MAKO GENOMICS

PGx Comprehensive Report

PATIENT: Gene Omics2

DOB:	1/1/1935	**SPECIMEN TYPE:**	Buccal Swab	**RECEIVED DATE:**	12/30/2016
GENDER:	Male	**COLLECTION DATE:**	1/18/2017	**REPORT GENERATED:**	10/19/2017
ETHNICITY:		**ACCESSION #:**	P1777777	**FACILITY/CLINIC:**	PGX HOUSE ACCOUNT
		ICD-10:	None Specified	**ORDERING PHYSICIAN:**	

TEST DETAILS SUMMARY

GENE	GENOTYPE	PHENOTYPE
CYP2C9	*1/*1	Normal Metabolizer
CYP2C19	*1/*17	Rapid Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity
Apolipoprotein E	ε3/ε4	Altered APOE function
CYP2D6	*1/*4 XN	Ultra-Rapid or Normal Metabolizer
CYP2B6	*1/*1	Normal Metabolizer
CYP1A2	*1A/*1F	Normal Metabolizer - Higher Inducibility
SLCO1B1	521T>C T/T	Normal Function
COMT	Val158Met G/G	High/Normal COMT Activity
OPRM1	A118G A/G	Altered OPRM1 Function
UGT2B15	*1/*2	Intermediate Metabolizer
MTHFR	1298A>C AA 677C>T CC	No Increased Risk of Hyperhomocysteinemia
MTHFR	677C>T CC	Normal MTHFR Activity
Factor II Factor V Leiden	20210G>A GG 1691G>A GG	No Increased Risk of Thrombosis

*Comprehensive Test Detail information available at end of the report

CURRENT MEDICATIONS SUMMARY

Medications Outside the Scope of the Report: Allegra, Lisinopril, Loratadine

SAFE TO USE AS DIRECTED

Adderall (Amphetamine)
Ibuprofen (Advil, Motrin)
Warfarin (Coumadin)

USE MEDICATIONS WITH CAUTION

Omeprazole (Prilosec)
Prilosec (Omeprazole)
Zoloft (Sertraline)

CAUTION CONSIDER ALTERNATIVES

*Guidance for additional medications available in Potentially Impacted Medications section

Current Patient Medications

Allegra, Lisinopril, Loratadine, Omeprazole, Warfarin, Ibuprofen, Zoloft, Adderall, Prilosec

Omeprazole
Prilosec

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

- Helicobacter pylori eradication: increase dose by 100-200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 100-200%.

Prilosec
Omeprazole

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

- Helicobacter pylori eradication: increase dose by 100-200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 100-200%.

Zoloft
Sertraline

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

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

Adderall
Amphetamine

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.

Ibuprofen
Advil, Motrin

Normal Sensitivity to Ibuprofen (CYP2C9: Normal Metabolizer) — INFORMATIVE

Individuals with a normal CYP2C9 activity (i.e normal metabolizers) can be prescribed ibuprofen according to standard label recommended-dosage and administration.

Warfarin
Coumadin

Less than normal Sensitivity to Warfarin (CYP2C9 *1/*1 VKORC1 -1639G>A G/G) — ACTIONABLE

Initiation Therapy: a dose increase may be required. Consider using the following warfarin dose range as provided in the FDA-approved label: **5-7 mg/day.** OR consider using a personalized dose calculated by a pharmacogenetic algorithm. The estimated time to reach steady state is 4-5 days.

Medications outside the scope of the report: Allegra, Lisinopril, Loratadine

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

Guidelines exist for adjusting dosage, increased vigilance or the patient has a moderate risk for the indicated condition.

The medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.

ACTIONABLE — Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA. EMA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as knowledge arises.

INFORMATIVE — There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

Risk Management

Type III Hyperlipoproteinemia

Not Associated with Type III Hyperlipoproteinemia

The patient is positive for the APOE c.388 T>C (Cys130Arg) mutation and negative for the APOE c.526 C>T (Arg176Cys) mutation. The patient's genotype is ε3/ε4 (frequency: 15-28%).
The APOE E3 is the normal APOE. The APOE E4 confers a limitation of HDL binding to its receptor, and is associated with increased plasma cholesterol, LDL, and triglycerides. Individuals that are heterozygous for this allele may have higher total cholesterol levels and elevated LDL cholesterol levels. The APOE ε3/ε4 genotype is associated with an increased risk for developing atherosclerosis and cardiovascular disease.
Consider dietary adjustments (very low fat diet) and lipid-lowering therapy based on lipid profiles and other risk factors.

