Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

### RELATED PROTOCOLS

- Cranial Electrotherapy Stimulation and Auricular Electrostimulation
- Cytochrome P450 Genotype-Guided Treatment Strategy
- Deep Brain Stimulation
- Vagus Nerve Stimulation

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals:  
  - Who are evaluated for diagnosis or risk of a mental illness | Interventions of interest are:  
  - Genetic testing for risk of a mental illness | Comparators of interest are:  
  - Standard care | Relevant outcomes include:  
  - Change in disease status  
  - Morbid events  
  - Functional outcomes  
  - Health status measures  
  - Quality of life  
  - Treatment-related morbidity |
| Individuals:  
  - Adult patients with major depressive disorder | Interventions of interest are:  
  - GeneSight® testing guided drug treatment  
  - NeuroIDgenetix® testing guided drug treatment  
  - Neuropharmagen® testing guided drug treatment | Comparators of interest are:  
  - Standard of care drug treatment | Relevant outcomes include:  
  - Symptoms  
  - Change in disease status  
  - Morbid events  
  - Functional outcomes  
  - Health status measures  
  - Quality of life  
  - Treatment-related morbidity |
| Individuals:  
  - With a mental health condition other than depression who are undergoing drug treatment | Interventions of interest are:  
  - Genetic testing for genes associated with medication pharmaco-kinetics and pharmaco-dynamics | Comparators of interest are:  
  - Standard of care drug treatment | Relevant outcomes include:  
  - Symptoms  
  - Change in disease status  
  - Morbid events  
  - Functional outcomes  
  - Health status measures  
  - Quality of life  
  - Treatment-related morbidity |
DESCRIPTION

Individual genes have been shown to be associated with the risk of psychiatric disorders and specific aspects of psychiatric drug treatment such as drug metabolism, treatment response, and risk of adverse events. Commercially available testing panels include several of these genes and are intended to aid in the diagnosis and management of mental health disorders.

SUMMARY OF EVIDENCE

For individuals who are evaluated for diagnosis or risk of a mental illness who receive genetic testing for risk of that disorder, the evidence includes various observational studies (cohort, case-control, genome-wide association study). Relevant outcomes are changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Most studies evaluated the association between genotype and mental health disorders or gene-drug interactions among patients with risk for mental health conditions. No studies were identified that evaluated whether testing for variants changed clinical management or affected health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult patients with major depressive disorder who receive GeneSight testing guided drug treatment, the evidence includes two randomized controlled trials (RCT). Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The two RCTs compared response (≥50% decrease in HAM-D17) and remission (HAM-D17 ≤7) with antidepressant therapy informed by GeneSight test results to standard of care (SOC)—antidepressant therapy selected without GeneSight test results. The Genomics Used to Improve DEpression Decisions (GUIDED) trial by Greden et al (2019) reported statistically significant improvement in response (26% of 560 vs. 20% of 607, p=.01) and remission (15% of 560 vs. 10% of 607, p=.007) in the GeneSight arm compared to SOC at eight weeks among patients with MDD using per protocol analysis. Per protocol cohort excluded 401 (22%) of 1799 randomized patients, and additional 231 patients from the per protocol cohort did not complete the study through the blinded week eight endpoint. The extent of missing data following randomization (35%) precludes conclusions on outcomes at eight weeks. In the small, single-center pilot study by Winner et al (2013), depression outcomes did not differ significantly between guided care and SOC groups at the 10-week follow-up and the study was underpowered to detect significant differences in outcomes between study arms. None of these trials provided adequate evidence. Both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult patients with major depressive disorder who receive NeuroIDgenetix testing guided drug treatment, the evidence includes two RCTs. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Bradley et al (2018) conducted a double-blind RCT among patients with MDD and reported statistically significant improvement in response (≥50% decrease in HAM-D17) in the NeuroIDgenetix arm (64% of 140) compared to SOC (46% of 121) at 12 weeks among a moderate and severe group of patients (p=.01) and significant improvement in remission (HAM-D17 ≤7) in the NeuroIDgenetix arm (35% of 40) compared to SOC (13% of 53) at 12 weeks among a severe group of patients only (p=.02). There was evidence suggesting selective reporting, as remission was reported for only those with severe depression and, contrary to the listing in clinicaltrials.gov, adverse drug events were not reported as the primary outcome. It was unclear if the analysis was based on intention-to-treat population and there was high loss to follow-up (15%). In the RCT conducted by Olson et al (2017), among patients with neuropsychiatric disorders those receiving SOC reported significantly more adverse events (53%) than those receiving NeuroIDgenetix guided care (28%), however, the study did not report the number of patients included in this analysis. The study did not describe the randomization procedure, and in clinicalTrials.gov neu-
rocognitive measures were listed as co-primary outcomes, which were not reported, suggesting possible selective reporting. None of these trials provided adequate evidence. The Olson et al (2017) study had major relevance limitations and both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult patients with major depressive disorder who receive Neuropharmagen testing guided drug treatment, the evidence includes two RCTs. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The two RCTs compared response (≥50% decrease in HAM-D17) and remission (HAM-D17 ≤7) with antidepressant therapy informed by Neuropharmagen test results to SOC—antidepressant therapy selected without Neuropharmagen test results. The single-blinded RCT by Han et al (2018) reported statistically significant improvement in response (72% of 52 vs. 44% of 48, p=.01) but no statistically significant improvement in remission (46% of 52 vs. 26% of 48, p=.07) in the Neuropharmagen arm compared to SOC at eight weeks among patients with MDD. The study reported early dropout of 25% in guided-care and 38% in the standard care arm and used last observation carried forward (LOCF) approach in intention to treat analysis of effectiveness. Use of LOCF assumes data are missing completely at random, which is unlikely to hold in this analysis. Also, the study did not report registration in any clinical trial database. The single-blinded RCT by Perez et al (2017) reported statistically not significant improvement in response (45% of 141 vs. 40% of 139, p=.39) and remission (34% of 141 vs. 33% of 139, p=.87) in the Neuropharmagen arm compared to SOC at 12 weeks among patients with major depressive disorder. Response and remission data were missing for 9% of patients in the guided care group and 14% of the standard care group. None of these trials provided adequate evidence. Both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a mental illness other than depression who are undergoing drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a systematic review and meta-analysis and RCTs evaluating associations between specific genes and outcomes of drug treatment. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review and meta-analysis by Hartwell et al (2020) included seven RCTs and reported no significant moderating effect of rs1799971, a single nucleotide polymorphism (SNP) that encodes a non-synonymous substitution (Asn40Asp) in the mu-opioid receptor gene, OPRM1 on response to naltrexone treatment of alcohol use disorder. Bradley et al (2018) conducted a double-blind RCT among patients with anxiety disorders and reported statistically significant improvement in response (≥50% decrease in HAM-A) in the NeuroIDgenetix arm (63% of 82) compared to SOC (50% of 95) at 12 weeks among a moderate and severe group of patients (p=.04). There was evidence suggesting selective reporting, as anxiety remission was not reported and, contrary to the listing in clinicaltrials.gov, adverse drug events were not reported as the primary outcome. It was unclear if the analysis was based on intention-to-treat population and among the randomized moderate and severe anxiety patients with only anxiety, 25% in the experimental arm and 17% in the standard care arm were lost to follow up over the 12 week period. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**POLICY**

