Premier Medical Laboratory Service (PMLS)
10 Jack Casey Ct, Fountain Inn SC 29644
Phone: 877-335-2455
Web: www.premedinc.com
Laboratory Director: Peter Zvejnieks, MD

Pain Management Pharmarcogenetic Testing Created for: JALENE DOUSE

Patient:	SAMPLE PATIENT	DOB:	0/0/0000
Accession #:	00000	Gender:	Male
Collection Date:	11/28/2016	Received Date:	12/1/2016
Ordered By:	TEST PHYSICIAN	Report Generated:	12/8/2016

Patient Medications

Current Medication List: Remeron

Medications Affected by Patient Genetic Results

Remeron (Mirtazapine) Evidence Level: 1

Normal Sensitivity to Mirtazapine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

Mirtazapine can be prescribed at standard label-recommended dosage and administration. Careful titration is recommended until a favorable response is achieved.

Test Details

	Assay	Results	Phenotype	Clinical Consequences
✓	CYP2C9	*1/*1	Normal Metabolizer	Consistent with a typical CYP2C9 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
!	CYP2C19	*1/*2	Intermediate Metabolizer	Consistent with a moderate deficiency in CYP2C19 activity. Potential risk for side effects or loss of efficacy with drug substrates.
!	CYP3A5	*1/*3	Intermediate Metabolizer	Consistent with an intermediate CYP3A5 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.
!	CYP3A4	*1B/*1B	Intermediate Metabolizer	Consistent with a moderate deficiency in 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.
⚑	CYP2D6	*2/*4 XN	Ultra-Rapid or Normal Metabolizer	Consistent with typical or increased CYP2D6 activity. Potential risk for side effects or loss of efficacy with drug substrates.

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Potentially Impacted Medications

Pain Medications		
Standard Precautions	**Use With Caution**	**Consider Alternatives**
Alfentanil (Alfenta)	Dihydrocodeine (Synalgos-DC)	Codeine (Codeine; Fioricet with Codeine)
Buprenorphine (Butrans, Buprenex)	Hydrocodone (Vicodin)	Tramadol (Ultram)
Carisoprodol (Soma)	Oxycodone (Percocet, Oxycontin)	
Celecoxib (Celebrex)		
Cyclobenzaprine (Flexeril, Amrix)		
Diclofenac (Voltaren)		
Fentanyl (Actiq)		
Flurbiprofen (Ansaid)		
Hydromorphone (Dilaudid, Exalgo)		
Ibuprofen (Advil, Motrin)		
Indomethacin (Indocin)		
Ketoprofen (Orudis)		
Ketorolac (Toradol)		
Levorphanol (Levo Dromoran)		
Meloxicam (Mobic)		
Meperidine (Demerol)		
Metaxalone (Skelaxin)		
Methocarbamol (Robaxin)		
Milnacipran (Savella)		
Morphine (MS Contin)		
Nabumetone (Relafen)		
Naproxen (Aleve)		
Oxymorphone (Opana, Numorphan)		
Piroxicam (Feldene)		
Sufentanil (Sufenta)		
Sulindac (Clinoril)		
Tapentadol (Nucynta)		

