What is the difference between "single-gene" testing and the weighted multi-gene approach used by the GeneSight® Psychotropic test?

Summary: Single-gene pharmacogenetic testing is a common way of analyzing gene-drug interactions for clinical implementation and personalizing patients' medication regimens. However, many medications are processed by multiple metabolic pathways, with genomic variability being capable of influencing the rate of metabolism and the likelihood of response or risk of side effects. The GeneSight Psychotropic test uses a weighted multi-gene approach that measures multiple genomic variants for each individual and weighs them together to provide comprehensive information about how an individual's genetic variation may impact their outcomes with certain psychotropic medications. This weighted multi-gene approach has been found to better predict antidepressant blood levels and clinical outcomes in comparison to single-gene pharmacogenetic testing.[1-4]

How is weighted multi-gene pharmacogenomic testing different from single-gene testing?

Weighted multi-gene pharmacogenomic testing is the process of simultaneously assessing the effects of variation found in multiple genes associated with medication metabolism or mechanism of action, and then conveying the results in an integrated fashion to help inform medication selection, or dosing.[5] This differs from single-gene pharmacogenetic testing which evaluates how genetic variation found in one gene associated with one or more medications may influence medication metabolism, efficacy, or tolerability.[6] While single-gene testing may help inform prescribing decisions in certain scenarios, it is worth acknowledging that the majority of commonly prescribed medications in psychiatric practice are metabolized by multiple enzymes where genetic variation may arise in these pathways resulting in variable medication breakdown, and potentially differential pharmacologic effects. This may limit the capability of single-gene testing information to improve patient outcomes in psychiatric practice, and trying to combine information from multiple single-gene test results may not be feasible for clinical implementation.

What is the weighted multi-gene approach used by the GeneSight Psychotropic test?

The GeneSight Psychotropic test addresses limitations of single-gene testing in psychiatric practice by employing a weighted multi-gene pharmacogenomic approach. This weighted multi-gene approach is comprised of evidence derived from comprehensive literature and data reviews, which is integrated into an algorithm to analyze and weigh the importance of multiple genes associated with a medication. For an overview of the data selection process, the inputs, and steps involved in the GeneSight algorithm, please see our GeneSight® Psychotropic Weighted Multi-Gene Algorithm white paper. (Figure 1A)

Based on an individual's genetic test results, the GeneSight weighted multi-gene algorithm generates a report categorizing 62 FDA approved medications into three color-coded categories according to the expected level of gene-drug interactions: green (use as directed), yellow (moderate gene-drug interaction), and red (significant gene-drug interaction). Report categorization and assignment of clinical consideration annotations provides insight into the weighted multi-gene effects of gene-drug interactions on medications to help inform on prescribing decisions. (Figure 1B)

Figure 1: The Algorithmic Process and example of weighted multi-gene Impact of Genetic Variability on *Drug X*

