GeneSight® Clinical Research Summary

GUIDED (Genomics Used to Improve DEpression Decisions)

Greden JF, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res. 2019; 111: 59-67.

https://pubmed.ncbi.nlm.nih.gov/30677646

Study Design: This was an 8 week, blinded, multi-center, randomized controlled trial of 1,167 subjects with major depressive disorder from 20 academic sites and 40 community sites. The trial was unblinded after the 8 week check-in, and the subjects were followed out to 24 weeks. The study assessed the impact of the GeneSight Psychotropic test on psychiatric treatment response compared to treatment as usual (TAU). The raters used the Hamilton Rating Scale for Depression (HAM-D17), and the subjects had to have a minimum score of 14 in order to be eligible for the study.

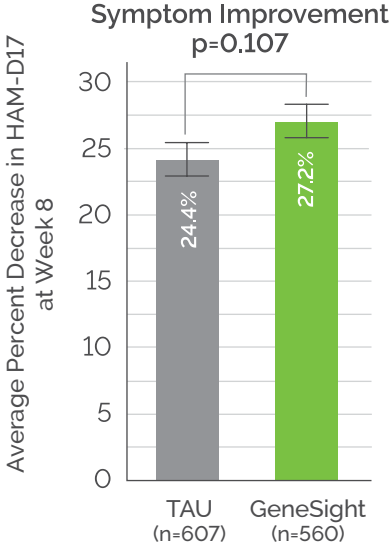
Study Endpoints: GUIDED compared two active treatment arms. The primary endpoint was symptom improvement with secondary endpoints of response and remission. Symptom improvement is defined as the change in HAM-D17 score, and this is based on the group average. Response is defined as a ≥50% reduction in HAM-D17 score, and remission is defined as a HAM-D17 score ≤7.

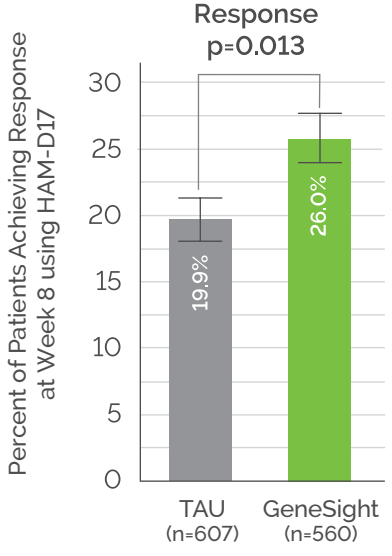
Study Limitations: The treating clinician was not blinded to study arm, the majority of the cohort was Caucasian, the primary results may not be generalizable for patients with mild depression, and the impact of polypharmacy on patient outcomes was not evaluated.

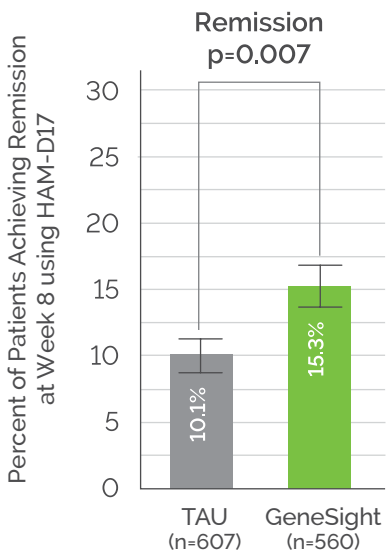
Key Findings:

Directional improvement in symptoms: On the primary endpoint of symptom improvement, the data trended toward but did not achieve statistical significance between GeneSight and TAU arms at week 8.

Significant improvement in response and remission: There were statistically significant and clinically meaningful increases in response and remission rates in the GeneSight arm versus the TAU arm at week 8.







The GeneSight effect on all endpoints was durable over 6 months: Symptom improvement, response, and remission continued to improve after unblinding at week 8 and up to 6 months for patients in the GeneSight arm.

Switching to a medication with no or moderate gene drug interactions improved patient outcomes: Symptom improvement, response, and remission were significantly improved when patients on a medication with significant gene-drug interactions were switched to a medication with no or moderate gene-drug interactions by week 8 compared to those who remained on medications with significant gene-drug interactions.