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Psychotropic Medications

Standard Precautions	Use With Caution	Consider Alternatives
Alprazolam (Xanax)	Amoxapine (Amoxapine)	Amitriptyline (Elavil)
Aripiprazole (Abilify)	Chlorpromazine (Thorazine)	Atomoxetine (Strattera)
Asenapine (Saphris)	Clobazam (Onfi)	Clomipramine (Anafranil)
Brexpiprazole (Rexulti)	Clonidine (Kapvay)	Desipramine (Norpramin)
Brivaracetam (Briviact)	Donepezil (Aricept)	Doxepin (Silenor)
Carbamazepine (Tegretol, Carbatrol, Epitol)	Fluphenazine (Prolixin)	Haloperidol (Haldol)
Citalopram (Celexa)	Fluvoxamine (Luvox)	Imipramine (Tofranil)
Clonazepam (Klonopin)	Maprotiline (Ludiomil)	Nortriptyline (Pamelor)
Clozapine (Clozaril)	Perphenazine (Trilafon)	Paroxetine (Paxil, Brisdelle)
Desvenlafaxine (Pristiq)	Phenobarbital (Luminal)	Protriptyline (Vivactil)
Dextromethorphan / Quinidine (Nuedexta)	Pimozide (Orap)	Risperidone (Risperdal)
Diazepam (Valium)	Primidone (Mysoline)	Trimipramine (Surmontil)
Duloxetine (Cymbalta)	Tetrabenazine (Xenazine)	Venlafaxine (Effexor)
Escitalopram (Lexapro)	Zonisamide (Zonegran)	
Eslicarbazepine (Aptiom)		
Ethosuximide (Zarontin)		
Ezogabine (Potiga)		
Felbamate (Felbatol)		
Flibanserin (Addyi)		
Fluoxetine (Prozac, Sarafem)		
Fosphenytoin (Cerebyx)		
Gabapentin (Neurontin)		
Galantamine (Razadyne)		
Guanfacine (Intuniv)		
Iloperidone (Fanapt)		
Lacosamide (Vimpat)		
Lamotrigine (Lamictal)		
Levetiracetam (Keppra)		
Levomilnacipran (Fetzima)		
Loxapine (Loxitane, Adasuve)		
Lurasidone (Latuda)		
Memantine (Namenda)		
Mirtazapine (Remeron)		
Nefazodone (Serzone)		
Olanzapine (Zyprexa)		
Oxcarbazepine (Trileptal, Oxtellar XR)		
Paliperidone (Invega)		
Perampanel (Fycompa)		
Phenytoin (Dilantin)		
Pimavanserin (Nuplazid)		
Pregabalin (Lyrica)		
Quetiapine (Seroquel)		
Rufinamide (Banzel)		
Sertraline (Zoloft)		
Thioridazine (Mellaril)		
Thiothixene (Navane)		
Tiagabine (Gabitril)		
Topiramate (Topamax)		
Trazodone (Oleptro)		
Trifluoperazine (Stelazine)		
Valproic Acid (Depakote, Depakene)		
Vigabatrin (Sabril)		
Vilazodone (Viibryd)		
Vortioxetine (Trintellix)		
Ziprasidone (Geodon)		

Other Medications

Standard Precautions	Use With Caution	Consider Alternatives
Azilsartan (Edarbi, Edarbyclor)	Dolasetron (Anzemet)	Clopidogrel (Plavix)
Carvedilol (Coreg)	Leflunomide (Arava)	Eliglustat (Cerdelga)
Cevimeline (Evoxac)	Methotrexate (Trexall)	Flecainide (Tambocor)
Chlorpropamide (Diabenese)	Mexiletine (Mexitil)	Metoprolol (Lopressor)
Darifenacin (Enablex)	Palonosetron (Aloxi)	Ondansetron (Zofran, Zuplenz)
Dexlansoprazole (Dexilant, Kapidex)	Propafenone (Rythmol)	
Esomeprazole (Nexium)	Tacrolimus (Prograf)	
Fesoterodine (Toviaz)	Voriconazole (Vfend)	
Fluvastatin (Lescol)		
Gefitinib (Iressa)		
Glimepiride (Amaryl)		
Glipizide (Glucotrol)		
Glyburide (Micronase)		
Irbesartan (Avapro)		
Lansoprazole (Prevacid)		
Lesinurad (Zurampic)		
Losartan (Cozaar, Hyzaar)		
Metoclopramide (Reglan)		
Mirabegron (Myrbetriq)		
Nateglinide (Starlix)		
Nebivolol (Bystolic)		
Omeprazole (Prilosec)		
Pantoprazole (Protonix)		
Prasugrel (Effient)		
Proguanil (Malarone)		
Propranolol (Inderal)		
Rabeprazole (Aciphex)		
Ranolazine (Ranexa)		
Tamsulosin (Flomax)		
Ticagrelor (Brilinta)		
Timolol (Timoptic)		
Tofacitinib (Xeljanz)		
Tolbutamide (Orinase)		
Tolterodine (Detrol)		
Torsemide (Demadex)		

