Comprehensive Pharmacogenetic Report Created for: FRANK

Patient:	FRANK	DOB:	9/16/1946
Accession #:	500088	Gender:	Male
Collection Date:		Received Date:	
Ordered By:	KWAME WILLIAMS	Report Generated:	4/26/2015

Current Patient Medications

Current Medication List: Acetaminophen, Amoxicillin, Carbamazepine, Codeine, Erythromycin, Indocin, Levaquin, Methylprednisolone, Penicillin, Phenobarbital, Simvastatin, Tetracycline

Medications Affected by Patient Genetic Results

Codeine (Codeine; Fioricet with Codeine)	Non-Response to Codeine (CYP2D6 *4/*6 Poor Metabolizer)	*	Greatly reduced morphine levels are expected, and the patient may not experience adequate pain relief when taking codeine. Avoid prescribing codeine, and consider alternative opioids other than tramadol, 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.
Indocin (Indomethacin)	Possible Sensitivity to Indomethacin (CYP2C9 *1/*3 Intermediate Metabolizer)	**	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.
Carbamazepine (Tegretol, Carbatrol)	Normal Response to Carbamazepine	**	**Pharmacogenetic guidance:** Carbamazepine, a drug with a narrow therapeutic window, is extensively metabolized by CYP3A4/5 to its active epoxide metabolite, which is further metabolized by epoxide hydrolase (EPHX1) to an inactive metabolite. Preliminary studies indicate that carbamazepine plasma concentrations are 30% higher in individuals with the CYP3A5*3/*3 genotype compared to those with CYP3A5*1/*1 or *1/*3 genotypes. The clinical impact of this change is poorly documented. **Polypharmacy guidance:** The dosage of carbamazepine should be decreased in patients receiving CYP3A4 inhibitors. Enzyme-inducing drugs significantly decrease carbamazepine levels, and dose adjustments are recommended when the drug is used with other inducers.
Phenobarbital (Luminal)	Normal Sensitivity to Phenobarbital (CYP2C19 *1/*1 Normal Metabolizer)	**	CYP2C19 is partly involved in the metabolism of phenobarbital, and this drug can be prescribed at standard label-recommended dosage and administration.

Pharmacogenetic interpretation cannot be provided for the following patient medications that are outside the scope of this report:

Acetaminophen, Amoxicillin, Erythromycin, Levaquin, Methylprednisolone, Penicillin, Simvastatin, Tetracycline

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

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

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.

Potentially Impacted Medications

Category	Class	Standard Precautions	Use With Caution	Consider Alternatives
Anticancer Agents	Antifolates		Methotrexate (Trexall)	
Cardiovascular	Angiotensin II Receptor Antagonists	Irbesartan (Avapro)		
	Antianginal Agents		Ranolazine (Ranexa)	
	Antiarrhythmics		Flecainide (Tambocor) Mexiletine (Mexitil) Propafenone (Rythmol)	
	Anticoagulants	Apixaban (Eliquis) Dabigatran Etexilate (Pradaxa) Fondaparinux (Arixtra) Rivaroxaban (Xarelto)	Warfarin (Coumadin)	
	Antiplatelets	Clopidogrel (Plavix) Prasugrel (Effient) Ticagrelor (Brilinta) Vorapaxar (Zontivity)		
	Beta Blockers	Labetalol (Normodyne, Trandate) Nebivolol (Bystolic) Propranolol (Inderal)	Carvedilol (Coreg) Timolol (Timoptic)	Metoprolol (Lopressor)
	Statins		Fluvastatin (Lescol)	
Diabetes	Sulfonylureas	Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Micronase) Tolbutamide (Orinase)		
Gastrointestinal	Antiemetics	Ondansetron (Zofran)	Metoclopramide (Reglan)	
	Proton Pump Inhibitors	Dexlansoprazole (Dexilant) Esomeprazole (Nexium) Lansoprazole (Prevacid) Omeprazole (Prilosec) Pantoprazole (Protonix) Rabeprazole (Aciphex)		
Infections	Antifungals	Voriconazole (Vfend)		

