DNALYSIS Biotechnology

PATIENT INFORMATION | SPECIMEN DETAILS

Medcheck Report

Current Patient Medications

Sertraline

Sertraline — Normal Sensitivity to Sertraline (CYP2C19: Intermediate Metabolizer) — ACTIONABLE

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

A medication has potentially reduced efficacy, increased toxicity or the patient has an increased risk for the indicated condition.	**ACTIONABLE**	Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA. EMA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as knowledge arises.
Guidelines exist for adjusting dosage, increased vigilance or the patient has a moderate risk for the indicated condition.		
The medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.	**INFORMATIVE**	There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

Risk Management

✓ Atrial Fibrillation

No increased risk of atrial fibrillation

The patient does not have a mutation in 4q25 variant rs2200733.

Unless other risk factors are present, noncarriers of 4q25 variant rs2200733 do not have an increased risk of atrial fibrillation.

No action is needed for this patient unless other cardiovascular risk factors are present.

⚠ Antipsychotic-Induced Tardive Dyskinesia

Increased Risk of Antipsychotic-Induced Tardive Dyskinesia

The patient does not carry the Taq1A variant (homozygous for the A2 allele).

The genotype results predict that the patient has normal dopamine receptor DRD2 density and functioning. The patient has increased risk for tardive dyskinesia when treated with antipsychotics.

Closely monitor the patient for signs of tardive dyskinesia.

✓ Antipsychotic-Induced Hyperprolactinemia

Normal Risk of Antipsychotic-Induced Hyperprolactinemia

The patient does not carry the Taq1A variant (homozygous for the A2 allele).

The genotype results predict that the patient has normal dopamine receptor DRD2 density and functioning. The patient has normal risk of hyperprolactinemia when treated with antipsychotics.

Monitor the patients closely for any signs of hyperprolactinemia.

✓ Antipsychotic-Induced Weight Gain

Low Risk of Antipsychotic-Induced Weight Gain

The patient does not carry the Taq1A variant (homozygous for the A2 allele).

The genotype results predict that the patient has normal dopamine receptor DRD2 density and functioning. The patient has a normal risk for weight gain when treated with antipsychotics.

Monitor the patient closely for signs of weight gain.

✓ Thrombosis

Protective Effect Against Thrombosis in Caucasians

The individual is positive for the Val34Leu variant of the FXIII-A1 gene. This genotype is associated with increased FXIII activity.

Coagulation Factor XIII is implicated in fibrin stabilization upon its activation by thrombin. The FXIII-A Leu34 form exhibits an accelerated activation. At high fibrinogen concentrations, fibrin clots are more susceptible to fibrinolysis.

The higher activity of FXIII-A Leu34 form, compared to the Val34 form, has been shown to confer protection against thrombotic events. Caucasian carriers of the FXIII-A 34 Leu allele have a reduced risk for venous thromboembolism and a modest reduction in risk for early myocardial infarction. Both venous thromboembolism and myocardial infarction are multi-factorial diseases likely to be under the influence of several genes, as well as environmental factors. Therefore, the existence of other genetic and non-genetic factors not assessed by this test may affect the risk assessment for this individual.

✓ Platelet Hyperactivity

Normal Response to Aspirin

The patient is negative for the ITGB3 176T>C (Leu59Pro) mutation. The genotype for the integrin β3 gene is wild-type, which is the most common genotype in the general population.

The wild-type genotype results confers a "normal" platelet reactivity, and is not associated with a resistance to the antithrombotic effects of aspirin. However, because the variability in response to antiplatelet drugs is multifactorial and not caused by single gene mutations, testing for the ITGB3 mutation alone should not be used as a diagnostic tool.

✓ Hyperhomocysteinemia - Depression

No Increased Risk of Hyperhomocysteinemia

The patient does not carry the MTHFR c.665C>T variant. MTHFR enzyme activity is normal.

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. With a normal MTHFR activity, this patient can process folate normally and is unlikely to have elevated plasma levels of homocysteine.

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.

✓ Nitric Oxide Production and Coronary Artery Disease

Normal Risk of Coronary Artery Disease

The patient does not carry the NOS3 G894T risk allele.

The endothelial nitric oxide synthase (NOS3) protein is involved in the synthesis of nitric oxide from L-arginine. The G allele of NOS3 G894T is associated with a normal basal nitric oxide production. The G/G genotype is not associated with an increased risk of developing coronary artery disease, hypertension and ischemic stroke.

No action is needed for this patient unless other cardiovascular risk factors are present.

✓ Alcohol Related Co-morbidities

Normal Alcohol and Acetaldehyde Metabolism After Alcohol Ingestion

ALDH2 rs671 A risk allele or the ADH1B rs1229984 T risk allele are absent.

Test results indicate normal alcohol dehydrogenase (ADH1B) activity and normal aldehyde dehydrogenase activity (ALDH2). ADH1B and ALDH2 play a role in alcohol metabolism. ADH1B is responsible for converting ethanol to acetaldehyde and ALDH2 subsequently converts this acetaldehyde into acetate.

Elevated and sustained aldehyde exposure after frequent alcohol consumption plays a key role in the pathogenesis of tissue and organ damage. In East Asians, abnormal ADH1B and/or ALDH2 activities appears to be associated with various health issues such as cancer, liver and cardiovascular diseases.

Consider optimal drinking habits by reducing the amount and the frequency of alcohol consumption.

⚠ Hyperlipidemia/Atherosclerotic Cardiovascular Disease

Slightly increased risk of cardiovascular disease

The patient carries a heterozygous mutation in LPA variant rs10455872 and is wild type for the other LPA variant rs3798220.

The patient's genotype is associated with elevated serum lipoprotein level and a smaller lipoprotein(a) isoform and may therefore may have an increased risk of atherosclerosis and coronary artery disease. Mutation in LPA variant rs10455872 is an independant marker of increased atherosclerosis disease risk and poor response to statins.

This patient may be at increased risk of atherosclerosis and coronary artery disease and may receive limited benefit from the cholesterol lowering statin treatment. Patient should be monitored for other coronary disease risk factors.

⚠ Calcium Channels Function and Bipolar Disorder

Risk of Bipolar Disorder: Caucasians - Increased; Asians - Unknown

The patient carries two copies of the rs1006737 A allele and the result for rs1051375 is indeterminate.

The patient carries a variant in the gene coding for the voltage-dependent calcium channel L-type, alpha 1C subunit (CACNA1C). This genotype is associated with an altered calcium gating, excessive neuronal depolarization and an altered mood regulation function. This genotype has been associated with higher rates of mood disorder recurrence and an increased risk of bipolar disorder in Caucasians. The result of CACNA1C variant rs1051375 is indeterminate and the risk of bipolar disorder cannot be predicted in Asians.

