GENEMARKERS

| PATIENT INFORMATION | | SPECIMEN DETAILS | | PROVIDER INFORMATION |
|---|---|---|---|---|
| **NAME:** | **959168507 NA** | **SPECIMEN TYPE:** | Buccal Swab | David Kisor PharmD |
| **ACC #:** | 959168507 | **COLLECTION DATE:** | 7/9/2019 | |
| **DOB:** | 7/12/2019 | **RECEIVED DATE:** | 7/12/2019 | |
| **SEX:** | Unknown | **REPORT DATE:** | 7/19/2019 | |

# Genemarkers PGXMarkers Panel Report

## Test Details

| Gene | Genotype | Phenotype | Clinical Consequences |
|---|---|---|---|
| ANKK1/DRD2 | DRD2:Taq1A A/G | Altered DRD2 function | Consistent with a reduced dopamine receptor D2 function. |
| COMT | Val158Met G/G | High/Normal COMT Activity | Consistent with a normal catechol O-methyltransferase (COMT) function. |
| CYP1A2 | *1A/*1L | 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. |
| CYP2B6 | *6/*6 | Poor Metabolizer | Consistent with a significant deficiency in CYP2B6 drug metabolism. Increased risk for side effects or loss of efficacy with drug substrates. |
| CYP2C19 | *1/*2 | Intermediate Metabolizer | Consistent with a moderate deficiency in CYP2C19 activity. Potential risk for side effects or loss of efficacy with drug substrates. |
| CYP2C9 | *1/*1 | Normal Metabolizer | Consistent with a typical CYP2C9 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates. |
| CYP2D6 | *1/*41 | 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/*1B | 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 | *1/*7 | Intermediate Metabolizer | Consistent with an intermediate CYP3A5 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. |
| 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. |
| HTR2C | -759C>T C/C | Homozygous for the C allele (rs3813929) | Consistent with altered satiety signaling mediated by the serotonin receptor 2C (HTR2C). Increased incidence of metabolic side effects (weight gain, hyperglycemia, hyperlipidemia) with atypical antipsychotic medications. |
| MTHFR | c.665C>T GG | Normal MTHFR Activity | The patient does not carry the MTHFR C677T mutation (wild-type) and the patient's MTHFR activity is normal. This is not associated with an increased risk of hyperhomocysteinemia. |
| MTHFR | c.1286A>C TT<br>c.665C>T GG | No Increased Risk of Hyperhomocysteinemia | The patient has a normal MTHFR function, and no elevation of plasma homocysteine levels is expected. The risk for venous thromboembolism is not increased. |
| 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. |
| 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 | -1639G>A G/G | Low Warfarin Sensitivity | VKORC1 is the site of action of warfarin. The patient may require an increase in warfarin dose. |

**Alleles Tested: ANKK1/DRD2** DRD2:Taq1A; **COMT** Val158Met; **CYP1A2** *1C, *1D, *1F, *1K, *1L, *1V, *1W; **CYP2B6** *6, *9; **CYP2C19** *2, *3, *4, *4B, *5, *6, *7, *8, *9, *17; **CYP2C9** *2, *3, *4, *5, *6, *8, *11; **CYP2D6** *2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *14A, *14B, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication); **CYP3A4** *1B, *2, *3, *12, *17, *22; **CYP3A5** *1D, *2, *3, *3B, *3C, *6, *7, *8, *9; **HTR2A** -1438G>A; **HTR2C** -759C>T; **MTHFR** c.1286A>C, c.665C>T; **OPRM1** A118G; **SLCO1B1** 521T>C, 388A>G; **VKORC1** -1639G>A

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# Risk Management

## ⚠ Antipsychotic-Induced Tardive Dyskinesia

### Moderate Risk of Antipsychotic-Induced Tardive Dyskinesia

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

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

Monitor the patient for any signs of tardive dyskinesia.

## ⚠ Antipsychotic-Induced Hyperprolactinemia

### Moderate Risk of Antipsychotic-induced Hyperprolactinemia

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

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

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

## ⚠ Antipsychotic-Induced Weight Gain

### Moderate Risk of Antipsychotic-Induced Weight Gain

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

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

Monitor patient closely for signs of weight gain.

