Client: LAB SOLUTIONS LLC
Sample #: 1
Chart #:
Provider:

Patient: RESPONSEcomp
DOB: 03/01/1999
Gender: M
Specimen Type: BUCCAL SWAB

Lab Acc#: 1603020248
Collected: 03/02/16 09:00
Received: 03/02/16 15:40
Reported: 03/13/16 10:59

Current Patient Medications

Current Medication List: Lortab, Zocor, Prilosec, Warfarin, Zoloft

Medications Affected by Patient Genetic Results

Lortab (Hydrocodone)

Possible Altered Response to Hydrocodone (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

Increased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 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.

Prilosec (Omeprazole)

Normal Response to Omeprazole (CYP2C19 *1/*1 Normal Metabolizer) Evidence Level: **Actionable**

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

Zoloft (Sertraline)

Normal Sensitivity to Sertraline (CYP2C19 *1/*1 Normal Metabolizer) Evidence Level: **Actionable**

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

Zocor (Simvastatin)

Intermediate Myopathy Risk (SLCO1B1 521T>C TC Intermediate Transporter Function) Evidence Level: **Actionable**

Simvastatin plasma concentrations are expected to be elevated. **Consider avoiding simvastatin,** and prescribe an alternative statin or another hypolipidemic drug, or consider prescribing simvastatin at a lower starting dose (20 mg/day). Routine creatine kinase (CK) monitoring is also advised. **The FDA recommends against the 80 mg daily dose.** Although the association between the SLCO1B1 521C>T variant and myopathy risk is not clearly established for other statins such as atorvastatin, pitavastatin, rosuvastatin, and pravastatin, caution is advised if high doses of these statins are used in this patient. Fluvastatin plasma levels are not affected by the SLCO1B1 521C>T variant.

Warfarin (Coumadin)

Moderate Sensitivity to Warfarin (CYP2C9 *1/*2 VKORC1 -1639G>A G/A) Evidence Level: **Actionable**

Initiation Therapy: a dose decrease may be required. Consider using the following warfarin dose range provided in the FDA-approved label: **3-4 mg/day.** OR consider using a personalized dose as calculated by a pharmacogenetic algorithm. The estimated time to reach steady state is 8-10 days.

Guidance Levels

Based upon the patient's genotype, a medication has potentially reduced efficacy or increased toxicity or the patient has an increased risk for the indicated condition.

Based upon the patient's genotype, guidelines exist for adjusting dosage or increased vigilance or the patient has a moderate risk for the indicated condition.

Based on this patient's genotype, the medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.

Evidence Levels

Actionable - Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA. EMEA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as new 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

Hyperlipidemia/Atherosclerotic Cardiovascular Disease

Increased risk of hyperlipidemia/atherosclerotic vascular disease

The patient is positive for the APOE 388 T>C (Arg112Cys) mutation and negative for the 526 C>T (Cys158Arg) 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.

The ε4 allele is associated with an increased risk of hyperlipidemia/atherosclerotic vascular disease, and individuals that are heterozygous for this allele may have higher total cholesterol levels and elevated LDL cholesterol levels.

Consider dietary adjustment (very low fat diet) and statins (or HMG-CoA reductase inhibitors).

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

No Increased Risk of Hyperhomocysteinemia

The patient carries one MTHFR C677T mutation and one A1298C mutation (compound heterozygous). MTHFR enzyme activity is reduced.

The patient's reduced MTHFR activity is not a risk factor for hyperhomocysteinemia. Unless other risk factors are present, the patient is not expected to have an increased risk for venous thromboembolism (VTE).

