Mehdi Dehghani, Ph.D, DABCC Laboratory Director • CLIA# 11D2071408, 45D2138167
333 Research Ct • Ste 200 • Peachtree Corners, GA 30092
t 678.250.9222 • tf 1.888.250.6228 • f 770.545.8592 • AlphaGenomix.com

Alpha Genomix Comprehensive Extended Created for: John Doe Jr.

Patient:	John Doe Jr.	DOB:	1/1/1900
Accession #:	12345678910	Gender:	
Collection Date:	8/27/2019	Received Date:	8/28/2019
Ordered By:	Alpha Genomix	Report Generated:	8/30/2019
Referred By:	Kevin Rosenblatt, MD, PhD		
Comments:			

Current Patient Medications

Current Medication List: Oxycodone, Warfarin, Gabapentin, Ibuprofen, Simvastatin, Morphine, Lorazepam

Medications Affected by Patient Genetic Results

✓ **Gabapentin (Neurontin®)**

Normal Response to Gabapentin — Evidence Level: **Informative**

Pharmacogenetic guidance: no genetically guided drug selection or dosing recommendations are available.
Polypharmacy guidance: Gabapentin is eliminated primarily through renal excretion and is not metabolized by CYPs. Genetic variations in these metabolizing enzymes are not expected to affect its efficacy or toxicity profiles. Gabapentin can be prescribed at standard label-recommended dosage and administration.

✓ **Ibuprofen (Advil®, Motrin®)**

Normal Sensitivity to Ibuprofen (CYP2C9 *1/*1 Normal Metabolizer) — Evidence Level: **Informative**

Individuals with a normal CYP2C9 activity (i.e normal metabolizers) can be prescribed ibuprofen according to standard label recommended-dosage and administration.

⚠ **Lorazepam (Ativan®)**

Possible Altered Response to Lorazepam (UGT2B15 *1/*2 Intermediate Metabolizer) — Evidence Level: **Informative**

Lorazepam clearance may be reduced in this patient. However, there is insufficient evidence whether this change results in a significant clinical effect. Consider monitoring the patient for increased sedation and adjust dosing accordingly.

⚠ **Morphine (MS Contin®)**

Altered Response to Morphine (COMT Val158Met G/G High/Normal COMT Activity) — Evidence Level: **Informative**

The patient does not carry the COMT Val158Met variant. The patient may require higher doses of morphine for adequate pain control. The dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

✓ **Oxycodone (Percocet®, Oxycontin®)**

Normal Response to Oxycodone (CYP2D6 *1/*4 Normal Metabolizer) — Evidence Level: **Actionable**

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

🚩 **Simvastatin (Zocor®)**

Intermediate Myopathy Risk (SLCO1B1 521T>C T/C Decreased Function) — Evidence Level: **Actionable**

Simvastatin plasma concentrations are expected to be elevated. **Consider avoiding simvastatin**, and prescribe an alternative statin or another hypolipidemic drug, or consider prescribing simvastatin at a lower starting dose (20 mg/day). Routine creatine kinase (CK) monitoring is also advised. **The FDA recommends against the 80 mg daily dose.** Although the association between the SLCO1B1 521T>C 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 521T>C variant.

✓ **Warfarin (Coumadin®)**

Average Dosing Requirements are Expected (CYP2C9 *1/*1; VKORC1 -1639G>A G/G) Evidence Level: **Actionable**

When initiating warfarin treatment for indications with a target INR of 2-3, consider one of the following methods to estimate dosing requirements:

FDA Label: CYP2C9 and VKORC1 genotype results indicate an expected therapeutic dose of 5-7 mg/day.

Pharmacogenomics algorithms/calculators available at www.warfarindosing.org:

Caucasians and Asians: Use the patient's demographics and other clinical factors along with CYP2C9 and VKORC1 genotypes to calculate the expected therapeutic dose.

Africans and African Americans: Use the patient's demographics and other clinical factors along with CYP2C9 and VKORC1 genotypes to calculate the expected therapeutic dose.

The provided recommendations in Africans and African Americans apply only when all the following CYP2C9 alleles are tested: *5, *6, *8, *11.

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

Antipsychotic-Induced Tardive Dyskinesia

Moderate Risk of Antipsychotic-Induced Tardive Dyskinesia

The patient carries one copy of the Taq1A variant (heterozygous for the A1 allele).