## ✓ 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.

## ✓ Hyperhomocysteinemia - Thrombosis

### No Increased Risk of Hyperhomocysteinemia

The patient does not carry the MTHFR c.665C>T variant or MTHFR c.1286A>C variant (wild-type). MTHFR enzyme activity is normal.

With a normal MTHFR activity, this patient is unlikely to have elevated plasma levels of homocysteine, which is a known risk factor for cardiovascular diseases and thrombosis. Unless other risk factors are present, the patient is not expected to have an increased risk for venous thromboembolism (VTE).

MTHFR enzyme activity is normal.

⊗ A medication has potentially reduced efficacy, increased toxicity or the patient has an increased risk for the indicated condition.

⚠ 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.

**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.

**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.

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# Potentially Impacted Medications

*The drugs that appear in this table are based solely on the patient's genetic results. Please note that there are available alternative medications that do not have PGx guidance and are not included within this report.*

| CATEGORY | DRUG CLASS | STANDARD PRECAUTIONS | USE WITH CAUTION | CONSIDER ALTERNATIVES |
|---|---|---|---|---|
| **Anesthesia** | **Injectable Anesthetics** | | Propofol (Diprivan®) | |
| **Anticancer Agents** | **Antifolates** | Methotrexate (Trexall®) | | |
| **Cardiovascular** | **Angiotensin II Receptor Antagonists** | Azilsartan (Edarbi®, Edarbyclor®)<br>Irbesartan (Avapro®)<br>Losartan (Cozaar®, Hyzaar®) | | |
| | **Antianginal Agents** | Ranolazine (Ranexa®) | | |
| | **Antiarrhythmics** | Flecainide (Tambocor®)<br>Mexiletine (Mexitil®)<br>Propafenone (Rythmol®) | | |
| | **Anticoagulants** | Warfarin (Coumadin®) | | |
| | **Antiplatelets** | | | Clopidogrel (Plavix®) |
| | **Beta Blockers** | Carvedilol (Coreg®)<br>Metoprolol (Lopressor®)<br>Nebivolol (Bystolic®)<br>Propranolol (Inderal®)<br>Timolol (Timoptic®) | | |
| | **Diuretics** | Torsemide (Demadex®) | | |
| | **Statins** | Atorvastatin (Lipitor®)<br>Fluvastatin (Lescol®)<br>Lovastatin (Mevacor®, Altoprev®, Advicor®)<br>Pitavastatin (Livalo®)<br>Pravastatin (Pravachol®)<br>Rosuvastatin (Crestor®)<br>Simvastatin (Zocor®) | | |
| | **Meglitinides** | Nateglinide (Starlix®)<br>Repaglinide (Prandin®, Prandimet®) | | |

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| CATEGORY | DRUG CLASS | STANDARD PRECAUTIONS | USE WITH CAUTION | CONSIDER ALTERNATIVES |
|---|---|---|---|---|
| **Diabetes** | **Sulfonylureas** | Chlorpropamide (Diabinese®)<br>Glimepiride (Amaryl®)<br>Glipizide (Glucotrol®)<br>Glyburide (Micronase®)<br>Tolbutamide (Orinase®) | | |
| **Gastrointestinal** | **Antiemetics** | Dolasetron (Anzemet®)<br>Dronabinol (Marinol®)<br>Fosnetupitant-Palonosetron (Akynzeo-i.v®)<br>Metoclopramide (Reglan®)<br>Netupitant-Palonosetron (Akynzeo-oral®)<br>Ondansetron (Zofran®, Zuplenz®)<br>Palonosetron (Aloxi®) | | |
| | **Proton Pump Inhibitors** | Dexlansoprazole (Dexilant®, Kapidex®)<br>Esomeprazole (Nexium®)<br>Lansoprazole (Prevacid®)<br>Omeprazole (Prilosec®)<br>Pantoprazole (Protonix®)<br>Rabeprazole (Aciphex®) | | |
| **Gaucher Disease** | **Endocrine-Metabolic Agents** | Eliglustat (Cerdelga®) | | |
| **Infections** | **Antifungals** | Voriconazole (Vfend®) | | |
| | **Antimalarials** | Proguanil (Malarone®) | | |
| | **Muscle Relaxants** | Carisoprodol (Soma®) | Tizanidine (Zanaflex®) | |
| | **NSAIDs** | Celecoxib (Celebrex®)<br>Diclofenac (Voltaren®)<br>Flurbiprofen (Ansaid®)<br>Ibuprofen (Advil®, Motrin®)<br>Indomethacin (Indocin®)<br>Meloxicam (Mobic®)<br>Piroxicam (Feldene®) | | |

