RealLab
diagnostics at its best

# Genotox Extensive Report

| | | | | | |
|---|---|---|---|---|---|
| Patient: | TEST GENOTOX | Accession #: | VGTX00001 | Received Date: | 1/1/2017 |
| Gender: | Female | Report Date: | 11/17/2017 | Collection Date: | 1/1/2017 |
| DOB: | 6/23/1944 | Ordered By: | MDx | Specimen Type: | Buccal Swab |

## Risk Management

### ⚠ Atrial Fibrillation

**Increased risk of atrial fibrillation**

The patient has a heterozygous mutation in 4q25 variant rs2200733.

Heterozygous mutations in 4q25 variant rs2200733 are associated with 1.7 times increase in risk of atrial fibrillation.

Closely monitor the patient for atrial fibrillations and for other cardiovascular disease risk factors.

### ⊗ 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.

### ✓ Hyperhomocysteinemia - Thrombosis

**No Increased Risk of Hyperhomocysteinemia**

The patient carries one MTHFR A1298C mutation (heterozygous). MTHFR enzyme activity is reduced (80% of normal activity).

The patient's slightly 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).

The patient's MTHFR activity is slightly reduced.

### ✓ Hyperlipidemia/Atherosclerotic Cardiovascular Disease

**No increased risk of cardiovascular disease**

The patient is a non carrier of the risk alleles in LPA gene for both the variants (rs3798220 and rs10455872).

The patient's genotype is associated with normal lipoprotein levels. The patient has no increased risk of atherosclerosis and cardiovascular disease as compared to the general population unless other risk factors are present.

No action is needed for this patient unless other genetic and non genetic risk factors (e.g. high blood pressure, smoking, diabetes, obesity, high blood cholesterol and excessive alcohol use) are present.

### ✓ Thrombophilia

**No Increased Risk of Thrombosis**

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

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

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

### ✓ 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.

| GUIDANCE LEVELS | EVIDENCE LEVELS | |
|---|---|---|
| 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. |

# Potentially Impacted Medications

| CATEGORY | DRUG CLASS | STANDARD PRECAUTIONS | USE WITH CAUTION | CONSIDER ALTERNATIVES |
|---|---|---|---|---|
| **Anticancer Agents** | **Antifolates** | Methotrexate (Trexall) | | |
| **Cardiovascular** | **Angiotensin II Receptor Antagonists** | Azilsartan (Edarbi, Edarbyclor)<br>Candesartan (Atacand)<br>Eprosartan (Teveten)<br>Irbesartan (Avapro)<br>Losartan (Cozaar, Hyzaar)<br>Olmesartan (Benicar)<br>Telmisartan (Micardis)<br>Valsartan (Diovan, Entresto) | | |
| | **Antianginal Agents** | Ranolazine (Ranexa) | | |
| | **Antiarrhythmics** | Flecainide (Tambocor)<br>Mexiletine (Mexitil)<br>Propafenone (Rythmol) | | |
| | **Anticoagulants** | Apixaban (Eliquis)<br>Dabigatran Etexilate (Pradaxa)<br>Edoxaban (Savaysa)<br>Fondaparinux (Arixtra)<br>Rivaroxaban (Xarelto) | Warfarin (Coumadin) | |
| | **Antiplatelets** | Clopidogrel (Plavix)<br>Prasugrel (Effient)<br>Ticagrelor (Brilinta)<br>Vorapaxar (Zontivity) | | |
| | **Beta Blockers** | Atenolol (Tenormin)<br>Bisoprolol (Zebeta)<br>Carvedilol (Coreg)<br>Labetalol (Normodyne, Trandate)<br>Metoprolol (Lopressor)<br>Nebivolol (Bystolic)<br>Propranolol (Inderal)<br>Timolol (Timoptic) | | |
| | **Diuretics** | Hydrochlorothiazide (Esidrix, Microzide)<br>Torsemide (Demadex) | | |
| | **Statins** | Atorvastatin (Lipitor)<br>Lovastatin (Mevacor, Altoprev, Advicor)<br>Pitavastatin (Livalo)<br>Pravastatin (Pravachol)<br>Rosuvastatin (Crestor)<br>Simvastatin (Zocor) | Fluvastatin (Lescol) | |

