Genetic Testing for Diagnosis and Management of Mental Health Conditions

Policy #   00402
Original Effective Date:  01/15/2014
Current Effective Date:  11/14/2022

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.

Note: Genetic Testing for Tamoxifen Treatment is addressed separately in medical policy 00269.

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:
  o selective serotonin reuptake inhibitors
  o selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
  o tricyclic antidepressants
  o 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, STA2R test, the GeneSight® Psychotropic panel, the Proove Opioid Risk assay, and the Mental Health DNA Insight panel for all indications to be investigational.*

**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
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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.

**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 3 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 item [HAM-D17]), 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 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 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 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 the 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, on 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 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 early dropout of 25% in guided-care and 38% in the SOC arm, and used a 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 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, 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...
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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>
<thead>
<tr>
<th>Recommendation for TCAs</th>
<th>Class of recommendation for amitriptyline and nortriptyline</th>
<th>Class of recommendation for other TCAsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased metabolism to less active</td>
<td>Avoid TCA due to potential lack of efficacy. If TCA strong optional</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>CYP2D6 metabolizer status</th>
<th>Metabolism impact</th>
<th>Dosage recommendation</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 rapid metabolizer</td>
<td>Normal metabolism of TCAs</td>
<td>Initiate TCA with recommended steady-state dose.</td>
<td>strong</td>
</tr>
<tr>
<td>CYP2D6 intermediate metabolizer</td>
<td>Reduced metabolism to less active compound results in higher plasma concentrations of active drug and increased probability of side effects.</td>
<td>Consider 25% reduced starting dose with monitoring to guide dose adjustments.</td>
<td>moderate</td>
</tr>
<tr>
<td>CYP2D6 poor metabolizer</td>
<td>Greatly reduced metabolism to less active compound results in higher plasma concentrations of active drug and increased</td>
<td>Avoid TCA due to potential side effects. If TCA is warranted, consider 50% reduced starting dose with monitoring to guide dose adjustments.</td>
<td>strong</td>
</tr>
</tbody>
</table>

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### Recommendations for Tertiary Amines Amytriptyline, Clomipramine, Doxepin, Imipramine, and Trimipramine

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications</th>
<th>Recommendation</th>
<th>Class of recommendation for amitriptyline</th>
<th>Class of recommendation for other tertiary amine TCAs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP2C19 ultrarapid and rapid metabolizer</strong></td>
<td>Increased metabolism of tertiary amines to secondary amines may affect efficacy and side effects</td>
<td>Avoid tertiary amines due to potential sub-optimal response. Consider secondary amines. If tertiary amines warranted, use monitoring to guide dose adjustments.</td>
<td>optional</td>
<td>optional</td>
</tr>
<tr>
<td><strong>CYP2C19 normal metabolizer</strong></td>
<td>Normal metabolism of tertiary amines</td>
<td>Initiate tertiary amine with recommended steady-state dose.</td>
<td>strong</td>
<td>strong</td>
</tr>
<tr>
<td><strong>CYP2C19 intermediate metabolizer</strong></td>
<td>Reduced metabolism of tertiary amines</td>
<td>Initiate tertiary amine with recommended steady-state dose.</td>
<td>strong</td>
<td>optional</td>
</tr>
<tr>
<td><strong>CYP2C19 poor metabolizer</strong></td>
<td>Greatly reduced metabolism of tertiary amines to secondary amines may affect efficacy and side effects</td>
<td>Avoid tertiary amines due to potential sub-optimal response. Consider secondary amines. If tertiary amines warranted, consider</td>
<td>moderate</td>
<td>optional</td>
</tr>
</tbody>
</table>
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.

