Manchester University

FOR ACADEMIC PURPOSES ONLY - NOT FOR CLINICAL USE

PATIENT INFORMATION		SPECIMEN DETAILS		ORDERED BY
NAME:	Patient ob793tc	**SPECIMEN TYPE:**		
ACC #:	ob793tc	**COLLECTION DATE:**		
DOB:	1/1/1900	**RECEIVED DATE:**		
SEX:		**REPORT DATE:**	11/11/2022	

Complete Panel

Risk Management

✓ Type III Hyperlipoproteinemia

Not Associated with Type III Hyperlipoproteinemia

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

✓ Hyperhomocysteinemia - Depression

No Increased Risk of Hyperhomocysteinemia

The patient carries one copy of the MTHFR c.665C>T variant (heterozygous). MTHFR enzyme activity is reduced (60% of normal activity).
Patients diagnosed with depression often have low folate levels and homocysteine is a highly sensitive marker of folate status. Functional folate deficiency is indicated by elevated homocysteine. The patient's small reduction in MTHFR activity is not a risk factor for hyperhomocysteinemia.
Patients diagnosed with depression: as lower folate levels are associated with poorer antidepressant response, and baseline levels of folate within the normal range predict antidepressant response, testing for homocysteine levels and serum folate levels may be informative for this patient before prescribing methylfolate as an antidepressant-augmenting agent.

✓ Thrombophilia

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 the MTHFR c.665C>T variant (heterozygous) and does not carry the MTHFR c.1286A>C variant. MTHFR enzyme activity is reduced (60% of normal activity).
Based on results for the MTHFR c.665C>T variant, the patient has a small reduction in MTHFR activity, which is not a risk factor for hyperhomocysteinemia. Hyperhomocysteinemia is associated with a risk for venous thromboembolism (VTE). Unless other risk factors are present, the patient is not expected to have an increased risk for VTE.
The patient's MTHFR activity is slightly reduced.

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

PATIENT INFORMATION	SPECIMEN DETAILS	ORDERED BY
NAME: Patient ob793tc	**SPECIMEN TYPE:**	
ACC #: ob793tc	**COLLECTION DATE:**	
DOB: 1/1/1900	**RECEIVED DATE:**	
SEX:	**REPORT DATE:** 11/11/2022	

Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Anticancer Agents	**Antifolates**		Methotrexate (Trexall®)	
Cardiovascular	**Angiotensin II Receptor Antagonists**	Candesartan (Atacand®) Eprosartan (Teveten®) Olmesartan (Benicar®) Telmisartan (Micardis®) Valsartan (Diovan®, Entresto®)		
	Antiarrhythmics	Amiodarone (Nexterone®, Pacerone®) Disopyramide (Norpace®) Quinidine (Quinidine®) Sotalol (Betapace®, Sorine®, Sotylize®)		
	Anticoagulants	Apixaban (Eliquis®) Betrixaban (Bevyxxa®) Dabigatran Etexilate (Pradaxa®) Edoxaban (Savaysa®) Fondaparinux (Arixtra®) Rivaroxaban (Xarelto®)		
	Antiplatelets	Prasugrel (Effient®) Ticagrelor (Brilinta®) Vorapaxar (Zontivity®)		Clopidogrel (Plavix®)
	Beta Blockers	Atenolol (Tenormin®) Bisoprolol (Zebeta®) Labetalol (Normodyne®, Trandate®)		
	Statins			Atorvastatin (Lipitor®) Lovastatin (Mevacor®, Altoprev®, Advicor®) Pitavastatin (Livalo®) Pravastatin (Pravachol®) Rosuvastatin (Crestor®) Simvastatin (Zocor®)
Diabetes	**Meglitinides**	Nateglinide (Starlix®)	Repaglinide (Prandin®, Prandimet®)	
	Sulfonylureas	Chlorpropamide (Diabinese®) Glimepiride (Amaryl®) Glipizide (Glucotrol®) Glyburide (Micronase®) Tolbutamide (Orinase®)		
	Antiemetics	Aprepitant (Emend-oral®) Fosaprepitant (Emend-IV®) Rolapitant (Varubi®)		

PATIENT INFORMATION	SPECIMEN DETAILS	ORDERED BY
NAME: Patient ob793tc	**SPECIMEN TYPE:**	
ACC #: ob793tc	**COLLECTION DATE:**	
DOB: 1/1/1900	**RECEIVED DATE:**	
SEX:	**REPORT DATE:** 11/11/2022	

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Gastrointestinal	Proton Pump Inhibitors	Dexlansoprazole (Dexilant®, Kapidex®) Esomeprazole (Nexium®) Lansoprazole (Prevacid®) Omeprazole (Prilosec®) Pantoprazole (Protonix®) Rabeprazole (Aciphex®)		
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®)		
Pain	Fibromyalgia Agents	Milnacipran (Savella®)		
	Muscle Relaxants	Cyclobenzaprine (Flexeril®, Amrix®) Metaxalone (Skelaxin®) Methocarbamol (Robaxin®) Tizanidine (Zanaflex®)	Carisoprodol (Soma®)	
	NSAIDs	Diclofenac (Voltaren®) Indomethacin (Indocin®) Ketoprofen (Orudis®) Ketorolac (Toradol®) Nabumetone (Relafen®) Naproxen (Aleve®) Sulindac (Clinoril®)		
	Opioids	Alfentanil (Alfenta®) Buprenorphine (Butrans®, Buprenex®) Fentanyl (Actiq®) Hydrocodone (Vicodin®) Hydromorphone (Dilaudid®, Exalgo®) Levorphanol (Levo Dromoran®) Meperidine (Demerol®) Oxymorphone (Opana®, Numorphan®) Sufentanil (Sufenta®) Tapentadol (Nucynta®)	Methadone (Dolophine®) Morphine (MS Contin®)	
	Antiaddictives		Bupropion (Wellbutrin®, Zyban®, Aplenzin®, Contrave®) Naltrexone (Vivitrol®, Contrave®)	

PATIENT INFORMATION	SPECIMEN DETAILS	ORDERED BY
NAME: Patient ob793tc	**SPECIMEN TYPE:**	
ACC #: ob793tc	**COLLECTION DATE:**	
DOB: 1/1/1900	**RECEIVED DATE:**	
SEX:	**REPORT DATE:** 11/11/2022	

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Psychotropic	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®)		
	Anticonvulsants	Cannabidiol (Epidiolex®) Carbamazepine (Tegretol®, Carbatrol®, Epitol®) Eslicarbazepine (Aptiom®) Ethosuximide (Zarontin®) Ezogabine (Potiga®) Felbamate (Felbatol®) Gabapentin (Neurontin®) Lacosamide (Vimpat®) Lamotrigine (Lamictal®) Levetiracetam (Keppra®) Oxcarbazepine (Trileptal®, Oxtellar XR®) Perampanel (Fycompa®) Pregabalin (Lyrica®) Rufinamide (Banzel®) Tiagabine (Gabitril®) Topiramate (Topamax®) Valproic Acid (Depakene®) Vigabatrin (Sabril®)	Brivaracetam (Briviact®) Phenobarbital (Luminal®) Primidone (Mysoline®) Zonisamide (Zonegran®)	
	Antidementia Agents	Memantine (Namenda®)		
	Antidepressants	Duloxetine (Cymbalta®) Levomilnacipran (Fetzima®) Mirtazapine (Remeron®) Trazodone (Oleptro®) Vilazodone (Viibryd®)	Citalopram (Celexa®) Escitalopram (Lexapro®) Sertraline (Zoloft®)	Amitriptyline (Elavil®) Clomipramine (Anafranil®) Doxepin (Silenor®) Imipramine (Tofranil®) Trimipramine (Surmontil®)
	Antipsychotics	Asenapine (Saphris®) Cariprazine (Vraylar®) Clozapine (Clozaril®) Fluphenazine (Prolixin®) Loxapine (Loxitane®, Adasuve®) Lurasidone (Latuda®) Olanzapine (Zyprexa®) Pimavanserin (Nuplazid®) Quetiapine (Seroquel®) Thiothixene (Navane®) Trifluoperazine (Stelazine®) Ziprasidone (Geodon®)		
	Benzodiazepines	Alprazolam (Xanax®) Clonazepam (Klonopin®)	Clobazam (Onfi®) Diazepam (Valium®)	
	Other Neurological Agents		Flibanserin (Addyi®)	

PATIENT INFORMATION	SPECIMEN DETAILS	ORDERED BY
NAME: Patient ob793tc	**SPECIMEN TYPE:**	
ACC #: ob793tc	**COLLECTION DATE:**	
DOB: 1/1/1900	**RECEIVED DATE:**	
SEX:	**REPORT DATE:** 11/11/2022	

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Rheumatology	Anti-Hyperuricemics and Anti-Gout Agents	Colchicine (Mitigare®) Febuxostat (Uloric®)		
	Immunomodulators	Apremilast (Otezla®) Tofacitinib (Xeljanz®)	Leflunomide (Arava®)	
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®) Terazosin (Hytrin®)		
	Antispasmodics for Overactive Bladder	Oxybutynin (Ditropan®) Solifenacin (Vesicare®) Trospium (Sanctura®)		
	Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra®) Sildenafil (Viagra®) Tadalafil (Cialis®) Vardenafil (Levitra®)		

Dosing Guidance

Amitriptyline
Elavil®

Increased Amitriptyline Exposure (CYP2C19: Poor Metabolizer) — ACTIONABLE

The patient's absent CYP2C19 activity is likely to result in a significantly decreased metabolism of amitriptyline to nortriptyline and a subsequent increase in amitriptyline exposure leading to side effects.

Psychiatric Conditions: Consider an alternative medication. If amitriptyline is warranted, consider a 50% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Neuropathic Pain: Amitriptyline can be prescribed according to standard recommended dosage and administration when lower doses are considered. If higher doses are warranted, consider a 50% reduction of the recommended dose and monitor patient for side effects.

Atorvastatin
Lipitor®

Increased Atorvastatin Exposure (SLCO1B1: Poor Function) — ACTIONABLE

The patient's genotype is associated with possible increased atorvastatin exposure. Patients may be at an increased myopathy risk.

Consider atorvastatin starting dose ≤20 mg. If doses >20 mg are needed, consider rosuvastatin or combination therapy (e.g., atorvastatin plus a non-statin guideline directed therapy).

Clomipramine
Anafranil®

Increased Clomipramine Exposure (CYP2C19: Poor Metabolizer) — INFORMATIVE

The patient's absent CYP2C19 activity is likely to result in a significantly decreased metabolism of clomipramine to desmethyl clomipramine and a subsequent increase in clomipramine exposure leading to side effects.

Psychiatric Conditions: Consider an alternative medication. If clomipramine is warranted, consider a 50% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Clopidogrel
Plavix®

Significantly Reduced Exposure to Clopidogrel Active Metabolite (CYP2C19: Poor Metabolizer) — ACTIONABLE

The patient's genotype is associated with possible decreased clopidogrel exposure. Patients may be at an increased risk for adverse cardiac and cerebrovascular events.

Cardiovascular and Neurovascular Indications:
Consider an alternative such as prasugrel (contraindicated in TIA/stroke) or ticagrelor.

Doxepin
Silenor®

Increased Doxepin Exposure (CYP2C19: Poor Metabolizer) — INFORMATIVE

The patient's absent CYP2C19 activity is likely to result in a significantly decreased metabolism of doxepin to desmethyl doxepin and a subsequent increase in doxepin exposure leading to side effects.

Psychiatric Conditions: Consider an alternative medication. If doxepin is warranted, consider a 50% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

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

Imipramine
Tofranil®

Increased Imipramine Exposure (CYP2C19: Poor Metabolizer) — INFORMATIVE

The patient's absent CYP2C19 activity is likely to result in a significantly decreased metabolism of imipramine to desipramine and a subsequent increase in imipramine exposure leading to side effects.

Psychiatric Conditions: Consider an alternative medication. If imipramine is warranted, consider a 50% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Lovastatin

Increased Lovastatin Exposure (SLCO1B1: Poor Function) — ACTIONABLE

Mevacor®, Altoprev®, Advicor®

The patient's genotype is associated with possible increased lovastatin exposure. Patients may be at an increased myopathy risk.
Consider an alternative statin based on disease-specific guidelines.

Pitavastatin
Livalo®

Increased Pitavastatin Exposure (SLCO1B1: Poor Function) — ACTIONABLE

The patient's genotype is associated with possible increased pitavastatin exposure. Patients may be at an increased myopathy risk.

Consider starting pitavastatin at doses ≤1 mg. If doses >1 mg are needed, consider an alternative statin or combination therapy (e.g., pitavastatin plus a non-statin guideline directed medical therapy).

Pravastatin
Pravachol®

Increased Pravastatin Exposure (SLCO1B1: Poor Function) — ACTIONABLE

The patient's genotype is associated with possible increased pravastatin exposure. Patients may be at an increased myopathy risk with doses >40 mg.

Consider starting pravastatin at doses ≤40 mg. If doses >40 mg are needed, consider increased monitoring, an alternative statin, or combination therapy (e.g., pravastatin plus a non-statin guideline directed medical therapy).

Rosuvastatin
Crestor®

Increased Rosuvastatin Exposure (SLCO1B1: Poor Function) — ACTIONABLE

The patient's genotype is associated with possible increased rosuvastatin exposure. Patients may be at an increased myopathy risk with doses >20 mg.

Consider starting rosuvastatin at doses ≤20 mg. If doses >20 mg are needed, consider combination therapy (e.g., rosuvastatin plus a non-statin guideline directed medical therapy).

Simvastatin
Zocor®

Increased Simvastatin Exposure (SLCO1B1: Poor Function) — ACTIONABLE

The patient's genotype is associated with possible increased simvastatin exposure. Patients may be at an increased myopathy risk.

Consider an alternative statin.

Trimipramine
Surmontil®

Increased Trimipramine Exposure (CYP2C19: Poor Metabolizer) — INFORMATIVE

The patient's absent CYP2C19 activity is likely to result in a significantly decreased metabolism of trimipramine to desmethyl trimipramine and a subsequent increase in trimipramine exposure leading to side effects.

Psychiatric Conditions: Consider an alternative medication. If trimipramine is warranted, consider a 50% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Voriconazole
Vfend®

Increased Sensitivity to Voriconazole (CYP2C19: Poor Metabolizer) — ACTIONABLE

Voriconazole plasma concentrations are expected to be high if a standard dose is used, which may increase the risk of adverse events (hepatotoxicity, visual disturbances/halucinations and neurologic disorders). Consider an alternative medication that is not dependent on CYP2C19 metabolism, such as isavuconazole, liposomal amphotericin B or posaconazole. If voriconazole is warranted, consider a decreased dose and careful therapeutic drug monitoring.

Brivaracetam
Briviact®

Possible Sensitivity to Brivaracetam (CYP2C19: Poor Metabolizer) — ACTIONABLE

Brivaracetam is primarily metabolized by hydrolysis and to a minor extent by hydroxylation, which is mediated by CYP2C19. In CYP2C19 poor metabolizers, the plasma concentration of brivaracetam is increased by 42%. Brivaracetam dose reduction may be required. Monitor the patient for any signs of adverse reaction or drug toxicity.