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|---|---|---|---|---|
| **Pain** | **Opioids** | Benzhydrocodone (Apadaz®)<br>Codeine (Codeine; Fioricet® with Codeine)<br>Dihydrocodeine (Synalgos-DC®)<br>Fentanyl (Actiq®)<br>Hydrocodone (Vicodin®)<br>Oxycodone (Percocet®, Oxycontin®)<br>Tramadol (Ultram®) | Methadone (Dolophine®)<br>Morphine (MS Contin®) | |
| | **Antiaddictives** | Lofexidine (Lucemyra®) | Naltrexone (Vivitrol®, Contrave®) | Bupropion (Wellbutrin®, Zyban®, Aplenzin®, Contrave®) |
| | **Anti-ADHD Agents** | Amphetamine (Adderall®, Evekeo®)<br>Clonidine (Kapvay®)<br>Dexmethylphenidate (Focalin®)<br>Dextroamphetamine (Dexedrine®)<br>Lisdexamfetamine (Vyvanse®)<br>Methylphenidate (Ritalin®, Aptensio XR®, Concerta®, Metadate ER®, Quillivant ER®) | Atomoxetine (Strattera®) | |
| | **Anticonvulsants** | Brivaracetam (Briviact®)<br>Fosphenytoin (Cerebyx®)<br>Lacosamide (Vimpat®)<br>Phenytoin (Dilantin®) | Phenobarbital (Luminal®)<br>Primidone (Mysoline®)<br>Zonisamide (Zonegran®) | |
| | **Antidementia Agents** | Donepezil (Aricept®)<br>Galantamine (Razadyne®) | | |

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|---|---|---|---|---|
| **Psychotropic** | **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>Maprotiline (Ludiomil®)<br>Mirtazapine (Remeron®)<br>Nefazodone (Serzone®)<br>Nortriptyline (Pamelor®)<br>Paroxetine (Paxil®, Brisdelle®)<br>Protriptyline (Vivactil®)<br>Sertraline (Zoloft®)<br>Trimipramine (Surmontil®)<br>Venlafaxine (Effexor®)<br>Vortioxetine (Trintellix®) | | |
| | **Antipsychotics** | Aripiprazole (Abilify®, Aristada®)<br>Brexpiprazole (Rexulti®)<br>Chlorpromazine (Thorazine®)<br>Fluphenazine (Prolixin®)<br>Haloperidol (Haldol®)<br>Iloperidone (Fanapt®)<br>Paliperidone (Invega®)<br>Perphenazine (Trilafon®)<br>Pimozide (Orap®)<br>Risperidone (Risperdal®)<br>Thioridazine (Mellaril®) | Clozapine (Clozaril®)<br>Olanzapine (Zyprexa®) | |
| | **Benzodiazepines** | Diazepam (Valium®) | Clobazam (Onfi®) | |
| | **Other Neurological Agents** | Deutetrabenazine (Austedo®)<br>Dextromethorphan / Quinidine (Nuedexta®)<br>Flibanserin (Addyi®)<br>Valbenazine (Ingrezza®) | Tetrabenazine (Xenazine®) | |

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| CATEGORY | DRUG CLASS | STANDARD PRECAUTIONS | USE WITH CAUTION | CONSIDER ALTERNATIVES |
|---|---|---|---|---|
| **Rheumatology** | **Anti-Hyperuricemics and Anti-Gout Agents** | Lesinurad (Zurampic®) | | |
| | **Immunomodulators** | Tofacitinib (Xeljanz®) | Leflunomide (Arava®) | |
| **Sjogren's Syndrome** | **Cholinergic Agonists** | Cevimeline (Evoxac®) | | |
| **Transplantation** | **Immunosuppressants** | | Tacrolimus (Prograf®) | |
| **Urologicals** | **Alpha-Blockers for Benign Prostatic Hyperplasia** | Tamsulosin (Flomax®) | | |
| | **Antispasmodics for Overactive Bladder** | Darifenacin (Enablex®)<br>Fesoterodine (Toviaz®)<br>Mirabegron (Myrbetriq®)<br>Tolterodine (Detrol®) | | |

# Dosing Guidance

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

### Decreased Response to Bupropion (CYP2B6: Poor Metabolizer) — INFORMATIVE

Bupropion is metabolized to its active metabolite hydroxybupropion by CYP2B6. This metabolite contributes to the therapeutic effects of bupropion when used as a smoking cessation agent or as an antidepressant. Individuals who are CYP2B6 poor metabolizers have significantly lower blood levels of hydroxybupropion which may result in a reduced response to bupropion treatment.