Bipolar disorder is a polygenic disorder and, as such, several genes are implicated in the etiology of the disease. Identification of one or more risk alleles in genes such as CACNA1C cannot replace standard clinical diagnostic tests, and this test should not be used as a diagnostic test for bipolar disorder.

⊗ Coronary Artery Disease

Significantly increased risk of coronary artery disease

The patient carries a total of 4 risk alleles in 9p21 region. There are homozygous mutations in both the variants of 9p21 (rs1333049 and rs10757278).

The risk of early onset coronary artery diseases is doubled as compared to non-carriers in patients with this genotype. Additionally, risk of abdominal aortic aneurysm is increased by 70% and the risk of coronary heart disease is increased by 60% as compared to non-carriers.

Patient needs to be monitored for cardiovascular health and for other genetic and non-genetic cardiovascular risk factors such as diabetes, hypertension, high cholesterol and alcohol use.

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 does not carry the MTHFR c.665C>T variant or MTHFR c.1286A>C variant. MTHFR enzyme activity is normal.

Based on results for the MTHFR c.665C>T and c.1286A>C variants, the patient has normal MTHFR activity and is unlikely to have elevated plasma levels of homocysteine. Hyperhomocysteinemia is associated with a risk for venous thromboembolism (VTE). Unless other risk factors are present, the patient is not expected to have an increased risk for VTE.

MTHFR enzyme activity is normal.

Potentially Impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Anesthesia	Depolarizing Muscle Relaxants	Succinylcholine		
	Inhaled Anesthetics	Desflurane Enflurane Halothane Isoflurane Sevoflurane		
Anticancer Agents	Anti-Estrogens			Tamoxifen
	Antifolates	Methotrexate		
	Detoxifying Agents	Rasburicase		
	Fluoropyrimidines	Capecitabine Fluorouracil		
	Platinum Compounds	Cisplatin		
	Protein Kinase Inhibitors	Dabrafenib Erdafitinib Gefitinib Pazopanib		
	Taxanes	Paclitaxel		
	Thiopurines	Azathioprine Mercaptopurine Thioguanine		
	Tubulin Inhibitors		Vincristine	
Cardiovascular	Angiotensin II Receptor Antagonists	Azilsartan Irbesartan Losartan		
	Antianginal Agents	Nitroglycerin Ranolazine		
	Antiarrhythmics		Flecainide Mexiletine Propafenone	
	Anticoagulants		Warfarin	
	Antiplatelets			Clopidogrel
	Beta Blockers	Carvedilol Nebivolol Propranolol	Metoprolol Timolol	
	Diuretics	Torsemide	Hydrochlorothiazide	
	Statins	Atorvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	Fluvastatin	

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Diabetes	Biguanides	Metformin		
	Meglitinides	Nateglinide Repaglinide		
	Thiazolidinediones	Pioglitazone Rosiglitazone		
Gastrointestinal	Antiemetics	Dolasetron Fosnetupitant / Palonosetron Netupitant / Palonosetron Palonosetron	Dronabinol Granisetron Metoclopramide Ondansetron	
	Proton Pump Inhibitors	Dexlansoprazole Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole		
Gaucher Disease	Endocrine-Metabolic Agents	Eliglustat		
Gynecology	Endometriosis Pain Agents	Elagolix		
Hematology	Hemostatic Agents		Avatrombopag Eltrombopag Lusutrombopag	
Infections	Antibiotics	Dapsone Methylene blue Nitrofurantoin Norfloxacin Silver Sulfadiazine Sulfamethoxazole		
	Antifungals	Flucytosine Voriconazole		
	Anti-HIV Agents	Abacavir Atazanavir Efavirenz		
	Antimalarials	Chloroquine Hydroxychloroquine Primaquine Quinine Tafenoquine		
	Anti-Tuberculosis	Isoniazid		
Multiple Sclerosis	Interferons	Peginterferon alfa-2a Peginterferon alfa-2b		
	Disease-Modifying Agents	Siponimod		
	Muscle Relaxants	Carisoprodol	Tizanidine	

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Pain	NSAIDs	Celecoxib Flurbiprofen Ibuprofen Lornoxicam Meloxicam Piroxicam		
	Opioids	Buprenorphine Dihydrocodeine Fentanyl Morphine Oxycodone	Benzhydrocodone Codeine Hydrocodone Methadone Tramadol	
Psychotropic	Antiaddictives	Bupropion Cocaine Vaccine Levodopa / Carbidopa Lofexidine	Acamprosate Disulfiram Naltrexone	
	Anti-ADHD Agents	Amphetamine Dextroamphetamine Lisdexamfetamine	Atomoxetine Dexmethylphenidate Methylphenidate	
	Anticonvulsants	Brivaracetam Carbamazepine Eslicarbazepine Fosphenytoin Lamotrigine Oxcarbazepine Phenytoin	Phenobarbital Primidone Topiramate Zonisamide	
	Antidementia Agents	Donepezil Galantamine		
	Antidepressants	Desvenlafaxine Escitalopram Fluoxetine Fluvoxamine Nefazodone Paroxetine Sertraline Vortioxetine	Amitriptyline Amoxapine Citalopram Clomipramine Desipramine Doxepin Imipramine Maprotiline Nortriptyline Protriptyline Trimipramine	Venlafaxine
	Antipsychotics	Aripiprazole Brexpiprazole Chlorpromazine Haloperidol Paliperidone Pimozide Quetiapine Risperidone	Clozapine Iloperidone Olanzapine Perphenazine Zuclopenthixol	Thioridazine
	Benzodiazepines	Diazepam Lorazepam Oxazepam	Clobazam	
	Mood Stabilizers	Lithium		

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Rheumatology	Other Neurological Agents	Deutetrabenazine Dextromethorphan / Quinidine Flibanserin Valbenazine	Tetrabenazine	
	Anti-Hyperuricemics and Anti-Gout Agents	Allopurinol Lesinurad Pegloticase Probenecid		
	Immunomodulators		Leflunomide	
	Other Antirheumatic Agents		Sulfasalazine	
Sjogren's Syndrome	Cholinergic Agonists	Cevimeline		
Sleep Disorder Agents	Narcoleptic Agents	Pitolisant		
Transplantation	Immunosuppressants	Tacrolimus		
Urologicals	Alpha-Blockers for Benign Prostatic Hyperplasia	Tamsulosin		
	Antispasmodics for Overactive Bladder	Darifenacin Fesoterodine Mirabegron Tolterodine		

Dosing Guidance

Clopidogrel

Reduced Response to Clopidogrel (CYP2C19: Intermediate Metabolizer) — ACTIONABLE

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

Tamoxifen

Decreased Response to Tamoxifen (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

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.

