2.04.110	Genetic Testing for Diagnosis and Management of Mental Health Conditions		
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Section:	2.0 Medicine	**Page:**	Page 1 of 30

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:

I. To confirm a diagnosis of a mental health disorder in an individual with symptoms
II. To predict future risk of a mental health disorder in an asymptomatic individual
III. To inform the selection or dose of medications used to treat mental health disorders, including but not limited to the following medications*:
   A. Selective serotonin reuptake inhibitors
   B. Selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
   C. Tricyclic antidepressants
   D. Antipsychotic drugs

Genetic testing panels for mental health disorders are considered **investigational** for **all** indications, including but not limited to the following:

I. Genecept Assay
II. GeneSight Psychotropic panel
III. Mental Health DNA Insight panel
IV. Proove Opioid Risk assay
V. STA²R test

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

***Note:** This policy does not address the use of Cytochrome P450 (CYP gene testing) for other drugs. See Blue Shield of California Medical Policy: Cytochrome P450 Genotype-Guided Treatment Strategy

Genetics Nomenclature Update

The Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence

Previous	Updated	Definition
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

There is no specific CPT code for these testing panels.

There are specific codes for some of the component tests:

- **81225**: CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
- **81226**: CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
- **81291**: MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)

The following CPT codes include the testing for *CYP3A4*:

- **81230**: CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22)
- **81231**: CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7)

The following PLA codes are specific for 2 tests:

- **0032U**: COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant (for the Catechol-O-Methyltransferase (COMT) Genotype)
- **0033U**: HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (e.g., citalopram metabolism) gene analysis, common variants (i.e., HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G]) (for the Serotonin Receptor Genotype)

The following CPT codes may be billed for this test:

- **0173U**: Psychiatry (i.e., depression anxiety) genomic analysis panel includes variant analysis of 14 genes
- **0175U**: Psychiatry (e.g., depression anxiety); genomic analysis panel, variant analysis of 15 genes

The remaining tests on the panel that are not currently codified in CPT would be reported with 1 unit of the following code:

- **81479**: Unlisted molecular pathology procedure

Description

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.

Related Policies

- Cranial Electrotherapy Stimulation and Auricular Electrostimulation
- Cytochrome P450 Genotype-Guided Treatment Strategy
- Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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);
- 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

Background

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 is from randomized controlled trials.

Literature Review

Testing For Diagnosis or Risk Of Mental Health Disorder

Clinical Context and Test Purpose

The purpose of testing for genes associated with increased risk of mental illness in patients who are currently asymptomatic is to identify those for whom an early intervention during a presymptomatic phase of the illness might facilitate improved outcomes.

The question addressed in this evidence review is: Does the use of testing for genes associated with increased risk of mental illness in patients who are currently asymptomatic improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is asymptomatic individuals who would consider intervention if a genetic variant is detected.

Interventions

The intervention of interest is testing for genes associated with increased risk of mental illness, either as a panel or single gene.

Comparators

At present, decisions about the management of mental illnesses are made when patients present with symptoms and are typically diagnosed based on clinical evaluation according to standard criteria (i.e., *Diagnostic and Statistical Manual of Mental Disorders*).

Outcomes
The primary outcome of interest is change in disease outcomes, which would result directly from changes in management that could be instituted because of earlier disease detection. Standardized outcome measures are available for many mental illnesses. Commonly used measures for the evaluation of depression in clinical trials are described in the next section.

Study Selection Criteria
Assessment of clinical utility of a genomic test cannot be made by a chain of evidence from clinical validity data alone. 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, randomized controlled trials (RCTs)are needed..

- We sought RCTs that reported the outcomes of pharmacogenetic testing to diagnose, assess the risk of developing, or to manage a mental health condition.
- We sought evidence on outcomes, with emphasis on efficacy outcomes, as the main purpose of genetic testing in mental health conditions to achieve clinically meaningful improvement compared with standard of care (SOC).
- We also included studies that reported only on adverse events, although for medications where adverse events tend to be mild, efficacy outcomes are of greater importance.

Review of Evidence
We did not find any RCT evaluating the use of genetic test results to inform decisions on mental health diagnoses or management of patients with risk for mental health conditions. Multiple cohort and case control studies examined the association between different genetic markers with different mental health disorders.[1,2,3,4,5,6,7,8,] However, those observational studies did not examine the effect of genetic testing on disease outcome among patients with risk for mental health conditions.

Section Summary: Testing for Diagnosis or Risk of Mental Health Disorder
No studies were identified that used genetic testing results to inform decisions on mental health diagnoses or management of patients with risk for mental health conditions. There is no clear clinical strategy for how the associations of specific genes and mental health disorders would be used to diagnose a specific patient or to manage a patient at higher risk of a specific disorder.

