STONE CLINICAL LABORATORIES

Shareef Nahas, Ph.D., FACMG, Laboratory Director • CLIA# 11D2071408

333 Research Ct • Ste 200 • Peachtree Corners, GA 30092

t 678.250.9222 • tf 1.888.250.6228 • f 770.545.8592 •

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Stone Clinical Laboratories Comprehensive Extended Created for: Johnny Doe

Patient:	Johnny Doe	DOB:	7/18/1969
Accession #:	1234562015	Gender:	Male
Collection Date:	1/8/2018	Received Date:	1/9/2018
Ordered By:	Dr. John Citizen	Report Generated:	1/12/2018
Comments:			

Current Patient Medications

Current Medication List: Lipitor, Soma, Celexa, Haldol, Percocet

Medications Affected by Patient Genetic Results

Lipitor (Atorvastatin)

Increased Myopathy Risk (SLCO1B1 521T>C C/C Poor 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.

Soma (Carisoprodol)

Normal Sensitivity to Carisoprodol (CYP2C19 *1/*1 Normal Metabolizer) Evidence Level: **Informative**

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

Celexa (Citalopram)

Delayed Response to Citalopram (SLC6A4 S/S Low Serotonin Transporter Expression) Evidence Level: **Informative**

The genotype predicts significantly decreased serotonin transporter levels resulting in less efficient transporter function. A longer titration period may be required to achieve maximal antidepressant response. The patient may respond to citalopram more slowly (up to 12 weeks) and may experience more side effects. The patient may benefit from non-selective antidepressants.

Haldol (Haloperidol)

Increased Sensitivity to Haloperidol (CYP2D6 *4M/*4M XN Poor Metabolizer) Evidence Level: **Actionable**

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.

Percocet (Oxycodone)

Possible Altered Response to Oxycodone (CYP2D6 *4M/*4M XN Poor Metabolizer) Evidence Level: **Actionable**

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).

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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.

Additional Risk Factors

Type III Hyperlipoproteinemia

Associated with Type III Hyperlipoproteinemia

The patient is negative for the APOE c.388 T>C (Cys130Arg) mutation and positive for the APOE c.526 C>T (Arg176Cys) mutation. The patient's genotype is ε2/ε2 (frequency: 0.2-2%).

Homozygosity for APOE ε2 allele is strongly associated with type III hyperlipoproteinemia. Over 90% of individuals presenting the type III hyperlipoproteinemia have the rare ε2/ε2 genotype. However, only 1-5% of individuals ε2/ε2 develop type III hyperlipoproteinemia. Although individuals with the APOE ε2/ε2 genotype are at a higher risk of premature vascular disease, they may never develop the disease because this genotype is only one of the risk factors.

In normolipidemic individuals, the APOE ε2 allele is associated with lower serum cholesterol concentrations, and may confer a protection against hypercholesterolemia.

Dietary adjustment and statin drugs are the preferred agents for lipid-lowering therapy. Useful drugs for treatment of type III hyperlipoproteinemia include nicotinic acid, fibric acid derivatives, and statins.

Thrombophilia

No Increased Risk of Thrombosis

The patient does not carry the Factor V Leiden G1691A mutation or Factor II G20210A mutation (wild-type).

The patient's risk of thrombosis is not increased (average risk of clotting is about 1 in 1000 for anyone in a year). However, because this test cannot find all of the inherited reasons for abnormal clotting, other factors may affect this risk assessment.

Unless other genetic and/or circumstantial risk factors are present (e.g., smoking or obesity…), estrogen-containing contraceptive and hormone replacement therapy can be used by the patient.

Hyperhomocysteinemia - Thrombosis

Increased Risk of Hyperhomocysteinemia

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

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

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

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Potentially Impacted Medications for: Johnny Doe

Category	Standard Precautions	Use With Caution	Consider Alternatives
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)	
Angiotensin II Receptor Antagonists	Azilsartan (Edarbi, Edarbyclor) Candesartan (Atacand) Eprosartan (Teveten) Irbesartan (Avapro) Olmesartan (Benicar) Telmisartan (Micardis) Valsartan (Diovan, Entresto)	Losartan (Cozaar, Hyzaar)	
Antiaddictives	Naltrexone (Vivitrol, Contrave)	Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave)	
Anti-ADHD Agents	Clonidine (Kapvay) Guanfacine (Intuniv)	Amphetamine (Adderall, Evekeo) Atomoxetine (Strattera) Dexmethylphenidate (Focalin) Dextroamphetamine (Dexedrine) Lisdexamfetamine (Vyvanse) Methylphenidate (Ritalin, Aptensio XR, Concerta, Metadate ER, Quillivant ER)	
Antianginal Agents		Ranolazine (Ranexa)	
Antiarrhythmics		Flecainide (Tambocor) Mexiletine (Mexitil) Propafenone (Rythmol)	
Anticoagulants	Apixaban (Eliquis) Betrixaban (Bevyxxa) Dabigatran Etexilate (Pradaxa) Edoxaban (Savaysa) Fondaparinux (Arixtra) Rivaroxaban (Xarelto)	Warfarin (Coumadin)	

