Genetic Testing for Diagnosis and Management of Mental Health Conditions

Policy # 00402
Original Effective Date: 01/15/2014
Current Effective Date: 11/13/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders is addressed separately in medical policy 00121.

Note: Cytochrome p450 Genotyping is addressed separately in medical policy 00169.

Note: Vagus Nerve Stimulation is addressed separately in medical policy 00134.

Note: Deep Brain Stimulation is addressed separately in medical policy 00024.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for diagnosis and management of mental health disorders in all situations, including but not limited to the following to be **investigational:***

- 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:
    - selective serotonin reuptake inhibitors
    - selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
    - tricyclic antidepressants
    - antipsychotic drugs.

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Based on review of available data, the Company considers genetic testing panels for mental health disorders, including but not limited to the Genecept™‡ Assay, STA^{2}R test, the GeneSight®‡ Psychotropic panel, the Proove Opioid Risk assay, and the Mental Health DNA Insight panel for all indications to be **investigational.***

When Services Are Not Covered

Based on review of available data, the Company considers repeat germline testing to be **not covered****.

Note:
Repeat germline testing that investigates the same genetic information is not reasonable and necessary as it is duplicative and not required for medical treatment decisions. Examples of germline tests include, but are not limited to, single gene testing, gene panel tests, whole exome or whole genome sequencing for inherited disorders and pharmacogenomic/cytochrome P450 testing.

Background/Overview

This evidence review 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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);
- STA^{2}R 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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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 individuals at 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 individuals with major depressive disorder (MDD) who receive GeneSight testing guided drug treatment, the evidence includes 4 randomized controlled trials (RCTs). Relevant outcomes are symptoms, change 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 [HAM-D17] or Patient Health Questionnaire-9 [PHQ-9]), remission (HAM-D17 ≤7 or PHQ-9 ≤5), and symptom improvement (mean % change in HAM-D17 or PHQ-9) with antidepressant therapy informed by GeneSight test results to antidepressant therapy selected without GeneSight test results (ie, standard of care [SOC]). The Precision Medicine in Mental Health Care (PRIME Care) RCT compared 24-week outcomes in adults with MDD who received either GeneSight-guided therapy or SOC.20, The study included 1,944 participants from

22 Veteran's Affairs medical centers who were randomly assigned to either pharmacogenomic-guided treatment (n=966) or SOC (n=978). Assessments were conducted at baseline and every 4 weeks until 24-weeks follow-up.

The authors reported a small and nonpersistent effect on the co-primary outcome of symptom remission. A significant difference in symptom remission rates on the PHQ-9 was reported favoring the GeneSight group at weeks 8 and 12, but no meaningful differences were detected at weeks 4, 18, or 24. The overall pooled effect over time for remission, however, remained favorable for the GeneSight group by a small margin (odds ratio [OR], 1.28; 95% CI, 1.05 to 1.5; p=.02) (Table 3). The other co-primary outcome, treatment initiation after pharmacogenomics testing, showed that more GeneSight-guided participants were likely to be prescribed an antidepressant in the first 30 days after testing (OR, 0.74; 95% CI, 0.6 to 0.92; p=.005). The pharmacogenomic-guided patients were less also likely to be classified as having no antidepressant and gene interaction compared to moderate or substantial interaction compared to SOC (OR, 2.08; 95% CI, 1.52 to 2.84; p=.005). The secondary outcomes of response rate (OR, 1.25; 95% CI, 1.07 to 1.46; p=.005) and symptom improvement (risk difference [RD], 0.56; 95% CI, 0.17 to 0.95; p=.005) on the PHQ-9 also demonstrated an overall pooled effect over time.

The PRIME trial exhibits a notable methodological limitation by lacking an intention-to-treat analysis. A power calculation was performed, indicating that each treatment arm necessitated 1000 participants to detect a 5% disparity in the remission rate, accounting for an estimated 20% loss to follow-up and possessing 80% statistical power. The trial fell short of achieving the desired recruitment level, and by the conclusion of the 24-week follow-up period, approximately 22% (n=196) of the GeneSight group and 20% (n=172) of the SOC group were lost to follow-up, exacerbating the recruitment issue. In the PRIME trial, solely the outcome assessors were subject to blinding, while both the participants and their treating clinicians were informed of the treatment allocation. Consequently, the potential placebo effect within this trial remains uncertain.