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

Monitor the patient for any signs of tardive dyskinesia.

Antipsychotic-Induced Hyperprolactinemia

Moderate Risk of Antipsychotic-induced Hyperprolactinemia

The patient carries one copy of the Taq1A variant (heterozygous for the A1 allele).

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

Monitor patient closely for signs of hyperprolactinemia. An evaluation of the risk-benefit profile of the antipsychotic medication may be required.

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Antipsychotic-Induced Weight Gain

Moderate Risk of Antipsychotic-Induced Weight Gain

The patient carries one copy of the Taq1A variant (heterozygous for the A1 allele).

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

Monitor patient closely for signs of weight gain.

Type III Hyperlipoproteinemia

Not Associated with Type III Hyperlipoproteinemia

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

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

No action is needed when a patient is normolipidemic.

Hyperhomocysteinemia - Depression

No Increased Risk of Hyperhomocysteinemia

The patient carries one copy of the MTHFR c.665C>T variant (heterozygous). MTHFR enzyme activity is reduced (60% of normal activity).

Patients diagnosed with depression often have low folate levels and homocysteine is a highly sensitive marker of folate status. Functional folate deficiency is indicated by elevated homocysteine. The patient's small reduction in MTHFR activity is not a risk factor for hyperhomocysteinemia.

Patients diagnosed with depression: as lower folate levels are associated with poorer antidepressant response, and baseline levels of folate within the normal range predict antidepressant response, testing for homocysteine levels and serum folate levels may be informative for this patient before prescribing methylfolate as an antidepressant-augmenting agent.

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Thrombophilia

Increased Risk of Thrombosis

The patient carries one copy (heterozygous) of the F5 c.1601G>A variant (also known as Factor V Leiden) and does not carry the F2 c.*97G>A variant (also known as Factor II 20210G>A).

The patient's risk of thrombosis is 3 to 8 times higher than average (average risk of clotting is about 1 in 1000 for anyone in a year). Other risk factors may have additive effects on thrombotic risk, increasing it further.

Anticoagulation:
Post-VTE patients with a low or moderate bleeding risk: long-term anticoagulation may be considered with periodic reevaluation to assess risks versus benefits.
Asymptomatic individual without a history of thrombosis: a short course of prophylactic anticoagulation may be considered in high-risk settings such as surgery, pregnancy, or prolonged immobilization. Decisions regarding prophylactic anticoagulation should be based on a risk/benefit assessment.

Estrogen-containing contraceptive and hormone replacement therapy:
Women with a positive history of thrombotic events or with an additional thrombotic risk factor: consider avoiding estrogen contraception and hormone replacement therapy.
Women with no history of thrombotic events (asymptomatic): consider informing of the risk of estrogen-containing contraceptives and hormone replacement therapy use; consider alternative forms of contraception and control of menopausal symptoms. These women should avoid additional life-style risk factors (e.g., smoking or obesity, or triggering events such as surgery or travel).
Women electing to use oral contraceptives: consider avoiding third-generation formulations because of their higher thrombotic risk.
Women who require short-term hormone replacement therapy for severe menopausal symptoms: consider low-dose transdermal preparations as they may have a lower thrombotic risk.

Hyperhomocysteinemia - Thrombosis

No Increased Risk of Hyperhomocysteinemia

The patient carries one copy of MTHFR c.665C>T variant and one copy of c.1286A>C variant (compound heterozygous). MTHFR enzyme activity is reduced.

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

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

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Potentially Impacted Medications for: John Doe Jr.

