GENOMIND®

PROFESSIONAL PGx™

*(Formerly known as the Genomind Genecept Assay)*

# Report Interpretation Guide

Genomind® Professional PGx™ is intended to assist health care professionals in the selection of safe and appropriate pharmaceuticals and other treatment modalities for patients with mental illness and other brain disorders. Our test allows clinicians to make personalized treatment decisions tailored to a patient's genetic background and helps to inform psychiatric treatments that:

- May have lower risk for side effects
- May be more likely to be effective
- Are individually dosed

These associations are based on an extensive review of the paper summarizing the literature related to common genetic polymorphisms and their influence on drug response. This literature is available at your request.

**Complimentary consults are available to clinicians for all reports.**
**We welcome you to reach out with any and all questions.**

**Disclaimer:** Genomind® Professional PGx™ provides a summary of the impact a patient's pharmacodynamic and pharmacokinetic genes can play in response to treatment. This report is not intended to recommend a particular course of treatment or medication for a patient. Prescribing health care professionals must use their independent medical judgment and are solely responsible for determining the most appropriate medication for their patients. The physician must consider other relevant clinical factors in determining which is the most appropriate medication. The test results in the The Genomind® Professional PGx™ are intended to be prognostic and not diagnostic. The understanding of the relationship between genetics and pharmacokinetics and pharmacodynamics changes periodically; this report will not be updated to to reflect new information. A white paper summarizing individudual gene-drug associations, strengh of evidence and effect size is available upon request from Genomind Customer Service.

## The Gene Variation results provide clinicians with the patient's genetic results and clinical significance of each gene.

| GENE RESULT | THERAPEUTIC IMPLICATIONS | GUIDE | CLINICAL IMPACT |
|---|---|---|---|
| **SLC6A4**<br><br>S/S<br>[Low Activity] | ***Serotonin Transporter (SLC6A4)*** *is a synaptic transporter protein responsible for serotonin reuptake*<br>• SSRIs act by blocking this transporter to produce a therapeutic response<br>• In Caucasians, **lower likelihood of remission and increased side effect risk with SSRIs**<br>• Potential for increased cortisol release in response to stress |  | **Assess alternatives to SSRIs** in Caucasians<br><br>**Therapeutic options: SNRIs** or other **non-SSRI antidepressants** may be considered if clinically indicated |
| **HTR2A**<br><br>G/G<br>[Normal response] | ***Serotonin Receptor 2A (HTR2A)*** *is a serotonin receptor which is a target for several serotonergic drugs*<br>• **This genotype confers normal activity** | | No known significant clinical impact |
| **ADRA2A**<br><br>C/G<br>[Improved response] | ***Alpha-2A Adrenergic Receptor (ADRA2A)*** *is a receptor which plays an important role in norepinephrine signaling*<br>• **Improved response to stimulants (mostly methylphenidate studies)** for symptoms of attention deficit/hyperactivity disorder in children and adolescents as compared to those with the C/C genotype |  | **Therapeutic options: methylphenidate** may be considered for attention deficit/hyperactivity disorder if clinically indicated |

## Gene Results

Provides the patient genotype for each of the gene variants on our panel. This color-coded genotype reflects the patient's inherited alleles or variants at a particular location within the tested gene, which is listed in bold font **(e.g., SLC6A4).**

### Red Genotype

The patient's genotype may be associated with altered drug metabolism or absorption, higher side effect risk or higher risk of inefficacy.

### Green Genotype

The patient's genotype has no known significant clinical impact, in that there are no known gene-drug interactions associated with this genotype.

### Blue Genotype

The patient's genotype may be associated with an improved response to a particular medication or class of medications.

## Therapeutic Implications

Provides more detailed information regarding the function of the gene variant tested and how the patient's genotype may affect medications.

## Guide

Icons indicate whether there is an interaction between the patient's genotype and any medication.

### Alert/Caution

Indicates an increased risk of side effects, altered drug metabolism or absorption, or inefficacy

### PGx Guided Option

Indicates targeted options based on the patient's genetic results

## Clinical Impact

Describes the patient's gene-drug interaction, including the specific therapeutic options or considerations based on present interactions.

## The Gene Drug Interaction Summary organizes information about how the patient's genetic profile interacts with medications commonly used in psychiatry.