The GUIDED trial reported statistically significant improvements in response and remission in the GeneSight arm compared to SOC at 8 weeks among individuals 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 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 individuals 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 (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 ITT population; there was also 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 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 individuals 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 (ie, 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 an early dropout of 25% in guided-care and 38% in the standard care arm and used the 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 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 individuals with MDD. Response and remission data were missing for 9% of individuals 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 individuals with anxiety disorders and reported statistically significant improvement in response (≥50% decrease in Hamilton Rating Scale for Anxiety [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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Clinical Pharmacogenetics Implementation Consortium

In 2009, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was established to develop practice guidelines on the use of genetic laboratory results to inform prescribing decisions. The panel consists of experts from the U. S., Europe, and Asia.

In 2015, the CPIC conducted a systematic literature review on the influence of *CYP2D6* and *CYP2C19* genotyping on selective serotonin reuptake inhibitor (SSRI) therapy. The CPIC provided dosing recommendations for SSRIs based on phenotypes that classified patients as ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. However, CPIC noted that patients on an effective and stable dose of SSRIs would not benefit from dose modifications based on *CYP2D6* and *CYP2C19* genotype results. Additionally, CPIC asserted that genetic testing is only one factor among several clinical factors that should be considered when determining a therapeutic approach.

In 2016, the CPIC conducted a systematic literature review of the influence of *CYP2D6* and *CYP2C19* genotype on the dosing of tricyclic antidepressants. Dosing recommendations for tricyclic antidepressants were provided, based on patient classifications of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers (Tables 1 and 2).

Table 1. Dosing Recommendations for Antidepressants Based on *CYP2D6* and *CYP2C19* Phenotype

Recommendations for TCAs				
Phenotype	**Implications**	**Recommendation**	**Class of recommendation for amitriptyline and nortripyline**	**Class of recommendation for other TCAs[a]**
CYP2D6 ultrarapid metabolizer	Increased metabolism to less active compound results in lower plasma concentrations of active drug and decreased probability of drug effectiveness.	Avoid TCA due to potential lack of efficacy. If TCA warranted, consider higher dose with monitoring to guide dose adjustments.	strong	optional
CYP2D6 rapid metabolizer	Normal metabolism of TCAs	Initiate TCA with recommended steady-state dose.	strong	strong
CYP2D6 intermediate metabolizer	Reduced metabolism to less active compound results in higher plasma concentration	Consider 25% reduced starting dose with monitoring to guide dose adjustments.	moderate	optional

	s of active drug and increased probability of side effects.			
CYP2D6 poor metabolizer	Greatly reduced metabolism to less active compound results in higher plasma concentrations of active drug and increased probability of side effects.	Avoid TCA due to potential side effects. If TCA is warranted, consider 50% reduced starting dose with monitoring to guide dose adjustments.	strong	optional
Recommendations for Tertiary Amines Amytriptyline, Clomipramine, Doxepin, Imipramine, and Trimipramine				
Phenotype	**Implications**	**Recommendation**	**Class of recommendation for amitriptyline**	**Class of recommendation for other tertiary amine TCAs**
CYP2C19 ultrarapid and rapid metabolizer	Increased metabolism of tertiary amines to secondary amines may	Avoid tertiary amines due to potential sub-optimal response. Consider secondary	optional	optional

	affect efficacy and side effects	amines. If tertiary amines warranted, use monitoring to guide dose adjustments.		
CYP2C19 normal metabolizer	Normal metabolism of tertiary amines	Initiate tertiary amine with recommended steady-state dose.	strong	strong
CYP2C19 intermediate metabolizer	Reduced metabolism of tertiary amines	Initiate tertiary amine with recommended steady-state dose.	strong	optional
CYP2C19 poor metabolizer	Greatly reduced metabolism of tertiary amines to secondary amines may affect efficacy and side effects	Avoid tertiary amines due to potential sub-optimal response. Consider secondary amines. If tertiary amines warranted, consider 50% reduced starting dose with monitoring to guide dose adjustments.	moderate	optional

[a] There is less clinical and pharmacokinetic evidence to support genotype-guided dose adjustments for TCAs other than amitriptyline or nortriptyline, though it may be reasonable to apply the same recommendations.

