism and renal excretion. The drug is metabolized both by glucuronidation (40%) and oxidative pathways (35%). The oxidative metabolism involves several cytochrome P450 enzymes (CYPs): CYP1A2, CYP2C8 and CYP2C9 as well as other non-CYP enzymes. Febuxostat is also glucuronidated primarily by UGT1A1 and UGT1A3. Preliminary studies indicate that febuxostat clearance is increased in subjects with UGT1A1*28 allele-UGT1A3*2a allele and decreased in those with the UGT1A1*6 allele. The clinical relevance of these changes is not known. Although serious skin and hypersensitivity reactions have been reported in patients taking febuxostat, there are no genetic biomarkers for predicting such reactions; no genotype-based recommendations are available. **Polypharmacy guidance:** Concomitant administration of febuxostat, a xanthine oxidase inhibitor, with substrate drugs such as theophylline, azathioprine or mercaptopurine could increase plasma concentrations of these drugs resulting in severe toxicity.

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.

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.

Fesoterodine
Toviaz®

Normal Sensitivity to Fesoterodine (CYP2D6: Intermediate Metabolizer)
ACTIONABLE

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

Finasteride
Proscar®

Normal Response to Finasteride
INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: Finasteride is extensively metabolized in humans by CYP3A4. The effects of potent or moderate CYP3A4 inhibitors on finasteride have not been studied. Because of the potential for drug-drug interactions, use caution when prescribing this drug to patients taking CYP3A4 enzyme inhibitors.

Flibanserin
Addyi®

Normal Exposure to Flibanserin (CYP2C19: Ultra-Rapid 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.

Fluconazole
Diflucan®

Normal Response to Fluconazole
ACTIONABLE

Pharmacogenetic guidance: Fluconazole not extensively metabolized and is eliminated primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug and 11% as metabolites. The pharmacokinetics of fluconazole is markedly affected by reduction in renal function. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Fluconazole is a moderate inhibitor of CYP3A4, CYP2C9 and CYP2C19 enzymes. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolized by CYP2C9, CYP2C19 or CYP3A4 should be monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of the drug due to its long half-life.

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.

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.

Flurbiprofen
Ansaid®

Normal Flurbiprofen Exposure (CYP2C9: Normal 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.

Fluvastatin
Lescol®

Normal Fluvastatin Exposure (CYP2C9: Normal Metabolizer)
INFORMATIVE

Fluvastatin plasma concentrations are not expected to increase, and unless other genetic or circumstantial risk factors are present, fluvastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. Other adverse events and predisposing factors include advanced age (≥65), diabetes, hypothyroidism, renal or hepatic impairments, high statin dose, CYP2C9 inhibitors, ABCG2 inhibitors, and female gender.

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.

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.

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.

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.

Fosphenytoin
Cerebyx®

Normal Sensitivity to Fosphenytoin (CYP2C9: Normal Metabolizer) — ACTIONABLE

Fosphenytoin is a prodrug of phenytoin. The genotype results indicate that the patient is a CYP2C9 normal metabolizer. Fosphenytoin can be prescribed at a standard loading dose and a standard maintenance dose. Evaluate response and serum concentrations 7-10 days after starting therapy.

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.

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.

Glimepiride
Amaryl®

Normal Exposure to Glimeperide — 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.

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.

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.

Granisetron
Sancuso®, Sustol®

Normal Response to Granisetron
ACTIONABLE

Pharmacogenetic guidance: Granisetron is extensively metabolized to 7-hydroxygranisetron and 9-desmethylgranisetron by CYP3A4, CYP3A5 and CYP1A1. A preliminary pharmacokinetic study conducted in pregnant women reported an increased granisetron clearance in carriers of the CYP1A1*2A increased function allele and a lower clearance of the drug in subjects with the CYP3A5*3/*3 genotype. The same study showed that genetic polymorphisms within the CYP3A4 or ABCB1 genes, had no effect on granisetron clearance while other reports in cancer patients found an association with granisetron efficacy and ABCB1 genetic polymorphisms. The significance of these preliminary findings is unclear and no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Inducers or inhibitors of CYP1A1 and CYP3A4 enzymes may affect the clearance of granisetron. However, the potential for an in vivo pharmacokinetic interaction with strong CYP3A4 inhibitors such as ketoconazole is not known. Administration of granisetron with metabolizing enzyme inducers, results in a 25% increase in granisetron clearance and the clinical significance of this change is not known.