Thioridazine

Increased Sensitivity to Thioridazine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

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.

Venlafaxine

Increased Exposure to Venlafaxine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient has a decreased CYP2D6 activity which may result in elevated plasma concentrations of venlafaxine at standard doses. Consider an alternative medication or consider prescribing venlafaxine at a reduced dose and be extra alert for adverse events; adjust the dose based on tolerability and therapeutic monitoring.

If therapeutic drug monitoring is utilized, the sum of venlafaxine and O-desmethylvenlafaxine (an active metabolite) plasma concentrations should be used for efficacy. While the sum of the parent and the active metabolite are informative for efficacy, a higher parent (venlafaxine) concentration may be associated with higher side effects, including QT prolongation.

Acamprosate

Decreased Response to Acamprosate (GRIN2B: Homozygous for rs2058878 T allele) — INFORMATIVE

The glutamate receptor, ionotropic, N-methyl D-aspartate 2B (GRIN2B) encodes the subunit N-methyl D-aspartate receptor subtype 2B of the glutamate receptor complex. These receptors are the predominant excitatory neurotransmitter receptors in the brain. The patient is homozygous for T allele of GRIN2B variant rs2058878. Preliminary studies indicate that the patient's genotype may associated with an unfavorable response to acamprosate treatment for alcoholism. Absence of the minor A allele was associated with higher risk of early relapse and shorter abstinence during the first 3 months of acamprosate treatment. Replication of these results in a larger cohort is still needed to validate these findings.

Amitriptyline

Increased Amitriptyline Exposure (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of amitriptyline to less active compounds and a subsequent increase in amitriptyline exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Neuropathic Pain: Amitriptyline therapy can be prescribed according to standard recommended dosage and administration when lower doses are considered. If higher doses are warranted, consider a 25% reduction of the recommended dose and monitor patient for side effects.

Amoxapine

Possible Increased Amoxapine Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

Like other tricyclic and tetracyclic antidepressants, amoxapine is metabolized by CYP2D6. However, the overall contribution of this enzyme in the metabolism of this drug is not well documented. 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.

Atomoxetine

Possible Atomoxetine Underexposure Leading to Decreased Response (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

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).

Avatrombopag

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

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.

Benzhydrocodone

Possible Altered Response to Benzhydrocodone (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

Benzhydrocodone is a prodrug of hydrocodone and is converted to active hydrocodone by intestinal enzymes. Decreased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 intermediate metabolizers. However, there is insufficient evidence whether these patients have decreased analgesia when taking benzhydrocodone. 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).

Citalopram

Decreased Response to Citalopram (FKBP5: Homozygous for rs4713916 G allele) — INFORMATIVE

FKBP5 is involved in the response to stress and in the pathogenesis of mood disorders. The patient does not carry the A allele of FKBP5 variant rs4713916. Preliminary studies indicate that this genotype is associated with a decreased response to citalopram.

Citalopram

Reduced Response to Citalopram (HTR2A: Heterozygous for the A allele (rs7997012)) — INFORMATIVE

The patient is heterozygous for HTR2A variant rs7997012. Preliminary studies report that heterozygous HTR2A variant rs7997012 may be associated with an unfavorable response to citalopram.

Citalopram

Possible Reduced Response to Citalopram (GRIK4: Reduced Response to Citalopram) — INFORMATIVE

The patient's genotype indicates the presence of one copy of the GRIK4 favorable allele and one copy of the GRIK4 unfavorable allele. The patient may or may not benefit from citalopram therapy.

Clobazam

Possible Sensitivity to Clobazam (CYP2C19: Intermediate Metabolizer) — ACTIONABLE

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

Clomipramine

Increased Clomipramine Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of clomipramine to less active compounds and a subsequent increase in clomipramine exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Clozapine

Non-Response to Clozapine (CYP1A2: Normal Metabolizer - Higher Inducibility) — INFORMATIVE

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

Codeine

Decreased Exposure to Codeine Active Metabolite (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient genotype is associated with decreased conversion of codeine to its active metabolite (morphine), which may result in decreased effectiveness.

Codeine can be prescribed at standard label-recommended age- or weight-based dosing. If no response and opioid use is warranted, consider a non-tramadol opioid. Alternative opioids may include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

Desipramine

Increased Desipramine Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of desipramine to less active compounds and a subsequent increase in desipramine exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Dexmethylphenidate

Unfavorable Response to Dexmethylphenidate (ADRA2A: Homozygous for C Allele) — INFORMATIVE

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.

Dexmethylphenidate

Decreased Response to Dexmethylphenidate (COMT: Intermediate COMT Activity) — INFORMATIVE

The patient's genotype result predicts a less optimal 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.

Disulfiram

Increased Sensitivity to Disulfiram (DBH: Reduced Dopamine Beta-Hydroxylase Activity) — INFORMATIVE

Dopamine β-hydroxylase (DBH) is the final enzyme in norepinephrine biosynthesis, catalyzing the oxidative hydroxylation of dopamine to norepinephrine. The patient carries one copy of the T allele of the DBH rs1611115 which is significantly associated with low DBH activity. Preliminary studies in alcohol-dependent patients indicate that this genotype is associated with increased side effects following disulfiram therapy. Replication of these results in a larger cohort is still needed to validate these findings.

Doxepin

Increased Doxepin Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of doxepin to less active compounds and a subsequent increase in doxepin exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Insomnia: Doxepin can be prescribed according to the standard recommended dosage and administration.

Dronabinol

Increased Dronabinol Exposure (CYP2C9: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype predicts a reduced CYP2C9 metabolic activity. Increased drug exposure may occur in this patient leading to prolonged sedation. Consider standard label-recommended dosing and close monitoring for adverse effects.

Eltrombopag

Increased Risk of Eltrombopag-Induced Thrombosis (F5: Moderate Thrombosis Risk) — ACTIONABLE

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.

Flecainide

Increased Exposure to Flecainide (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype may be associated with an increased flecainide exposure following standard dosing. Consider prescribing a lower flecainide dose for therapeutic indications. When compared to a CYP2D6 normal metabolizer, an intermediate metabolizer may require a 25% dose reduction. Careful titration with ECG recording and monitoring of flecainide plasma concentrations are recommended until a favorable clinical response is achieved.

Dose adjustments are not required when flecainide is utilized for diagnostic uses.