To avoid non-response, an increased dose of bupropion or an alternative medication may be considered in CYP2B6 poor metabolizers. Therapeutic monitoring of hydroxybupropion levels may be considered to guide dosing adjustment. **Because Bupropion is associated with a risk of seizures that is dose-related, it is advised to increase bupropion dose gradually and to carefully monitor the patient's response.**

Zhu A Z X AZ, Cox L S LS, Nollen N N, Faseru B B, Okuyemi K S KS, Ahluwalia J S JS, Benowitz N L NL, Tyndale R F RF. CYP2B6 and bupropion's smoking-cessation pharmacology: the role of hydroxybupropion., Clin. Pharmacol. Ther. 2012 11;92(6):771-7.
Lee Anna M AM, Jepson Christopher C, Hoffmann Ewa E, Epstein Leonard L, Hawk Larry W LW, Lerman Caryn C, Tyndale Rachel F RF. CYP2B6 genotype alters abstinence rates in a bupropion smoking cessation trial., Biol. Psychiatry 2007 09;62(6):635-41.
Høiseth Gudrun G, Haslemo Tore T, Uthus Linda H LH, Molden Espen E. Effect of CYP2B6*6 on Steady-State Serum Concentrations of Bupropion and Hydroxybupropion in Psychiatric Patients: A Study Based on Therapeutic Drug Monitoring Data., Ther Drug Monit 2015 09;37(5):589-93.

## Clopidogrel
*Plavix®*

### 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.

Scott S A SA, Sangkuhl K K, Gardner E E EE, Stein C M CM, Hulot J-S JS, Johnson J A JA, Roden D M DM, Klein T E TE, Shuldiner A R AR, . Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy., Clin. Pharmacol. Ther. 2011 07;90(2):328-32.

## Atomoxetine
*Strattera®*

### Possible Atomoxetine Underexposure Leading to Decreased Response (CYP2D6: Normal 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).

Brown JT, Bishop JR, Sangkuhl K, Nurmi EL, Mueller DJ, Dinh JC, Gaedigk A, Klein TE, Caudle KE, McCracken JT, de Leon J, Leeder JS. Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther 2019 Feb;():.

## Clobazam
*Onfi®*

### 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.

Onfi [package insert]. Deerfield, IL: Lundbeck Inc.; 2013.
Seo Takayuki T, Nagata Rie R, Ishitsu Takateru T, Murata Tsukasa T, Takaishi Chisato C, Hori Masaharu M, Nakagawa Kazuko K. Impact of CYP2C19 polymorphisms on the efficacy of clobazam therapy., Pharmacogenomics 2008 05;9(5):527-37.
Kosaki Kenjiro K, Tamura Kazuyo K, Sato Reiko R, Samejima Hazuki H, Tanigawara Yusuke Y, Takahashi Takao T. A major influence of CYP2C19 genotype on the steady-state concentration of N-desmethylclobazam., Brain Dev. 2004 11;26(8):530-4.

## Clozapine
*Clozaril®*

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

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

Bolla Emilio E, Bortolaso Paola P, Ferrari Marco M, Poloni Nicola N, Callegari Camilla C, Marino Franca F, Lecchini Sergio S, Vender Simone S, Cosentino Marco M. Are CYP1A2*1F and *1C associated with clozapine tolerability?: a preliminary investigation., Psychiatry Res 2011 10 30;189(3):483.
Ferrari Marco M, Bolla Emilio E, Bortolaso Paola P, Callegari Camilla C, Poloni Nicola N, Lecchini Sergio S, Vender Simone S, Marino F, Cosentino Franca M. Association between CYP1A2 polymorphisms and clozapine-induced adverse reactions in patients with schizophrenia., Psychiatry Res 2012 12 30;200(2-3):1014-7.
Ozdemir V V, Kalow W W, Okey A B AB, Lam M S MS, Albers L J LJ, Reist C C, Fourie J J, Posner P P, Collins E J EJ, Roy R R. Treatment-resistance to clozapine in association with ultrarapid CYP1A2 activity and the C-->A polymorphism in intron 1 of the CYP1A2 gene: effect of grapefruit juice and low-dose fluvoxamine., J Clin Psychopharmacol 2001 12;21(6):603-7.
Koonrungsesomboon N, Khatsri R, Wongchompoo P, Teekachunhatean S. The impact of genetic polymorphisms on CYP1A2 activity in humans: a systematic review and meta-analysis. Pharmacogenomics J 2017 Dec;():.