| CATEGORY | DRUG CLASS | STANDARD PRECAUTIONS | USE WITH CAUTION | CONSIDER ALTERNATIVES |
|---|---|---|---|---|
| Diabetes | Biguanides | Metformin (Glucophage) | | |
| | Meglitinides | Nateglinide (Starlix)<br>Repaglinide (Prandin, Prandimet) | | |
| | Sulfonylureas | Chlorpropamide (Diabenese)<br>Glimepiride (Amaryl)<br>Glipizide (Glucotrol)<br>Glyburide (Micronase)<br>Tolbutamide (Orinase) | | |
| Gastrointestinal | Antiemetics | Aprepitant (Emend-oral)<br>Dolasetron (Anzemet)<br>Dronabinol (Marinol)<br>Fosaprepitant (Emend-i.v)<br>Granisetron (Sancuso, Sustol)<br>Metoclopramide (Reglan)<br>Netupitant-Palonosetron (Akynzeo)<br>Ondansetron (Zofran, Zuplenz)<br>Palonosetron (Aloxi)<br>Rolapitant (Varubi) | | |
| | Proton Pump Inhibitors | Dexlansoprazole (Dexilant, Kapidex)<br>Esomeprazole (Nexium)<br>Lansoprazole (Prevacid)<br>Omeprazole (Prilosec)<br>Pantoprazole (Protonix)<br>Rabeprazole (Aciphex) | | |
| Infections | Antifungals | Amphotericin B (AmBisome, Abelcet)<br>Anidulafungin (Eraxis)<br>Caspofungin (Cancidas)<br>Fluconazole (Diflucan)<br>Isavuconazonium (Cresemba)<br>Itraconazole (Sporanox)<br>Micafungin (Mycamine)<br>Posaconazole (Noxafil)<br>Voriconazole (Vfend) | | |
| | Anti-HIV Agents | Dolutegravir (Tivicay, Triumeq)<br>Raltegravir (Isentress, Dutrebis) | | |
| | Antimalarials | Proguanil (Malarone) | | |

| CATEGORY | DRUG CLASS | STANDARD PRECAUTIONS | USE WITH CAUTION | CONSIDER ALTERNATIVES |
|---|---|---|---|---|
| Pain | Fibromyalgia Agents | Milnacipran (Savella) | | |
| | Muscle Relaxants | Carisoprodol (Soma)<br>Cyclobenzaprine (Flexeril, Amrix)<br>Metaxalone (Skelaxin)<br>Methocarbamol (Robaxin)<br>Tizanidine (Zanaflex) | | |
| | NSAIDs | Ibuprofen (Advil, Motrin)<br>Ketoprofen (Orudis)<br>Ketorolac (Toradol)<br>Nabumetone (Relafen)<br>Naproxen (Aleve)<br>Sulindac (Clinoril) | Celecoxib (Celebrex)<br>Diclofenac (Voltaren)<br>Flurbiprofen (Ansaid)<br>Indomethacin (Indocin)<br>Meloxicam (Mobic)<br>Piroxicam (Feldene) | |
| | Opioids | Alfentanil (Alfenta)<br>Buprenorphine (Butrans, Buprenex)<br>Codeine (Codeine; Fioricet with Codeine)<br>Dihydrocodeine (Synalgos-DC)<br>Hydromorphone (Dilaudid, Exalgo)<br>Levorphanol (Levo Dromoran)<br>Meperidine (Demerol)<br>Oxycodone (Percocet, Oxycontin)<br>Oxymorphone (Opana, Numorphan)<br>Sufentanil (Sufenta)<br>Tapentadol (Nucynta)<br>Tramadol (Ultram) | Fentanyl (Actiq)<br>Hydrocodone (Vicodin)<br>Morphine (MS Contin) | |
| | Antiaddictives | Naltrexone (Vivitrol, Contrave) | Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave) | |
| | Anti-ADHD Agents | Atomoxetine (Strattera)<br>Clonidine (Kapvay)<br>Guanfacine (Intuniv) | Amphetamine (Adderall, Evekeo)<br>Dexmethylphenidate (Focalin)<br>Dextroamphetamine (Dexedrine)<br>Lisdexamfetamine (Vyvanse)<br>Methylphenidate (Ritalin, Aptensio XR, Concerta, Metadate ER, Quillivant ER) | |