Hyperhomocysteinemia - Depression

No Increased Risk of Hyperhomocysteinemia

The patient does not carry the MTHFR C677T variant. MTHFR enzyme activity is normal.
Patients diagnosed with depression often have low folate levels and homocysteine is a highly sensitive marker of folate status. Functional folate deficiency is indicated by elevated homocysteine. With a normal MTHFR activity, this patient can process folate normally and is unlikely to have elevated plasma levels of homocysteine.
Patients diagnosed with depression: as lower folate levels are associated with poorer antidepressant response, and baseline levels of folate within the normal range predict antidepressant response, testing for homocysteine levels and serum folate levels may be informative for this patient before prescribing methylfolate as an antidepressant-augmenting agent.

Thrombophilia

No Increased Risk of Thrombosis

The patient does not carry the Factor V Leiden G1691A mutation or Factor II G20210A mutation (wild-type).
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.
Unless other genetic and/or circumstantial risk factors are present (e.g., smoking or obesity...), estrogen-containing contraceptive and hormone replacement therapy can be used by the patient.

Hyperhomocysteinemia - Thrombosis

No Increased Risk of Hyperhomocysteinemia

The patient does not carry the MTHFR C677T or MTHFR A1298C mutation (wild-type). MTHFR enzyme activity is normal.
With a normal MTHFR activity, this patient is unlikely to have elevated plasma levels of homocysteine, which is a known risk factor for cardiovascular diseases and thrombosis. Unless other risk factors are present, the patient is not expected to have an increased risk for venous thromboembolism (VTE).
MTHFR enzyme activity is normal.

Potentially Impacted Medications

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

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Gastrointestinal	Antiemetics	Aprepitant (Emend-oral) Dronabinol (Marinol) Fosaprepitant (Emend-i.v) Granisetron (Sancuso, Sustol) Metoclopramide (Reglan) Rolapitant (Varubi)	Dolasetron (Anzemet) Netupitant-Palonosetron (Akynzeo) Palonosetron (Aloxi)	Ondansetron (Zofran, Zuplenz)
	Proton Pump Inhibitors	Rabeprazole (Aciphex)	Dexlansoprazole (Dexilant, Kapidex) Esomeprazole (Nexium) Lansoprazole (Prevacid) Omeprazole (Prilosec) Pantoprazole (Protonix)	
Infections	Antifungals	Amphotericin B (AmBisome, Abelcet) Anidulafungin (Eraxis) Caspofungin (Cancidas) Fluconazole (Diflucan) Isavuconazonium (Cresemba) Itraconazole (Sporanox) Micafungin (Mycamine) Posaconazole (Noxafil)		Voriconazole (Vfend)
	Anti-HIV Agents	Dolutegravir (Tivicay, Triumeq) Raltegravir (Isentress, Dutrebis)		
	Antimalarials	Proguanil (Malarone)		
Pain	Fibromyalgia Agents	Milnacipran (Savella)		
	Muscle Relaxants	Cyclobenzaprine (Flexeril, Amrix) Metaxalone (Skelaxin) Methocarbamol (Robaxin)	Carisoprodol (Soma) Tizanidine (Zanaflex)	
	NSAIDs	Celecoxib (Celebrex) Diclofenac (Voltaren) Flurbiprofen (Ansaid) Ibuprofen (Advil, Motrin) Indomethacin (Indocin) Ketoprofen (Orudis) Ketorolac (Toradol) Meloxicam (Mobic) Nabumetone (Relafen) Naproxen (Aleve) Piroxicam (Feldene) Sulindac (Clinoril)		
	Opioids	Alfentanil (Alfenta) Buprenorphine (Butrans, Buprenex) Hydromorphone (Dilaudid, Exalgo) Levorphanol (Levo Dromoran) Meperidine (Demerol) Methadone (Dolophine) Oxymorphone (Opana, Numorphan) Sufentanil (Sufenta) Tapentadol (Nucynta)	Dihydrocodeine (Synalgos-DC) Fentanyl (Actiq) Hydrocodone (Vicodin) Morphine (MS Contin) Oxycodone (Percocet, Oxycontin)	Codeine (Codeine; Fioricet with Codeine) Tramadol (Ultram)
	Antiaddictives	Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave) Naltrexone (Vivitrol, Contrave)		