Dosing Guidance

Amitriptyline (Elavil) Evidence Level: 1

Moderate Sensitivity to Amitriptyline (CYP2C19 *1/*2 Intermediate Metabolizer)

Amitriptyline should be used with caution in patients with reduced CYP2C19 activity. Consider a lower starting dose, and increase dosing over several days until an optimal response is achieved.

Amitriptyline (Elavil) Evidence Level: 1

Possible Non-Response to Amitriptyline (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Amoxapine (Amoxapine) Evidence Level: 2

Possible Non-Response to Amoxapine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Atomoxetine (Strattera) Evidence Level: 2

Possible Non-Response to Atomoxetine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Chlorpromazine (Thorazine) Evidence Level: 2

Possible Non-Response to Chlorpromazine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Clobazam (Onfi) Evidence Level: 1

Possible Sensitivity to Clobazam (CYP2C19 *1/*2 Intermediate Metabolizer)

In CYP2C19 intermediate metabolizers, plasma levels of the active metabolite N-desmethylclobazam were 2-fold higher than those found in CYP2C19 normal metabolizers. The dose adjustment for intermediate metabolizers is not well established, and therefore the recommendation for poor metabolizers is proposed. The starting dose should be 5 mg/day, and dose titration should proceed slowly according to weight. Patients should be titrated initially to 10 mg /day (≤30 kg body weight) or 20 mg/day (>30 kg body weight). If necessary and based upon clinical response, an additional titration to the maximum doses 20 mg/day (≤30 kg body weight) or 40 mg/day (>30 kg body weight) may be started on day 21.

Clomipramine (Anafranil) Evidence Level: 1

Moderate Sensitivity to Clomipramine (CYP2C19 *1/*2 Intermediate Metabolizer)

Clomipramine should be used with caution in patients with reduced CYP2C19 activity. Consider a lower starting dose, and increase dosing over several days until an optimal response is achieved.

Clomipramine (Anafranil) Evidence Level: 1

Possible Non-Response to Clomipramine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Clonidine (Kapvay) Evidence Level: 2

Possible Altered Response to Clonidine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

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

Clopidogrel (Plavix) Evidence Level: 1

Reduced Response to Clopidogrel (CYP2C19 *1/*2 Intermediate Metabolizer)

Consider alternative therapy. Examples of alternative drugs: prasugrel (contraindicated in TIA/Stroke patients), ticagrelor, aspirin, aspirin plus dipyridamole.

Codeine (Codeine; Fioricet with Codeine) Evidence Level: 1

Possible Increased Response to Codeine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer. Codeine is converted into its active metabolite morphine by CYP2D6. Since this patient may be a ultra-rapid metabolizer, greatly increased morphine levels may occur, and the patient may be at high risk of toxicity when taking codeine. 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) Evidence Level: 1

Possible Non-Response to Desipramine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Dihydrocodeine (Synalgos-DC) Evidence Level: 1

Possible Altered Response to Dihydrocodeine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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) Evidence Level: 2

Possible Altered Response to Dolasetron (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Donepezil (Aricept) Evidence Level: 2

Possible Altered Response to Donepezil (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Doxepin (Silenor) Evidence Level: 1

Moderate Sensitivity to Doxepin (CYP2C19 *1/*2 Intermediate Metabolizer)

Doxepin should be used with caution in patients with reduced CYP2C19 activity. Consider a lower starting dose, and increase dosing over several days until an optimal response is achieved.