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®) Tamsulosin (Flomax®) Terazosin (Hytrin®)		
Angiotensin II Receptor Antagonists	Azilsartan (Edarbi®, Edarbyclor®) Candesartan (Atacand®) Eprosartan (Teveten®) Irbesartan (Avapro®) Losartan (Cozaar®, Hyzaar®) Olmesartan (Benicar®) Telmisartan (Micardis®) Valsartan (Diovan®, Entresto®)		
Antiaddictives	Lofexidine (Lucemyra®)	Bupropion (Wellbutrin®, Zyban®, Aplenzin®, Contrave®) Naltrexone (Vivitrol®, Contrave®)	
Anti-ADHD Agents	Amphetamine (Adderall®, Evekeo®) Clonidine (Kapvay®) Dextroamphetamine (Dexedrine®) Guanfacine (Intuniv®) Lisdexamfetamine (Vyvanse®)	Atomoxetine (Strattera®) Dexmethylphenidate (Focalin®) 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®) Cannabidiol (Epidiolex®) Carbamazepine (Tegretol®, Carbatrol®, Epitol®) Eslicarbazepine (Aptiom®) Ethosuximide (Zarontin®) Ezogabine (Potiga®) Felbamate (Felbatol®) Fosphenytoin (Cerebyx®) Gabapentin (Neurontin®) Lacosamide (Vimpat®) Lamotrigine (Lamictal®) Levetiracetam (Keppra®) Oxcarbazepine (Trileptal®, Oxtellar XR®) Perampanel (Fycompa®) Phenobarbital (Luminal®) Phenytoin (Dilantin®) Pregabalin (Lyrica®) Primidone (Mysoline®) Rufinamide (Banzel®) Tiagabine (Gabitril®) Topiramate (Topamax®) Valproic Acid (Depakote®, Depakene®) Vigabatrin (Sabril®) Zonisamide (Zonegran®)		
Antidementia Agents	Donepezil (Aricept®) Galantamine (Razadyne®) Memantine (Namenda®)		
Antidepressants	Amitriptyline (Elavil®) Amoxapine (Amoxapine®) Clomipramine (Anafranil®) Desipramine (Norpramin®) Desvenlafaxine (Pristiq®) Doxepin (Silenor®) Duloxetine (Cymbalta®) Fluoxetine (Prozac®, Sarafem®) Imipramine (Tofranil®) Levomilnacipran (Fetzima®) Maprotiline (Ludiomil®) Mirtazapine (Remeron®) Nefazodone (Serzone®) Nortriptyline (Pamelor®) Paroxetine (Paxil®, Brisdelle®) Protriptyline (Vivactil®) Sertraline (Zoloft®) Trazodone (Oleptro®) Trimipramine (Surmontil®) Venlafaxine (Effexor®) Vilazodone (Viibryd®) Vortioxetine (Trintellix®)	Citalopram (Celexa®) Escitalopram (Lexapro®) Fluvoxamine (Luvox®)	

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Category	Standard Precautions	Use With Caution	Consider Alternatives
Antiemetics	Aprepitant (Emend-oral®) Dolasetron (Anzemet®) Dronabinol (Marinol®) Fosaprepitant (Emend-i.v®) Fosnetupitant-Palonosetron (Akynzeo-i.v®) Metoclopramide (Reglan®) Netupitant-Palonosetron (Akynzeo-oral®) Palonosetron (Aloxi®) Rolapitant (Varubi®)	Granisetron (Sancuso®, Sustol®) 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®)		
Anti-HIV Agents	Dolutegravir (Tivicay®, Triumeq®) Raltegravir (Isentress®, Dutrebis®)		Atazanavir (Reyataz®, Evotaz®)
Anti-Hyperuricemics and Anti-Gout Agents	Colchicine (Mitigare®) Febuxostat (Uloric®) Lesinurad (Zurampic®)		
Antimalarials	Proguanil (Malarone®)		
Antiplatelets	Clopidogrel (Plavix®) Prasugrel (Effient®) Ticagrelor (Brilinta®) Vorapaxar (Zontivity®)		