Bupropion

Altered Bupropion Exposure (CYP2B6: Intermediate Metabolizer) — INFORMATIVE

Wellbutrin®, Zyban®, Aplenzin®, Contrave®

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

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

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

Carisoprodol
Soma®

Altered Sensitivity to Carisoprodol (CYP2C19: Poor Metabolizer) — **INFORMATIVE**

CYP2C19 poor metabolizers have a lower capacity to metabolize carisoprodol to meprobamate, and may therefore have an increased risk of developing concentration-dependent side effects such as drowsiness and hypotension when receiving standard doses of carisoprodol. Carisoprodol should be used with caution in patients with reduced CYP2C19 activity. Because there is insufficient data to allow calculation of dose adjustment, consider reducing the dose or using an alternative medication.

Citalopram
Celexa®

Increased Sensitivity to Citalopram (CYP2C19: Poor Metabolizer) — **ACTIONABLE**

At standard label-recommended dosage, citalopram plasma concentrations levels are expected to be high and adverse events may occur. Consider a 50% reduction of the recommended starting dose to help prevent concentration-dependent adverse events. Dose escalations over 20 mg/day for CYP2C19 poor metabolizers are not recommended. An alternative medication may also be considered.

Clobazam
Onfi®

Increased Sensitivity to Clobazam (CYP2C19: Poor Metabolizer) — **ACTIONABLE**

In CYP2C19 poor metabolizers, plasma levels of the active metabolite N-desmethylclobazam were 5-fold higher than those found in CYP2C19 normal metabolizers. Therefore, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight. Patients should be titrated initially to 10 mg /day (≤30 kg body weight) or 20 mg/day (>30 kg body weight). If necessary and based upon clinical response, an additional titration to the maximum doses 20 mg/day (≤30 kg body weight) or 40 mg/day (>30 kg body weight) may be started on day 21.

Diazepam
Valium®

Increased Sensitivity to Diazepam (CYP2C19: Poor Metabolizer) — **INFORMATIVE**

CYP2C19 poor metabolizers have a lower capacity to metabolize diazepam and its active metabolite nordiazepam. Therefore, they may experience more concentration-dependent side effects, such as increased or prolonged sedation, if treated with standard doses of diazepam. Diazepam should be used with caution in these patients, and a reduced dose or longer dosing interval may be needed.

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).

Escitalopram
Lexapro®

Increased Sensitivity to Escitalopram (CYP2C19: Poor Metabolizer) — **ACTIONABLE**

At standard label-recommended dosage, escitalopram plasma concentrations levels are expected to be high and adverse events may occur. Consider a 50% reduction of the recommended starting dose to help prevent concentration-dependent adverse events. An alternative medication may also be considered.

Flibanserin
Addyi®

Increased Exposure to Flibanserin (CYP2C19: Poor 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. CYP2C19 poor metabolizers have increased flibanserin exposure compared to CYP2C19 normal metabolizers. As this change in exposure may increase the risk of hypotension, syncope, and CNS depression, advise and monitor patient more closely for serious adverse effects.

Leflunomide
Arava®

Increased Exposure to Leflunomide (CYP2C19: Poor Metabolizer) — INFORMATIVE

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

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

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.

Methotrexate
Trexall®

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

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

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.

Phenobarbital
Luminal®

Possible Sensitivity to Phenobarbital (CYP2C19: Poor Metabolizer) — INFORMATIVE

CYP2C19 is partly involved in the metabolism of phenobarbital, and although CYP2C19 poor metabolizers have a 20% lower clearance of phenobarbital than normal metabolizers, no significant changes in clinical outcome has been reported with this antiepileptic drug. Therefore, phenobarbital can be prescribed at standard label-recommended dosage and administration with a closer monitoring for adverse events.

Primidone

Possible Sensitivity to Primidone (CYP2C19: Poor Metabolizer) — INFORMATIVE

Mysoline®

CYP2C19 is partly involved in the metabolism of primidone and although CYP2C19 poor metabolizers have a 20% lower clearance of phenobarbital (active metabolite) than normal metabolizers, no significant changes in clinical outcome has been reported with this antiepileptic drug. Therefore, primidone can be prescribed at standard label-recommended dosage and administration with a closer monitoring for adverse events.

Repaglinide

Prandin®, Prandimet®

Possible Sensitivity to Repaglinide (SLCO1B1: Poor Function) — INFORMATIVE

The patient carries two copies of the the SLCO1B1 521T>C variant. This genotype is associated with reduced transporter function. Patients with this genotype are probably more susceptible to the blood glucose-lowering effect of repaglinide than those with other genotypes. Based on preliminary findings, the optimal starting dose of repaglinide may be lower in these patients. Selecting a lower starting dose may reduce the time needed to reach the correct maintenance dose, potentially with a smaller risk of hypoglycaemia. Repaglinide dose should be adjusted according to the actual blood glucose-lowering response.

Sertraline

Zoloft®

Increased Sensitivity to Sertraline (CYP2C19: Poor Metabolizer) — INFORMATIVE

At standard label-recommended dosage, sertraline levels are expected to be high, and adverse events may occur. **Consider a 50% decrease of the initial dose and titrate based on the clinical response and tolerability.** An alternative medication may also be considered.

Tacrolimus

Prograf®

Insufficient Response to Tacrolimus (CYP3A5: Normal Metabolizer) — ACTIONABLE

The genotype result predicts that the patient expresses the CYP3A5 protein. Therefore, the patient may metabolize tacrolimus more rapidly, resulting in low tacrolimus trough levels. Studies have shown patients with this genotype may be at increased risk for acute transplant rejection while taking a standard dose of tacrolimus. Therefore, increasing starting dose 1.5 to 2 times recommended starting dose with close monitoring is strongly recommended to achieve therapeutic effect. Total starting dose should not exceed 0.3mg/kg/day.

Zonisamide

Zonegran®

Possible Sensitivity to Zonisamide (CYP2C19: Poor Metabolizer) — INFORMATIVE

CYP2C19 is partly involved in the metabolism of zonisamide, and although preliminary studies show that CYP2C19 poor metabolizers have a slightly lower (30%) zonisamide clearance than normal metabolizers, no significant change in the clinical outcome has been reported with this antiepileptic drug. Therefore, zonisamide can be prescribed at standard label -recommended dosage and administration with a closer monitoring for adverse events.

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®

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.

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.

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.

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.

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.

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.

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.

Clonazepam
Klonopin®

Normal Response to Clonazepam — **INFORMATIVE**

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

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.

Clozapine
Clozaril®

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

Clozapine can be prescribed at standard label-recommended dosage and administration. Careful titration is recommended with monitoring until a favorable response is achieved. Extrinsic factors such as diet (cruciferous vegetables, heavy coffee consumption, char-grilled meats) smoking, and certain medications (omeprazole, modafinil, carbamazepine) are known to increase CYP1A2 activity.

Colchicine
Mitigare®

Normal Response to Colchicine — **INFORMATIVE**

Pharmacogenetic guidance: Colchicine in eliminated both by renal excretion and metabolism. While 50% of the absorbed dose is 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.

Dexlansoprazole
Dexilant®, Kapidex®

Increased Exposure to Dexlansoprazole (CYP2C19: Poor Metabolizer) — INFORMATIVE

The patient's genotype is associated with an increased dexlansoprazole exposure following standard dosing. Consider prescribing dexlansoprazole at standard label-recommended dosage and administration. Once efficacy is achieved, in the setting of chronic PPI therapy (beyond 12 weeks), consider a 50% reduction in the daily dose to minimize the risk of adverse events from prolonged acid suppression.

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®

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.

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.

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.

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.

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.

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
Avodart®

Normal Response to Dutasteride — INFORMATIVE

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®

Slightly Increased Exposure to Esomeprazole (CYP2C19: Poor Metabolizer) — INFORMATIVE

The patient's genotype may be associated with a slightly increased esomeprazole exposure following standard dosing. 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.

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.

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.

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.

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.

✓ 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.

✓ Glimepiride
Amaryl®

Normal Exposure to Glimepiride — **ACTIONABLE**

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

✓ 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.

✓ 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.

✓ Hydrocodone

Good Response to Hydrocodone (OPRM1: Normal OPRM1 Function) — **INFORMATIVE**

Vicodin®

The patient does not carry the OPRM1 118A>G variant. Acute postoperative and cancer pain: the patient is expected to experience good analgesia with standard or increased hydrocodone doses, without an increase in side effects.

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.

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.

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.

Lansoprazole
Prevacid®

Increased Exposure to Lansoprazole (CYP2C19: Poor Metabolizer) — ACTIONABLE

The patient's genotype is associated with an increased lansoprazole exposure following standard dosing. Consider prescribing lansoprazole at standard label-recommended dosage and administration. Once efficacy is achieved, in the setting of chronic PPI therapy (beyond 12 weeks), consider a 50% reduction in the daily dose to minimize the risk of adverse events from prolonged acid suppression.

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®

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.

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.

✓ 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.

✓ Methylphenidate

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

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

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.

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 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: Poor Function)
INFORMATIVE

The patient carries two copies of the SLCO1B1 521T>C variant, which is associated with reduced transporter function. While the exposure of nateglinide may be slightly elevated in patients with this genotype, this change is not associated with any significant clinical effect. Nateglinide can be prescribed at label-recommended standard dosage and administration.

Olanzapine
Zyprexa®

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

Olanzapine can be prescribed at standard label-recommended dosage and administration. Careful titration is recommended with monitoring until a favorable response is achieved. Extrinsic factors such as diet (cruciferous vegetables, heavy coffee consumption, char-grilled meats) smoking, and certain medications (omeprazole, modafinil, carbamazepine) are known to increase CYP1A2 activity.

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.

Omeprazole
Prilosec®

Increased Exposure to Omeprazole (CYP2C19: Poor Metabolizer) — ACTIONABLE

The patient's genotype is associated with an increased omeprazole exposure following standard dosing. Consider prescribing omeprazole at standard label-recommended dosage and administration. Once efficacy is achieved, in the setting of chronic PPI therapy (beyond 12 weeks), consider a 50% reduction in the daily dose to minimize the risk of adverse events from prolonged acid suppression.

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.

Pantoprazole
Protonix®

Increased Exposure to Pantoprazole (CYP2C19: Poor Metabolizer) — ACTIONABLE

The patient's genotype is associated with an increased pantoprazole exposure following standard dosing. Consider prescribing pantoprazole at standard label-recommended dosage and administration. Once efficacy is achieved, in the setting of chronic PPI therapy (beyond 12 weeks), consider a 50% reduction in the daily dose to minimize the risk of adverse events from prolonged acid suppression.

Perampanel
Fycompa®

Normal Response to Perampanel — INFORMATIVE

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

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.

✓ Posaconazole
Noxafil®

Normal Response to Posaconazole — ACTIONABLE

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.

✓ 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.

✓ 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.

✓ 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®

Slightly Increased Exposure to Rabeprazole (CYP2C19: Poor Metabolizer) — INFORMATIVE

The patient's genotype may be associated with a slightly increased rabeprazole exposure following standard dosing. 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.

✓ Rilpivirine
Intelence®

Normal Exposure to Rilpivirine — ACTIONABLE

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.

✓ 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.

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.

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

Normal Response to Sulindac — INFORMATIVE

Clinoril®

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.

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.

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.

✓ Tizanidine
Zanaflex®

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

Tizanidine can be prescribed at standard label-recommended dosage and administration. Careful titration is recommended with monitoring until a favorable response is achieved. Extrinsic factors such as diet (cruciferous vegetables, heavy coffee consumption, char-grilled meats) smoking, and certain medications (omeprazole, modafinil, carbamazepine) are known to increase CYP1A2 activity.

✓ 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.

✓ 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.

✓ 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

Normal Response to Trifluoperazine — INFORMATIVE

Stelazine®

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.

Valproic Acid
Depakene®

Normal Response to Valproic acid — INFORMATIVE

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

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

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).

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.).

Test Details

Gene	Genotype	Phenotype	Alleles Tested
CYP2C19	*5/*5	Poor Metabolizer	*2, *3, *4A, *4B, *5, *6, *7, *8, *17
CYP3A5	*1/*1	Normal Metabolizer	*3, *6, *7
CYP3A4	*2/*2	Intermediate Metabolizer	*2, *17, *22
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity	-1639G>A
APOE	ε3/ε3	Normal APOE function	ε2, ε4, (ε3 is reference)
CYP2C9	Indeterminate	Unknown Phenotype	*2, *3, *4, *5, *6, *8, *11, *12, *13, *15, *25
CYP2D6	Indeterminate	Unknown Phenotype	*2, *3, *4, *4M, *6, *7, *9, *10, *11, *12, *14, *15, *17, *18, *19, *20, *29, *41, *114
CYP2B6	*1/*6	Intermediate Metabolizer	*6, *9, *18, *18.002
CYP1A2	*1A/*1A	Normal Metabolizer- Possible Inducibility	*1C, *1F, *1K, *1L, *7, *11
COMT	Val158Met G/G	High/Normal COMT Activity	Val158Met
OPRM1	A118G A/A	Normal OPRM1 Function	A118G
SLCO1B1	*5/*5	Poor Function	*5
F2 F5	rs1799963 GG rs6025 CC	Normal Risk of Thrombosis	rs1799963, rs6025
MTHFR	c.1286A>C AA c.665C>T CT	No Increased Risk of Hyperhomocysteinemia	c.1286A>C, c.665C>T
MTHFR	c.665C>T CT	Reduced MTHFR Activity	c.1286A>C, c.665C>T

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

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

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

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

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

APOE Monograph

Clinical Utility

Apolipoproteins (APO) are structural constituents of lipoprotein particles that have critical roles in blood lipid metabolism and transport. Apolipoprotein E (APOE) is a major constituent of triglyceride-rich chylomicrons, very low-density lipoproteins (VLDL), and some subclasses of high-density lipoproteins (HDL). APOE acts as a lipid carrier and transports cholesterol from the cells in the blood vessel wall to the liver for excretion. It also binds to several cell surface receptors to support membrane homeostasis and injury repair in the brain. Defects in APOE can result in hyperlipidemia, which is an important risk factor in the genesis of atherosclerosis and subsequent development of cardiovascular disease (CVD).

Assay Interpretation

There are three common APOE alleles designated ε2, ε3, and ε4, resulting from combinations of the two common variants c.388T>C (rs429358, p.Cys130Arg) and c.526 C>T (rs7412, p.Arg176Cys). These alleles result in E2, E3, and E4 protein isoforms, respectively. The approximate allele frequencies for most populations are 8-12% for ε2, 74-78% for ε3, and 14-15% for ε4.

The reference ranges for both mutations of APOE are c.388T/T and c.526C/C. This is consistent with a ε3/ε3 genotype and a normal APOE function.

Clinical Implications

The apolipoprotein E3 is considered the normal isoform and is associated with normal lipid metabolism. The apolipoprotein E2 isoform shows defective binding of remnants to hepatic lipoprotein and delayed clearance from plasma. It is associated with a slower conversion of intermediate-density lipoproteins (IDL) to low-density lipoproteins (LDL), lower cholesterol, and higher triglycerides, compared to the normal apolipoprotein E3 isoform. The apolipoprotein E4 isoform results in the down regulation of the LDL receptor and is associated with increased total cholesterol, triglycerides, and LDL.

