diagnostics GNP

PATIENT INFORMATION		SPECIMEN DETAILS		ORDERED BY
NAME:		**SPECIMEN TYPE:**	Buccal Swab	
ACC #:	PHI12031	**COLLECTION DATE:**	10/31/2017	
DOB:	6/2/1990	**RECEIVED DATE:**	11/6/2017	
SEX:	Male	**REPORT DATE:**	11/10/2017	

General Gene Panel

Test Details

Gene	Genotype	Phenotype	Clinical Consequences
ABCG2	421C>A C/C	**Normal Function**	Consistent with a normal ABCG2 transporter function. The patient's risk for statin-induced adverse events is normal.
ANKK1/DRD2	DRD2:Taq1A G/G	**Unaltered DRD2 function**	Consistent with a normal dopamine receptor D2 function.
Apolipoprotein E	ε3/ε3	**Normal APOE function**	Not associated with type III hyperlipoproteinemia - No increased risk of cardiovascular disease
COMT	Val158Met G/G	**High/Normal COMT Activity**	Consistent with a normal catechol O-methyltransferase (COMT) function.
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.
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.
CYP2C19	*1/*1	**Normal Metabolizer**	Consistent with a typical CYP2C19 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP2C9	*2/*3	**Poor Metabolizer**	Consistent with a significant deficiency in CYP2C9 activity. Increased risk for side effects or loss of efficacy with drug substrates.
CYP2D6	*1/*2 XN	**Ultra-Rapid Metabolizer**	Consistent with a significant increase in CYP2D6 activity. Potential risk for side effects or loss of efficacy with drug substrates.
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.
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.
DPYD	*1/*1	**Normal Metabolizer**	Consistent with a typical DPD activity and a typical risk of side effects with conventional doses of fluoropyridines.
DRD2	-241A>G T/T	**Homozygous for rs1799978 T Allele**	Associated with a favorable response to Risperidone.
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.
HTR2A	-1438G>A C/T	**Heterozygous for the T Allele (rs6311)**	The patient carries one copy of the variant allele at rs6311 which may be associated with greater serotonin 2A receptor gene expression.
HTR2A	rs7997012 A/A	**Homozygous for the A allele (rs7997012)**	Possible increased response to citalopram and escitalopram
HTR2C	2565G>C G/G	**Homozygous for the G allele (rs1414334)**	This genotype is not associated with risperidone- and clozapine-induced metabolic syndrome.
HTR2C	-759C>T C/C	**Homozygous for the C allele (rs3813929)**	Consistent with altered satiety signaling mediated by the serotonin receptor 2C (HTR2C). Increased incidence of metabolic side effects (weight gain, hyperglycemia, hyperlipidemia) with atypical antipsychotic medications.

ITGB3	176T>C T/C	**Increased Platelet Reactivity**	The patient carries the 176T>C mutation of the integrin β3 gene which is associated with an increased platelet reactivity.
LPA	rs10455872 A/A rs3798220 T/T	**No increased risk of cardiovascular disease**	The patient is a non carrier of the risk alleles in LPA gene for both the variants (rs3798220 and rs10455872).
MTHFR	677C>T TT	**Reduced MTHFR Activity**	The patient carries two MTHFR C677T mutations (homozygous). MTHFR enzyme activity is severely reduced (30% of normal activity) and the risk of hyperhomocysteinemia is severely increased.
MTHFR	1298A>C AA 677C>T TT	**Increased Risk of Hyperhomocysteinemia**	The patient's significantly reduced MTHFR activity is a risk factor for hyperhomocysteinemia, especially in the presence of low serum folate levels. Mild to moderate hyperhomocysteinemia appears to be associated with an increased risk for venous thromboembolism (VTE).
OPRM1	A118G A/A	**Normal OPRM1 Function**	Consistent with a normal OPRM1 receptor signaling efficiency induced by exogenous opioids. This is associated with a good analgesia following standard opioid doses and a poor response to naltrexone.
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.
TPMT	*1/*1	**Normal Metabolizer**	Consistent with a typical TPMT activity and a typical risk of side effects with conventional doses of thiopurines.
VKORC1	-1639G>A A/A	**High Warfarin Sensitivity**	VKORC1 is the site of action of warfarin. The patient may require a substantial decrease in warfarin dose.