Category	Standard Precautions	Use With Caution	Consider Alternatives
Antipsychotics	Aripiprazole (Abilify®, Aristada®) Asenapine (Saphris®) Brexpiprazole (Rexulti®) Cariprazine (Vraylar®) Chlorpromazine (Thorazine®) Fluphenazine (Prolixin®) Haloperidol (Haldol®) Iloperidone (Fanapt®) Loxapine (Loxitane®, Adasuve®) Lurasidone (Latuda®) Paliperidone (Invega®) Perphenazine (Trilafon®) Pimavanserin (Nuplazid®) Pimozide (Orap®) Quetiapine (Seroquel®) Risperidone (Risperdal®) Thioridazine (Mellaril®) Thiothixene (Navane®) Trifluoperazine (Stelazine®) Ziprasidone (Geodon®)	Clozapine (Clozaril®) Olanzapine (Zyprexa®)	
Antispasmodics for Overactive Bladder	Darifenacin (Enablex®) Fesoterodine (Toviaz®) Mirabegron (Myrbetriq®) Oxybutynin (Ditropan®) Solifenacin (Vesicare®) Tolterodine (Detrol®) Trospium (Sanctura®)		
Benzodiazepines	Alprazolam (Xanax®) Clobazam (Onfi®) Clonazepam (Klonopin®) Diazepam (Valium®)	Lorazepam (Ativan®) Oxazepam (Serax®)	
Beta Blockers	Atenolol (Tenormin®) Bisoprolol (Zebeta®) Carvedilol (Coreg®) Labetalol (Normodyne®, Trandate®) Metoprolol (Lopressor®) Nebivolol (Bystolic®) Propranolol (Inderal®) Timolol (Timoptic®)		
Diuretics	Torsemide (Demadex®)		
Fibromyalgia Agents	Milnacipran (Savella®)		
Fluoropyrimidines	Capecitabine (Xeloda®) Fluorouracil (Adrucil® (iv); Carac® (topical); Efudex® (topical))		
Histone Deacetylase Inhibitors		Belinostat (Beleodaq®)	
Immunomodulators	Apremilast (Otezla®) Leflunomide (Arava®) Tofacitinib (Xeljanz®)		

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Category	Standard Precautions	Use With Caution	Consider Alternatives
Immunosuppressants	Tacrolimus (Prograf®)		
Meglitinides	Nateglinide (Starlix®) Repaglinide (Prandin®, Prandimet®)		
Muscle Relaxants	Carisoprodol (Soma®) Cyclobenzaprine (Flexeril®, Amrix®) Metaxalone (Skelaxin®) Methocarbamol (Robaxin®)	Tizanidine (Zanaflex®)	
NSAIDs	Celecoxib (Celebrex®) Diclofenac (Voltaren®) Flurbiprofen (Ansaid®) Ibuprofen (Advil®, Motrin®) Indomethacin (Indocin®) Ketoprofen (Orudis®) Ketorolac (Toradol®) Meloxicam (Mobic®) Nabumetone (Relafen®) Naproxen (Aleve®) Piroxicam (Feldene®) Sulindac (Clinoril®)		
Opioids	Alfentanil (Alfenta®) Benzhydrocodone (Apadaz®) Buprenorphine (Butrans®, Buprenex®) Codeine (Codeine; Fioricet® with Codeine) Dihydrocodeine (Synalgos-DC®) Fentanyl (Actiq®) Hydrocodone (Vicodin®) Hydromorphone (Dilaudid®, Exalgo®) Levorphanol (Levo Dromoran®) Meperidine (Demerol®) Oxycodone (Percocet®, Oxycontin®) Oxymorphone (Opana®, Numorphan®) Sufentanil (Sufenta®) Tapentadol (Nucynta®) Tramadol (Ultram®)	Methadone (Dolophine®) Morphine (MS Contin®)	
Other Neurological Agents	Deutetrabenazine (Austedo®) Dextromethorphan / Quinidine (Nuedexta®) Flibanserin (Addyi®) Valbenazine (Ingrezza®)	Tetrabenazine (Xenazine®)	
Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra®) Sildenafil (Viagra®) Tadalafil (Cialis®) Vardenafil (Levitra®)		

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Category	Standard Precautions	Use With Caution	Consider Alternatives
Protein Kinase Inhibitors	Erdafitinib (Balversa®) Gefitinib (Iressa®)	Erlotinib (Tarceva®) Nilotinib (Tasigna®) Pazopanib (Votrient®)	
Proton Pump Inhibitors	Dexlansoprazole (Dexilant®, Kapidex®) Esomeprazole (Nexium®) Lansoprazole (Prevacid®) Omeprazole (Prilosec®) Pantoprazole (Protonix®) Rabeprazole (Aciphex®)		
Statins	Fluvastatin (Lescol®)	Atorvastatin (Lipitor®) Lovastatin (Mevacor®, Altoprev®, Advicor®) Pitavastatin (Livalo®) Pravastatin (Pravachol®) Rosuvastatin (Crestor®)	Simvastatin (Zocor®)
Sulfonylureas	Chlorpropamide (Diabinese®) Glimepiride (Amaryl®) Glipizide (Glucotrol®) Glyburide (Micronase®) Tolbutamide (Orinase®)		
Topoisomerase inhibitors		Irinotecan (Camptosar®) Irinotecan liposomal (Onivyde®)	

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Dosing Guidance for: John Doe Jr.