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Category	Standard Precautions	Use With Caution	Consider Alternatives
Anticonvulsants	Brivaracetam (Briviact) Carbamazepine (Tegretol, Carbatrol, Epitol) Eslicarbazepine (Aptiom) Ethosuximide (Zarontin) Ezogabine (Potiga) Felbamate (Felbatol) Gabapentin (Neurontin) Lacosamide (Vimpat) Lamotrigine (Lamictal) Levetiracetam (Keppra) Oxcarbazepine (Trileptal, Oxtellar XR) Perampanel (Fycompa) Phenobarbital (Luminal) Pregabalin (Lyrica) Primidone (Mysoline) Rufinamide (Banzel) Tiagabine (Gabitril) Topiramate (Topamax) Valproic Acid (Depakote, Depakene) Vigabatrin (Sabril) Zonisamide (Zonegran)	Fosphenytoin (Cerebyx) Phenytoin (Dilantin)	
Antidementia Agents	Memantine (Namenda)	Donepezil (Aricept) Galantamine (Razadyne)	
Antidepressants	Desvenlafaxine (Pristiq) Fluoxetine (Prozac, Sarafem) Levomilnacipran (Fetzima) Mirtazapine (Remeron) Sertraline (Zoloft) Trazodone (Oleptro) Vilazodone (Viibryd)	Amoxapine (Amoxapine) Citalopram (Celexa) Duloxetine (Cymbalta) Escitalopram (Lexapro) Fluvoxamine (Luvox) Maprotiline (Ludiomil) Nefazodone (Serzone) Vortioxetine (Trintellix)	Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Imipramine (Tofranil) Nortriptyline (Pamelor) Paroxetine (Paxil, Brisdelle) Protriptyline (Vivactil) Trimipramine (Surmontil) Venlafaxine (Effexor)
Antiemetics	Aprepitant (Emend-oral) Dolasetron (Anzemet) Fosaprepitant (Emend-i.v) Netupitant-Palonosetron (Akynzeo) Palonosetron (Aloxi) Rolapitant (Varubi)	Dronabinol (Marinol) Granisetron (Sancuso, Sustol) Metoclopramide (Reglan) Ondansetron (Zofran, Zuplenz)	
Antifolates		Methotrexate (Trexall)	
Antifungals	Amphotericin B (AmBisome, Abelcet) Anidulafungin (Eraxis) Caspofungin (Cancidas) Fluconazole (Diflucan) Isavuconazonium (Cresemba) Itraconazole (Sporanox) Micafungin (Mycamine) Posaconazole (Noxafil) Voriconazole (Vfend)		

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Category	Standard Precautions	Use With Caution	Consider Alternatives
Anti-HIV Agents	Dolutegravir (Tivicay, Triumeq) Raltegravir (Isentress, Dutrebis)		
Anti-Hyperuricemics and Anti-Gout Agents	Colchicine (Mitigare) Febuxostat (Uloric)	Lesinurad (Zurampic)	
Antimalarials	Proguanil (Malarone)		
Antiplatelets	Clopidogrel (Plavix) Prasugrel (Effient) Ticagrelor (Brilinta) Vorapaxar (Zontivity)		
Antipsychotics	Asenapine (Saphris) Cariprazine (Vraylar) Loxapine (Loxitane, Adasuve) Lurasidone (Latuda) Paliperidone (Invega) Pimavanserin (Nuplazid) Quetiapine (Seroquel) Thiothixene (Navane) Trifluoperazine (Stelazine) Ziprasidone (Geodon)	Aripiprazole (Abilify, Aristada) Brexpiprazole (Rexulti) Chlorpromazine (Thorazine) Clozapine (Clozaril) Fluphenazine (Prolixin) Iloperidone (Fanapt) Olanzapine (Zyprexa) Perphenazine (Trilafon) Pimozide (Orap)	Haloperidol (Haldol) Risperidone (Risperdal) Thioridazine (Mellaril)
Antispasmodics for Overactive Bladder	Fesoterodine (Toviaz) Mirabegron (Myrbetriq) Oxybutynin (Ditropan) Solifenacin (Vesicare) Trospium (Sanctura)	Darifenacin (Enablex) Tolterodine (Detrol)	
Benzodiazepines	Alprazolam (Xanax) Clobazam (Onfi) Clonazepam (Klonopin) Diazepam (Valium) Lorazepam (Ativan) Oxazepam (Serax)		
Beta Blockers	Atenolol (Tenormin) Bisoprolol (Zebeta) Labetalol (Normodyne, Trandate) Nebivolol (Bystolic) Propranolol (Inderal)	Carvedilol (Coreg) Timolol (Timoptic)	Metoprolol (Lopressor)
Diuretics		Torsemide (Demadex)	
Fibromyalgia Agents	Milnacipran (Savella)		
Immunomodulators	Apremilast (Otezla) Leflunomide (Arava) Tofacitinib (Xeljanz)		
Immunosuppressants		Tacrolimus (Prograf)	
Meglitinides		Nateglinide (Starlix) Repaglinide (Prandin, Prandimet)	

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Category	Standard Precautions	Use With Caution	Consider Alternatives
Muscle Relaxants	Carisoprodol (Soma) Cyclobenzaprine (Flexeril, Amrix) Metaxalone (Skelaxin) Methocarbamol (Robaxin)	Tizanidine (Zanaflex)	
NSAIDs	Ketoprofen (Orudis) Ketorolac (Toradol) Nabumetone (Relafen) Naproxen (Aleve) Sulindac (Clinoril)	Celecoxib (Celebrex) Diclofenac (Voltaren) Flurbiprofen (Ansaid) Ibuprofen (Advil, Motrin) Indomethacin (Indocin) Meloxicam (Mobic) Piroxicam (Feldene)	
Opioids	Alfentanil (Alfenta) Buprenorphine (Butrans, Buprenex) Dihydrocodeine (Synalgos-DC) Hydromorphone (Dilaudid, Exalgo) Levorphanol (Levo Dromoran) Meperidine (Demerol) Methadone (Dolophine) Oxymorphone (Opana, Numorphan) Sufentanil (Sufenta) Tapentadol (Nucynta)	Fentanyl (Actiq) Hydrocodone (Vicodin) Morphine (MS Contin) Oxycodone (Percocet, Oxycontin)	Codeine (Codeine; Fioricet with Codeine) Tramadol (Ultram)
Other Neurological Agents	Flibanserin (Addyi)	Deutetrabenazine (Austedo) Dextromethorphan / Quinidine (Nuedexta) Tetrabenazine (Xenazine) Valbenazine (Ingrezza)	
Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra) Sildenafil (Viagra) Tadalafil (Cialis) Vardenafil (Levitra)		
Proton Pump Inhibitors	Dexlansoprazole (Dexilant, Kapidex) Esomeprazole (Nexium) Lansoprazole (Prevacid) Omeprazole (Prilosec) Pantoprazole (Protonix) Rabeprazole (Aciphex)		
Statins		Atorvastatin (Lipitor) Fluvastatin (Lescol) Lovastatin (Mevacor, Altoprev, Advicor) Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor)	Simvastatin (Zocor)

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Category	Standard Precautions	Use With Caution	Consider Alternatives
Sulfonylureas		Chlorpropamide (Diabenese) Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Micronase) Tolbutamide (Orinase)	

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Dosing Guidance for: Johnny Doe

Amitriptyline (Elavil) Evidence Level: **Actionable**

Increased Sensitivity to Amitriptyline (CYP2D6 *4M/*4M XN 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.

