INTRODUCTION

One in six Americans develop Major Depressive Disorder (MDD) in their lifetime.¹ 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%.² 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.³ 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 genes involved in pharmacokinetics and pharmacodynamics to weigh their combined influence on patient response to psychotropic medications. This combinatorial approach used only by GeneSight has been demonstrated to drive improved patient outcomes in multiple clinical studies. GeneSight guides 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. 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. Taking this into consideration, GeneSight 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 superior to the analysis of any one gene in isolation or panel of individual genes.⁴,⁵

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 (antidepressant, antipsychotic, anxiolytic, hypnotic, and/or mood stabilizing medications).

ANALYTICAL VALIDITY

GeneSight has robust analytical performance across all tested genes, demonstrating high rates of accuracy, precision, repeatability, and reproducibility across multiple platforms.⁶ 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 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

GeneSight accurately categorizes patients by their likelihood of responding to a specific medication due to gene-drug compatibility, 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.⁵ In contrast to GeneSight results, single-gene analyses predominantly failed to accurately predict patient outcomes.⁴,⁵

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CLINICAL UTILITY

Multiple peer-reviewed publications (Table 1) demonstrate the clinical utility of GeneSight-guided therapy. The studies evaluate key endpoints using the HAM-D17* scale to objectively measure meaningful outcomes in MDD: remission (HAM-D17 score ≤7), response (HAM-D17 reduction ≥50%), and symptom improvement (reduction in HAM-D17).

“Genomics Used to Improve DEpression Decisions” (GUIDED) is the largest, double 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 GeneSight-guided care improves outcomes in patients with MDD who have failed at least 1 medication compared to TAU. The study concluded that patients with combinatorial pharmacogenomics-guided therapy were:

- 50% more likely to achieve remission (p=0.007),
- 30% more likely to achieve treatment response (p=0.013), and
- 11% more likely to achieve symptom improvement (p=0.107) than TAU at 8 weeks.

Remission, response, and symptom improvement continued to progress in the GeneSight-guided arm through week 24, demonstrating the long-term durability of the results.

“Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment” (IMPACT) is a naturalistic, one-arm study with 1,871 patients that compared outcomes in patients with moderate-to-severe depression who were treated by primary care providers (PCPs) to patients who were treated by psychiatrists. Patients treated by PCPs had significantly greater improvement in response (p<0.01, 95% CI 1.2-1.8), remission (p<0.01, 95% CI 1.4-2.3), and symptoms (32% vs 24%, P<0.0005) from baseline to visit 2 compared to patients treated by psychiatrists. All analyses were adjusted for patient depression severity (i.e., BDI score*) and number of medications.

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 guided by GeneSight results versus TAU. Patients with GeneSight-guided care saw improved patient depression scores and higher physician confidence with treatment decisions. These studies are consistent with the findings reported in GUIDED and IMPACT, showing that the clinical use of GeneSight significantly improves patient outcomes.

HEALTHCARE UTILIZATION & ECONOMICS

A key cost driver in mental illness is patients’ failure 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 costly.

Benitez J et al (2018) is a retrospective case-control analysis (Table 2) conducted by an outside consulting group in conjunction with Optum Health that compared medical and pharmacy claims from members with psychiatric disorders (n=683) who received GeneSight-guided care versus physician-matched controls receiving TAU, and calculated payer amounts for each cohort over a 24-month episode-of-care period. The GeneSight-guided cohort with MDD (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 tested equaled $1,231 with a per-member-per-month savings of $0.05.

Two earlier studies (Table 2), one in partnership with Union Health Service and another with Medco Health Solutions (now Express Scripts), produced similar findings showing that the utilization of GeneSight led to significant cost-savings of $1,000 in pharmacy spend and more than $1,500 in other healthcare-related costs annually per patient tested.

MEDICARE COVERAGE

GeneSight received a favorable technical assessment by MolDX in October 2014, resulting in a positive coverage determination. GeneSight is the only combinatorial pharmacogenomic 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.

* The Hamilton Depression Rating Scale (HAM-D) determines a patient’s level of depression before, during, and after treatment. It is administered by a clinician. Since its development in 1960, the scale has been widely used in clinical practice and become a standard in pharmaceutical trials.

The Beck Depression Inventory (BDI) score is a self-reported and widely used indicator of depression severity that monitors change over time.
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 clinically-proven tool that **improves remission by 50% and treatment response rates by 30%**, while reducing healthcare costs by more than $3,400 annually per patient tested, year over year ($1,231 when test cost included). 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 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 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.

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

### Table 1: Clinical Utility Key Findings

| Study Name | Study Type | GeneSight-guided arm performed better in all three endpoints (remission, response, and symptom improvement) with 50% improvement in remission rates, 30% improvement in response rates, and a greater reduction in symptoms relative to the TAU arm. This is the first time a technology has demonstrated improvement in outcomes relative to an active drug arm for depression. A subanalysis was performed of patients in both study arms taking ≥1 red-category (incongruent) medication(s) prior to any changes at baseline. Patients who switched to green- or yellow-category (congruent) medications were compared to patients who remained on or added additional incongruent medication(s) at week 8, showing that patients on congruent medications experienced greater remission (p=0.0067), response (p=0.0364), and symptom improvement (p=0.0018).
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| Study Name | Study Type | Patients treated by primary care physicians compared to psychiatrists exhibited 19.5% vs 12.0% (p=0.0005) greater remission, 30.1% vs 22.3% (p<0.0005) higher response rates, and 31.7% vs 24.9% (p<0.0005) improvement in symptoms. GeneSight testing aided in medication selection for patients with moderate-to-severe MDD, resulting in a significant reduction in depressive symptoms after 8–12 weeks.