**Table 2. Dosing Recommendations for Amitriptyline Based on Both CYP2D6 and CYP2C19 Phenotypes**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CYP2D6 ultrarapid metabolizer</th>
<th>CYP2D6 normal metabolizer</th>
<th>CYP2D6 intermediate metabolizer</th>
<th>CYP2D6 poor metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 ultrapid or rapid metabolizer</td>
<td>Avoid amitriptyline. (optional)</td>
<td>Consider alternative drug. (optional)</td>
<td>Consider alternative drug. (optional)</td>
<td>Avoid amitriptyline. (optional)</td>
</tr>
<tr>
<td>CYP2C19 normal metabolizer</td>
<td>Avoid amitriptyline. If amitriptyline is warranted, consider higher target dose. (strong)</td>
<td>Initiate therapy with recommended starting dose. (strong)</td>
<td>Consider 25% reduction of recommended starting dose. (moderate)</td>
<td>Avoid amitriptyline. If amitriptyline is warranted, consider 50% reduction of recommended starting dose. (strong)</td>
</tr>
<tr>
<td>CYP2C19 intermediate metabolizer</td>
<td>Avoid amitriptyline. (optional)</td>
<td>Initiate therapy with recommended starting dose. (strong)</td>
<td>Consider 25% reduction of recommended starting dose. (optional)</td>
<td>Avoid amitriptyline. If amitriptyline is warranted,</td>
</tr>
</tbody>
</table>
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| CYP2C19 poor metabolizer | Avoid amitryptiline. (optional) | Avoid amitryptiline. If amitryptiline is warranted, consider 50% reduction of recommended starting dose. (optional) | Avoid amitryptiline. (optional) |

*a* classification of recommendation appears in parenthesis after every recommendation

*b* Recommendations from studies focused on amitryptiline; however, since tricyclic antidepressants have comparable pharmacokinetic properties, these guidelines may apply to other tertiary amines.

**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-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**

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Title</th>
<th>Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03170362</td>
<td>PRIME Care (Precision Medicine In Mental Health Care)</td>
<td>1,944</td>
<td>Mar 2022</td>
</tr>
<tr>
<td>NCT03749629</td>
<td>Comparative Effectiveness of Pharmacogenomics for Treatment of Depression (CEPIO-D)</td>
<td>201</td>
<td>Mar 2022</td>
</tr>
<tr>
<td>NCT03674138</td>
<td>Pharmacogenomic-Guided Antidepressant Drug Prescribing in Cancer Patients</td>
<td>99</td>
<td>Oct 2022</td>
</tr>
<tr>
<td>NCT04615234</td>
<td>Towards Precision Medicine in Psychiatry: Clinical Validation of a Combinatorial Pharmacogenomic Approach (PANDORA)</td>
<td>300</td>
<td>Mar 2023</td>
</tr>
<tr>
<td>NCT04909749a</td>
<td>CDDOM Oneome Rightmed Depression Study</td>
<td>350</td>
<td>Jun 2023</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Description</th>
<th>NCT Number</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02573168a</td>
<td>A Three-arm, Parallel Group, Multicenter, Double-blind, Randomized Controlled Trial Evaluating the Impact of GeneSight Psychotropic and Enhanced-GeneSight Psychotropic, on Change in Weight Following Antipsychotic Treatment in Patients Suffering From Disorders Indicated for Antipsychotic Utilization</td>
<td>103</td>
<td>Sep 2020</td>
</tr>
<tr>
<td>NCT03228953</td>
<td>Impact of Comprehensive Pharmacogenomic Testing on the Treatment of Major Depressive Disorder</td>
<td>206</td>
<td>May 2021 (status unknown)</td>
</tr>
<tr>
<td>NCT04207385</td>
<td>Accurate Clinical Study of Medication in Patients With Depression Via Pharmacogenomics (PGx) and Therapeutic Drug Monitoring (TDM) of Venlafaxine</td>
<td>160</td>
<td>Nov 2021 (status unknown)</td>
</tr>
</tbody>
</table>

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

References


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Policy History
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01/09/2014 Medical Policy Committee review
01/15/2014 Medical Policy Implementation Committee approval. New policy.
08/07/2014 Medical Policy Committee review
08/06/2015 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
09/20/2022 Coding update
10/06/2022 Medical Policy Committee review
10/11/2022 Medical Policy Implementation Committee approval. No change to coverage.

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12/07/2022 Coding update
03/19/2023 Coding update
06/06/2023 Coding update
Next Scheduled Review Date: 10/2023

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 2021 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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CPT is a registered trademark of the American Medical Association.
Genetic Testing for Diagnosis and Management of Mental Health Conditions

Policy # 00402
Original Effective Date: 01/15/2014
Current Effective Date: 11/14/2022

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

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Add code effective 01/01/2023: 81418</td>
</tr>
<tr>
<td></td>
<td>Add code effective 04/01/2023: 0380U</td>
</tr>
<tr>
<td></td>
<td>Add code effective 07/01/2023: 0392U</td>
</tr>
<tr>
<td>HCPCS Codes</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 DX Codes</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*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.

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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.