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GUIDED: Patients on Medications with Gene-Drug Interactions (GDIs)

Thase ME, et al. Impact of pharmacogenomics on clinical outcomes for patients taking medications with gene-drug interactions in a randomized controlled trial. J Clin Psychiatry. 2019; 80(6): 19m12910.

https://pubmed.ncbi.nlm.nih.gov/31721487

Study Design: This is a post hoc analysis of the GUIDED study. It was performed on patients taking medications subject to gene-drug interactions at baseline (yellow and red categories). This excludes the 31% of patients entering the study on medications with no gene-drug interactions (green category).

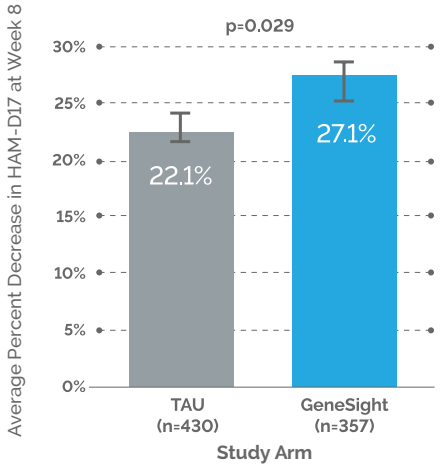
Study Endpoints: Symptom improvement, response, and remission were measured using HAM-D17. Symptom improvement is defined as the change in HAM-D17 score, and this is based on the group average. Response is defined as a ≥50% reduction in HAM-D17 score, and remission is defined as a HAM-D17 score ≤7.

Study Limitations: This analysis did not assess non-genetic factors that may contribute to medication failure or the utility of pharmacogenomic testing to inform multiple medication trials compared to TAU.

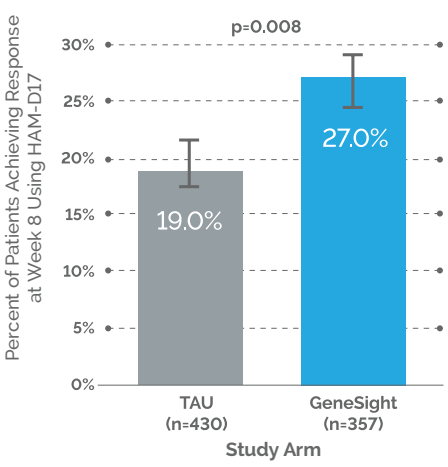
Key Findings:

Significant improvement in symptom reduction, response, and remission: Among patients taking medications with gene-drug interactions at baseline, the GeneSight arm experienced a significant improvement in symptoms, response rates, and remission rates at week 8 compared to TAU.

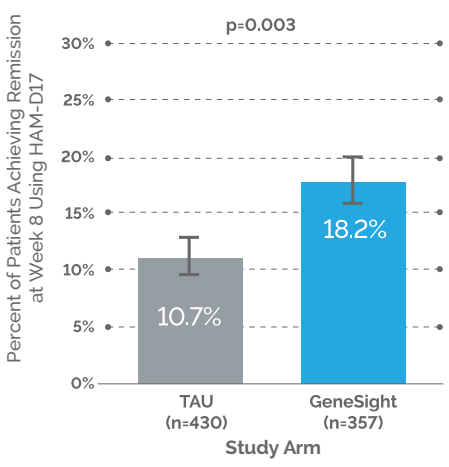
SYMPTOM IMPROVEMENT



RESPONSE



REMISSION



Outcomes Continued to Improve Over Time: Symptom improvement, response, and remission continued to improve after unblinding at week 8 and through week 24 for patients in the GeneSight arm who were taking medications with gene-drug interactions at baseline.