Atazanavir (Reyataz®, Evotaz®) Evidence Level: **Actionable**

Increased Risk of Severe Hyperbilirubinemia (UGT1A1 *28/*28 Poor Metabolizer)

The genotype results predict decreased UGT1A1 activity. Inform the patient that some patients stop atazanavir because of hyperbilirubinemia or jaundice (yellowing of eyes and skin). Patients with this genotype have high possibility of developing atazanavir-associated severe hyperbilirubinemia. Consider an alternative agent, particularly where jaundice would be of concern to the patient.

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

Possible Atomoxetine Underexposure Leading to Decreased Response (CYP2D6 *1/*4 Normal Metabolizer)

The genotype result indicates that the patient is likely to have an insufficient response due to inadequate drug exposure following standard dosing. Consider the following dosing strategy:

- Initiate treatment at 40 mg/day, increase to 80 mg/day after 3 days and maintain dose.
- If after 2 weeks, optimal clinical response is not observed and adverse events are not present, consider a dose increase to 100 mg/day.
- If after 2 weeks, optimal clinical response is not observed and adverse events are not present, consider therapeutic drug monitoring 1-2 hours post dose. If the plasma concentration is less than 200 ng/ml consider a dose increase to a target of 400 ng/ml. Doses greater than 100 mg/day may be needed to achieve a targeted therapeutic concentration. (Therapeutic range: 200-1000 ng/ml).

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

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

Avatrombopag (Doptelet®) Evidence Level: **Actionable**

Increased Risk of Avatrombopag-Induced Thrombosis (F2 rs1799963 GG; F5 rs6025 CT)

The patient carries one copy (heterozygous) of the F5 c.1601G>A variant (also known as Factor V Leiden), which is a known risk factor for thromboembolism. Consider potential increased risk of thrombosis when administering this drug and monitor the patient closely for any signs of thrombosis or thromboembolism.

Belinostat (Beleodaq®) Evidence Level: **Actionable**

Increased risk for belinostat toxicity (UGT1A1 *28/*28 Poor Metabolizer)

Since UGT1A1 metabolizes up to 90% of belinostat, patients homozygous for reduced function UGT1A1 alleles may have belinostat systemic exposures greater than those seen at doses of 1000 mg/m2 which is also the maximum tolerated dose. **Therefore, consider prescribing a lower starting dose of 750 mg/m2 to minimize dose-limiting toxicities.** It is also recommended to carefully monitor the patient for increased side effects and to titrate the drug according to the patient's tolerance.

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

Decreased Response to Bupropion for Smoking Cessation (ANKK1 DRD2:Taq1A A/G 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.

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

Possibly Decreased Response to Bupropion (CYP2B6 *1/*6 Intermediate Metabolizer)

Bupropion is metabolized to its active metabolite hydroxybupropion by CYP2B6. This metabolite contributes to the therapeutic effects of bupropion when used as a smoking cessation agent or as an antidepressant. Individuals who are CYP2B6 intermediate metabolizers may or may not have lower blood levels of hydroxybupropion which may or may not result in a reduced response to bupropion treatment. Bupropion can be prescribed at standard label-recommended dosage with careful monitoring of the patient's response. Therapeutic monitoring of hydroxybupropion levels may be considered to guide dosing adjustment.

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

Delayed Response to Citalopram (SLC6A4 S/Lg 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.

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

Non-Response to Clozapine (CYP1A2 *1F/*1F Normal Metabolizer - Higher Inducibility)

Smokers have a high risk for non-response at standard doses and may require higher doses. There is an association between high clozapine doses and the risk of seizures, and therefore careful monitoring is recommended during dosing adjustment. Smoking cessation will increase plasma drug levels, leading to adverse events. Therefore, therapeutic drug monitoring accompanied by dose reduction is recommended in patients who have quit smoking.

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.