Category	Class	Standard Precautions	Use With Caution	Consider Alternatives
Pain	Fibromyalgia Agents	Milnacipran (Savella)		
	Muscle Relaxants	Carisoprodol (Soma) Cyclobenzaprine (Flexeril, Amrix) Metaxalone (Skelaxin) Methocarbamol (Robaxin)		
	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) Dihydrocodeine (Synalgos-DC) Fentanyl (Actiq) Hydromorphone (Dilaudid, Exalgo) Levorphanol (Levo Dromoran) Meperidine (Demerol) Morphine (MS Contin) Oxymorphone (Opana, Numorphan) Sufentanil (Sufenta) Tapentadol (Nucynta)	Hydrocodone (Vicodin) Oxycodone (Percocet, Oxycontin)	Codeine (Codeine; Fioricet with Codeine) Tramadol (Ultram)

Category	Class	Standard Precautions	Use With Caution	Consider Alternatives
Psychotropic	Anti-ADHD Agents		Atomoxetine (Strattera)	
	Anticonvulsants	Carbamazepine (Tegretol, Carbatrol) Eslicarbazepine Acetate (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	Memantine (Namenda)	Donepezil (Aricept) Galantamine (Razadyne)	
	Antidepressants	Citalopram (Celexa) Desvenlafaxine (Pristiq) Escitalopram (Lexapro) Fluoxetine (Prozac, Sarafem) Levomilnacipran (Fetzima) Mirtazapine (Remeron) Sertraline (Zoloft) Vilazodone (Viibryd)	Amoxapine (Amoxapine) Duloxetine (Cymbalta) Fluvoxamine (Luvox) Maprotiline (Ludiomil) Nefazodone (Serzone) Paroxetine (Paxil, Brisdelle) Vortioxetine (Brintellix)	Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Imipramine (Tofranil) Nortriptyline (Pamelor) Protriptyline (Vivactil) Trimipramine (Surmontil) Venlafaxine (Effexor)
	Antipsychotics	Asenapine (Saphris) Clozapine (Clozaril) Lurasidone (Latuda) Olanzapine (Zyprexa) Paliperidone (Invega) Quetiapine (Seroquel) Thiothixene (Navane) Trazodone (Oleptro) Trifluoperazine (Stelazine) Ziprasidone (Geodon)	Aripiprazole (Abilify) Chlorpromazine (Thorazine) Fluphenazine (Prolixin) Iloperidone (Fanapt) Perphenazine (Trilafon) Pimozide (Orap) Tetrabenazine (Xenazine)	Haloperidol (Haldol) Risperidone (Risperdal) Thioridazine (Mellaril)
	Benzodiazepines	Clobazam (Onfi) Clonazepam (Klonopin) Diazepam (Valium)		
Rheumatology	Immunomodulators	Apremilast (Otezla) Leflunomide (Arava) Tofacitinib (Xeljanz)		
Transplantation	Immunosupressants	Tacrolimus (Prograf)		

Category	Class	Standard Precautions	Use With Caution	Consider Alternatives
Urologicals	5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia	Dutasteride (Avodart) Finasteride (Proscar)		
	Alpha-Blockers for Benign Prostatic Hyperplasia	Alfuzosin (UroXatral) Doxazosin (Cardura) Silodosin (Rapaflo) Terazosin (Hytrin)	Tamsulosin (Flomax)	
	Antispasmodics for Overactive Bladder	Fesoterodine (Toviaz) Mirabegron (Myrbetriq) Oxybutynin (Ditropan) Solifenacin (Vesicare) Trospium (Sanctura)	Darifenacin (Enablex) Tolterodine (Detrol)	
	Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra) Sildenafil (Viagra) Tadalafil (Cialis) Vardenafil (Levitra)		