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Psychotropic	Anti-ADHD Agents	Amphetamine (Adderall, Evekeo) Dexmethylphenidate (Focalin) Dextroamphetamine (Dexedrine) Guanfacine (Intuniv) Lisdexamfetamine (Vyvanse) Methylphenidate (Ritalin, Aptensio XR, Concerta, Metadate ER, Quillivant ER)	Clonidine (Kapvay)	Atomoxetine (Strattera)
	Anticonvulsants	Brivaracetam (Briviact) Cannabidiol (Epidiolex) Carbamazepine (Tegretol, Carbatrol, Epitol) Eslicarbazepine (Aptiom) Ethosuximide (Zarontin) Ezogabine (Potiga) Felbamate (Felbatol) Fosphenytoin (Cerebyx) Gabapentin (Neurontin) Lacosamide (Vimpat) Lamotrigine (Lamictal) Levetiracetam (Keppra) Oxcarbazepine (Trileptal, Oxtellar XR) Perampanel (Fycompa) Phenobarbital (Luminal) Phenytoin (Dilantin) Pregabalin (Lyrica) Primidone (Mysoline) Rufinamide (Banzel) Stiripentol (Diacomit) Tiagabine (Gabitril) Topiramate (Topamax) Valproic Acid (Depakote, Depakene) Vigabatrin (Sabril) Zonisamide (Zonegran)		
	Antidementia Agents	Galantamine (Razadyne) Memantine (Namenda)	Donepezil (Aricept)	
	Antidepressants	Desvenlafaxine (Pristiq) Duloxetine (Cymbalta) Fluoxetine (Prozac, Sarafem) Levomilnacipran (Fetzima) Mirtazapine (Remeron) Nefazodone (Serzone) Trazodone (Oleptro) Vilazodone (Viibryd) Vortioxetine (Trintellix)	Amoxapine (Amoxapine) Fluvoxamine (Luvox) Maprotiline (Ludiomil) Sertraline (Zoloft)	Amitriptyline (Elavil) Citalopram (Celexa) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Escitalopram (Lexapro) Imipramine (Tofranil) Nortriptyline (Pamelor) Paroxetine (Paxil, Brisdelle) Protriptyline (Vivactil) Trimipramine (Surmontil) Venlafaxine (Effexor)

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
	Antipsychotics	Aripiprazole (Abilify, Aristada) Asenapine (Saphris) Brexpiprazole (Rexulti) Cariprazine (Vraylar) Iloperidone (Fanapt) Loxapine (Loxitane, Adasuve) Lurasidone (Latuda) Paliperidone (Invega) Pimavanserin (Nuplazid) Quetiapine (Seroquel) Thioridazine (Mellaril) Thiothixene (Navane) Trifluoperazine (Stelazine) Ziprasidone (Geodon)	Chlorpromazine (Thorazine) Clozapine (Clozaril) Fluphenazine (Prolixin) Olanzapine (Zyprexa) Perphenazine (Trilafon) Pimozide (Orap)	Haloperidol (Haldol) Risperidone (Risperdal)
	Benzodiazepines	Alprazolam (Xanax) Clobazam (Onfi) Clonazepam (Klonopin)	Diazepam (Valium) Lorazepam (Ativan) Oxazepam (Serax)	
	Other Neurological Agents	Deutetrabenazine (Austedo) Dextromethorphan / Quinidine (Nuedexta) Flibanserin (Addyi) Valbenazine (Ingrezza)	Tetrabenazine (Xenazine)	
Rheumatology	Anti-Hyperuricemics and Anti-Gout Agents	Colchicine (Mitigare) Febuxostat (Uloric) Lesinurad (Zurampic)		
	Immunomodulators	Apremilast (Otezla) Leflunomide (Arava) Tofacitinib (Xeljanz)		
Transplantation	Immunosupressants	Tacrolimus (Prograf)		
Urologicals	5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia	Dutasteride (Avodart) Finasteride (Proscar)		
	Alpha-Blockers for Benign Prostatic Hyperplasia	Alfuzosin (UroXatral) Doxazosin (Cardura) Silodosin (Rapaflo) Tamsulosin (Flomax) Terazosin (Hytrin)		
	Antispasmodics for Overactive Bladder	Darifenacin (Enablex) Fesoterodine (Toviaz) Mirabegron (Myrbetriq) Oxybutynin (Ditropan) Solifenacin (Vesicare) Tolterodine (Detrol) Trospium (Sanctura)		
	Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra) Sildenafil (Viagra) Tadalafil (Cialis) Vardenafil (Levitra)		