1 - Type III Hyperlipoproteinemia

Result Interpretation: APOE genotyping can be used to confirm the diagnosis of suspected type III hyperlipoproteinemia. Patients with symptoms (xanthomas) and with a lipid profile consistent with type III hyperlipidemia are candidates for APOE genotype analysis. Homozygosity for the APOE ε2 allele is strongly associated with type III hyperlipoproteinemia. Over 90% of individuals presenting the clinical type III hyperlipoproteinemia have the rare ε2/ε2 genotype. These individuals have an increased risk of premature vascular disease.

Only 1-5% of individuals with the APOE ε2/ε2 genotype develop type III hyperlipoproteinemia, suggesting that other genetic, hormonal, or environmental factors must contribute the expression of this disease. Despite the accumulation of remnants in the circulation, most (>95%) APOE ε2 homozygous subjects are normolipidemic or even hypolipidemic because of low LDL cholesterol levels. Other non-ε2/ε2 APOE genotypes (ε3/ε3, ε2/ε3 ε2/ε4 ε3/ε4 ε4/ε4) are not associated with type III hyperlipoproteinemia.

Summary: patients with a lipid profile (tendinous/tuberous xanthomas, elevated cholesterol, triglycerides, very low density lipoprotein (VLDL)) consistent with type III hyperlipoproteinemia are candidates for APOE genotyping. Most patients with type III hyperlipoproteinemia are homozygous for the APOE ε2 allele and homozygosity for ε2 allele is the only genotype associated with type III hyperlipoproteinemia. Factors in addition to the defective receptor binding activity of the apolipoprotein E2 isoform are necessary for manifestation of this disorder and only 1-5% of APOE ε2 homozygotes develop type III hyperlipoproteinemia.

2 - Atherosclerotic Cardiovascular Disease

Result Interpretation: genetic testing of APOE genotyping has been proposed for individual cardiovascular risk assessment and/or to predict the response to statin therapy. APOE genotyping can be informative in individuals with premature coronary heart disease or a family history of premature coronary heart disease. The APOE ε4 allele has been linked to pure elevations of low-density lipoproteins (LDL), and the ε4/ε4 and ε3/ε4 genotypes are associated with increased serum cholesterol levels.

Although the evidence is not fully consistent, it has been estimated that having the ε3/ε4 or ε4/ε4 genotype is associated with on average a 30 -40% increased risk of cardiovascular disease relative to the common ε3/ε3 genotype.

There is some evidence that having an ε2/ε2 or ε2/ε3 genotype may be associated with a lower CVD risk in Caucasians normolipidemic patients. A proposed explanation of such observation is the association between APOE2 allele and lower Lp(a) concentrations.

Summary: the APOE ε4 allele results in the down regulation of the LDL receptor and is associated with increased total cholesterol, triglycerides, and LDL. Several studies indicate that the ε3/ε4, ε2/ε4 or ε4/ε4 genotypes are associated with increased plasma cholesterol levels. The presence of the ε3/ε4 or ε4/ε4 genotype has been suggested as a risk factor for atherosclerosis and coronary heart disease. Thus, the APOE genotype may be useful and informative in individuals with a family history of coronary heart disease as an additional tool for assessing their risk in conjunction with other clinical or laboratory findings. No clinical practice guidelines or position statements from U.S. professional associations were identified that recommended the use of APOE genotyping in cardiovascular risk assessment, including but not limited to the following: the 2013 American College of Cardiology/American Heart Association guidelines for the assessment of cardiovascular risk in asymptomatic patients; the 2009 U.S. Preventive Services Task Force (USPSTF) recommendations on the use of nontraditional risk factors for the assessment of coronary heart disease; the American Diabetes Association and the American College of Cardiology Foundation consensus conference publication.

References

1: Eichner JE et al. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol. 2002 Mar 15;155(6):487-95. **2**: Koch W et al. Apolipoprotein E gene epsilon2/epsilon3/epsilon4 polymorphism and myocardial infarction: case-control study in a large population sample. Int J Cardiol. 2008 Mar 28;125(1):116-7. **3**: Hanis CL et al. Effects of the apolipoprotein E polymorphism on levels of lipids, lipoproteins, and apolipoproteins among Mexican-Americans in Starr County, Texas. Arterioscler Thromb. 1991 Mar-Apr;11(2):362-70. **4**: Klos KL et al. Linkage analysis of plasma ApoE in three ethnic groups: multiple genes with context-dependent effects. Ann Hum Genet. 2005 Mar;69(Pt 2):157-67. **5**: Bennet AM et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA. 2007 Sep 19;298(11):1300-11. **6**: Ciftdoğan DY et al. The association of apolipoprotein E polymorphism and lipid levels in children with a family history of premature coronary artery disease. J Clin Lipidol. 2012 Jan-Feb;6(1):81-7. **7**: Kofler BM et al. Apolipoprotein E genotype and the cardiovascular disease risk phenotype: impact of sex and adiposity (the FINGEN study). Atherosclerosis. 2012 Apr;221(2):467-70. **8**: Carvalho-Wells AL et al. Interactions between age and apoE genotype on fasting and postprandial triglycerides levels. Atherosclerosis. 2010 Oct;212(2):481-7. **9**: Sima A et al. Apolipoprotein E polymorphism--a risk factor for metabolic syndrome. Clin Chem Lab Med. 2007;45(9):1149-53. **10**: Granér M et al. Apolipoprotein E polymorphism is associated with both carotid and coronary atherosclerosis in patients with coronary artery disease. Nutr Metab Cardiovasc Dis. 2008 May;18 (4):271-7. **11**: Utermann G et al. Polymorphism of apolipoprotein E and occurrence of dysbetalipoproteinaemia in man. Nature. 1977 Oct 13;269(5629):604-7. **12** : Blum CB. Type III Hyperlipoproteinemia: Still Worth Considering? Prog Cardiovasc Dis. 2016 Sep - Oct;59(2):119-124. **13**: Harold D et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet. 2009 Oct;41(10):1088-93. **14**: Hopkins PN et al. Type III dyslipoproteinemia in patients heterozygous for familial hypercholesterolemia and apolipoprotein E2. Evidence for a gene-gene interaction. Arterioscler Thromb. 1991 Sep-Oct;11(5):1137-46. **15**: Wilson PW et al. Apolipoprotein E alleles and risk of coronary disease. A meta-analysis. Arterioscler Thromb Vasc Biol. 1996 Oct;16(10):1250-5. **16**: Brscic E et al. Acute myocardial infarction in young adults: prognostic role of angiotensin-converting enzyme, angiotensin II type I receptor, apolipoprotein E, endothelial constitutive nitric oxide synthase, and glycoprotein IIIa genetic polymorphisms at medium-term follow-up. Am Heart J. 2000 Jun;139(6):979-84. **17**: Humphries SE et al. Apolipoprotein E4 and coronary heart disease in middle-aged men who smoke: a prospective study. Lancet. 2001 Jul 14;358(9276):115-9. **18**: Zhu H et al. The association of apolipoprotein E (APOE) gene polymorphisms with atherosclerosis susceptibility: a meta-analysis. Minerva Cardioangiol. 2016 Feb;64(1):47-54. **19**: Song Y et al. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. Ann Intern Med. 2004 Jul 20;141(2):137-47. **20**: Xu H et al. Meta-analysis of apolipoprotein E gene polymorphism and susceptibility of myocardial infarction. PLoS One. 2014 Aug 11;9(8):e104608. **21**: Schaefer JR. Unraveling hyperlipidemia type III (dysbetalipoproteinemia), slowly. Eur J Hum Genet. 2009 May;17(5):541-2. **22**: Khan TA et al. Apolipoprotein E genotype, cardiovascular biomarkers and risk of stroke: systematic review and meta-analysis of 14,015 stroke cases and pooled analysis of primary biomarker data from up to 60,883 individuals. Int J Epidemiol. 2013 Apr;42(2):475-92. **23**: Zhang MD et al. Apolipoprotein E gene polymorphism and risk for coronary heart disease in the Chinese population: a meta-analysis of 61 studies including 6634 cases and 6393 controls. PLoS One. 2014 Apr 22;9(4):e95463. **24**: Cheema AN et al. APOE gene polymorphism and risk of coronary stenosis in Pakistani population. Biomed Res Int. 2015;2015:587465. **25**: Zhang Y et al. Meta-analysis for the Association of Apolipoprotein E ε2/ε3/ε4 Polymorphism with Coronary Heart Disease. Chin Med J (Engl). 2015 May 20;128(10):1391-8. **26**: Zhao QR et al. Association between apolipoprotein E polymorphisms and premature coronary artery disease: a meta-analysis. Clin Chem Lab Med. 2017 Feb 1;55(2):284-298. **27**: Xu M et al. Apolipoprotein E Gene Variants and Risk of Coronary Heart Disease: A Meta-Analysis. Biomed Res Int. 2016;2016:3912175. **28**: Moriarty PM et al. Lipoprotein(a) Mass Levels Increase Significantly According to APOE Genotype: An Analysis of 431 239 Patients. Arterioscler Thromb Vasc Biol. 2017 Mar;37(3):580-588. **29**: Mack S et al. A genome-wide association meta-analysis on lipoprotein(a) concentrations adjusted for apolipoprotein(a) isoforms. J Lipid Res. 2017 May 16.

COMT Monograph

Clinical Utility

Catechol-O-Methyltransferase (COMT) is an enzyme responsible for the metabolism of catecholamines and catechol-estrogens in the central nervous system and other organs. Dopamine is cleared mainly by COMT in the frontal cortex, and a reduced activity of this enzyme results in higher synaptic levels of dopamine, which affects prefrontal cortex cognitive response to certain drugs. A single nucleotide polymorphism of the COMT gene produces an amino acid change from valine to methionine (Val158Met) and reduces the enzyme activity by 3- to 4-fold.

Assay Interpretation

The most well studied COMT genetic variant (rs4680; 472G>A) is the one resulting in a valine to methionine change at codon 158. The variant allele called the Met allele is found in 30-47% of Caucasians, 23% of Africans, and 27-32% of Asians. The phenotype is defined by the presence of the reduced activity Met allele (A variant). The wild-type genotype (Val/Val; GG) predicts a high/normal COMT activity, the heterozygous genotype (Val/Met; GA) predicts an intermediate COMT activity, and the homozygous (Met/Met; AA) results in a low COMT activity.

The reference range for COMT metabolic status is COMT Val158Met GG (Val/Val) (wild-type), which is consistent with a high/normal COMT activity.

Clinical Implications

Several complex associations with the Val158Met variant as a risk factor for numerous diseases have been found, but seem to have limited predictive value. The response to some psychotropic medications seems to be dependent to some extent upon the COMT status. In general, the wild-type genotype result predicts a good response to methylphenidate and amphetamines in the treatment of attention deficit hyperactivity disorder. In the treatment of pain, patients who are homozygous for the Met allele require lower doses of morphine to achieve analgesia.

References

1: De Gregori et al. Genetic variability at COMT but not at OPRM1 and UGT2B7 loci modulates morphine analgesic response in acute postoperative pain. Eur J Clin Pharmacol. 2013 May 19. 2 : Hamidovic et al. Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. Psychiatr Genet. 2010 Jun;20(3):85-92. 3 : Blasi et al. Effect of catechol-O-methyltransferase val158met genotype on attentional control. J Neurosci. 2005 May 18;25(20):5038-45. 4 : Mattay et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A. 2003 May 13;100(10):6186-91.

CYP1A2 Monograph

Clinical Utility

The cytochrome P450 1A2 (CYP1A2) accounts for 13% of total CYP in the human liver, and is responsible for metabolizing 8-10% of commonly used drugs as well as natural compounds such as caffeine. A large inter-individual variability in the elimination of drugs that are metabolized by CYP1A2 has been observed, which has been ascribed to genetic variations and environmental factors. CYP1A2 activity is highly inducible (increased) by environmental factors including smoking (tobacco), some drugs, and several dietary compounds (cruciferous vegetables).

Assay Interpretation

More than 20 different alleles have been characterized for the CYP1A2 gene, and some have been shown to affect enzyme activity and its sensitivity towards inducers (inducibility). The CYP1A2*1F is the most studied allele and results in a rapid metabolizer phenotype in the presence of inducers, while CYP1A2*1K and *1C alleles result in enzymes that are less active and less sensitive to induction. The CYP1A2*1F allele is found in 25-50% of Caucasians, 30% of Asians, and 50% of Ethiopians. The genotype-phenotype relationship for CYP1A2 is not well established, and can be expressed in terms of metabolic capacity as well as sensitivity towards induction (inducibility). Individuals are predicted to have CYP1A2 normal, intermediate, or poor metabolic capacity, with high, possible, or low inducibility depending on their genotype.

The reference range for CYP1A2 metabolic status is CYP1A2 *1A/ *1A, which is consistent with a normal metabolizer that is possibly inducible.

Clinical Implications

CYP1A2 genotype can help identify patients with high or low sensitivity to inducing agents, especially those released during smoking. T**he clinical relevance of this sensitivity becomes important in patients who are smokers or who quit smoking.** Patients with the highly inducible genotype CYP1A2*1F/*1F can experience loss of response to drug substrates while they are exposed to dietary or environmental inducers, and therefore may require higher doses.

The following drugs used in the management of pain and various psychiatric conditions are metabolized extensively by CYP1A2 and are sensitive to its function: clozapine (Clozaril), duloxetine (Cymbalta), olanzapine (Zyprexa), and tizanidine (Zanaflex). CYP1A2 also metabolizes other important drugs such as melatonin, ondansetron (Zofran), pirfenidone (Esbriet), pomalidomide (Pomalyst), ramelteon (Rozerem), ropivacaine (Naropin), and tasimelteon (Hetlioz).

CYP1A2 metabolism is highly sensitive to inhibition and induction, and the occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, response, and safety profiles of many CYP1A2 drug substrates.

Inhibitors

Some known **strong** CYP1A2 inhibitors include: ciprofloxacin (Cipro), enoxacin (Penetrex), fluvoxamine (Luvox) and zafirlukast (Accolate).

Some known **moderate to weak** CYP1A2 inhibitors include: allopurinol (Zyloprim), mexiletine (Mexitil), norfloxacin (Norflox), peginterferon alfa-2a (Pegasys), obeticholic acid (Ocaliva), oral contraceptives, ticlopidine (Ticlid), vemurafenib (Zelboraf) and zileuton (Zyflo).

Inducers

Known CYP1A2 inducers include: carbamazepine (Tegretol), montelukast (Singulair), moricizine (Ethmozine), omeprazole (Prilosec), phenobarbital, phenytoin (Dilantin), primidone (Mysoline) and rifampin (Rifadin).

Some dietary and environmental compounds found in charcoal-grilled food, cigarette smoke and cruciferous vegetables can also increase CYP1A2 activity.

