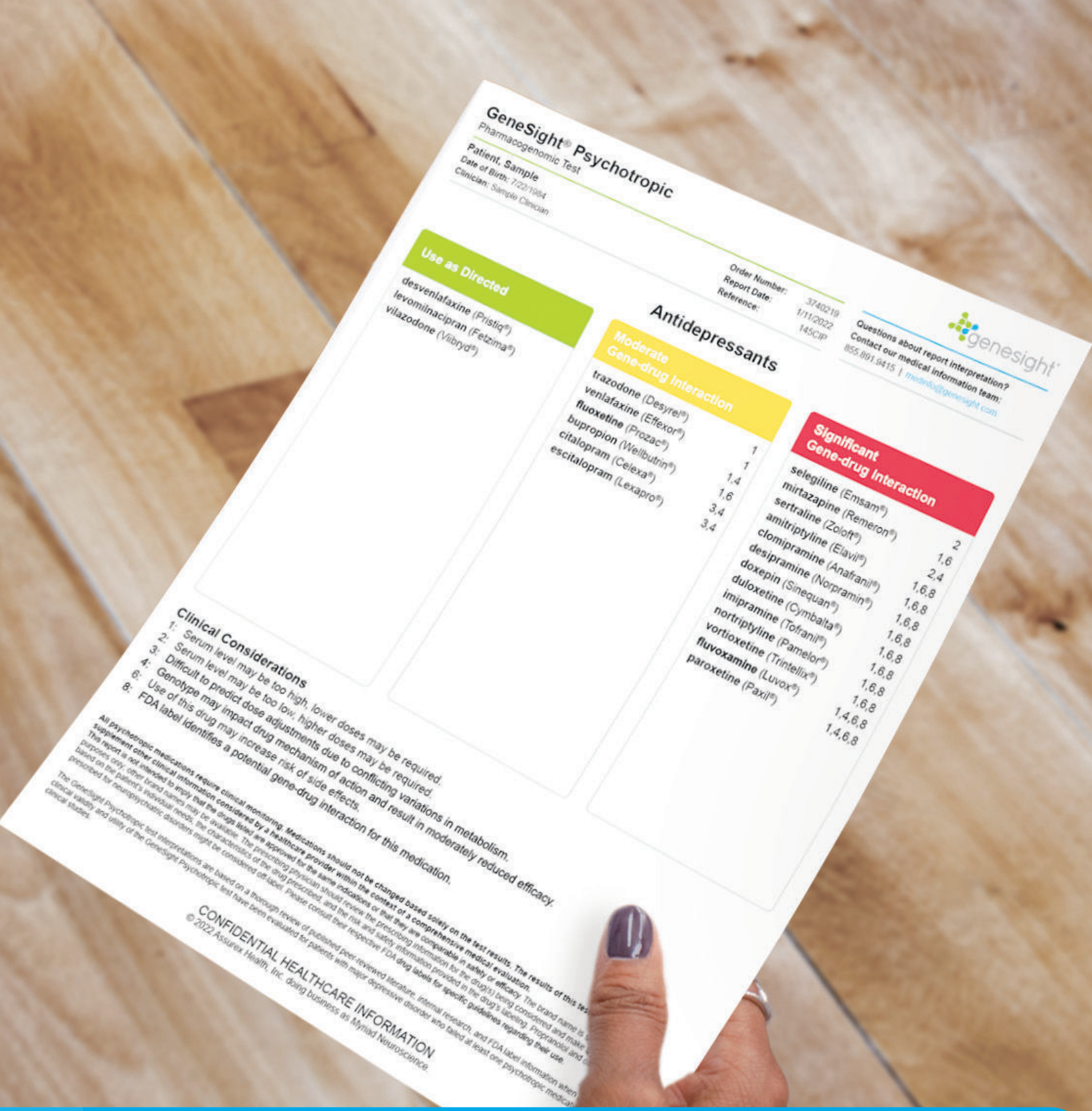


Interpreting the GeneSight® Psychotropic Report

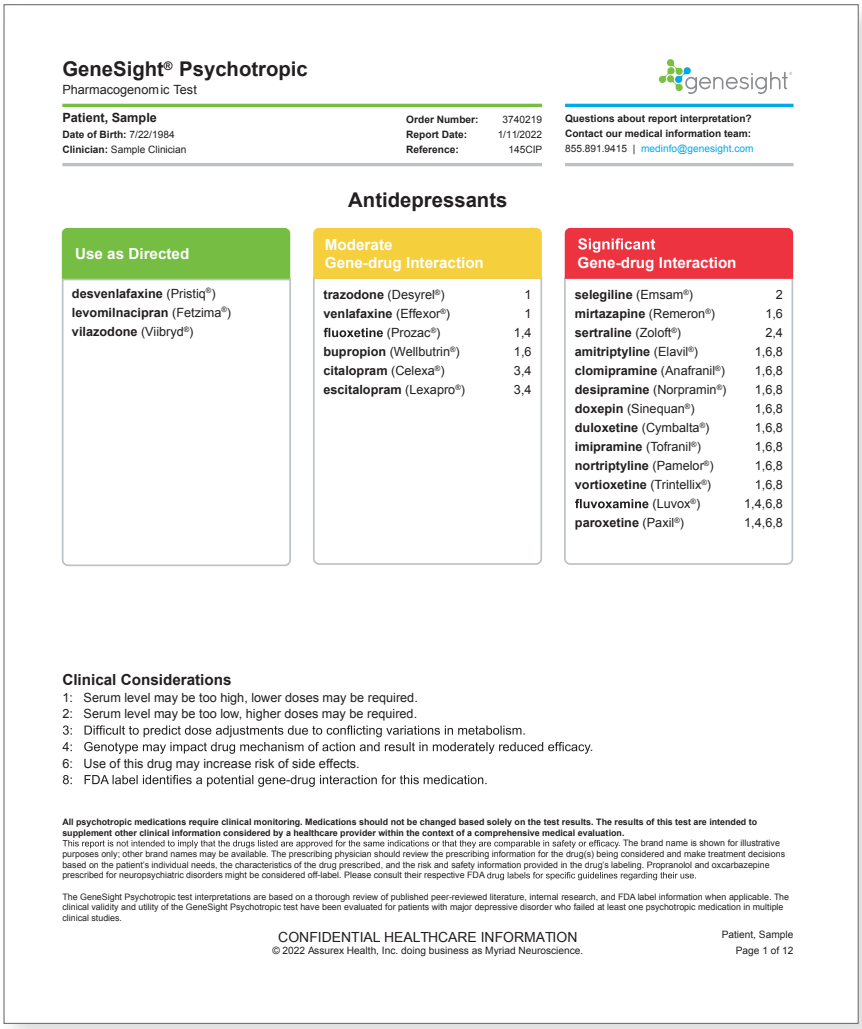
Clinician Report Interpretation Resource

genesight®

The GeneSight® Psychotropic test evaluates a person's DNA to determine how they may metabolize or respond to certain medications.

The GeneSight test may help inform medication selection and dosing. The results of the test show which medications may require dose adjustments, may be less likely to work, or may have an increased risk of side effects based on the patient's genetic results.

On the GeneSight Psychotropic Test, three color-coded categories are used to assist in report interpretation.



GeneSight® Psychotropic
Pharmacogenomic Test

genesight

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

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

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

Antidepressants

Use as Directed	Moderate Gene-drug Interaction		Significant Gene-drug Interaction	
desvenlafaxine (Pristiq®)	**trazodone** (Desyrel®)	1	**selegiline** (Emsam®)	2
levomilnacipran (Fetzima®)	**venlafaxine** (Effexor®)	1	**mirtazapine** (Remeron®)	1,6
vilazodone (Viibryd®)	**fluoxetine** (Prozac®)	1,4	**sertraline** (Zoloft®)	2,4
	bupropion (Wellbutrin®)	1,6	**amitriptyline** (Elavil®)	1,6,8
	citalopram (Celexa®)	3,4	**clomipramine** (Anafranil®)	1,6,8
	escitalopram (Lexapro®)	3,4	**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.

CONFIDENTIAL HEALTHCARE INFORMATION

green

Use as Directed

These medications are not associated with any known genetic issues that would be expected to change patient medication outcomes. However, these medications are not guaranteed to work and may not always be the best options, as there are many other factors that influence medication response and susceptibility to side effects, including drug-drug interactions, diet, environmental factors, age, etc.

yellow

Moderate Gene-drug Interaction

These medications may require dose adjustments in order to have the desired effect, may be less likely to work, or may cause side effects.

red

Significant Gene-drug Interaction

These medications are likely to require dose adjustments in order to have the desired effect, may be less likely to work, or may cause side effects. Genetics are expected to have a greater impact on medications in the significant gene-drug interaction category than those that fall into the moderate gene-drug interaction category.