Dosing Guidance

Amitriptyline
Elavil

Possible Non-Response to Amitriptyline (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider an alternative drug, or prescribe amitriptyline at increased dose and monitor the plasma concentrations of amitriptyline and metabolites (there is insufficient data to calculate dose adjustment).

Amitriptyline
Elavil

Increased Sensitivity to Amitriptyline (CYP2C19: Rapid Metabolizer) — INFORMATIVE

Consider an alternative drug, or consider prescribing amitriptyline at standard dose and monitor the plasma concentrations of amitriptyline and nortriptyline to guide dose adjustments.

Atomoxetine
Strattera

Possible Non-Response to Atomoxetine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — INFORMATIVE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: the patient may fail to achieve adequate plasma levels of atomoxetine if the drug is prescribed at standard recommended doses. Consider prescribing atomoxetine with careful titration and monitoring for reduced efficacy. There is insufficient data to calculate dose adjustment. Or consider an alternative medication.

Citalopram
Celexa

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

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

Clomipramine
Anafranil

Possible Non-Response to Clomipramine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider an alternative drug, or prescribe clomipramine at an increased dose and monitor the plasma concentrations of clomipramine and desmethylclomipramine.

Clomipramine
Anafranil

Increased Sensitivity to Clomipramine (CYP2C19: Rapid Metabolizer) — INFORMATIVE

Consider an alternative drug, or consider prescribing clomipramine at standard dose and monitor the plasma concentrations of clomipramine and desmethyl-clomipramine to guide dose adjustments.

Codeine
Codeine; Fioricet with Codeine

Possible Increased Response to Codeine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

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

Desipramine
Norpramin

Possible Non-Response to Desipramine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider an alternative drug, or prescribe desipramine at an increased dosage and observe the patient for decreased efficacy. Adjust dosage in response to desipramine and metabolites plasma concentrations and clinical response.

Doxepin
Silenor

Possible Non-Response to Doxepin (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider an alternative drug, or increase doxepin dose by 100%. Adjust maintenance dose according to nordoxepin plasma concentrations.

Doxepin
Silenor

Increased Sensitivity to Doxepin (CYP2C19: Rapid Metabolizer) — INFORMATIVE

Consider an alternative drug, or consider prescribing doxepin at standard dose and monitor the plasma concentrations of doxepin and desmethyl-doxepin to guide dose adjustments.

Escitalopram
Lexapro

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

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

Flecainide
Tambocor

Altered Response to Flecainide (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: titrate carefully and consider adjusting dose in response to plasma concentration and ECG monitoring, OR consider an alternative drug. Examples of alternatives drugs not affected by CYP2D6 include: sotalol, disopyramide, quinidine, and amiodarone.

Haloperidol
Haldol

Possible Non-Response to Haloperidol (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider an alternative drug, or prescribe haloperidol at standard dose and adjust dosage to achieve a favorable clinical response. Be alert to decreased haloperidol plasma concentrations.

Imipramine
Tofranil

Possible Non-Response to Imipramine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider an alternative drug, or consider increasing the imipramine dose and adjust the dosage in response to imipramine and desipramine plasma concentrations.

Imipramine
Tofranil

Increased Sensitivity to Imipramine (CYP2C19: Rapid Metabolizer) — INFORMATIVE

Consider an alternative drug, or consider prescribing imipramine at the standard dose and monitor the plasma concentrations of imipramine and desipramine to guide dose adjustments.

Metoprolol
Lopressor

Possible Non-Responder to Metoprolol (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: the patient may experience a decrease in the pharmacological effect when taking metoprolol at standard dosage. Heart Failure: Consider alternative beta-blockers such as bisoprolol or carvedilol, or prescribe metoprolol at a higher dose. Other indications: Consider alternative beta-blockers such as bisoprolol or atenolol, or prescribe metoprolol at a higher dose. If metoprolol is prescribed, titrate the dose to a maximum of 250% of the normal dose in response to efficacy and adverse events.