La Crosse Clinical Study

Hall-Flavin DK, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenet Genomics. 2013; 23(10): 535-548.

https://pubmed.ncbi.nlm.nih.gov/24018772

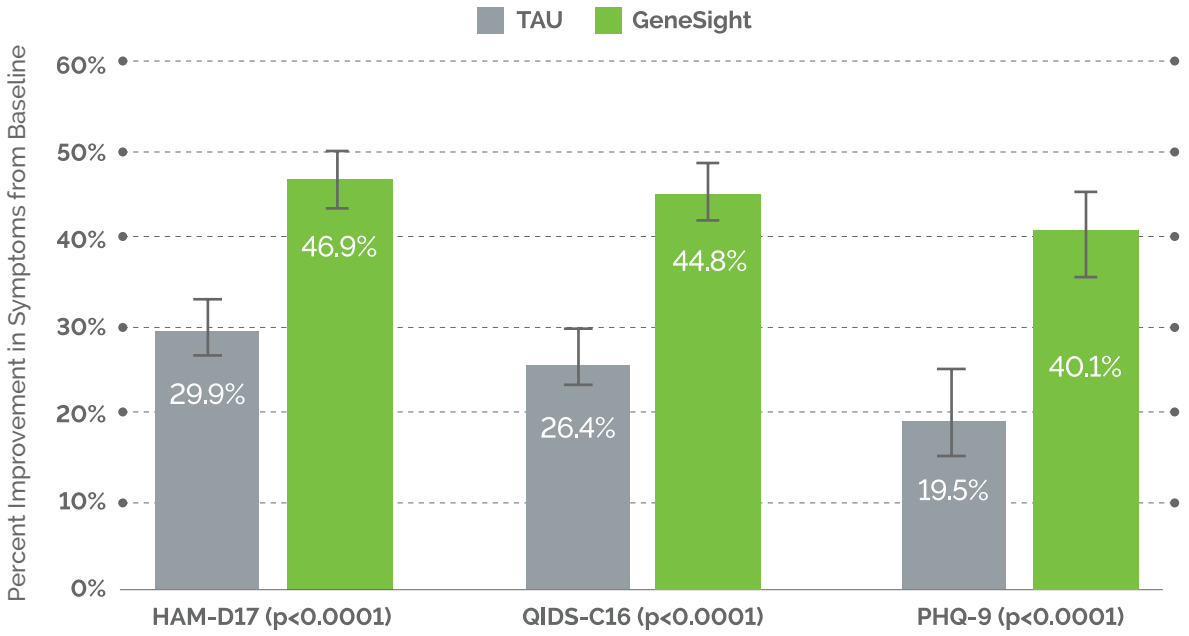
Study Design: This was a prospective, open-label study of 165 subjects with a primary diagnosis of major depressive disorder. Subjects had to have a minimum score of 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D17). Subjects were also assessed using the Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C16) and the Patient Health Questionnaire (PHQ-9). The study compared patient outcomes between GeneSight group and treatment as usual group (TAU) at week 8.

Study Endpoints: Symptom improvement, response and remission were measured across the three scales. Symptom improvement is defined as the change in the scale score, and this is based on the group average. Response is defined as a ≥50% reduction in the scale score. Remission is defined as a HAM-D17 score ≤7, a QIDS-C16 score <6, or a PHQ-9 score <5.

Study Limitations: This study had a relatively small sample size and was not blinded.

Key Findings:

Significant improvement in depression scores: Greater reduction in symptoms was observed across the duration of the study for the GeneSight group, showing 70% relative improvement in depressive symptoms compared to TAU at 8 weeks (QIDS-C16).



Higher response rates: Patients in the GeneSight group were 2.1 times more likely to respond to their medications compared to those in the TAU group.

Higher physician and patient satisfaction: Almost three times as many physicians in the GeneSight group perceived their patients to be very highly satisfied with their care compared to the TAU group. Physician reporting of confidence in choice of medication and treatment and satisfaction with care was also substantially higher in the GeneSight group.

Pine Rest Clinical Study

Winner JG, et al. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med. 2013; 16(89): 219-227.

https://pubmed.ncbi.nlm.nih.gov/24229738

Study Design: This was a blinded, randomized controlled trial of 49 subjects with a primary diagnosis of major depressive disorder. Subjects had to have a minimum score of 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D17). It compared patient outcomes between the GeneSight group and the treatment as usual group (TAU) at week 10.