Amoxapine (Amoxapine) Evidence Level: **Informative**

Possible Sensitivity to Amoxapine (CYP2D6 *4M/*4M XN 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; therapy must be initiated cautiously and adjusted according to the patient's response.

Amphetamine (Adderall, Evekeo) Evidence Level: **Informative**

Poor Response to Amphetamine salts (COMT Val158Met A/A Low COMT Activity)

The patient's genotype result predicts a reduced therapeutic response to amphetamine stimulants. If prescribed, amphetamines should be administered at the lowest effective dose, and dosage should be individually adjusted.

Amphetamine (Adderall, Evekeo) Evidence Level: **Informative**

Possible Increased Exposure to Amphetamine (CYP2D6 *4M/*4M XN Poor Metabolizer)

There is little evidence documenting the exposure of amphetamine in subjects with reduced CYP2D6 activity such as CYP2D6 poor metabolizers. Although the drug's plasma concentrations may be elevated in these subjects, the clinical relevance of this change is not well documented. Consider initiating therapy with lower doses and monitor the patient more frequently during drug titration. Consider adjusting the dose based on clinical response and tolerability. An alternative therapy may also be considered in patients with decreased tolerability.

Aripiprazole (Abilify, Aristada) Evidence Level: **Actionable**

Increased Sensitivity to Aripiprazole (CYP2D6 *4M/*4M XN Poor Metabolizer)

CYP2D6 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 CYP2D6 poor metabolizers who are administered a strong CYP3A4 inhibitor should be reduced to one-quarter (25%) of the usual dose.

Monthly dosing (intramuscular): for *Abilify Maintena*, 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. For *Aristada*, reduce the dose to the next lower strength (662 mg instead of 882 mg and 441 mg instead of 662 mg); no dosage adjustment is necessary in patients taking 441 mg *Aristada*, if tolerated. For *Abilify Maintena*, reduce the monthly dose to 200 mg if a CYP3A4 inhibitor is prescribed to CYP2D6 poor metabolizers receiving 300 mg of aripiprazole. For *Aristada*, reduce dose to 441 mg and avoid use at 662 mg or 882 mg dose if a CYP3A4 inhibitor is prescribed to CYP2D6 poor metabolizers for more than 14 days. No dosage adjustment is necessary in patients taking 441 mg *Aristada*, if tolerated.

Every 6 weeks or two months dosing with *Aristada* (intramuscular): reduce the dose to a lower strength of 441 mg every 4 weeks. If a strong CYP3A4 inhibitor is coadministered for more than 14 days, avoid using the 662 mg, 882 mg or 1064 mg doses and consider the lower dose strenght of 441 mg every 4 weeks.

Atomoxetine (Strattera) Evidence Level: **Actionable**

Increased Sensitivity to Atomoxetine (CYP2D6 *4M/*4M XN 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.

Atorvastatin (Lipitor) Evidence Level: **Informative**

Increased Myopathy Risk (SLCO1B1 521T>C C/C Poor Function)

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.

Brexpiprazole (Rexulti) Evidence Level: **Actionable**

Increased Sensitivity to Brexpiprazole (CYP2D6 *4M/*4M XN Poor Metabolizer)

The exposure to brexpiprazole in CYP2D6 poor metabolizers is 120% higher than the exposure in CYP2D6 normal metabolizers. Because the incidence of akathisia is dose-related in patients suffering from schizophrenia or major depressive disorders, **it is recommended to prescribe half of the usual doses of brexpiprazole to CYP2D6 poor metabolizers.** Careful titration is recommended until a favorable response is achieved.

Adjunctive Treatment of Major Depression Disorder: the recommended starting doses should be reduced by half (0.25 mg or 0.5 mg once daily). The daily maintenance doses and maximum recommended dose are 0.5-1 mg and 1.5 mg, respectively. Schizophrenia: the recommended starting dose is 0.5 mg once daily. The daily maintenance doses and maximum recommended dose are 1-2 mg and 2 mg, respectively.

Dose adjustments with comedications: Administer **a quarter of the usual dose** if a strong/moderate CYP3A4 inhibitor is coadministered. Double usual dose over 1 to 2 weeks if a strong CYP3A4 inducer is coadministered.

Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave) Evidence Level: **Informative**

Decreased Response to Bupropion for Smoking Cessation (ANKK1 DRD2:Taq1A A/A Altered DRD2 function)

Smoking Cessation: The patient's genotype result is associated with a positive response to nicotine replacement therapy and a lesser response to bupropion treatment.

Carvedilol (Coreg) Evidence Level: **Actionable**

Moderate Sensitivity to Carvedilol (CYP2D6 *4M/*4M XN 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) Evidence Level: **Actionable**

High Sensitivity to Celecoxib (CYP2C9 *8/*8 Poor Metabolizer)

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

Cevimeline (Evoxac) Evidence Level: **Actionable**

Increased Sensitivity to Cevimeline (CYP2D6 *4M/*4M XN Poor Metabolizer)

Cevimeline is metabolized by CYP2D6. However, the overall contribution of this enzyme in the metabolism of this drug is not well documented. Lack of CYP2D6 activity may result in higher cevimeline concentrations potentially leading to higher adverse events. There are no established dosing adjustments for CYP2D6 poor metabolizers therefore, cevimeline must be initiated cautiously and dosing may be adjusted according to the patient's response.