Nortriptyline
Pamelor

Possible Non-Response to Nortriptyline (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider an alternative drug, or prescribe nortriptyline at an increased dose and monitor the plasma concentration of nortriptyline and hydroxynortriptyline.

Ondansetron
Zofran, Zuplenz

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

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: a substantially decreased antiemetic effect has been reported in these patients when taking standard doses of this medication. Consider prescribing an alternative drug not metabolized by CYP2D6 such as granisetron.

Paroxetine

Paxil, Brisdelle

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

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: there is a risk for decreased efficacy at standard dosage. If a standard dose is prescribed to a CYP2D6 ultra-rapid metabolizer, suboptimal plasma concentrations of the drug are likely. Consider an alternative medication.

Protriptyline

Vivactil

Possible Non-Response to Protriptyline (CYP2D6: Ultra-Rapid or Normal Metabolizer) — INFORMATIVE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider alternative drugs or prescribe protriptyline at increased dosage and observe the patient for decreased efficacy. Adjust dosage in response to protriptyline and metabolites plasma concentrations and clinical response.

Risperidone

Risperdal

Possible Non-Response to Risperidone (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider an alternative drug, or prescribe risperidone, be extra alert to insufficient response, and adjust dosage in response to clinical response and adverse events.

Tramadol

Ultram

Possible Increased Response to Tramadol (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, and is at high risk of toxicity when taking tramadol at standard dosing. Consider reducing tramadol dose by 30%. Careful monitoring for side effects (nausea, vomiting, constipation, respiratory depression, confusion, urinary retention) and weekly titration are recommended. In case of toxicity, consider alternative opioids other than codeine, or a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

The accelerated conversion of tramadol to its active metabolite can result in high and unsafe levels of this metabolite in breast milk potentially causing life threatening respiratory depression in the breastfed infant. Use of tramadol should be avoided in breastfeeding mothers.

Trimipramine

Surmontil

Possible Non-Response to Trimipramine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider an alternative drug, or consider prescribing trimipramine at an increased dose, then adjust dosage in response to trimipramine plasma concentrations.

Trimipramine

Surmontil

Increased Sensitivity to Trimipramine (CYP2C19: Rapid Metabolizer) — INFORMATIVE

Consider an alternative drug, or consider prescribing trimipramine at standard dose and monitor the plasma concentrations of trimipramine and desmethyl-trimipramine to guide dose adjustments.

Venlafaxine

Effexor

Possible Non-Response to Venlafaxine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: consider an alternative drug, or increase the venlafaxine dose to a maximum of 150% of the normal dose and monitor venlafaxine and O-desmethylvenlafaxine plasma concentrations.

Voriconazole

Vfend

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

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

Amoxapine

Amoxapine

Possible Non-Response to Amoxapine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — INFORMATIVE

Like other tricyclic and tetracyclic antidepressants, amoxapine is metabolized by CYP2D6. However, the overall contribution of this enzyme in the metabolism of this drug is not well documented. Based on the genotype result, this patient may be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: patients with increased CYP2D6 function may metabolize amoxapine more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations. There are no established dosing adjustments for patients with increased CYP2D6 function; therapy must be initiated cautiously and adjusted according to the patient's response.

Carisoprodol

Soma

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

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

Chlorpromazine

Thorazine

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

Chlorpromazine is metabolized by CYP2D6, CYP3A4 and flavin-containing monooxygenases. Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: subjects with increased CYP2D6 function will metabolize chlorpromazine more rapidly which can result in sub-therapeutic drug concentrations. Consider a standard dose and adjust dosage according to the patient's tolerability and response. Higher doses may be necessary to achieve efficacy.

Clonidine

Kapvay

Possible Altered Response to Clonidine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — INFORMATIVE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers. Approximately 40-60% of an orally administered dose of clonidine is eliminated unchanged by the kidneys, with the remainder undergoing hepatic metabolism. CYP2D6 plays a major role in clonidine oxidative metabolism, followed by CYP3A and CYP1A2. **Preliminary studies that individuals with high CYP2D6 activity, have increased clonidine clearance and may require higher doses to reach target therapeutic plasma concentrations and respond to therapy.** There is insufficient data to calculate dose adjustments and careful titration is recommended until a favorable response is achieved in this patient. An alternative medication not metabolized by CYP2D6 can also be considered if the patient fails to respond to higher doses of clonidine.