Doxepin (Silenor) Evidence Level: 1

Possible Non-Response to Doxepin (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Eliglustat (Cerdelga) Evidence Level: 1

Possible Non-Response to Eliglustat (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The patient 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) Evidence Level: 1

Altered Response to Flecainide (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Fluphenazine (Prolixin) Evidence Level: 2

Possible Non-response to Fluphenazine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Fluvoxamine (Luvox) Evidence Level: 2

Possible Reduced Response to Fluvoxamine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Haloperidol (Haldol) Evidence Level: 1

Possible Non-Response to Haloperidol (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Hydrocodone (Vicodin) Evidence Level: 2

Possible Altered Response to Hydrocodone (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Imipramine (Tofranil) Evidence Level: 1

Moderate Sensitivity to Imipramine (CYP2C19 *1/*2 Intermediate Metabolizer)

Imipramine should be used with caution in patients with reduced CYP2C19 activity. Consider a lower starting dose, and increase dosing over several days until an optimal response is achieved.

Imipramine (Tofranil) Evidence Level: 1

Possible Non-Response to Imipramine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Leflunomide (Arava) Evidence Level: 2

Increased Sensitivity to Leflunomide (CYP2C19 *1/*2 Intermediate Metabolizer)

Leflunomide is metabolized by CYP2C19 and CYP1A2 to its active metabolite teriflunomide. Preliminary studies indicate that patients with decreased CYP2C19 activity have a higher risk of developing gastrointestinal side effects and hepatotoxicity. There is insufficient data to calculate dose adjustment. If leflunomide is prescribed at standard dosing, monitor closely the patient's response and be alert to increased side effects. Full blood cell count (CBC) and liver function parameters should be checked no more than 6 months before beginning treatment, and every month for the initial 6 months of therapy. Blood pressure should be checked before beginning treatment and periodically thereafter.

Maprotiline (Ludiomil) Evidence Level: 2

Possible Non-response to Maprotiline (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

Like other tricyclic and tetracyclic antidepressants, maprotiline is metabolized by CYP2D6 as well as CYP1A2. Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, although the result is not definitive. The following recommendations apply for CYP2D6 ultra-rapid metabolizers: patients with increased CYP2D6 function may metabolize 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.**

Methotrexate (Trexall) Evidence Level: 2

Increased risk for methotrexate toxicity (MTHFR 677C>T CT Reduced MTHFR Activity)

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) Evidence Level: 1

Possible Non-Responder to Metoprolol (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Mexiletine (Mexitil) Evidence Level: 2

Altered Response to Mexiletine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Nortriptyline (Pamelor) Evidence Level: 1

Possible Non-Response to Nortriptyline (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Ondansetron (Zofran, Zuplenz) Evidence Level: 2

Possible Non-Response to Ondansetron (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Oxycodone (Percocet, Oxycontin) Evidence Level: 1

Possible Altered Response to Oxycodone (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Palonosetron (Aloxi) Evidence Level: 2

Possible Altered Response to Palonosetron (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Paroxetine (Paxil, Brisdelle) Evidence Level: 1

Possible Reduced Response to Paroxetine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Perphenazine (Trilafon) Evidence Level: 1

Possible Non-Response to Perphenazine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Phenobarbital (Luminal) Evidence Level: 2

Possible Sensitivity to Phenobarbital (CYP2C19 *1/*2 Intermediate Metabolizer)

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

Pimozide (Orap) Evidence Level: 1

Possible Non-Response to Pimozide (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Primidone (Mysoline) Evidence Level: 2

Possible Sensitivity to Primidone (CYP2C19 *1/*2 Intermediate Metabolizer)

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

Propafenone (Rythmol) Evidence Level: 1

Altered Response to Propafenone (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Protriptyline (Vivactil) Evidence Level: 1

Possible Non-Response to Protriptyline (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Risperidone (Risperdal) Evidence Level: 1

Possible Non-Response to Risperidone (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Tacrolimus (Prograf) Evidence Level: 1

Insufficient Response to Tacrolimus (CYP3A5 *1/*3 Intermediate Metabolizer)

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

Tetrabenazine (Xenazine) Evidence Level: 1

Unknown Sensitivity to Tetrabenazine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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.