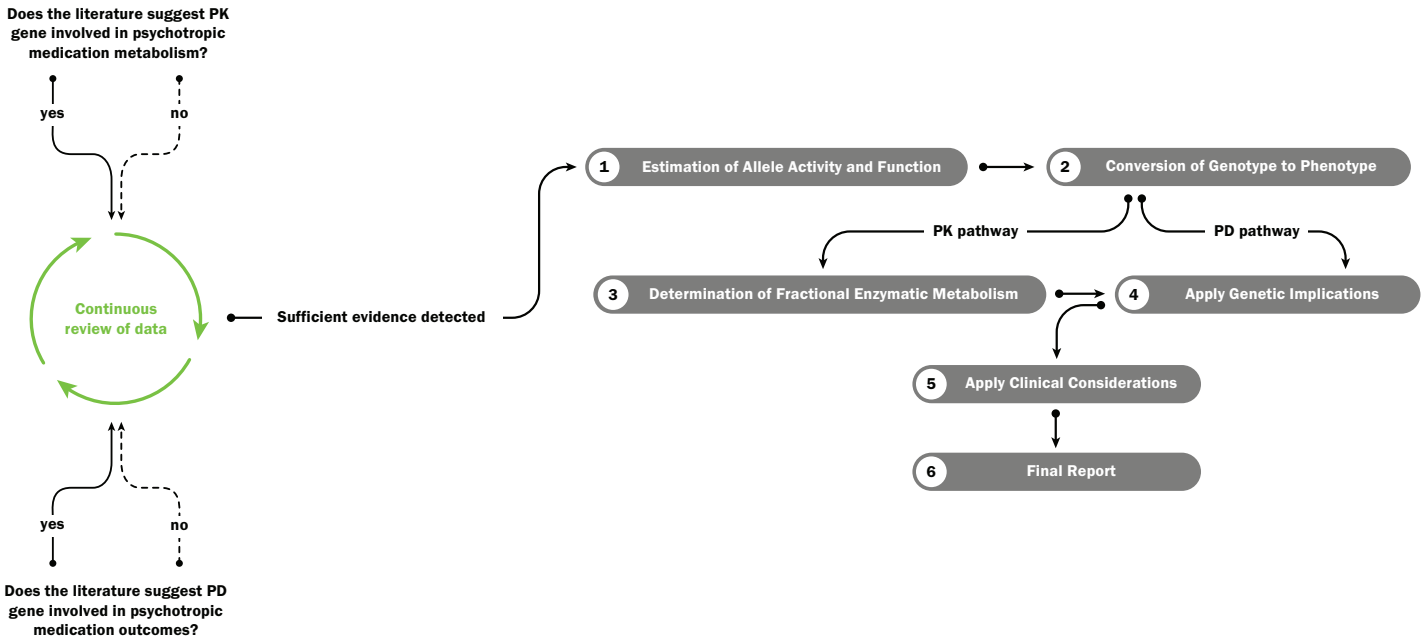

Figure 1A: Algorithmic Process

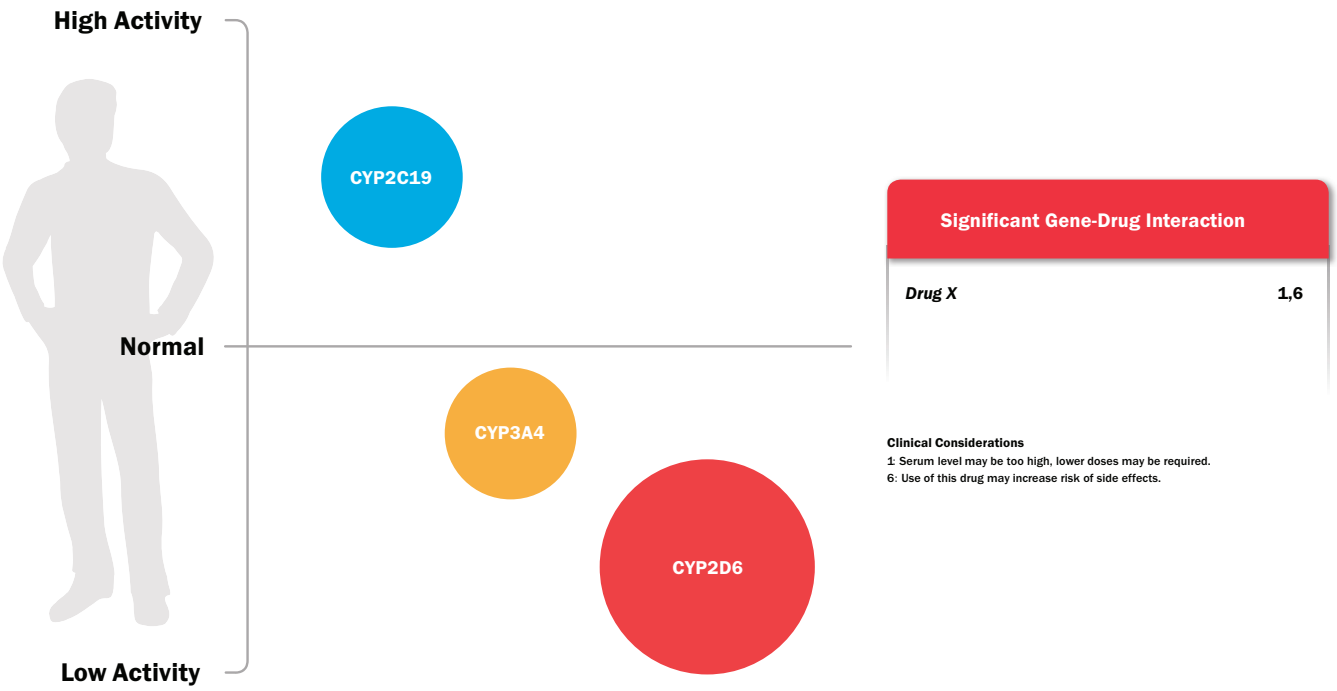

Figure 1B: Example of weighted multi-gene impact of genetic variability on Drug X

Are there examples showing the importance of weighted multi-gene pharmacogenomic testing compared to single-gene testing?