## Leflunomide
*Arava®*

### Increased Sensitivity 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.

Wiese Michael D MD, Schnabl Matthew M, O'Doherty Catherine C, Spargo Llewellyn D LD, Sorich Michael J MJ, Cleland Leslie G LG, Proudman Susanna M SM. Polymorphisms in cytochrome P450 2C19 enzyme and cessation of leflunomide in patients with rheumatoid arthritis., Arthritis Res. Ther. 2014 07;14(4):R163.
Bohanec Grabar Petra P, Grabnar Iztok I, Rozman Blaz B, Logar Dusan D, Tomsic Matija M, Suput Dasa D, Trdan Tina T, Peterlin Masic Lucija L, Mrhar Ales A, Dolzan Vita V. Investigation of the influence of CYP1A2 and CYP2C19 genetic polymorphism on 2-Cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-2-butenamide (A77 1726) pharmacokinetics in leflunomide-treated patients with rheumatoid arthritis., Drug Metab. Dispos. 2009 09;37(10):2061-8.

## Methadone
*Dolophine®*

### Increased Sensitivity to Methadone (CYP2B6: Poor Metabolizer)
**INFORMATIVE**

Increased S-methadone plasma concentrations with associated-cardiotoxicity may occur. Consider a lower initial dose, and adjust dosing based on the clinical response. CYP2B6 poor metabolizers require lower maintenance doses than normal metabolizers. Consider an alternative medication in patients with other arrhythmias or a family history of long QT syndrome.

Dobrinas Maria M, Crettol Séverine S, Oneda Beatrice B, Lahyani Rachel R, Rotger Margalida M, Choong Eva E, Lubomirov Rubin R, Csajka Chantal C, Eap Chin B CB. Contribution of CYP2B6 alleles in explaining extreme (S)-methadone plasma levels: a CYP2B6 gene resequencing study., Pharmacogenet Genomics 2013 01;23(2):84-93.
Kharasch Evan D ED, Regina Karen J KJ, Blood Jane J, Friedel Christina C. Methadone Pharmacogenetics: CYP2B6 Polymorphisms Determine Plasma Concentrations, Clearance, and Metabolism., Anesthesiology 2015 10;123(5):1142-53.
Kringen Marianne K MK, Chalabianloo Fatemeh F, Bernard Jean-Paul JP, Bramness Jørgen G JG, Molden Espen E, Høiseth Gudrun G. The combined effect of CYP2B6 genotype and other candidate genes on a steady-state serum concentration of methadone in opioid maintenance treatment., Ther Drug Monit 2017 07;():.

## Morphine
*MS Contin®*

### Altered Response to Morphine (COMT: High/Normal COMT Activity)
**INFORMATIVE**

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

Rakvåg Trude T TT, Ross Joy R JR, Sato Hiroe H, Skorpen Frank F, Kaasa Stein S, Klepstad Pål P. Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain., Mol Pain 2008 02 18;4:64.
Rakvåg Trude Teoline TT, Klepstad Pål P, Baar Cecilie C, Kvam Tor-Morten TM, Dale Ola O, Kaasa Stein S, Krokan Hans Einar HE, Skorpen Frank F. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients., Pain 2005 06;116(1-2):73-8.
Matic Maja M, Simons Sinno H P SH, van Lingen Richard A RA, van Rosmalen Joost J, Elens Laure L, de Wildt Saskia N SN, Tibboel Dick D, van Schaik Ron H N RH. Rescue morphine in mechanically ventilated newborns associated with combined OPRM1 and COMT genotype., Pharmacogenomics 2014 08;15(10):1287-95.