### Class
Indicates the class of medications (e.g., SSRIs, anxiolytics, opioids, etc.).

### Medication
Includes each medication in the class listed in alphabetical order by generic name.

### Pharmacodynamic Associations
Describes any interactions between the patient's pharmacodynamic gene results and medications. It presents **PGx Guided Options** or **Alert/Caution** based on interactions that impact efficacy or increase side effect risk.

#### III. GENE DRUG INTERACTION SUMMARY

| CLASS | MEDICATION | PHARMACODYNAMIC ASSOCIATIONS | PHARMACODYNAMIC GENE | DRUG EXPOSURE | PHARMACOKINETIC GENE |
|---|---|---|---|---|---|
| | **ANTIDEPRESSANTS** | | | | |
| SSRIs | **Citalopram** (Celexa®) | Lower odds of remission or response and increased side effects in Caucasians<br>Higher odds of remission or response in Asians | SLC6A4,BDNF | ↑ | 2C19, P-gp |
| SSRIs | **Escitalopram** (Lexapro®) | Lower odds of remission or response and increased side effects in Caucasians<br>Higher odds of remission or response in Asians | SLC6A4,BDNF | ↑ | 2C19, P-gp |
| SSRIs | **Fluoxetine** (Prozac®) | Lower odds of remission or response and increased side effects in Caucasians<br>Higher odds of remission or response in Asians | SLC6A4,BDNF | ↑ | 2D6, 2C9 |
| SSRIs | **Fluvoxamine** (Luvox®) | Lower odds of remission or response and increased side effects in Caucasians<br>Higher odds of remission or response in Asians | SLC6A4,BDNF | ↑ | 2D6, 1A2, P-gp |
| SSRIs | **Paroxetine** (Paxil®) | Lower odds of remission or response and increased side effects in Caucasians<br>Higher odds of remission or response in Asians | SLC6A4,BDNF | ↑ | 2D6, P-gp |
| SSRIs | **Sertraline** (Zoloft®) | Lower odds of remission or response and increased side effects in Caucasians<br>Higher odds of remission or response in Asians | SLC6A4,BDNF | | 2C19, 2B6 |

**Medication has FDA biomarker guidance available** - https://www.fda.gov/downloads/drugs/scienceresearch/UCM578588.pdf

**Medication has CPIC or DPWG biomarker guidance available** - https://cpicgx.org/guidelines, https://www.pharmgkb.org/page/dpwg

### Pharmacodynamic Gene
Provides the name of the pharmacodynamic gene associated with the interaction, if present. In this example, this individual's SLC6A4 gene is associated with lower odds of remission or response with SSRIs (in Caucasians).

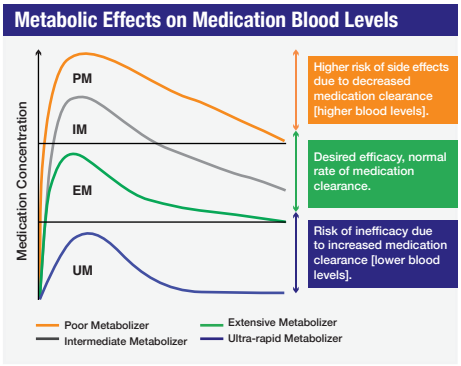
### Drug Exposure
Shows the direction of any changes in drug exposure that may occur based on the patient's pharmacokinetic genetic profile. Exposure is a measure of blood levels over time, and dependent on drug absorption, metabolism, or blood-brain barrier penetration.

| | |
|---|---|
| **Drug Exposure** | The exposure to this drug may be altered based on the patient's genetics. Direction of arrow indicates expected changes in blood levels or brain levels. |
| **Reduced Drug Exposure with 1A2 inducers** | The exposure to this drug may be significantly reduced in the presence of psychotropic or environmental inducers (e.g., smoking, drinking >3 cups of coffee/day). |

# Genotype/Metabolic Effects



## The figure below represents the relative impact of pharmacokinetic gene variation on drug serum levels.




| | Wild-Type Genotypes | Alternative Genotypes | |
|---|---|---|---|
| **SLC6A4** | L(A)/L(G) or L(A)/S | L(A)/L(A) | L(G)/L(G) or L(G)/S or S/S |
| **CACNA1C** | G/G | G/A | A/A |
| **ANK3** | C/C | C/T | T/T |
| **5HT2C** | C/C | C/T | T/T |
| **MC4R** | C/C | C/A | A/A |
| **DRD2** | C/C | C/DEL | DEL/DEL |
| **COMT** | Val/Met | Val/Val | Met/Met |
| **ADRA2A** | C/C | C/G | G/G |
| **MTHFR (C677T)** | C/C | C/T | T/T |
| **MTHFR (A1298C)** | A/A | A/C | C/C |
| **OPRM1** | A/A | A/G | G/G |
| **GRIK1** | A/A | A/C | C/C |
| **ABCB1(rs20332583)** | A/A | A/G | G/G |
| **ABCB1 (C3435T)** | G/G | G/A | A/A |
| **BDNF** | Val/Val | Val/Met | Met/Met |
| **HTR2A** | G/G | G/A | A/A |