Dosing Guidance

Amitriptyline (Elavil)	Increased Sensitivity to Amitriptyline (CYP2D6 *4/*6 Poor Metabolizer)	*Select an alternative drug, or consider prescribing amitriptyline at a reduced dose (50% reduction) with monitoring of plasma concentrations of amitriptyline and nortriptyline.
Clomipramine (Anafranil)	Increased Sensitivity to Clomipramine (CYP2D6 *4/*6 Poor Metabolizer)	*Consider an alternative drug, or prescribe clomipramine at 50% of the recommended standard starting dose. Monitor plasma concentrations of clomipramine and desmethylclomipramine, and titrate accordingly until a favorable response is achieved.
Codeine (Codeine; Fioricet with Codeine)	Non-Response to Codeine (CYP2D6 *4/*6 Poor Metabolizer)	*Greatly reduced morphine levels are expected, and the patient may not experience adequate pain relief when taking codeine. Avoid prescribing codeine, and consider alternative opioids other than tramadol, 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)	Increased Sensitivity to Desipramine (CYP2D6 *4/*6 Poor Metabolizer)	*Consider an alternative drug, or prescribe desipramine at 50% of recommended standard starting dose. Monitor plasma concentrations of desipramine and metabolites and titrate accordingly until a favorable response is achieved.
Doxepin (Silenor)	Increased Sensitivity to Doxepin (CYP2D6 *4/*6 Poor Metabolizer)	*Consider an alternative drug or reduce doxepin starting dose by 50%. Adjust maintenance dose according to nordoxepin plasma concentrations.
Haloperidol (Haldol)	Increased Sensitivity to Haloperidol (CYP2D6 *4/*6 Poor Metabolizer)	*Haloperidol is metabolized by CYP2D6, CYP3A4, and other enzymes. **Decreased CYP2D6 activity results in higher haloperidol concentrations, potentially leading to more adverse events.** Consider an alternative drug, or prescribe haloperidol at 50% of the usual starting dose, then adjust dosage to achieve a favorable clinical response.
Imipramine (Tofranil)	Increased Sensitivity to Imipramine (CYP2D6 *4/*6 Poor Metabolizer)	*Consider an alternative drug, or consider a 50% reduction of the imipramine recommended starting dose, then titrate in response to imipramine and desipramine plasma concentrations.
Metoprolol (Lopressor)	Significantly Increased Sensitivity to Metoprolol (CYP2D6 *4/*6 Poor Metabolizer)	*Based on the genotype result, this patient is at risk of excessive beta-blockade when taking metoprolol at standard dosage. Heart Failure: Consider alternative beta-blockers such as bisoprolol or carvedilol, or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, a poor metabolizer may require a 75% dose reduction. Other indications: Consider alternative beta-blockers such as bisoprolol or atenolol, or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, a poor metabolizer may require a 75% dose reduction. If metoprolol is prescribed, be alert to adverse events (e.g., bradycardia or cold extremities).
Nortriptyline (Pamelor)	Increased Sensitivity to Nortriptyline (CYP2D6 *4/*6 Poor Metabolizer)	*Select an alternative drug, or consider prescribing nortriptyline at a reduced dose (50% reduction) with monitoring of plasma concentrations of nortriptyline and metabolites.

Protriptyline (Vivactil)	Increased Sensitivity to Protriptyline (CYP2D6 *4/*6 Poor Metabolizer)	*Consider alternative or prescribe protriptyline at 50% of recommended standard starting dose. Monitor plasma concentrations of protriptyline and metabolites and titrate accordingly until a favorable response is achieved.
Risperidone (Risperdal)	Significantly Increased Sensitivity to Risperidone (CYP2D6 *4/*6 Poor Metabolizer)	*Consider an alternative drug, OR prescribe risperidone at a reduced dose, be extra alert of adverse events, and adjust dosage in response to clinical response and tolerability.
Thioridazine (Mellaril)	Increased Sensitivity to Thioridazine (CYP2D6 *4/*6 Poor Metabolizer)	*Reduced cytochrome CYP2D6 activity results in elevated plasma levels of thioridazine, would be expected to augment the prolongation of the QTc interval associated with thioridazine, and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes-type arrhythmias. Such an increased risk may result also from the additive effect of coadministering thioridazine with other agents that prolong the QTc interval. Therefore, thioridazine is contraindicated in patients with reduced levels of CYP2D6 activity.
Tramadol (Ultram)	Non-Response to Tramadol (CYP2D6 *4/*6 Poor Metabolizer)	*The patient will not experience adequate pain relief when taking tramadol. Avoid prescribing tramadol, and 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)	Increased Sensitivity to Trimipramine (CYP2D6 *4/*6 Poor Metabolizer)	*Consider an alternative drug, or consider a 50% reduction of the trimipramine recommended starting dose, then titrate in response to trimipramine plasma concentrations.
Venlafaxine (Effexor)	Significantly Increased Sensitivity to Venlafaxine (CYP2D6 *4/*6 Poor Metabolizer)	*The patient has an increased risk of side effects when taking standard doses of venlafaxine. Consider an alternative drug, OR prescribe venlafaxine, be extra alert of adverse events, and adjust dosage in response to clinical response and tolerability. Monitor O-desmethylvenlafaxine plasma concentrations.
Amoxapine (Amoxapine)	Possible Sensitivity to Amoxapine (CYP2D6 *4/*6 Poor 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. Decreased CYP2D6 activity may result in higher amoxapine concentrations potentially leading to higher adverse events. There are no established dosing adjustments for patients with decreased CYP2D6 function therefore, therapy must be initiated cautiously and adjusted according to the patient's response.

