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

EFFECTIVE DATE: 10|13|2015
POLICY LAST UPDATED: 01|04|2021

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

MEDICAL CRITERIA

BlueCHiP for Medicare

GeneSight® Psychotropic panel testing is covered when the following clinical conditions are met:

- Diagnosis of moderate to severe depression, and
- Failed at least one prior medication.

Commercial Products

Not applicable

PRIOR AUTHORIZATION

BlueCHiP for Medicare and Commercial Products

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 BlueCHiP for Medicare and recommended for Commercial Products 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

BlueCHiP for Medicare

GeneSight Psychotropic gene panel testing 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 the effects of the technology on health outcomes:

- Genecept Assay (Genomind)
- 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)

Commercial Products

The following tests are not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes:

- 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 of 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)
- STA2R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical Reference Laboratory)
- GeneSight® Psychotropic panel (Assurex Health)
- Proove Opioid Risk panel (Proove Biosciences)
- Mental Health DNA Insight™ panel (Pathway Genomics)
- IDgenetix-branded tests (AltheaDx)

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 the effects of the technology on health outcomes.

For adult patients with major depressive disorder who have had inadequate response to antidepressant therapy who receive GeneSight® testing guided drug treatment, the evidence includes 2 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 2 RCTs compared response (≥50% decrease in HAM-D17) and remission (HAMD-17≤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=0.01) and remission (15% of 560 vs 10% of 607, p=0.007) in the GeneSight® arm compared to SOC at 8 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 8 endpoint. The extent of missing data following randomization (35%) precludes conclusions on outcomes at 8 weeks. In the small single center 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 the effects of the technology on health outcomes.

For adult patients with major depressive disorder who have had inadequate response to antidepressant therapy who receive NeuroIDgenetix® testing guided drug treatment, the evidence includes 2 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. 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 moderate and severe group of patients (p=0.01) and significant improvement in remission (HAMD-17≤7) in the NeuroIDgenetix® arm (35% of 40) compared to SOC (13% of 53) at 12 weeks among severe group of patients only (p=0.02). 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 was 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 neurocognitive 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 the studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine the effects of the technology on health outcomes.

For adult patients with major depressive disorder who have had inadequate response to antidepressant therapy who receive Neuropharmagen® testing guided drug treatment, the evidence includes 2 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 2 RCTs compared response (≥50% decrease in HAM-D17) and remission (HAMD-17≤7) with antidepressant therapy informed by Neuropharmagen ® test results to standard of care (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=0.01) and not statistically significant improvement in remission (46% of 52 vs 26% of 48, p=0.07) 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 intention to treat analysis of effectiveness. Use of LOCF assumes data are missing completely at random (MCAR), 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=0.39) and remission (34% of 141 vs 33% of 139, p=0.87) in the Neuropharmagen® arm compared to SOC at 12 weeks among patients with MDD. Response and remission data were missing for 9% 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 the effects of the technology on health outcomes.

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-A17) in the NeuroIDgenetix® arm (63% of 82) compared to SOC (50% of 95) at 12 weeks among moderate and severe group of patients (p=0.04). There was evidence suggesting selective reporting, as anxiety remission was not

reported and contrary to the listing in clinicaltrials.gov adverse drug events was 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 the effects of the technology on health outcomes.

BlueCHiP for Medicare
GeneSight Psychotropic is a pharmacogenomic test that analyzes 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 may be considered medically necessary in testing for drug selection in the treatment of moderate to severe depression.

CODING

BlueCHiP for Medicare and Commercial Products
There is not a specific CPT code for the testing referenced in this policy. Therefore, claims should be filed with Unlisted CPT code **81479.**

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

RELATED POLICIES

Genetic Testing Services

PUBLISHED

Provider Update, March 2021
Provider Update, February 2020
Provider Update, January 2019
Provider Update, November 2017
Provider Update, September 2016