# Manufacturer Dosing Recommendations

## This table lists Genomind® Professional PGx™ drugs with dosing guidelines and recommendations based on genetic variation provided by:

**FDA** — **U.S. Food & Drug Administration**
https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm

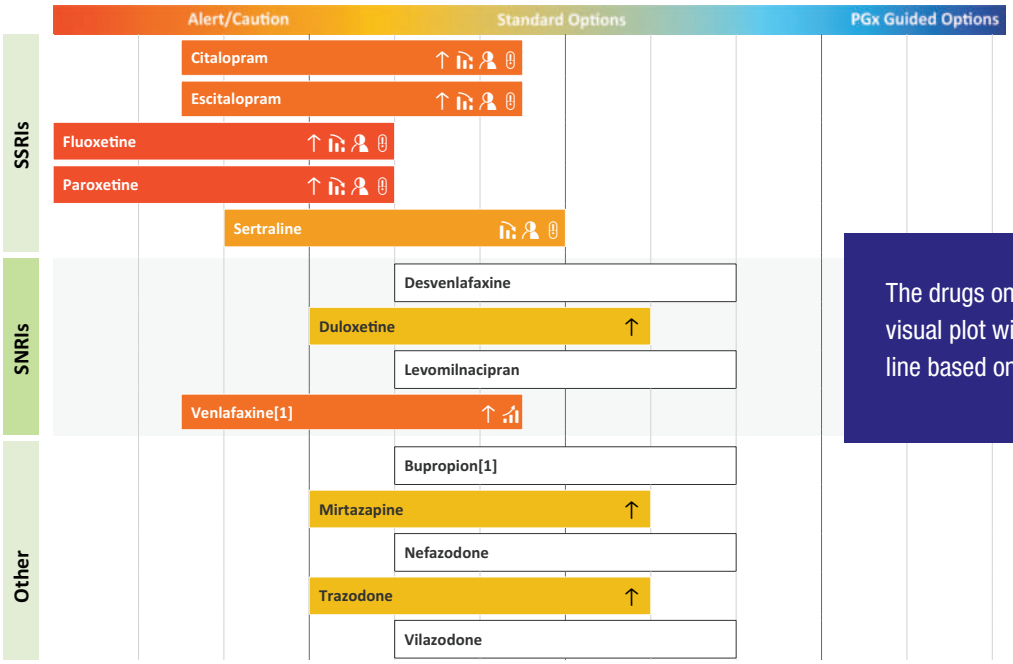
**CPIC** — **Clinical Pharmacogenetics Implementation Consortium**
https://cpicpgx.org/guidelines/

**DPWG** — **Dutch Pharmacogenetics Working Group**
https://www.pharmgkb.org/page/dpwg

| FDA | CPIC | DPWG |
|---|---|---|
| aripiprazole | amitriptyline | amitriptyline |
| atomoxetine | amoxapine | aripiprazole |
| brexpiprazole | atomoxetine | atomoxetine |
| carbamazepine | carbamazepine | citalopram |
| celecoxib | citalopram | clomipramine |
| citalopram | clomipramine | clopidogrel |
| clobazam | clopidogrel | codeine |
| clopidogrel | codeine | doxepin |
| codeine | desipramine | escitalopram |
| deutetrabenazine | doxepin | esomeprazole |
| eliglustat | escitalopram | flecainide |
| iloperidone | fluvoxamine | haloperidol |
| oxcarbazepine | imipramine | imipramine |
| pimozide | nortriptyline | lansoprazole |
| propafenone | ondansetron | metoprolol |
| tetrabenazine | oxcarbazepine | nortriptyline |
| thioridazine | paroxetine | omeprazole |
| valbenazine | phenytoin | oxycodone |
| vortioxetine | protriptyline | pantoprazole |
| warfarin | sertraline | paroxetine |
| | tacrolimus | phenytoin |
| | tamoxifen | propafenone |
| | trimipramine | risperidone |
| | voriconazole | sertraline |
| | warfarin | tamoxifen |
| | | tramadol |
| | | venlafaxine |

## The diagnosis-specific Summary Page will provide a visual plot of drugs for depression, treatment-resistant depression, ADHD, bipolar and anxiety related disorders, and pain management. Providers have access to all summary pages.

