Pharmacogenomic Test

Patient, Sample
Date of Birth: 7/22/1984
Clinician: Sample Clinician

Order Number:	3740219
Report Date:	1/11/2022
Reference:	145CIP

# genesight

Questions about report interpretation? Contact our medical information team: 855.891.9415 | medinfo@genesight.com

## Use as Directed

desvenlafaxine (Pristiq®) levomilnacipran (Fetzima®) vilazodone (Viibryd®)

Moderate	
Gene-drug	Interaction

Antidepressants

trazodone (Desyrel®)	1
venlafaxine (Effexor®)	1
fluoxetine (Prozac®)	1,4
bupropion (Wellbutrin®)	1,6
citalopram (Celexa®)	3,4
escitalopram (Lexapro®)	3,4

## Significant Gene-drug Interaction

selegiline (Emsam®)	2
mirtazapine (Remeron®)	1,6
sertraline (Zoloft®)	2,4
amitriptyline (Elavil®)	1,6,8
clomipramine (Anafranil®)	1,6,8
desipramine (Norpramin®)	1,6,8
doxepin (Sinequan®)	1,6,8
duloxetine (Cymbalta®)	1,6,8
imipramine (Tofranil®)	1,6,8
nortriptyline (Pamelor®)	1,6,8
vortioxetine (Trintellix®)	1,6,8
fluvoxamine (Luvox®)	1,4,6,8
paroxetine (Paxil®)	1,4,6,8

#### **Clinical Considerations**

- 1: Serum level may be too high, lower doses may be required.
- 2: Serum level may be too low, higher doses may be required.
- 3: Difficult to predict dose adjustments due to conflicting variations in metabolism.
- 4: Genotype may impact drug mechanism of action and result in moderately reduced efficacy.
- 6: Use of this drug may increase risk of side effects.
- 8: FDA label identifies a potential gene-drug interaction for this medication.

All psychotropic medications require clinical monitoring. Medications should not be changed based solely on the test results. The results of this test are intended to supplement other clinical information considered by a healthcare provider within the context of a comprehensive medical evaluation.

This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs, the characteristics of the drug prescribed, and the risk and safety information provided in the drug's labeling. Propranolol and oxcarbazepine prescribed for neuropsychiatric disorders might be considered off-label. Please consult their respective FDA drug labels for specific guidelines regarding their use.

The GeneSight Psychotropic test interpretations are based on a thorough review of published peer-reviewed literature, internal research, and FDA label information when applicable. The clinical validity and utility of the GeneSight Psychotropic test have been evaluated for patients with major depressive disorder who failed at least one psychotropic medication in multiple clinical studies.

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## **Anxiolytics and Hypnotics**

## Use as Directed

alprazolam (Xanax®) buspirone (BuSpar®) clonazepam (Klonopin®) eszopiclone (Lunesta®) lemborexant (Dayvigo®) suvorexant (Belsomra®) temazepam (Restoril®) zolpidem (Ambien®)

Moderate	
Gene-drug	Interaction

chlordiazepoxide (Librium®)	
clorazepate (Tranxene®)	
lorazepam (Ativan®)	
oxazepam (Serax®)	

Significant	
Gene-drug	Interaction

diazepam (Valium®)	1,6
propranolol (Inderal®)	1,6,8

### **Clinical Considerations**

- 1: Serum level may be too high, lower doses may be required.
- 6: Use of this drug may increase risk of side effects.
- 8: FDA label identifies a potential gene-drug interaction for this medication.