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.

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.

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.

Ibuprofen
Advil®, Motrin®

Normal Ibuprofen Exposure (CYP2C9: Normal 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.

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.

Irbesartan
Avapro®

Normal Irbesartan Exposure (CYP2C9: Normal Metabolizer) — INFORMATIVE

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

Isavuconazonium
Cresemba®

Normal Response to Isavuconazonium — ACTIONABLE

Pharmacogenetic guidance: Isavuconazonium sulfate is a prodrug that is rapidly hydrolyzed in plasma by butylcholinesterase into its active moiety isavuconazole. Isavuconazole is extensively metabolized CYP3A4 and CYP3A5 and Common genetic polymorphism of these metabolizing enzymes gene are not expected to affect isavuconazole exposure. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Isavuconazole is a sensitive CYP3A4 substrate and its use with strong CYP3A4 inhibitors or inducers contraindicated.

Itraconazole
Sporanox®

Normal Response to Itraconazole — ACTIONABLE

Pharmacogenetic guidance: Itraconazole is extensively metabolized to several metabolites by CYP3A4. The main metabolite is hydroxy-itraconazole, which has in vitro antifungal activity comparable to itraconazole; trough plasma concentrations of this metabolite are about twice those of itraconazole. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Coadministration of itraconazole with potent CYP3A4 inducers may decrease the bioavailability of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be reduced. Therefore, administration of potent CYP3A4 inducers with itraconazole is not recommended and the use of these drugs should be avoided 2 weeks before and during treatment with itraconazole. Potent CYP3A4 inhibitors may increase the bioavailability of itraconazole and these drugs should be used with caution when coadministered with this antifungal. Itraconazole inhibit the metabolism of drugs metabolized by CYP3A4 or transported by P-glycoprotein, which may result in increased plasma concentrations of these drugs and/or their active metabolite(s) when they are coadministered. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. When using concomitant medication, it is recommended that the corresponding label be consulted for information on possible contraindications or need for dose adjustments.

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.

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.

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.

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.

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.

Leflunomide
Arava®

Normal Exposure to Leflunomide (CYP2C19: Ultra-Rapid Metabolizer)
INFORMATIVE

Leflunomide can be prescribed according to standard label-recommended dosage and administration.

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

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.

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.

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.

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.

Lisdexamfetamine
Vyvanse®

Good Response to Lisdexamfetamine (COMT: High/Normal COMT Activity)
INFORMATIVE

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

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.

PATIENT INFORMATION

NAME: Demo Patient
ACC #: DEMO
DOB: 1/1/1900
SEX:

Losartan
Cozaar®, Hyzaar®

Normal Response to Losartan (CYP2C9: Normal Metabolizer) — INFORMATIVE

Losartan is metabolized to its active metabolite by CYP2C9 and CYP3A4. The patient's genotype predicts a normal exposure to losartan and its active metabolite. Losartan can be prescribed at label-recommended dosage and administration.

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), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.

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.

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.

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.

Meloxicam
Mobic®

Normal Meloxicam Exposure (CYP2C9: Normal 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.

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.

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.

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.

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.

Methotrexate
Trexall®

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

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

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

Good Response to Methylphenidate (COMT: High/Normal COMT Activity) — INFORMATIVE

The patient's genotype result predicts a higher likelihood of 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.

Micafungin
Mycamine®

Normal Response to Micafungin — ACTIONABLE

Pharmacogenetic guidance: Micafungin is metabolized by arylsulfatase, catechol-O-methyltransferase and cytochrome P450 enzymes. Even though micafungin is a substrate for and a weak inhibitor of CYP3A in vitro, hydroxylation by CYP3A is not a major pathway for micafungin metabolism in vivo. No genetically guided drug selection or dosing recommendations are available.