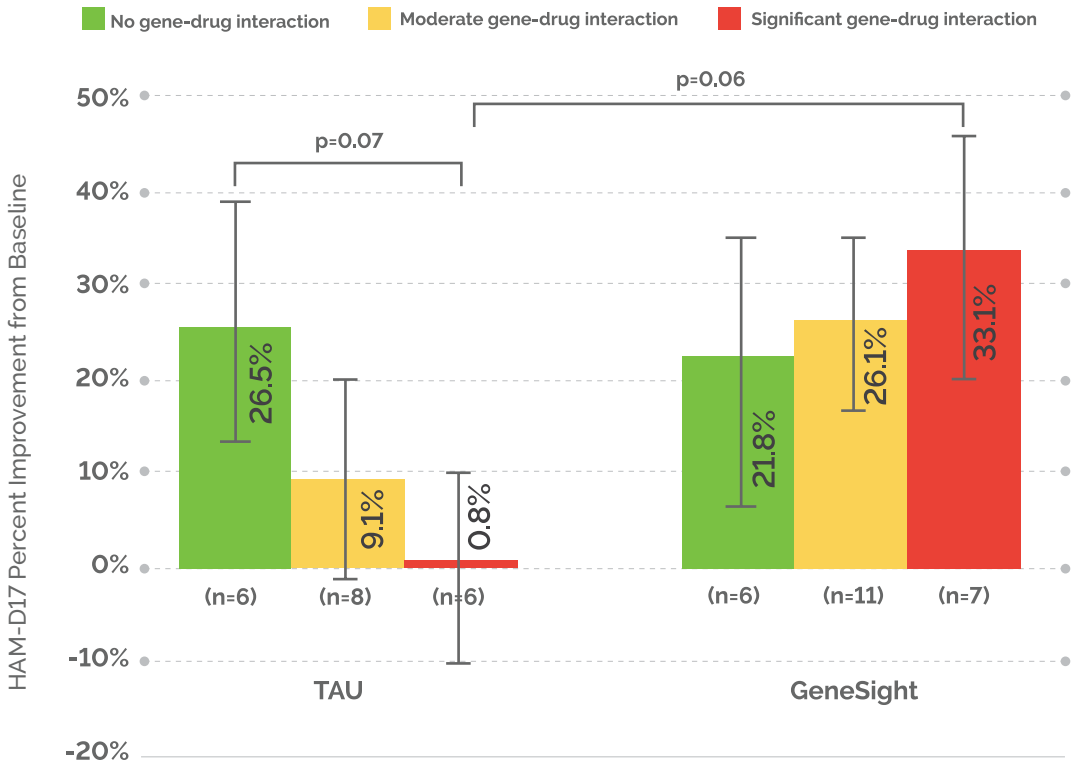
Study Endpoints: Symptom improvement, response, and remission were measured using HAM-D17. Symptom improvement is defined as the change in HAM-D17 score, and this is based on the group average. Response is defined as a ≥50% reduction in HAM-D17 score, and remission is defined as a HAM-D17 score ≤7.

Study Limitations: The treating clinician was not blinded to study arm, the study was underpowered, and the results were not statistically significant.

Key Findings:

GeneSight accurately predicted patient outcomes based on gene-drug interactions: GeneSight accurately predicted those patients who were more likely to have poor depression outcomes due to gene-drug interactions. TAU subjects who had been prescribed medications with significant gene-drug interactions had almost no improvement in depressive symptoms over the 10 weeks of the trial.

Medications with no or moderate gene-drug interactions improved patient outcomes: When subjects who had been on medications with significant gene-drug interactions were switched to medications with no or moderate gene-drug interactions based on their GeneSight report, the subjects experienced a 33.1% improvement in symptoms (HAM-D17) at ten weeks compared to TAU subjects taking medications with significant gene-drug interactions, who had 0.8% improvement.



Hamm Clinical Study

Hall-Flavin DK, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. 2012; 2(10): e172.