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## GeneSight<sup>®</sup> Psychotropic

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## Use as Directed

asenapine (Saphris®) cariprazine (Vraylar®) lumateperone (Caplyta®) lurasidone (Latuda®) paliperidone (Invega®) thiothixene (Navane<sup>®</sup>) ziprasidone (Geodon®)

**Antipsychotics** 

fluphenazine (Prolixin®)	1
olanzapine (Zyprexa®)	1
quetiapine (Seroquel®)	1
clozapine (Clozaril®)	1,8
haloperidol (Haldol®)	1,8

## Significant **Gene-drug Interaction**

chlorpromazine (Thorazine®)	1,6
aripiprazole (Abilify®)	1,6,8
brexpiprazole (Rexulti®)	1,6,8
iloperidone (Fanapt®)	1,6,8
perphenazine (Trilafon®)	1,6,8
risperidone (Risperdal®)	1,6,8
thioridazine (Mellaril®)	1,6,9

### Clinical Considerations

- 1: Serum level may be too high, lower doses may be required.
- 6: Use of this drug may increase risk of side effects.
- 8: FDA label identifies a potential gene-drug interaction for this medication.
- 9: Per FDA label, this medication is contraindicated for this genotype.

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## **Mood Stabilizers**

Use as Directed	Moderate Gene-drug Interaction	Significant Gene-drug Interaction
lamotrigine (Lamictal®) oxcarbazepine (Trileptal®) valproic acid/divalproex (Depakote®)		carbamazepine (Tegretol®) 6,8
No Proven Genetic Markers		

Clinical Considerations

gabapentin (Neurontin<sup>®</sup>) 10

- 6: Use of this drug may increase risk of side effects.
- 8: FDA label identifies a potential gene-drug interaction for this medication.
- 10: While this medication does not have clinically proven genetic markers that allow it to be categorized, it may be an effective choice based on other clinical factors.

lithium (Eskalith®) 10

All psychotropic medications require clinical monitoring. Medications should not be changed based solely on the test results. The results of this test are intended to supplement other clinical information considered by a healthcare provider within the context of a comprehensive medical evaluation.

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topiramate (Topamax<sup>®</sup>) 10

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## Stimulants

Use as Directed	Moderate Gene-drug Interaction	Significant Gene-drug Interaction			
	dexmethylphenidate 4 (Focalin <sup>®</sup> )				
	methylphenidate4(Ritalin®, Concerta®)				
No Proven Genetic Markers					
	dextroamphetamine (Dexedrine <sup>®</sup> ) 10	lisdexamfetamine (Vyvanse®) 10			

## Non-stimulants

Liso as Directed	Moderate Gene-drug Interaction	Significant Gene-drug Interaction
guanfacine (Intuniv®)	viloxazine (Qelbree®) 1	atomoxetine (Strattera <sup>®</sup> ) 1,5,8

No Proven Genetic Markers

clonidine (Kapvay®) 10

#### **Clinical Considerations**

- 1: Serum level may be too high, lower doses may be required.
- 4: Genotype may impact drug mechanism of action and result in moderately reduced efficacy.
- 5: CYP2D6 genotype indicates that this patient may experience increased frequency of side effects but also greater symptom improvement in those who find the treatment tolerable.
- 8: FDA label identifies a potential gene-drug interaction for this medication.
- 10: While this medication does not have clinically proven genetic markers that allow it to be categorized,

it may be an effective choice based on other clinical factors.

All psychotropic medications require clinical monitoring. Medications should not be changed based solely on the test results. The results of this test are intended to supplement other clinical information considered by a healthcare provider within the context of a comprehensive medical evaluation.

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## GeneSight<sup>®</sup> Psychotropic

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HTR2A

SLC6A4

S/S

G/G

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## **Patient Genotypes and Phenotypes**

#### Pharmacodynamic Genes

#### ADRA2A C/C

#### **Moderately Reduced Response**

This patient is homozygous for the C allele of the -1291G>C polymorphism in the adrenergic alpha-2A receptor gene. This genotype suggests a moderately reduced response to certain ADHD medications.

## HLA-A\*3101

T/T

#### **Higher Risk**

This patient is homozygous for the T allele of the rs1061235 A>T polymorphism indicating presence of the HLA-A\*3101 allele or certain HLA-A\*33 alleles. This genotype suggests a higher risk of serious hypersensitivity reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms when taking certain mood stabilizers.

#### HLA-B\*1502 Not Present

Normal Risk

This patient does not carry the HLA-B\*1502 allele or a closely related \*15 allele. Absence of HLA-B\*1502 and the closely related \*15 alleles suggests normal risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.