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.

Mirabegron

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

Myrbetriq®

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

✓ **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.

✓ **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 an 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.

✓ **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.

✓ **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.

✓ **Nateglinide**
Starlix®

Normal Nateglinide Exposure (CYP2C9: Normal Metabolizer) — INFORMATIVE

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

✓ **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.

✓ **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.

✓ **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.

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.

Ondansetron
Zofran®, Zuplenz®

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

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

Oxcarbazepine
Trileptal®, Oxtellar XR®

Normal Response to Oxcarbazepine — 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). 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%.

Oxybutynin
Ditropan®

Normal Response to Oxybutynin — INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: Oxybutynin is extensively metabolized in humans by CYP3A4, and coadministration of a CYP3A4 strong inhibitor (itraconazole) increases oxybutynin serum concentrations. Therefore, use caution when prescribing this drug to patients taking CYP3A4 enzyme inhibitors.

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.

Paliperidone
Invega®

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

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

Palonosetron
Aloxi®

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

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

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.

Perampanel

Normal Response to Perampanel — INFORMATIVE

Fycompa®

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%.

Phenobarbital
Luminal®

Normal Sensitivity to Phenobarbital (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

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

Phenytoin
Dilantin®

Normal Sensitivity to Phenytoin (CYP2C9: Normal Metabolizer) — ACTIONABLE

The genotype results indicate that the patient is a CYP2C9 substrate normal metabolizer. Phenytoin can be prescribed at a standard loading dose and a standard maintenance dose. Evaluate response and serum concentrations 7-10 days after starting therapy.

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.

Pimozide
Orap®

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

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.

Piroxicam
Feldene®

Normal Piroxicam Exposure (CYP2C9: Normal 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.

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), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.)

Posaconazole

Normal Response to Posaconazole — ACTIONABLE

Noxafil®

Pharmacogenetic guidance: Posaconazole is cleared primarily as unchanged drug. The excreted metabolites in urine and feces account for approximately 17% of the administered dose. The metabolic pathways for posaconazole include direct glucuronidation, minor oxidation and dealkylation. CYP3A4 (and possibly CYP1A1 and CYP3A5), UGT1A4, and P-glycoprotein are enzymes and transporters that play a role in the elimination of this antifungal. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** UGT and P-glycoprotein inhibitors or inducers may affect posaconazole plasma concentrations. Concomitant use of posaconazole and these agents should be avoided unless the benefit to the patient outweighs the risk.

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
Pravachol®

Normal Myopathy Risk (SLCO1B1: Normal Function) — INFORMATIVE

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), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.)

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.

Primidone
Mysoline®

Normal Sensitivity to Primidone (CYP2C19: Ultra-Rapid 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.

Proguanil
Malarone®

Normal Exposure to Proguanil — INFORMATIVE

Pharmacogenetic guidance: Proguanil is a pro-drug that is primarily metabolized by CYP2C19 to its active metabolite, cycloguanil. Preliminary studies indicate that individuals with reduced CYP2C19 function, have reduced cycloguanil exposure compared to subjects with normal CYP2C19 function, but there is considerable overlap of cycloguanil and proguanil metabolic ratios across CYP2C19 metabolizer status. The clinical relevance of this change is not well understood and there is insufficient data to calculate dose adjustments. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: Co-administration of proguanil with a strong CYP2C19 inhibitor may result in lower cycloguanil (higher proguanil) exposure.

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.

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.

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.

Rabeprazole
Aciphex®

Normal Exposure to Rabeprazole (CYP2C19: Ultra-Rapid Metabolizer)
INFORMATIVE

The patient's genotype is associated with a decreased rabeprazole exposure following standard dosing. There is not enough data to determine the effect of this patient's genotype on efficacy or adverse events for rabeprazole. Consider prescribing rabeprazole at standard label-recommended dosage and administration.