- Symptom reduction (27.9%) was consistent with GUIDED, wherein there was a 27.2% improvement in symptoms.
- Although study did not include a control arm, rates of response and remission were also similar to the intervention arm of GUIDED.

| Study Name | Study Type | Pilot study for the larger GUIDED study. In GeneSight-guided arm vs TAU arm: remission rates more than doubled (20.0% vs 8.3%; OR=2.75; 95% CI:0.48-15.80), response rates were 73% higher (36.0% vs 20.8%; OR=2.14; 95% CI:0.59-7.69), and mean percent improvement in depressive symptoms was higher (30.8% vs 20.7%; p=0.28). TAU subjects taking red-category medications at baseline had almost no improvement (0.8%) in depressive symptoms at week 10 vs the 33.1% improvement (p<0.0005) in GeneSight-guided subjects who started on a red-category medication and the 26.4% improvement in GeneSight-guided subjects overall (p=0.08).

| Study Name | Study Type | Greater reduction in depression scores from baseline to week 8 visit observed in GeneSight arm vs TAU: QIDS-C16 (p<0.0001), HAM-D17 (p=0.0001), and PHQ-9 (p<0.0001).

In GeneSight-guided arm vs TAU arm at 8 weeks: QIDS-C16 remission rates were higher (p=0.03) and response rates were higher (HAM-D-17, p<0.05; QIDS-C16, p<0.05; PHQ-9, p<0.05).

Participants in TAU group who at baseline were prescribed red-category medications experienced the least improvement compared with other unguided TAU participants (HAMD-17, p<0.05).

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| Study Name | Study Type | GeneSight subjects achieved greater reduction in depressive symptoms between baseline and week 8 visit compared to TAU subjects (p=0.0024).

| Study Name | Study Type | Providing clinicians with the GeneSight interpretive report improved the proportion of antidepressant responders by 71% as compared with unguided patients.

Results from each study were highly consistent in independent populations and results were statistically significant.
### Table 2: Healthcare Utilization & Economics Key Findings

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Type</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Benitez J, Per Med 2019 (n=683)</td>
<td>Retrospective case-control analysis</td>
<td>Evaluated 683 patients who had failed at least 1 prior medication for depression, of which 205 had GeneSight and 478 received TAU. Calculated spending over 12-month period after GeneSight testing to compare costs, as well as spending associated with pharmacy (CNS and other) and visits (inpatient, outpatient, and professional). For patients with MDD, individuals who received GeneSight had total costs of $18,741 compared to $24,791 in TAU arm representing total cost savings of $6,050. This result was highly statistically significant after controlling for pre-test differences (p&lt;0.00005). Savings in the GeneSight cohort were attributed to outpatient, inpatient, and pharmacy cost categories ($3,265, $3,032; and $792 less than those incurred by the TAU cohort). Pre-to-post-comparison yielded savings of $1,231 for the GeneSight cohort versus TAU, including the test cost (p=0.960). Using GeneSight in the depression subpopulation yielded a $0.05 PMPM savings over the episode-of-care ($0.15 excluding the GeneSight test cost).</td>
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</table>

| Winner JG, Trans Psychiatry 2013 (n=96) | Retrospective | Subjects whose regimen included a medication in the red category of the GeneSight report had 69% more total healthcare visits (p=0.005), 87% 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 green or yellow category. Mean healthcare-related costs calculated for red-category subjects during the previous 12-month period were higher at $3,827, compared to $3,435 for green-category subjects (p=0.024) and $3,426 for yellow-category subjects (p=0.027), yielding an average annual increase in healthcare costs of $5,188 for subjects on GeneSight red-category medications. Since 30% of patients are taking red-category medications, the healthcare saving of testing all subjects to help these patients is $1,956 annually. |

| Winner JG, Curr Med Res Opin 2015 (n=2,168; n=10,880 for TAU group; 5-to-1 match) | Prospective, comparative cohort study | Patients who received GeneSight-guided care saved $1,035.60 in total medication costs over 1 year compared to 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-guided 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). GeneSight-guided group showed improvement in adherence (17% greater) compared to TAU group (1% decrease) (p<0.0001). Discontinuation rates decreased by 7.3% in GeneSight group compared to 0.3% increase among TAU patients (p<0.0001). Approximately one in five patients in GeneSight group were on 1 less medication by the last 90 days of the post-test period compared to TAU group (p<0.0001). |

### REFERENCES

19. Local Coverage Determination (LCD): MolDX: GeneSight
20. Local Coverage Determination (LCD): MolDX: GeneSight
22. Local Coverage Determination (LCD): MolDX: GeneSight
23. Local Coverage Determination (LCD): MolDX: GeneSight
24. Local Coverage Determination (LCD): MolDX: GeneSight