Fluvastatin

Possible Increased Fluvastatin Exposure (CYP2C9: Intermediate Metabolizer) — INFORMATIVE

Increased fluvastatin plasma concentrations due to reduced CYP2C9 activity may occur, resulting in myopathy/hepatotoxicity. Consider monitoring the patient for treatment-related adverse effects, and adjust dose based on tolerability and response. Other adverse events and predisposing factors include advanced age (65 and older), diabetes, hypothyroidism, renal or hepatic impairments, high statin dose, CYP2C9 inhibitors, ABCG2 inhibitors, and female sex.

Granisetron

Unfavorable Response to Standard Granisetron Dosing (ABCB1: Variant Allele Not Present) — INFORMATIVE

The genotype result predicts that the patient has normal ABCB1 transporter expression. Patients with this genotype may experience decreased efficacy. No dose adjustments are recommended.

Hydrochlorothiazide

Unfavorable Response to Hydrochlorothiazide in African Americans (12q15: Heterozygous for the T allele (rs7297610)) — INFORMATIVE

The genotype results indicate that the patient carries one copy of the rs7297610 variant allele. This genotype is associated with decreased blood pressure responses to hydrochlorothiazide (HCTZ) in African-American patients. Consider monitoring for unresponsiveness.

Hydrocodone

Possible Decreased Exposure to Hydrocodone Active Metabolite (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

The patient genotype may be associated with a reduced conversion of hydrocodone to an active metabolite (hydromorphone), which may result in decreased effectiveness.

Hydrocodone can be prescribed at standard label-recommended age- or weight-based dosing. If no response and opioid use is warranted, consider a non-codeine or non-tramadol opioid. Alternative opioids may include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

Iloperidone

Moderate Sensitivity to Iloperidone (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

Because iloperidone is associated with QTc prolongation, caution is warranted when prescribing the drug in patients with reduced CYP2D6 activity. Iloperidone must be titrated slowly from a low starting dose to avoid orthostatic hypotension. 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

Increased Imipramine Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of imipramine to less active compounds and a subsequent increase in imipramine exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Leflunomide

Increased Exposure to Leflunomide (CYP2C19: Intermediate Metabolizer) — INFORMATIVE

Leflunomide is metabolized by CYP2C19 and CYP1A2 to its active metabolite teriflunomide. Preliminary studies indicate that patients with decreased CYP2C19 activity have a higher risk of developing gastrointestinal side effects and hepatotoxicity. There is insufficient data to calculate dose adjustment. If leflunomide is prescribed at standard dosing, monitor closely the patient's response and be alert to increased side effects.

Full blood cell count (CBC) and liver function parameters should be checked no more than 6 months before beginning treatment, and every month for the initial 6 months of therapy. Blood pressure should be checked before beginning treatment and periodically thereafter.

Lusutrombopag

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

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.

Maprotiline

Possible Increased Maprotiline Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

Like other tricyclic and tetracyclic antidepressants, maprotiline is metabolized by CYP2D6 as well as CYP1A2. Decreased CYP2D6 activity results in higher maprotiline concentrations potentially leading to higher adverse events. There are no established dosing adjustments for patients with decreased CYP2D6 function therefore, therapy must be initiated at a low dosage and gradually adjusted according to the patient's response. The lowest effective dosage should always be considered during maintenance therapy.

Methadone

Decreased Response to Methadone in African-Americans (OPRD1: Homozygous for rs678849 T allele) — INFORMATIVE

Preliminary studies in African Americans patients who are addicted to opioids and taking methadone treatment, indicate that patients with the TT genotype are more likely to have positive opioid drug screens than individuals with the CC genotype. These preliminary findings require confirmation in an independent population.

Methylphenidate

Unfavorable Response to Methylphenidate (ADRA2A: Homozygous for C Allele) — INFORMATIVE

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.

Methylphenidate

Decreased Response to Methylphenidate (COMT: Intermediate COMT Activity) — INFORMATIVE

The patient's genotype result predicts a less optimal 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.

Metoclopramide

Possible Sensitivity to Metoclopramide (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

There is no data documenting the changes in plasma concentrations of metoclopramide in CYP2D6 intermediate metabolizers. Metoclopramide can be prescribed at standard label-recommended dosage and administration with careful monitoring for possible increase of side effects.

Metoprolol

Increased Exposure to Metoprolol (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype may be associated with an increased metoprolol exposure following standard dosing. When compared to a normal metabolizer, an intermediate metabolizer may require a 50% dose reduction. If metoprolol is prescribed, be alert to adverse events (e.g., bradycardia or cold extremities).

Mexiletine

Increased Sensitivity to Mexiletine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

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.

Naltrexone

Altered Response to Naltrexone (OPRM1: Normal OPRM1 Function) — INFORMATIVE

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.

Nortriptyline

Increased Nortriptyline Exposure (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of nortriptyline to less active compounds and a subsequent increase in nortriptyline exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Olanzapine

Non-Response to Olanzapine (CYP1A2: Normal Metabolizer - Higher Inducibility) — INFORMATIVE

There is little evidence regarding the impact of CYP1A2 genetic variants on olanzapine response. Smokers may be at risk for non-response at standard doses. Careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels, leading to adverse events. Therefore, therapeutic drug monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

Ondansetron

Unfavorable Response to Standard Ondansetron Dosing (ABCB1: Variant Allele Not Present) — INFORMATIVE

The genotype result predicts that the patient has normal ABCB1 transporter expression. Patients with this genotype may experience decreased efficacy. No dose adjustments are recommended.

Perphenazine

Possible Sensitivity to Perphenazine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

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.

Phenobarbital

Possible Sensitivity to Phenobarbital (CYP2C19: Intermediate Metabolizer) — INFORMATIVE

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

Primidone

Possible Sensitivity to Primidone (CYP2C19: Intermediate Metabolizer) — INFORMATIVE

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

Propafenone

Increased Exposure to Propafenone (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

The patient's genotype may be associated with an increased propafenone exposure following standard dosing. There is insufficient data to allow calculation of dose adjustment. Titrate carefully and adjust the dose in response to plasma concentration and ECG monitoring. An alternative medication such as sotalol, disopyramide, quinidine or amiodarone may also be considered.

Dose adjustments with co-medications: concurrent use of propafenone along with CYP3A4 inhibitors and CYP2D6 inhibitors may significantly increase the plasma concentration of propafenone increasing the risk of proarrhythmia and other adverse events. Therefore, avoid simultaneous use of propafenone with both a CYP2D6 inhibitor and a CYP3A4 inhibitor.

Protriptyline

Possible Increased Protriptyline Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

Like other tricyclic and tetracyclic antidepressants, protriptyline is metabolized by CYP2D6. Decreased CYP2D6 activity results in higher protriptyline concentrations potentially leading to higher adverse events. There are no established dosing adjustments for patients with decreased CYP2D6 function. Therefore, therapy must be initiated at a low dosage and gradually adjusted according to the patient's response. The lowest effective dosage should always be considered during maintenance therapy.