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#### **Reduced Response**

This patient is homozygous for the short promoter polymorphism of the serotonin transporter gene. The short promoter allele is reported to decrease expression of the serotonin transporter compared to the homozygous long promoter allele. The patient may have a moderately decreased likelihood of response to selective serotonin reuptake inhibitors due to the presence of the short form of the gene.

This individual is homozygous variant for the G allele of the

with an increased risk of adverse drug reactions with certain

selective serotonin reuptake inhibitors.

-1438G>A polymorphism for the Serotonin Receptor Type 2A. They

carry two copies of the G allele. This genotype has been associated



**Increased Sensitivity** 

PD

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## **Patient Genotypes and Phenotypes**

#### **Pharmacokinetic Genes**

#### CES1A1 GLY/GLY

Extensive (Normal) Metabolizer

CES1A1 - GLY allele enzyme activity: Normal CES1A1 - GLY allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype. This patient is expected to have normal enzyme activity.

#### CYP1A2 \*1/\*1

#### Extensive (Normal) Metabolizer

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

#### CYP2B6 \*1/\*1

#### Extensive (Normal) Metabolizer

CYP2B6\*1 allele enzyme activity: Normal CYP2B6\*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

#### CYP2C19 \*17/\*17

#### **Ultrarapid Metabolizer**

Intermediate Metabolizer

CYP2C19\*17 allele enzyme activity: Increased CYP2C19\*17 allele enzyme activity: Increased

This genotype is most consistent with the ultrarapid metabolizer phenotype. This patient may have increased enzyme activity as compared to individuals with the normal phenotype.

#### CYP2C9

#### \*1/\*2

CYP2C9\*1 allele enzyme activity: Normal

CYP2C9\*2 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

**CYP2D6** \*10/\*10

CYP2D6\*10 allele enzyme activity: Reduced CYP2D6\*10 allele enzyme activity: Reduced

This genotype is most consistent with the poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

#### CYP3A4 \*1/\*1

#### Extensive (Normal) Metabolizer

CYP3A4\*1 allele enzyme activity: Normal CYP3A4\*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

#### UGT1A4 \*1/\*1

#### **Extensive (Normal) Metabolizer**

Intermediate Metabolizer

UGT1A4\*1 allele enzyme activity: Normal UGT1A4\*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype. The patient is expected to have normal enzyme activity.

#### UGT2B15

#### \*2/\*2

UGT2B15\*2 allele enzyme activity: Reduced UGT2B15\*2 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.





**Poor Metabolizer** 



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## Additional Genotypes

Not Included in Categorizing Medications

Genotypes reported in this section have not been shown to be reliable markers of medication outcomes

#### COMT VAL/MET

This patient is heterozygous for the Val158Met polymorphism in the catechol-o-methyltransferase gene. They have one copy of the Met allele and one copy of the Val allele.

A summary of the studies that have assessed the potential effect of COMT genotype on response to psychotropic medications can be found here: https://genesight.com/comt.

To categorize medications on this pharmacogenomic test, a gene must have a variant that has been shown to have a significant impact on medication outcomes, as demonstrated in multiple well-designed studies. Studies assessing the gene in this section have not shown that it is a reliable marker of medication outcomes. Therefore, this gene does not currently meet the criteria for categorizing medications. The patient's genotype is provided for informational purposes only.



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\* This gene-drug interaction is recognized by the FDA or CPIC.