Alleles Tested: **ABCG2** 421C>A; **ANKK1/DRD2** DRD2:Taq1A; **Apolipoprotein E** ε2, ε4, (ε3 is reference); **COMT** Val158Met; **CYP1A2** *1F; **CYP2B6** *6, *9; **CYP2C19** *2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *17; **CYP2C9** *2, *3; **CYP2D6** *2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication); **CYP3A4** *1B, *22; **CYP3A5** *3, *3C, *6, *7; **DPYD** *2A, *9A, *9B, rs67376798 A, *13; **DRD2** -241A>G; **Factor II** 20210G>A; **Factor V Leiden** 1691G>A; **HTR2A** -1438G>A, rs7997012; **HTR2C** -759C>T, 2565G>C; **ITGB3** 176T>C; **LPA** rs3798220, rs10455872; **MTHFR** 1298A>C, 677C>T; **OPRM1** A118G; **SLCO1B1** 521T>C; **TPMT** *3A, *3B, *3C; **VKORC1** -1639G>A

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Report Overview

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

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Risk Management

Hyperuricemia and Gout

Normal Risk of Gout

The patient carries two copies of ABCG2 rs2231142 C allele.

The ABCG2 rs2231142 C allele is associated with normal ABCG2 activity and subsequent normal renal elimination of uric acid. The patient's genotype is associated with a normal risk of hyperuricemia and gout.

No action is needed for this patient unless other genetic or non-genetic risk factors are present.

Antipsychotic-Induced Tardive Dyskinesia

Increased Risk of Antipsychotic-Induced Tardive Dyskinesia

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

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

Closely monitor the patient for signs of tardive dyskinesia.

Antipsychotic-Induced Hyperprolactinemia

Normal Risk of Antipsychotic-Induced Hyperprolactinemia

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

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

Monitor the patients closely for any signs of hyperprolactinemia.

Antipsychotic-Induced Weight Gain

Low Risk of Antipsychotic-Induced Weight Gain

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

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

Monitor the patient closely for signs weight gain.

Type III Hyperlipoproteinemia

Not Associated with Type III Hyperlipoproteinemia

The patient is negative for both the APOE c.388 T>C (Cys130Arg) and c.526 C>T (Arg176Cys) mutations. The patient's genotype is wild-type, which is the most common genotype in the general population (frequency: >60%).

A patient with wild-type genotype does not have a defect in the apolipoprotein E (APOE), which is an integral structure of lipoprotein particles that have critical roles in blood lipid metabolism and transport. The APOE ε3/ε3 genotype is not associated with increased risk of cardiovascular disease.

No action is needed when a patient is normolipidemic.

Platelet Hyperactivity

Possible Altered Response to Aspirin

The patient carries one ITGB3 176T>C (Leu59Pro) mutation.

Preliminary studies have found an association between the 176T>C mutation of the integrin β3 gene and the possible resistance to the antithrombotic effects of aspirin. However, because the variability in response to antiplatelet drugs is multifactorial and not caused by single gene mutations, testing for the ITGB3 mutation alone should not be used as a diagnostic tool.

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Hyperhomocysteinemia - Depression

Increased Risk of Hyperhomocysteinemia

The patient carries two MTHFR C677T mutations (homozygous). MTHFR enzyme activity is severely reduced (30% 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. This patient exhibits significantly reduced MTHFR activity, which is a risk factor for hyperhomocysteinemia. Low MTHFR activity may further exacerbate folate deficiency in patients with depression and may increase the risk of depressive relapse or delay the response to antidepressants.

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, this patient is likely to benefit from methylfolate as an antidepressant-augmenting agent. Testing for homocysteine levels and serum folate levels may be informative for this patient. Although methylfolate may substantially benefit this patient, it should not replace the antidepressant therapy and methylfolate should always be used as an adjuvant to antidepressant medication.

