FEP Medical Policy Manual

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

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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

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.

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 patients 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

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), *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

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 patients with risk for mental health conditions. No studies were identified that evaluated whether testing for variants changed clinical management or affected health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For adult patients with major depressive disorder who have had inadequate response to antidepressant therapy who receive GeneSight testing guided drug treatment, the evidence includes 2 randomized controlled trials (RCT). Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The 2 RCTs compared response (≥50% decrease in HAM-D17) and remission (HAMD-17≤7) with antidepressant therapy informed by GeneSight test results to standard of care (SOC)<97>antidepressant therapy selected without GeneSight test results. The Genomics Used to Improve DEpression Decisions (GUIDED) trial by Greden *et al* (2019) reported statistically significant improvement in response (26% of 560 vs 20% of 607, p=0.01) and remission (15% of 560 vs 10% of 607, p=0.007) in the GeneSight arm compared to SOC at 8 weeks among patients with MDD using per protocol analysis. Per protocol cohort excluded 401 (22%) of 1799 randomized patients, and additional 231 patients from the per protocol cohort did not complete the study through the blinded week 8 endpoint. The extent of missing data following randomization (35%) precludes conclusions on outcomes at 8 weeks. In the small single center study by Winner *et al* (2013), depression outcomes did not differ significantly between guided care and SOC groups at the 10-week follow-up and the study was underp-owered to detect significant differences in outcomes between study arms. None of these trials provided adequate evidence. Both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine the effects of the technology on health outcomes.

For adult patients with major depressive disorder who have had inadequate response to antidepressant therapy who receive NeuroIDgenetix testing guided drug treatment, the evidence includes 2 randomized controlled trials (RCT). Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Bradley *et al* (2018) conducted a double-blind RCT among patients with MDD and reported statistically significant improvement in response (≥50% decrease in HAM-D17) in the NeuroIDgenetix arm (64% of 140) compared to SOC (46% of 121) at 12 weeks among moderate and severe group of patients (p=0.01) and significant improvement in remission (HAMD-17≤7) in the NeuroIDgenetix arm (35% of 40) compared to SOC (13% of 53) at 12 weeks among severe group of patients only (p=0.02). There was evidence suggesting selective reporting, as remission was reported for only those with severe depression and contrary to the listing in clinicaltrials.gov adverse drug events was not reported as the primary outcome. It was unclear if the analysis was based on intention-to-treat population and there was high loss to follow-up (15%). In the RCT conducted by Olson *et al* (2017), among patients with neuropsychiatric disorders those receiving SOC reported significantly more adverse events (53%) than those receiving NeuroIDgenetix guided care (28%), however, the study did not report the number of patients included in this analysis. The study did not describe the randomization procedure and in ClinicalTrials.gov neurocognitive measures were listed as co-primary outcomes, which were not reported, suggesting possible selective reporting. None of these trials provided adequate evidence. The Olson et al (2017) study had major relevance limitations and both the studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine the effects of the technology on health outcomes.

For adult patients with major depressive disorder who have had inadequate response to antidepressant therapy who receive Neuropharmagen testing guided drug treatment, the evidence includes 2 randomized controlled trials (RCT). Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The 2 RCTs compared response (≥50% decrease in HAM-D17) and remission (HAMD-17≤7) with antidepressant therapy informed by Neuropharmagen test results to standard of care (SOC)<97>antidepressant therapy selected without Neuropharmagen test results. The single-blinded RCT by Han *et al* (2018) reported statistically significant improvement in response (72% of 52 vs 44% of 48, p=0.01) and not statistically significant improvement in remission (46% of 52 vs 26% of 48, p=0.07) in the Neuropharmagen arm compared to SOC at 8 weeks among patients with MDD. The study reported early dropout of 25% in guided-care and 38% in the standard care arm and used last observation carried forward (LOCF) approach in intention to treat analysis of effectiveness. Use of LOCF assumes data are missing completely at random (MCAR), which is unlikely to hold in this analysis. Also, the study did not report registration in any clinical trial database. The single-blinded RCT by Perez *et al* (2017) reported statistically not significant improvement in response (45% of 141 vs 40% of 139, p=0.39) and remission (34% of 141 vs 33% of 139, p=0.87) in the Neuropharmagen arm

compared to SOC at 12 weeks among patients with MDD. Response and remission data were missing for 9% patients in the guided care group and 14% of the standard care group. None of these trials provided adequate evidence. Both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a mental illness other than depression who are undergoing drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a systematic review and meta-analysis and RCTs evaluating associations between specific genes and outcomes of drug treatment. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review and meta-analysis by Hartwell *et al* (2020) included 7 RCTs and reported no significant moderating effect of rs1799971, a single nucleotide polymorphism (SNP) that encodes a non-synonymous substitution (Asn40Asp) in the mu-opioid receptor gene, *OPRM1* on response to naltrexone treatment of alcohol use disorder. Bradley *et al* (2018) conducted a double-blind RCT among patients with anxiety disorders and reported statistically significant improvement in response (≥50% decrease in HAM-A17) in the NeuroIDgenetix arm (63% of 82) compared to SOC (50% of 95) at 12 weeks among moderate and severe group of patients (p=0.04). There was evidence suggesting selective reporting, as anxiety remission was not reported and contrary to the listing in clinicaltrials.gov adverse drug events was not reported as the primary outcome. It was unclear if the analysis was based on intention-to-treat population and among the randomized moderate and severe anxiety patients with only anxiety, 25% in the experimental arm and 17% in the standard care arm were lost to follow up over the 12 week period. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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.[30] 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.[31] 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.[32,] Dosing recommendations for tricyclic antidepressants were provided, based on patient classifications of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers (Table 1 and 2).

Table 1. Dosing Recommendations for Antidepressants Based on *CYP2D6* and *CYP2C19* Phenotype[32,]

Recommendations for Tricyclic Antidepressants				
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.

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.

Evaluation of Genomic Applications in Practice and Prevention

In 2007, the EGAPP Working Group commissioned the Agency for Healthcare Research and Quality to conduct a systematic review on *CYP450* testing in patients receiving SSRIs.[33,] Based on results from the review, EGAPP "found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are complete."

International Society of Psychiatric Genetics

In 2018, the International Society of Psychiatric Genetics published a review and recommendations from its Residency Education Committee regarding genetic issues relevant to psychiatric training programs.[34,] The Committee only recommends genetic testing as part of a diagnostic workup for patients with autism spectrum disorders or intellectual disability. In regards to pharmacogenetic testing, the Committee states that the "efficacy of these pharmacogenomic profiles requires further investigation in controlled studies."

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™ 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.