## **Gene-drug Interactions**

Use as Directed									
	CES1A1 Normal	CYP1A2 Normal	CYP2B6 Normal	CYP2C19 Ultrarapid	CYP2C9 Intermediate	CYP2D6 Poor	CYP3A4 Normal	UGT1A4 Normal	UGT2B15 Intermediate
Antidepressants									
desvenlafaxine (Pristiq®)							0		
levomilnacipran (Fetzima®)				•		٠	0		
vilazodone (Viibryd®)				•		•	0		
Anxiolytics and hypnotics									
alprazolam (Xanax®)							0		
buspirone (BuSpar®)						•	0		
clonazepam (Klonopin®)							0		
eszopiclone (Lunesta®)					•		0		
lemborexant (Dayvigo®)							0		
suvorexant (Belsomra®)							0		
temazepam (Restoril®)			0		•		0		•
zolpidem (Ambien®)		0		•		٠	0		
Antipsychotics									
asenapine (Saphris®)		0				•	0	0	
cariprazine (Vraylar®)						٠	0		
lumateperone (Caplyta®)							0		
lurasidone (Latuda®)							0		
paliperidone (Invega®)						٠	0		
thiothixene (Navane®)		0							
ziprasidone (Geodon®)		0					0		
Mood stabilizers									
lamotrigine (Lamictal®)								0	
oxcarbazepine (Trileptal®)									
valproic acid/divalproex (Depakote®)			0		•			0	
Non-stimulants									
guanfacine (Intuniv®)							0		

 Variation was found in patient genotype that may impact medication metabolism.

 This gene is associated with medication metabolism, but the predicted patient phenotype is normal.



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## Gene-drug Interactions

Moderate Gene-drug In	teraction								
	CES1A1 Normal	CYP1A2 Normal	CYP2B6 Normal	CYP2C19 Ultrarapid	CYP2C9 Intermediate	CYP2D6 Poor	CYP3A4 Normal	UGT1A4 Normal	UGT2B15 Intermediate
Antidepressants									
bupropion (Wellbutrin®)			0			٠	0		
citalopram (Celexa®)				• *		٠	0		
escitalopram (Lexapro®)				• *		•	0		
fluoxetine (Prozac®)				•	•	•	0		
trazodone (Desyrel®)		0				•	0		
venlafaxine (Effexor®)				•		• *	0		
Anxiolytics and hypnotics									
chlordiazepoxide (Librium®)		0					0		
clorazepate (Tranxene®)		0					0		
lorazepam (Ativan®)									
oxazepam (Serax®)									
Antipsychotics									
clozapine (Clozaril®)		0				• *	0	0	
fluphenazine (Prolixin®)		0			•	٠	0		
haloperidol (Haldol®)		0				٠	0	0	
olanzapine (Zyprexa®)		0				٠	0	0	
quetiapine (Seroquel®)						٠	0		
Stimulants									
dexmethylphenidate (Focalin®)	0								
methylphenidate (Ritalin <sup>®</sup> , Concerta <sup>®</sup> )	0								
Non-stimulants									
viloxazine (Qelbree®)						•			

#### Significant Gene-drug Interaction

Significant Gene-drug interaction									
	CES1A1 Normal	CYP1A2 Normal	CYP2B6 Normal	CYP2C19 Ultrarapid	CYP2C9 Intermediate	CYP2D6 Poor	CYP3A4 Normal	<b>UGT1A4</b> Normal	UGT2B15 Intermediate
Antidepressants									
amitriptyline (Elavil®)				• *		• *			
clomipramine (Anafranil®)		0		• *		• *	0		
desipramine (Norpramin®)						• *			

 Variation was found in patient genotype that may impact medication metabolism. \* This gene-drug interaction is recognized by the FDA or CPIC.

• This gene is associated with medication metabolism, but the predicted patient phenotype is normal.

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## **Gene-drug Interactions**