Genetic Testing to Inform Medication Selection for Patients with Depression
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition. The first step in assessing a medical test is to formulate the clinical context and purpose of the test.

Clinical Context and Test Purpose
The purpose of pharmacogenetic testing in patients with depression is to inform antidepressant selection in order to improve symptoms (i.e., clinical response) and, preferably, to achieve remission of depression.

Major Depressive Disorder (MDD) is a mood disorder characterized by pervasive sadness, lack of interest and enjoyment in most activities, feelings of low self-worth, sleep disturbance, over-or under-eating, suicidal thoughts and suicide attempts. The goal of treatment is remission of depression. While response to treatment is defined as 50% or greater reduction of symptoms; the patient who has responded, but is not in remission, may still bear a considerable burden of depression. Moreover, the risk of recurrence is greater than when remission is achieved. The main categories of treatment for MDD are psychotherapy, pharmacotherapy, and brain stimulation therapies. These may be used in combination. First generation antidepressants are tricyclic antidepressants and monoamine oxidase inhibitors. Classes of second generation

antidepressants are: selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and atypical agents.

Individuals who fail to achieve remission of MDD after 2 vigorous trials of anti-depressant medications have a poor prognosis. The Sequenced Treatment Alternatives to Relieve Depression * (STAR*D) found that only about half of patients reached remission after 2 treatments.[9] Individuals may stop treatment due to side effects of anti-depressants, which can include drowsiness; insomnia/agitation; orthostatic hypotension; QTc prolongation; gastrointestinal toxicity; weight gain; and sexual dysfunction.

Pharmacogenomic testing is proposed to identify which antidepressant medications would be most effective or have the least side effects based on genetic variants that affect drug metabolism.

The question addressed in this evidence review is: Does pharmacogenomic testing in patients with depression improve the net health outcome?

Populations
Adult patients who have a diagnosis of major depressive disorder. MDD is defined by the presence of 5 or more of the symptoms below for a period of at least 2 weeks. At least 1 symptom must be: (1) lack of interest or enjoyment in most activities, almost every day; or (2) depressed mood almost every day for most of the day. In addition at least 4 of the symptoms below must be present almost every day.

- Sleep disturbance, insomnia or excessive sleepiness
- Over-or under-eating with significant weight gain or loss
- Observable psychomotor agitation or retardation
- Fatigue or loss of energy
- Difficulty concentrating or making decisions
- Feelings of worthlessness or inappropriate guilt
- Thoughts of death or suicide, or suicide attempt.

The symptoms are not attributable to another medical condition, or behavioral disorder or substance abuse.[10]

Interventions
Three commercially available pharmacogenetic tests for antidepressant selection are reviewed here: GeneSight, NeurolDgenetix, and Neuropharmagen. Each test has its own proprietary algorithm for assessing genes associated with drug pharmacokinetics and pharmacodynamics. Each of these tests also has a proprietary format for reporting results and categorizing likely responsiveness or intolerance to available antidepressants.

All are laboratory developed tests and not subject to U.S. Food and Drug Administration (FDA) regulation. However, recently, the FDA has raised concerns about pharmacogenetic tests that claim to predict medication response where drug labeling does not describe a predictive relationship between genetic variation and drug response. The FDA has reportedly reached out to firms marketing such tests, including tests of antidepressant response, with concerns about claims of clinical benefit.[11]

Comparators
The comparator is antidepressant drug selection without pharmacogenetic testing. At present there is no definitive algorithm for selecting next line treatment after failure to respond to initial treatment.

Outcomes
This evidence review assesses whether genetic testing for the management of depression is clinically useful. The balance of benefits and harms must be better when the test is used to

manage the condition than when no test is used. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid adverse events.
There are standardized outcome measures for depression (e.g., Hamilton Rating Scale for Depression [HAM-D], Montgomery-Asberg Depression Rating Scale [MADRS] and Beck's Depression Inventory [BDI]). Scoring for the HAM-D and MADRS are shown in Table 1.

HAM-D and MADRS are physician scored scales that rate the presence and intensity of attributes of depression. The HAM-D, introduced by Max Hamilton in 1960, is the progenitor of depression measurement scales. Attributes rated include depressive mood, guilt feelings, insomnia, suicidal ideas or attempts, work and activity. However, shortcomings of HAM-D are incomplete overlap with DSM criteria for MDD and weak item-level inter-rarer reliability.[12.] None-the-less, HAM-D has moderate to high correlation with other depression scales. Various versions have been developed, intended to make the instrument easier to use. The 17-item HAM-D (HAM-D17) is the most commonly used instrument in trials of depression drugs[13.]. The MADRS is the next most commonly used instrument in trials of depression drugs. Attributes scored include sadness, pessimism, inability to feel and suicidal thoughts. As with HAM-D, MADRS has incomplete overlap with DSM criteria for MDD. MADRS is reported to correlate to other depression scales, including the HAM-D17. MADRS is generally reported to be more sensitive to treatment related change and to have better inter-rater reliability than HAM-D17; perhaps because of its more uniform structure.[13.]