Eltrombopag (Promacta®) Evidence Level: **Actionable**

Increased Risk of Eltrombopag-Induced Thrombosis (F5 rs6025 CT Moderate Thrombosis Risk)

Venous and arterial thromboses have been reported in adult patients being treated with eltrombopag, more frequently in patients with hepatitis C and chronic liver disease. Other risk factors that can potentially increase the risk of thrombosis include but are not limited to splenectomy, immobilization, surgery, anti-phospholipid antibody syndrome and use of estrogen-containing contraceptives. The presence of the F5 c.1601G>A variant (also known as Factor V Leiden) in this patient represents an additional risk factor for thrombosis. Eltrombopag should be used with caution in this patient with closer monitoring of platelet count.

Erlotinib (Tarceva®) Evidence Level: **Actionable**

Increased Risk of Hyperbilirubinemia (UGT1A1 *28/*28 Poor Metabolizer)

The genotype results predict a severely decreased UGT1A1 activity. The patient is expected to have a decreased capacity to conjugate bilirubin which is associated with mild hyperbilirubinemia. By inhibiting further UGT1A1 enzyme activity, erlotinib contributes to the increased susceptibility to unconjugated hyperbilirubinemia in subjects with this genotype. Consider prescribing erlotinib at standard doses and with caution. Monitor closely the patient for signs of hyperbilirubinemia.

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

Delayed Response to Escitalopram (SLC6A4 S/Lg 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.

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

Delayed Response to Fluvoxamine (SLC6A4 S/Lg 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.

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

Unfavorable Response to Standard Granisetron Dosing (ABCB1 3435C>T C/T Heterozygous- Variant Allele 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.

Irinotecan (Camptosar®) Evidence Level: **Actionable**

Increased Risk of Irinotecan Toxicity (UGT1A1 *28/*28 Poor Metabolizer)

The patient carries two UGT1A1 decreased function alleles. This genotype predicts a significant decrease in UGT1A1 activity which is associated with an increased risk of irinotecan-associated hematological or gastrointestinal toxicity. **Consider reducing the initial dose by 30%**. If the patient tolerates this initial dose, the dose can be increased, based on the patient's tolerance and neutrophil count.

Irinotecan liposomal (Onivyde®) Evidence Level: **Actionable**

Increased Risk of Irinotecan Liposomal (Onivyde) Toxicity (UGT1A1 *28/*28 Poor Metabolizer)

The patient carries two decreased function alleles and has decreased UGT1A1 activity (30% of normal). The patient has an increased risk of neutropenia, diarrhea, and asthenia when treated with standard doses of irinotecan liposomal (Onivyde). Patient should be monitored closely for any of these signs. **Consider a lower starting dose of 50 mg/m2 in patients who are homozygous for UGT1A1 *28 allele (or homozygous for other decreased function alleles such as *6, *27, *37).**

Onivyde, a liposomal formulation of irinotecan, cannot substitute for other drugs containing irinotecan.

Lorazepam (Ativan®) Evidence Level: **Informative**

Possible Altered Response to Lorazepam (UGT2B15 *1/*2 Intermediate Metabolizer)

Lorazepam clearance may be reduced in this patient. However, there is insufficient evidence whether this change results in a significant clinical effect. Consider monitoring the patient for increased sedation and adjust dosing accordingly.

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

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

Lusutrombopag (Mulpleta®) Evidence Level: **Actionable**

Increased Risk of Lusutrombopag-Induced Thrombosis (F2 rs1799963 GG; F5 rs6025 CT)

The patient carries one copy (heterozygous) of the F5 c.1601G>A variant (also known as Factor V Leiden), which is a known risk factor for thromboembolism. Consider potential increased risk of thrombosis when administering this drug and monitor the patient closely for any signs of thrombosis or thromboembolism.

Methadone (Dolophine®) Evidence Level: **Informative**

Possible Sensitivity to Methadone (CYP2B6 *1/*6 Intermediate Metabolizer)

Based on currently available evidence, S-methadone plasma concentrations may increase, resulting in higher risk of cardiac arrhythmias and QTc prolongation. Consider lower starting doses of methadone, and adjust dosing based on the clinical response.

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

Increased Risk for Methotrexate Toxicity (MTHFR c.665C>T GA Reduced MTHFR Activity)

The patient carries one copy of the MTHFR c.665C>T variant resulting in a reduced MTHFR activity. **Malignancy:** Leukemia or lymphoma patients who are treated with methotrexate standard regimens might have an increased likelihood of treatment interruptions due to methotrexate toxicity. Monitor the 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. **Nonmalignant conditions:** a limited number of studies found an association between individuals carrying the MTHFR c.665C>T variant 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**

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.