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

Test Details			
Gene	**Genotype**	**Phenotype**	**Alleles Tested**
ANKK1/DRD2	DRD2:Taq1A GG	Unaltered DRD2 function	DRD2:Taq1A
Apolipoprotein E	ε3/ε4	Increased Risk of Hyperlipidemia/Atherosclerotic Vascular Disease	ε2, ε4
COMT	Val158Met GG	High/Normal COMT Activity	Val158Met
CYP1A2	*1A/*1F	Normal Metabolizer - Higher Inducibility	*1C, *1D, *1F, *1K, *1L, *1V, *1W
CYP2B6	*1/*1	Normal Metabolizer	*6, *9
CYP2C19	*1/*1	Normal Metabolizer	*2, *3, *4, *4B, *6, *7, *8, *9, *10
CYP2C8	*1A/*3	Intermediate Metabolizer	*2, *3, *4, *5, *7, *8
CYP2C9	*1/*2	Intermediate Metabolizer	*2, *3, *4, *5, *6, *8, *11, *27
CYP2D6	*1/*1 XN	Rapid Metabolizer	*2, *3, *6, *7, *8, *9, *10, *14A, *14B, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1/*1	Normal Metabolizer	*1B, *3, *12, *17, *22
CYP3A5	*3/*3	Poor Metabolizer	*2, *3, *3C, *6, *8, *9
DPYD	*1/*1	Normal DPD Activity	*2A, *2B, rs115232898 G, *8, *9A, *9B, *10, *11, rs67376798 A, *13
Factor II	20210G>A GG	Normal Thrombosis Risk	20210G>A
Factor V Leiden	1691G>A GG	Normal Thrombosis Risk	1691G>A
MTHFR	677C>T CT	Reduced MTHFR Activity	677C>T
MTHFR	1298A>C AC	Reduced MTHFR Activity	1298A>C
OPRM1	A118G AA	Normal OPRM1 Function	A118G
SLCO1B1	521T>C TC	Intermediate Transporter Function	521T>C, 388A>G
UGT2B15	*2/*2	Poor Metabolizer	*2
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity	-1639G>A

Potentially Impacted Medications				
Category	**Drug Class**	**Standard Precautions**	**Use With Caution**	**Consider Alternatives**
Anticancer Agents	Antifolates		Methotrexate (Trexall)	
	Dihydropyrimidines	Capecitabine (Xeloda) Fluorouracil (Adrucil (iv); Carac (topical); Efudex (topical))		
	Taxanes		Paclitaxel (Taxol, Abraxane)	
Cardiovascular	Angiotensin II Receptor Antagonists	Irbesartan (Avapro)		
	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	Carvedilol (Coreg) Labetalol (Normodyne, Trandate) Nebivolol (Bystolic) Propranolol (Inderal) Timolol (Timoptic)		Metoprolol (Lopressor)
	Statins	Lovastatin (Mevacor)	Atorvastatin (Lipitor) Fluvastatin (Lescol) Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor)	Simvastatin (Zocor)
Diabetes	Sulfonylureas	Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Micronase) Tolbutamide (Orinase)		
Gastrointestinal	Antiemetics	Metoclopramide (Reglan)	Dolasetron (Anzemet) Palonosetron (Aloxi)	Ondansetron (Zofran)
	Proton Pump Inhibitors	Dexlansoprazole (Dexilant, Kapidex) Esomeprazole (Nexium) Lansoprazole (Prevacid) Omeprazole (Prilosec) Pantoprazole (Protonix) Rabeprazole (Aciphex)		
Infections	Antifungals	Voriconazole (Vfend)		

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	Ibuprofen (Advil, Motrin) Ketoprofen (Orudis) Ketorolac (Toradol) Nabumetone (Relafen) Naproxen (Aleve) Sulindac (Clinoril)	Celecoxib (Celebrex) Diclofenac (Voltaren) Flurbiprofen (Ansaid) 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)	
	Anti-ADHD Agents	Amphetamine (Adderall) Dexmethylphenidate (Focalin) Dextroamphetamine (Dexedrine) Guanfacine (Intuniv) Lisdexamfetamine (Vyvanse) Methylphenidate (Ritalin)	Clonidine (Kapvay)	Atomoxetine (Strattera)