Raltegravir
Isentress®, Dutrebis®

Normal Response to Raltegravir
ACTIONABLE

Pharmacogenetic guidance: Raltegravir is eliminated mainly through metabolism by UGT1A1. Although UGT1A1 poor metabolizers or patients taking inhibitors of UGT1A1 activity have increased plasma levels of raltegravir, these changes are not clinically significant. No dosing adjustments are required for raltegravir in patients who carry genetic variants of UGT1A1. **Polypharmacy guidance:** Coadministration of raltegravir with drugs that are strong inducers of UGT1A1, such as rifampin, may result in reduced plasma concentrations of this drug.

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.

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.

Rilpivirine

Normal Exposure to Rilpivirine
ACTIONABLE

Intelence®

Pharmacogenetic guidance: Rilpivirine is primarily eliminated by metabolism via CYP3A4. No genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance**: Co-administration of rilpivirine with drugs that induce or inhibit CYP3A4 may affect the plasma concentrations of rilpivirine.

Risperidone
Risperdal®

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

Although the patient's genotype is associated with changes in the concentrations of both risperidone and its active metabolite, no relationship has been determined between the plasma concentrations of these active substances and the clinical effectiveness or tolerability.

Consider initiating according to standard label-recommended dosage and administration. Dosing is individualized based on the patient's tolerability and clinical response. The patient's genotype may be associated with a lower maintenance dose.

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.

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.

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), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.)

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.

Sildenafil
Viagra®

Normal Response to Sildenafil — INFORMATIVE

Pharmacogenetic guidance: Preliminary findings indicate that sildenafil exposure is 1.5 times higher in individuals with CYP3A5*3/*3 genotype compared to those with CYP3A5*1/*1 genotype. The clinical significance of this change is unknown. **Polypharmacy guidance:** Sildenafil is metabolized by CYP3A4 (major route) and CYP2C9 (minor route). **In patients taking strong CYP3A inhibitors, sildenafil exposure is significantly increased, and it is recommended not to exceed a maximum single dose of 25 mg in a 48-hour period.** Inducers of CYP3A may decrease the concentration of the drug.

✓ **Silodosin**
Rapaflo®

Normal Response to Silodosin — INFORMATIVE

Pharmacogenetic guidance: silodosin is extensively metabolized by CYP3A4 into pharmacologically inactive metabolites. no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** silodosin is contraindicated with potent CYP3A4 inhibitors, as the risk for serious adverse events is increased at higher concentrations. Use caution when this drug is prescribed with CYP3A4 moderate inhibitors, as drug levels may increase.

✓ **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), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.

✓ **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.

✓ **Solifenacin**
Vesicare®

Normal Response to Solifenacin — INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Coadministration of a CYP3A4 strong inhibitor increases solifenacin serum concentrations significantly. **Therefore, it is recommended not to exceed a 5 mg daily dose of solifenacin when coadministered with strong CYP3A4 inhibitors, as the risk for QTc prolongation induced by this drug is increased at higher concentrations.** Although the effects of moderate CYP3A4 inhibitors were not examined, use caution when this drug is administered with moderate CYP3A4 inhibitors.

✓ **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.

✓ **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.

✓ **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.

✓ **Tacrolimus**
Prograf®

Typical response to Tacrolimus (CYP3A5: Poor Metabolizer) — ACTIONABLE

The genotype result predicts that the patient does not express the CYP3A5 protein. Therefore, there is no risk that the patient may metabolize tacrolimus more rapidly. Careful titration of tacrolimus in response to therapeutic drug monitoring is recommended until a favorable response is achieved.

Tadalafil
Cialis®

Normal Response to Tadalafil
INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** Tadalafil is extensively metabolized by CYP3A4. **Tadalafil for Use as Needed** — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of vardenafil is 10 mg, not to exceed once every 72 hours. **Tadalafil for Once Daily Use** — For patients taking concomitant strong inhibitors of CYP3A4, the maximum recommended dose is 2.5 mg. Although specific interactions have not been studied, other CYP3A4 moderate inhibitors would likely increase tadalafil exposure. The exposure of tadalafil is reduced when coadministered with rifampin or other CYP3A4 inducers. This can be anticipated to decrease the efficacy of tadalafil for once-daily use, though the magnitude of decreased efficacy is unknown.