Table 1: Measures of Depression in Adults

Outcome Measure	Description	Scale	Clinically Meaningful Difference
Hamilton Rating Scale for Depression	Physician scored. Rates presence and intensity of symptoms. Symptom domains include depressive mood, guilt, insomnia, suicidality, work and activity. 17 item version is most common (HAM-D17).	0 to 7 normal (no depression); 8 to 13 mild depression; 14 to 18 moderate depression; 19 to 22 severe depression; 23 or greater very severe depression	The goal of treatment is remission, typically defined as 7 or less. But 2 or less has been suggested as optimal. Response is 50% reduction from baseline
Montgomery-Asberg Depression Rating Scale	Physician scored. Presence and intensity of symptoms. Symptom domains include sadness; pessimism; inability to feel; suicidality	0 to 6 normal (no depression); 7 to 19 mild depression; 20 to 34 moderate depression; 35 to 59 severe depression; 60 or greater very severe depression	No consensus to define remission. Thresholds for remission have ranged from 6 to 12 in trials.

Secondary endpoints are:

- Clinical Global Impression (CGI)
- Sheehan Disability Scale (SDS)

The CGI and SDS may supplement depression rating scales, by assessing severity of illness and functional impairment, respectively. However, the measurement properties of these instruments are not well characterized.

The CGI "asks that the clinician rate the patient relative to their experience with other patients with the same diagnosis, with or without collateral information." There are 3 components: Severity of Illness (CGI-S), Improvement (CGI-I), and the efficacy index, each rated on a scale of 1 to 7. Severity of Illness ranges from 1="not ill at all" to 7 "among the most extremely ill." A comparative meta-analysis of change in CGI in antidepressant trials found that, among double-blind trials, the CGI-S was more conservative than HAM-D and MADRS in showing change in

severity of depression.[14] There is little evidence available on the validity and reliability of these measures.[13]

The SDS was developed as a simple tool to address the "desynchrony between psychiatric symptoms and disability": that some " very symptomatic patients who still functioned reasonably well socially and at work, while other patients with less severe and less frequent symptoms were quite disabled."[15] The SDS is a self-reported 3-item instrument used to assess the impact of symptoms on the individual's work, family and social life. Each item is scored on an 11 point scale with 0 indicating no impairment and 10 extreme impairment, with a score greater than 5 suggesting functional impairment. A study of 1001 primary care patients showed that almost half of patients with elevated SDS score had a psychiatric disorder diagnosis.[16] No MICD has been set for assessing change in SDS score.[13]

Follow-up Duration
Typically, short term response for established classes of antidepressants is assessed in studies of 6-8 weeks duration, based on mechanism of pharmacologic response. As rapid-acting anti-depressants become available, a week or even less could be sufficient.

Maintenance, the ability of a treatment to reduce recurrence of MDD, is equally important. At least 6 months of follow up is typically required to assess the ability of an agent to reduce recurrence.

Study Selection Criteria
Assessment of clinical utility of a genomic test cannot be made by a chain of evidence from clinical validity data alone. 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, RCTs are needed.

- We sought RCTs that reported the outcomes of pharmacogenetic testing to diagnose, assess the risk of developing, or to manage a mental health condition.
- We sought evidence on outcomes, with emphasis on efficacy outcomes, as the main purpose of genetic testing in mental health conditions to achieve clinically meaningful improvement compared with SOC.
- We also included studies that reported only on adverse events, although for medications where adverse events tend to be mild, efficacy outcomes are of greater importance.

Review of Evidence
GeneSight® test

Systematic Reviews
A systematic review and meta-analysis (Brown et al 2019) of prospective, 2 arm studies to examine the clinical utility of using GeneSight to inform treatment decisions for patients with MDD included 2 RCTs (Winner et al 2013 and Greden et al 2019) and 2 open label studies (Hall-Flavin et al 2012 and Hall-Flavin et al 2013).[17,18,19,20,21] Given that the Brown meta-analysis includes a mix of randomized studies and nonrandomized studies, the results will not be discussed here. The Winner and Greden RCTs included in the Brown meta-analysis are discussed below.