Treatment with clonidine can cause dose related decreases in blood pressure and heart rate Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Titrate Clonidine slowly in patients with a history of hypotension, and those with underlying conditions that may be worsened by hypotension and bradycardia.

Clopidogrel

Plavix

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

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

Clozapine

Clozaril

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

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

Dexlansoprazole

Dexilant, Kapidex

Insufficient Response to Dexlansoprazole (CYP2C19: Rapid Metabolizer) — INFORMATIVE

- Helicobacter pylori eradication: increase dose by 200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 200%.

Diazepam

Valium

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

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

Dihydrocodeine

Synalgos-DC

Possible Altered Response to Dihydrocodeine (CYP2D6: Ultra-Rapid or Normal Metabolizer) **INFORMATIVE**

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

Dolasetron

Anzemet

Possible Altered Response to Dolasetron (CYP2D6: Ultra-Rapid or Normal Metabolizer) **INFORMATIVE**

The reduction of dolasetron to its active metabolite hydrodolasetron is mediated by a carbonyl reductase. Hydrodolasetron is further eliminated by multiple routes, including renal excretion and by glucuronidation or hydroxylation by CYP2D6. Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower hydroxydolasetron plasma concentrations at standard dosing. However, the clinical significance of this change remains unclear. Dolasetron can be prescribed at standard label-recommended dosage and administration. Monitor the patient for possible decreased efficacy.

Donepezil

Aricept

Possible Altered Response to Donepezil (CYP2D6: Ultra-Rapid or Normal Metabolizer) **INFORMATIVE**

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: when compared to a normal metabolizer, a ultra-rapid metabolizers has a 24% increase in donepezil clearance. The clinical significance of this increase is not well documented. Consider using a standard dosing regimen and adjust dosage in response to clinical response and tolerability.

Esomeprazole

Nexium

Insufficient Response to Esomeprazole (CYP2C19: Rapid Metabolizer) **INFORMATIVE**

- Helicobacter pylori eradication: increase dose by 50-100% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 50-100%.

Fentanyl

Actiq

Altered Response to Fentanyl (OPRM1: Altered OPRM1 Function) **INFORMATIVE**

The patient carries one copy of the OPRM1 118A>G mutation. Acute postoperative and cancer pain: the patient's genotype has been shown to be associated with reduced analgesia at standard fentanyl doses. Therefore, the patient may require higher doses of this drug. 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.

Fluphenazine

Prolixin

Possible Non-response to Fluphenazine (CYP2D6: Ultra-Rapid or Normal Metabolizer) **INFORMATIVE**

Fluphenazine is metabolized by CYP2D6, CYP1A2 and other enzymes and based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: **patients with increased CYP2D6 function will metabolize fluphenazine more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations.** There are no established dosing adjustments for patients with increased CYP2D6 function therefore, therapy must be initiated cautiously with oral or parenteral fluphenazine hydrochloride. When the pharmacological effects and an appropriate dosage are apparent, an equivalent dose of fluphenazine decanoate (IM or SC) may be administered and subsequent dosage adjustments may be necessary.

Fluvoxamine

Luvox

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

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: there is a risk for decreased efficacy at standard dosage. If a standard dose is prescribed to a CYP2D6 ultra-rapid metabolizer, suboptimal plasma concentrations of the drug are likely. There is insufficient data to calculate dose adjustments and careful titration is recommended until a favorable response is achieved. An alternative medication not metabolized by CYP2D6 can also be considered.

Hydrocodone

Vicodin

Altered Response to Hydrocodone (OPRM1: Altered OPRM1 Function) **INFORMATIVE**

Acute postoperative and cancer pain: the patient's genotype has been shown to be associated with reduced analgesia and increased opioid side effects at standard or high hydrocodone doses. If the patient fails to respond to increased hydrocodone doses, an alternative opioid may be considered.

Hydrocodone
Vicodin

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

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

Lansoprazole
Prevacid

Insufficient Response to Lansoprazole (CYP2C19: Rapid Metabolizer) — INFORMATIVE

- Helicobacter pylori eradication: increase dose by 200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 200%.