| CATEGORY | DRUG CLASS | STANDARD PRECAUTIONS | USE WITH CAUTION | CONSIDER ALTERNATIVES |
|---|---|---|---|---|
| Psychotropic | Anticonvulsants | Brivaracetam (Briviact)<br>Carbamazepine (Tegretol, Carbatrol, Epitol)<br>Eslicarbazepine (Aptiom)<br>Ethosuximide (Zarontin)<br>Ezogabine (Potiga)<br>Felbamate (Felbatol)<br>Gabapentin (Neurontin)<br>Lacosamide (Vimpat)<br>Lamotrigine (Lamictal)<br>Levetiracetam (Keppra)<br>Oxcarbazepine (Trileptal, Oxtellar XR)<br>Perampanel (Fycompa)<br>Phenobarbital (Luminal)<br>Pregabalin (Lyrica)<br>Primidone (Mysoline)<br>Rufinamide (Banzel)<br>Tiagabine (Gabitril)<br>Topiramate (Topamax)<br>Valproic Acid (Depakote, Depakene)<br>Vigabatrin (Sabril)<br>Zonisamide (Zonegran) | Fosphenytoin (Cerebyx)<br>Phenytoin (Dilantin) | |
| | Antidementia Agents | Donepezil (Aricept)<br>Galantamine (Razadyne)<br>Memantine (Namenda) | | |
| | Antidepressants | Amitriptyline (Elavil)<br>Amoxapine (Amoxapine)<br>Citalopram (Celexa)<br>Clomipramine (Anafranil)<br>Desipramine (Norpramin)<br>Desvenlafaxine (Pristiq)<br>Doxepin (Silenor)<br>Duloxetine (Cymbalta)<br>Escitalopram (Lexapro)<br>Fluoxetine (Prozac, Sarafem)<br>Fluvoxamine (Luvox)<br>Imipramine (Tofranil)<br>Levomilnacipran (Fetzima)<br>Maprotiline (Ludiomil)<br>Mirtazapine (Remeron)<br>Nefazodone (Serzone)<br>Nortriptyline (Pamelor)<br>Paroxetine (Paxil, Brisdelle)<br>Protriptyline (Vivactil)<br>Sertraline (Zoloft)<br>Trazodone (Oleptro)<br>Trimipramine (Surmontil)<br>Venlafaxine (Effexor)<br>Vilazodone (Viibryd)<br>Vortioxetine (Trintellix) | | |

| CATEGORY | DRUG CLASS | STANDARD PRECAUTIONS | USE WITH CAUTION | CONSIDER ALTERNATIVES |
|---|---|---|---|---|
| | Antipsychotics | Aripiprazole (Abilify, Aristada)<br>Asenapine (Saphris)<br>Brexpiprazole (Rexulti)<br>Cariprazine (Vraylar)<br>Chlorpromazine (Thorazine)<br>Clozapine (Clozaril)<br>Fluphenazine (Prolixin)<br>Haloperidol (Haldol)<br>Iloperidone (Fanapt)<br>Loxapine (Loxitane, Adasuve)<br>Lurasidone (Latuda)<br>Olanzapine (Zyprexa)<br>Paliperidone (Invega)<br>Perphenazine (Trilafon)<br>Pimavanserin (Nuplazid)<br>Pimozide (Orap)<br>Quetiapine (Seroquel)<br>Risperidone (Risperdal)<br>Thioridazine (Mellaril)<br>Thiothixene (Navane)<br>Trifluoperazine (Stelazine)<br>Ziprasidone (Geodon) | | |
| | Benzodiazepines | Alprazolam (Xanax)<br>Clobazam (Onfi)<br>Clonazepam (Klonopin)<br>Diazepam (Valium) | | |
| | Other Neurological Agents | Deutetrabenazine (Austedo)<br>Dextromethorphan / Quinidine (Nuedexta)<br>Flibanserin (Addyi)<br>Valbenazine (Ingrezza) | Tetrabenazine (Xenazine) | |
| Rheumatology | Anti-Hyperuricemics and Anti-Gout Agents | Colchicine (Mitigare)<br>Febuxostat (Uloric)<br>Lesinurad (Zurampic) | | |
| | Immunomodulators | Apremilast (Otezla)<br>Leflunomide (Arava)<br>Tofacitinib (Xeljanz) | | |
| Transplantation | Immunosupressants | Tacrolimus (Prograf) | | |