Category	Drug Class	Standard Precautions	Use With Caution	Consider Alternatives
Psychotropic	Anticonvulsants	Carbamazepine (Tegretol, Carbatrol) Eslicarbazepine (Aptiom) Ethosuximide (Zarontin) Ezogabine (Potiga) Felbamate (Felbatol) Gabapentin (Neurontin) Lacosamide (Vimpat) Lamotrigine (Lamictal) Levetiracetam (Keppra) Oxcarbazepine (Trileptal) 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) Vilazodone (Viibryd) Vortioxetine (Brintellix)	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) Asenapine (Saphris) Iloperidone (Fanapt) Lurasidone (Latuda) Paliperidone (Invega) Quetiapine (Seroquel) Thioridazine (Mellaril) Thiothixene (Navane) Trazodone (Oleptro) Trifluoperazine (Stelazine) Ziprasidone (Geodon)	Chlorpromazine (Thorazine) Clozapine (Clozaril) Fluphenazine (Prolixin) Olanzapine (Zyprexa) Perphenazine (Trilafon) Pimozide (Orap) Tetrabenazine (Xenazine)	Haloperidol (Haldol) Risperidone (Risperdal)
	Benzodiazepines	Alprazolam (Xanax) Clobazam (Onfi) Clonazepam (Klonopin) Diazepam (Valium)	Lorazepam (Ativan) Oxazepam (Serax)	
Rheumatology	Immunomodulators	Apremilast (Otezla) Leflunomide (Arava) Tofacitinib (Xeljanz)		

Category	Drug Class	Standard Precautions	Use With Caution	Consider Alternatives
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 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

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

Amoxapine (Amoxapine)

Possible Non-Response to Amoxapine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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 therefore, therapy must be initiated cautiously and adjusted according to the patient's response.

Atomoxetine (Strattera)

Non-Response to Atomoxetine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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.

Atorvastatin (Lipitor)

Increased Myopathy Risk (SLCO1B1 521T>C TC Intermediate Transporter Function) Evidence Level: **Informative**

The reduced SLCO1B1 function may result in elevated atorvastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high atorvastatin doses in this patient should be avoided. If atorvastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications, and female gender.

Celecoxib (Celebrex)

Possible Sensitivity to Celecoxib (CYP2C9 *1/*2 Intermediate Metabolizer) Evidence Level: **Informative**

Celecoxib can be prescribed at standard label-recommended dosage and administration. Evaluate response the first week and be alert to gastrointestinal adverse events.

Chlorpromazine (Thorazine)

Possible Non-Response to Chlorpromazine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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.

Clomipramine (Anafranil)

Non-Response to Clomipramine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

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

Clonidine (Kapvay)

Possible Altered Response to Clonidine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

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.

Clozapine (Clozaril)

Non-Response to Clozapine (CYP1A2 *1A/*1F Normal Metabolizer - Higher Inducibility) Evidence Level: **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.

Codeine (Codeine; Fioricet with Codeine)

Increased Response to Codeine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Codeine is converted into its active metabolite morphine by CYP2D6. Since this patient is a rapid metabolizer, greatly increased morphine levels are expected, and the patient is at high risk of toxicity when taking codeine. 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 *1/*1 XN Rapid Metabolizer) Evidence Level: **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.

Diclofenac (Voltaren)

Possible Sensitivity to Diclofenac (CYP2C9 *1/*2 Intermediate Metabolizer) Evidence Level: **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 intermediate 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 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Increased conversion of dihydrocodeine to the more active metabolite dihydromorphine is expected in CYP2D6 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 *1/*1 XN Rapid Metabolizer) Evidence Level: **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 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 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

When compared to a normal metabolizer, a 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.

Doxepin (Silenor)

Non-Response to Doxepin (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

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

Flecainide (Tambocor)

Altered Response to Flecainide (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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.

Fluphenazine (Prolixin)

Possible Non-response to Fluphenazine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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)

Possible Sensitivity to Flurbiprofen (CYP2C9 *1/*2 Intermediate Metabolizer) Evidence Level: **Informative**

The patient may have high plasma levels of the drug. Flurbiprofen can be prescribed at standard label-recommended dosage and administration with closer monitoring for gastrointestinal side effects.

Fluvastatin (Lescol)

Possible Sensitivity to Fluvastatin (CYP2C9 *1/*2 Intermediate Metabolizer) Evidence Level: **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 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

There is a risk for decreased efficacy at standard dosage. If a standard dose is prescribed to a CYP2D6 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)

Moderate Sensitivity to Fosphenytoin (CYP2C9 *1/*2 Intermediate Metabolizer) Evidence Level: **Actionable**

The genotype results indicate that the patient is a CYP2C9 substrate intermediate metabolizer. Plasma concentrations of phenytoin are likely to increase, resulting in an increased risk of mild to moderate neurological toxicity. Consider a standard loading dose, and reduce the maintenance dose by 25%. Evaluate response and serum concentrations after 7-10 days. Be alert to neurological concentration-related adverse events.