Interpreting the Clinical Considerations

All medications start in the "Use as Directed" category on the report. Based on an individual's genetic variation, medications may be moved to the Moderate or Significant Gene-drug Interaction categories, depending on how significantly the variation is expected to impact outcomes with that medication. Medications in the Moderate or Significant Gene-drug Interaction categories on the report do not necessarily need to be avoided. The clinical considerations, which are denoted by numbers next to the medications, explain the rationale for a medication's classification and can be used to help inform treatment decisions.

Clincial 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.

Clinical Considerations 1 and 2 reflect an issue with how a medication is metabolized, which means the individual has variation in one or more pharmacokinetic genes. This may affect how much medication is in an individual's system and may require a lower or higher dose. For medications that may require a higher dose, it is not advising to start the individual on a high dose of the medication, but rather to start at a standard dose while being aware that dose increases may be needed to get the desired benefit.

3: Difficult to predict dose adjustments due to conflicting variations in metabolism.

Clinical Consideration 3 also provides information about a medication's metabolism. This clinical consideration indicates that there are conflicting variations in the metabolism of that medication, thus making it difficult to predict a dose adjustment. The most common example is when there are two genes that contribute a relatively similar amount to the overall metabolism of the medication, but one has increased activity and the other has decreased activity. If a medication with clinical consideration 3 is chosen, it may be appropriate to consider starting on a lower dose and increasing the dose based upon how the individual is doing.

4: Genotype may impact drug mechanism of action and result in moderately reduced efficacy.

Clinical consideration 4 indicates that an individual may have a moderately reduced response to certain medications. This is due to variation in a pharmacodynamic gene, and thus reflects an issue with the drug's mechanism of action. Since pharmacodynamic genes do not affect metabolism, it is unlikely that adjusting the dose will improve 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.

Clinical Consideration 5 specifically applies to atomoxetine (Strattera®) when an individual is a CYP2D6 poor metabolizer. This is based on evidence which shows that CYP2D6 poor metabolizers treated with atomoxetine experienced an increased frequency of side effects but also significantly greater improvement in ADHD symptoms compared to extensive (normal) metabolizers.[1]

6: Use of this drug may increase risk of side effects.

Clinical Consideration 6 indicates that an individual may have an increased risk for side effects when taking this medication. This can be due to variation in one or more pharmacokinetic genes that may predict slower than normal metabolism of certain medications, which may result in higher levels of medication in the system. It could also be due to an effect caused by one of the pharmacodynamic genes.

7: Serum level may be too low in smokers.

Clinical Consideration 7 only applies if the individual is a smoker and indicates that smoking may increase the metabolism of that medication. This is because smoking induces CYP1A2 in individuals who already have an increased activity for this enzyme.[2-5] The reaction is not caused by the nicotine, but rather by inhaling the burning hydrocarbons.[4] When you see clinical consideration 2 coupled with clinical consideration 7, it means that if the individual is a smoker, they are expected to metabolize that medication even more quickly than someone who is an ultrarapid metabolizer and does not smoke.

8: FDA label identifies a potential gene-drug interaction for this medication.

When medications have **Clinical Consideration 8**, it means the FDA label contains information that may be relevant for the patient based on their genetic results. This may include information about dosing or more general information to consider.

9: Per FDA label, this medication is contraindicated for this genotype.

Clinical Consideration 9 indicates that per the FDA label, this medication is contraindicated for an individual with this genotype.

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.

Clinical Consideration 10 is associated with medications in the gray "No Proven Genetic Markers" category, meaning that genetic markers have not yet been discovered to reliably predict treatment outcomes with these medications. Due to this lack of evidence, we are not currently able to categorize them or provide actionable recommendations. However, these medications may be effective choices based on other clinical factors. Medications that fall into the "No Proven Genetic Markers" category and receive a clinical consideration of 10 are the same for all individuals.

No Proven Genetic Markers		
gabapentin (Neurontin®) 10	**lithium** (Eskalith®) 10	**topiramate** (Topamax®) 10

Interpreting the Patient Genotypes and Phenotypes

The patient genotypes and phenotypes section of the report provides a list of all the genes tested on the GeneSight® Psychotropic report along with the individual's specific genetic result (genotype) and the characteristic associated with that genetic result (phenotype). **The patient genotypes and phenotypes are broken down into two categories:**

Pharmacodynamic Genes PD

Pharmacodynamic genes provide information about how a medication works on the body. Variation in these genes may affect likelihood of response or risk of side effects with certain medications.

ADRA2A
ADRA2A encodes the alpha-2A adrenergic receptor, which is a norepinephrine receptor. Individuals with the C/C genotype may have a moderately reduced response to certain stimulants, specifically methylphenidate and dexmethylphenidate. If an individual with this genotype is having a less than optimal response to these medications, increasing the dose may not necessarily improve efficacy.