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

Increased Risk of Hyperhomocysteinemia

The patient carries two MTHFR C677T mutations (homozygous) and no MTHFR A1298C mutation. MTHFR enzyme activity is severely reduced (30% of normal activity).

The patient's significantly reduced MTHFR activity is a risk factor for hyperhomocysteinemia, especially in the presence of low serum folate levels. Mild to moderate hyperhomocysteinemia appears to be associated with an increased risk for venous thromboembolism (VTE).

Testing total plasma homocysteine level may be beneficial. Hyperhomocysteinemia can be treated with nutritional supplementation.

Hyperlipidemia/Atherosclerotic Cardiovascular Disease

No increased risk of cardiovascular disease

The patient is a non carrier of the risk alleles in LPA gene for both the variants (rs3798220 and rs10455872).

The patient's genotype is associated with normal lipoprotein levels. The patient has no increased risk of atherosclerosis and cardiovascular disease as compared to the general population unless other risk factors are present.

No action is needed for this patient unless other genetic and non genetic risk factors (e.g. high blood pressure, smoking, diabetes, obesity, high blood cholesterol and excessive alcohol use) are present.

Current Patient Medications

Venlafaxine, Fluoxetine, Clorazepate, Clomipramine, Lithium

Clomipramine
Anafranil

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

Consider an alternative drug, or prescribe clomipramine at an increased dose and monitor the plasma concentration of clomipramine and desmethylclomipramine.

Venlafaxine
Effexor

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

The patient is unlikely to achieve adequate serum levels of venlafaxine and O-desmethylvenlafaxine when taking standard doses of venlafaxine. Consider an alternative drug, or increase the venlafaxine dose to a maximum of 150% of the normal dose and monitor venlafaxine and O-desmethylvenlafaxine plasma concentrations.

Fluoxetine
Prozac, Sarafem

Normal Sensitivity to Fluoxetine (CYP2D6: Ultra-Rapid Metabolizer) — **INFORMATIVE**

Fluoxetine is metabolized to its active metabolite norfluoxetine and to other metabolites by multiple enzymes including CYP2D6, CYP2C19, CYP2C9, and CYP3A4. Compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower fluoxetine plasma concentrations at standard dosing. However, the clininal significance of this change remains unclear. Consider prescribing fluoxetine at standard dosage and monitor the patient for decreased efficacy.

Medications outside the scope of the report: Clorazepate, Lithium

Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Anesthesia	**Injectable Anesthetics**	Propofol (Diprivan)		
Anticancer Agents	**Antifolates**		Methotrexate (Trexall)	
	Dihydropyrimidines	Capecitabine (Xeloda) Fluorouracil (Adrucil (iv); Carac (topical); Efudex (topical))		
	Thiopurines	Azathioprine (Azasan, Imuran) Mercaptopurine (Purinethol, Purixan) Thioguanine (Tabloid)		
Cardiovascular	**Angiotensin II Receptor Antagonists**	Azilsartan (Edarbi, Edarbyclor) Candesartan (Atacand) Eprosartan (Teveten) Irbesartan (Avapro) Olmesartan (Benicar) Telmisartan (Micardis) Valsartan (Diovan, Entresto)	Losartan (Cozaar, Hyzaar)	
	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	Clopidogrel (Plavix) Prasugrel (Effient) Ticagrelor (Brilinta) Vorapaxar (Zontivity)		
	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) Lovastatin (Mevacor, Altoprev, Advicor) Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor) Simvastatin (Zocor)	Fluvastatin (Lescol)	

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CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Diabetes	Meglitinides	Repaglinide (Prandin, Prandimet)	Nateglinide (Starlix)	
	Sulfonylureas		Chlorpropamide (Diabenese) Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Micronase) Tolbutamide (Orinase)	
Gastrointestinal	Antiemetics	Aprepitant (Emend-oral) Fosaprepitant (Emend-i.v) Granisetron (Sancuso, Sustol) Metoclopramide (Reglan) Rolapitant (Varubi)	Dolasetron (Anzemet) Dronabinol (Marinol) Netupitant-Palonosetron (Akynzeo) Palonosetron (Aloxi)	Ondansetron (Zofran, Zuplenz)
	Proton Pump Inhibitors	Dexlansoprazole (Dexilant, Kapidex) Esomeprazole (Nexium) Lansoprazole (Prevacid) Omeprazole (Prilosec) Pantoprazole (Protonix) Rabeprazole (Aciphex)		
Gaucher Disease	Endocrine-Metabolic Agents	Imiglucerase (Cerezyme) Miglustat (Zavesca) Taliglucerase alfa (Elelyso) Velaglucerase alfa (Vpriv)		Eliglustat (Cerdelga)
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)		

