DRAFT Medical Coverage Policy | Genetic Testing for Diagnosis and Management of Mental Health Conditions

EFFECTIVE DATE: 03/01/2023
POLICY LAST UPDATED: 11/16/2022

OVERVIEW

Individual genes have been shown to be associated with 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.

The following tests are addressed in this policy:

- Genecept Assay (Genomind)
- GeneSight Psychotropic panel (Myriad Neuroscience)
- Mental Health DNA Insight panel (Pathway Genomics)
- NeuroIDgenetix (AltheaDx)
- Neuropharmagen (AB-Biotics)
- Proove Opioid Risk Assay (Proove Biosciences)
- Psychotropic Pharmacogenomics Gene Panel (Mayo Clinic)
- STA²R - SureGene Test for Antipsychotic and Antidepressant Response (SureGene)

MEDICAL CRITERIA

Medicare Advantage Plans
GeneSight® Psychotropic Panel - CPT code 0345U (Code Effective 10/01/2022. For Dates of Service prior to 10/1/2022, CPT Code 81479 must be used)
NeuroIDgenetix - CPT code 81479

The GeneSight® Psychotropic Panel and NeuroIDgenetix services may be considered medically necessary when ALL six (6) of the following criteria are met:

1. Individual has at least ONE of the following conditions:
   A. Major Depressive Disorder (MDD); or,
   B. Schizophrenia; or,
   C. Schizophreniform disorder; or,
   D. Bipolar disorder; or,
   E. Social phobia, generalized; or,
   F. Panic disorder [episodic paroxysmal anxiety]; or,
   G. Anxiety disorders; or,
   H. Post-traumatic stress disorder; or,
   I. Obsessive-compulsive personality disorder; or,
   J. Attention-deficit hyperactivity disorder; and,
2. Medication therapy is being considered or is already being administered; and,
3. Non-genetic factors are used to make preliminary drug selection; and,
4. Documentation that the test is required to define safe use of drug in the individual; and,
5. Must meet criteria A or B, below:
   A. Initial Testing: Must meet ALL FIVE of the following criteria:

1) When medication therapy is being considered (has not already been administered), documentation must include that testing is required to define safe use of drug in the individual; and,
2) Medication is medically necessary, appropriate and approved for use with specific patient diagnosis; and,
3) Medication is known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable; and,
4) Selection of medication must be derived from clinical factors/necessity rather than from testing; and,
5) Test results are necessary for safe administration or dosing of medication; and,

B. Additional Testing: Documented medical necessity for additional testing; and,

6. Must meet criteria A or B, below:
   A. More than one gene is reasonable and necessary for the safe use of the drug being considered or in use; or,
   B. More than one drug is in consideration or use that is associated with a gene-drug interaction

Psychotropic Pharmacogenomics Gene Panel – CPT Code 81479

The Psychotropic Pharmacogenomics Gene Panel may be considered medically necessary when ALL six (6) of the following criteria are met:

1. Individual has at least ONE of the following conditions:
   A. Schizophrenia; or,
   B. Schizophreniform disorder; or,
   C. Bipolar disorder; or.
   D. Social phobia, generalized; or,
   E. Panic disorder [episodic paroxysmal anxiety]; or,
   F. Anxiety disorders; or,
   G. Post-traumatic stress disorder; or,
   H. Obsessive-compulsive personality disorder; or,
   I. Attention-deficit hyperactivity disorder; and,
2. Medication therapy is being considered or is already being administered; and,
3. Non-genetic factors are used to make preliminary drug selection; and,
4. Documentation that the test is required to define safe use of drug in the individual; and,
5. Must meet criteria A or B, below:
   A. Initial Testing: Must meet ALL FIVE of the following criteria:
      1) When medication therapy is being considered (has not already been administered), documentation must include that testing is required to define safe use of drug in the individual; and,
      2) Medication is medically necessary, appropriate and approved for use with specific patient diagnosis; and,
      3) Medication is known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable; and,
      4) Selection of medication must be derived from clinical factors/necessity rather than from testing; and,
      5) Test results are necessary for safe administration or dosing of medication; and,
   B. Additional Testing: Documented medical necessity for additional testing; and,
6. Must meet criteria A or B, below:
   A. More than one gene is reasonable and necessary for the safe use of the drug being considered or in use; or,
   B. More than one drug is in consideration or use that is associated with a gene-drug interaction

Commercial Products
Not applicable

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products
Aside from the GeneSight® Psychotropic Panel (CPT code 0345U), there is no specific CPT code for the services in this policy and an Unlisted CPT code should be used (See Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Prior authorization is required for Medicare Advantage Plans and is obtained via the online tool for participating providers. See the Related Policies section.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans
GeneSight® Psychotropic panel, NeuroIDgenetix, and Psychotropic Pharmacogenomics gene panel will be considered medically necessary when the medical criteria listed above are met.

The following tests are not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- Genecept Assay (Genomind)
- Mental Health DNA Insight Panel (Pathway Genomics)
- Neuropharmagen (AB-Biotics)
- Proove Opioid Risk Assay (Proove Biosciences)
- STA²R - SureGene Test for Antipsychotic and Antidepressant Response (SureGene)

Commercial Products
The following tests are not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- Genecept Assay (Genomind)
- GeneSight Psychotropic panel (Assurex Health)
- NeuroIDgenetix (AltheaDx)
- Mental Health DNA Insight Panel (Pathway Genomics)
- Neuropharmagen (AB-Biotics)
- Proove Opioid Risk Assay (Proove Biosciences)
- STA²R - SureGene Test for Antipsychotic and Antidepressant Response (SureGene)

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for laboratory tests or not medically necessary/not covered benefits/coverage.