Lorazepam
Ativan

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

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

Maprotiline
Ludiomil

Possible Non-response to Maprotiline (CYP2D6: Ultra-Rapid or Normal Metabolizer) — INFORMATIVE

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

Mexiletine
Mexitil

Altered Response to Mexiletine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — INFORMATIVE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: because mexiletine plasma concentrations may be decreased, consider adjusting dose in response to mexiletine plasma concentration and ECG monitoring, until a favorable response in achieved.

Morphine
MS Contin

Altered Response to Morphine (OPRM1: Altered OPRM1 Function) — INFORMATIVE

The patient carries one copy of the OPRM1 118A>G mutation. Acute postoperative and cancer pain: the patient's genotype has been shown to be associated with possible reduced analgesia at standard morphine doses and decreased risk for nausea and vomiting during the first 24-hour postoperative period. Therefore, the patient may require higher doses of this drug. The dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

Morphine
MS Contin

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

The patient does not carry the COMT Val158Met mutation. 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.

Netupitant-Palonosetron
Akynzeo

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

Netupitant: Netupitant is extensively metabolized to three major metabolites (desmethyl, N-oxide and a hydroxy-methyl derivatives). Metabolism is mediated primarily by CYP3A4 and to a lesser extent by CYP2C9 and CYP2D6. No genetically guided drug selection or dosing recommendations are available for this drug. Netupitant can be prescribed at standard label-recommended dosage and administration.
Palonosetron: Palonosetron is eliminated by multiple routes including metabolism. While CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in its metabolism to two inactive metabolites. Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower palonosetron plasma concentrations at standard dosing. However, the clinical significance of this change remains unclear. Palonosetron can be prescribed at standard label-recommended dosage and administration. Monitor the patient for possible decreased efficacy.

Olanzapine
Zyprexa

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

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

Omeprazole
Prilosec

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

- Helicobacter pylori eradication: increase dose by 100-200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 100-200%.

Oxazepam
Serax

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

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

Oxycodone
Percocet, Oxycontin

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

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

Palonosetron
Aloxi

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

Palonosetron is eliminated by multiple routes including metabolism. While CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in its metabolism to two inactive metabolites. Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower palonosetron plasma concentrations at standard dosing. However, the clinical significance of this change remains unclear. Palonosetron can be prescribed at standard label-recommended dosage and administration. Monitor the patient for possible decreased efficacy.

Pantoprazole
Protonix

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

- Helicobacter pylori eradication: increase dose by 400% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase of 400%.

Perphenazine
Trilafon

Possible Non-Response to Perphenazine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: subjects with increased CYP2D6 function will metabolize perphenazine more rapidly, which can result in sub-therapeutic drug concentrations. Consider a dose increase with close monitoring until a favorable response is achieved.

Pimozide
Orap

Possible Non-Response to Pimozide (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: there is insufficient data to calculate dose adjustment, and if pimozide is prescribed at standard dosing, monitor response and be alert to reduced efficacy. Standard starting dose: 1 to 2 mg/day (adult) or 0.05 mg/kg/day (children). Doses may be increased to a maximum of 10 mg/day or 0.2 mg/kg/day.

Propafenone
Rythmol

Altered Response to Propafenone (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers:titrate carefully and consider adjusting dose in response to plasma concentration and ECG monitoring, OR consider an alternative drug. Examples of alternatives drugs not affected by CYP2D6 include: sotalol, disopyramide, quinidine, and amiodarone.

Sertraline

Zoloft

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

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

Tetrabenazine

Xenazine

Unknown Sensitivity to Tetrabenazine (CYP2D6: Ultra-Rapid or Normal Metabolizer) — ACTIONABLE