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CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Pain	Fibromyalgia Agents	Milnacipran (Savella)		
	Muscle Relaxants	Carisoprodol (Soma) Cyclobenzaprine (Flexeril, Amrix) Metaxalone (Skelaxin) Methocarbamol (Robaxin)	Tizanidine (Zanaflex)	
	NSAIDs	Ketoprofen (Orudis) Ketorolac (Toradol) Nabumetone (Relafen) Naproxen (Aleve) Sulindac (Clinoril)	Celecoxib (Celebrex) Diclofenac (Voltaren) Flurbiprofen (Ansaid) Ibuprofen (Advil, Motrin) Indomethacin (Indocin) Meloxicam (Mobic) Piroxicam (Feldene)	
	Opioids	Alfentanil (Alfenta) Buprenorphine (Butrans, Buprenex) Fentanyl (Actiq) Hydromorphone (Dilaudid, Exalgo) Levorphanol (Levo Dromoran) Meperidine (Demerol) Methadone (Dolophine) Oxymorphone (Opana, Numorphan) Sufentanil (Sufenta) Tapentadol (Nucynta)	Dihydrocodeine (Synalgos-DC) Hydrocodone (Vicodin) Morphine (MS Contin) Oxycodone (Percocet, Oxycontin)	Codeine (Codeine; Fioricet with Codeine) Tramadol (Ultram)
	Antiaddictives	Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave)	Naltrexone (Vivitrol, Contrave)	
	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)

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

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
	Benzodiazepines	Alprazolam (Xanax) Clobazam (Onfi) Clonazepam (Klonopin) Diazepam (Valium)		
	Other Neurological Agents	Deutetrabenazine (Austedo) Dextromethorphan / Quinidine (Nuedexta) Flibanserin (Addyi) Valbenazine (Ingrezza)	Tetrabenazine (Xenazine)	
Rheumatology	Anti-Hyperuricemics and Anti-Gout Agents	Allopurinol (Zyloprim, Liopurin, Aloprim) Colchicine (Mitigare) Febuxostat (Uloric)	Lesinurad (Zurampic)	
	Immunomodulators	Apremilast (Otezla) Leflunomide (Arava) Tofacitinib (Xeljanz)		
	Other Antirheumatic Agents		Sulfasalazine (Azulfidine, Sulfazine)	
Sjogren's Syndrome	Cholinergic Agonists	Cevimeline (Evoxac)		
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

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

Consider an alternative drug, or prescribe amitriptyline at an increased dose and monitor the plasma concentration of amitriptyline and metabolites.

Atomoxetine
Strattera

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

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.

Clomipramine
Anafranil

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

Consider an alternative drug, or prescribe clomipramine at an increased dose and monitor the plasma concentration of clomipramine and desmethylclomipramine.

Codeine
Codeine; Fioricet with Codeine

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

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

Desipramine
Norpramin

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

Consider an alternative drug, or prescribe desipramine at increased dosage and observe the patient for decreased efficacy. Adjust dosage in response to desipramine and metabolites plasma concentrations and clinical response.

Doxepin
Silenor

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

Consider an alternative drug or increase doxepin dose by 100%. Adjust maintenance dose according to nordoxepin plasma concentrations.

Eliglustat
Cerdelga

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

CYP2D6 ultra-rapid metabolizers may not reach adequate concentrations of eliglustat to achieve a therapeutic effect. Eliglustat should not be prescribed in patients who are CYP2D6 ultra-rapid metabolizers. An alternative medication may be considered.