One example highlighting the importance of weighted multi-gene pharmacogenomic testing is with (es)citalopram. (Es)citalopram is extensively metabolized by CYP2C19, in which genetic variation can result in changes in (es)citalopram blood levels.[7-13] The correlation between CYP2C19 genetic variation and altered (es)citalopram blood levels has led to subsequent CYP2C19 single gene-drug interaction recommendations by the Clinical Pharmacogenetics Implementation Consortium (CPIC) with (es)citalopram, and Food and Drug Administration (FDA) with citalopram, specifically.[14,15] However, data have also shown involvement of CYP3A4 and CYP2D6 in the metabolism of (es)citalopram (Figure 2).[15-22] Multiple studies have evaluated the impact of genetic polymorphisms in multiple CYP enzymes on (es)citalopram blood levels including a post-hoc analysis of the GUIDED study.[1,19-21] This post hoc analysis evaluated the ability of the GeneSight weighted multi-gene approach to predict (es)citalopram blood levels compared to CPIC single-gene recommendations. Results showed that the weighted multi-gene approach used by the GeneSight Psychotropic test was a better predictor of (es)citalopram blood levels than CYP2C19 single-gene testing, and also identified more patients who could benefit from clinically actionable recommendations in contrast to CYP2C19 single-gene testing and CPIC classifications.[1]

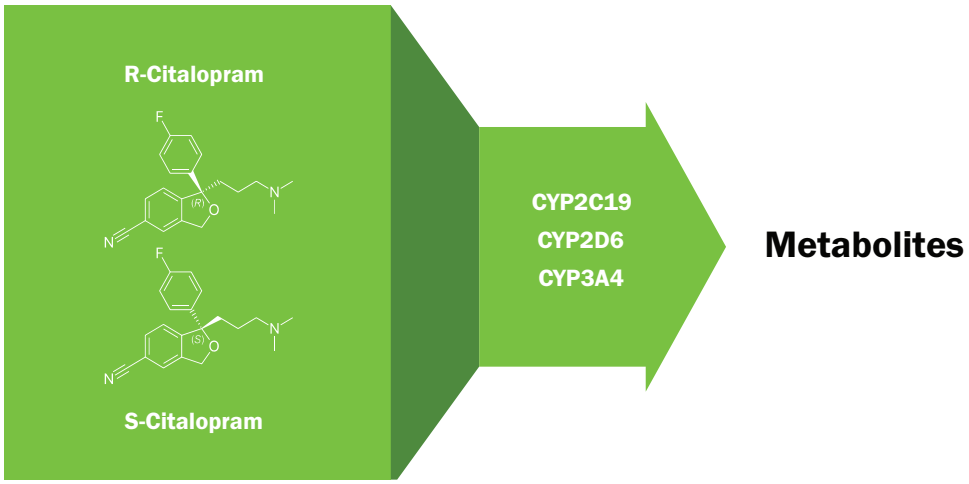

Figure 2: Citalopram/escitalopram metabolic pathway

Another example highlighting the value of weighted multi-gene pharmacogenomic testing is with sertraline (Figure 3). Multiple cytochrome P450 (CYP450) enzymes have been characterized in the metabolism of sertraline, along with evidence supporting that genetic variation in these enzymatic pathways results in altered sertraline blood levels.[23-34] Previously, CPIC guidelines provided gene-drug interaction recommendations for sertraline with only CYP2C19.[35] However, during an updated evidence review, recommendations for both CYP2C19 and CYP2B6 were provided for sertraline.[14] A post hoc analysis of the GUIDED study evaluated the ability of the GeneSight weighted multi-gene approach to predict sertraline blood levels when looking at the weighted assessment of CYP2C19, CYP2B6, and CYP3A4 variation in the algorithm compared to CYP2C19 single-gene testing, showing that the weighted multi-gene algorithm was a significant predictor of variation in sertraline blood levels.[2] These findings support the importance of a weighted multi-gene pharmacogenomic approach with sertraline in comparison to single-gene recommendations.