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Chlorpromazine (Thorazine) Evidence Level: **Informative**

Increased Sensitivity to Chlorpromazine (CYP2D6 *4M/*4M XN 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.

Chlorpropamide (Diabenese) Evidence Level: **Informative**

Possible Sensitivity to Chlorpropamide (CYP2C9 *8/*8 Poor Metabolizer)

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

Citalopram (Celexa) Evidence Level: **Informative**

Delayed Response to Citalopram (SLC6A4 S/S Low Serotonin Transporter Expression)

The genotype predicts significantly decreased serotonin transporter levels resulting in less efficient transporter function. A longer titration period may be required to achieve maximal antidepressant response. The patient may respond to citalopram more slowly (up to 12 weeks) and may experience more side effects. The patient may benefit from non-selective antidepressants.

Clomipramine (Anafranil) Evidence Level: **Actionable**

Increased Sensitivity to Clomipramine (CYP2D6 *4M/*4M XN 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.

Clozapine (Clozaril) Evidence Level: **Informative**

Possible Non-Response to Clozapine (CYP1A2 *1A/*1C Normal Metabolizer- Possible Inducibility)

Smokers may be at 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 may 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) Evidence Level: **Actionable**

Non-Response to Codeine (CYP2D6 *4M/*4M XN 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.

Darifenacin (Enablex) Evidence Level: **Actionable**

Possible Sensitivity to Darifenacin (CYP2D6 *4M/*4M XN 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.

Desipramine (Norpramin) Evidence Level: **Actionable**

Increased Sensitivity to Desipramine (CYP2D6 *4M/*4M XN 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.

Deutetrabenazine (Austedo) Evidence Level: **Actionable**

Increased Sensitivity to Deutetrabenazine (CYP2D6 *4M/*4M XN Poor Metabolizer)

For treating chorea associated with Huntington's disease: The exposure to deutetrabenazine active metabolites alpha- and and beta-dihydrotetrabenazine is expected to be increased in CYP2D6 poor metabolizers (approximately 3-fold compared to CYP2D6 normal metabolizers) and clinically relevant QT prolongation might be expected in some patients at highest therapeutic doses. Therefore, the maximum recommended dosage of deutetrabenazine in CYP2D6 poor metabolizers is 36 mg per day. Individualization of dose with careful weekly titration is required. The first week's starting dose is 6 mg once daily then this dose should be slowly titrated at weekly intervals by 6 mg per day based on tolerability and up to a maximum recommended daily dosage of 36 mg (18 mg twice daily).

Dexmethylphenidate (Focalin) Evidence Level: **Informative**

Poor Response to Dexmethylphenidate (COMT Val158Met A/A Low COMT Activity)

The patient's genotype result predicts a reduced therapeutic response to dexmethylphenidate. Dosage should be individualized according to the needs and response of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

Dexmethylphenidate (Focalin) Evidence Level: **Informative**

Unfavorable Response to Dexmethylphenidate (ADRA2A C-1291G C/C Homozygous for C Allele)

The patient carries two C alleles of the ADRA2A –1291 C>G polymorphism. Preliminary studies suggest that this genotype may be associated with an unfavorable response to dexmethylphenidate in children and adolescents with the attention-deficit and hyperactivity disorder of inattentive type.

Dextroamphetamine (Dexedrine) Evidence Level: **Informative**

Poor Response to Dextroamphetamine (COMT Val158Met A/A Low COMT Activity)

The patient's genotype result predicts a reduced therapeutic response to amphetamine stimulants. If prescribed, dextroamphetamine should be administered at the lowest effective dose, and dosage should be individually adjusted.

Dextroamphetamine (Dexedrine) Evidence Level: **Informative**

Possible Increased Exposure to Dextroamphetamine (CYP2D6 *4M/*4M XN Poor Metabolizer)

There is little evidence documenting the exposure of dextroamphetamine in subjects with reduced CYP2D6 activity such as CYP2D6 poor metabolizers. Although the drug's plasma concentrations may be elevated in these subjects, the clinical relevance of this change is not well documented. Consider initiating therapy with lower doses and monitor the patient more frequently during drug titration. Consider adjusting the dose based on clinical response and tolerability. An alternative therapy may also be considered in patients with decreased tolerability.

Dextromethorphan / Quinidine (Nuedexta) Evidence Level: **Actionable**

Altered Sensitivity to Dextromethorphan-Quinidine (CYP2D6 *4M/*4M XN Poor Metabolizer)

Patients with Pseudobulbar Affect: the quinidine component of dextromethorphan-quinidine is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone. Quinidine does not further inhibit CYP2D6 metabolism in poor metabolizers (PMs) and this component may expose PMs to an unnecessary risk since quinidine is not adding any benefit. Prescribers should consider the potential risk for quinidine-related adverse events relative to the benefit of administering the dextromethorphan-quinidine combination product (vs. dextromethorphan alone) in known CYP2D6 poor metabolizers.

Diclofenac (Voltaren) Evidence Level: **Informative**

Possible Sensitivity to Diclofenac (CYP2C9 *8/*8 Poor 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 poor 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) Evidence Level: **Informative**

Possible Altered Response to Donepezil (CYP2D6 *4M/*4M XN 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.

Doxepin (Silenor) Evidence Level: **Actionable**

Increased Sensitivity to Doxepin (CYP2D6 *4M/*4M XN Poor Metabolizer)

Consider an alternative drug or reduce doxepin starting dose by 50%. Adjust maintenance dose according to nordoxepin plasma concentrations.

Dronabinol (Marinol) Evidence Level: **Informative**

Possible Sensitivity to Dronabinol (CYP2C9 *8/*8 Poor Metabolizer)

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

Duloxetine (Cymbalta) Evidence Level: **Informative**

Possible Sensitivity to Duloxetine (CYP2D6 *4M/*4M XN 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.

