How Do I Use the Gene-Drug Interaction Chart?

What is the gene-drug interaction chart?

Healthcare providers and patients often inquire about how they can determine which genes may affect outcomes with each medication. The gene-drug interaction chart provides supplementary information about which pharmacokinetic genes are involved in the metabolism of each medication. 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 interpretative pages, which serve as the primary resource to help inform treatment decisions.

How do I interpret the gene-drug interaction chart?

The pharmacokinetic genes on the GeneSight report are listed across the top of the chart, and medications are listed in a column on the left side. Any dot (either shaded, unshaded, or half-shaded) 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. A half-shaded dot means that the phenotype is dependent upon smoking status, with smokers being ultrarapid metabolizers and non-smokers being normal metabolizers. Medication categorization in this chart is according to non-smokers. Refer to the sections labeled Smokers to see medication categories for individuals who smoke.

Gene-drug Interactions

Use as Directed

	CES1A1 Normal	CYP1A2 Smoking Dependent	CYP2B6 Ultrarapid	CYP2C19 Poor	CYP2C9 Normal	CYP2D6 Normal	CYP3A4 Normal	UGT1A4 Normal	UGT2B15 Intermediate
Antidepressants									
desipramine (Norpramin®)						○			
desvenlafaxine (Pristiq®)				●			○		
duloxetine (Cymbalta®)		◐				○			

Moderate Gene-drug Interaction

	CES1A1 Normal	CYP1A2 Smoking Dependent	CYP2B6 Ultrarapid	CYP2C19 Poor	CYP2C9 Normal	CYP2D6 Normal	CYP3A4 Normal	UGT1A4 Normal	UGT2B15 Intermediate
Antidepressants									
clomipramine (Anafranil®)		◐		●*		○	○		
fluoxetine (Prozac®)				●	○	○	○		
fluvoxamine (Luvox®)		◐				○			
selegiline (Emsam®)		◐	●	●			○		
venlafaxine (Effexor®)				●	○	○	○		

Significant Gene-drug Interaction

	CES1A1 Normal	CYP1A2 Smoking Dependent	CYP2B6 Ultrarapid	CYP2C19 Poor	CYP2C9 Normal	CYP2D6 Normal	CYP3A4 Normal	UGT1A4 Normal	UGT2B15 Intermediate
Antidepressants									
amitriptyline (Elavil®)				●*		○			
bupropion (Wellbutrin®)			●			○	○		
citalopram (Celexa®)				●*		○	○		

● 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.

◐ This phenotype may be ultrarapid due to smoking. Smoking status may change the medication category. Refer to sections labeled Smokers to see medication categories for individuals who smoke.

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

Why do I sometimes see shaded dots for medications that are in the green "Use as Directed" category?

When you see shaded dots in the green "Use as Directed" category, it means that although the patient has variation in one or more genes, it is unlikely to impact their 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. For example, buspirone (Buspar®) is metabolized by CYP3A4 and CYP2D6.[1–3] Since CYP2D6 plays a very minor role in Buspar® metabolism, variation in this gene will not likely change the way Buspar® is metabolized, and therefore Buspar® will remain in the green category even when CYP2D6 has a shaded dot.

Another reason a medication in the green category could have shaded dots is that the enzymes involved have opposite phenotypes and therefore compensate for one another. For example, vilazodone (Viibryd®) is metabolized by three different enzymes: CYP2C19, CYP3A4, and CYP2D6.[4] In the example below, the patient is ultrarapid for CYP2C19, poor for CYP2D6, and extensive (normal) for CYP3A4. Since CYP2C19 and CYP2D6 have phenotypes in opposite directions, the enzymes very likely compensate for one another, and Viibryd® remains in the green category.

Use as Directed

	CES1A1 Normal	CYP1A2 Smoking Dependent	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®)						●	○		

Why are there sometimes no dots for medications in the red "Significant Gene-Drug Interaction" category?

In this uncommon situation, the medication does not have any known pharmacokinetic markers but does have pharmacodynamic markers. Since the gene-drug interaction chart includes only pharmacokinetic genes, the medication will not have any dots. Thus, the reason the medication falls in the red category is due to the effect of the pharmacodynamic gene. The only medication on GeneSight Psychotropic that creates this situation is oxcarbazepine (Trileptal®).

Significant Gene-drug Interaction

	CES1A1 Normal	CYP1A2 Smoking Dependent	CYP2B6 Normal	CYP2C19 Ultrarapid	CYP2C9 Intermediate	CYP2D6 Poor	CYP3A4 Normal	UGT1A4 Normal	UGT2B15 Intermediate
Mood stabilizers									
carbamazepine (Tegretol®)			○				●		
lamotrigine (Lamictal®)								○	
oxcarbazepine (Trileptal®)									

Conclusions

The gene-drug interaction chart provides additional information to healthcare providers and patients about which pharmacokinetic genes are involved in the metabolism of each medication. The GeneSight test takes into consideration the unique metabolic pathways and mechanisms of action for each medication and integrates genetic information from all relevant pharmacokinetic and pharmacodynamic genes to categorize medications into the green, yellow, and red categories.

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References

1. FDA Label.. Buspirone. (2010).
2. M. Zhu, W. Zhao, H. Jimenez, D. Zhang, S. Yeola, R. Dai, N. Vachharajani, J. M. Cytochrome P450 3A-mediated metabolism of buspirone in human liver microsomes. Drug Metab. Dispos. 33, 500-507 (2005).
3. N. Raghavan, D. Zhang, M. Zhu, J Zeng, L. C. CYP2D6 catalyzes 5-hydroxylation of 1-(2-pyrimidinyl)-piperazine, an active metabolite of several psychoactive drugs, in human liver microsomes. Drug Metab. Dispos. 33, 203-208 (2005).
4. FDA Label. Vilazodone. (2011).