References

1: Metabolic Drug Interactions. RH Levy, KE Thummel, WF Trager. Publisher: Lippincott Williams & Wilkins (March 15, 2000). 2: Zhou et al. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev. 2009;41(2):89-295 3 : Thorn et al. PharmGKB summary: very important pharmacogene information for CYP1A2. Pharmacogenet Genomics. 2012 Jan;22(1):73-7. 4 : Aklillu et al. Genetic polymorphism of CYP1A2 in Ethiopians affecting induction and expression: characterization of novel haplotypes with single-nucleotide polymorphisms in intron 1. Mol Pharmacol. 2003 Sep;64(3):659-69. 5 : Zhou et al. Structure, function, regulation and polymorphism and the clinical significance of human cytochrome P450 1A2. Drug Metab Rev. 2010 May;42(2):268-354.

CYP2B6 Monograph

Clinical Utility

The cytochrome P450 2B6 (CYP2B6) enzyme is responsible for the metabolism of 4% of frequently used medications. It is expressed primarily in the liver and also in the brain. This enzyme is highly polymorphic: to date, a large number of variants have been identified. The CYP2B6 assay identifies some common variants that are associated with variability in enzyme activity, which has important clinical implications for efavirenz dosing.

Assay Interpretation

Genetic polymorphism in CYP2B6 result in different enzyme isoforms that are fully active (normal function), partially active (decreased function), inactive (no function), or have increased activity (increased function). The CYP2B6*1 allele is considered wild-type and encodes a functionally active enzyme (normal). Common decreased function alleles include the *6, *7, and *9 alleles. The *4 and *22 alleles are increased function alleles while the *18 allele is a no-function allele. Of note, common functional polymorphisms in CYP2B6 alter enzyme activity in a substrate-dependent manner. For most substrates, activity of the *9 variant is exceptionally low, activity of the *4 variant is similar or greater than that of the *1, while the activity of the *6 variant lies between *9 and *4, depending on substrate.

The most clinically relevant decreased function allele is the CYP2B6*6 allele. It is found in 7-18%, 10-17%, 23% and 33% of Caucasians, Asians, Mexican-Americans and African-Americans, respectively. The CYP2B6*18 allele is found only in individuals of African descent, with a frequency of 4-7%.

An individual carrying two normal function alleles is considered a normal metabolizer. An individual carrying one normal function allele and one decreased function allele OR one normal function allele and one no function allele OR one increased function allele and one decreased function allele OR one increased function allele and one no function allele is considered an intermediate metabolizer. An individual carrying two decreased function alleles OR two no function alleles OR one decreased function allele and one no function allele is considered a poor metabolizer. An individual carrying one normal function allele and one increased function allele is considered a rapid metabolizer. An individual carrying two increased function alleles is considered an ultra-rapid metabolizer.

The reference range for CYP2B6 metabolic status is CYP2B6 *1/ *1, which is consistent with a normal metabolizer.

Clinical Implications

CYP2B6 plays a role in the metabolism of the following drugs: artemisinin, bupropion (Wellbutrin), cyclophosphamide (Cytoxan), efavirenz (Sustiva), ketamine (Ketalar), meperidine (Demerol), methadone (Dolophine), nevirapine (Viramune), propofol (Diprivan), and selegiline (Eldepryl).

The impact of CYP2B6 polymorphism on pharmacokinetics and clinical response have been documented in adult and pediatric patients taking efavirenz. Patients who are intermediate or poor metabolizers are likely to have higher dose-adjusted trough concentrations of efavirenz following standard treatment when compared with normal metabolizers. Therefore, these patients are subject to increased risk of CNS adverse events. Decreased initial dosage and therapeutic monitoring are recommended for intermediate and poor metabolizers. Patients who are rapid or ultra-rapid metabolizers are likely to have slightly higher efavirenz clearance with no clinically significant effect on efficacy or toxicity. Efavirenz can be initiated with standard dosing for normal, rapid and ultra-rapid metabolizers. Specific dosing strategies for pediatric patients have been published by a panel of experts (Department of Human and Health Services-Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV). These are based and on CYP2B6 genotype, weight, age and comorbidities.

Inhibitors or inducers of the CYP2B6 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2B6 inhibitors or inducers.

Inhibitors

Some known CYP2B6 inhibitors include: clopidogrel (Plavix), darunavir (Prezista), prasugrel (Effient), ritonavir (Norvir), thiotepa (Tepadina), ticlopidine (Ticlid) and voriconazole (Vfend).

Inducers

Some CYP2B6 inducers include: artemether (Coartem), carbamazepine (Tegretol), dabrafenib (Tafinlar), efavirenz (Sustiva), metamizole, nevirapine (Viramune), phenobarbital, phenytoin (Dilantin), rifampin (Rimactane), ritonavir (Norvir) and St. John's wort.

References

1: CYP2B6 Allele Nomenclature: www.cypallele.ki.se/cyp2b6.htm. **2**: Li J, Menard V, Benish RL, Jurevic RJ, Guillemette C, Stoneking M, Zimmerman PA, Mehlotra RK. Worldwide variation in human drug-metabolism enzyme genes CYP2B6 and UGT2B7: implications for HIV/AIDS treatment. Pharmacogenomics. 2012 Apr;13 (5):555-70. **3**: Li Y, Coller JK, Hutchinson MR, Klein K, Zanger UM, Stanley NJ, Abell AD, Somogyi AA. The CYP2B6*6 allele significantly alters the N-demethylation of ketamine enantiomers in vitro. Drug Metab Dispos. 2013 Jun;41(6):1264-72. **4**: Zanger and Klein. Zanger UM, Klein K. Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance. Front Genet. 2013 Mar 5;4:24. Front Genet. 2013;4:24. **5**: Zanger UM, Klein K, Saussele T, Blievernicht J, Hofmann MH, Schwab M. Polymorphic CYP2B6: molecular mechanisms and emerging clinical significance. Pharmacogenomics. 2007 Jul;8(7):743-59. 6: Zhu AZ, Cox LS, Nollen N, Faseru B, Okuyemi KS, Ahluwalia JS, Benowitz NL, Tyndale RF. CYP2B6 and bupropion's smoking-cessation pharmacology: the role of hydroxybupropion. Clin Pharmacol Ther. 2012 Dec;92(6):771-7. **7**: Benowitz NL, Zhu AZ, Tyndale RF, Dempsey D, Jacob P 3rd. Influence of CYP2B6 genetic variants on plasma and urine concentrations of bupropion and metabolites at steady state. Pharmacogenet Genomics. 2013 Mar;23 (3):135-41. **8**: Desta Z, Gammal RS, Gong L, Whirl-Carrillo M, Gaur AH, Sukasem C, Hockings J, Myers A, Swart M, Tyndale R, Masimirembwa C, Iwuchukwu OF, Chirwa S, Lennox J, Gaedigk A, Klein T, Haas DW. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2B6 and Efavirenz-containing Antiretroviral Therapy. Clin Pharmacol Ther. 2019 Apr 21. **9**: Bloom AJ, Wang PF, Kharasch ED. Nicotine oxidation by genetic variants of CYP2B6 and in human brain microsomes. Pharmacol Res Perspect. 2019 Mar 11;7(2):e00468. **10**: Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed (6/19/2019) [p257-267].

CYP2C19 Monograph

Clinical Utility

The cytochrome P450 2C19 (CYP2C19) is involved in the metabolism of 10% of clinically important medications. This enzyme is highly polymorphic and more than 30 different alleles have been identified in various ethnicities. The CYP2C19 assay identifies common and rare variants that are associated with variability in CYP2C19 enzyme, which has important pharmacological and toxicological implications for antidepressants, benzodiazepines, antiplatelets, and proton-pump inhibitors.

Assay Interpretation

CYP2C19 enzyme activity defines a normal or abnormal (intermediate, poor, rapid or ultra-rapid) metabolizer status for a given individual. Several variant alleles have been identified and result in different isoforms of the CYP2C19 enzyme that functionally exhibit normal function, reduction function, no function or increased function. The CYP2C19*1 allele is considered wild-type/reference allele and CYP2C19 *11, *13 and *18 encodes a functionally active enzyme (normal function allele). The alleles *2, *3 *4-*8, *22, *24, and *35-*37 encode an inactive enzyme and are referred to as no function alleles while the *9, *10, *16,*19, *25 and *26 alleles are classified as reduced function alleles. The CYP2C19*17 is an increased function allele.

A new joint statement by the Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP), provides a two-tiered classification of CYP2C19 alleles for inclusion during clinical testing. Tier 1 alleles that should be included in all clinical tests, include CYP2C19 *2, *3 and *17. Tier 2 alleles which may also be included in clinical tests include CYP2C19 *4A, *4B, *5, *6, *7, *8, *9, *10 and *35.

The CYP2C19 genotype-phenotype relationship is established based on the allele's function. An Individual with two normal function alleles is considered a normal metabolizer while an individual carrying two no function alleles is considered a poor metabolizer. An individual carrying one normal function allele with one no function allele or one no function allele with one increased function allele is classified as an intermediate metabolizer. Individuals with two increased function alleles are considered ultra-rapid metabolizers and carriers of one increased function allele with one normal function allele are referred to as rapid metabolizers. Because of limited evidence, individuals carrying two decreased function alleles OR those carrying one normal or increased function allele with one decreased function allele are provisionally categorized as intermediate metabolizers.

The reference range for CYP2C19 metabolic status is CYP2C19 *1/*1 genotype, which is consistent with a normal metabolizer.

Clinical Implications

There is substantial evidence linking the CYP2C19 polymorphisms to variability in the pharmacological and safety profiles of the following therapies used in psychiatric conditions and pain management: amitriptyline (Elavil), sertraline (Zoloft), clobazam (Onfi), citalopram (Celexa), escitalopram (Lexapro), diazepam (Valium), imipramine (Tofranil), and carisoprodol (Soma). CYP2C19 plays a minor role in the elimination of methadone (Dolophine).

Cardiovascular medications that are metabolized by CYP2C19 include the prodrug clopidogrel (Plavix), propranolol (Inderal), and cilostazol (Pletal). Proton-pump inhibitors such as omeprazole (Prilosec), esomeprazole (Nexium), lansoprazole (Prevacid), dexlansoprazole (Dexilant), and pantoprazole (Protonix) are major substrates of CYP2C19.

Brivaracetam (Briviact) is primarily metabolized by hydrolysis and by hydroxylation. The hydrolysis reaction is mediated by amidase and the hydroxylation is mediated by CYP2C19. Brivaracetam exposure is increased by 22% and 42%, in CYP2C19 intermediate and poor metabolizers, respectively. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may therefore require dose reduction to avoid concentration-dependent toxicity.

CYP2C19 is significantly involved in the metabolism of voriconazole (Vfend) and the disposition of this antifungal is affected by CYP2C19 genetic polymorphisms. The CPIC dosing guideline for voriconazole recommends selecting an alternative agent that is not dependent on CYP2C19 metabolism in adults who are CYP2C19 ultrarapid metabolizers, rapid metabolizers or poor metabolizers. In pediatric patients, an alternative agent should be used in patients who are ultrarapid metabolizers or poor metabolizers.

Inhibitors or inducers of CYP2C19 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2C19 inhibitors or inducers.

Inhibitors

Some known CYP2C19 inhibitors include: armodafinil (Nuvigil), delavirdine (Rescriptor), esomeprazole (Nexium), etravirine (Intelence), felbamate (Felbatol), fluconazole (Diflucan), fluoxetine (Prozac), fluvoxamine (Luvox), moclobemide (Manerix), modafinil (Provigil), omeprazole (Prilosec), oxcarbazepine (Trileptal), ticlopidine (Ticlid), topiramate (Topamax) and voriconazole (Vfend).

Inducers

Some known CYP2C19 inducers include: apalutamide (Erleada), artemether (Coartem), carbamazepine (Tegretol), efavirenz (Sustiva), enzalutamide (Xtandi), fosphenytoin (Cerebyx), phenobarbital, phenytoin (Dilantin), primidone (Mysoline), rifampin (Rifadin) and St. John's wort.

References

1: Preskorn SH. Clinically important differences in the pharmacokinetics of the ten newer "atypical" antipsychotics: Part 2: Metabolism and elimination. J Psychiatr Pract. 2012 Sep;18(5):361-8. **2**: Preskorn SH. Clinically important differences in the pharmacokinetics of the ten newer "atypical" antipsychotics: part 1. J Psychiatr Pract. 2012 May;18(3):199-204. **3**: Hicks et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants. Clin Pharmacol Ther. 2013 Jan 16 **4**: Swen et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther. 2011 May;89(5):662-73. **5**: Wilffert et al. KNMP working group Pharmacogenetics. From evidence based medicine to mechanism based medicine. Reviewing the role of pharmacogenetics. Int J Clin Pharm. 2011 Feb;33(1):3-9. **6**: Psychiatric Pharmacogenomics. David A. Mrazek. Publisher: Oxford University Press, USA; 1 edition (May 28, 2010). **7**: Briviact Prescribing Label (label approved on 02/18/2016). **8**: Moriyama B, Obeng AO, Barbarino J, Penzak SR, Henning SA, Scott SA, Agúndez JA, Wingard JR, McLeod HL, Klein TE, Cross S, Caudle KE, Walsh TJ. Clinical Pharmacogenetics Implementation Consortium (CPIC®) Guideline for CYP2C19 and Voriconazole Therapy. Clin Pharmacol Ther. 2016 Dec 16. **9**: Pratt VM, Del Tredici AL, Hachad H, Ji Y, Kalman LV, Scott SA, Weck KE. Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology. J Mol Diagn. 2018 May;20 (3):269-276. **10**: Lima JJ, Thomas CD, Barbarino J, Desta Z, Van Driest SL, El Rouby N, Johnson JA, Cavallari LH, Shakhnovich V, Thacker DL, Scott SA, Schwab M, Uppugunduri CRS, Formea CM, Franciosi JP, Sangkuhl K, Gaedigk A, Klein TE, Gammal RS, Furuta T. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C19 and Proton Pump Inhibitor Dosing. Clin Pharmacol Ther. 2020 Aug 8.

CYP2C9 Monograph

Clinical Utility

The cytochrome P450 2C9 (CYP2C9) is involved in the metabolism of 15% of clinically important medications. This enzyme is highly polymorphic: to date, 60 alleles have been identified. The CYP2C9 assay identifies some common variants that are associated with variability in CYP2C9 enzyme activity, which has important pharmacological and toxicological implications for anticonvulsants, anticoagulants, and certain antidiabetics.

Assay Interpretation

CYP2C9 enzyme activity defines a normal or abnormal (intermediate and poor) metabolizer status for a given individual. Several variant alleles have been identified and result in different CYP2C9 isoforms that functionally are fully active, partially active, or inactive. The CYP2C9 *1 (wild-type) and CYP2C9*9 alleles encode functionally active enzymes. A number of CYP2C9 alleles such as *2, *4, *5, *8, *11, *12 and *31 encode partially active enzymes and are classified as decreased function alleles. Other CYP2C9 alleles such as *3, *6, *13, *15 and *25 are considered no -function alleles encoding inactive enzymes. Many other alleles with an unknown/uncertain functional effect have also been identified and can be revealed from testing.