Eliglustat (Cerdelga) Evidence Level: **Actionable**

Increased Sensitivity to Eliglustat (CYP2D6 *4M/*4M XN Poor Metabolizer)

Eliglustat plasma concentrations are expected to be high in CYP2D6 poor metabolizers, which may increase the risk of dose-dependent adverse events. Consider prescribing eliglustat at half the recommended dose: 84 mg orally once daily. Appropriate adverse events monitoring is recommended.

Dose adjustments with comedications: Co-administration of eliglustat with drugs that inhibit CYP2D6 and CYP3A may significantly increase the exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac interval, which could result in cardiac arrhythmias. Eliglustat is not recommended if a moderate/weak CYP3A inhibitor is co-administered. Eliglustat is contraindicated if a strong CYP3A inhibitor is co-administered or a strong/moderate CYP2D6 inhibitor AND a strong CYP3A inhibitor are co-administered.

Escitalopram (Lexapro) Evidence Level: **Informative**

Delayed Response to Escitalopram (SLC6A4 S/S Low Serotonin Transporter Expression)

The genotype predicts significantly decreased serotonin transporter levels resulting in less efficient transporter function. A longer titration period may be required to achieve maximal antidepressant response. The patient may respond to escitalopram more slowly (up to 12 weeks) and may experience more side effects. The patient may benefit from non-selective antidepressants.

Fentanyl (Actiq) Evidence Level: **Informative**

Altered Response to Fentanyl (OPRM1 A118G G/G Altered OPRM1 Function)

The results show that the patient carries two copies of the OPRM1 118A>G mutation. Acute postoperative and cancer pain: the patient's genotype has been shown to be associated with reduced analgesia at standard fentanyl doses. Therefore, the patient may require higher doses of this drug. Because fentanyl has a narrow therapeutic window, it is advised to carefully titrate this drug to a tolerable dose that provides adequate analgesia with minimal side effects.

Flecainide (Tambocor) Evidence Level: **Actionable**

Significantly Increased Sensitivity to Flecainide (CYP2D6 *4M/*4M XN 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) Evidence Level: **Informative**

Increased Sensitivity to Fluphenazine (CYP2D6 *4M/*4M XN 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) Evidence Level: **Actionable**

Increased Sensitivity to Flurbiprofen (CYP2C9 *8/*8 Poor Metabolizer)

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

Fluvastatin (Lescol) Evidence Level: **Actionable**

Increased Sensitivity to Fluvastatin (CYP2C9 *8/*8 Poor 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) Evidence Level: **Informative**

Delayed Response to Fluvoxamine (SLC6A4 S/S Low Serotonin Transporter Expression)

The genotype predicts significantly decreased serotonin transporter levels resulting in less efficient transporter function. A longer titration period may be required to achieve maximal antidepressant response. The patient may respond to fluvoxamine more slowly (up to 12 weeks) and may experience more side effects. The patient may benefit from non-selective antidepressants.

Fluvoxamine (Luvox) Evidence Level: **Informative**

Increased Sensitivity to Fluvoxamine (CYP2D6 *4M/*4M XN Poor Metabolizer)

At standard label-recommended dosage, fluvoxamine levels are expected to be high and adverse events may occur. Consider a 25-50% reduction of recommended starting dose to help prevent concentration-dependent adverse events and titrate based on the clinical response and tolerability. An alternative medication may also be considered.

Fosphenytoin (Cerebyx) Evidence Level: **Actionable**

High Sensitivity to Fosphenytoin (CYP2C9 *8/*8 Poor Metabolizer)

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

Galantamine (Razadyne) Evidence Level: **Informative**

Possible Sensitivity to Galantamine (CYP2D6 *4M/*4M XN 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.

Gefitinib (Iressa) Evidence Level: **Actionable**

Possible Increased Exposure to Gefitinib (CYP2D6 *4M/*4M XN Poor Metabolizer)

Gefitinib undergoes extensive hepatic metabolism in humans by CYP3A4 and CYP2D6. CYP2D6 metabolizes gefitinib to its major active metabolite, O--desmethyl gefitinib. CYP2D6 poor metabolizers may have a higher exposure to gefitinib compared to normal metabolizers. Gefitinib can be prescribed at label-recommended dosage and administration. The patient should be closely monitored for adverse events related to higher exposure of gefitinib.

Glimepiride (Amaryl) Evidence Level: **Actionable**

Possible Sensitivity to Glimepiride (CYP2C9 *8/*8 Poor Metabolizer)

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

Glipizide (Glucotrol) Evidence Level: **Informative**

Possible Sensitivity to Glipizide (CYP2C9 *8/*8 Poor Metabolizer)

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

Glyburide (Micronase) Evidence Level: **Actionable**

Possible Sensitivity to Glyburide (CYP2C9 *8/*8 Poor Metabolizer)

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

Granisetron (Sancuso, Sustol) Evidence Level: **Informative**

Unfavorable Response to Standard Granisetron Dosing (ABCB1 3435C>T C/C Variant Allele Not Present)

The genotype result predicts that the patient has high ABCB1 transporter expression. An increased risk of vomiting has been reported in patients with high ABCB1 transporter expression when taking standard doses of granisetron. Monitor for decreased response.

Haloperidol (Haldol) Evidence Level: **Actionable**

Increased Sensitivity to Haloperidol (CYP2D6 *4M/*4M XN 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.

Hydrocodone (Vicodin) Evidence Level: **Informative**

Possible Altered Response to Hydrocodone (CYP2D6 *4M/*4M XN 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).

Hydrocodone (Vicodin) Evidence Level: **Informative**

Altered Response to Hydrocodone (OPRM1 A118G G/G Altered OPRM1 Function)

The patient carries two copies of the OPRM1 118A>G mutation. Acute postoperative and cancer pain: the patient's genotype has been shown to be associated with reduced analgesia and increased opioid side effects at standard or high hydrocodone doses. If the patient fails to respond to increased hydrocodone doses, an alternative opioid may be considered.