| CATEGORY | DRUG CLASS | STANDARD PRECAUTIONS | USE WITH CAUTION | CONSIDER ALTERNATIVES |
|---|---|---|---|---|
| Urologicals | 5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia | Dutasteride (Avodart)<br>Finasteride (Proscar) | | |
| | Alpha-Blockers for Benign Prostatic Hyperplasia | Alfuzosin (UroXatral)<br>Doxazosin (Cardura)<br>Silodosin (Rapaflo)<br>Tamsulosin (Flomax)<br>Terazosin (Hytrin) | | |
| | Antispasmodics for Overactive Bladder | Darifenacin (Enablex)<br>Fesoterodine (Toviaz)<br>Mirabegron (Myrbetriq)<br>Oxybutynin (Ditropan)<br>Solifenacin (Vesicare)<br>Tolterodine (Detrol)<br>Trospium (Sanctura) | | |
| | Phosphodiesterase Inhibitors for Erectile Dysfunction | Avanafil (Stendra)<br>Sildenafil (Viagra)<br>Tadalafil (Cialis)<br>Vardenafil (Levitra) | | |

# Dosing Guidance

## Amphetamine
*Adderall, Evekeo*

**Poor Response to Amphetamine salts (COMT: Low COMT Activity)** — INFORMATIVE

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

## Bupropion
*Wellbutrin, Zyban, Aplenzin, Contrave*

**Decreased Response to Bupropion for Smoking Cessation (ANKK1: Altered DRD2 function)** — INFORMATIVE

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

## Celecoxib
*Celebrex*

**Possible Sensitivity to Celecoxib (CYP2C9: Intermediate Metabolizer)** — INFORMATIVE

Celecoxib can be prescribed at standard label-recommended dosage and administration. Evaluate response the first week and be alert to gastrointestinal adverse events.

## Dexmethylphenidate
*Focalin*

**Poor Response to Dexmethylphenidate (COMT: Low COMT Activity)** — INFORMATIVE

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

## Dextroamphetamine
*Dexedrine*

**Poor Response to Dextroamphetamine (COMT: Low COMT Activity)** — INFORMATIVE

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

## Diclofenac
*Voltaren*

**Possible Sensitivity to Diclofenac (CYP2C9: Intermediate Metabolizer)** — INFORMATIVE

Diclofenac is extensively metabolized by hydroxylation and direct glucuronidation. About 50% of diclofenac is eliminated as a 4-hydroxymetabolite, a reaction mediated by CYP2C9. Other CYP enzymes including CYP2C8, CYP2C19 and CYP3A4 are also involved in the formation of a 5-hydroxymetabolite. A substantial portion of the drug is also directly glucuronidated by UGT2B7 and UGT2B4. Individuals with decreased CYP2C9 activity (i.e intermediate metabolizers) should be closely monitored for increased gastrointestinal adverse events when prescribed diclofenac and lower doses may be more appropriate for these patients.

## Fentanyl
*Actiq*

**Altered Response to Fentanyl (OPRM1: Altered OPRM1 Function)** — INFORMATIVE

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

## Flurbiprofen
*Ansaid*

**Possible Sensitivity to Flurbiprofen (CYP2C9: Intermediate Metabolizer)** — INFORMATIVE

The patient may have high plasma levels of the drug. Flurbiprofen can be prescribed at standard label-recommended dosage and administration with closer monitoring for gastrointestinal side effects.