## Naltrexone
*Vivitrol®, Contrave®*

### 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.

Kranzler Henry R HR, Armeli Stephen S, Covault Jonathan J, Tennen Howard H. Variation in OPRM1 moderates the effect of desire to drink on subsequent drinking and its attenuation by naltrexone treatment., Addict Biol 2013 01;18(1):193-201.
Chamorro Antonio-Javier AJ, Marcos Miguel M, Mirón-Canelo José-Antonio JA, Pastor Isabel I, González-Sarmiento Rogelio R, Laso Francisco-Javier FJ. Association of μ-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis., Addict Biol 2012 04;17(3):505-12.
Coller Janet K JK, Cahill Sharon S, Edmonds Carolyn C, Farquharson Aaron L AL, Longo Marie M, Minniti Rinaldo R, Sullivan Thomas T, Somogyi Andrew A AA, White Jason M JM. OPRM1 A118G genotype fails to predict the effectiveness of naltrexone treatment for alcohol dependence., Pharmacogenet. Genomics 2011 11;21(12):902-5.

## Olanzapine
*Zyprexa®*

### Increased Risk of Weight Gain with Olanzapine (HTR2C: Homozygous for the C allele (rs3813929))
**INFORMATIVE**

Genetic variations in the Serotonin 2C Receptor (HTR2C) gene in known to be partially involved in the adverse effects associated with atypical antipsychotic medications. The patient is homozygous for C allele of HTR2C variant rs3813929. Patients with this genotype may have an increased risk of weight gain when treated with olanzapine.

Godlewska B R BR, Olajossy-Hilkesberger L L, Ciwoniuk M M, Olajossy M M, Marmurowska-Michałowska H H, Limon J J, Landowski J J. Olanzapine-induced weight gain is associated with the -759C/T and -697G/C polymorphisms of the HTR2C gene., Pharmacogenomics J. 2009 07;9(4):234-41.
Ellingrod Vicki L VL, Perry Paul J PJ, Ringold John C JC, Lund Brian C BC, Bever-Stille Kristy K, Fleming Frank F, Holman Timothy L TL, Miller Del D. Weight gain associated with the -759C/T polymorphism of the 5HT2C receptor and olanzapine., Am. J. Med. Genet. B Neuropsychiatr. Genet. 2005 03;134B(1):76-8.
Daray Federico Manuel FM, Rodante Demián D, Carosella Laura G LG, Silva María Elena ME, Martínez Melina M, Fernández Busch María V MV, Faccone Diego F DF, Rothlin Rodolfo P RP, Maffía Paulo C PC. -759C>T Polymorphism of the HTR2C Gene is Associated with Second Generation Antipsychotic-Induced Weight Gain in Female Patients with Schizophrenia., Pharmacopsychiatry 2017 03;50(1):14-18.

## Olanzapine

*Zyprexa®*

### Possible Non-Response to Olanzapine (CYP1A2: Normal Metabolizer- Possible 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.

Perera Vidya V, Gross Annette S AS, Polasek Thomas M TM, Qin Yan Y, Rao Gauri G, Forrest Alan A, Xu Junzhe J, McLachlan Andrew J AJ. Considering CYP1A2 phenotype and genotype for optimizing the dose of olanzapine in the management of schizophrenia., Expert Opin Drug Metab Toxicol 2013 08;9(9):1115-37.
Laika B B, Leucht S S, Heres S S, Schneider H H, Steimer W W. Pharmacogenetics and olanzapine treatment: CYP1A2*1F and serotonergic polymorphisms influence therapeutic outcome., Pharmacogenomics J 2010 01;10(1):20-9.
Koonrungsesomboon N, Khatsri R, Wongchompoo P, Teekachunhatean S. The impact of genetic polymorphisms on CYP1A2 activity in humans: a systematic review and meta-analysis. Pharmacogenomics J 2017 Dec;():.