Aripiprazole (Abilify)	Increased Sensitivity to Aripiprazole (CYP2D6 *4/*6 Poor Metabolizer)	***Poor metabolizers have a significantly reduced capacity to metabolize aripiprazole and its active metabolite, and should receive lower doses**. Careful titration is recommended until a favorable response is achieved. Daily dosing (oral or intramuscular): aripiprazole dose should initially be reduced to one-half (**50%**) of the usual dose, then adjusted to achieve a favorable clinical response. Reduce the **maximum dose to 10 mg/day** (67% of the maximum recommended daily dose). The dose of aripiprazole for poor metabolizers who are administered a strong CYP3A4 inhibitor should be reduced to one-quarter (25%) of the usual dose. Monthly dosing (intramuscular): the starting and maintenance monthly recommended dose is lower than the usually recommended dose, and should be **300 mg**. Some patients may benefit from a reduction to 200 mg. Reduce the monthly dose to 200 mg if a CYP3A4 inhibitor is prescribed to CYP2D6 poor metabolizers receiving 300 mg of aripiprazole.
Atomoxetine (Strattera)	Increased Sensitivity to Atomoxetine (CYP2D6 *4/*6 Poor Metabolizer)	*When given a standard atomoxetine dose, CYP2D6 poor metabolizers are likely to have higher plasma levels of the drug, which may lead to a higher rate of adverse events. **Careful titration and dosing adjustment are recommended with monitoring for toxicity until a favorable response is achieved**. In children and adolescents up to 70 kg body weight, atomoxetine should be initiated at standard dosing of 0.5 mg/kg/day, and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. In children and adolescents over 70 kg body weight and adults, atomoxetine should be initiated at standard dosing of 40 mg/day, and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.
Carvedilol (Coreg)	Moderate Sensitivity to Carvedilol (CYP2D6 *4/*6 Poor Metabolizer)	*Carvedilol can be prescribed at standard label-recommended dosage and administration. CYP2D6 poor metabolizers may experience dizziness during up-titration. Careful titration is recommended with monitoring until a favorable response is achieved.
Celecoxib (Celebrex)	Possible Sensitivity to Celecoxib (CYP2C9 *1/*3 Intermediate Metabolizer)	**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)	Increased Sensitivity to Chlorpromazine (CYP2D6 *4/*6 Poor Metabolizer)	**Chlorpromazine is metabolized by CYP2D6, CYP3A4 and flavin-containing monooxygenases. Decreased CYP2D6 activity results in higher chlorpromazine concentrations potentially leading to higher adverse events. Consider prescribing chlorpromazine at a lower starting dose and then adjust dosage to achieve a favorable clinical response.
Darifenacin (Enablex)	Possible Sensitivity to Darifenacin (CYP2D6 *4/*6 Poor Metabolizer)	*Darifenacin exposure is increased 30% in CYP2D6 poor metabolizers. Although dose adjustment may not be needed in these patients, monitor patients for increased side effects when darifenacin is prescribed at standard label-recommended dosage and administration.