Ibuprofen (Advil, Motrin) Evidence Level: **Informative**

Possible Sensitivity to Ibuprofen (CYP2C9 *8/*8 Poor Metabolizer)

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

Shareef Nahas, Ph.D., FACMG, Laboratory Director • CLIA# 11D2071408
333 Research Ct • Ste 200 • Peachtree Corners, GA 30092
t 678.250.9222 • tf 1.888.250.6228 • f 770.545.8592 •
stoneclinicallaboratories.com

Iloperidone (Fanapt) Evidence Level: **Actionable**

Increased Sensitivity to Iloperidone (CYP2D6 *4M/*4M XN 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.

Imipramine (Tofranil) Evidence Level: **Actionable**

Increased Sensitivity to Imipramine (CYP2D6 *4M/*4M XN 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.

Indomethacin (Indocin) Evidence Level: **Informative**

Possible Sensitivity to Indomethacin (CYP2C9 *8/*8 Poor Metabolizer)

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

Lesinurad (Zurampic) Evidence Level: **Actionable**

Possible Sensitivity to Lesinurad (CYP2C9 *8/*8 Poor Metabolizer)

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

Lisdexamfetamine (Vyvanse) Evidence Level: **Informative**

Poor Response to Lisdexamfetamine (COMT Val158Met A/A Low COMT Activity)

The patient's genotype result predicts a reduced therapeutic response to amphetamine stimulants. If prescribed, lisdexamfetamine should be administered at the lowest effective dose, and dosage should be individually adjusted.

Lisdexamfetamine (Vyvanse) Evidence Level: **Informative**

Possible Increased Exposure to Lisdexamfetamine Active Metabolite (CYP2D6 *4M/*4M XN Poor Metabolizer)

There is little evidence documenting the exposure of lisdexamfetamine and its active metabolite dextroamphetamine in subjects with reduced CYP2D6 activity such as CYP2D6 poor metabolizers. Although dextroamphetamine plasma concentrations may be elevated in these subjects, the clinical relevance of this change is not well documented. Consider initiating therapy with lower doses and monitor the patient more frequently during drug titration. Consider adjusting the dose based on clinical response and tolerability. An alternative therapy may also be considered in patients with decreased tolerability.

Losartan (Cozaar, Hyzaar) Evidence Level: **Informative**

Possible Decreased Response to Losartan (CYP2C9 *8/*8 Poor Metabolizer)

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

Lovastatin (Mevacor, Altoprev, Advicor) Evidence Level: **Informative**

Increased Myopathy Risk (SLCO1B1 521T>C C/C Poor Function)

The reduced SLCO1B1 function may result in elevated lovastatin acid plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high lovastatin doses in this patient should be avoided. If lovastatin 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.

Shareef Nahas, Ph.D., FACMG, Laboratory Director • CLIA# 11D2071408
333 Research Ct • Ste 200 • Peachtree Corners, GA 30092
t 678.250.9222 • tf 1.888.250.6228 • f 770.545.8592 •
stoneclinicallaboratories.com

Maprotiline (Ludiomil) Evidence Level: **Informative**

Increased Sensitivity to Maprotiline (CYP2D6 *4M/*4M XN 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) Evidence Level: **Informative**

Increased sensitivity to Meloxicam (CYP2C9 *8/*8 Poor Metabolizer)

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

Methotrexate (Trexall) Evidence Level: **Informative**

Increased risk for methotrexate toxicity (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.

Methylphenidate (Ritalin, Aptensio XR, Concerta, Metadate ER, Quillivant ER) Evidence Level: **Informative**

Poor Response to Methylphenidate (COMT Val158Met A/A Low COMT Activity)

The patient's genotype result predicts a reduced therapeutic response to methylphenidate. Dosage should be individualized according to the needs and response of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

Methylphenidate (Ritalin, Aptensio XR, Concerta, Metadate ER, Quillivant ER) Evidence Level: **Informative**

Unfavorable Response to Methylphenidate (ADRA2A C-1291G C/C Homozygous for C Allele)

The patient carries two C alleles of the ADRA2A –1291 C>G polymorphism. Preliminary studies suggest that this genotype may be associated with an unfavorable response to methylphenidate in children and adolescents with the attention-deficit and hyperactivity disorder of inattentive type.

Metoclopramide (Reglan) Evidence Level: **Informative**

Increased Sensitivity to Metoclopramide (CYP2D6 *4M/*4M XN 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 is recommended. Patients with renal disease are at increased risk of CNS adverse events.

Metoprolol (Lopressor) Evidence Level: **Actionable**

Significantly Increased Sensitivity to Metoprolol (CYP2D6 *4M/*4M XN 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).

Shareef Nahas, Ph.D., FACMG, Laboratory Director • CLIA# 11D2071408
333 Research Ct • Ste 200 • Peachtree Corners, GA 30092
t 678.250.9222 • tf 1.888.250.6228 • f 770.545.8592 •
stoneclinicallaboratories.com

Mexiletine (Mexitil) Evidence Level: **Actionable**

Significantly Increased Sensitivity to Mexiletine (CYP2D6 *4M/*4M XN 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.

Morphine (MS Contin) Evidence Level: **Informative**

Altered Response to Morphine (COMT Val158Met A/A Low COMT Activity)

The patient carries two COMT Val158Met mutations, which translates to a reduced COMT function. The patient may require lower 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.

Morphine (MS Contin) Evidence Level: **Informative**

Altered Response to Morphine (OPRM1 A118G G/G Altered OPRM1 Function)

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

Nateglinide (Starlix) Evidence Level: **Informative**

Possible Sensitivity to Nateglinide (CYP2C9 *8/*8 Poor Metabolizer)

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

Nefazodone (Serzone) Evidence Level: **Informative**

Possible Sensitivity to Nefazodone (CYP2D6 *4M/*4M XN 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.

Nortriptyline (Pamelor) Evidence Level: **Actionable**

Increased Sensitivity to Nortriptyline (CYP2D6 *4M/*4M XN 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.