## Phenobarbital

*Luminal®*

### 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.

Lee Soon Min SM, Chung Jae Yong JY, Lee Young Mock YM, Park Min Soo MS, Namgung Ran R, Park Kook In KI, Lee Chul C. Effects of cytochrome P450 (CYP)2C19 polymorphisms on pharmacokinetics of phenobarbital in neonates and infants with seizures., Arch. Dis. Child. 2012 05;97(6):569-72.
Mamiya K K, Hadama A A, Yukawa E E, Ieiri I I, Otsubo K K, Ninomiya H H, Tashiro N N, Higuchi S S. CYP2C19 polymorphism effect on phenobarbitone. Pharmacokinetics in Japanese patients with epilepsy: analysis by population pharmacokinetics., Eur. J. Clin. Pharmacol. 2000 07;55(11-12):821-5.
Yukawa E E, Mamiya K K. Effect of CYP2C19 genetic polymorphism on pharmacokinetics of phenytoin and phenobarbital in Japanese epileptic patients using Non-linear Mixed Effects Model approach., J Clin Pharm Ther 2006 06;31(3):275-82.
Anderson, Gail D. "Chemisry, Biotransformation, and Pharmacokinetics." Antiepileptic Drugs. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002. 496-03. Print.

## Primidone

*Mysoline®*

### 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.

Fincham, Richard W., and Dorothy D. Schottelius. "Primidone." Antiepileptic Drugs. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002. 621-36. Print.

## Propofol

*Diprivan®*

### Possible Altered Propofol Response (CYP2B6: Poor Metabolizer)

INFORMATIVE

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

Mastrogianni Orthodoxia O, Gbandi Emma E, Orphanidis Amvrosios A, Raikos Nikolaos N, Goutziomitrou Evangelia E, Kolibianakis Efstratios M EM, Tarlatzis Basil C BC, Goulas Antonis A. Association of the CYP2B6 c.516G>T polymorphism with high blood propofol concentrations in women from northern Greece., Drug Metab. Pharmacokinet. 2014 04;29(2):215-8.
Murayama N N, Minoshima M M, Shimizu M M, Guengerich F P FP, Yamazaki H H. Involvement of human cytochrome P450 2B6 in the omega- and 4-hydroxylation of the anesthetic agent propofol., Xenobiotica 2007 07;37(7):717-24.
Court M H MH, Duan S X SX, Hesse L M LM, Venkatakrishnan K K, Greenblatt D J DJ. Cytochrome P-450 2B6 is responsible for interindividual variability of propofol hydroxylation by human liver microsomes., Anesthesiology 2001 01;94(1):110-9.

## Tacrolimus

*Prograf®*

### Insufficient Response to Tacrolimus (CYP3A5: Intermediate Metabolizer)

ACTIONABLE

The genotype result predicts that the patient expresses the CYP3A5 protein. Therefore, the patient may metabolize tacrolimus more rapidly, resulting in low tacrolimus trough levels. Studies have shown patients with this genotype may be at increased risk for acute transplant rejection while taking a standard dose of tacrolimus. Therefore, increasing starting dose 1.5 to 2 times recommended starting dose with close monitoring is strongly recommended to achieve therapeutic effect. Total starting dose should not exceed 0.3mg/kg/day.

Birdwell K A KA, Decker B B, Barbarino J M JM, Peterson J F JF, Stein C M CM, Sadee W W, Wang D D, Vinks A A AA, He Y Y, Swen J J JJ, Leeder J S JS, van Schaik Rhn R, Thummel K E KE, Klein T E TE, Caudle K E KE, MacPhee I A M IA. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing., Clin. Pharmacol. Ther. 2015 06;98(1):19-24.

## 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.

Xenazine [package insert]. Deerfield, IL: Lundbeck Inc.; 2011.

## Tizanidine
*Zanaflex®*

**Possible Non-Response to Tizanidine (CYP1A2: Normal Metabolizer- Possible 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.

Backman Janne T JT, Schröder Marika T MT, Neuvonen Pertti J PJ. Effects of gender and moderate smoking on the pharmacokinetics and effects of the CYP1A2 substrate tizanidine., Eur J Clin Pharmacol 2008 01;64(1):17-24.

Granfors MT, Backman JT, Neuvonen M, Ahonen J, Neuvonen PJ. Fluvoxamine drastically increases concentrations and effects of tizanidine: a potentially hazardous interaction. Clin Pharmacol Ther 2004 Apr;75(4):331-41.

Al-Ghazawi M, Alzoubi M, Faidi B. Pharmacokinetic comparison of two 4 mg tablet formulations of tizanidine. Int J Clin Pharmacol Ther 2013 Mar;51(3):255-62.