A new joint statement by the Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP), provides a two-tiered classification of CYP2C9 alleles for clinical testing. Tier 1 alleles that should be included in all tests, these include CYP2C9 *2, *3, 5. *6, *8 and *11. Tier 2 alleles which may also be included in clinical tests include CYP2C9 *12, *13 and *15.

The genotype-phenotype relationship is established based on the allele's function. Individuals with two normal function alleles are considered normal (extensive) metabolizers (AS = 2.0). Individuals with one normal function allele with one decreased function allele are considered intermediate metabolizers (AS = 1.5). Individuals with one normal function allele and one no-function allele or two decreased function alleles are considered intermediate metabolizers (AS = 1.0). Individuals with one decreased function allele and one no function allele are considered poor metabolizers (AS = 0.5). Individuals with two no-function alleles are considered poor metabolizers (AS = 0). The phenotype of carriers of one or two CYP2C9 unknown/uncertain function alleles cannot be predicted accurately (unknown phenotype).

The reference range for CYP2C9 metabolic status is CYP2C9 *1/*1 genotype, which is consistent with an AS of 2.0 and a normal metabolizer.

Clinical Implications

Abnormal CYP2C9 activity affects the therapeutic outcome of a variety of drugs used to treat cardiovascular and other conditions. Following the administration of drug substrates, the clinical manifestation in a poor or an intermediate metabolizer depends on the characteristics of the drug (i.e., the amount of drug/metabolites that is cleared by the enzyme), and the safety and pharmacological profiles of the drug and its metabolites. Within the medications used to treat cardiovascular conditions, there is compelling evidence that the response to certain angiotensin II inhibitors, statins, and anticoagulants is altered in individuals exhibiting abnormal CYP2C9 activity.

CYP2C9 plays a role in the metabolism of the following psychotropic drugs: fluoxetine (Prozac), phenytoin (Dilantin), and primidone (Mysoline). Several NSAIDs and Cox-2 inhibitors are substrates of CYP2C9, and patients with reduced CYP2C9 activity may have higher plasma levels of celecoxib (Celebrex), flurbiprofen (Ocufen), piroxicam (Feldene), or meloxicam (Mobic). CYP2C9 plays a minor role in the elimination of diclofenac (Voltaren), sulindac (Clinoril), and naproxen (Aleve).

Cardiovascular medications that are metabolized by CYP2C9 include warfarin (Coumadin), fluvastatin (Lescol), losartan (Cozaar), and irbesartan (Avapro).

The FDA has added a contraindication on the use of siponimod (Mayzent) in patients with a CYP2C9 *3/*3 genotype.

Inhibitors or inducers of the CYP2C9 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2C9 inhibitors or inducers.

Inhibitors

Some known CYP2C9 inhibitors include: amiodarone (Cordarone), capecitabine (Xeloda), chloramphenicol, cimetidine (Tagamet), co-trimoxazole (Septra), danazol (Danocrine), delavirdine (Rescriptor), disulfiram (Antabuse), efavirenz (Sustiva), etravirine (Intelence), fluconazole (Diflucan), 5-fluorouracil (Adrucil), fluoxetine (Prozac), fluvastatin (Lescol), fluvoxamine (Luvox), gemfibrozil (Lopid), lomitapide (Juxtapid), metronidazole (Flagyl), miconazole (Oravig), oxandrolone (Oxandrin), phenytoin (Dilantin), sulfamethoxazole (Bactrim), sulfinpyrazone (Anturane), tamoxifen (Nolvadex), tigecycline (Tygacil), toremifene (Fareston), voriconazole (Vfend) and zafirlukast (Accolate).

Inducers

Some known CYP2C9 inducers include: alpelisib (Piqray), apalutamide (Erleada), aprepitant (Emend), bosentan (Tracleer), carbamazepine (Tegretol), dabrafenib (Tafinlar), elvitegravir (Genvoya, Stribild), enzalutamide (Xtandi), phenobarbital, phenytoin (Dilantin), primidone (Mysoline), rifampin (Rifadin, Rimactane), rifapentine (Priftin), ritonavir (Norvir) and St. John's wort.

References

1: Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, Rongen GA, van Schaik RH, Schalekamp T, Touw DJ, van der Weide J, Wilffert B, Deneer VH, Guchelaar HJ. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther. 2011 May;89(5):662-73. **2**: Wilffert B, Swen J, Mulder H, Touw D, Maitland-Van der Zee AH, Deneer V; KNMP working group Pharmacogenetics. From evidence based medicine to mechanism based medicine. Reviewing the role of pharmacogenetics. Int J Clin Pharm. 2011 Feb;33(1):3-9. **3**: Wang B, Wang J, Huang SQ, Su HH, Zhou SF. Genetic polymorphism of the human cytochrome P450 2C9 gene and its clinical significance. Curr Drug Metab. 2009 Sep;10(7):781-834. **4**: Wyatt JE, Pettit WL, Harirforoosh S. Pharmacogenetics of nonsteroidal anti-inflammatory drugs. Pharmacogenomics J. 2012 Dec;12(6):462-7. **5**: Pratt VM, Cavallari LH, Del Tredici AL, Hachad H, Ji Y, Moyer AM, Scott SA, Whirl-Carrillo M, Weck KE. Recommendations for Clinical CYP2C9 Genotyping Allele Selection: A Joint Recommendation of the Association for Molecular Pathology and College of American Pathologists. J Mol Diagn. 2019 May 7. **6**: Daly AK, Rettie AE, Fowler DM, Miners JO. Pharmacogenomics of CYP2C9: Functional and Clinical Considerations. J Pers Med. 2017 Dec 28;8(1). **7**: Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA, Lee MT, Gage BF, Kimmel SE, Perera MA, Anderson JL, Pirmohamed M, Klein TE, Limdi NA, Cavallari LH, Wadelius M. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther. 2017 Sep;102(3):397-404. **8**: Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther. 2020 Mar 19. **9**: Karnes JH, Rettie AE, Somogyi AA, Huddart R, Fohner AE, Formea CM, Ta Michael Lee M, Llerena A, Whirl-Carrillo M, Klein TE, Phillips EJ, Mintzer S, Gaedigk A, Caudle KE, Callaghan JT. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. Clin Pharmacol Ther. 2021 Feb;109(2):302-309.

CYP2D6 Monograph

Clinical Utility

The cytochrome P450 2D6 (CYP2D6) is involved in the metabolism of 20% of clinically important medications. This enzyme is highly polymorphic: more than 100 different variants have been identified. The CYP2D6 assay identifies common variants that are associated with variability in CYP2D6 enzyme activity, which has important pharmacological and toxicological implications for antidepressants, antipsychotics, opioids, beta-blockers, and antiarrhythmics.

Assay Interpretation

CYP2D6 enzyme activity defines a normal or abnormal (intermediate, poor, or ultra-rapid) metabolizer status for a given individual. Many alleles have been identified and result in different CYP2D6 isoforms that functionally have normal activity, decreased activity, no activity or in some cases unknown activity. The CYP2D6*1 (reference or wild-type allele) is inferred when no variants tested by the assay are detected. Genotyping tests usually interrogate for both sequence variants and structural variants and results are used to infer CYP2D6 alleles or haplotypes as defined by PharmVar. Sequence variants include single nucleotide polymorphisms (SNPs) and small insertions and deletions. Structural variations include entire gene deletions (CYP2D6*5), gene duplication/multiplication (CYP2D6*1xN, *2xN and *4xN), and hybrids with the CYP2D7 gene. Moreover, alleles that contain hybrids can be found on their own (as single entities) or in combination with other gene copies (tandems).

Commonly detected alleles include those with normal function (e.g. CYP2D6 *1, *2 and *35), increased function (e.g. CYP2D6*1xN, *2xN), reduced function (e.g. CYP2D6*9, *10, *10-*36, *17, *29, and *41) and no-function (e.g. CYP2D6 *3, *4, *4N, *5, *6, *7, *8, *11, *12, *36, *4xN).

The genotype-phenotype relationship is established using a scoring system that assigns an activity value to every CYP2D6 allele, in order to assign a predicted phenotype. For a given genotype, the activity values of the constituent alleles are added together to calculate the CYP2D6 activity score. This activity score (AS) is then used to assign a predicted phenotype. The AS system was first published in 2008 and was recently refined by an expert group that included both the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) members. The group reviewed recent findings and heterogeneities in phenotype assignment.

The consensus method jointly recommended by CPIC and the DPWG redefined the translation of CYP2D6 diplotypes to phenotype as follows:

- CYP2D6 ultra-rapid metabolizers (UMs) when the calculated AS is > 2.25
- CYP2D6 normal metabolizers (NMs) when the calculated AS = x is within the range of $1.25 \leq x \leq 2.25$
- CYP2D6 intermediate metabolizers (IMs) when the calculated AS = x is within the range of $0 < x < 1.25$
- CYP2D6 poor metabolizers (PMs) when the calculated AS = 0

After literature review, the standardization expert group also obtained consensus to 'downgrade' the activity value for the CYP2D6*10 allele from 0.5 to 0.25 to better reflect the level of enzyme reduction that is observed with this allele. The group proposed the following activity value when the functional effect of the CYP2D6 allele is known:

- fully functional CYP2D6 alleles are assigned an activity value of 1.0 (e.g. CYP2D6 *2, *35).
- reduced function CYP2D6 alleles (except CYP2D6*10) have an activity value of 0.5 (Note that the value of 0.5 does not indicate a 50% reduction in activity, but signals decreased function, i.e., has functional activity somewhere between no-function and full function).
- CYP2D6*10 reduced function allele is assigned an activity value of 0.25.
- non-functional CYP2D6 alleles are assigned an activity value of 0 (e.g. CYP2D6 *4, *5, *36, *36xN, *4x2N).

For alleles with two or more gene copies, the value of the allele is multiplied by the number of gene copies (e.g. AS of CYP2D6*1x3N = 3 calculated as the AS of *1 which is 1 multiplied by 3). For a tandem, the sum of each allele value is used to assign the score (e.g. AS of CYP2D6*36-*10 = 0.25 calculated as the sum of AS of CYP2D6*36 which is 0 and AS of CYP2D6*10 which is 0.25).

The reference range for CYP2D6 metabolic status is a CYP2D6 *1/ *1 genotype, which is consistent with an AS of 2.0 and a normal metabolizer status.

Clinical Implications

There is substantial evidence linking the CYP2D6 polymorphisms to variability in the pharmacological and safety profiles of the following psychotropics: desipramine (Norpramin), imipramine (Tofranil), amitriptyline (Elavil), nortriptyline (Pamelor), haloperidol (Haldol), trimipramine (Surmontil), venlafaxine (Effexor), doxepin (Silenor), aripiprazole (Abilify), atomoxetine (Strattera), risperidone (Risperdal), clomipramine (Anafranil), and pimozide (Orap).

CYP2D6 polymorphisms have been shown to affect the pharmacological and safety profiles of the following analgesics: codeine, tramadol (Ultram), and hydrocodone (Vicodin). Codeine and tramadol are prodrugs that need to be activated by CYP2D6. Poor metabolizers are at high risk of therapy failure when given codeine or tramadol. On the other hand, ultra-rapid metabolizers may experience increased toxicity when given standard dosage of codeine or tramadol. Because CYP3A4 is also involved in the metabolism of oxycodone, patients with abnormal CYP2D6 activity may still experience adequate analgesia when taking this drug. CYP2D6 polymorphism has been shown to affect dihydrocodeine (Synalgos-DC) pharmacokinetics and can potentially alter the response to this drug.

Morphine, oxymorphone (Opana), hydromorphone (Dilaudid), butorphanol (Stadol), fentanyl (Duragesic), buprenorphine (Butrans), methadone (Dolophine), morphine (Avinza), and tapentadol (Nucynta) are not substrates of CYP2D6, and the patient's response to these drugs is not expected to be affected by polymorphisms in this enzyme.

Several important cardiovascular medications are metabolized by CYP2D6, and include: metoprolol (Lopressor), flecainide (Tambocor), and propafenone (Rythmol).

Eliglustat (Cerdelga) is a glucosylceramide synthase inhibitor used for the long-term treatment of adult patients with Gaucher disease type 1. Both the FDA-approved drug label and the EMA Summary of Product Characteristics for this drug state that CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of eliglustat to achieve a therapeutic effect. Therefore this drug should not be used in these individuals. Patients who are CYP2D6 intermediate and normal metabolizers have a recommended dose of 84 mg twice daily, while poor metabolizers have a recommended dose of 84 mg once daily.

Cevimeline (Evoxac) is a muscarinic agonist indicated for the treatment of symptoms of dry mouth in patients with Sjögrens Syndrome. Both CYP2D6 and CYP3A are responsible for the metabolism of cevimeline, and this drug should be used with caution in individuals who are CYP2D6 poor metabolizers, as they may be at a higher risk of adverse events.

Inhibitors of the CYP2D6 enzyme may modify its activity and change the patient’s metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2D6 inhibitors. Although there are no known clinical inducers of CYP2D6, the pharmacokinetics of a drug substrate can be affected by inducers of other enzymes (such as CYP3A) that are involved in the metabolism of that drug.

Inhibitors

Some known **strong and moderate** CYP2D6 inhibitors include: abiraterone (Zytiga), bupropion (wellbutrin), cinacalcet (Sensipar), cobicistat (Stribild), dacomitinib (Vizimpro), duloxetine (Cymbalta), ecstasy, fluoxetine (Prozac), paroxetine (Paxil), quinidine (Quinidex), rolapitant (Varubi), terbinafine (Lamisil), mirabegron (Myrbetriq), panobinostat (Farydak), peginterferon alfa-2b (Sylatron) and tipranavir/ritonavir (Aptivus).

Some known **weak** CYP2D6 inhibitors include: amiodarone (Cordarone), celecoxib (Celebrex), clobazam (Onfi), desvenlafaxine (Pristiq), diltiazem (Cardiazem), diphenhydramine (Benadryl), Echinacea, escitalopram (Lexapro), febuxostat (Uloric), gefitinib (Iressa), hydralazine (Apresoline), hydroxychloroquine (Plaquenil), imatinib (Gleevec), lorcaserin (Belviq), methadone (Dolophine), perphenazine (Trilafon), propafenone (Rythmol), ranitidine (Zantac), ritonavir (Norvir), sertraline (Zoloft), telithromycin (Ketek), venlafaxine (Effexor) and verapamil (Isoptin, Covera-HS).