Flecainide
Tambocor

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

Titrate carefully and consider adjusting the 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

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

Consider an alternative drug, or prescribe haloperidol at the standard dose and adjust dosage to achieve a favorable clinical response. Be alert to decreased haloperidol plasma concentrations.

Imipramine
Tofranil

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

Consider an alternative drug or consider prescribing imipramine at an increased dose, then adjust dosage in response to imipramine and desipramine plasma concentrations.

Metoprolol
Lopressor

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

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

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

Consider an alternative drug, or prescribe nortriptyline at an increased dose and monitor the plasma concentration of amitriptyline and hydroxynortriptyline.

Ondansetron
Zofran, Zuplenz

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

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

Paroxetine
Paxil, Brisdelle

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

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

Protriptyline
Vivactil

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

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

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

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

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

The patient 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

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

Consider an alternative drug, or consider prescribing trimipramine at an increased dose, then adjust dosage in response to trimipramine plasma concentrations.

Venlafaxine
Effexor

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

The patient is unlikely to achieve adequate serum levels of venlafaxine and O-desmethylvenlafaxine when taking standard doses of venlafaxine. Consider an alternative drug, or increase the venlafaxine dose to a maximum of 150% of the normal dose and monitor venlafaxine and O-desmethylvenlafaxine plasma concentrations.

Amoxapine
Amoxapine

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

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

Celecoxib
Celebrex

High Sensitivity to Celecoxib (CYP2C9: Poor Metabolizer) — **ACTIONABLE**

Consider starting at half the lowest recommended dose, and evaluate response the first week. Be alert to gastrointestinal adverse events. Consider alternative medication for the management of Juvenile Rheumatoid Arthritis.

Chlorpromazine
Thorazine

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

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

Chlorpropamide
Diabenese

Possible Sensitivity to Chlorpropamide (CYP2C9: Poor Metabolizer) — **INFORMATIVE**

Subjects with reduced CYP2C9 activity may have increased chlorpropamide plasma drug concentrations at standard doses, leading to hypoglycemic episodes. Because there is insufficient data to whether such changes have a significant clinical impact, chlorpropamide can be prescribed according to standard label-recommended dosage and administration, with frequent monitoring of plasma glucose levels.

Clonidine
Kapvay

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

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.

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.

Diclofenac
Voltaren

Possible Sensitivity to Diclofenac (CYP2C9: Poor Metabolizer) — **INFORMATIVE**

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. Individuals with decreased CYP2C9 activity (i.e poor metabolizers) should be closely monitored for increased gastrointestinal adverse events when prescribed diclofenac and lower doses may be more appropriate for these patients.

Dihydrocodeine
Synalgos-DC

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

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

Dolasetron
Anzemet

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

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

Donepezil
Aricept

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

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

Dronabinol
Marinol

Possible Sensitivity to Dronabinol (CYP2C9: Poor Metabolizer) — **INFORMATIVE**

The patient has a substantial reduction in CYP2C9 metabolic activity (CYP2C9 poor metabolizer). Increased drug exposure may occur in this patient leading to prolonged sedation. Consider standard label-recommended dosing and close monitoring for adverse effects.

Fluphenazine
Prolixin

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

Fluphenazine is metabolized by CYP2D6, CYP1A2 and other enzymes. **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.

Flurbiprofen
Ansaid

Increased Sensitivity to Flurbiprofen (CYP2C9: Poor Metabolizer) — **ACTIONABLE**

At standard dosage, plasma concentrations of flurbiprofen are expected to be high, resulting in an increased risk of gastrointestinal toxicity. Administer flurbiprofen with caution and reduce dose if necessary.

Fluvastatin
Lescol

Increased Sensitivity to Fluvastatin (CYP2C9: Poor Metabolizer) — **ACTIONABLE**

Increased fluvastatin plasma concentrations due to reduced CYP2C9 activity may occur, resulting in myotoxicity/hepatotoxicity. Consider monitoring the patient for treatment-related adverse effects, and adjust dose as needed. Other adverse events and predisposing factors include advanced age (≥65), diabetes, hypothyroidism, renal or hepatic impairments, high statin dose, CYP2C9 inhibitors, ABCG2 inhibitors, and female gender.