https://pubmed.ncbi.nlm.nih.gov/23047243

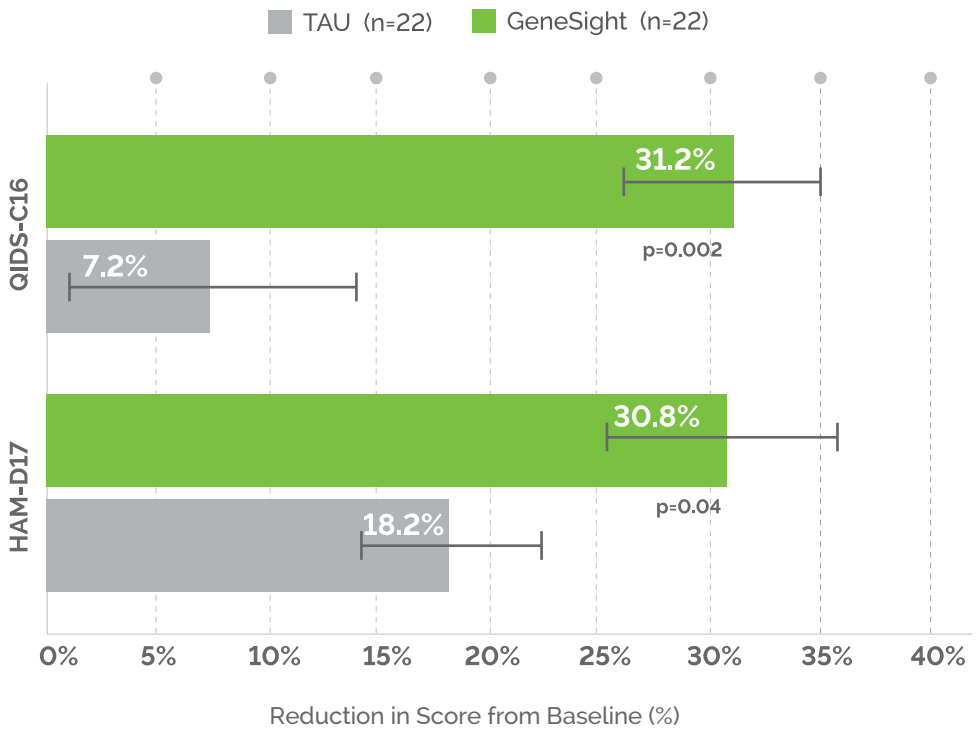
Study Design: This was a prospective, open-label study of 44 subjects with a primary diagnosis of major depressive disorder. Subjects had to have a minimum score of 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D17). Subjects were also assessed using the Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C16). The study compared patient outcomes between the GeneSight group and the treatment as usual group at week 8.

Study Endpoints: Symptom improvement was measured using HAM-D17 and QIDS-C16. Symptom improvement is defined as the change in the scale score.

Study Limitations: This study had a small sample size and was not blinded.

Key Findings:

Greater symptom improvement: Patients in the GeneSight group experienced a 4-fold greater improvement in depressive symptoms at week 8 (QIDS-C16) compared to those in the treatment as usual (TAU) group.



With GeneSight, clinicians prescribed medications with no to moderate gene-drug interactions more often: Patients in the GeneSight group were more often prescribed medications with no to moderate gene-drug interactions vs. medications with significant gene-drug interactions.

Clinical Utility of Combinatorial Pharmacogenomics

Altar CA, et al. Clinical utility of combinatorial pharmacogenomics-guided antidepressant therapy: evidence from three clinical studies. Mol Neuropsychiaty. 2015; 1(3): 145-155.

https://pubmed.ncbi.nlm.nih.gov/27606312

Meta-Analysis Design: This was a meta-analysis of three previous prospective two-arm studies (La Crosse, Pine Rest, and Hamm) with a total of 258 patients with a primary diagnosis of major depressive disorder. Subjects had to have a minimum score of 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D17). It compared outcomes between the GeneSight group and the treatment as usual group (TAU).

Study Endpoints: Symptom improvement, response, and remission were measured using HAM-D17 in each of the studies. Symptom improvement is defined as the change in HAM-D17 score, and this is based on the group average. Response is defined as a ≥50% reduction in HAM-D17 score, and remission is defined as a HAM-D17 score ≤7.