Tamsulosin
Flomax®

Normal Response to Tamsulosin (CYP2D6: Intermediate Metabolizer)
ACTIONABLE

Tamsulosin plasma concentrations may be elevated in CYP2D6 intermediate metabolizers. However, there is insufficient data related to the clinical impact of this change, and therefore this drugs can be prescribed at standard label-recommended dosage and administration.

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.

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.

Terazosin
Hytrin®

Normal Response to Terazosin
INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available. **Polypharmacy guidance:** The enzymes involved in metabolizing terazosin have not been characterized.

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).

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.

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.

Tofacitinib
Xeljanz®

Normal Exposure to Tofacitinib
INFORMATIVE

Pharmacogenetic guidance: Tofacitinib is metabolized primarily by CYP3A4 with some contribution from CYP2C19. Genetic variations in the CYP2C19 gene do not significantly influence tofacitinib exposure. Tofacitinib may be prescribed at standard dosing, but consider a dose reduction if a CYP2C19 poor metabolizer is also prescribed a CYP3A4 inhibitor such as ketoconazole, erythromycin, diltiazem, troleandomycin, nefazodone, fluconazole, verapamil or HIV protease inhibitors. **Polypharmacy guidance**: Tofacitinib dose should be reduced if a patient is taking strong CYP3A4 inhibitors (e.g., ketoconazole), or if a patient is taking a moderate CYP3A4 inhibitor (e.g., alprazolam) with a strong CYP2C19 inhibitor (e.g., fluconazole).

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.

Tolterodine
Detrol®

Normal Sensitivity to Tolterodine (CYP2D6: Intermediate Metabolizer)
INFORMATIVE

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

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.

Torsemide
Demadex®

Normal Torsemide Exposure (CYP2C9: Normal Metabolizer)
INFORMATIVE

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

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.

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.

Trospium
Sanctura®

Normal Response to Trospium
INFORMATIVE

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: CYP enzymes do not contribute significantly to the elimination of trospium. No major drug-drug interactions are expected with CYP inhibitors or inducers.

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.

Valproic Acid
Depakote®, 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.

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.

Vardenafil
Levitra®

Normal Response to Vardenafil
ACTIONABLE

Pharmacogenetic guidance: Preliminary findings indicate that vardenafil exposure is 3 times higher in individuals with CYP3A5*3/*3 genotype compared to those with CYP3A5*1/*1 genotype. The clinical impact of this change is unknown. **Polypharmacy guidance:** The dosage of vardenafil may require adjustment in patients receiving strong CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, atazanavir, or clarithromycin, as well as in patients receiving moderate CYP3A4 inhibitors such as erythromycin. **For ritonavir, a single dose of 2.5 mg vardenafil should not be exceeded in a 72-hour period. For indinavir, saquinavir, atazanavir, or ketoconazole: 400 mg daily. For itraconazole: 400 mg daily. For clarithromycin: a single dose of 2.5 mg vardenafil should not be exceeded in a 24-hour period. For ketoconazole: 200 mg daily. For itraconazole: 200 mg daily. For erythromycin: a single dose of 5 mg vardenafil should not be exceeded in a 24-hour period.** Inducers of CYP3A4 may decrease the concentrations of vardenafil.

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.

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.

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).

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.

Warfarin
Coumadin®

Average Dosing Requirements are Expected (CYP2C9 *1/*1; 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.

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.).