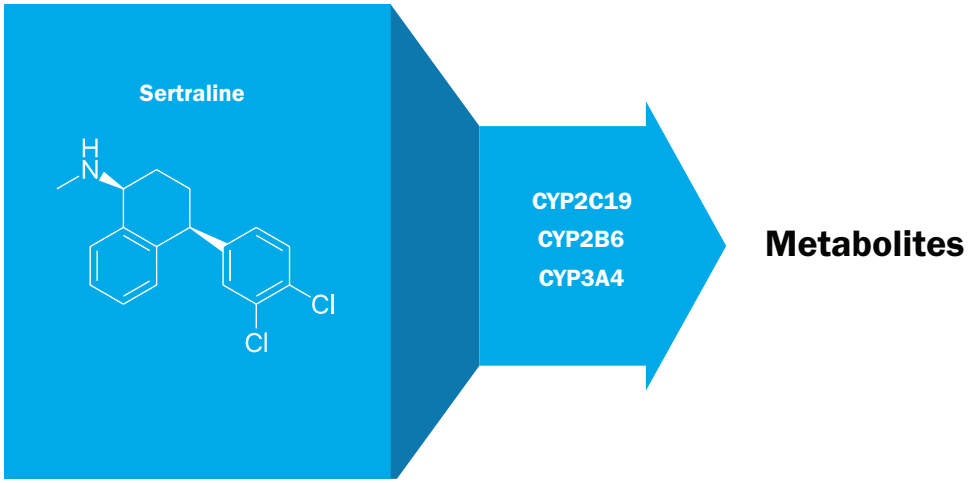

Figure 3: Sertraline metabolic pathway

Does weighted multi-gene pharmacogenomic testing predict better patient outcomes than single-gene testing?

Single-gene pharmacogenetic testing in depression has historically produced mixed results regarding clinical outcomes[36], although recent guidelines have brought attention to clinically important single gene-drug interactions[14-37] A potential reason for the lack of overwhelming evidence for single-gene testing in depression is that the effects of multiple genes assessed together may give a more complete pharmacologic picture for a given medication.[5] Therefore, an important question clinically is, "Do the effects of multiple genes, assessed through a weighted multi-gene approach, predict improved patient outcomes compared to each gene individually?"

To address this question, two analyses have been published evaluating the ability of the weighted multi-gene approach used by the GeneSight Psychotropic test to predict patient outcomes compared to single-gene testing.[3,4] The first analysis used combined data from the standard of care arms of three prospective clinical outcomes trials of the GeneSight Psychotropic test. By assessing the standard of care (i.e., control arm or treatment as usual) group of patients, no patient or patient's healthcare provider was aware of their pharmacogenomic information, thus creating blinded outcomes.

In this analysis, patients were separated into groups based on the primary metabolizing enzyme of their medication, and single-gene phenotypes (i.e., CYP2D6 ultrarapid metabolizer, extensive (normal) metabolizer, intermediate metabolizer, and poor metabolizer) were assessed for improvement in HAM-D17 from baseline. When only CYP2D6 genotype was considered for medications primarily, though not exclusively, metabolized by CYP2D6, the individual phenotypes were not predictive of patient outcomes, suggesting that single-gene testing was unable to accurately predict patient outcomes.[3] However, when the same analysis was performed using the weighted multi-gene approach of the GeneSight Psychotropic test, significant differences were found. Patients taking medications in the red Significant Gene-Drug Interaction category showed significantly less improvement in their symptoms compared to those taking medications in the green Use as Directed or yellow Moderate Gene-Drug Interaction categories.[3] This analysis showed that the GeneSight test predicted which patients were likely to have poor depression outcomes with their treatment regimen.