Olanzapine (Zyprexa) Evidence Level: **Informative**

Possible Non-Response to Olanzapine (CYP1A2 *1A/*1C Normal Metabolizer- Possible Inducibility)

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, Zuplenz) Evidence Level: **Informative**

Lack of Benefit from Ondansetron Treatment in Early Onset Alcoholism (SLC6A4 S/S Low Serotonin Transporter Expression)

Ondansetron has been shown to be effective in inhibiting heavy drinking behaviors in patients with early onset alcoholism. This patient carries two short or S alleles of SLC6A4 5-HTTLPR variant. Preliminary studies demonstrate that use of ondansetron may not benefit patients with this genotype. The abstinence rates from alcohol and the number of drinks per drinking day were not significantly different between patients treated with placebo or ondansetron.

Ondansetron (Zofran, Zuplenz) Evidence Level: **Informative**

Unfavorable Response to Standard Ondansetron Dosing (ABCB1 3435C>T C/C Variant Allele Not Present)

The genotype result predicts that the patient has high ABCB1 transporter expression. An increased risk of vomiting has been reported in patients with high ABCB1 transporter expression when taking standard doses of ondansetron. Monitor for decreased response.

Oxycodone (Percocet, Oxycontin) Evidence Level: **Actionable**

Possible Altered Response to Oxycodone (CYP2D6 *4M/*4M XN 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) Evidence Level: **Informative**

Increased Sensitivity to Paroxetine (CYP2D6 *4M/*4M XN Poor Metabolizer)

At standard label-recommended dosage, paroxetine levels are expected to be high, and adverse events may occur. Consider an alternative medication. If paroxetine is warranted, consider a 50% decrease of the initial dose and titrate based on the clinical response and tolerability. Some studies show that compared to normal metabolizers, poor metabolizers may experience more sexual dysfunction.

Perphenazine (Trilafon) Evidence Level: **Actionable**

Increased Sensitivity to Perphenazine (CYP2D6 *4M/*4M XN 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) Evidence Level: **Actionable**

High Sensitivity to Phenytoin (CYP2C9 *8/*8 Poor Metabolizer)

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

Pimozide (Orap) Evidence Level: **Actionable**

Increased Sensitivity to Pimozide (CYP2D6 *4M/*4M XN 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) Evidence Level: **Informative**

Increased Sensitivity to Piroxicam (CYP2C9 *8/*8 Poor Metabolizer)

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

Pitavastatin (Livalo) Evidence Level: **Informative**

Increased Myopathy Risk (SLCO1B1 521T>C C/C Poor Function)

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) Evidence Level: **Informative**

Increased Myopathy Risk (SLCO1B1 521T>C C/C Poor Function)

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) Evidence Level: **Actionable**

Increased Sensitivity to Propafenone (CYP2D6 *4M/*4M XN Poor Metabolizer)

Consider reducing propafenone initial dose, and monitor ECG and plasma concentrations. Compared to normal metabolizers, poor metabolizers may require a 70% dose reduction of the initial dose.

Dose adjustments with comedications: increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated beta-adrenergic blocking activity. Concurrent use of propafenone along with CYP3A4 inhibitors and CYP2D6 inhibitors may significantly increase the plasma concentration of propafenone and thereby increase the risk of proarrhythmia and other adverse events. Therefore, avoid simultaneous use of propafenone with a CYP3A4 inhibitor.

Protriptyline (Vivactil) Evidence Level: **Informative**

Increased Sensitivity to Protriptyline (CYP2D6 *4M/*4M XN 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.

Ranolazine (Ranexa) Evidence Level: **Actionable**

Increased Sensitivity to Ranolazine (CYP2D6 *4M/*4M XN 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.

Repaglinide (Prandin, Prandimet) Evidence Level: **Informative**

Possible Sensitivity to Repaglinide (SLCO1B1 521T>C C/C Poor Function)

The patient carries two copies of the SLCO1B1 rs4149056 C allele, which is associated with reduced transporter function. Patients homozygous for the SLCO1B1 rs4149056 C allele are probably more susceptible to the blood glucose-lowering effect of repaglinide than those with other genotypes. Based on preliminary findings, the optimal starting dose of repaglinide may be lower in these patients. Selecting a lower starting dose may reduce the time needed to reach the correct maintenance dose, potentially with a smaller risk of hypoglycaemia. Repaglinide dose should be adjusted according to the actual blood glucose-lowering response.

Risperidone (Risperdal) Evidence Level: **Actionable**

Significantly Increased Sensitivity to Risperidone (CYP2D6 *4M/*4M XN 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.

Rosuvastatin (Crestor) Evidence Level: **Informative**

Increased Myopathy Risk (SLCO1B1 521T>C C/C)

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) Evidence Level: **Actionable**

High Myopathy Risk (SLCO1B1 521T>C C/C Poor Function)

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.

Tacrolimus (Prograf) Evidence Level: **Actionable**

Insufficient Response to Tacrolimus (CYP3A5 *1/*1 Normal 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.

Tamsulosin (Flomax) Evidence Level: **Actionable**

Increased Sensitivity to Tamsulosin (CYP2D6 *4M/*4M XN 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) Evidence Level: **Actionable**

Increased Sensitivity to Tetrabenazine (CYP2D6 *4M/*4M XN Poor Metabolizer)

For treating chorea associated with Huntington's disease: Individualization of dose with careful weekly titration is required. The first week's starting dose is 12.5 mg daily; second week, 25 mg (12.5 mg twice daily); then slowly titrate at weekly intervals by 12.5 mg to a tolerated dose. **The maximum daily dose in CYP2D6 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.

Thioridazine (Mellaril) Evidence Level: **Actionable**

Increased Sensitivity to Thioridazine (CYP2D6 *4M/*4M XN 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.

Timolol (Timoptic) Evidence Level: **Actionable**

Increased Sensitivity to Timolol (CYP2D6 *4M/*4M XN 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.