Significant Gene-drug	Interactic	on (Conti	nued)						
	CES1A1 Normal	CYP1A2 Normal	CYP2B6 Normal	CYP2C19 Ultrarapid	CYP2C9 Intermediate	CYP2D6 Poor	CYP3A4 Normal	UGT1A4 Normal	UGT2B15 Intermediate
Antidepressants									
doxepin (Sinequan®)		0		• *	•	• *	0	0	
duloxetine (Cymbalta®)		0				٠			
fluvoxamine (Luvox®)		0				• *			
imipramine (Tofranil®)		0		• *		• *	0		
mirtazapine (Remeron®)		0				• *	0		
nortriptyline (Pamelor®)						• *			
paroxetine (Paxil®)						• *	0		
selegiline (Emsam®)		0	0				0		
sertraline (Zoloft®)			0	•*		*	0		
vortioxetine (Trintellix®)			0	•	•	• *	0		
Anxiolytics and hypnotics									
diazepam (Valium®)		0	0				0		•
propranolol (Inderal®)		0				۲			
Antipsychotics									
aripiprazole (Abilify®)						• *	0		
brexpiprazole (Rexulti®)						• *	0		
chlorpromazine (Thorazine®)		0				٠	0		
iloperidone (Fanapt®)						• *	0		
perphenazine (Trilafon®)		0				• *	0		
risperidone (Risperdal®)						• *	0		
thioridazine (Mellaril®)		0		•		• *	0		
Mood stabilizers									
carbamazepine (Tegretol®)			0				0		
Non-stimulants									
atomoxetine (Strattera®)						• *			

#### No Proven Genetic Markers

	CES1A1 Normal	CYP1A2 Normal	CYP2B6 Normal	CYP2C19 Ultrarapid	CYP2C9 Intermediate	CYP2D6 Poor	CYP3A4 Normal	UGT1A4 Normal	UGT2B15 Intermediate
Stimulants									
amphetamine salts (Adderall®)						*			

 Variation was found in patient genotype that may impact medication metabolism. \* This gene-drug interaction is recognized by the FDA or CPIC.

• This gene is associated with medication metabolism, but the predicted patient phenotype is normal.

## GeneSight<sup>®</sup> Psychotropic

Pharmacogenomic Test

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D Clinician: Sample Clinician