The second analysis evaluated the ability of the weighted multi-gene approach used by the GeneSight Psychotropic test to predict patient outcomes (and medication blood levels) compared to CPIC single-gene guideline recommendations for CYP2D6 and CYP2C19. This post-hoc study analyzed patients from GUIDED taking any medication included on the GeneSight test and a subset of patients taking a medication with single-gene CPIC guidelines. The predictive ability of each pharmacogenetic approach was measured according to medication congruence and correlation with treatment outcomes (symptom improvement, response, and remission). For GeneSight, medications were considered congruent if they were in the no or moderate gene-drug interaction categories, while incongruent medications were those in the significant gene-drug interaction category. For single-gene guidelines, congruent medications were those with no actionable therapeutic recommendations. Medications with no available guidelines were also considered congruent as there are no published guidelines to say that those medications have a meaningful gene-drug interaction. Medications with actionable recommendations in single-gene guidelines were considered incongruent. Congruence analyses were conducted for all medications on the GeneSight report, and a subset of medications with CPIC single-gene guidelines, specifically. The results showed that only the weighted multi-gene approach used by the GeneSight Psychotropic test, not single-gene analysis, was able to predict symptom improvement, response, and remission.[4] (Figure 4)

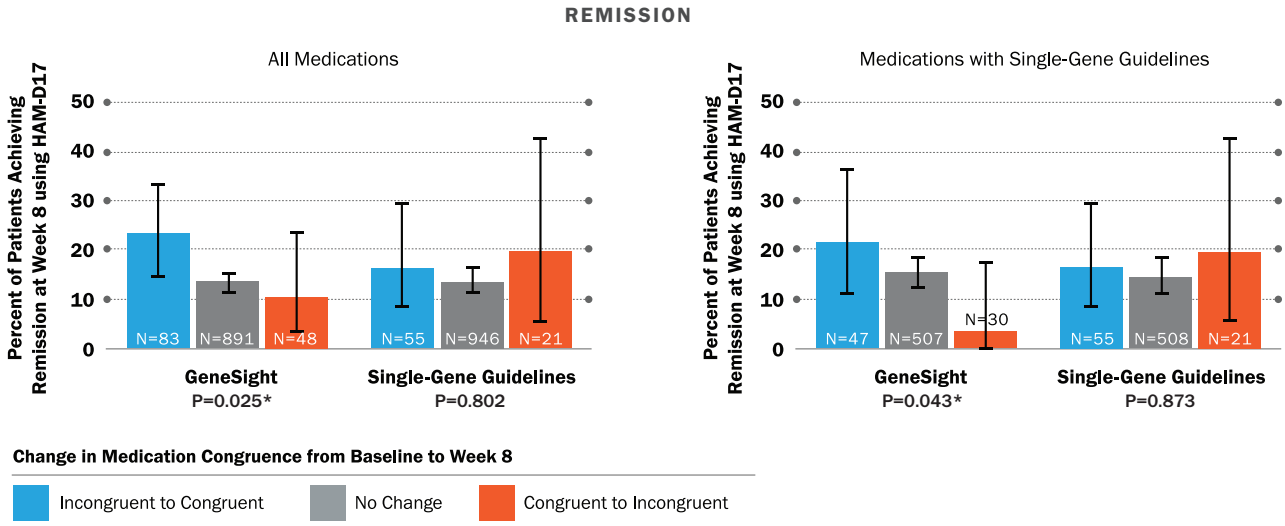

Figure adapted from Rothschild et al. Remission defined as HAMD-17 score of ≤ 7

**Statistically significant correlation between patient outcomes and medication congruence. Statistically significant results seen for GeneSight weighted multi-gene approach for other outcomes assessed (symptom improvement and response rates)*

Data based on CPIC guidelines available at the time of publication and may not reflect current CPIC guidelines

Figure 4: Patient outcomes according to medication congruence- Remission Rates

Conclusion

The GeneSight test employs a unique method of predicting patient medication outcomes using a weighted multi-gene pharmacogenomic approach. Weighted multi-gene pharmacogenomics uses knowledge of each medication's unique set of pharmacokinetic and pharmacodynamic characteristics to incorporate and appropriately weigh genetic variation at multiple loci to produce better predictions of patient outcomes than testing solely for the primary metabolic pathway of a medication.

For more information, contact the GeneSight Medical Information Department at:

PHONE: 855.891.9415
EMAIL: medinfo@genesight.com

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