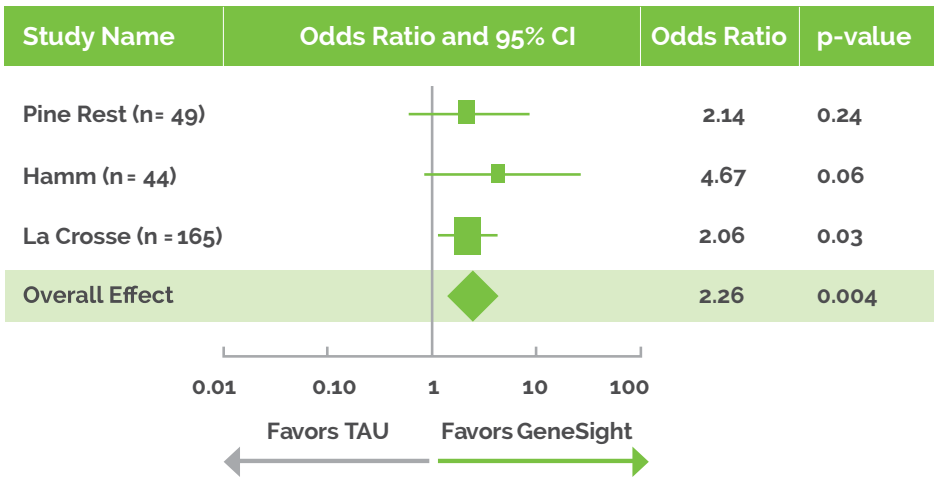
Study Limitations: This analysis included both open-label studies and a blinded RCT. The treating clinician was not blinded to study arm in the blinded RCT, and the majority of the subjects in all studies was Caucasian.

Key Findings:

The GeneSight test accurately predicted which patients were likely to have poor depression outcomes due to gene-drug interactions. TAU subjects who at baseline were prescribed medications identified by the GeneSight test as having significant gene-drug interactions improved only 12%, while patients taking medications with no or moderate gene-drug interactions improved by 28.5% and 32.5%, respectively.

Patients in the GeneSight group were more likely to achieve response compared to TAU: The odds of a clinical response were increased 2.3-fold among all GeneSight subjects compared to all TAU subjects. The odds of remission were also increased for the GeneSight group compared to TAU, but this was not statistically significant (OR=1.8; p=0.07).

ODDS OF CLINICAL RESPONSE: HAM-D17*



*Minimum Score of 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D17).

Clinical Validity of Combinatorial Pharmacogenomics

Altar CA, et al. Clinical validity: combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes. Pharmacogenomics J. 2015; 15(5): 443-451.

https://pubmed.ncbi.nlm.nih.gov/25686762

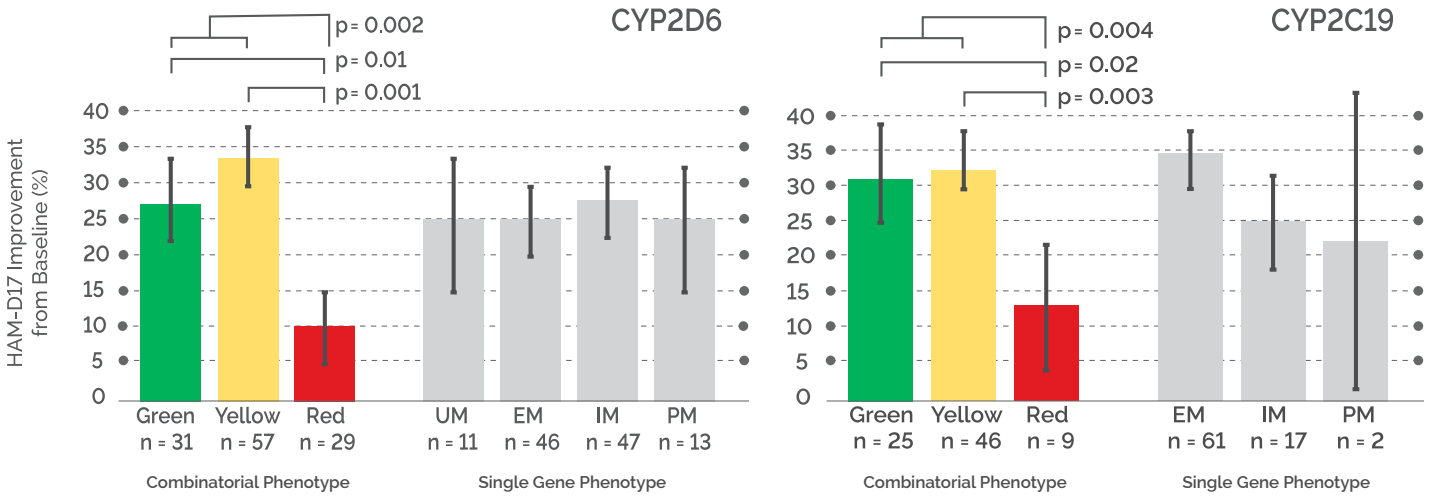
Meta-Analysis Design: This analysis used combined data from the treatment as usual (TAU) arms from three previous prospective two-arm studies (La Crosse, Pine Rest, and Hamm) with a total of 119 patients with a primary diagnosis of major depressive disorder. Subjects had to have a minimum score of 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D17). Outcome predictions were compared between GeneSight testing and single-gene testing.