## Fluvastatin
*Lescol*

**Possible Sensitivity to Fluvastatin (CYP2C9: Intermediate Metabolizer)** — ACTIONABLE

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

## Fosphenytoin
*Cerebyx*

**Moderate Sensitivity to Fosphenytoin (CYP2C9: Intermediate Metabolizer)** — ACTIONABLE

The genotype results indicate that the patient is a CYP2C9 substrate intermediate metabolizer. Plasma concentrations of phenytoin are likely to increase, resulting in an increased risk of mild to moderate neurological toxicity. Consider a standard loading dose, and reduce the maintenance dose by 25%. Evaluate response and serum concentrations after 7-10 days. Be alert to neurological concentration-related adverse events.

## Hydrocodone
*Vicodin*

**Altered Response to Hydrocodone (OPRM1: Altered OPRM1 Function)** — INFORMATIVE

Acute postoperative and cancer pain: the patient's genotype has been shown to be associated with reduced analgesia and increased opioid side effects at standard or high hydrocodone doses. If the patient fails to respond to increased hydrocodone doses, an alternative opioid may be considered.

## Indomethacin
*Indocin*

**Possible Sensitivity to Indomethacin (CYP2C9: Intermediate Metabolizer)** — INFORMATIVE

Indomethacin is metabolized mainly by O-demethylation to its inactive metabolite O-desmethylindomethacin, a reaction catalyzed by CYP2C9. At standard doses, indomethacin plasma concentrations may be higher in individuals with decreased CYP2C9 function. Although indomethacin can be prescribed at standard label recommended-dosage and administration, a closer monitoring for signs of gastrointestinal toxicity during long-term administration is recommended.

## Lisdexamfetamine
*Vyvanse*

**Poor Response to Lisdexamfetamine (COMT: Low COMT Activity)** — INFORMATIVE

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

## Meloxicam
*Mobic*

**Possible Sensitivity to Meloxicam (CYP2C9: Intermediate Metabolizer)** — INFORMATIVE

Meloxicam plasma concentrations may be higher in individual with decreased CYP2C9 function. A reduction in meloxicam dosage may be needed with a closer monitoring for signs of gastrointestinal toxicity during long-term administration.

## Methylphenidate
*Ritalin, Aptensio XR, Concerta, Metadate ER, Quillivant ER*

**Poor Response to Methylphenidate (COMT: Low COMT Activity)** — INFORMATIVE

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

## Morphine
*MS Contin*

**Altered Response to Morphine (OPRM1: Altered OPRM1 Function)** — INFORMATIVE

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

## Morphine
*MS Contin*

**Altered Response to Morphine (COMT: Low COMT Activity)** — INFORMATIVE

The patient carries two COMT Val158Met mutations, which translates to a reduced COMT function. The patient may require lower doses of morphine for adequate pain control. The dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

## Phenytoin
*Dilantin*

**Moderate Sensitivity to Phenytoin (CYP2C9: Intermediate Metabolizer)** — ACTIONABLE

The genotype results indicate that the patient is a CYP2C9 substrate intermediate metabolizer. Plasma concentrations of phenytoin are likely to increase, resulting in an increased risk of mild to moderate neurological toxicity. Consider a standard loading dose, and reduce the maintenance dose by 25%. Evaluate response and serum concentrations after 7-10 days. Be alert to neurological concentration-related adverse events.

## Piroxicam
*Feldene*

**Possible Sensitivity to Piroxicam (CYP2C9: Intermediate Metabolizer)** — INFORMATIVE

Piroxicam plasma concentrations may be higher in individual with decreased CYP2C9 function. Although piroxicam can be prescribed at standard label-recommended dosage and administration, a closer monitoring for signs of gastrointestinal toxicity during long-term administration is recommended.