References

1: Swen et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther. 2011 May;89(5):662-73. **2**: Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part II. Clin Pharmacokinet. 2009;48(12):761-804. **3**: Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part I. Clin Pharmacokinet. 2009;48(11):689-723. **4**: Preskorn SH. Clinically important differences in the pharmacokinetics of the ten newer "atypical" antipsychotics: Part 2. Metabolism and elimination. J Psychiatr Pract. 2012 Sep;18(5):361-8. **5**: Preskorn SH. Clinically important differences in the pharmacokinetics of the ten newer "atypical" antipsychotics: part 1. J Psychiatr Pract. 2012 May;18(3):199-204. **6**: D'Empaire et al. Antidepressant treatment and altered CYP2D6 activity: are pharmacokinetic variations clinically relevant? J Psychiatr Pract. 2011 Sep;17(5):330-9. **7**: Hicks et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants. Clin Pharmacol Ther. 2013 Jan 16. **8**: Gaedigk et al. The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. Clin Pharmacol Ther. 2008 Feb;83(2):234-42. **9**: Crews et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. Clin Pharmacol Ther. 2012 Feb;91(2):321-6. **10**: Meyer et al. Absorption, distribution, metabolism and excretion pharmacogenomics of drugs of abuse. Pharmacogenomics. 2011 Feb;12(2):215-3. **11**: Evoxac FDA Prescribing Label. **12**: Cerdelga FDA Prescribing Label. **13**: Brown JT, Bishop JR, Sangkuhl K, Nurmi EL, Mueller DJ, Dinh JC, Gaedigk A, Klein TE, Caudle KE, McCracken JT, de Leon J, Leeder JS. Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther. 2019 Feb 22. **14**: Pharmacogene Variation (PharmVar) Consortium. PharmVar CYP2D6. https://www.pharmvar.org/gene/CYP2D6. Published 2019. Accessed January 6, 2020. **15**: Nofziger C, Turner AJ, Sangkuhl K, et al. PharmVar GeneFocus: CYP2D6. Clin Pharmacol Ther. 2020;107(1):154-170. **16**: Gaedigk A. Complexities of CYP2D6 gene analysis and interpretation. Int Rev Psychiatry. 2013;25(5):534-553. **17**: Pharmacogene Variation (PharmVar) Consortium. Structural Variation CYP2D6. 2019:9. https://a.storyblok.com/f/70677/x/2de9d1f5e1/cyp2d6_structural-variation_v1-7.pdf. Accessed January 6, 2020. **18**: Caudle KE, Sangkuhl K, Whirl-Carrillo M, et al. Standardizing CYP2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. Clin Transl Sci. October 2019.

CYP3A4 Monograph

Clinical Utility

The cytochrome P450 3A4 and 3A5 (CYP3A4 and CYP3A5) account for 40-80% of total CYP in human liver and intestine, respectively. Most importantly, CYP3A enzymes metabolize 50% of commonly used drugs. CYP3A4 and CYP3A5 enzymes have overlapping substrate specificity, and the contribution of CYP3A5 in the overall metabolism is smaller than the one for CYP3A4. The overall CYP3A metabolism status is expected to affect drugs that have a narrow therapeutic index.

Assay Interpretation

A limited number of variants identified within the CYP3A4 and CYP3A5 genes have been associated with significant alterations in enzyme activity and subsequent variability in therapeutic response. For CYP3A5, individuals with the less prevalent “normal metabolizer phenotype” may metabolize drugs faster than those with the more common “poor metabolizer phenotype”. This may result in increased toxicity or loss of efficacy.

The CYP3A4*1B variant is the most studied, and results in an enzyme with a moderately decreased activity. It occurs in 50% of African-Americans, 3-5% of Caucasians, and <1% of Asians. The CYP3A4*2, *3, *12, and *17 are also considered decreased activity alleles. Recently, the CYP3A4 *22 allele has been characterized as a decreased function allele that can be clinically relevant (associated with a decreased clearance of certain substrates). The genotype-phenotype relationship for CYP3A4 is not well established, and individuals are predicted to have a CYP3A4 normal or intermediate metabolic capacity.

The reference range for CYP3A4 metabolic status is CYP3A4 *1/ *1, which is consistent with a normal metabolizer.

The variant results in an enzyme with no activity, and is the most common variant in the general population. This variant is found on all the CYP3A5*3 alleles. The CYP3A5 *6 and *7 are also no function alleles. The functional effects of the CYP3A5 alleles *2, *4, *5 *8, and *9 are not well established. The CYP3A5 *1 functional allele produces an active enzyme, and is found in 5% of Caucasians, 20% of Asians, and 15-50% of Africans. Individuals with two CYP3A5 no function alleles are classified as poor metabolizers while those carrying one copy of a functional CYP3A5*1 allele are considered intermediate metabolizers. A subject carrying two copies of the functional CYP3A5*1 allele is considered a normal metabolizer. **CYP3A5 poor metabolizers represent 50% of Asians and 90% of Caucasians.**

The reference range for CYP3A5 metabolic status is CYP3A5 *1/*1, which is consistent with a normal metabolizer. This genotype is the least prevalent in Caucasians and Asians.

Clinical Implications

CYP3A4 and CYP3A5 genotypes can help identify patients with high or low overall CYP3A activity. Although these two enzymes metabolize many drugs, the response of only a few (such as narrow therapeutic index drugs) is expected to change significantly by genetic polymorphisms. Fentanyl (Duragesic) is a narrow therapeutic drug that is mainly metabolized by CYP3A. There is limited evidence suggesting that the response to this drug is altered in individuals with abnormal CYP3A activity.

The following drugs used in pain management and various psychiatric conditions are metabolized extensively by CYP3A: fentanyl (Duragesic), oxycodone (Oxycontin), buprenorphine (Suboxone), carbamazepine (Tegretol), quetiapine (Seroquel), ziprasidone (Geodon), alprazolam (Xanax), midazolam (Versed), triazolam (Halcion), nefazodone (Serzone), trazodone (Oleptro), vilazodone (Vibryd), zaleplon (Sonata), and zolpidem (Ambien). CYP3A contributes to a small extent in the elimination of methadone (Dolophine).

Within the major therapeutic classes used in cardiovascular conditions, the following drugs are substantially metabolized by CYP3A: atorvastatin (Lipitor), simvastatin (Zocor), lovastatin (Mevacor), nifedipine (Procardia), verapamil (Verelan), nicardipine (Cardene), felodipine (Plendil), nisoldipine (Sular), clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), cilostazol (Pletal), amiodarone (Cordarone), quinidine (Qualaquin), disopyramide (Norpace), losartan (Cozaar), rivaroxaban (Xarelto), and apixaban (Eliquis).

CYP3A metabolism is highly sensitive to inhibition and induction when a patient is taking multiple drugs. In this case, occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, as well as the responses and safety profiles of many CYP3A drug substrates.

Inhibitors

Some known **strong** CYP3A inhibitors include: boceprevir (Victrelis), clarithromycin (Biaxin), clofazimine (Lamprene), conivaptan (Vaprisol), grapefruit juice (high dose), idelalisib (Zydelig), itraconazole (Sporanox), ketoconazole (Nizoral), lopinavir, (Kaletra), nefazodone (Serzone), nelfinavir (Viracept), paritaprevir (Technivie), posaconazole (Noxafil), ribociclib (Kisqali), ritonavir (Norvir), saquinavir (Invirase), telaprevir (Incivek), telithromycin (Ketek), tipranavir (aptivus), troleandomycin (TAO) and voriconazole (Vfend).

Some known **moderate** CYP3A inhibitors include: amprenavir (agenerase), aprepitant (Emend), atazanavir (Reyataz), ciprofloxacin (Cipro), darunavir (Prezista), diltiazem (cardizem), erythromycin (Eryc), fosamprenavir (Lexiva), fluconazole (Diflucan), grapefruit juice (low dose), imatinib (Gleevec), quinupristin/dalfopristin (Synercid) and verapamil (Isoptin, Covera-HS).

Some known **weak** CYP3A inhibitors include: amiodarone (Cordarone), amlodipine (Norvasc), atorvastatin (Lipitor), bicalutamide (Casodex), cilostazol (Pletal), cimetidine (Tagamet), fluoxetine (Prozac), fluvoxamine (Luvox), ranitidine (Zantac), ranolazine (Ranexa), sertraline (Zoloft) and ticagrelor (Brilinta).

Inducers

Some known **strong** CYP3A inducers include: apalutamide (Erleada), carbamazepine (Tegretol), enzalutamide (Xtandi), fosphenytoin (Cerebyx), lumacaftor (Orkambi), phenobarbital, phenytoin (Dilantin), primidone (Mysoline), rifampin (Rifadin), rifapentine (Priftin) and St. John's wort.

Some known **moderate** CYP3A inducers include: artemether (Coartem), bosentan (Tracleer), dabrafenib (Tafinlar), efavirenz (Sustiva), etravirine (Intelence), ivosidenib (tibsovo), modafinil (Provigil), nafcillin (Unipen), nevirapine (Viramune) and rifabutin (Mycobutin).

Some known **weak** CYP3A inducers include: aprepitant (Emend), clobazam (Onfi), dexamethasone (Decadron), Echinacea, fosamprenavir (Lexiva), lesinurad (Zurampic), methylprednisolone (Medrol), midostaurin (Rydapt), oxcarbazepine (Trileptal), pioglitazone (Actos) and rufinamide (Banzel).

References

1- Metabolic Drug Interactions. RH Levy, KE Thummel, WF Trager. Publisher: Lippincott Williams & Wilkins (March 15, 2000). 2: Zhou et al. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev. 2009;41(2):89-295 3- Isoherranen et al. The influence of CYP3A5 expression on the extent of hepatic CYP3A inhibition is substrate-dependent: an in vitro-in vivo evaluation. Drug Metab Dispos. 2008 Jan;36(1):146-54. 4- Williams et al. A significant drug-metabolizing role for CYP3A5? Drug Metab Dispos. 2003 Dec;31(12):1526-30. 5- Elens et al. A new functional CYP3A4 intron 6 polymorphism significantly affects tacrolimus pharmacokinetics in kidney transplant recipients. Clin Chem. 2011 Nov;57(11):1574-83. 6- Elens et al. Effect of a new functional CYP3A4 polymorphism on calcineurin inhibitors' dose requirements and trough blood levels in stable renal transplant patients. Pharmacogenomics. 2011 Oct;12 (10):1383-96. 7-Lamba et al. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev. 2002 Nov 18;54(10):1271-94.

CYP3A5 Monograph

Clinical Utility

The cytochrome P450 3A4 and 3A5 (CYP3A4 and CYP3A5) account for 40-80% of total CYP in human liver and intestine, respectively. Most importantly, CYP3A enzymes metabolize 50% of commonly used drugs. CYP3A4 and CYP3A5 enzymes have overlapping substrate specificity, and the contribution of CYP3A5 in the overall metabolism is smaller than the one for CYP3A4. The overall CYP3A metabolism status is expected to affect drugs that have a narrow therapeutic index.

Assay Interpretation

A limited number of variants identified within the CYP3A4 and CYP3A5 genes have been associated with significant alterations in enzyme activity and subsequent variability in therapeutic response. For CYP3A5, individuals with the less prevalent “normal metabolizer phenotype” may metabolize drugs faster than those with the more common “poor metabolizer phenotype”. This may result in increased toxicity or loss of efficacy.

The CYP3A4*1B variant is the most studied, and results in an enzyme with a moderately decreased activity. It occurs in 50% of African-Americans, 3-5% of Caucasians, and <1% of Asians. The CYP3A4*2, *3, *12, and *17 are also considered decreased activity alleles. Recently, the CYP3A4 *22 allele has been characterized as a decreased function allele that can be clinically relevant (associated with a decreased clearance of certain substrates). The genotype-phenotype relationship for CYP3A4 is not well established, and individuals are predicted to have a CYP3A4 normal or intermediate metabolic capacity.

The reference range for CYP3A4 metabolic status is CYP3A4 *1/ *1, which is consistent with a normal metabolizer.

The variant results in an enzyme with no activity, and is the most common variant in the general population. This variant is found on all the CYP3A5*3 alleles. The CYP3A5 *6 and *7 are also no function alleles. The functional effects of the CYP3A5 alleles *2, *4, *5 *8, and *9 are not well established. The CYP3A5 *1 functional allele produces an active enzyme, and is found in 5% of Caucasians, 20% of Asians, and 15-50% of Africans. Individuals with two CYP3A5 no function alleles are classified as poor metabolizers while those carrying one copy of a functional CYP3A5*1 allele are considered intermediate metabolizers. A subject carrying two copies of the functional CYP3A5*1 allele is considered a normal metabolizer. **CYP3A5 poor metabolizers represent 50% of Asians and 90% of Caucasians.**

The reference range for CYP3A5 metabolic status is CYP3A5 *1/*1, which is consistent with a normal metabolizer. This genotype is the least prevalent in Caucasians and Asians.

Clinical Implications

CYP3A4 and CYP3A5 genotypes can help identify patients with high or low overall CYP3A activity. Although these two enzymes metabolize many drugs, the response of only a few (such as narrow therapeutic index drugs) is expected to change significantly by genetic polymorphisms. Fentanyl (Duragesic) is a narrow therapeutic drug that is mainly metabolized by CYP3A. There is limited evidence suggesting that the response to this drug is altered in individuals with abnormal CYP3A activity.

The following drugs used in pain management and various psychiatric conditions are metabolized extensively by CYP3A: fentanyl (Duragesic), oxycodone (Oxycontin), buprenorphine (Suboxone), carbamazepine (Tegretol), quetiapine (Seroquel), ziprasidone (Geodon), alprazolam (Xanax), midazolam (Versed), triazolam (Halcion), nefazodone (Serzone), trazodone (Oleptro), vilazodone (Vibryd), zaleplon (Sonata), and zolpidem (Ambien). CYP3A contributes to a small extent in the elimination of methadone (Dolophine).

Within the major therapeutic classes used in cardiovascular conditions, the following drugs are substantially metabolized by CYP3A: atorvastatin (Lipitor), simvastatin (Zocor), lovastatin (Mevacor), nifedipine (Procardia), verapamil (Verelan), nicardipine (Cardene), felodipine (Plendil), nisoldipine (Sular), clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), cilostazol (Pletal), amiodarone (Cordarone), quinidine (Qualaquin), disopyramide (Norpace), losartan (Cozaar), rivaroxaban (Xarelto), and apixaban (Eliquis).

CYP3A metabolism is highly sensitive to inhibition and induction when a patient is taking multiple drugs. In this case, occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, as well as the responses and safety profiles of many CYP3A drug substrates.

Inhibitors

Some known **strong** CYP3A inhibitors include: boceprevir (Victrelis), clarithromycin (Biaxin), clofazimine (Lamprene), conivaptan (Vaprisol), grapefruit juice (high dose), idelalisib (Zydelig), itraconazole (Sporanox), ketoconazole (Nizoral), lopinavir, (Kaletra), nefazodone (Serzone), nelfinavir (Viracept), paritaprevir (Technivie), posaconazole (Noxafil), ribociclib (Kisqali), ritonavir (Norvir), saquinavir (Invirase), telaprevir (Incivek), telithromycin (Ketek), tipranavir (aptivus), troleandomycin (TAO) and voriconazole (Vfend).

Some known **moderate** CYP3A inhibitors include: amprenavir (agenerase), aprepitant (Emend), atazanavir (Reyataz), ciprofloxacin (Cipro), darunavir (Prezista), diltiazem (cardizem), erythromycin (Eryc), fosamprenavir (Lexiva), fluconazole (Diflucan), grapefruit juice (low dose), imatinib (Gleevec), quinupristin/dalfopristin (Synercid) and verapamil (Isoptin, Covera-HS).