Diclofenac (Voltaren)	Possible Sensitivity to Diclofenac (CYP2C9 *1/*3 Intermediate Metabolizer)	**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.
Donepezil (Aricept)	Possible Altered Response to Donepezil (CYP2D6 *4/*6 Poor Metabolizer)	**When compared to a normal metabolizer, a poor metabolizer has a 30% decrease in donepezil clearance. The clinical significance of this decrease is not well documented. Consider using a standard dosing regimen, be alert for adverse events, and adjust dosage in response to clinical response and tolerability.
Duloxetine (Cymbalta)	Possible Sensitivity to Duloxetine (CYP2D6 *4/*6 Poor Metabolizer)	**Limited data suggest that duloxetine plasma concentrations might be increased in CYP2D6 poor metabolizers. Therefore, duloxetine can be prescribed at standard label-recommended dosage, and careful titration is recommended until a favorable response is achieved.
Flecainide (Tambocor)	Significantly Increased Sensitivity to Flecainide (CYP2D6 *4/*6 Poor Metabolizer)	*Consider prescribing a lower flecainide dose. When compared to a CYP2D6 normal metabolizer, a poor metabolizer may require a 50% dose reduction. Careful titration with ECG recording and monitoring of flecainide plasma concentrations are recommended until a favorable clinical response is achieved.
Fluphenazine (Prolixin)	Increased Sensitivity to Fluphenazine (CYP2D6 *4/*6 Poor Metabolizer)	**Fluphenazine is metabolized by CYP2D6, CYP1A2 and other enzymes. **Decreased CYP2D6 activity may result in higher fluphenazine concentrations potentially leading to higher adverse events such as extrapyramidal symptoms**. There are no established dosing adjustments for patients lacking 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/*3 Intermediate Metabolizer)	**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/*3 Intermediate Metabolizer)	*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)	Increased Sensitivity to Fluvoxamine (CYP2D6 *4/*6 Poor Metabolizer)	*At standard label-recommended dosage, fluvoxamine levels are expected to be high and adverse events may occur. Careful titration is recommended until a favorable response is achieved. When compared to a CYP2D6 normal metabolizer, a poor metabolizer may require a 25 to 50% dose reduction to help prevent concentration-dependent adverse events.

Fosphenytoin (Cerebyx)	Moderate Sensitivity to Fosphenytoin (CYP2C9 *1/*3 Intermediate Metabolizer)	***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.
Galantamine (Razadyne)	Possible Sensitivity to Galantamine (CYP2D6 *4/*6 Poor Metabolizer)	****A CYP2D6 poor metabolizer has a drug exposure that is approximately 50% higher than the exposure in a normal metabolizer. Although dosage adjustment is not necessary in a patient identified as a CYP2D6 poor metabolizer as the dose of drug is individually titrated to tolerability, a slower titration can be considered as it may improve tolerability.
Hydrocodone (Vicodin)	Possible Altered Response to Hydrocodone (CYP2D6 *4/*6 Poor Metabolizer)	****Decreased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 poor metabolizers. However, there is insufficient evidence whether poor metabolizers have decreased analgesia when taking hydrocodone. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 may also be considered (i.e., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone).
Iloperidone (Fanapt)	Increased Sensitivity to Iloperidone (CYP2D6 *4/*6 Poor Metabolizer)	*Iloperidone **dose should be reduced by one-half and titrated slowly to avoid orthostatic hypotension**. Because iloperidone is associated with QTc prolongation, caution is warranted when prescribing the drug in patients with reduced CYP2D6 activity. If patients taking iloperidone experience symptoms that could indicate the occurrence of cardiac arrhythmias (e.g., dizziness, palpitations, or syncope), the prescriber should initiate further evaluation, including cardiac monitoring.
Indomethacin (Indocin)	Possible Sensitivity to Indomethacin (CYP2C9 *1/*3 Intermediate Metabolizer)	****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.
Maprotiline (Ludiomil)	Increased Sensitivity to Maprotiline (CYP2D6 *4/*6 Poor Metabolizer)	****Like other tricyclic and tetracyclic antidepressants, maprotiline is metabolized by CYP2D6 as well as CYP1A2. Compared to CYP2D6 normal metabolizers, CYP2D6 poor metabolizers have higher exposure to maprotiline at therapeutic doses which may increase the risk of concentration-dependent toxicities. There are no established dosing adjustments for patients with decreased CYP2D6 function however, it is recommended to initiate maprotiline therapy at a low dosage and gradually adjust the dosing according to the patient's response. The lowest effective dosage should always be considered during maintenance therapy.
Meloxicam (Mobic)	Possible Sensitivity to Meloxicam (CYP2C9 *1/*3 Intermediate Metabolizer)	****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 Sensitivity to Methotrexate (MTHFR 677C>T TT Reduced MTHFR Activity)	**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.
Metoclopramide (Reglan)	Increased Sensitivity to Metoclopramide (CYP2D6 *4/*6 Poor Metabolizer)	**Metoclopramide is metabolized at a slower rate in CYP2D6 poor metabolizers which results in significantly higher serum concentrations of the drug. Considering the CNS and extrapyramidal adverse effects of metoclopramide, close monitoring for toxicity and eventually a dose decrease are recommended. Patients with renal disease at increased risk.
Mexiletine (Mexitil)	Significantly Increased Sensitivity to Mexiletine (CYP2D6 *4/*6 Poor Metabolizer)	*Consider prescribing a lower mexiletine dose. A slow titration with ECG recording and monitoring of mexiletine plasma concentrations are recommended until a favorable clinical response is achieved.
Nefazodone (Serzone)	Possible Sensitivity to Nefazodone (CYP2D6 *4/*6 Poor Metabolizer)	**Nefazodone is metabolized by CYP3A4 to its active metabolite m-chlorophenylpiperazine and other metabolites. The m-chlorophenylpiperazine metabolite which may contribute to adverse events, is further metabolized by CYP2D6. Individuals lacking CYP2D6 activity have higher levels of m-chlorophenylpiperazine metabolite and may experience more moderate and transient side effects when starting therapy. Consider prescribing nefazodone at a lower dose and adjust dose according to the patient's tolerability and clinical response.
Oxycodone (Percocet, Oxycontin)	Possible Altered Response to Oxycodone (CYP2D6 *4/*6 Poor Metabolizer)	*Decreased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 poor metabolizers. However, there is insufficient evidence whether poor metabolizers have decreased analgesia when taking oxycodone. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 may also be considered (i.e., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone).
Paroxetine (Paxil, Brisdelle)	Possible Sensitivity to Paroxetine (CYP2D6 *4/*6 Poor Metabolizer)	*At standard label-recommended dosage, paroxetine levels are expected to be high, and adverse events may occur. Careful titration is recommended until a favorable response is achieved. When compared to a CYP2D6 normal metabolizer, a poor metabolizer may require a 50% dose reduction. Some studies show that compared to normal metabolizers, poor metabolizers may experience more sexual dysfunction. No differences between genotypes are seen for other common paroxetine-induced side effects.

