BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.110 Genetic Testing for Diagnosis and Management of Mental Health Conditions

Effective Policy Date: October 1, 2023

Original Policy Date: March 2014

Related Policies:

2.01.50 - Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders
2.04.38 - Cytochrome P450 Genotype-Guided Treatment Strategy

Genetic Testing for Diagnosis and Management of Mental Health Conditions

Description

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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.

OBJECTIVE

The objective of this evidence review is to assess whether the use of genetic tests for diagnosis or management improves the net health outcome of individuals with mental health disorders. Assessment of the clinical utility of a pharmacogenomic test requires direct evidence from intervention studies that compare health outcomes of individuals managed with and without the test.

POLICY STATEMENT

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

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

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, are considered **investigational** for all indications.

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

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

Examples of commercially available panels include the following:

- Genecept™ Assay (Genomind);
- 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), cytochrome P450 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

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) trial did not find a statistically significant difference between GeneSight guided treatment and SOC in the primary outcome of remission at 24 weeks follow-up, but significant differences in the secondary outcome of symptom score improvement and treatment response were observed, favoring the GeneSight group. However, this trial had a high loss to follow-up (21%) and had inadequate participant recruitment based on a priori sample size estimation and power analysis. 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 intention to treat (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

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.[38,] 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.[39,] 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.[40,] 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[40,]

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 concentrations of active drug and increased probability of side effects.	Consider 25% reduced starting dose with monitoring to guide dose adjustments.	moderate	optional
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 affect efficacy and side effects	Avoid tertiary amines due to potential sub-optimal response. Consider secondary amines. If tertiary amines warranted, use monitoring to guide dose adjustments.	optional	optional
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.[41,42,] 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2014	New policy	The Genecept€ž assay is investigational for all indications.
September 2014	Replace policy	Policy updated with literature review. Policy expanded to include other genetic testing panels; title of policy changed to "Genetic Testing for Mental Health Conditions., Rationale extensively revised. Reference 1, 2, 7-11, 19-26, 28-44 added. Policy statement changed to indicated that individual genetic tests and genetic testing panels for mental health disorders are investigational.
December 2016	Replace policy	Policy updated with literature review. References 3, 14, 21, 27, 32, 37, 43-44, 50 and 54 added. Policy statements changed to clarify which categories of genetic testing the policy address; intent of policy statements unchanged.
September 2018	Replace policy	Policy updated with literature review through April 9, 2018; references 6, 32, 35, 37-44, 51 and 68-70 added. Policy statements changed to specify drugs used to treat mental health conditions (previously from policy 2.04.38: SSRIs, SNRIs, tricyclic antidepressants, and antipsychotic drugs). Title changed to "Genetic Testing for Diagnosis and Management of Mental Health Conditions.,
September 2019	Replace policy	Policy updated with literature review through April 23, 2019; references added. Previously, the population in the second indication was "individuals with a mental illness who are undergoing drug treatment." This single indication was changed to 2 indications with the following populations: 1) "individuals with depression who are adequately controlled with drug treatment" and 2) "individuals with a mental illness other than depression who are undergoing drug treatment".
September 2020	Replace policy	Policy updated with literature review through April 24, 2020; references added. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through May 26, 2021; references added. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through June 2, 2022; references added. Policy statements unchanged.
September 2023	Replace policy	Policy updated with literature review through May 29, 2023; references added and updated. Policy statements unchanged.