IV. DEPRESSION SUMMARY




The drugs on the "Depression Summary" visual plot will be shifted from the center line based on the patient's genetic results.

### Alert/Caution

Drugs will be shifted to the left if the patient has genetic variations which may reduce efficacy, increase likelihood of side effects, or alter drug metabolism or absorption. The extent to which the drug is shifted reflects the degree of risk.

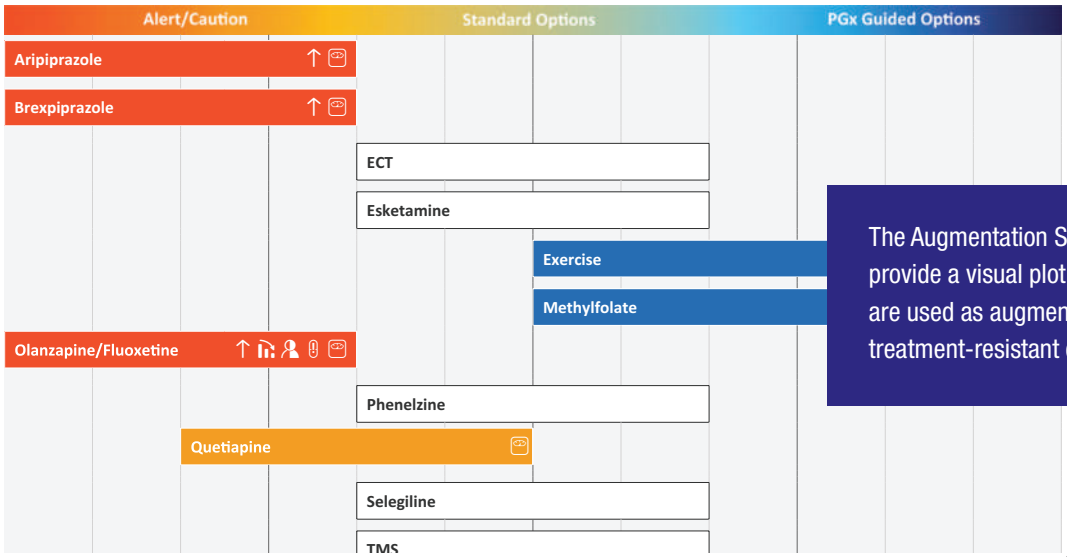
### Standard Options

Drugs that are not shifted indicate that there are no gene-drug interactions for the patient.

### PGx Options

Drugs will be shifted to the right if the patient has genetic variations which may increase likelihood of efficacy.

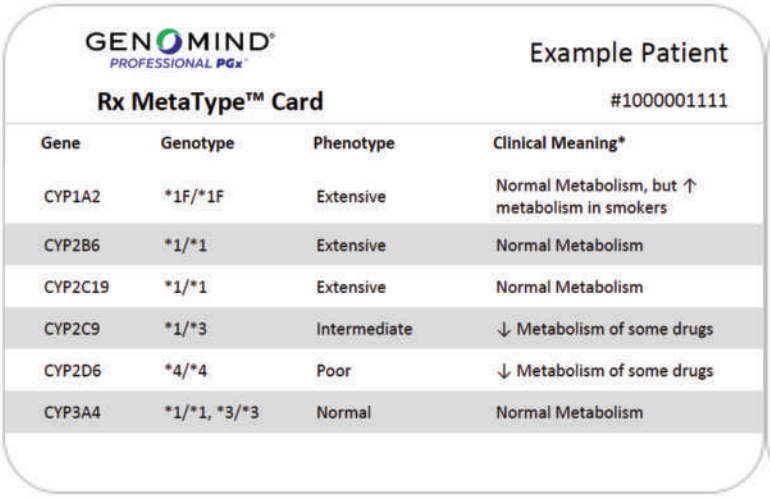
IV. DEPRESSION AUGMENTATION SUMMARY




The Augmentation Summary page will provide a visual plot of therapies that are used as augmentation agents or for treatment-resistant depression.