Study Endpoints: Symptom improvement was measured using HAM-D17 in each of the studies. This is defined as the change in HAM-D17 score, and this is based on the group average.

Study Limitations: This analysis had a relatively small sample size, and the majority of the subjects were Caucasian.

Key Findings:

Single-gene phenotyping failed to identify patients with differential outcomes to medications. When patients were separated into groups based on the primary metabolizing enzyme of their medication, the phenotypes were not predictive of patient outcomes. However, when the same patients were analyzed using the GeneSight test, patients who were likely to have poor depression outcomes could be predicted.



The GeneSight test accurately predicted which patients were likely to have poor depression outcomes due to gene-drug interactions. TAU subjects taking medications identified by the GeneSight test as having significant gene-drug interactions showed significantly less improvement in symptoms compared to those taking medications with no or moderate gene-drug interactions.

Impact Clinical Study

Tanner JA, et al. Combinatorial pharmacogenomics and improved patient outcomes in depression: treatment by primary care providers or psychiatrists. J Psychiatr Res. 2018; 104: 157-162.

https://pubmed.ncbi.nlm.nih.gov/30081389

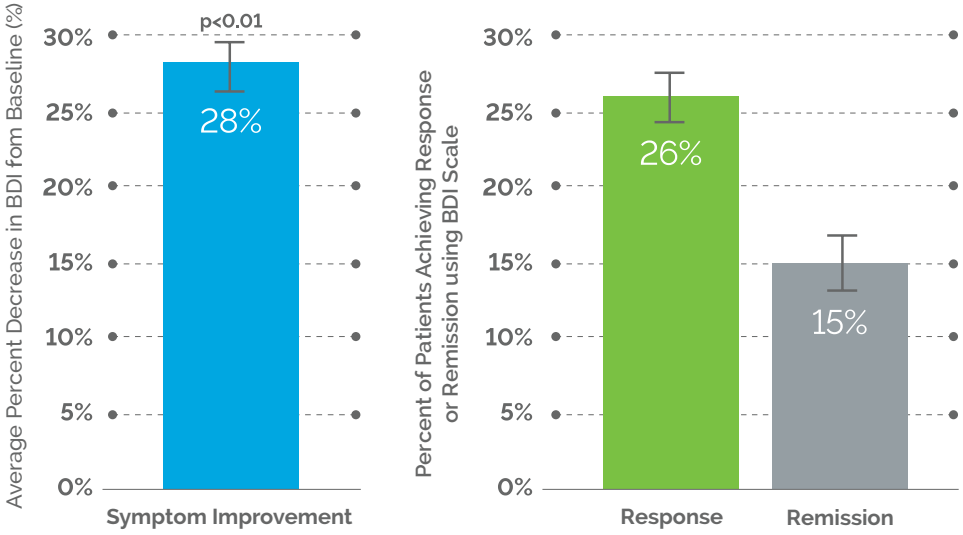
Study Design: This was an 8-12 week, prospective, naturalistic study that assessed 1,871 patients who had moderate-to-severe depression and were treated by primary care providers or psychiatrists. The study assessed the impact of the GeneSight Psychotropic test on patient outcomes using the Beck Depression Inventory. Patients had to have a BDI score ≥20 to be included in the study.

Study Endpoints: Symptom improvement, response and remission were measured using the BDI scale. Symptom improvement is defined as the percent change in BDI score. Response is defined as a ≥50% decrease in BDI score and remission is defined as a BDI score ≤10.

Study Limitations: This study did not have a control arm and was not blinded.

Key Findings:

Significant improvement in depressive symptoms: Patients who received the GeneSight test experienced a 28% reduction in depressive symptoms at follow-up compared to baseline.



Significantly greater improvements among patients treated by PCPs: Symptom improvement, response, and remission were significantly better among patients treated by primary care providers (n=810) compared to psychiatrists (n=1,061).

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