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## **Test Information**

The buccal swab sample was collected on 1/9/2022 and received in the laboratory on 1/10/2022. Genomic DNA is isolated and the relevant genomic regions are amplified by polymerase chain reaction (PCR). Analysis of CYP2D6 deletion and duplication, HLA-B\*1502 and SLC6A4 is completed by electrophoresis of PCR products. Analysis of CES1A1, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6 CYP3A4, ADRA2A, COMT, HTR2A, rs1061235 (indicating presence of the HLA-A\*3101 allele or certain HLA-A\*33 alleles), UGT1A4 and UGT2B15 is completed by using iPLEX MassARRAY® technology (Agena Bioscience). The following genetic variants may be detected in the assay: CES1A1 Gly143Glu (NM 001025194.1:c.428G>A); CYP1A2 -3860G>A (NG 008431.1:g.28338G>A), -2467T>delT (NM 000761.4:c.-1635delT), -739T>G (NM 000761.4:c.-10+103T>G), -729C>T (NM 000761.4:c.-10+113C>T), -163C>A (NM 000761.4:c.-9-154C>A), 125C>G (NM\_000761.4:c.125C>G), 558C>A (NM\_000761.4:c.558C>A), 2116G>A (NM\_000761.4:c.1042G>A), 2473G>A (NM\_000761.4:c.1130G>A) , 2499A>T (NM 000761.4:c.1156A>T), 3497G>A (NM 000761.4:c.1217G>A), 3533G>A (NM 000761.4:c.1253+1G>A), 5090C>T (NM 000761.4:c.1291C>T), 5166G>A (NM 000761.4:c.1367G>A), 5347C>T (NM 000761.4:c.1548C>T); CYP2B6 \*4(NM 000767.4:c.785A>G), \*6 (NM 000767.4:c.516G>T; c.785A>G), \*9 (NM\_000767.4:c.516G>T); CYP2C19 \*2 (NM\_000769.2:c.681G>A), \*3(NM\_000769.2:c.636G>A), \*4 (NM\_000769.2:c.1A>G), \*5 (NM\_000769.2:c.1297C>T),\*6 (NM 000769.2:c.395G>A), \*7 (NM 000769.2:c.819+2T>A), \*8 (NM 000769.2:c.358T>C), \*17 (NM 000769.2:c. -806C>T); CYP2C9 \*2 (NM 000771.3:c.430C>T), \*3 (NM\_000771.3:c.1075A>C), \*4 (NM\_000771.3:c.1076T>C), \*5 (NM\_000771.3:c.1080C>G), \*6 (NM\_000771.3:c.817delA); CYP2D6 \*2 (NM\_000106.5:c.886C>T; c.1457G>C), \*2A (NM\_000106.5:c.-1584C>G; c.886C>T; c.1457G>C), \*3 (NM\_000106.5:c.775delA), \*4 (NM\_000106.5:c.506-1G>A; c.100C>T; c.1457G>C), \*5 (CYP2D6 Deletion), \*6 (NM 000106.5:c.454delT),\*7 (NM 000106.5:c.971A>C), \*8 (NM 000106.5:c.505G>T; c.886C>T; c.1457G>C), \*9 (NM\_000106.5:c.841\_843delAAG), \*10 (NM\_000106.5:c.100C>T; c.1457G>C), \*11 (NM\_000106.6:c.181-1G>C; NM\_000106.5:c.886C>T; c.1457G>C), \*12 (NM\_000106.5:c.124G>A, c.886C>T; c.1457G>C), \*14 (NM\_000106.5:c.505G>A; c.886C>T; c.1457G>C), \*15 (NM\_000106.6:c.137dup), \*17 (NM\_000106.5:c.320C>T; c.886C>T; c.1457G>C), \*41 (NM\_000106.5:c.985+39G>A; c.886C>T; c.1457G>C), gene duplication: CYP3A4 \*13 (NM\_017460.5:c.1247C>T), \*15A (NM\_017460.5:c.485G>A), \*22 (NM\_017460.5:c.522-191C>T); ADRA2A -1291G>C (NM\_000681.3:c.-1252G>C); COMT Val158Met (NM\_007310.2:c.322G>A); HLA-B\*1502; rs1061235 (NM\_002116.7:c.\*66A>T); HTR2A -1438G>A (NM\_000621.4:c.-998G>A); SLC6A4 L, S; UGT1A4 \*3 (NM\_007120.2:c.142T>G); UGT2B15 \*2 (NM\_001076.3:c.253G>T). The following rare genetic variants have not been observed by the Assurex Health Inc. Laboratory: CYP1A2 125C>G, 558C>A; CYP2C19\*7. \*1 is the reference allele and is reported by default if the other tested alleles are not detected.

This test was developed and its performance characteristics determined by Assurex Health. It has not been cleared or approved by the U.S. Food and Drug Administration. These interpretations are based upon data available in scientific literature and prescribing information for the relevant drugs. Interpretations are, in some instances, based on data regarding the pharmacokinetic, pharmacodynamic and pharmacogenomics properties of a drug derived from non-clinical studies (e.g. in vitro studies). Findings from studies performed in a non-clinical setting or clinical studies involving healthy subjects are not necessarily indicative of clinical performance in a particular patient. References used to inform medication categorizations can be found here: https://genesight.com/references.

This report was reviewed and verified on 1/11/2022 by:

Nina King

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#### **Disclaimer of Liability**

The information contained in this report is provided as a service and does not constitute medical advice. At the time of report generation this information is believed to be current and is based upon published research; however, research data evolves and amendments to the prescribing information of the drugs listed will change over time. While this report is believed to be accurate and complete as of the date issued, THE DATA IS PROVIDED "AS IS", WITHOUT WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION, THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. As medical advice must be tailored to the specific circumstances of each case, the treating healthcare provider has ultimate responsibility for all treatment decisions made with regard to a patient including any made on the basis of a patient's genotype. GeneSight Psychotropic is covered by U.S. Patent No. 9,111,028

Genetic testing was completed by a CLIA and CAP accredited laboratory in the United States located at:

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Laboratory Director: Nina King, PhD

#### **Customer Service**

Please contact 855.891.9415 or medinfo@genesight.com for assistance with report interpretation. For all other inquires please contact 866.757.9204 or support@genesight.com.

GeneSight Psychotropic Test Version: 4.1