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

Tizanidine

Zanaflex

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

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

Test Details

Gene	Genotype	Phenotype	Clinical Consequences
CYP2C9	*1/*1	**Normal Metabolizer**	Consistent with a typical CYP2C9 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP2C19	*1/*17	**Rapid Metabolizer**	Consistent with a significant increase in CYP2C19 activity. Potential risk for side effects or loss of efficacy with drug substrates.
CYP3A5	*3/*3	**Poor Metabolizer**	Consistent with a poor CYP3A5 activity. This phenotype is the most common in the general population. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
CYP3A4	*1/*1	**Normal Metabolizer**	Consistent with a typical CYP3A4 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
VKORC1	-1639G>A G/G	**Low Warfarin Sensitivity**	VKORC1 is the site of action of warfarin. The patient may require an increase in warfarin dose.
Apolipoprotein E	ε3/ε4	**Altered APOE function**	Not associated with type III hyperlipoproteinemia - Increased risk of cardiovascular disease
CYP2D6	*1/*4 XN	**Ultra-Rapid or Normal Metabolizer**	Consistent with typical or increased CYP2D6 activity. Potential risk for side effects or loss of efficacy with drug substrates.
CYP2B6	*1/*1	**Normal Metabolizer**	Consistent with a typical CYP2B6 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP1A2	*1A/*1F	**Normal Metabolizer - Higher Inducibility**	Consistent with a typical CYP1A2 activity in absence of inducing substances. Rapid Metabolism occurs in presence of inducers such as barbiturates, cruciferous vegetables, carbamazepine, rifampin and smoking.
SLCO1B1	521T>C T/T	**Normal Function**	Consistent with a typical SLCO1B1 transporter function. The patient's risk for statin-induced myopathy is not increased.
COMT	Val158Met G/G	**High/Normal COMT Activity**	Consistent with a normal catechol O-methyltransferase (COMT) function.
OPRM1	A118G A/G	**Altered OPRM1 Function**	Consistent with a reduced OPRM1 receptor signaling efficiency induced by exogenous opioids. This is associated with a possible reduced analgesia following standard opioid doses and a favorable response to naltrexone.
UGT2B15	*1/*2	**Intermediate Metabolizer**	Consistent with a moderately decreased UGT2B15 glucuronidation function. Potential risk for side effects with drug substrates.
MTHFR	1298A>C AA 677C>T CC	**No Increased Risk of Hyperhomocysteinemia**	With a normal MTHFR activity, this patient is unlikely to have elevated plasma levels of homocysteine, which is a known risk factor for cardiovascular diseases and thrombosis. Unless other risk factors are present, the patient is not expected to have an increased risk for venous thromboembolism (VTE).
MTHFR	677C>T CC	**Normal MTHFR Activity**	The patient does not carry the MTHFR C677T mutation (wild-type) and the patient's MTHFR activity is normal. This is not associated with an increased risk of hyperhomocysteinemia.
Factor II **Factor V Leiden**	20210G>A GG 1691G>A GG	**No Increased Risk of Thrombosis**	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.

Alleles Tested: Apolipoprotein E ε2, ε4, (ε3 is reference); **COMT** Val158Met; **CYP1A2** *1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W; **CYP2B6** *7, *16, *5, *6, *9, *18, *22; **CYP2C19** *2, *3, *4, *4B, *5, *6, *7, *8, *9, *17; **CYP2C9** *2, *3, *4, *5, *6, *11; **CYP2D6** *2, *3, *4, *4M, *6, *7, *8, *9, *10, *11, *12, *14A, *14B, *15, *17, *29, *41, *5 (gene deletion), XN (gene duplication); **CYP3A4** *1B, *12, *17, *22; **CYP3A5** *2, *3, *3B, *3C, *6, *7; **Factor II** 20210G>A; **Factor V Leiden** 1691G>A; **MTHFR** 1298A>C, 677C>T; **OPRM1** A118G; **SLCO1B1** 521T>C; **UGT2B15** *2; **VKORC1** -1639G>A

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

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

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. Mako Medical Laboratories developed this test and its performance characteristics. This test has not been cleared or approved by the U.S. Food and Drug Administration. 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.

The pharmacogenetic assay involves non-FDA approved interpretational software and genotype-phenotype associations performed by Translational Software. A qualified designee within Mako Medical Laboratories uses Translational Software to generate and subsequently review the report.

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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.

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Patient Information Card

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

REPORT DETAILS

Patient: Gene Omics2
DOB: 1/1/1935
ACC #: P1777777

Pharmacogenetic Test Summary

CYP2C19	*1/*17	Rapid Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*1/*4 XN	Ultra-Rapid or Normal Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity
MTHFR	1298A>C AA 677C>T CC	No Increased Risk of Hyperhomocysteinemia
MTHFR	677C>T CC	Normal MTHFR Activity
Factor II Factor V Leiden	20210G>A GG 1691G>A GG	No Increased Risk of Thrombosis

For a complete report contact Mako Medical Laboratories, LLC
www.makomedical.com