Perphenazine (Trilafon)	Increased Sensitivity to Perphenazine (CYP2D6 *4/*6 Poor Metabolizer)	*Patients with a decreased CYP2D6 function will eliminate perphenazine more slowly, which can result in higher drug concentrations and possibly more adverse events (extrapyramidal symptoms). Consider close monitoring and dose reduction to avoid toxicity.
Phenytoin (Dilantin)	Moderate Sensitivity to Phenytoin (CYP2C9 *1/*3 Intermediate Metabolizer)	*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)	Increased Sensitivity to Pimozide (CYP2D6 *4/*6 Poor Metabolizer)	*The pimozide concentrations observed in poor CYP2D6 metabolizers are expected to be high, and the time to achieve steady-state pimozide concentrations is expected to be long (approximately 2 weeks). Consequently, CYP2D6 poor metabolizers are at an increased risk of QT prolongation at standard doses of pimozide. In CYP2D6 poor metabolizers, pimozide doses should not exceed 4 mg/day in adults or 0.05 mg/kg/day in children, and doses should not be increased earlier than 14 days.
Piroxicam (Feldene)	Possible Sensitivity to Piroxicam (CYP2C9 *1/*3 Intermediate Metabolizer)	**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.
Propafenone (Rythmol)	Increased Sensitivity to Propafenone (CYP2D6 *4/*6 Poor Metabolizer)	*Consider reducing the propafenone dose, and monitor ECG. Compared to normal metabolizers, poor metabolizers may require a 70% dose reduction. Consider monitoring for plasma concentrations.
Ranolazine (Ranexa)	Increased Sensitivity to Ranolazine (CYP2D6 *4/*6 Poor Metabolizer)	*Ranolazine is metabolized mainly by CYP3A4, and to a lesser extent by CYP2D6. At 500 mg twice daily, subjects lacking CYP2D6 activity (poor metabolizers) had 62% higher ranolazine exposure than subjects with normal CYP2D6 activity. The corresponding difference at 1000 mg twice daily dose was 25%. **The risk for increased exposure leading to adverse events is higher in patients lacking CYP2D6 activity (i.e., poor metabolizers).** The recommended initial oral dose is 375 mg twice daily. **A slower up titration and additional monitoring is recommended in these patients.** Exposure related side effects might include nausea, vomiting, syncope, and dizziness. If a patient experiences treatment-related adverse events, down titration of the dose to 500 mg or 375 mg twice daily may be required. If symptoms do not resolve after dose reduction, treatment should be discontinued. **Ranolazine is a QTc prolonging drug.** Caution should be observed when treating: 1- patients with a history of congenital or a family history of long QT syndrome, 2- patients with known acquired QT interval prolongation, and 3- patients treated with drugs affecting the QTc interval. Administration of CYP3A4 inhibitors increases the exposure of ranolazine significantly. As a consequence, the QTc prolongation by ranolazine in the presence of potent CYP3A inhibitors is significantly elevated relative to when the drug is administered alone.