Tramadol (Ultram) Evidence Level: 1

Possible Increased Response to Tramadol (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

Based on the genotype result, this patient MAY be a CYP2D6 ultra-rapid metabolizer, and is at high risk of toxicity when taking tramadol at standard dosing. Consider reducing tramadol dose by 30%. Careful monitoring for side effects 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) Evidence Level: 1

Moderate Sensitivity to Trimipramine (CYP2C19 *1/*2 Intermediate Metabolizer)

Trimipramine should be used with caution in patients with reduced CYP2C19 activity. Consider a lower starting dose, and increase dosing over several days until an optimal response is achieved.

Trimipramine (Surmontil) Evidence Level: 1

Possible Non-Response to Trimipramine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Venlafaxine (Effexor) Evidence Level: 1

Possible Non-Response to Venlafaxine (CYP2D6 *2/*4 XN Ultra-Rapid or Normal Metabolizer)

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

Voriconazole (Vfend) Evidence Level: 1

Moderate Sensitivity to Voriconazole (CYP2C19 *1/*2 Intermediate Metabolizer)

Voriconazole should be used with caution in patients with reduced CYP2C19 activity. Monitor closely voriconazole plasma concentrations, and adjust the dose accordingly.

Zonisamide (Zonegran) Evidence Level: 2

Possible Sensitivity to Zonisamide (CYP2C19 *1/*2 Intermediate Metabolizer)

CYP2C19 is partly involved in the metabolism of zonisamide, and although preliminary studies show that CYP2C19 intermediate metabolizers have a slightly lower (15%) zonisamide clearance than normal metabolizers, no significant change in the clinical outcome has been reported with this antiepileptic drug. Therefore, zonisamide can be prescribed at standard label-recommended dosage and administration with a closer monitoring for adverse events.

Premier Medical Laboratory Service (PMLS)
10 Jack Casey Ct, Fountain Inn SC 29644
Phone: 877-335-2455
Web: www.premedinc.com
Laboratory Director: Peter Zvejnieks, MD

Additional Notes

Results of genotyping should be interpreted in the full context of the patient's clinical history, including hepatic and renal function, life style, co-administration of other drugs, and other pre-existing conditions. Drug metabolism is known to be affected by non-genetic factors. As thus DNA testing does not replace the necessity for clinical drug monitoring.

Test Methodologies and Limitations

PCR based microarray assays are utilized to detect the listed allelic characteristics, including common and rare variants most well characterized at analytical sensitivities and specificities > 99%. Note that the absence of a detectable genetic mutation or polymorphism does not rule out the possibility that a patient has an intermediate or poor metabolizer phenotype. These assays do not detect polymorphisms other than those listed. These assays have been developed and performance characteristics determined by PMLS. Rare false positive or false negative results may occur. These assays have not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance is not necessary. These tests are used for clinical purposes and should not be considered as investigational.

TESTED ALLELES:

CYP2C19 *2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *17; **CYP2C9** *2, *3, *4, *5, *6, *11; **CYP2D6** *2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication); **CYP3A4** *1B, *2, *3, *12, *17; **CYP3A5** *1D, *2, *3, *3B, *3C, *6, *7, *8, *9

Patient Reference

For more information:
877-335-2455
www.premedinc.com

Pharmacogenetic Test Results

Patient: JALENE DOUSE DOB 4/3/1995

CYP2C19	*1/*2	Intermediate Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*2/*4 XN	Ultra-Rapid or Normal Metabolizer
CYP3A4	*1B/*1B	Intermediate Metabolizer
CYP3A5	*1/*3	Intermediate Metabolizer