## Tetrabenazine
*Xenazine*

**Normal Sensitivity to Tetrabenazine (CYP2D6: Normal 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 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.

## Warfarin
*Coumadin*

**Moderate Sensitivity to Warfarin (CYP2C9 *1/*3 VKORC1 -1639G>A G/A)** — ACTIONABLE

Initiation Therapy: a dose decrease may be required. Consider using the following warfarin dose range provided in the FDA -approved label: **3-4 mg/day.** OR consider using a personalized dose as calculated by a pharmacogenetic algorithm. The estimated time to reach steady state is 8-10 days.

# Pharmacogenetic Test Results

| Gene | Genotype | Phenotype | Clinical Consequences |
|---|---|---|---|
| 12q15 | rs7297610 C/C | Homozygous for the C allele (rs7297610) | Favorable response to hydrochlorothiazide in African Americans |
| 4q25 | rs2200733 C/T | Heterozygous for rs2200733 variant | The patient has a heterozygous mutation in 4q25 variant rs2200733. Heterozygous mutations in rs2200733 are associated with a 1.7 times increase in atrial fibrillation risk. |
| 9p21 | rs10757278 G/G<br>rs1333049 C/C<br>rs2383206 G/G | 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). |
| ANKK1/DRD2 | DRD2:Taq1A A/G | Altered DRD2 function | Consistent with a reduced dopamine receptor D2 function. |
| Apolipoprotein E | ε3/ε3 | Normal APOE function | Not associated with type III hyperlipoproteinemia - No increased risk of cardiovascular disease |
| C11orf65 | rs11212617 A/A | Homozygous for the A allele (rs11212617) | Normal glycemic response to metformin |
| COMT | Val158Met A/A | Low COMT Activity | Consistent with a significantly reduced catechol O-methyltransferase (COMT) function. |
| CYP1A2 | *1A/*1V | Normal Metabolizer- Possible Inducibility | Consistent with a typical CYP1A2 activity in absence of inducing substances. Rapid metabolism may occur in presence of inducers such as barbiturates, cruciferous vegetables, carbamazepine, rifampin and smoking. |
| CYP2C19 | *1/*1 | Normal Metabolizer | Consistent with a typical CYP2C19 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates. |
| CYP2C9 | *1/*3 | Intermediate Metabolizer | Consistent with a moderate deficiency in CYP2C9 activity. Potential risk for side effects or loss of efficacy with drug substrates. |
| CYP2D6 | *1/*2 | Normal Metabolizer | Consistent with a typical CYP2D6 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates. |
| 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 a poor CYP3A5 activity. This phenotype is the most common in the general population. 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. |
| Factor II<br>Factor V Leiden | 20210G>A GG<br>1691G>A GG | No Increased Risk of Thrombosis | The patient's risk of thrombosis is not increased (average risk of clotting is about 1 in 1000 for anyone in a year). However, because this test cannot find all of the inherited reasons for abnormal clotting, other factors may affect this risk assessment. |
| LPA | rs10455872 A/A<br>rs3798220 T/T | No increased risk of cardiovascular disease | The patient is a non carrier of the risk alleles in LPA gene for both the variants (rs3798220 and rs10455872). |
| MTHFR | 1298A>C AC<br>677C>T CC | No Increased Risk of Hyperhomocysteinemia | The patient's slightly 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). |
| OPRM1 | A118G A/G | Altered OPRM1 Function | Consistent with a reduced OPRM1 receptor signaling efficiency induced by exogenous opioids. This is associated with a possible reduced analgesia following standard opioid doses and a favorable response to naltrexone. |
| SLC47A2 | -130G>A G/A | Moderately Increased Function | Normal renal and secretion clearance of metformin |
| SLCO1B1 | 521T>C T/T | Normal Function | Consistent with a typical SLCO1B1 transporter function. The patient's risk for statin-induced myopathy is not increased. |

| | | | |
|---|---|---|---|
| **VKORC1 and CYP2C9** | -1639G>A G/A, *1/*3 | **Moderate Sensitivity to Warfarin** | The CYP2C9 and VKORC1 genotype results predict a moderate sensitivity to warfarin. Plasma concentrations of warfarin are likely to increase, and inhibition of clotting may be intensified, resulting in an increased risk of side effects. The estimated time to reach steady state is 8-10 days. |