CYP: cytochrome P450; TCA: tricyclic antidepressants.

Table 2. Dosing Recommendations for Amitriptyline Based on Both *CYP2D6* and *CYP2C19* Phenotypes[a,b]

Phenotype	***CYP2D6* ultrarapid metabolizer**	***CYP2D6* normal metabolizer**	***CYP2D6* intermediate metabolizer**	***CYP2D6* poor metabolizer**
CYP2C19 ultrarapid or rapid metabolizer	Avoid amitryptyline. (optional)	Consider alternative drug. (optional)	Consider alternative drug. (optional)	Avoid amitryptyline. (optional)
CYP2C19 normal metabolizer	Avoid amitryptyline. If amitryptyline is warranted, consider higher target dose, (strong)	Initiate therapy with recommended starting dose. (strong)	Consider 25% reduction of recommended starting dose. (moderate)	Avoid amitryptyline. If amitryptyline is warranted, consider 50% reduction of recommended starting dose. (strong)
CYP2C19 intermediate metabolizer	Avoid amitryptyline. (optional)	Initiate therapy with recommended starting dose. (strong)	Consider 25% reduction of recommended starting dose.(optional)	Avoid amitryptyline. If amitryptyline is warranted, consider 50% reduction of

				recommended starting dose. (optional)
CYP2C19 poor metabolizer	Avoid amitryptyline. (optional)	Avoid amitryptyline. If amitryptyline is warranted, consider 50% reduction of recommended starting dose. (moderate)	Avoid amitryptyline. (optional)	Avoid amitryptyline. (optional)

[a] classification of recommendation appears in parenthesis after every recommendation
[b] Recommendations from studies focused on amitryptyline; however, since tricyclic antidepressants have comparable pharmacokinetic properties, these guidelines may apply to other tertiary amines.
CYP: cytochrome P450.

International Society of Psychiatric Genetics

In 2019, The International Society of Psychiatric Genetics (ISPG) issued recommendations on the use of pharmacogenetic testing in the management of psychiatric disorders, and in 2020 published the evidence review used to inform the recommendations. The recommendations state: "we recommend HLA [human leukocyte antigen]-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups. Evidence to support widespread use of other pharmacogenetic tests at this time is still inconclusive, but when pharmacogenetic testing results are already available, providers are encouraged to integrate this information into their medication selection and dosing decisions. Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial."

The ISPG also included the following considerations regarding pharmacogenetic testing:

- Common genetic variants alone are not sufficient to cause psychiatric disorders such as depression, bipolar disorder, substance dependence, or schizophrenia. Genotypes from large numbers of common variants can be combined to produce an overall genetic risk

score which can identify individuals at higher or lower risk, but at present it is not clear that this has clinical value.

- There is growing evidence that rare, pathogenic variants with large effects on brain function play a causative role in a significant minority of individuals with psychiatric disorders and may be a major cause of illness in some families. Identification of known pathogenic variants may help diagnose rare conditions that have important medical and psychiatric implications for individual patients and may inform family counseling. Identification of de novo mutations and copy number variants (CNVs) may also have a place in the management of serious psychiatric disorders. CNV testing may also prove useful for persons requesting counseling on familial risk. While the Committee did not reach consensus on widespread use of CNV testing in adult-onset disorders, most agreed that such tests may have value in cases that present atypically or in the context of intellectual disability, autism spectrum disorder, learning disorders, or certain medical syndromes.
- Professional counseling can play an important role in the decision to undergo genetic testing and in the interpretation of genetic test results. We recommend that diagnostic or genome-wide genetic testing should include counseling by a professional with expertise in both mental health and the interpretation of genetic tests. Consultation with a medical geneticist is recommended, if available, when a recognized genetic disorder is identified or when findings have reproductive or other broad health implications.
- Whenever genome-wide testing is performed, the possibility of incidental (secondary) findings must be communicated in a clear and open manner. Procedures for dealing with such findings should be made explicit and should be agreed with the patient or study participant in advance. The autonomy of competent individuals regarding preferences for notification of incidental findings should be respected.
- Genetic test results, like all medical records, are private data and must be safeguarded against unauthorized disclosure with advanced encryption and computer security systems.
- We advocate the development and dissemination of education programs and curricula to enhance knowledge of genetic medicine among trainees and mental health professionals, increase public awareness of genetics and genetic testing, and reduce stigma.
- Expanded research efforts are needed to identify relevant genes and clarify the proper role of genetic testing and its clinical utility in psychiatric care.