Sulfasalazine

Decreased Response to Sulfasalazine For the Treatment of Rheumatoid Arthritis (ABCG2: Normal Function) — INFORMATIVE

Rheumatoid Arthritis: The patient carries two copies of ABCG2 rs2231142 C allele. Preliminary data suggests that this genotype may be associated with decreased plasma levels of sulfasalazine which may decrease the likelihood of response to this drug.

Tetrabenazine

Normal Sensitivity to Tetrabenazine (CYP2D6: Intermediate Metabolizer) — ACTIONABLE

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 intermediate metabolizers of CYP2D6 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.

Timolol

Possible Sensitivity to Timolol (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

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

Possible Non-Response to Tizanidine (CYP1A2: Normal Metabolizer - Higher Inducibility) — INFORMATIVE

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

Topiramate

Decreased Response to Topiramate (alcoholism treatment) (GRIK1: Heterozygous for rs2832407 C allele) — INFORMATIVE

Glutamate receptor, ionotropic, kainate 1 (GRIK1) belongs to the kainate family of glutamate receptors, which are the predominant excitatory neurotransmitter receptors in the brain. The patient is heterozygous for the C allele of GRIK1 variant rs2832407. Topiramate treatment did not reduce heavy alcohol drinking in patients with this genotype when compared to a placebo. Replication of these results in a larger cohort is still needed to validate these findings.

Tramadol

Decreased Exposure to Tramadol Active Metabolite (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

The patient genotype is associated with decreased conversion of tramadol to its active metabolite (O-desmethyltramadol), which may result in decreased effectiveness.

Tramadol can be prescribed at standard label-recommended age- or weight-based dosing and monitoring. If no response and opioid use is warranted, consider a non-codeine opioid. Alternative opioids may include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

Trimipramine

Increased Trimipramine Exposure (CYP2D6: Intermediate Metabolizer) — INFORMATIVE

The patient is predicted to be a CYP2D6 intermediate metabolizer which is likely to result in decreased metabolism of trimipramine to less active compounds and a subsequent increase in trimipramine exposure leading to side effects.

Psychiatric Conditions: Consider a 25% reduction of the recommended dose and use therapeutic drug monitoring to guide dose adjustments.

Vincristine

Increased Risk of Vincristine-Induced Peripheral Neuropathy During Later Treatment Phases (CEP72: Decreased CEP72 expression) — INFORMATIVE

Test results indicate that the patient carries two copies of the CEP72 rs924607 T risk allele. Preliminary studies in adults patients with acute lymphoblastic leukemia, indicate that individuals with this genotype have an increased risk and severity of vincristine-related peripheral neuropathy after prolonged treatment. These preliminary findings, found in patients who received chronic vincristine treatment, require further confirmation. The CEP72 rs924607 genotype cannot be used to predict the risk of vincristine-induced neurotoxicity during the early phase of treatment (induction). Other genetic and non-genetic risk factors may contribute to the patient's susceptibility to vincristine neurotoxicity and include the total cumulative vincristine dose, dosing frequency, concomitant use of CYP3A4 inhibitors, hepatic function impairment, comorbid hereditary neuropathy and Caucasian ancestry. Consider closer monitoring and adjust dosing based on the patient's tolerance.

Warfarin

Dosing Adjustments are Expected (CYP2C9 *1/*2; VKORC1 -1639G>A G/A; CYP4F2 c.1297G>A A/A; CYP2C g.96405502G>A G/A) — 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 3-4 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. Consider an additional 5-10% increase to the calculated dose.

Africans (NOT African Americans): Use the patient's demographics and other clinical factors along with CYP2C9 and VKORC1 genotypes to calculate the expected therapeutic dose.

African Americans: Use the patient's demographics and other clinical factors along with CYP2C9 and VKORC1 genotypes to calculate the expected therapeutic dose. Consider an additional 10-25% decrease to the calculated dose.

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

Zonisamide

Possible Sensitivity to Zonisamide (CYP2C19: Intermediate Metabolizer)

INFORMATIVE

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

Zuclopenthixol

Increased Exposure to Zuclopenthixol (CYP2D6: Intermediate Metabolizer)

ACTIONABLE

The patient's genotype may be associated with an increased zuclopenthixol exposure following standard dosing. Consider a 25% dose reduction or consider an alternative medication. Examples of alternative medications include flupenthixol, clozapine, olanzapine or quetiapine.

Test Details

Gene	Genotype	Phenotype	Clinical Consequences
12q15	rs7297610 C/T	Heterozygous for the T allele (rs7297610)	Unfavorable response to hydrochlorothiazide in African Americans
4q25	rs2200733 C/C	Wild-type for rs2200733	The patient is non carrier of 4q25 variants and are not associated increased risk atrial fibrillation unless other cardiovascular risk factors are present.
9p21	rs10757278 G/G rs1333049 C/C	Significantly increased risk of coronary artery disease	The patient carries a total of 4 risk alleles in 9p21 region. There are homozygous mutations in both the variants of 9p21 (rs1333049 and rs10757278).
ABCB1	3435C>T C/C	Variant Allele Not Present	Consistent with high transporter expression.
ABCG2	421C>A C/C	Normal Function	Consistent with a normal ABCG2 transporter function. The patient's risk for statin-induced adverse events is normal.
ACYP2	rs1872328 G/G	Homozygous for rs1872328 G allele	
ADRA2A	C-1291G C/C	Homozygous for C Allele	Non-carriers of the G allele of ADRA2A C-1291G variant, may have a limited reduction of inattentive symptoms when administered Methylphenidate or Dexmethylphenidate.
ALDH2 ADH1B	706A>G C/C 1369G>A G/G	Normal Alcohol and Acetaldehyde Metabolism After Alcohol Ingestion	East Asians: ALDH2 rs671 A allele or the ADH1B rs1229984 T allele associated with increased risk of alcohol related co-morbidities are absent.
ANKK1/DRD2	DRD2:Taq1A C/C	Unaltered DRD2 function	Consistent with a normal dopamine receptor D2 function.
BDNF	434C>T T/T	Homozygous for rs6265 T allele	Consistent with reduced activity-dependent secretion of BDNF from neurons and impaired BDNF signaling.
C11orf65	rs11212617 C/C	Homozygous for the C allele (rs11212617)	Increased glycemic response to metformin
CACNA1C	5361G>A Indeterminate	Unknown phenotype	Test results were obtained for CACNA1C but one or more analytes failed.
CACNA1C	270344G>A A/A 5361G>A Indeterminate	Risk of Bipolar Disorder: Caucasians - Increased; Asians - Unknown	The patient carries a variant in the gene coding for the voltage-dependent calcium channel L-type, alpha 1C subunit (CACNA1C). This genotype is associated with an altered calcium gating, excessive neuronal depolarization and an altered mood regulation function. This genotype has been associated with higher rates of mood disorder recurrence and an increased risk of bipolar disorder in Caucasians. The result of CACNA1C variant rs1051375 is indeterminate and the risk of bipolar disorder cannot be predicted in patients of Asian origin.
CACNA1S	No Pathogenic Variant Detected	Uncertain Susceptibility to Malignant Hyperthermia	No CACNA1S malignant hyperthermia pathogenic variant, as designated by the European Malignant Hyperthermia Group (EMHG), was detected in this individual. A negative genetic test cannot be assumed to indicate normal CACNA1S-related phenotypes and should be interpreted in context of clinical findings, family history and other laboratory data.
CEP72	rs924607 T/T	Decreased CEP72 expression	Increased Risk of Vincristine-Induced Peripheral Neuropathy During Later Treatment Phases
COMT	Val158Met A/G	Intermediate COMT Activity	Consistent with a reduced catechol O-methyltransferase (COMT) function.
CYP1A2	*1F/*1F	Normal Metabolizer - Higher Inducibility	Consistent with a typical CYP1A2 activity in absence of inducing substances. Rapid Metabolism occurs in presence of inducers such as barbiturates, cruciferous vegetables, carbamazepine, rifampin and smoking.
CYP2B6	*1/*4	Rapid Metabolizer	Consistent with increased CYP2B6-mediated drug metabolism. Potential risk for side effects or loss of efficacy with drug susbtrates.