HLA-A*3101
The human leukocyte antigen (HLA) complex, encoded by the HLA gene family, plays a critical role in immunity. Presence of the T allele (either T/T or A/T genotype) is associated with 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 (DRESS), when taking certain mood stabilizers, specifically carbamazepine.

HLA-B*1502
Presence of genetic variation in HLA-B*1502 is associated with a higher risk of serious dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), when taking certain mood stabilizers, including carbamazepine, oxcarbazepine, and lamotrigine.

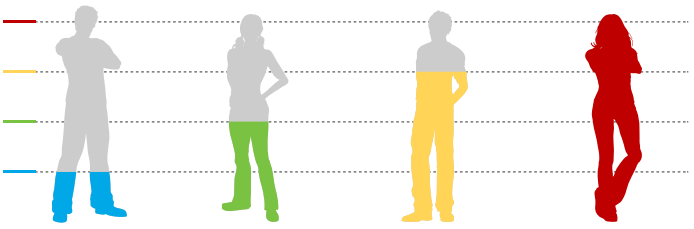
HTR2A
HTR2A encodes for the Serotonin Receptor Type 2A, which is responsible for serotonin signaling. Studies show an increased risk of adverse effects with certain SSRIs, particularly paroxetine, in individuals who have the G/G genotype.

SLC6A4
SLC6A4 encodes for the serotonin transporter, which is the main site of action for SSRIs. SLC6A4 has two main versions: the long (L) allele and the short (S) allele. Studies have shown that the short allele results in less serotonin transporters than the long allele. Individuals who have the S allele may be less likely to respond to certain SSRIs based on this genotype. Additionally, due to the lower number of transporters, increasing the dose may not necessarily improve efficacy.

Pharmacokinetic Genes PK

Pharmacokinetic genes provide information about how the body works on the medication. Variation in these genes may affect the metabolism of a medication. The following PK genes are included on the GeneSight test: **CES1A1, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, UGT1A4, and UGT2B15.**

These genes are categorized based on average enzyme activity into one of four metabolizer phenotypes on the GeneSight Psychotropic report.



Ultrarapid Metabolizer
Breaks down medication rapidly. May not get enough medication at normal doses.

Extensive (Normal) Metabolizer
Breaks down medication normally. Has normal amounts of medication at normal doses.

Intermediate Metabolizer
Breaks down medication slowly. May have too much medication at normal doses.

Poor Metabolizer
Breaks down medication very slowly. May experience side effects at normal doses.

The GeneSight test uses a combinatorial approach that measures multiple genomic variants for each individual and weighs them in combination in order to categorize the medications on the report and provide clinical considerations when applicable.

Additional Genotypes

The genotype for COMT, or catechol-o-methyltransferase, is provided for informational purposes only. This gene has not been shown to be a reliable marker of medication outcomes, and therefore, it is not used to categorize medications on the report.

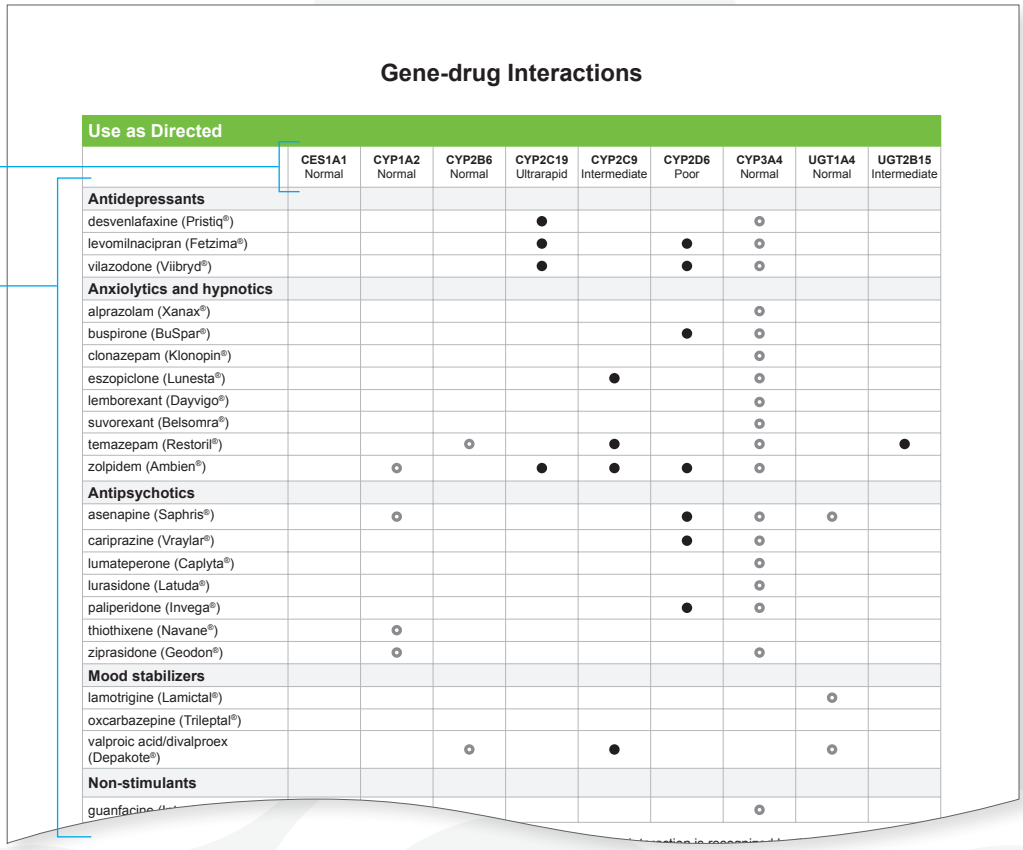
Interpreting the Gene-drug Interaction Chart

