INTRODUCTION

One in six Americans develop Major Depressive Disorder (MDD) in their lifetime. Medications serve as the primary course of care for this condition; yet, fewer than half of all depressed patients respond well to their first prescription. This high failure rate is compounded by the fact that six weeks are typically necessary to observe the effectiveness of MDD medications, a timeline aggravated by the common approach of starting patients on low doses and making gradual increases in order to avoid significant side effects. Patients also become less responsive and less adherent with each subsequent medication, and the likelihood of an adverse event increases. This inefficient trial-and-error approach results in patients suffering through successive medication trials and a surge in depression-related medical expenditures and pharmaceutical costs with each treatment attempt.

GENESIGHT® PSYCHOTROPIC

GeneSight Psychotropic is a pharmacogenomic test that analyzes clinically important genetic variations that may affect a patient’s response to psychiatric medications. The test informs clinicians about which medications may require dose adjustments, may be less likely to work, or may have an increased risk of side effects based on a patient’s genetic makeup. This combinatorial approach has been evaluated in multiple clinical studies, and GeneSight is the only psychiatric pharmacogenomic test backed by such extensive research. GeneSight supports prescribing clinicians by placing each medication into one of three color-coded categories: “Use as Directed” in green, “Moderate Gene-Drug Interaction” in yellow, or “Significant Gene-Drug Interaction” in red. Selecting medications with no or moderate gene-drug interactions for each patient improves outcomes and reduces the risk of adverse events.

Most neuropsychiatric medications are processed through multiple metabolic pathways, each of which may be influenced by genomic variation. Taking this into consideration, GeneSight measures multiple genomic variants for each patient and weighs them in combination — rather than one at a time — to provide comprehensive, genetically-driven recommendations for each medication. Integrated combinatorial analysis is superior to the analysis of any one gene in isolation or panel of individual genes.

INTENDED USE POPULATION

GeneSight is intended to support medication selection for patients with MDD who have experienced an inadequate response (lack of clinical improvement or intolerable side-effects) to at least 1 psychotropic treatment.

ANALYTICAL VALIDITY

GeneSight has robust analytical performance across all tested genes, demonstrating high rates of accuracy, precision, repeatability, and reproducibility across multiple platforms. Overall, the accuracy of genotype results produced by this combinatorial pharmacogenomic test was 99.8%. Further, the GeneSight laboratory confirms the initial and continued accuracy of its test through three processes: initial assay validation, semi-annual external and internal proficiency testing, and New York State Department of Health test approval.

CLINICAL VALIDITY

An important measure of clinical validity for pharmacogenomic testing is the ability to predict medication blood levels, which shows altered metabolism. Historically, individual genes and their specific impact on metabolic activity have been the focus. However, we now know that most medications are metabolized by multiple metabolic pathways. Shelton et al. (n=191) showed that analyzing multiple genes and their combined influence on metabolic activity, as is done on the GeneSight test, predicts citalopram blood levels in patients with MDD better than historical single-gene analysis. GeneSight factors in the combined impact of genetic variations in multiple genes, predicting medication blood levels more accurately than single-gene testing. As such, the combinatorial approach used by GeneSight identified more patients who could benefit from clinically actionable recommendations in contrast to single-gene testing.
In addition, GeneSight accurately predicted patient outcomes based on gene-drug interactions, as demonstrated by the strong association between the patients’ color-coded groupings and clinical outcomes. In a pooled analysis of treatment-as-usual (TAU) subjects in three clinical studies, those subjects who entered the studies on red-category medications showed 61.5% less improvement in depressive symptoms over 8-10 weeks compared with those prescribed yellow- or green-category medications. In contrast to GeneSight results, single-gene analyses predominantly failed to accurately predict patient outcomes.

CLINICAL UTILITY

Multiple peer-reviewed publications have evaluated the clinical utility of the GeneSight test. The studies evaluate key endpoints using the 17-item Hamilton Depression Rating Scale (HAM-D17) to objectively measure meaningful outcomes in MDD: symptom improvement (change in HAM-D17 score, based on group average), response (HAM-D17 score reduction ≥50%), and remission (HAM-D17 score ≤7).

"Genomics Used to Improve DEpression Decisions" (GUIDED) is the largest, patient- and rater-blinded randomized controlled trial of pharmacogenomics in mental health with 1,167 patients and 60 study sites, including many of the nation’s leading academic institutions. GUIDED provides level 1 evidence showing that compared to TAU at 8 weeks, patients with MDD who have failed at least 1 medication and who were in the GeneSight group had improvements in symptoms (p=0.107), response (p=0.013), and remission (p=0.007). Patient outcomes continued to progress in the GeneSight cohort through week 24, demonstrating the long-term durability of the results.