Zonisamide
Zonegran®

Normal Sensitivity to Zonisamide (CYP2C19: Ultra-Rapid Metabolizer) — INFORMATIVE

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

4U Health

PATIENT INFORMATION

NAME: **Demo Patient**
ACC #: DEMO
DOB: 1/1/1900
SEX:

Test Details

Gene	Genotype	Phenotype	Alleles Tested
ANKK1/DRD2	DRD2:Taq1A G/G	**Unaltered DRD2 function**	DRD2:Taq1A
Apolipoprotein E	ε3/ε3	**Normal APOE function**	ε2, ε4, (ε3 is reference)
COMT	Val158Met G/G	**High/Normal COMT Activity**	Val158Met
CYP1A2	*1A/*1L	**Normal Metabolizer- Possible Inducibility**	*1C, *1D, *1F, *1K, *1L, *1V, *1W
CYP2B6	*1/*6	**Intermediate Metabolizer**	*6, *9
CYP2C19	*17/*17	**Ultra-Rapid Metabolizer**	*2, *3, *4A, *4B, *6, *7, *8, *9, *10, *17
CYP2C9	*1/*1	**Normal Metabolizer**	*2, *3, *4, *5, *6, *8, *11, *27
CYP2D6	*10/*17	**Intermediate Metabolizer**	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *114, *14, *17, *29, *35, *41
CYP3A4	*1/*1B	**Normal Metabolizer**	*1B, *22
CYP3A5	*3/*6	**Poor Metabolizer**	*2, *3, *6, *7
F2 **F5**	rs1799963 GG rs6025 CC	**Normal Risk of Thrombosis**	rs1799963, rs6025
ITGB3	176T>C T/T	**Normal Platelet Reactivity**	176T>C
LPA	rs10455872 A/A rs3798220 T/T	**No increased risk of cardiovascular disease**	rs3798220, rs10455872
MTHFR	c.665C>T GG	**Normal MTHFR Activity**	c.1286A>C, c.665C>T
MTHFR	c.1286A>C GT c.665C>T GG	**No Increased Risk of Hyperhomocysteinemia**	c.1286A>C, c.665C>T
OPRM1	A118G A/A	**Normal OPRM1 Function**	A118G
SLCO1B1	521T>C T/T	**Normal Function**	521T>C
TPMT	*1/*1	**Normal Metabolizer**	*2, *3A, *3B, *3C
VKORC1	-1639G>A G/G	**Low Warfarin Sensitivity**	-1639G>A

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

Limitation: *This test will not detect all the known mutations that result in altered or inactive tested genes. Absence of a detectable gene mutation or polymorphism does not rule out the possibility that a patient has intermediate or high sensitivity phenotypes due to the presence of an undetected polymorphism or due to drug-drug interactions. There may be other genetic factors impacting individual patient dosing that are not included in this test.*

Disclaimer: *This test was developed and its performance characteristics determined by Vision Laboratories. It has not been cleared or approved by the US Food and Drug Administration (FDA). The FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. Only a physician, pharmacist or other healthcare professional should advise a patient on the use of information in this report.*

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.

4U Health

PATIENT INFORMATION

NAME: **Demo Patient**
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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.

Lab Director: Lekh Sharma, Ph.D., MT (AAB), TC (NRCC) | CLIA: 44D2080585 | 6130 Shallowford Road, 100, Chattanooga TN 37421 | visionlaboratories.com | 1.844.484.3522

4U Health

REPORT DETAILS
Name: Demo Patient
DOB: 1/1/1900
ACC #: DEMO

Pharmacogenetic Test Summary

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CYP2C19	*17/*17	Ultra-Rapid Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*10/*17	Intermediate Metabolizer
CYP3A4	*1/*1B	Normal Metabolizer
CYP3A5	*3/*6	Poor Metabolizer
Factor II	rs1799963 GG	Normal Thrombosis Risk
Factor V Leiden	rs6025 CC	Normal Thrombosis Risk
ITGB3	176T>C T/T	Normal Platelet Reactivity
LPA	rs10455872 A/A	Wild-type for rs10455872
LPA	rs3798220 T/T	Wild-type for rs3798220
MTHFR	c.665C>T GG	Normal MTHFR Activity
MTHFR	c.1286A>C GT	Reduced MTHFR Activity
OPRM1	A118G A/A	Normal OPRM1 Function
SLCO1B1	521T>C T/T	Normal Function
TPMT	*1/*1	Normal Metabolizer
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity

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