The gene-drug interaction chart provides supplementary information about which pharmacokinetic genes are involved in the metabolism of each medication.

The pharmacokinetic genes on the GeneSight® report are listed across the top of the chart.

Medications are listed in a column on the left side.

- Any dot (either shaded or unshaded) signifies that the enzyme is involved in the metabolism of the associated medication.
- A shaded dot means that variation was found in the patient's genotype that may impact medication metabolism.
- An unshaded dot indicates that the gene is associated with medication metabolism, but the predicted patient phenotype is normal.



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®)				●			○		
levomilnacipran (Fetzima®)				●		●	○		
vilazodone (Viibryd®)				●		●	○		
Anxiolytics and hypnotics									
alprazolam (Xanax®)							○		
buspirone (BuSpar®)						●	○		
clonazepam (Klonopin®)							○		
eszopiclone (Lunesta®)					●		○		
lemborexant (Dayvigo®)							○		
suvorexant (Belsomra®)							○		
temazepam (Restoril®)			○		●		○		●
zolpidem (Ambien®)		○		●	●	●	○		
Antipsychotics									
asenapine (Saphris®)		○				●	○	○	
cariprazine (Vraylar®)						●	○		
lumateperone (Caplyta®)							○		
lurasidone (Latuda®)							○		
paliperidone (Invega®)						●	○		
thiothixene (Navane®)		○							
ziprasidone (Geodon®)		○					○		
Mood stabilizers									
lamotrigine (Lamictal®)								○	
oxcarbazepine (Trileptal®)									
valproic acid/divalproex (Depakote®)			○		●			○	
Non-stimulants									
guanfacine							○		

It is not mandatory to refer to the gene-drug interaction chart when using the GeneSight test to inform patient medication selection. It is simply intended to augment the patient results on the pages where the medications are categorized and the clinical considerations are provided, which serve as the primary resource to help inform treatment decisions.

The format of the gene-drug interaction chart is similar to the earlier pages of the GeneSight report where medications are categorized into the green, yellow, and red categories.

There are situations where an individual may have shaded dots in the green "Use as Directed" category. This means that although the individual has variation in one or more genes, it is unlikely to impact their overall metabolism of that particular medication. This could mean that while an enzyme is involved in the metabolism of the medication, its role is not clinically significant enough to warrant a change in dosing or there may be compensation among the enzymes known to metabolize the medication, which results in the medication not being moved from the green "Use as Directed" category.

The results of the GeneSight test are intended to supplement other clinical factors considered by a healthcare provider during a comprehensive medical assessment to help inform treatment decisions.

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The GeneSight® Psychotropic test can provide information that your patients can't.

Questions or Comments?

Medical Information
855.891.9415
medinfo@genesight.com

Visit **GeneSight.com** to learn more.

Not all patients who receive the GeneSight test will have improved outcomes. The GeneSight test is intended to supplement a clinician's comprehensive medical assessment.

1. Michelson D, et al. 2007. J Am Acad Child Adolesc Psychiatry.
2. Dobrinas M, et al. 2011. Clin Pharmacol Ther.
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4. Zevin S, and Benowitz N. 1999. Clin Pharmacokinet.
5: Tantcheva-Poór I, Zaigler M, Rietbrock S, and Fuhr U. 1999. Pharmacogenetics.

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