Haloperidol (Haldol)

Non-Response to Haloperidol (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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.

Hydrocodone (Vicodin)

Possible Altered Response to Hydrocodone (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

Increased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 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.

Imipramine (Tofranil)

Non-Response to Imipramine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

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

Indomethacin (Indocin)

Possible Sensitivity to Indomethacin (CYP2C9 *1/*2 Intermediate Metabolizer) Evidence Level: **Informative**

Indomethacin is metabolized mainly by O-demethylation to its inactive metabolite O-desmethylindomethacin, a reaction catalyzed by CYP2C9. At standard doses, indomethacin plasma concentrations may be higher in individuals with decreased CYP2C9 function. Although indomethacin can be prescribed at standard label recommended-dosage and administration, a closer monitoring for signs of gastrointestinal toxicity during long-term administration is recommended.

Lorazepam (Ativan)

Possible Altered Response to Lorazepam (UGT2B15 *2/*2 Poor Metabolizer) Evidence Level: **Informative**

Lorazepam clearance is 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 *1/*1 XN Rapid Metabolizer) Evidence Level: **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 lower dose and gradually increased in small increments according to the patient's response.**

Meloxicam (Mobic)

Possible Sensitivity to Meloxicam (CYP2C9 *1/*2 Intermediate Metabolizer) Evidence Level: **Informative**

Meloxicam plasma concentrations may be higher in individual with decreased CYP2C9 function. A reduction in meloxicam dosage may be needed with a closer monitoring for signs of gastrointestinal toxicity during long-term administration.

Methotrexate (Trexall)

Increased risk for methotrexate toxicity (MTHFR 677C>T CT Reduced MTHFR Activity) Evidence Level: **Informative**

The patient carries the MTHFR 677 T allele resulting in a reduced MTHFR activity. **Malignancy:** Leukemia or lymphoma patients who are treated with methotrexate standard regimens might have an increased likelihood of treatment interruptions due to methotrexate toxicity. Consider at least a 25% 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.

Metoprolol (Lopressor)

Possible Non-Responder to Metoprolol (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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.

Mexiletine (Mexitil)

Altered Response to Mexiletine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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 Val158Met GG High/Normal COMT Activity) Evidence Level: **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)

Altered Response to Naltrexone (OPRM1 A118G AA Normal OPRM1 Function) Evidence Level: **Informative**

Treatment of alcohol dependence: the patient has the wild-type genotype for OPRM1 that is associated with a poorer outcome with naltrexone therapy. Naltrexone-treated patients not carrying the 118A> G mutation are less likely to respond to this drug, and may have higher relapse rates than those who are carriers of this mutation.

Nortriptyline (Pamelor)

Non-Response to Nortriptyline (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

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

Olanzapine (Zyprexa)

Non-Response to Olanzapine (CYP1A2 *1A/*1F Normal Metabolizer - Higher Inducibility) Evidence Level: **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.

Ondansetron (Zofran)

Non-Response to Ondansetron (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Informative**

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

Oxazepam (Serax)

Possible Altered Response to Oxazepam (UGT2B15 *2/*2 Poor Metabolizer) Evidence Level: **Informative**

Oxazepam clearance is 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 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

Increased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 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.

Paclitaxel (Taxol, Abraxane)

Increased risk for peripheral neuropathy (CYP2C8 *1A/*3 Intermediate Metabolizer) Evidence Level: **Informative**

The genotype results predict that the patient has decreased CYP2C8-mediated paclitaxel metabolism which results in a higher exposure to this drug when used at standard dosing regimens. The presence of the CYP2C8*3 allele has been associated with an increased risk of paclitaxel-induced peripheral neuropathy (Grade 2 and higher). Peripheral neuropathy is a toxicity associated with paclitaxel therapy and is correlated with drug exposure. Dosing adjustment and a more closer monitoring may be needed for this patient to avoid severe peripheral neuropathy. African-American patients who are carriers of CYP2C8*3 allele have a higher risk of peripheral neuropathy than Caucasians with similar genotype.

Palonosetron (Aloxi)

Possible Altered Response to Palonosetron (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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 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.