CYP2C	g.96405502G>A G/A	**High Sensitivity**	Consistent with a deficiency in CYP2C (rs12777823) enzyme activity in African Americans. Exercise caution if CYP2C (rs12777823) drug substrates are prescribed.
CYP2C19	*1/*35	**Intermediate Metabolizer**	Consistent with a moderate deficiency in CYP2C19 enzyme activity.
CYP2C8	*1A/*1A	**Normal Metabolizer**	Consistent with a typical CYP2C8 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP2C9	*1/*2	**Intermediate Metabolizer**	Consistent with a moderate deficiency in CYP2C9 enzyme activity.
CYP2D6	*1/*4	**Intermediate Metabolizer**	Consistent with a moderate deficiency in CYP2D6 enzyme activity.
CYP3A4	*1/*1	**Normal Metabolizer**	Consistent with a typical CYP3A4 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
CYP3A5	*3/*3	**Poor Metabolizer**	Consistent with an absence of CYP3A5 enzyme expression (Non-Expresser). This phenotype is the most common in the general population.
CYP4F2	c.1297G>A A/A	**Reduced Activity**	Consistent with a deficiency in CYP4F2 protein expression, resulting in reduced vitamin K metabolism.
DBH	-1021C>T C/T	**Reduced Dopamine Beta-Hydroxylase Activity**	Consistent with a low dopamine beta-hydroxylase activity and a reduced conversion of dopamine to norepinephrine.
DPYD	Activity Score: 2	**Normal Metabolizer**	Consistent with a typical DPD activity.
DRD2	-241A>G T/C	**Heterozygous for rs1799978 C allele**	Associated with a favorable response to Risperidone.
F13A1	c.103G>T T/T	**Homozygous for F13A1 Leu Allele**	The patient carries two copies of the thrombo-protective Leu 34 variant allele of the FXIII A1 gene.
F2 **F5**	rs1799963 GG rs6025 CT	**Increased Risk of Thrombosis**	The patient's genotypes for F5 c.1601G>A variant (also known as Factor V Leiden) and F2 c.97G>A variant (also known as Factor II 20210G>A) predict an increased risk for thrombosis. Consider avoiding estrogen-containing preparations. A short course of prophylactic anticoagulation may be considered in high-risk settings such as surgery.
FKBP5	rs4713916 G/G	**Homozygous for rs4713916 G allele**	Consistent with a possible non-response to citalopram.
G6PD	B/B	**Normal Function**	Consistent with a typical G6PD function. This genotype predicts a >60% of normal G6PD function. Low risk of drug-induced acute hemolytic anemia.
GRIK1	rs2832407 A/C	**Heterozygous for rs2832407 C allele**	Glutamate receptor, ionotropic, kainate 1 (GRIK1) belongs to the kainate family of glutamate receptors, which are the predominant excitatory neurotransmitter receptors in the brain. The patient carries one copy of the GRIK1 rs2832407 C allele.
GRIK4	83-10039T>C T/C	**Reduced Response to Citalopram**	Consistent with a possible non-response to citalopram.
GRIN2B	rs2058878 T/T	**Homozygous for rs2058878 T allele**	Increased risk of early relapse and shorter abstinence in alcoholics when treated with Acamprosate.
HCP5	rs2395029 T/T	**HLA-B*57:01 Negative**	In Caucasians and Hispanics: the absence of the HCP5 rs2395029 G allele, indicates the absence of the HLA-B*57:01 risk allele, which is consistent with normal or reduced risk of drug-induced hypersensitivity reactions with specific medications.
HLA-A	rs1061235 A/A	**HLA-A*31:01 Negative**	The absence of the rs1061235 risk allele T, indicates the absence of the HLA-A*31:01 risk allele, which is consistent with normal or reduced risk of drug-induced hypersensitivity reactions with specific medications.
HLA-B	neg/neg	**HLA-B*15:02, *57:01, and *58:01 Negative**	Consistent with normal or reduced risk of drug-induced hypersensitivity reactions with specific medications.