| Summary Icon | Icon Description |
|---|---|
| Weight Gain | Greater than average risk of weight gain with 2nd generation antipsychotics. |
| Ethnic Dependent Response | The genetic interaction with this drug differs based on the patient's ethnicity (refer to Drug Interaction Summary for more specific information). |
| Decreased Efficacy | Patient may be less likely to respond to this medication. |
| Increased Efficacy | Patient may be more likely to respond to this medication. |
| Decreased Sensitivity (May need ↑ doses) | Decreased sensitivity to opioids. Higher doses may be considered. |
| Increased Sensitivity (May need ↓ doses) | Increased sensitivity to opioids. Lower doses may be just as effective. |
| Do Not Initiate | This drug should not be used if patient is treatment naïve to the drug. |
| Side Effects Risk | Patient may be more likely to experience adverse events with this medication. |
| Drug Exposure [2] | The exposure to this drug may be altered based on the patient's genetics. Direction of arrow indicates expected changes in blood levels or brain levels. |
| Reduced Drug Exposure with 1A2 inducers | The exposure to this drug may be significantly reduced in the presence of psychotropic or environmental inducers (e.g., smoking, drinking >3 cups of coffee/day). |

## Patient's Genomind® Rx MetaType™ Card



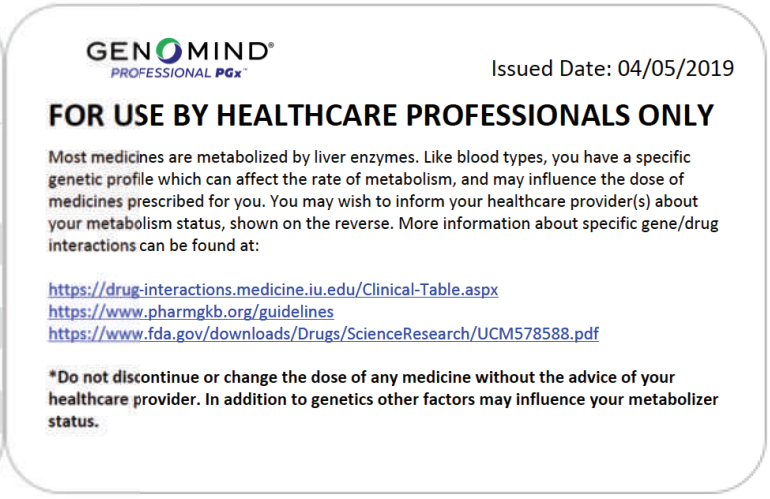
GENOMIND® PROFESSIONAL PGx™

Example Patient

Rx MetaType™ Card

#1000001111

| Gene | Genotype | Phenotype | Clinical Meaning* |
|---|---|---|---|
| CYP1A2 | *1F/*1F | Extensive | Normal Metabolism, but ↑ metabolism in smokers |
| CYP2B6 | *1/*1 | Extensive | Normal Metabolism |
| CYP2C19 | *1/*1 | Extensive | Normal Metabolism |
| CYP2C9 | *1/*3 | Intermediate | ↓ Metabolism of some drugs |
| CYP2D6 | *4/*4 | Poor | ↓ Metabolism of some drugs |
| CYP3A4 | *1/*1, *3/*3 | Normal | Normal Metabolism |



GENOMIND® PROFESSIONAL PGx™

Issued Date: 04/05/2019

**FOR USE BY HEALTHCARE PROFESSIONALS ONLY**

Most medicines are metabolized by liver enzymes. Like blood types, you have a specific genetic profile which can affect the rate of metabolism, and may influence the dose of medicines prescribed for you. You may wish to inform your healthcare provider(s) about your metabolism status, shown on the reverse. More information about specific gene/drug interactions can be found at:

https://drug-interactions.medicine.iu.edu/Clinical-Table.aspx
https://www.pharmgkb.org/guidelines
https://www.fda.gov/downloads/Drugs/ScienceResearch/UCM578588.pdf

***Do not discontinue or change the dose of any medicine without the advice of your healthcare provider. In addition to genetics other factors may influence your metabolizer status.**

**The Genomind® RxMetaType™ Card will be provided for every patient tested with the Genomind® Professional PGx™ and includes the following information:**

### Gene
CYP450 genes tested

### Genotype
Patient's genotype with specific allele combination for each gene

### Phenotype
Enzyme activity associated with the patient's genotype

### Clinical Meaning
Expected impact of patient's genotype on drug metabolism