Koonrungsesomboon N, Khatsri R, Wongchompoo P, Teekachunhatean S. The impact of genetic polymorphisms on CYP1A2 activity in humans: a systematic review and meta-analysis. Pharmacogenomics J 2017 Dec;():.

## Zonisamide
*Zonegran®*

**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.

Okada Yusuke Y, Seo Takayuki T, Ishitsu Takateru T, Wanibuchi Atsuko A, Hashimoto Nami N, Higa Yoko Y, Nakagawa Kazuko K. Population estimation regarding the effects of cytochrome P450 2C19 and 3A5 polymorphisms on zonisamide clearance., Ther Drug Monit 2008 08;30(4):540-3.

**PATIENT INFORMATION**

**NAME:** **959168507 NA**
**ACC #:** 959168507
**DOB:** 7/12/2019
**SEX:** Unknown

**Disclaimer**

Genemarkers personnel are not medical doctors and this report is not medical advice. Treatment for any condition depends highly on individual circumstances. Medical research and knowledge about medical and health issues is constantly evolving. Dose schedules for medications are continually revised, as new side effects are recognized. The user of this report has the responsibility to seek proper professional advice and to consult up-to-date published product information, data sheets provided by the manufacturers, codes of conduct, and safety regulations.

Genemarkers has tested samples only a) to identify whether a sample has genotypes that correspond with increased or decreased drug metabolism, and b) if any of those genotypes appear in the test sample, to list medications with dosing guidelines that may be impacted by those genotypes. Genemarkers makes no representation or warranty, expressed or implied, as to anything other than its testing process. Genemarkers disclaims responsibility for any loss, risk, or liability arising from the use of this report. For any liability, Genemarkers may have as to its testing procedures, Genemarkers is not responsible for damages in excess of the fees Genemarkers has received for its testing work.

**Methodology**

Genomic DNA was isolated from the specimen provided and the relevant genomic regions were amplified by polymerase chain reaction (PCR). This test was developed and its performance determined by Genemarkers laboratory. It has not been cleared or approved by the U.S. Food and Drug Administration. Since FDA is not required for clinical use of this test, Genemarkers laboratory has established and validated the test's accuracy and precision, pursuant to the requirement of CLIA '88.

**Limitations**

PCR based assays detect listed alleles, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity > 99%. Variants tested are listed in the table below. Rare variants may not have been observed at Genemarkers. Other known variants not listed are not detected.

**Laboratory Certification**

Genemarkers laboratory is licensed and/or accredited under CLIA to perform High Complexity Testing. CLIA ID Number 23D2061638.

**Reviewed By**: Jeanne Ohrnberger, PhD

GENEMARKERS

**PATIENT INFORMATION**

**NAME:** **959168507 NA**
**ACC #:** 959168507
**DOB:** 7/12/2019
**SEX:** Unknown

# 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.

GENEMARKERS

**REPORT DETAILS**
**Name:** 959168507 NA
**DOB:** 7/12/2019
**ACC #:** 959168507

**Pharmacogenetic Test Summary**

| | | |
|---|---|---|
| ANKK1/DRD2 | DRD2:Taq1A A/G | Altered DRD2 function |
| COMT | Val158Met G/G | High/Normal COMT Activity |
| CYP1A2 | *1A/*1L | Normal Metabolizer- Possible Inducibility |
| CYP2B6 | *6/*6 | Poor Metabolizer |
| CYP2C19 | *1/*2 | Intermediate Metabolizer |
| CYP2C9 | *1/*1 | Normal Metabolizer |
| CYP2D6 | *1/*41 | Normal Metabolizer |
| CYP3A4 | *1/*1B | Normal Metabolizer |
| CYP3A5 | *1/*7 | Intermediate Metabolizer |
| HTR2A | -1438G>A C/T | Heterozygous for the T Allele (rs6311) |
| HTR2C | -759C>T C/C | Homozygous for the C allele (rs3813929) |
| MTHFR | c.665C>T GG | Normal MTHFR Activity |
| MTHFR | c.1286A>C TT | Normal MTHFR Activity |
| OPRM1 | A118G A/A | Normal OPRM1 Function |
| SLCO1B1 | 521T>C T/T | Normal Function |
| VKORC1 | -1639G>A G/G | Low Warfarin Sensitivity |

For a complete report contact Genemarkers
**http://www.genemarkersllc.com/**

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