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

Altered Response to Morphine (COMT Val158Met G/G High/Normal COMT Activity)

The patient does not carry the COMT Val158Met variant. The patient may require higher doses of morphine for adequate pain control. The dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

Naltrexone (Vivitrol®, Contrave®) Evidence Level: **Informative**

Altered Response to Naltrexone (OPRM1 A118G A/A Normal OPRM1 Function)

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

Nilotinib (Tasigna®) Evidence Level: **Actionable**

Increased risk of hyperbilirubinemia (UGT1A1 *28/*28 Poor Metabolizer)

Carriers of UGT1A1 alleles that reduce enzyme activity are expected to have a decreased capacity to conjugate bilirubin which is associated with mild hyperbilirubinemia. By inhibiting further UGT1A1 enzyme activity, nilotinib contributes to the increased susceptibility to unconjugated hyperbilirubinemia in subjects carrying reduced UGT1A1 function alleles. Monitor serum liver tests (ALT, AST, and bilirubin) more carefully. Nilotinib dose can be adjusted based on bilirubin levels.

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

Non-Response to Olanzapine (CYP1A2 *1F/*1F Normal Metabolizer - Higher 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**

Unfavorable Response to Standard Ondansetron Dosing (ABCB1 3435C>T C/T Heterozygous- Variant Allele 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.

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

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

Ondansetron has been shown to be effective in inhibiting heavy drinking behaviors in patients with early onset alcoholism. The patient carries one Lg and one S allele of SLC6A4 5HTTLPR 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.

Oxazepam (Serax®) Evidence Level: **Informative**

Possible Altered Response to Oxazepam (UGT2B15 *1/*2 Intermediate Metabolizer)

Oxazepam clearance may be reduced in this patient. However, there is insufficient evidence whether this change results in a significant clinical effect. Consider monitoring the patient for increased sedation and adjust dosing accordingly.

Pazopanib (Votrient®) Evidence Level: **Actionable**

Increased risk of hyperbilirubinemia (UGT1A1 *28/*28 Poor Metabolizer)

Carriers of UGT1A1 alleles that reduce enzyme activity are expected to have a decreased capacity to conjugate bilirubin which is associated with mild hyperbilirubinemia. By inhibiting further UGT1A1 enzyme activity, pazopanib contributes to the increased susceptibility to unconjugated hyperbilirubinemia in subjects carrying reduced UGT1A1 function alleles. Monitor serum liver tests (ALT, AST, and bilirubin) more carefully. Dose can be adjusted based on bilirubin levels.

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

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

Propofol (Diprivan®) Evidence Level: **Informative**

Possible Altered Propofol Response (CYP2B6 *1/*6 Intermediate Metabolizer)

Preliminary studies indicate that the patient's genotype may be associated with higher propofol exposure at standard dosing. This CYP2B6 genotype along with other factors such as old age (>65 years) and associated comorbidities may contribute to delayed emergence from anesthesia. There is insufficient data to allow calculation of dose adjustment; careful monitoring during post-surgery is recommended. The dosing regimen needs to be individualized for each patient, considering the patient's prior propofol dose requirements, age and comorbidities.

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

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

Intermediate Myopathy Risk (SLCO1B1 521T>C T/C Decreased 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 521T>C 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 521T>C variant.

Tamoxifen (Nolvadex®, Soltamox®) Evidence Level: **Informative**

Decreased Response to Tamoxifen (CYP2D6 *1/*4 Normal Metabolizer)

Adjuvant treatment of estrogen receptor-positive breast cancer: based on the CYP2D6 genotype results, this patient is expected to have low endoxifen (active metabolite of tamoxifen) concentrations. This is associated with a reduced response to this drug and poor treatment outcomes.

Consider alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or an aromatase inhibitor along with ovarian function suppression in premenopausal women.