HTR2A	-1438G>A C/T	**Heterozygous for the T Allele (rs6311)**	The patient carries one copy of the variant allele at rs6311 which may be associated with greater serotonin 2A receptor gene expression.
HTR2A	102C>T G/A	**Heterozygous for the A allele (rs6313)**	
HTR2A	rs7997012 A/G	**Heterozygous for the A allele (rs7997012)**	Reduced response to citalopram and escitalopram
HTR2C	114138144C>G G/G	**Homozygous for the G allele (rs1414334)**	This genotype is not associated with risperidone- and clozapine-induced metabolic syndrome.
IFNL3	rs12979860 C/C	**Favorable Genotype Response**	Increased likelihood of response to Peginterferon-based regimens resulting in a greater chance of sustained virologic response.
ITGB3	176T>C T/T	**Normal Platelet Reactivity**	The patient does not carry the 176T>C mutation of the integrin β3 gene. Unless other genetic or circumstantial risk factors are present, he is not expected to have an increased platelet reactivity.
LPA	rs10455872 A/G rs3798220 T/T	**Slightly increased risk of cardiovascular disease**	The patient carries a heterozygous mutation in LPA variant rs10455872. The other LPA variant rs3798220 is wild type.The patient may be associated with elevated serum lipoprotein level and a smaller lipoprotein(a) isoform and may therefore may have an increased risk of atherosclerosis and coronary artery disease.
MC4R	g.60215554C>A C/C	**Homozygous for C allele (rs489693)**	Normal MC4R function
MTHFR	c.665C>T CC	**Normal MTHFR Activity**	The patient does not carry the MTHFR c.665C>T variant, and the patient's MTHFR activity is normal. This is not associated with an increased risk of hyperhomocysteinemia.
MTHFR	c.1286A>C AA c.665C>T CC	**No Increased Risk of Hyperhomocysteinemia**	The patient does not carry the MTHFR c.665C>T or c.1286A>C variant. Therefore, the patient has normal MTHFR function, and no elevation of plasma homocysteine levels is expected.
NAT2	*4/*6	**Intermediate Metabolizer**	Consistent with a moderate deficiency in NAT2 enzyme activity.
NOS3	G894T G/G	**Normal Basal Nitric Oxide Production**	The G/G genotype is not associated with an increased risk of developing coronary artery disease, hypertension and ischemic stroke.
NUDT15	*1/*1	**Normal Metabolizer**	Consistent with a typical NUDT15 activity.
OPRD1	rs678849 T/T	**Homozygous for rs678849 T allele**	Consistent with a possible favorable response to buprenorphine and a decreased response to methadone in African-Americans treated for opioid dependence.
OPRK1	rs6473797 T/T	**Homozygous for rs6473797 T allele**	Consistent with an enanced therapeutic response to cocaine vaccine in Caucasians treated for cocaine dependence.
OPRM1	A118G A/A	**Normal OPRM1 Function**	Consistent with a normal OPRM1 receptor signaling efficiency induced by exogenous opioids. This is associated with a good analgesia following standard opioid doses and a poor response to naltrexone.
RARG	rs2229774 C/C	**Normal Function**	Normal receptor function and normal repression of topoisomerase-II beta (TOP2B) expression
RYR1	No Pathogenic Variant Detected	**Uncertain Susceptibility to Malignant Hyperthermia**	No RYR1 malignant hyperthermia pathogenic variant, as designated by the European Malignant Hyperthermia Group (EMHG), was detected in this individual. A negative genetic test cannot be assumed to indicate normal RYR1-related phenotypes and should be interpreted in context of clinical findings, family history and other laboratory data.
SLC28A3	rs7853758 C/C	**Normal Function**	Normal SLC28A3 influx transporter function
SLC47A2	-130G>A G/G	**Normal Function**	Normal renal and secretion clearance of metformin
SLCO1B1	521T>C T/T	**Normal Function**	Consistent with a typical SLCO1B1 transporter function.
TPMT	*1/*1	**Normal Metabolizer**	Consistent with a typical TPMT activity.

UGT1A1	rs887829 C/C	**rs887829 (*28 and *37 proxy) variant absent**	Consistent with a typical UGT1A1 glucuronidation function.
UGT1A1	*1/*1	**Normal Metabolizer**	Consistent with a typical UGT1A1 glucuronidation function.
UGT1A6	rs17863783 G/G	**Normal Metabolizer**	Consistent with typical UGT1A6 glucuronidation metabolism.
UGT2B15	*1/*1	**Normal Metabolizer**	Consistent with a typical UGT2B15 glucuronidation function. This test did not identify risks for side effects with drug substrates.
VKORC1	-1639G>A G/A	**Intermediate Warfarin Sensitivity**	Consistent with a moderately decreased VKORC1 expression. Exercise caution with coumarin anticoagulants.

Alleles Tested: 12q15 rs7297610; **4q25** rs2200733; **9p21** rs10757278, rs1333049; **ABCB1** 3435C>T; **ABCG2** 421C>A; **ACYP2** rs1872328; **ADH1B** 706A>G; **ADRA2A** C-1291G; **ALDH2** 1369G>A; **ANK3** rs10994336; **ANKK1/DRD2** DRD2:Taq1A; **BDNF** 434C>T; **C11orf65** rs11212617; **CACNA1C** 270344G>A, 5361G>A; **CACNA1S** See Variant Results section for this gene.; **CEP72** rs924607; **COMT** Val158Met; **CYP1A2** *1C, *1F, *1K, *1L; **CYP2B6** *4, *5, *6, *7, *9, *16, *18, *19, *20, *22; **CYP2C** g.96405502G>A; **CYP2C19** *2, *3, *4A, *4B, *5, *6, *7, *8, *9, *10, *11, *13, *15, *17, *24, *25, *35; **CYP2C8** *2, *3, *4; **CYP2C9** *2, *3, *4, *5, *6, *8, *9, *11, *12, *13, *14, *15, *18, *27, *31; **CYP2D6** *2, *4, *4M, *6, *7, *8, *9, *10, *14, *17, *29, *31, *33, *35, *38, *40, *41, *49, *50, *51, *53, *54, *56A, *56B, *57, *62, *72, *84, *100, *114, *5 (gene deletion), XN (gene duplication); **CYP3A4** *2, *3, *12, *17, *22; **CYP3A5** *3, *6, *7; **CYP4F2** c.1297G>A; **DBH** -1021C>T; **DPYD** 475994del, 85T>C, 703C>T, 2657G>A, 2983G>T, 1905+1G>A, , 1601C>T, 496A>G, , 1627T>C, , 2846A>T, 1236G>A, 1003C>A, 557A>G, c.1156G>T, c.1129-5923C>G; **DRD2** -241A>G; **F13A1** c.103G>T; **Factor II** rs1799963; **Factor V Leiden** rs6025; **FKBP5** rs4713916; **G6PD** A, A-(202), A-(968), Asahi, Canton, Chatham, Cosenza, Kalyan-Kerala, Mediterranean, Orissa, Sao Borja; **GRIK1** rs2832407; **GRIK4** 83-10039T>C; **GRIN2B** rs2058878; **HCP5** rs2395029; **HLA-A** rs1061235; **HLA-B** 1502, 5701; **HTR2A** 102C>T, -1438G>A, rs7997012; **HTR2C** 114138144C>G; **IFNL3** rs12979860; **ITGB3** 176T>C; **LPA** rs3798220, rs10455872; **MC4R** g.60215554C>A; **MTHFR** c.1286A>C, c.665C>T; **NAT2** *5, *5A, *5B, *6, *6A, *6C, *7; **NOS3** G894T; **NUDT15** *2, *3, *4, *5; **OPRD1** rs678849; **OPRK1** rs6473797; **OPRM1** A118G; **RARG** rs2229774; **RYR1** See Variant Results section for this gene.; **SLC28A3** rs7853758; **SLC47A2** -130G>A; **SLCO1B1** 521T>C; **TPMT** *2, *3A, *3B, *3C, *4, *8; **UGT1A1** *6, *27, *80; **UGT1A6** rs17863783; **UGT2B15** *2; **VKORC1** -1639G>A

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

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

Lab Disclaimer: DNAlysis Biotechnology developed the Genotype test. The performance characteristics of this test were determined by DNAlysis Biotechnology. It has not been cleared or approved by the U.S. Food and Drug Administration.