- Pharmacogenetic testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 3.

Table 3. Summary of Key Trials

NCT Number	Title	Enrollment	Completion Date
Ongoing			
NCT04615234	Towards Precision Medicine in Psychiatry: Clinical Validation of a Combinatorial Pharmacogenomic Approach (PANDORA)	300	Mar 2023
NCT04909749[a]	CDDOM Oneome Rightmed Depression Study	350	Jun 2023
NCT04500301	Pharmacogenomic Testing to Personalize Supportive Oncology	120	Feb 2024
NCT05669391	Pharmacogenomics on Individualized Precise Treatment of Patients With Depression	120	Dec 2026
Unpublished			
NCT02573168[a]	A Three-arm, Parallel Group, Multicentre, Double-blind, Randomized Controlled Trial Evaluating the Impact of GeneSight	103	Sep 2020

	Psychotropic and Enhanced-GeneSight Psychotropic, on Change in Weight Following Antipsychotic Treatment in Patients Suffering From Disorders Indicated for Antipsychotic Utilization		
NCT04207385	Accurate Clinical Study of Medication in Patients With Depression Via Pharmacogenomics (PGx) and Therapeutic Drug Monitoring (TDM) of Venlafaxine	160	Nov 2021 (status unknown)
NCT03749629	Comparative Effectiveness of Pharmacogenomics for Treatment of Depression (CEPIO-D)	201	Mar 2022

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. 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
2. 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
3. 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
4. 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
5. 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

6. Schröter 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
7. 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
8. 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
9. Bonin L. Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis. 2021; https://www.uptodate.com/contents/pediatric-unipolar-depression-epidemiology-clinical-features-assessment-and-diagnosis?topicRef=1231&source=related_link.
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. Browin VK. DNA test for antidepressants raises questions from FDA. Bloomberg. August 14 2019. https://www.bloomberg.com/news/articles/2019-08-14/dna-test-for-depression-drugs-raise-fda-doubts-cratering-myriad?in_source=embedded-checkout-banner.
12. Rohan KJ, Rough JN, Evans M, et al. A protocol for the Hamilton Rating Scale for Depression: Item scoring rules, Rater training, and outcome accuracy with data on its application in a clinical trial. J Affect Disord. Aug 2016; 200: 111-8. PMID 27130960
13. 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.
14. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. Sep 2001; 16(9): 606-13. PMID 11556941
15. Costantini L, Pasquarella C, Odone A, et al. Screening for depression in primary care with Patient Health Questionnaire-9 (PHQ-9): A systematic review. J Affect Disord. Jan 15 2021; 279: 473-483. PMID 33126078
16. Spielmans GI, McFall JP. A comparative meta-analysis of Clinical Global Impressions change in antidepressant trials. J Nerv Ment Dis. Nov 2006; 194(11): 845-52. PMID 17102709
17. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. Jun 1996; 11 Suppl 3: 89-95. PMID 8923116