If aromatase inhibitors are contraindicated, a higher FDA approved dose of tamoxifen (40 mg/day) can be considered, although a higher dose increases but does not normalize endoxifen concentrations. Consider avoiding the co-administration of this drug with strong, moderate or weak CYP2D6 inhibitors. An increased risk of thromboembolic events is associated with tamoxifen therapy. The risks and benefits of this drug should be carefully considered in women with a history of thromboembolic events or with other coexisting risk factors for thrombosis.

Tetrabenazine (Xenazine®) Evidence Level: **Actionable**

Normal Sensitivity to Tetrabenazine (CYP2D6 *1/*4 Normal 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 normal metabolizers is 100 mg, with a maximum single dose of 37.5 mg**. If serious adverse events occur, titration should be stopped and the dose of tetrabenazine should be reduced. If the adverse event(s) do not resolve, consider withdrawal of tetrabenazine.

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

Possible Non-Response to Tizanidine (CYP1A2 *1F/*1F Normal Metabolizer - Higher 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.

Mehdi Dehghani, Ph.D, DABCC Laboratory Director • CLIA# 11D2071408, 45D2138167
333 Research Ct • Ste 200 • Peachtree Corners, GA 30092
t 678.250.9222 • tf 1.888.250.6228 • f 770.545.8592 • AlphaGenomix.com

Test Details for: John Doe Jr.

Gene	Genotype	Phenotype	Alleles Tested
ABCB1	2677G>A indeterminate	Unknown phenotype	3435C>T, 2677G>A, 2677G>T
ABCB1	2677G>T G/T	Heterozygous- Variant Allele Present	3435C>T, 2677G>A, 2677G>T
ABCB1	3435C>T C/T	Heterozygous- Variant Allele Present	3435C>T, 2677G>A, 2677G>T
ADRA2A	C-1291G C/C	Homozygous for C Allele	C-1291G
ANKK1/DRD2	DRD2:Taq1A A/G	Altered DRD2 function	DRD2:Taq1A
Apolipoprotein E	ε3/ε3	Normal APOE function	ε2, ε4
COMT	Val158Met G/G	High/Normal COMT Activity	Val158Met
CYP1A2	*1F/*1F	Normal Metabolizer - Higher Inducibility	*1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W
CYP2B6	*1/*6	Intermediate Metabolizer	*16, *18, *2, *28, *3, *5, *6, *7, *9
CYP2C19	*1/*1	Normal Metabolizer	*10, *17, *2, *3, *4, *4B, *5, *6, *7, *8, *9
CYP2C9	*1/*1	Normal Metabolizer	*11, *2, *27, *3, *5, *6, *8
CYP2D6	*1/*4	Normal Metabolizer	*10, *11, *12, *14A, *14B, *17, *2, *29, *3, *35, *4, *41, *4M, *56A, *56B, *6, *7, *8, *9, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1/*1	Normal Metabolizer	*12, *17, *2, *22, *3
CYP3A5	*3/*3	Poor Metabolizer	*1D, *3, *3C, *6, *7
DPYD	*1/*9A	Normal Metabolizer	85T>C, 2657G>A, 1905+1G>A, 1679T>G, 2846A>T
DRD2	-241A>G T/T	Homozygous for rs1799978 T allele	-241A>G, rs2283265
DRD2	rs2283265 C/A	Heterozygous for rs2283265 A allele	-241A>G, rs2283265
Factor II	rs1799963 GG	Normal Thrombosis Risk	rs1799963
Factor V Leiden	rs6025 CT	Moderate Thrombosis Risk	rs6025
MTHFR	c.1286A>C GT	Reduced MTHFR Activity	c.1286A>C
MTHFR	c.665C>T GA	Reduced MTHFR Activity	c.665C>T
OPRK1	rs6473797 C/T	Heterozygous for rs6473797 T allele	rs6473797
OPRM1	A118G A/A	Normal OPRM1 Function	A118G
SLC6A4	S/Lg	Low Serotonin Transporter Expression	La, Lg, S
SLCO1B1	521T>C T/C	Decreased Function	521T>C, 388A>G
SULT4A1	rs138060 A/C	Heterozygous for C Allele	rs138097, rs138060
SULT4A1	rs138097 A/G	Heterozygous for A Allele	rs138097, rs138060
UGT1A1	*28/*28	Poor Metabolizer	*27, *28, *6
UGT2B15	*1/*2	Intermediate Metabolizer	*2
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity	-1639G>A

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, 45D2138167