Greden et al. also reported on patients who entered GUIDED on medications with significant gene-drug interactions, or red-category medications. Symptoms (33.5% vs 21.1%, p=0.002), response (28.5% vs 16.7%, p=0.036), and remission (21.5% vs 8.5%, p=0.007) were significantly improved in patients who were switched from medications with significant gene-drug interactions (red category) to medications with moderate or no gene-drug interactions (yellow or green category) by week 8.

Forester et al. analyzed GUIDED data in a post hoc analysis specifically focusing on patients 65 years and older (n=206). This analysis showed that among older adults with depression, those in the GeneSight cohort had improved outcomes compared to TAU. At week 8, symptom improvement was not significantly different in the GeneSight cohort than in the TAU cohort (Δ = 8.1%, t=1.64, df=187; p=0.102); however, the GeneSight cohort showed significantly improved response (Δ = 13.6%, t=2.16, df=187; p = 0.032) and remission (Δ = 12.7%, t=2.49, df=189; p=0.014) rates compared to TAU. By week 8, more than twice as many patients in the GeneSight cohort than in TAU were on medications predicted to have no gene-drug interactions (χ² = 19.3, df=2; p<0.001).

A subsequent post hoc analysis by Thase et al. (n=787) assessed outcomes for patients who entered the GUIDED study on medications with any predicted gene-drug interactions (red and yellow categories) and compared the GeneSight cohort to the TAU group. This study measured clinical utility more directly than any previously published study, by identifying the individuals who carry genetic variants causing gene-drug interactions with a current medication. Symptoms (27.1% vs 22.1%, p=0.029), response (27.0% vs 19.0%, p=0.008), and remission (18.2% vs 10.7%, p=0.003) were significantly improved in the GeneSight cohort compared to TAU. The patients who had their medications switched from baseline to week 8 were also compared for the two study arms. Medication switches were defined as the clinician stopping at least 1 medication and adding at least 1 different medication. Those in the GeneSight arm experienced significantly improved symptoms (30% vs 22.3%, p=0.011), response (29.8% vs 19.4%, p=0.011), and remission (20.3% vs 11.1%, p=0.008) compared to the TAU arm.

Previous research has suggested that the 6-item Hamilton Depression Rating Scale (HAM-D6) is more sensitive than HAM-D17 at detecting differences between antidepressants and placebo. The HAM-D6 focuses on 6 core symptoms related to MDD and omits those like insomnia and weight loss that could be related to something other than MDD. Dunlop et al. conducted a post hoc analysis of GUIDED (n=1,298) demonstrating that the HAM-D6 had improved outcomes when comparing two active MDD treatment arms, as within the GUIDED trial. Analyses were performed for the full cohort and for a subset

*The Hamilton Depression Rating Scale (HAM-D) determines a patient’s level of depression before, during, and after treatment. Since its development in 1960, the scale has been widely used in clinical practice and has become a standard in pharmaceutical trials.
of patients who at baseline were taking medications with moderate or significant gene-drug interactions (yellow- and red-category medications). Symptoms (Δ=4.4%, p=0.023), response (Δ=7.0%, p=0.004), and remission (Δ=4.6%, p=0.031) were significantly improved in the full cohort when comparing the GeneSight arm to the TAU group using the HAM-D6 rating scale. Symptoms (Δ=7.3%, p=0.004), response (Δ=10.0%, p=0.001), and remission (Δ=7.9%, p=0.005) were also significantly improved in the subset of patients taking medications with gene-drug interactions when comparing the GeneSight and TAU arms at week 8 using HAM-D6. The study concluded that future biomarker-guided trials comparing active treatment arms may benefit from using the HAM-D6 scale.

“Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment” (IMPACT) is a naturalistic, one-arm study with 1,871 patients that compared outcomes in patients who were treated for moderate-to-severe depression using GeneSight by either primary care providers (PCPs) or psychiatrists. All analyses were adjusted for patient depression severity (i.e., BDI score*) and number of medications. Patients treated by PCPs had significantly greater improvement in symptoms (32% vs 25%, p<0.01), response (30% vs 22%, p<0.01), and remission (20% vs 12%, p<0.01) from baseline to visit 2 compared to patients treated by psychiatrists. This shows that use of GeneSight is as effective or even more effective when ordered by a PCP instead of a psychiatrist.