Tamsulosin (Flomax)	Increased Sensitivity to Tamsulosin (CYP2D6 *4/*6 Poor Metabolizer)	*Tamsulosin is metabolized at a slower rate in CYP2D6 poor metabolizers, which results in significantly higher serum concentrations of tamsulosin. Therefore, this drug should be used with caution in patients known to be CYP2D6 poor metabolizers, particularly at a daily dose higher than 0.4 mg.
Tetrabenazine (Xenazine)	Increased Sensitivity to Tetrabenazine (CYP2D6 *4/*6 Poor 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 poor metabolizers is 50 mg with a maximum single dose of 25 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.
Timolol (Timoptic)	Increased Sensitivity to Timolol (CYP2D6 *4/*6 Poor Metabolizer)	*Potentiated systemic beta-blockade (e.g., bradycardia) has been reported during timolol treatment by patients with decreased CYP2D6 activity. Monitor patient for treatment-related adverse effects.
Tolterodine (Detrol)	Possible Sensitivity to Tolterodine (CYP2D6 *4/*6 Poor Metabolizer)	**Tolterodine is metabolized at a slower rate in CYP2D6 poor metabolizers, which results in significantly higher serum concentrations of tolterodine and negligible concentrations of its active metabolite (5-hydroxymethytolterodine). Considering the antimuscarinic potency of tolterodine and its active metabolite, and the protein binding of these compounds, tolterodine accounts for the major part of the clinical effect in poor metabolizers, and the same dosage can be applied irrespective of phenotype status. Patients with congenital or acquired QT prolongation: the effect of tolterodine on the QT interval prolongation is greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day, and is more pronounced in CYP2D6 poor metabolizers than normal metabolizers. This should be considered when tolterodine is prescribed to patients with a known history of QT prolongation, or patients who are taking Class IA or Class III antiarrhythmics.
Vortioxetine (Brintellix)	Increased Sensitivity to Vortioxetine (CYP2D6 *4/*6 Poor Metabolizer)	*CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive carboxylic acid metabolite. CYP2D6 poor metabolizers have approximately twice the vortioxetine plasma concentrations of normal metabolizers. **Vortioxetine starting dose should be reduced by one-half. The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers.** Consider 5 mg/day for patients who do not tolerate higher doses.
Warfarin (Coumadin)	Very High Sensitivity to Warfarin (CYP2C9 *1/*3 VKORC1 -1639G>A A/A)	*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.

Test Details			
Gene	**Genotype**	**Phenotype**	**Alleles Tested**
CYP2C19	*1/*1	Normal Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *17
CYP2C9	*1/*3	Intermediate Metabolizer	*2, *3, *4, *5, *6, *11
CYP2D6	*4/*6	Poor Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1/*1	Normal Metabolizer	*1B, *2, *3, *12, *17
CYP3A5	*2/*3/*3	Poor Metabolizer	*1D, *2, *3, *3B, *3C, *6, *7, *8, *9
Factor II	20210G>A GG	Normal Thrombosis Risk	20210G>A
Factor V Leiden	1691G>A GG	Normal Thrombosis Risk	1691G>A
MTHFR	1298A>C AA	Normal MTHFR Activity	1298A>C
MTHFR	677C>T TT	Reduced MTHFR Activity	677C>T
VKORC1	-1639G>A A/A	High Warfarin Sensitivity	-1639G>A, 698C>T, 1173C>T, 1542G>C, 2255C>T, 358C>T, 3730G>A, 5808T>G

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

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

Disclaimer: The information presented on this report is provided as general educational health information. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Only a physician, pharmacist or other healthcare professional should advise a patient on the use of the medications prescribed. CQuentia Labs developed this test and its performance characteristics. This test has not been cleared or approved by the U.S. Food and Drug Administration. The pharmacogenetic report is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to dose guidelines does not necessarily assure a successful medical outcome.

Laboratory Certification: CLIA # 11D2074759