Fluvoxamine
Luvox

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

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.

Fosphenytoin
Cerebyx

High Sensitivity to Fosphenytoin (CYP2C9: Poor Metabolizer) — **ACTIONABLE**

In CYP2C9 poor metabolizers, the plasma concentrations of phenytoin are expected to increase, resulting in an increased risk of severe neurological toxicity. This risk increases further in individuals who are also CYP2C19 poor metabolizers. **Consider a standard loading dose, and reduce the maintenance dose by 50%**. Evaluate response and serum concentrations after 7-10 days. **Be alert to neurological concentration-related adverse events.**

Glimepiride
Amaryl

Possible Sensitivity to Glimepiride (CYP2C9: Poor Metabolizer) — **ACTIONABLE**

Subjects with reduced CYP2C9 activity may have increased glimepiride plasma drug concentrations at standard doses, leading to hypoglycemic episodes. Because there is insufficient data to whether such changes have a significant clinical impact, glimepiride can be prescribed according to standard label-recommended dosage and administration, with frequent monitoring of plasma glucose levels.

Glipizide
Glucotrol

Possible Sensitivity to Glipizide (CYP2C9: Poor Metabolizer) — **INFORMATIVE**

Subjects with reduced CYP2C9 activity may have increased glipizide plasma drug concentrations at standard doses, leading to hypoglycemic episodes. Because there is insufficient data to whether such changes have a significant clinical impact, glipizide can be prescribed according to standard label-recommended dosage and administration, with frequent monitoring of glucose plasma levels.

Glyburide
Micronase

Possible Sensitivity to Glyburide (CYP2C9: Poor Metabolizer) — **ACTIONABLE**

Subjects with reduced CYP2C9 activity may have increased glyburide plasma drug concentrations at standard doses, leading to hypoglycemic episodes. Because there is insufficient data to whether such changes have a significant clinical impact, glyburide can be prescribed according to standard label-recommended dosage and administration with frequent monitoring of glucose plasma levels.

Hydrocodone
Vicodin

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

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

Ibuprofen
Advil, Motrin

Possible Sensitivity to Ibuprofen (CYP2C9: Poor Metabolizer) — **INFORMATIVE**

Ibuprofen is extensively metabolized into hydroxylate or carboxylate metabolites by CYP2C8 and CYP2C9. Diminished ibuprofen clearance has been found in CYP2C9 poor metabolizers and those with decreased CYP2C8 activity. This change in clearance may result in elevated concentrations of the drug inadvertently leading to adverse events. Although, dosage adjustment is not necessary in a patient identified as a CYP2C9 poor metabolizer, a lower dose and a closer monitoring for increased gastrointestinal adverse events may be considered.

Indomethacin
Indocin

Possible Sensitivity to Indomethacin (CYP2C9: Poor Metabolizer) — **INFORMATIVE**

Indomethacin is metabolized mainly by O-demethylation to its inactive metabolite O-desmethylindomethacin, a reaction catalyzed by CYP2C9. At standard dosage, plasma concentrations of indomethacin are expected to be high resulting in an increased risk of gatrointestinal toxicity. To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.

Lesinurad
Zurampic

Possible Sensitivity to Lesinurad (CYP2C9: Poor Metabolizer) — **ACTIONABLE**

The patient has a substantial reduction in CYP2C9 metabolic activity (CYP2C9 poor metabolizer). Increased drug exposure may occur in this patient leading to an increased risk for adverse events. Consider using lesinurad with caution and with close monitoring for adverse effects.

