EXECUTIVE SUMMARY

GeneSight® is a proprietary pharmacogenomic test which improves patient outcomes by identifying neuropsychiatric medications likely to be ineffective or poorly tolerated by a patient. Unlike other tests, GeneSight uses a “combinatorial” pharmacogenomic approach, which analyzes and weights multiple genomic variants in combination to provide comprehensive, individualized medication recommendations for each patient. In three clinical studies and two health economic studies, when compared to standard of care, GeneSight Psychotropic has been shown to:

- Reduce depressive symptoms by more than 70%¹
- Double patients’ odds of response to treatment²
- Double patients’ odds of remission³
- Substantially reduce health care costs by more than $2500 per patient per year⁴,⁵

INTRODUCTION

One in six Americans develop Major Depressive Disorder (MDD) in their lifetime.⁶ 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 and overall treatment failure rates exceed 50%.⁷ 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 “start low, go slow” dosing approach used 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.⁸ 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 uses a proprietary algorithm to analyze 12 different genes to weigh their combined influence on patient response to more than 55 different psychotropic medications. This proprietary combinatorial approach used only by GeneSight has been demonstrated to drive improved patient outcomes in multiple clinical studies. GeneSight guides clinician prescribing 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. This categorization enables physicians to select genetically appropriate medications for each patient, increasing the likelihood of response and reducing the risk of adverse events.

Most neuropsychiatric medications are processed through multiple metabolic pathways, and genomic variants influence both metabolism and response. Unlike other tests, GeneSight uses a combinatorial pharmacogenomic approach, which measures multiple genomic variants for each patient and weights them in combination — rather than one at a time — to provide comprehensive, genetically-driven recommendations for each medication. Integrated combinatorial analysis is significantly superior to the analysis of any one gene in isolation or panel of individual genes.⁹,¹⁰
INTENDED USE POPULATION

GeneSight Psychotropic is intended to support treatment selection for patients who are candidates for antidepressant, antipsychotic, anxiolytic, hypnotic, and/or mood stabilizing medications according to standard treatment guidelines.

ANALYTICAL VALIDITY

GeneSight Psychotropic possesses robust analytical validity across all tested genes, specifically demonstrating high rates of accuracy, precision, repeatability, and reproducibility across multiple platforms. The genes included in the GeneSight assay were compared against the gold standard of DNA sequencing for each applicable gene, providing an overall concordance rate of 99.99%. Further, the GeneSight laboratory confirms the initial and continued accuracy of its tests through three processes: initial assay validation, semi-annual external and internal proficiency testing, and New York State Department of Health test approval.

CLINICAL VALIDITY

The GeneSight test accurately stratifies patients by their likelihood of responding to a specific medication, and shows a strong association between the patients’ color-coded categories and clinical outcomes. In a pooled analysis of fully blinded, treatment-as-usual 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. Conversely, single gene analyses predominantly failed to accurately predict patient outcomes.

CLINICAL UTILITY

Multiple peer-reviewed publications demonstrate the clinical utility of the GeneSight Psychotropic assay and of combinatorial pharmacogenomics-guided therapy. Three two-armed prospective studies each independently demonstrated positive improvement in patient response. These prospective studies assessed changes between clinical scores in patients whose treatment was guided by GeneSight results versus Treatment as Usual (TAU). Patients with treatments guided by the GeneSight test saw improved patient depression scores, higher physician confidence with treatment decisions, better healthcare resource utilization, and a reduction in disability claims, absenteeism, and medication costs.

Improved patient response was clearly illustrated by the Number Needed to Treat (NNT). NNT measures the impact of an intervention by estimating the number of patients who need to be treated in order to have an impact on one person. The NNT to show an antidepressant response for subjects guided by GeneSight Psychotropic above that for TAU subjects was 6.07 based on the unweighted, pooled NNT estimate across all three studies. This was an improvement from the NNT (8.7) of selective serotonin reuptake inhibitor (SSRI) antidepressants. This reduction in NNT demonstrates that matching the right medication to the right patient improves medication efficacy by 43% over treatment as usual.

These studies validate the hypothesis that the clinical use of GeneSight Psychotropic significantly improves patient outcomes. Indeed, using GeneSight Psychotropic to guide depression treatment demonstrated a 71% improvement in patient response, including more than doubling the odds of remission in a randomized control trial.
### Study Name | Study Type | Key Findings
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**Pine Rest**<sup>3</sup> | Prospective, patient and rater-blinded, randomized control trial (RCT) | Response rates in the GeneSight Psychotropic-guided arm were 73% higher compared to the unguided treatment as usual (TAU) arm (36.0% versus 20.8%, respectively). Remission rates more than doubled in the GeneSight-guided arm compared to the TAU arm (20.0% versus 8.3%, respectively).

**Hamm**<sup>2</sup> | Prospective 2-armed cohort | GeneSight Psychotropic subjects achieved greater reduction in depression symptoms between baseline and week 8 visits compared to TAU subjects (p = 0.0024). Absolute response and remission rates more than doubled in GeneSight Psychotropic arm compared to TAU arm.