Genetic testing for diagnosis and management of mental health disorders is considered **investigational** in all situations, including but not limited to the following:

- To confirm a diagnosis of a mental health disorder in an individual with symptoms.
• To predict future risk of a mental health disorder in an asymptomatic individual.
• To inform the selection or dose of medications used to treat mental health disorders, including but not limited to the following medications:
  o selective serotonin reuptake inhibitors
  o selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
  o tricyclic antidepressants
  o antipsychotic drugs.

Genetic testing panels for mental health disorders, including but not limited to the Genecept Assay, STA2R test, the GeneSight Psychotropic panel, the Proove Opioid Risk assay and the Mental Health DNA Insight panel, are considered investigational for all indications.

POLICY GUIDELINES

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical protocol updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including
the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

MEDICARE ADVANTAGE
For Medicare Advantage, GeneSight® Psychotropic panel (Assurex Health) and NeuroIDgenetix multigene panel to treat Major Depressive Disorder may be considered medically necessary.

BACKGROUND
This protocol assesses whether genetic testing for the diagnosis and management of mental health conditions is clinically useful. To make a clinical management decision that improves the net health outcome; the balance of benefits and harms must be better when the test is used to manage the condition than when another test or no test is used. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes compared to managing the condition with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug.

Therefore, assessment of clinical utility of a pharmacogenetic test cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the use of the pharmacogenomic test to make management decisions alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype. Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with or without the test. Because these are intervention studies, the preferred evidence is from randomized controlled trials.

REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The tests discussed in this section are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Examples of commercially available panels include the following:

- Genecept™ Assay (Genomind);
- STA²R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical Reference Laboratory). Specific variants included in the panel were not easily identified from the manufacturer’s website.
- GeneSight® Psychotropic panel (Assurex Health);
• Mental Health DNA Insight™ panel (Pathway Genomics);
• IDgenetix-branded tests (AltheaDx).

Also, many labs offer genetic testing for individual genes, including MTFHR (GeneSight Rx and other laboratories), CYP450 variants, and SULT4A1.

AltheaDx offers a number of IDgenetix-branded tests, which include several panels focusing on variants that affect medication pharmacokinetics for a variety of disorders, including psychiatric disorders.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