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NAME:		**SPECIMEN TYPE:**	Buccal Swab	
ACC #:	PHI12031	**COLLECTION DATE:**	10/31/2017	
DOB:	6/2/1990	**RECEIVED DATE:**	11/6/2017	
SEX:	Male	**REPORT DATE:**	11/10/2017	

Losartan
Cozaar, Hyzaar

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

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

Maprotiline
Ludiomil

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

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

Meloxicam
Mobic

Increased sensitivity to Meloxicam (CYP2C9: Poor Metabolizer) — INFORMATIVE

CYP2C9 poor metabolizers have a higher risk of experiencing gastrointestinal toxicities when taking meloxicam at standard doses. To minimize the potential risk of adverse events in these patients, **the lowest effective dose should be used for the shortest possible duration.**

Methotrexate
Trexall

Increased risk for methotrexate toxicity (MTHFR: Reduced MTHFR Activity) — INFORMATIVE

The patient carries two MTHFR 677 T alleles, resulting in a significantly reduced MTHFR activity. **Malignancy:** Leukemia or lymphoma patients who are treated with methotrexate standard regimens may have an increased risk of overall toxicity (including mucositis, thrombocytopenia, and hepatic toxicity), and an increased severity of mucositis. Consider at least a 50% reduction in methotrexate starting dose, followed by titration based on toxicity. 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 the MTHFR 677 T allele 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.

Mexiletine
Mexitil

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

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 (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.

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.

Nateglinide
Starlix

Possible Sensitivity to Nateglinide (CYP2C9: Poor Metabolizer) — INFORMATIVE

The patient's genotype predicts a reduced CYP2C9 activity, which may result in a slightly increased risk for hypoglycemia. Nateglinide can be prescribed at label-recommended dosage and administration with additional monitoring of the patient's response.

Netupitant-Palonosetron
Akynzeo

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

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

Olanzapine
Zyprexa

Increased Risk of Weight Gain with Olanzapine (HTR2C: Homozygous for the C allele (rs3813929)) — **INFORMATIVE**

Genetic variations in the Serotonin 2C Receptor (HTR2C) gene in known to be partially involved in the adverse effects associated with atypical antipsychotic medications. The patient is homozygous for C allele of HTR2C variant rs3813929. Patients with this genotype may have an increased risk of weight gain when treated with olanzapine.

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.

Oxycodone
Percocet, Oxycontin

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

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

Palonosetron
Aloxi

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

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

Perphenazine
Trilafon

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

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.

Phenytoin
Dilantin

High Sensitivity to Phenytoin (CYP2C9: Poor Metabolizer) — **ACTIONABLE**

In CYP2C9 poor metabolizers, the plasma concentrations of phenytoin are expected to increase, resulting in an increased risk of severe neurological toxicity. This risk increases further in individuals who are also CYP2C19 poor metabolizers. **Consider a standard loading dose, and reduce the maintenance dose by 50%**. Evaluate response and serum concentrations after 7-10 days. **Be alert to neurological concentration-related adverse events.**

Pimozide
Orap

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

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.

Piroxicam
Feldene

Increased Sensitivity to Piroxicam (CYP2C9: Poor Metabolizer) — **INFORMATIVE**

At standard dosage, plasma concentrations of piroxicam are expected to be high, resulting in an increased risk of gastrointestinal toxicity. Administer piroxicam with caution and reduce dose if necessary.

Propafenone
Rythmol

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

There is insufficient data to allow calculation of dose adjustment. Titrate carefully and adjust the dose in response to plasma concentration and ECG monitoring. OR consider alternative drug such as sotalol, disopyramide, quinidine, or amiodarone.

Sulfasalazine
Azulfidine, Sulfazine

Decreased Response to Sulfasalazine For the Treatment of Rheumatoid Arthritis (ABCG2: Normal Function) — **INFORMATIVE**

Rheumatoid Arthritis: The patient carries two copies of ABCG2 rs2231142 C allele. Preliminary data suggests that this genotype may be associated with decreased plasma levels of sulfasalazine which may decrease the likelihood of response to this drug.

Tetrabenazine
Xenazine

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

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

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.

Tolbutamide
Orinase

Possible Sensitivity to Tolbutamide (CYP2C9: Poor Metabolizer) — **ACTIONABLE**

Subjects with reduced CYP2C9 activity may have increased tolbutamide plasma drug concentrations at standard doses, leading to hypoglycemic episodes. Because there is insufficient data to whether such changes have a significant clinical impact, tolbutamide can be prescribed according to standard label-recommended dosage and administration, with frequent monitoring of glucose plasma levels.