Three earlier two-armed prospective studies independently demonstrated improvement in patient outcomes. These prospective studies assessed changes in clinical scores between patients whose treatment was supported by GeneSight results versus TAU. Patients with GeneSight-informed care saw improved patient depression scores and higher physician confidence with treatment decisions. Recently, these three studies joined GUIDED in a meta-analysis by Brown et al. to evaluate whether a pharmacogenomic intervention can improve patient outcomes when compared to treatment as usual. With 1,556 patients, the GeneSight cohort had better results in every category over the control group: symptom improvement (Δ=10.08%, p=0.019), response (RR=1.40, p<0.001), and remission (RR=1.49, p=0.001). Many societies consider meta-analyses very important and often regard them as the strongest level of evidence upon which to guide practice decisions.

**HEALTHCARE UTILIZATION & ECONOMICS**

A key cost driver in mental illness is patients’ failure to respond to prescribed treatments. Due to the time it takes to determine whether a response has occurred and the significant side effects associated with many of these medications, patients often become increasingly resistant to further treatment attempts. In essence, the current trial-and-error prescribing approach lends itself to patient non-adherence and related poor outcomes, driving patients away from potentially effective treatments. Such an approach lacks timeliness and efficacy, and is costly.

Benitez et al. (2018) is a retrospective case-control analysis conducted with Optum Health that compared medical and pharmacy claims from members with psychiatric disorders (n=683) who received GeneSight-informed care versus controls receiving TAU. Payer amounts were calculated for each cohort over a 24-month episode-of-care period. The GeneSight cohort with depression (n=323) saved $2,203 in medical costs and $1,228 in pharmacy costs for total potential savings per patient annually of more than $3,400. Once the price of the test was included in the analysis, the savings per patient equaled $1,231 (p=0.960) with a per-member-per-month (PMPM) savings of $0.05.

Two earlier studies, one in partnership with Union Health Service and another with Medco Health Solutions (now Express Scripts), similarly showed that utilization of GeneSight led to significant pharmaceutical and other healthcare-related cost savings annually per patient tested. Patients who received the GeneSight test saved $1,000 on average in pharmacy spend compared to TAU. There was also an average annual increase in healthcare utilization costs of $5,188 for individuals taking medications with significant gene-drug interactions compared to those taking medications with no or moderate gene-drug interactions.

Tanner et al. analyzed pharmacy claims for a cohort of GeneSight tested patients (n=1,662) whose clinician recently augmented or switched their antidepressant or antipsychotic medication(s). Patients whose clinicians prescribed medications consistent with the test report, i.e., those with no or moderate gene-drug interactions (green- or yellow-category medications), saved $1,061 CAD per member per year (PMPY) on prescription medication costs compared to patients whose medications were incongruent with the test report (p<0.0001). The greatest cost savings were for patients who were 65 years or older, when their medications were congruent with the test report. This analysis used data from the Winner et al. Curr Med Res Opin 2015 study. The costs of prescription medications were translated from U.S. calculations into the Canadian healthcare system.

---

* The Beck Depression Inventory (BDI) score is a self-reported indicator of depression severity that monitors change over time.
MEDICARE COVERAGE

GeneSight received a favorable technical assessment by MolDX in October 2014, resulting in a positive coverage determination. Unlike testing for single genes, GeneSight’s combinatorial approach has demonstrated improved clinical and economic outcomes in numerous peer-reviewed publications. 

SUMMARY

Depression is a leading cause of disability and economic burden, and has traditionally lagged behind other areas of medicine in innovation. The current approach of trial-and-error to identify appropriate treatments is ineffective for patients and costly to the healthcare system.

GeneSight is a decision-support tool that may improve symptoms, response, and remission, while reducing healthcare costs by approximately $3,400 annually per patient tested, year over year ($1,231 when test cost included, p=0.960). GeneSight was developed in recognition that many genetic factors are involved in the ultimate efficacy of a given medication, and that the interactions among these factors are as important as the specific genes involved. In other words, assuming that a single gene or even a collection of single genes can accurately predict patient outcomes is where other approaches fall short. The combinatorial approach used by GeneSight recognizes that each medication’s metabolic pathway is unique and that genomic variants influence both metabolism and response. The GeneSight test is intended to supplement other information considered by a healthcare provider within the context of a

REFERENCES

17. GRADE working group, https://www.gradeworkinggroup.org/.