BACKGROUND

This policy 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.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The tests discussed in this section are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA 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)
- GeneSight® Psychotropic panel (Assurex Health)
- IDgenetix-branded tests (AltheaDx)
- Mental Health DNA Insight™ panel (Pathway Genomics)
- Neuropharmagen (AB-Biotics)
- Proove Opioid Risk Assay (Proove Biosciences)
- Psychotropic Pharmacogenomics gene panel (Mayo Clinic)
- STA2R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical Reference Laboratory)

Commercial Plans

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 (MDD) who receive GeneSight testing guided drug treatment, the evidence includes 3 randomized controlled trials (RCTs). Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The RCTs compared response (≥50% decrease in Hamilton Depression Rating Scale 17 item (HAM-D17)) and remission (HAM-D17 ≤7), and symptom improvement (Mean % change in HAM-D17) with antidepressant therapy informed by GeneSight test results to antidepressant therapy selected without GeneSight test results (standard of Care (SOC)). The Genomics Used to Improve Depression Decisions (GUIDED) trial 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 8 weeks among patients with MDD. However, depending on the population (intention to treat [ITT] or per protocol), up to one third of GUIDED randomized participants were missing from the reported results; the extent of missing data following randomization precludes conclusions on outcomes at 8 weeks. The Genomic Applications Partnership Program - Major Depressive Disorder (GAPP-MDD) trial, also comparing GeneSight guided treatment with SOC, found no statistically significant differences between groups in response, remission, or symptom improvement at 8 weeks follow-up, although like the GUIDED trial a high proportion (up to 69%) of randomized participants were excluded from outcome analysis and the study was not adequately powered to detect between-group differences. In the third trial, a small, single-center pilot study by Winner et al (2013), depression outcomes did not differ significantly between GeneSight-guided care and SOC groups at the 10-week follow-up, though the study was underpowered to detect significant differences in outcomes between study arms. All of these trials have major limitations in design and conduct and in consistency and precision, thus none provided adequate evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult patients with MDD who receive NeuroIDgenetix testing guided drug treatment, the evidence includes 2 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 (p=.02). There was evidence of reporting bias, and it was unclear if the analysis was based on intention-to-treat (ITT) 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, on ~~in~~ clinicalTrials.gov, neurocognitive measures were listed as co-primary outcomes. Since these outcomes were not reported, selective reporting is also possible. 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 MDD who receive Neuropharmagen testing guided drug treatment, the evidence includes 2 RCTs. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The 2 RCTs compared response (≥50% decrease in HAM-D17) and remission (HAM-D17 ≤7) with antidepressant therapy informed by Neuropharmagen test results to antidepressant therapy selected without Neuropharmagen test results (i.e. SOC). 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 8 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 the ITT 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 non-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 MDD. Response and remission data were missing for 9% of patients in the guided care group and 14% in the SOC 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 7 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 of reporting bias, and, it was unclear if the analysis was based on the ITT population. Furthermore, among the randomized moderate and severe anxiety patients with only anxiety, 25% in the experimental arm and 17% in the SOC 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.

Medicare Advantage Plans

GeneSight® Psychotropic panel**,** NeuroIDgenetix and the Psychotropic Pharmacogenomics Gene Panel are pharmacogenomic tests that analyze clinically important genetic variations in DNA. The results can inform physicians about genes that may impact how a particular patient metabolizes or responds to certain medications. GeneSight® Psychotropic panel, NeuroIDgenetix and the Psychotropic Pharmacogenomics Gene Panel may be considered medically necessary when medical criteria are met in testing for drug selection in the treatment of mental health conditions.

Documentation Requirements

The medical record must clearly reflect the following:

- The patient has a diagnosis for which pharmacologic therapy is reasonable and necessary, and the drug or drugs that the clinician is considering using must be reasonable and necessary for the treatment of the patient's diagnosis.
- The clinician has made an initial personalized decision for the patient based on the patient's diagnosis, the patient's other medical conditions, other medications the patient is taking, professional judgement, clinical science and basic science pertinent to the drug (e.g. mechanism of action, side effects), the patient's past medical history and when pertinent family history and the patient's preferences and values.
- The provider performing the service must have a record of what drug(s) is/are being considered and for what indication(s).

CODING

The following CPT code is covered for Medicare Advantage Plans when criteria is met and not medically necessary for Commercial Products:

GeneSight® Psychotropic Panel

0345U Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6

(Code: Effective 10/01/2022. For Dates of Service prior to 10/1/2022, Unlisted CPT code 81479 must be used.)

While there may be specific CPT codes for some of the components of the GeneSight® Psychotropic panel testing, claims for the entire panel must be filed with CPT code 0345U or 81479 according to the Dates of Service outlined above.

Medicare Advantage Plans and Commercial Products
*For all other testing referenced in this policy:
There is not a specific CPT code, therefore, claims should be filed with Unlisted CPT code **81479.**
81479 Unlisted molecular pathology procedure

While there may be specific CPT codes for some of the components of the panel testing in this policy, claims for the entire panel must be filed with the Unlisted CPT code noted above.

RELATED POLICIES
Genetic Testing Services

PUBLISHED
Provider Update, January 2023
Provider Update, February 2022
Provider Update, March 2021
Provider Update, February 2020
Provider Update, January 2019

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3. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Pharmacogenomics Testing, Noridian Healthcare Solutions, LLC (L38335))
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