Translational Software Disclaimer: The information presented on this report is provided as general educational health information. The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Only a physician, pharmacist or other healthcare professional should advise a patient on the use of the medications prescribed.

The pharmacogenetic assay involves use of reporting software and genotype-phenotype associations performed by Translational Software (www.translationalsoftware.com). The software has not been evaluated by the Food and Drug Administration. The software, and the report generated by the software, is not intended to diagnose, treat, cure, or prevent any disease. A qualified designee within the lab uses Translational Software to generate and subsequently review the report. The pharmacogenetic report is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to dose guidelines does not necessarily assure a successful medical outcome.

Approved By: Laboratory Manager
Thenusha Naidoo
MS 0000990

DNALYSIS Biotechnology

Patient Information Card

This is a summary genetic report for your patient to share with other healthcare providers. The card can be cut out along the dashed line and carried with the patient.

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REPORT DETAILS

Pharmacogenetic Test Summary

12q15	rs7297610 C/T	Heterozygous for the T allele (rs7297610)
4q25	rs2200733 C/C	Wild-type for rs2200733
9p21	rs10757278 G/G	Homozygous for rs10757278 Variant
9p21	rs1333049 C/C	Homozygous for rs1333049 Variant
ABCB1	3435C>T C/C	Variant Allele Not Present
ABCG2	421C>A C/C	Normal Function
ACYP2	rs1872328 G/G	Homozygous for rs1872328 G allele
ADH1B	706A>G C/C	Normal function
ADRA2A	C-1291G C/C	Homozygous for C Allele
ALDH2	1369G>A G/G	Normal function
ANK3	rs10994336 C/C	Homozygous for rs10994336 C allele
ANKK1/DRD2	DRD2:Taq1A C/C	Unaltered DRD2 function
BDNF	434C>T T/T	Homozygous for rs6265 T allele
C11orf65	rs11212617 C/C	Homozygous for the C allele (rs11212617)
CACNA1C	270344G>A A/A	Homozygous for rs1006737 A allele
CACNA1C	5361G>A Indeterminate	Unknown phenotype
CACNA1S	No Pathogenic Variant Detected	Uncertain Susceptibility to Malignant Hyperthermia
CEP72	rs924607 T/T	Decreased CEP72 expression
COMT	Val158Met A/G	Intermediate COMT Activity
CYP1A2	*1F/*1F	Normal Metabolizer - Higher Inducibility
CYP2B6	*1/*4	Rapid Metabolizer
CYP2C	g.96405502G>A G/A	High Sensitivity
CYP2C19	*1/*35	Intermediate Metabolizer
CYP2C8	*1A/*1A	Normal Metabolizer
CYP2C9	*1/*2	Intermediate Metabolizer
CYP2D6	*1/*4	Intermediate Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
CYP4F2	c.1297G>A A/A	Reduced Activity

DBH	-1021C>T C/T	Reduced Dopamine Beta-Hydroxylase Activity
DPYD	Activity Score: 2	Normal Metabolizer
DRD2	-241A>G T/C	Heterozygous for rs1799978 C allele
F13A1	c.103G>T T/T	Homozygous for F13A1 Leu Allele
Factor II	rs1799963 GG	Normal Thrombosis Risk
Factor V Leiden	rs6025 CT	Moderate Thrombosis Risk
FKBP5	rs4713916 G/G	Homozygous for rs4713916 G allele
G6PD	B/B	Normal Function
GRIK1	rs2832407 A/C	Heterozygous for rs2832407 C allele
GRIK4	83-10039T>C T/C	Reduced Response to Citalopram
GRIN2B	rs2058878 T/T	Homozygous for rs2058878 T allele
HCP5	rs2395029 T/T	HLA-B*57:01 Negative
HLA-A	rs1061235 A/A	HLA-A*31:01 Negative
HLA-B	neg/neg	HLA-B*15:02, *57:01, and *58:01 Negative
HTR2A	rs7997012 A/G	Heterozygous for the A allele (rs7997012)
HTR2A	-1438G>A C/T	Heterozygous for the T Allele (rs6311)
HTR2A	102C>T G/A	Heterozygous for the A allele (rs6313)
HTR2C	114138144C>G G/G	Homozygous for the G allele (rs1414334)
IFNL3	rs12979860 C/C	Favorable Genotype Response
ITGB3	176T>C T/T	Normal Platelet Reactivity
LPA	rs3798220 T/T	Wild-type for rs3798220
LPA	rs10455872 A/G	Heterozygous for rs10455872 variant
MC4R	g.60215554C>A C/C	Homozygous for C allele (rs489693)
MTHFR	c.665C>T CC	Normal MTHFR Activity
MTHFR	c.1286A>C AA	Normal MTHFR Activity
NAT2	*4/*6	Intermediate Metabolizer
NOS3	G894T G/G	Normal Basal Nitric Oxide Production
NUDT15	*1/*1	Normal Metabolizer
OPRD1	rs678849 T/T	Homozygous for rs678849 T allele
OPRK1	rs6473797 T/T	Homozygous for rs6473797 T allele
OPRM1	A118G A/A	Normal OPRM1 Function
RARG	rs2229774 C/C	Normal Function
RYR1	No Pathogenic Variant Detected	Uncertain Susceptibility to Malignant Hyperthermia

SLC28A3	rs7853758 C/C	Normal Function
SLC47A2	-130G>A G/G	Normal Function
SLCO1B1	521T>C T/T	Normal Function
TPMT	*1/*1	Normal Metabolizer
UGT1A1	*1/*1	Normal Metabolizer
UGT1A1	rs887829 C/C	rs887829 (*28 and *37 proxy) variant absent
UGT1A6	rs17863783 G/G	Normal Metabolizer
UGT2B15	*1/*1	Normal Metabolizer
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity

For a complete report contact DNAlysis Biotechnology
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