**La Crosse**<sup>1</sup> | Prospective 2-armed cohort | Greater reduction in depression scores from baseline to the week 8 visit was observed in the GeneSight Psychotropic arm for all measures of depression vs TAU: QIDS-C16 (p < 0.0001), HAM-D17 (p < 0.0001), and PHQ-9 (p < 0.0001). For all measures, faster reduction of symptoms was observed in GeneSight Psychotropic subjects compared to TAU subjects (QIDS-C16 and HAM-D17 [p < 0.0001], PHQ-9 [p = 0.002]). Physicians changed medications more frequently in the GeneSight Psychotropic group (57.9%) than in the TAU group (25.9%) (p = 0.0007).

**Pooled**<sup>11</sup> | Meta-analysis | Overall improvement in patient response rates across the meta-analysis of 258 patients was 71% using a relative benefit ratio metric. Results from each study were highly consistent in independent populations and results were statistically significant. For the combined analysis, the two-arm benefit ratio for response was both clinically impactful in size and highly significant (p = 0.005).

### HEALTHCARE UTILIZATION & ECONOMICS

Multiple studies have demonstrated that a key cost driver in mental illness is the failure for patients to respond to prescribed treatments. Unfortunately, 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, efficacy, and is unnecessarily costly. Two studies, one in partnership with Union Health Service and another with Medco Health Solutions (now Express Scripts), demonstrate utilization of GeneSight Psychotropic leads to significant cost-savings of $1,000 in drug spend and more than $1,500 in other healthcare-related costs annually per patient tested, totaling $2,500 in annual savings year over year.

### Study Name | Study Type | Key Findings
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**Union Health Service**<sup>4</sup> | Retrospective | Subjects whose regimen included a medication in the red category of the GeneSight Psychotropic report had 69% more total healthcare visits (p = 0.005), 67% more general medical visits (p = 0.02), greater than 3-fold more medical absence days (p = 0.06), and greater than 4-fold more disability claims (p = 0.004) compared to subjects taking medications in the green or yellow category. Mean healthcare related costs calculated for red category subjects during the previous 12-month period were higher at $8,627, compared to $3,453 for green category subjects (p = 0.0024) and $3,426 for yellow category subjects (p = 0.027), yielding an average annual increase in healthcare cost of $5,188 for subjects on GeneSight Psychotropic red category medications. Since 30% of patients are taking “red bin medications” the healthcare saving of testing all subjects to help these patients is $1,556 annually.<sup>2</sup>

**Medco (now Express Scripts)**<sup>5</sup> | Prospective, comparative cohort study | Patients who received GeneSight Psychotropic saved $1,035.60 in total medication costs over one year compared to the non-tested standard of care cohort. 79% of clinicians made decisions congruent with report recommendations (e.g., switching from a red category medication to a green category medication). Among GeneSight Psychotropic tested patients whose clinicians made decisions congruent with report recommendations, overall post-test medication costs per tested member per year (PMPY) were $2,774.53 lower than PMPY costs for incongruent decisions ($7,289.96 vs. $10,064.49; p < 0.0001). The GeneSight Psychotropic tested group showed improvement in adherence (17% greater) compared to TAU group (1% decrease) (p < 0.0001). Discontinuation rates decreased by 7.3% in GeneSight Psychotropic group compared to a 0.3% increase among TAU patients (p < 0.0001). Approximately one in five patients in the GeneSight Psychotropic group were on one less medication by the last 90 days of the post-test period compared to the TAU group (p < 0.0001).
MEDICARE COVERAGE

GeneSight Psychotropic received a favorable technical assessment by MolDX in October 2014, resulting in a positive Coverage Determination. GeneSight is the only combinatorial assay that has been approved by Medicare and, unlike testing for single genes, has demonstrated improved clinical and economic outcomes in numerous peer-reviewed publications.

CLINICAL GUIDANCE

Magellan HealthSM, a leading managed care plan and service provider in behavioral health and employee assistance programs covering over 60M risk-based and ASO members, has evaluated the GeneSight published clinical data and considers GeneSight Psychotropic as “evidence informed.” Magellan considers all other interventions in psychiatric pharmacogenomics as “investigational.”

SUMMARY

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

GeneSight Psychotropic is a clinically-proven tool that improves treatment response rates by 71% and reduces healthcare costs by more than $2500 annually per patient tested, year over year. 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 likewise nearly as important as the genes involved themselves. 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 is the only successful route, as it recognizes that each medication’s metabolic pathway is wholly unique with multiple factors affecting the ultimate effectiveness or lack of effectiveness of the particular medication chosen.

Compared to the usual treatment approach, GeneSight Psychotropic:

- Improves treatment response rates by 71%
- Doubles patients’ odds of response to treatment
- Doubles the likelihood of remission
- Improves medication adherence by 17%
- Reduces medication discontinuation rates by 7.3%
- Reduces polypharmacy by 1 medication for every 5 patients tested
- Saves more than $2,500 in drug spend and healthcare-related costs annually per patient tested, year over year
- Used by more than 20,000 healthcare providers to treat over 500,000 patients

In summary, GeneSight provides objective, evidence-based measures for selecting appropriate medications, thereby improving patient outcomes while reducing medical utilization and disability claims.

REFERENCES