Paroxetine (Paxil, Brisdelle)

Reduced Response to Paroxetine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

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

Perphenazine (Trilafon)

Possible Non-Response to Perphenazine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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)

Moderate Sensitivity to Phenytoin (CYP2C9 *1/*2 Intermediate Metabolizer) Evidence Level: **Actionable**

The genotype results indicate that the patient is a CYP2C9 substrate intermediate metabolizer. Plasma concentrations of phenytoin are likely to increase, resulting in an increased risk of mild to moderate neurological toxicity. Consider a standard loading dose, and reduce the maintenance dose by 25%. 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 *1/*1 XN Rapid Metabolizer) Evidence Level: **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)

Possible Sensitivity to Piroxicam (CYP2C9 *1/*2 Intermediate Metabolizer) Evidence Level: **Informative**

Piroxicam plasma concentrations may be higher in individual with decreased CYP2C9 function. Although piroxicam can be prescribed at standard label-recommended dosage and administration, a closer monitoring for signs of gastrointestinal toxicity during long-term administration is recommended.

Pitavastatin (Livalo)

Increased Myopathy Risk (SLCO1B1 521T>C TC Intermediate Transporter Function) Evidence Level: **Informative**

The reduced SLCO1B1 function may result in elevated pitavastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high pitavastatin doses in this patient should be avoided. If pitavastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications, and female gender.

Pravastatin (Pravachol)

Increased Myopathy Risk (SLCO1B1 521T>C TC Intermediate Transporter Function) Evidence Level: **Informative**

The reduced SLCO1B1 function may result in elevated pravastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high pravastatin doses in this patient should be avoided. If pravastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications, and female gender.

Propafenone (Rythmol)

Altered Response to Propafenone (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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.

Protriptyline (Vivactil)

Non-Response to Protriptyline (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

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 *1/*1 XN Rapid Metabolizer) Evidence Level: **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.

Rosuvastatin (Crestor)

Increased Myopathy Risk (SLCO1B1 521T>C TC) Evidence Level: **Informative**

The reduced SLCO1B1 function may result in elevated rosuvastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high rosuvastatin doses in this patient should be avoided. If rosuvastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications, and female gender.

Simvastatin (Zocor)

Intermediate Myopathy Risk (SLCO1B1 521T>C TC Intermediate Transporter Function) Evidence Level: **Actionable**

Simvastatin plasma concentrations are expected to be elevated. **Consider avoiding simvastatin,** and prescribe an alternative statin or another hypolipidemic drug, or consider prescribing simvastatin at a lower starting dose (20 mg/day). Routine creatine kinase (CK) monitoring is also advised. **The FDA recommends against the 80 mg daily dose.** Although the association between the SLCO1B1 521C>T variant and myopathy risk is not clearly established for other statins such as atorvastatin, pitavastatin, rosuvastatin, and pravastatin, caution is advised if high doses of these statins are used in this patient. Fluvastatin plasma levels are not affected by the SLCO1B1 521C>T variant.

Tetrabenazine (Xenazine)

Unknown Sensitivity to Tetrabenazine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **Actionable**

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 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 *1A/*1F Normal Metabolizer - Higher Inducibility) Evidence Level: **Informative**

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

Tramadol (Ultram)

Increased Response to Tramadol (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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 and weekly titration are recommended. If 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.

Trimipramine (Surmontil)

Non-Response to Trimipramine (CYP2D6 *1/*1 XN Rapid Metabolizer) Evidence Level: **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 *1/*1 XN Rapid Metabolizer) Evidence Level: **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.

Warfarin (Coumadin)

Moderate Sensitivity to Warfarin (CYP2C9 *1/*2 VKORC1 -1639G>A G/A) Evidence Level: **Actionable**

Initiation Therapy: a dose decrease may be required. Consider using the following warfarin dose range provided in the FDA-approved label: **3-4 mg/day.** OR consider using a personalized dose as calculated by a pharmacogenetic algorithm. The estimated time to reach steady state is 8-10 days.

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 within 95.0-99.9%.

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. LabSolutions developed this test and its performance characteristics. This test has not been cleared or approved by the U.S. Food and Drug Administration, however, FDA approval or clearance is currently not required for clinical use of this test. 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 LabSolutions uses Translational Software to generate and subsequently review the report.

Laboratory Certification: CLIA # 11D2065318