Tizanidine (Zanaflex) Evidence Level: **Informative**

Possible Non-Response to Tizanidine (CYP1A2 *1A/*1C Normal Metabolizer- Possible Inducibility)

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

Tolbutamide (Orinase) Evidence Level: **Actionable**

Possible Sensitivity to Tolbutamide (CYP2C9 *8/*8 Poor Metabolizer)

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

Tolterodine (Detrol) Evidence Level: **Informative**

Possible Sensitivity to Tolterodine (CYP2D6 *4M/*4M XN 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.

Torsemide (Demadex) Evidence Level: **Informative**

Possible Sensitivity to Torsemide (CYP2C9 *8/*8 Poor Metabolizer)

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

Tramadol (Ultram) Evidence Level: **Actionable**

Non-Response to Tramadol (CYP2D6 *4M/*4M XN 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) Evidence Level: **Actionable**

Increased Sensitivity to Trimipramine (CYP2D6 *4M/*4M XN 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.

Shareef Nahas, Ph.D., FACMG, Laboratory Director • CLIA# 11D2071408
333 Research Ct • Ste 200 • Peachtree Corners, GA 30092
t 678.250.9222 • tf 1.888.250.6228 • f 770.545.8592 •
stoneclinicallaboratories.com

Valbenazine (Ingrezza) Evidence Level: **Actionable**

Increased Sensitivity to Valbenazine (CYP2D6 *4M/*4M XN Poor Metabolizer)

The initial dose is 40 mg once daily. Based on tolerability, this dose may be maintained in CYP2D6 poor metabolizers to reduce the risk of exposure-related adverse events. Valbenazine may prolong the QT interval. The exposure to valbenazine and its major active metabolite in CYP2D6 poor metabolizers is significantly higher than the exposure in CYP2D6 normal metabolizers. Because the drug's QTc prolongation effect is concentration-dependent, it is appropriate to consider a reduced recommended dose based on the patient's tolerability. Other exposure-related adverse events include somnolence. Careful titration is recommended until a favorable response is achieved.

Dose adjustments with comedications: reduce the daily recommended dose to 40 mg if a strong CYP3A4 inhibitor is coadministered. Concomitant use with CYP3A4 inducers should be avoided.

Venlafaxine (Effexor) Evidence Level: **Actionable**

Significantly Increased Sensitivity to Venlafaxine (CYP2D6 *4M/*4M XN 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.

Vortioxetine (Trintellix) Evidence Level: **Actionable**

Increased Sensitivity to Vortioxetine (CYP2D6 *4M/*4M XN 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) Evidence Level: **Actionable**

Very High Sensitivity to Warfarin (CYP2C9 *8/*8 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.

STONE CLINICAL LABORATORIES

Shareef Nahas, Ph.D., FACMG, Laboratory Director • CLIA# 11D2071408

333 Research Ct • Ste 200 • Peachtree Corners, GA 30092

t 678.250.9222 • tf 1.888.250.6228 • f 770.545.8592 •

stoneclinicallaboratories.com

Test Details for: Johnny Doe

Gene	Genotype	Phenotype	Alleles Tested
ABCB1	2677G>A G/G	Variant Allele Not Present	3435C>T, 2677G>A, 2677G>T
ABCB1	2677G>T G/G	Variant Allele Not Present	3435C>T, 2677G>A, 2677G>T
ABCB1	3435C>T C/C	Variant Allele Not Present	3435C>T, 2677G>A, 2677G>T
ADRA2A	C-1291G C/C	Homozygous for C Allele	C-1291G
ANKK1/DRD2	DRD2:Taq1A A/A	Altered DRD2 function	DRD2:Taq1A
Apolipoprotein E	ε2/ε2	Altered APOE function	ε2, ε4
COMT	Val158Met A/A	Low COMT Activity	Val158Met, c.1-98A>G
CYP1A2	*1A/*1C	Normal Metabolizer- Possible Inducibility	*1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W
CYP2B6	*1/*1	Normal Metabolizer	*7, *16, *2, *3, *5, *6, *9, *18, *28
CYP2C19	*1/*1	Normal Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *17
CYP2C9	*8/*8	Poor Metabolizer	*2, *3, *5, *6, *8, *11, *27
CYP2D6	*4M/*4M XN	Poor Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *11, *12, *14A, *14B, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1/*1	Normal Metabolizer	*2, *3, *12, *17, *22
CYP3A5	*1/*1	Normal Metabolizer	*1D, *2, *3, *3C, *6, *7, *8, *9
DRD2	-241A>G T/T	Homozygous for rs1799978 T Allele	-241A>G, , rs2283265, 957C>T, 939T>C
DRD2	rs2283265 C/C	Homozygous for rs2283265 C allele	-241A>G, , rs2283265, 957C>T, 939T>C
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
OPRK1	36G>T C/C	Homozygous for G Allele (36G>T)	36G>T, rs6989250
OPRK1	rs6989250 C/C	Homozygous for rs6989250 C Allele	36G>T, rs6989250
OPRM1	A118G G/G	Altered OPRM1 Function	A118G
SLC6A4	S/S	Low Serotonin Transporter Expression	La, S, Lg
SLCO1B1	521T>C C/C	Poor Function	521T>C, 388A>G
SULT4A1	rs138060 C/C	Homozygous for C Allele	rs138097, rs138060
SULT4A1	rs138097 G/G	Homozygous for G Allele	rs138097, rs138060
UGT2B15	*1/*1	Normal Metabolizer	*2
VKORC1	-1639G>A A/A	High Warfarin Sensitivity	-1639G>A, 1173C>T

Disclaimer: Only a physician, pharmacist or other healthcare professional should advise a patient on the use of information in this report.

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

Limitations: This test will not detect all the known mutations that result in altered or inactive tested genes. Absence of a detectable gene mutation or polymorphism does not rule out the possibility that a patient has intermediate or high sensitivity phenotypes due to the presence of an undetected polymorphism or due to drug-drug interactions.

Laboratory Certification: CLIA #11D2071408