Some known **weak** CYP3A inhibitors include: amiodarone (Cordarone), amlodipine (Norvasc), atorvastatin (Lipitor), bicalutamide (Casodex), cilostazol (Pletal), cimetidine (Tagamet), fluoxetine (Prozac), fluvoxamine (Luvox), ranitidine (Zantac), ranolazine (Ranexa), sertraline (Zoloft) and ticagrelor (Brilinta).

Inducers

Some known **strong** CYP3A inducers include: apalutamide (Erleada), carbamazepine (Tegretol), enzalutamide (Xtandi), fosphenytoin (Cerebyx), lumacaftor (Orkambi), phenobarbital, phenytoin (Dilantin), primidone (Mysoline), rifampin (Rifadin), rifapentine (Priftin) and St. John's wort.

Some known **moderate** CYP3A inducers include: artemether (Coartem), bosentan (Tracleer), dabrafenib (Tafinlar), efavirenz (Sustiva), etravirine (Intelence), ivosidenib (tibsovo), modafinil (Provigil), nafcillin (Unipen), nevirapine (Viramune) and rifabutin (Mycobutin).

Some known **weak** CYP3A inducers include: aprepitant (Emend), clobazam (Onfi), dexamethasone (Decadron), Echinacea, fosamprenavir (Lexiva), lesinurad (Zurampic), methylprednisolone (Medrol), midostaurin (Rydapt), oxcarbazepine (Trileptal), pioglitazone (Actos) and rufinamide (Banzel).

References

1- Metabolic Drug Interactions. RH Levy, KE Thummel, WF Trager. Publisher: Lippincott Williams & Wilkins (March 15, 2000). 2: Zhou et al. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev. 2009;41(2):89-295 3- Isoherranen et al. The influence of CYP3A5 expression on the extent of hepatic CYP3A inhibition is substrate-dependent: an in vitro-in vivo evaluation. Drug Metab Dispos. 2008 Jan;36(1):146-54. 4- Williams et al. A significant drug-metabolizing role for CYP3A5? Drug Metab Dispos. 2003 Dec;31(12):1526-30. 5- Elens et al. A new functional CYP3A4 intron 6 polymorphism significantly affects tacrolimus pharmacokinetics in kidney transplant recipients. Clin Chem. 2011 Nov;57(11):1574-83. 6- Elens et al. Effect of a new functional CYP3A4 polymorphism on calcineurin inhibitors' dose requirements and trough blood levels in stable renal transplant patients. Pharmacogenomics. 2011 Oct;12 (10):1383-96. 7-Lamba et al. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev. 2002 Nov 18;54(10):1271-94.

Factor II Monograph

Clinical Utility

The F2 gene encodes the coagulation factor II, or prothrombin. It is a vitamin K–dependent proenzyme that functions in the blood coagulation cascade. It is a precursor to thrombin, which converts fibrinogen into fibrin, which in turn strengthens a protective clot.

The F2 c.*97G>A variant (also known as Factor II 20210G>A) in the F2 gene results in increased levels of plasma prothrombin and a concurrent increased risk for thrombosis. Prothrombin-related thrombophilia is characterized by venous thromboembolism (VTE). This risk of thrombosis is also increased when variants exist for other coagulation factors such as F5 c.1601G>A variant (also known as Factor V Leiden), or in presence of non-genetic risk factors such as obesity, injury, surgery, smoking, pregnancy, use of estrogen-containing contraceptives, or replacement therapy. The clinical expression of prothrombin-related thrombophilia is variable, and many individuals may never develop thrombosis, while others may experience venous thrombotic events or pregnancy complications.

Assay Interpretation

The Factor II thrombophilia is the second most common inherited risk factor for thrombosis. The F2 c.*97G>A variant (also known as Factor II 20210G>A) is associated with a hypercoagulable state. In the United States, the prevalence of this variant is 1.1% in Caucasians and Hispanics and 0.3% in African-Americans. The prevalence of heterozygosity is 2%-5% in whites and 0%-0.3% in African-Americans. The prevalence of homozygosity is approximately one in 10,000.

The reference range for F2 c.*97G>A variant is F2 c.*97G>A G/G.

Clinical Implications

The F2 c.*97G>A variant is associated with an elevation of plasma prothrombin levels to about 30% above normal in heterozygotes and to 70% above normal in homozygotes. Heterozygotes are at a 2- to 5-fold increased risk of an initial VTE. The risk for VTE in F2 c.*97G>A homozygotes is not well defined but is presumed to be higher than in F2 c.*97G>A heterozygotes. F2 c.*97G>A homozygotes tend to develop thrombosis more frequently and at a younger age. Individuals who are doubly heterozygotes for F5 c.1601G>A variant and F2 c.*97G>A variant have an estimated 20-fold increased risk when compared to individuals without either variant suggesting a multiplicative elevation in risk. Certain circumstantial factors can increase the risk of thrombosis, and include: travel, central venous catheter use, pregnancy, oral contraceptive use, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), organ transplantation, injury, age, and surgery.

References

1: Kujovich JL. Prothrombin-Related Thrombophilia. 2006 Jul 25 [updated 2014 Aug 14]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. **2**: Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA; ACMG Factor V. Leiden Working Group. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. Genet Med. 2001 Mar-Apr;3(2):139-48. **3**: Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: routine testing for Factor V Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic venous thromboembolism and their adult family members. Genet Med. 2011 Jan;13(1):67-76. **4**: Segal JB, Brotman DJ, Necochea AJ, Emadi A, Samal L, Wilson LM, Crim MT, Bass EB. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. JAMA. 2009 Jun 17;301(23):2472-85. **5**: Zhang S, Taylor AK, Huang X, Luo B, Spector EB, Fang P, Richards CS; ACMG Laboratory Quality Assurance Committee. Venous thromboembolism laboratory testing (factor V Leiden and factor II c.*97G>A), 2018 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018 Oct 5. **6**: Promacta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017. **7**: Dopletet [package insert]. Durham, NC: Dova Pharmaceuticals, Inc.; 2018. **8**: Mulpleta [package insert]. Florham Park, NJ: Shionogi, Inc.; 2018.

Factor V Leiden Monograph

Clinical Utility

The F5 gene encodes the coagulation factor V. In normal conditions, Factor V is inactivated during the clotting process by the activated protein C (APC). In subjects with Factor V Leiden thrombophilia, a variant in the gene produces a Factor V that cannot be inactivated normally by APC. As a result, the clotting process remains active longer than usual, leading to more thrombin generation. This hypercoagulable state is also increased when other variants exist in other coagulation factors such as F2 c.*97G>A variant (also known as Factor II 20210G>A), or in the presence of non-genetic risk factors such as obesity, injury, surgery, smoking, pregnancy, or use of estrogen-containing contraceptive or estrogen containing replacement therapy. The clinical expression of Factor V Leiden thrombophilia is variable. Many individuals may never develop thrombosis, while others may experience venous thrombotic events or pregnancy complications. Certain circumstantial factors can increase the risk of thrombosis, and include: travel, central venous catheter use, pregnancy, oral contraceptive use, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), organ transplantation, injury, age, and surgery. These factors are associated with the first thrombotic episode in at least 50% of individuals with a F5 c.1601G>A variant.

Assay Interpretation

The F5 c.1601G>A variant (also known as Factor V Leiden) is the most common known inherited risk factor for thrombosis. The F5 c.1601G>A variant refers to a base change (from G to A at position 1691) in the gene. As a result, Factor V is inactivated to a lesser extent and persists for longer in the circulation, leading to hypercoagulability. In the US, the frequency of the F5 c.1601G>A variant varies by ethnicity, with about 5% of Caucasians, 2% of Hispanics, and 1% of African-Americans having one variant. Only 1 in 5000 individuals have two F5 c.1601G>A variants.

The reference range for F5 c.1601G>A variant is F5 c.1601G>A G/G.

Clinical Implications

About 1 in 1000 people in the U.S. experience a first venous thromboembolism (VTE) each year. VTE is caused by inherited and environmental factors, and while the F5 c.1601G>A variant is present in only 15-20% of individuals with a first VTE, it is found in 50% of individuals with recurrent VTE or estrogen-related thrombosis. The risk for VTE is increased 3- to 8-fold in F5 c.1601G>A heterozygotes and 9- to 80-fold in homozygotes. This risk is increased further if other genetic or circumstantial factors are present. A heterozygote individual for both the F5 c.1601G>A variant and the F2 c.*97G>A variant (compound heterozygote) has an even greater risk of VTE (20-fold) than an individual with a variant in only one factor. This illustrates the multiplicative effect of these two factors on overall thrombotic risk.

References

1: Kujovich JL. Factor V Leiden Thrombophilia. 1999 May 14 [updated 2018 Jan 4]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. **2**: Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA; ACMG Factor V. Leiden Working Group. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. Genet Med. 2001 Mar-Apr;3(2):139-48. **3**: Rosendaal FR, Reitsma PH. Genetics of venous thrombosis. J Thromb Haemost. 2009 Jul;7 Suppl 1:301-4. **4**: Bezemer ID, van der Meer FJ, Eikenboom JC, Rosendaal FR, Doggen CJ. The value of family history as a risk indicator for venous thrombosis. Arch Intern Med. 2009 Mar 23;169(6):610-5. **5**: Segal JB, Brotman DJ, Necochea AJ, Emadi A, Samal L, Wilson LM, Crim MT, Bass EB. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. JAMA. 2009 Jun 17;301(23):2472-85. **6**: Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: routine testing for Factor V Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic venous thromboembolism and their adult family members. Genet Med. 2011 Jan;13(1):67-76. **7**: Zhang S, Taylor AK, Huang X, Luo B, Spector EB, Fang P, Richards CS; ACMG Laboratory Quality Assurance Committee. Venous thromboembolism laboratory testing (factor V Leiden and factor II c.*97G>A), 2018 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018 Oct 5. **8**: Promacta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017. **9**: Dopletet [package insert]. Durham, NC: Dova Pharmaceuticals, Inc.; 2018. **10**: Mulpleta [package insert]. Florham Park, NJ: Shionogi, Inc.; 2018.

MTHFR Monograph

Clinical Utility

Methylenetetrahydrofolate reductase (MTHFR) is involved in folate metabolism and is essential for the remethylation of homocysteine. Two common variants in the MTHFR gene: c.665C>T (legacy name 677C>T) and c.1286A>C (legacy name 1298A>C), result in an enzyme with decreased activity, which is linked to increased plasma homocysteine levels (i.e. hyperhomocysteinemia). Mild to moderate hyperhomocysteinemia has been identified as a risk factor for venous thromboembolism and other cardiovascular diseases such as coronary heart disease and stroke. Other conditions in which hyperhomocysteinemia is found, include recurrent pregnancy loss, placental infarction and birth defects. However, the causal role of MTHFR variants in these conditions is not well established.

Assay Interpretation

The approximate minor allele frequencies for most populations are 30-50% for the MTHFR c.1286A>C variant and 18-30% for the MTHFR c.665C>T variant. Heterozygotes and homozygotes for the MTHFR c.665C>T variant have 60% and 30% of normal MTHFR activity, respectively. Heterozygotes and homozygotes for the MTHFR c.1286A>C variant have 80% and 60% of normal MTHFR activity, respectively.

The reference ranges for both variants of MTHFR are c.665C>T C/C and c.1286A>C A/A. This is consistent with a normal MTHFR activity.

Clinical Implications

The MTHFR assay provides information about potential causes of elevated homocysteine, and approaches for addressing it.

- Homozygosity for the MTHFR c.665C>T variant (individual with MTHFR c.665C>T T/T genotype) predisposes for hyperhomocysteinemia (especially during times of folate insufficiency) and an increase in premature cardiovascular disease. Measurement of total plasma homocysteine is informative in this case.
- Compound heterozygosity (individual with MTHFR c.665C>T C/T and MTHFR c.1286A>C A/C genotypes) is not associated with an increase in plasma homocysteine level. Measurement of total plasma homocysteine is informative in this case.
- Heterozygosity or homozygosity for the MTHFR c.1286A>C A>C variant alone (individual with MTHFR c.1286A>C A/C or MTHFR c.1286A>C C/C genotypes) does not increase homocysteine levels. Similarly, heterozygosity for the MTHFR c.665C>T variant alone (individuals with MTHFR c.665C>T C/T genotype) does not increase homocysteine levels.
- Hyperhomocysteinemia related to MTHFR genetic variants has been associated with neural tube defects, stillbirths and recurrent pregnancy loss. However, because hyperhomocysteinemia is multifactorial, involving a combination of other genetic, physiologic and environmental factors, the presence of MTHFR variants in an individual should not be used alone to predict the risk of these conditions.
- MTHFR in depression: Low MTHFR activity may exacerbate folate deficiency in patients with depression and may increase the risk of depressive relapse or delay the response to antidepressants. Testing for homocysteine levels and serum folate levels are recommended in patients with depression. Methylfolate may substantially benefit patients with hyperhomocysteinemia and depression when used as an adjuvant to antidepressant medication.
- The response to methotrexate, a drug used in cancer and autoimmune diseases, is affected by the presence of MTHFR genetic variants. Methotrexate intolerance is observed in individuals that are heterozygous or homozygous for the MTHFR c.665C>T variant.

References

1: van der Put. A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? Am J Hum Genet. 1998 May;62(5):1044-51. 2: Lewis et al. Meta-analysis of MTHFR 677C->T polymorphism and coronary heart disease: does totality of evidence support causal role for homocysteine and preventive potential of folate? BMJ. 2005 Nov5;331(7524):1053. 3: Kluijtmans et al. Molecular genetic analysis in mild hyperhomocysteinemia: a common mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for cardiovascular disease. Am J Hum Genet. 1996 Jan;58(1):35-41. 4: Hickey et al. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. Genet Med. 2013 Feb;15(2):153-6. 5: Grody et al. ACMG Factor V. Leiden Working Group. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. Genet Med. 2001 Mar-Apr;3(2):139-48. 6: Gatt et al. Hyperhomocysteinemia and venous thrombosis. Semin Hematol. 2007 Apr;44(2):70-6. 7: De Mattia E, Toffoli G. C677T and A1298C MTHFR polymorphisms, a challenge for antifolate and fluoropyrimidine-based therapy personalisation. Eur J Cancer. 2009 May;45(8):1333-51. 8: Toffoli et al. Pharmacogenetic relevance of MTHFR polymorphisms. Pharmacogenomics. 2008 Sep;9(9):1195-206. 9: Clarke et al. MTHFR Studies Collaborative Group. Homocysteine and coronary heart disease: meta-analysis of MTHFR case-control studies, avoiding publication bias. PLoS Med. 2012 Feb;9 (2) 10: Weisberg I, Tran P, Christensen B, Sibani S, Rozen R. A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. Mol Genet Metab. 1998 Jul;64(3):169-72. 11: Weisberg et al. The 1298A-->C polymorphism in methylenetetrahydrofolate reductase (MTHFR): in vitro expression and association with homocysteine. Atherosclerosis. 2001 Jun;156(2):409-15. 12: Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, Baer L, Dalton ED, Sacco GR, Schoenfeld D, Pencina M, Meisner A, Bottiglieri T, Nelson E, Mischoulon D, Alpert JE, Barbee JG, Zisook S, Fava M. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. Am J Psychiatry. 2012 Dec;169(12):1267-74. 13: Coppen A, Bolander-Gouaille C. Treatment of depression: time to consider folic acid and vitamin B12. J Psychopharmacol. 2005 Jan;19(1):59-65. 14: Reynolds EH. Methylfolate as adjunctive treatment in major depression. Am J Psychiatry. 2013 May;170(5):560. 15: Lewis SJ, Araya R, Leary S, Smith GD, Ness A. Folic acid supplementation during pregnancy may protect against depression 21 months after pregnancy, an effect modified by MTHFR C677T genotype. Eur J Clin Nutr. 2012 Jan;66(1):97-103. 16: Delport D, Schoeman R, van der Merwe N, van der Merwe L, Fisher LR, Geiger D, Kotze MJ. Significance of dietary folate intake, homocysteine levels and MTHFR 677 C>T genotyping in South African patients diagnosed with depression: test development for clinical application. Metab Brain Dis. 2014 Jun;29(2):377-84. 17: Shelton RC, Sloan Manning J, Barrentine LW, Tipa EV. Assessing Effects of l-Methylfolate in Depression Management: Results of a Real-World Patient Experience Trial. Prim Care Companion CNS Disord. 2013;15(4). 18: Mischoulon D, Lamon-Fava S, Selhub J, Katz J, Papakostas GI, Iosifescu DV,Yeung AS, Dording CM, Farabaugh AH, Clain AJ, Baer L, Alpert JE, Nierenberg AA, Fava M. Prevalence of MTHFR C677T and MS A2756G polymorphisms in major depressive disorder, and their impact on response to fluoxetine treatment. CNS Spectr. 2012 Jun;17 (2):76-86.