Torsemide
Demadex

Possible Sensitivity to Torsemide (CYP2C9: Poor Metabolizer) — **INFORMATIVE**

The patient's genotype predicts a reduced CYP2C9 function, which may result in reduced torsemide clearance. There is insufficient data to whether such change has a significant clinical impact and whether the diuretic effects are more pronounced in patients with this phenotye. Torsemide can be prescribed at label-recommended dosage and administration with additional monitoring of the patient's response.

Warfarin
Coumadin

Very High Sensitivity to Warfarin (CYP2C9 *2/*3 VKORC1 -1639G>A A/A) — **ACTIONABLE**

Initiation Therapy: The expected therapeutic **dose is substantially lower than the usual one.** Consider using the following warfarin dose range provided in the FDA-approved label: **0.5-2 mg/day.** OR consider using a personalized dose as calculated by a pharmacogenetic algorithm. The estimated time to reach steady state is more than 2-4 weeks. Frequent INR monitoring is recommended.

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SEX:	Male	**REPORT DATE:**	11/10/2017	

Caution: It is important to note that the combination of genetic metabolizer and non-genetic factors, such as, but not limited to: body size, age, inhibition caused by interference of drugs or food, liver function, and kidney function produce the overall response to a given drug dose.

Methods: This specimen was analyzed for gene mutations by real-time PCR (TaqMan SNP Genotyping, Thermo Fisher) developed by Phi Life Sciences, LLC. These assays were validated following the 1988 CLIA standards. Performance characteristics were validated by Phi Life Sciences Laboratory with analytical specificity and sensitivity of >99% for detection of the variants above.

Lab Disclaimer: The FDA has neither cleared nor approved these assays, nor is FDA pre-market review required. These tests are used for clinical purposes and should not be regarded as investigational or for research only. Diagnosis and treatment decisions are the sole responsibility of the practitioner and does not replace the need for clinical and therapeutic drug monitoring. Hence, the interpretation and commentary are provided to the practitioner for educational purposes only and should not be taken as diagnostic or treatment recommendations.

Laboratory Director: Catherine Li, MD

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.

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ACC #:	PHI12031	**COLLECTION DATE:**	10/31/2017	
DOB:	6/2/1990	**RECEIVED DATE:**	11/6/2017	
SEX:	Male	**REPORT DATE:**	11/10/2017	

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

Name:
DOB: 6/2/1990
ACC #: PHI12031

Pharmacogenetic Test Summary

ABCG2	421C>A C/C	Normal Function
ANKK1/DRD2	DRD2:Taq1A G/G	Unaltered DRD2 function
Apolipoprotein E	ε3/ε3	Normal APOE function
COMT	Val158Met G/G	High/Normal COMT Activity
CYP1A2	*1A/*1F	Normal Metabolizer - Higher Inducibility
CYP2B6	*1/*1	Normal Metabolizer
CYP2C19	*1/*1	Normal Metabolizer
CYP2C9	*2/*3	Poor Metabolizer
CYP2D6	*1/*2 XN	Ultra-Rapid Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
DPYD	*1/*1	Normal Metabolizer
DRD2	-241A>G T/T	Homozygous for rs1799978 T Allele
Factor II	20210G>A GG	Normal Thrombosis Risk
Factor V Leiden	1691G>A GG	Normal Thrombosis Risk
HTR2A	-1438G>A C/T	Heterozygous for the T Allele (rs6311)
HTR2A	rs7997012 A/A	Homozygous for the A allele (rs7997012)
HTR2C	2565G>C G/G	Homozygous for the G allele (rs1414334)
HTR2C	-759C>T C/C	Homozygous for the C allele (rs3813929)
ITGB3	176T>C T/C	Increased Platelet Reactivity
LPA	rs10455872 A/A	Wild-type for rs10455872
LPA	rs3798220 T/T	Wild-type for rs3798220
MTHFR	677C>T TT	Reduced MTHFR Activity
MTHFR	1298A>C AA	Normal MTHFR Activity
OPRM1	A118G A/A	Normal OPRM1 Function
SLCO1B1	521T>C T/T	Normal Function
TPMT	*1/*1	Normal Metabolizer
VKORC1	-1639G>A A/A	High Warfarin Sensitivity