18. Leon AC, Olfson M, Portera L, et al. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med. 1997; 27(2): 93-105. PMID 9565717
19. 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
20. Oslin DW, Lynch KG, Shih MC, et al. Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder: The PRIME Care Randomized Clinical Trial. JAMA. Jul 12 2022; 328(2): 151-161. PMID 35819423
21. 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
22. Tiwari AK, Zai CC, Altar CA, et al. Clinical utility of combinatorial pharmacogenomic testing in depression: A Canadian patient- and rater-blinded, randomized, controlled trial. Transl Psychiatry. Mar 14 2022; 12(1): 101. PMID 35288545
23. 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
24. Noordam R, Avery CL, Visser LE, et al. Identifying genetic loci affecting antidepressant drug response in depression using drug-gene interaction models. Pharmacogenomics. Jun 2016; 17(9): 1029-40. PMID 27248517
25. International Conference on Harmonization. Statistical principles for clinical trials: E9. 1998. https://www.fda.gov/media/71336/download.
26. Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. Int J Epidemiol. Oct 1992; 21(5): 837-41. PMID 1468842
27. 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
28. 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
29. 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

30. 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
31. Pérez 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
32. 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
33. Lachin JM. Fallacies of last observation carried forward analyses. Clin Trials. Apr 2016; 13(2): 161-8. PMID 26400875
34. Hartwell EE, Feinn R, Morris PE, et al. Systematic review and meta-analysis of the moderating effect of rs1799971 in OPRM1, the mu-opioid receptor gene, on response to naltrexone treatment of alcohol use disorder. Addiction. Aug 2020; 115(8): 1426-1437. PMID 31961981
35. Kampangkaew JP, Spellicy CJ, Nielsen EM, et al. Pharmacogenetic role of dopamine transporter (SLC6A3) variation on response to disulfiram treatment for cocaine addiction. Am J Addict. Jul 2019; 28(4): 311-317. PMID 31087723
36. Naumova D, Grizenko N, Sengupta SM, et al. DRD4 exon 3 genotype and ADHD: Randomised pharmacodynamic investigation of treatment response to methylphenidate. World J Biol Psychiatry. Jul 2019; 20(6): 486-495. PMID 29182037
37. Jukic MM, Smith RL, Haslemo T, et al. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. Lancet Psychiatry. May 2019; 6(5): 418-426. PMID 31000417
38. Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. Feb 2014; 15(2): 209-17. PMID 24479687
39. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. Aug 2015; 98(2): 127-34. PMID 25974703
40. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. Jul 2017; 102(1): 37-44. PMID 27997040
41. International Society of Psychiatric Genetics. Genetic Testing and Psychiatric Disorders: A Statement from the International Society of Psychiatric Genetics.

42. Bousman CA, Bengesser SA, Aitchison KJ, et al. Review and Consensus on Pharmacogenomic Testing in Psychiatry. Pharmacopsychiatry. Jan 2021; 54(1): 5-17. PMID 33147643

Policy History

Original Effective Date: 01/15/2014
Current Effective Date: 11/13/2023

01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. New policy.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. Title changed from Genecept Assay to Genetic Testing for Mental Health Conditions. Entire policy rewritten.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Policy statements changed to clarify which categories of genetic testing the policy addresses.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. No change to coverage.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Policy statements changed to specify drugs used to treat mental health conditions (SSRIs, SNRIs, tricyclic antidepressants, and antipsychotic drugs). Title changed to "Genetic Testing for Diagnosis and Management of Mental Health Conditions."
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. No change to coverage.
10/01/2020	Medical Policy Committee review
10/07/2020	Medical Policy Implementation Committee approval. No change to coverage.
10/07/2021	Medical Policy Committee review
10/13/2021	Medical Policy Implementation Committee approval. No change to coverage.
12/20/2021	Coding update
03/02/2022	Coding update
03/25/2022	Coding update

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT Codes	0029U, 0031U, 0032U, 0033U, 0345U, 0347U, 0348U, 0349U, 0350U 0392U, 81225, 81226, 81230, 81291, 81401, 81418, 81479 Add codes effective 10/01/2023: 0411U, 0419U Delete code effective 12/01/2023: 81231 Delete code effective 12/11/2023: 0380U Add code effective 01/01/2024: 0423U, 0437U
HCPCS Codes	No codes
ICD-10 DX Codes	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.