OPRM1 Monograph

Clinical Utility

"Mu" opioid receptors are the most important site of action of opioid drugs. Single polymorphisms in the human mu-opioid receptor (OPRM1) have been investigated for their role in human nociception, opiate efficacy, and addiction.

Assay Interpretation

The variant mostly studied is a single substitution at position 118, from an adenine to a guanine (A118G). This variant reduces the OPRM1 receptor signaling efficiency induced by exogenous opioids. Reduced OPRM1 mRNA expression levels were observed in carriers of the G variant. The variant allele (G) is present in 7-15% of Caucasians, 1.5% of African-Americans, and up to 48.5% of Asians. The major interest of this particular SNP is due to its pharmacological and physiological consequences; however the exact mechanism by which the altered receptor influences opioid analgesia is still unresolved. The presence of the G allele seems to reduce the effect of exogenous agonists but increase the effects of exogenous antagonists.

The reference range for the A118G SNP is A118G AA, and is associated with a normal OPRM1 receptor signaling efficiency.

Clinical Implications

The presence of the G allele (A118G) seems to be associated with pain sensitivity as well as opioid dosage requirements. But only weak evidence of these associations is available to date. It is suggested that patients carrying the G allele report higher intensity pain. In terms of drug response, patients with the G allele have a favorable response to the anti-addictive drug naltrexone. Several studies conducted in post-surgical settings or in cancer analgesia showed that G allele carriers require slightly higher doses of morphine or fentanyl. This association still needs to be confirmed in larger studies and does not hold in other situations such as labor pain.

References

1: Wu et al. Polymorphism of the micro-opioid receptor gene (OPRM1 118A>G) affects fentanyl-induced analgesia during anesthesia and recovery. Mol Diagn Ther. 2009;13(5):331-7. 2: Menon et al. The human μ-opioid receptor gene polymorphism (A118G) is associated with head pain severity in a clinical cohort of female migraine with aura patients. J Headache Pain. 2012Oct;13(7):513-9. 3: Olsen et al. Pain intensity the first year after lumbar disc herniation is associated with theA118G polymorphism in the opioid receptor mu 1 gene: evidence of a sex and genotype interaction. J Neurosci. 2012 Jul 18;32(29):9831-4. 4: Reyes-Gibby et al. Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene. Pain. 2007 Jul;130(1-2):25-30. 5: Lötsch et al. Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers. Pharmacogenet Genomics. 2009 Jun;19(6):429-36. 6: Walter C, Lötsch J. Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment. Pain. 2009 Dec;146(3):270-5. 7: Zhang et al. Association of human micro-opioid receptor gene polymorphism A118G with fentanyl analgesia consumption in Chinese gynaecological patients. Anaesthesia. 2010Feb;65(2):130-5. 8: Zhang et al. Study of the OPRM1 A118G genetic polymorphism associated with postoperative nausea and vomiting induced by fentanyl intravenous analgesia. Minerva Anestesiol. 2011 Jan;77 (1):33-9. 9: Oertel et al. The mu-opioid receptor gene polymorphism 118A>G depletes alfentanil-induced analgesia and protects against respiratory depression in homozygous carriers. Pharmacogenet Genomics. 2006 Sep;16(9):625-36. 10: Zwisler et al. Lack of Association of OPRM1 and ABCB1 Single-Nucleotide Polymorphisms to Oxycodone Response in Postoperative Pain. J Clin Pharmacol. 2011 Mar 24. 11: Klepstad et al. Influence from genetic variability on opioid use for cancer pain: a European genetic association study of 2294 cancer pain patients. Pain. 2011 May;152(5):1139-45. 12: Kadiev E, et al. Role of pharmacogenetics in variable response to drugs: focus on opioids. Expert Opin Drug Metab Toxicol. 2008 Jan;4(1):77-91. 13: Vuilleumier et al. Pharmacogenomic considerations in opioid analgesia. Pharmgenomics Pers Med. 2012;5:73-87. 14: Walter et al. μ-opioid receptor gene variant OPRM1 118 A>G: a summary of its molecular and clinical consequences for pain. Pharmacogenomics. 2013 Nov;14(15):1915-25. 15: Thorsell A. The μ-opioid receptor and treatment response to naltrexone. Alcohol Alcohol. 2013 Jul-Aug;48(4):402-8. 16: Setiawan et al. Influence of the OPRM1 A118G polymorphism on alcohol-induced euphoria, risk for alcoholism and the clinical efficacy of naltrexone. Pharmacogenomics. 2012 Jul;13(10):1161-72. 17: Kranzler et al. Variation in OPRM1 moderates the effect of desire to drink on subsequent drinking and its attenuation by naltrexone treatment. Addict Biol. 2013 Jan;18 (1):193-201. 18: Chamorro et al. Association of μ-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis. Addict Biol. 2012 May;17(3):505-12.

SLCO1B1 Monograph

Clinical Utility

The SLCO1B1 gene encodes a liver-specific transporter involved in the removal of endogenous compounds (bile acids, bilirubin) and drugs such as statins from the blood to the liver. Some variants of the SLCO1B1 gene result in a low-functioning protein, which impairs statin clearance, and may lead to an increased risk of muscle pain, tenderness, or weakness, called myopathy. Certain medications can potently inhibit SLCO1B1, causing clinically significant drug interactions.

Assay Interpretation

The functional SLCO1B1 activity (phenotype) is estimated from the genotype at 521T>C. Non-carriers of the 521T>C variant are predicted to have a SLCO1B1 normal function, those with one copy of the 521T>C variant have a SLCO1B1 decreased function, and those with two copies of the variant have poor SLCO1B1 function.

There are several variants of the SLCO1B1 that define over 15 alleles. One relatively common variant 521T>C (rs4149056) results in SLCO1B1 decreased function, which affects the transport of drug substrates such as statins. This variant is present alone on the *5 allele and in presence with another variant (388A>G; rs2306283) on the *15 allele. Both alleles are low-activity alleles (reduced hepatic uptake), and have a combined frequency of 15-20% in Caucasians, 10-15% in Asians, and 2% in sub-Saharan Africans and African-Americans.

The reference range for the 521T>C mutation of SLCO1B1 is 521 TT. This is consistent with normal SLCO1B1 function.

Clinical Implications

All statins are substrates of SLCO1B1, but the effects of SLCO1B1 genetic polymorphism differ between individual statins. The effect is the largest on simvastatin, and individuals with the 521T>C variant have increased levels of the active simvastatin form. The variant is strongly associated with simvastatin-induced myopathy (with or without CK elevation), especially with high-dose simvastatin therapy. More than 60% of the myopathy cases could be attributed to its presence. The clinical spectrum of statin-induced myopathy ranges from a mild and common myalgia to a life-threatening and rare rhabdomyolysis. Other known risk factors for statin-induced myopathy include a high-statin dose, interacting drugs that raise statin levels, age, hypothyroidism, and certain inherited muscle disorders.

At therapeutic doses, the apparent sensitivity levels of the five statins to the presence of the 521T>C variant are simvastatin>pitavastatin>atorvastatin>pravastatin>rosuvastatin. Carriers of the 521 T>C variant should avoid high-dose simvastatin therapy. These patients can take other statins, such as atorvastatin, pitavastatin, rosuvastatin, or pravastatin, but at reduced doses. Fluvastatin is not affected by the 521 T>C variant and could therefore be considered a suitable alternative.

Other drugs that are substrates of SLCO1B1 transporter include enalapril, olmesartan, valsartan, atrasentan, repaglinide, nateglinide, methotrexate, and bosentan. However, there is insufficient evidence documenting the impact of the 521 T>C variant on the systemic exposure and safety profile of these drugs.

Inhibitors

Inhibitors of SLCO1B1 transporter may alter its activity and result in increased levels of drug substrates. These include boceprevir (Victrelis), clarithromycin (Biaxin), cyclosporine (Gengraf, Neoral, Restasis, Sandimmune), eltrombopag (Promacta), gemfibrozil (Lopid), paritaprevir (Technivie), protease inhibitors, simeprevir (Olysio), telaprevir (Incivek) and teriflunomide (Aubagio).

Inducers

Inducers of SLCO1B1 transporter include: apalutamide (Erleada).

References

1: FDA Zocor Prescribing Label: http://www.accessdata.fda.gov 2: 1: Wilke et al. Clinical Pharmacogenomics Implementation Consortium (CPIC). The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. Clin Pharmacol Ther. 2012 Jul;92(1):112-7. 2: Feng et al. Individualized risk for statin-induced myopathy: current knowledge, emerging challenges and potential solutions. Pharmacogenomics.2012 Apr;13 (5):579-94. 3: Elsby et al. Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. Clin Pharmacol Ther. 2012 Nov;92(5):584-98. 4: SEARCH Collaborative Group, Link E. SLCO1B1 variants and statin-induced myopathy--a genome wide study. N Engl J Med. 2008 Aug 21;359(8):789-99. 5: Nies et al. Genetics is a major determinant of expression of the human hepatic uptake transporter OATP1B1, but not of OATP1B3 and OATP2B1. Genome Med. 2013 Jan 11;5(1):1. 6 : Niemi M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther. 2010 Jan;87(1):130-3. 7 : Niemi et al. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. Pharmacol Rev. 2011 Mar;63(1):157-81. 8: Neuvonen et al. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther. 2006 Dec;80(6):565-81.

VKORC1 Monograph

Clinical Utility

The Vitamin K epoxide reductase complex, subunit 1 (VKORC1) is the target of anticoagulants such as warfarin, acenocoumarol and phenprocoumon. VKORC1 catalyzes the conversion of oxidized Vitamin K to reduced Vitamin K. By inhibiting this conversion, warfarin leads to decreased availability of the reduced Vitamin K that serves as a cofactor for gamma-glutamyl carboxylase and blocks the formation of functionally-active clotting factors, resulting in reduced coagulation. Polymorphisms within the VKORC1 gene result in variable expression levels of the VKORC1 enzyme and altered response towards coumarin anticoagulants. VKORC1 genetic testing defines three clinical phenotypes: high, moderate, and low sensitivity to warfarin. VKORC1 genetic testing is usually used in conjunction with CYP2C9 and CYP4F2 genetic testing to optimize warfarin dosing and minimize the risks of bleeding or thrombotic complications.

Assay Interpretation

Several relevant variants in the VKORC1 gene have been identified and correlate well with warfarin dose requirements. In Europeans, the genotype for a single variant (-1694G>A; rs9923231) accounts for 25% of variability in warfarin dose requirements, with the minor A allele associated with lower doses. This association is also observed in East Asians, where the minor allele occurs more frequently than in Europeans (88% vs 41%). In Africans, the minor allele frequency for VKORC1 -1639G>A is 10% which is considerably lower than in Europeans. Several studies in Africans and African-Americans identified common variants that are associated with higher warfarin dose requirements in patients of African descent.

The reference range for VKORC1 -1639G>A is G/G and is associated with a normal VKORC1 enzyme expression phenotype.

Clinical Implications

The common VKORC1 -1639G>A variant is associated with low-dose warfarin requirements. When CYP2C9 and VKORC1 genotypes are combined with other patient-specific parameters such as demographic (age, weight, height), clinical (disease, co-medications), and environmental factors (smoking), they account for 50% of warfarin dose variation between individuals. Several validated warfarin pharmacogenetic dosing algorithms have been developed and are available to calculate initial and maintenance warfarin doses in both adults and children. Moreover, the FDA prescribing label for warfarin includes genotype-specific dose ranges based on CYP2C9 and VKORC1 genotypes.

References

1: Food and Drug Administration: Coumadin® Label accessed on Jan 2013. **2:** Gage et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther. 2008 Sep;84(3):326-31 **3:** Schelleman et al. New genetic variant that might improve warfarin dose prediction in African Americans. Br J Clin Pharmacol. 2010 Sep;70(3):393-9 **4:** Johnson et al. Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clin Pharmacol Ther. 2011 Oct;90(4):625-9. **5:** Klein et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. International Warfarin Pharmacogenetics Consortium. N Engl J Med. 2009 Feb 19;360 (8):753-64 **6:** Rieder et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. 2005 Jun 2;352(22):2285-93. **7:** Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA, Lee MT, Gage BF, Kimmel SE, Perera MA, Anderson JL, Pirmohamed M, Klein TE, Limdi NA, Cavallari LH, Wadelius M. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther. 2017 Sep;102(3):397-404.

PATIENT INFORMATION	SPECIMEN DETAILS	ORDERED BY
NAME: Patient ob793tc	**SPECIMEN TYPE:**	
ACC #: ob793tc	**COLLECTION DATE:**	
DOB: 1/1/1900	**RECEIVED DATE:**	
SEX:	**REPORT DATE:** 11/11/2022	

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.

Manchester University

REPORT DETAILS

Patient: Patient ob793tc
DOB: 1/1/1900
ACC #: ob793tc

Pharmacogenetic Test Summary

CYP2C19	*5/*5	Poor Metabolizer
CYP2C9	Indeterminate	Unknown Phenotype
CYP2D6	Indeterminate	Unknown Phenotype
CYP3A4	*2/*2	Intermediate Metabolizer
CYP3A5	*1/*1	Normal Metabolizer
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity
MTHFR	c.1286A>C AA c.665C>T CT	No Increased Risk of Hyperhomocysteinemia
MTHFR	c.665C>T CT	Reduced MTHFR Activity

For a complete report contact Manchester University Master of Science in Pharmacogenomics Program
www.manchester.edu/pgx

Powered By Translational software