REFERENCES

1. Genesight website: Genetic Testing - Personalized Treatment | Genesight
2. Koyama E, Zai CC, Bryushkova L, et al. Predicting risk of suicidal ideation in youth using a multigene panel for impulsive aggression. Psychiatry Res. Mar 2020; 285: 112726. PMID 31870620
3. Ghafouri-Fard S, Taheri M, Omrani MD, et al. Application of Single-Nucleotide Polymorphisms in the Diagnosis of Autism Spectrum Disorders: A Preliminary Study with Artificial Neural Networks. J Mol Neurosci. Aug 2019; 68(4): 515-521. PMID 30937628
4. Ran L, Ai M, Wang W, et al. Rare variants in SLC6A4 cause susceptibility to major depressive disorder with suicidal ideation in Han Chinese adolescents and young adults. Gene. Feb 05 2020; 726: 144147. PMID 31629822
5. Wan L, Zhang G, Liu M, et al. Sex-specific effects of methylenetetrahydrofolate reductase polymorphisms on schizophrenia with methylation changes. Compr Psychiatry. Oct 2019; 94: 152121. PMID 31476590
6. Zhu D, Yin J, Liang C, et al. CACNA1C (rs1006737) may be a susceptibility gene for schizophrenia: An updated meta-analysis. Brain Behav. Jun 2019; 9(6): e01292. PMID 31033230
7. Schroter K, Brum M, Brunkhorst-Kanaan N, et al. Longitudinal multi-level biomarker analysis of BDNF in major depression and bipolar disorder. Eur Arch Psychiatry Clin Neurosci. Mar 2020; 270(2): 169-181. PMID 30929061
8. Chen X, Wang M, Zhang Q, et al. Stress response genes associated with attention deficit hyperactivity disorder: A case-control study in Chinese children. Behav Brain Res. May 02 2019; 363: 126-134. PMID 30707907

9. Zhang L, Hu XZ, Benedek DM, et al. Genetic predictor of current suicidal ideation in US service members deployed to Iraq and Afghanistan. J Psychiatr Res. Jun 2019; 113: 65-71. PMID 30904785
10. Gaynes BN, Warden D, Trivedi MH, et al. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr Serv. Nov 2009; 60(11): 1439-45. PMID 19880458
11. Bonin L. Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis. 2019; https://www.uptodate.com/contents/pediatric-unipolar-depression-epidemiology-clinical-features-assessment-and-diagnosis?topicRef=1231&source=related_link. Accessed Apr 30, 2019.
12. Source Bloomberg news, August 14 2019.
13. Food and Drug Administration. Major Depressive Disorder: Developing Drugs for Treatment. Guidance Document 2018; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/major-depressive-disorder-developing-drugs-treatment. Accessed May 30,2019.
14. CADTH Common Drug Reviews. Aripiprazole (Abilify): Depression, Major Depressive Disorder (MDD). Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, Copyright (c) CADTH 2016.; 2016.
15. Brown L, Vranjkovic O, Li J, et al. The clinical utility of combinatorial pharmacogenomic testing for patients with depression: a meta-analysis. Pharmacogenomics. Jun 2020; 21(8): 559-569. PMID 32301649
16. Winner JG, Carhart JM, Altar CA, et al. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med. Nov 2013; 16(89): 219-27. PMID 24229738
17. Greden JF, Parikh SV, Rothschild AJ, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res. Apr 2019; 111: 59-67. PMID 30677646
18. Hall-Flavin DK, Winner JG, Allen JD, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. Oct 16 2012; 2: e172. PMID 23047243
19. Hall-Flavin DK, Winner JG, Allen JD, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenet Genomics. Oct 2013; 23(10): 535-48. PMID 24018772
20. Bradley P, Shiekh M, Mehra V, et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility. J Psychiatr Res. Jan 2018; 96: 100-107. PMID 28992526
21. Olson MC, Maciel A, Gariepy JF, et al. Clinical Impact of Pharmacogenetic-Guided Treatment for Patients Exhibiting Neuropsychiatric Disorders: A Randomized Controlled Trial. Prim Care Companion CNS Disord. Mar 16 2017; 19(2). PMID 28314093
22. Vilches S, Tuson M, Vieta E, et al. Effectiveness of a Pharmacogenetic Tool at Improving Treatment Efficacy in Major Depressive Disorder: A Meta-Analysis of Three Clinical Studies. Pharmaceutics. Sep 02 2019; 11(9). PMID 31480800
23. Han C, Wang SM, Bahk WM, et al. A Pharmacogenomic-based Antidepressant Treatment for Patients with Major Depressive Disorder: Results from an 8-week, Randomized, Single-blinded Clinical Trial. Clin Psychopharmacol Neurosci. Nov 30 2018; 16(4): 469-480. PMID 30466219
24. Perez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. BMC Psychiatry. Jul 14 2017; 17(1): 250. PMID 28705252
25. Espadaler J, Tuson M, Lopez-Ibor JM, et al. Pharmacogenetic testing for the guidance of psychiatric treatment: a multicenter retrospective analysis. CNS Spectr. Aug 2017; 22(4): 315-324. PMID 27098095
26. Lachin JM. Fallacies of last observation carried forward analyses. Clin Trials. Apr 2016; 13(2): 161-8. PMID 26400875

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