**Alleles Tested: 12q15** rs7297610; **4q25** rs2200733; **9p21** rs10757278, rs1333049, rs2383206; **ANKK1/DRD2** DRD2:Taq1A; **Apolipoprotein E** ε2, ε4, (ε3 is reference); **C11orf65** rs11212617; **COMT** Val158Met; **CYP1A2** *1C, *1D, *1F, *1K, *1L, *1V, *1W; **CYP2C19** *2, *3, *4, *4B, *5, *6, *7, *8, *17; **CYP2C9** *2, *3, *4, *5, *6, *8, *11, *27; **CYP2D6** *2, *3, *4, *4M, *6, *7, *9, *10, *14A, *14B, *17, *29, *41, *5 (gene deletion), XN (gene duplication); **CYP3A4** *1B, *2, *3, *22; **CYP3A5** *2, *3, *3C, *6, *7, *9; **Factor II** 20210G>A; **Factor V Leiden** 1691G>A; **LPA** rs3798220, rs10455872; **MTHFR** 1298A>C, 677C>T; **OPRM1** A118G; **SLC47A2** -130G>A; **SLCO1B1** 521T>C, 388A>G; **VKORC1** -1639G>A

**Electronically Signed By:** on GMT

**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%. For reports containing results for CYP2B6: CYP2B6 SNP rs2279343 was tested by Sanger Sequencing at Genewiz LLC, 115 Corporate Boulevard, South Plainfield, NJ 07080.

**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. Genotox Laboratories developed this test and its performance characteristics. This test has not been cleared or approved by the U.S. Food and Drug Administration. The pharmacogenetic report is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to dose guidelines does not necessarily assure a successful medical outcome.

**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.

**Laboratory Certification:** CLIA # 45D2044559

# 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.

RealLab diagnostics at its best

**REPORT DETAILS**

**Name:** TEST GENOTOX
**DOB:** 6/23/1944
**ACC #:** VGTX00001

**Pharmacogenetic Test Summary**

| | | |
|---|---|---|
| 12q15 | rs7297610 C/C | Homozygous for the C allele (rs7297610) |
| 4q25 | rs2200733 C/T | Heterozygous for rs2200733 variant |
| 9p21 | rs10757278 G/G<br>rs1333049 C/C<br>rs2383206 G/G | Significantly increased risk of coronary artery disease |
| ANKK1/DRD2 | DRD2:Taq1A A/G | Altered DRD2 function |
| Apolipoprotein E | ε3/ε3 | Normal APOE function |
| C11orf65 | rs11212617 A/A | Homozygous for the A allele (rs11212617) |
| COMT | Val158Met A/A | Low COMT Activity |
| CYP1A2 | *1A/*1V | Normal Metabolizer- Possible Inducibility |
| CYP2C19 | *1/*1 | Normal Metabolizer |
| CYP2C9 | *1/*3 | Intermediate Metabolizer |
| CYP2D6 | *1/*2 | Normal Metabolizer |
| CYP3A4 | *1/*1 | Normal Metabolizer |
| CYP3A5 | *3/*3 | Poor Metabolizer |
| Factor II<br>Factor V Leiden | 20210G>A GG<br>1691G>A GG | No Increased Risk of Thrombosis |
| LPA | rs10455872 A/A<br>rs3798220 T/T | No increased risk of cardiovascular disease |
| MTHFR | 1298A>C AC<br>677C>T CC | No Increased Risk of Hyperhomocysteinemia |
| OPRM1 | A118G A/G | Altered OPRM1 Function |
| SLC47A2 | -130G>A G/A | Moderately Increased Function |
| SLCO1B1 | 521T>C T/T | Normal Function |
| VKORC1 and CYP2C9 | -1639G>A G/A,<br>*1/*3 | Moderate Sensitivity to Warfarin |