Randomized Controlled Trials
Two randomized controlled trials compared response and remission with antidepressant therapy informed by gene test results to SOC—antidepressant therapy selected without gene test results.

Greden et al (2019) presented results for the GUIDED trial in which patients with MDD were randomized to receive treatment guided by results from a genotyping test (GeneSight) or through standard physician assessment (Table 2).[19] GeneSight evaluates 8 genes (59 variants) in relation to 38 psychotropic medications and the potential for gene-drug interactions. Based on results from the genotype test, the medications are categorized as either congruent ('use as directed' or 'use with caution') or incongruent ('use with increased caution and with more

frequent monitoring') for a particular patient. The primary outcome was symptom improvement, measured by a change in HAM-D. Secondary outcomes were response (≥50% decrease in HAM-D, Quick Inventory of Depressive Symptomatology [QIDS], or Patient Health Questionnaire [PHQ]) and remission (score of ≤7 HAM-D, ≤5 QIDS, and <5 PHQ). The study randomized 1799 patients, after post-randomization exclusions, according to the text 1541 patients remained in what was labeled the "intention to treat" cohort, but the "intention to treat" results reported in Figure 2 included only 1299 participants. Overall, approximately one third of randomized participants were missing from the reported results on response and remission. The participant flow chart included in the Supplement describes missing data as occurring because of 'lost-to-follow-up' (n=18 before randomization; n=48 between baseline and week 4; n=24 between week 4 and week 8); 'discontinued' due to inclusion/exclusion violations, HAM-D or QIDS scores, out of window visits, withdrawal of consent, or 'other' (n=383 before randomization; n=86 between baseline and week 4; n=73 between week 4 and week 8).The text reports that 'Analyses were performed for patients who completed the study through week 8.' These exclusions and analysis methods do not conform with definitions of intent-to-treat and there were no sensitivity analyses for the missing data provided.[22,23] While the results significantly favored the GeneSight informed group, the extent of missing data precludes conclusions on outcomes.

A pilot RCT by Winner et al (2013) evaluated the effect of providing the GeneSight test on the management of psychotropic medications used for MDD in a single outpatient psychiatric practice (see Table 2).[18] Fifty-one subjects were enrolled and randomized to treatment as usual or treatment guided by GeneSight testing. All subjects underwent GeneSight testing, though results were not given to the physicians in the treatment as a usual group until after study completion. At 10-week follow-up, treating physicians dose-adjusted subjects' medication regimens with the same likelihood in the GeneSight group (53%) and the treatment as usual group (58%; p=.66). However, patients in the GeneSight group who were initially on a medication classified as "use with caution and with more frequent monitoring" were more likely than those with the same classification in the unguided group to have a medication change or dose adjustment (100% vs. 50% respectively; p=.02). Depression outcomes, measured by the HAM-D17 score, did not differ significantly between groups at the 10-week follow-up (see Table 3). This trial's small size may have limited the ability to detect a significant effect, as the authors estimated that 92 patients per arm would be required. The GeneSight directed arm and the standard care arm included 26 and 25 patients, respectively, in this pilot study for a larger trial.

Table 2: Summary Characteristics of RCTs Assessing GeneSight Test

Study	Country	Sites	Dates	Participants	Intervention Active	Comparator
Greden et al (2019)[19] (GUIDED)	U.S.	60	2014-2017	Patients with MDD based on QIDS ≥11; failure of at least 1 medication	Treatment guided by GeneSight (n=681)* *Per protocol 1398 of 1799 randomized	SOC (n=717)* *Per protocol cohort is 1398 of 1799 randomized
Winner et al (2013)[18]	U.S.	1	NR	Patients with major depressive disorder, HAM-D17 >14 (moderate)	Treatment guided by GeneSight (n=26)	SOC (n=25)

HAM-D17: Hamilton Depression Rating Scale 17 item; NR: not reported; QIDS: Quick Inventory of Depressive Symptomatology; RCT: randomized controlled trial; SOC: standard of care

Table 3: Summary of Results of RCTs Assessing GeneSight

Study	N	Outcomes		
			Response ≥50% decrease in HAM-D17	Remission: HAM-D17 ≤7
Greden et al (2019)[19]		8 weeks	p	p

Study	N	Outcomes			
		Response ≥50% decrease in HAM-D17		Remission: HAM-D17 ≤7	
GeneSight	560	26.0%		15.3%	
Standard Care	607	19.9%	.01	10.1%	.007
Winner et al (2013)[18]		10 weeks			
GeneSight	26	36%		20%	
Standard Care	25	20.8%		8.3%	
		OR 2.14 (95% CI 0.59-7.79)		OR 2.75 (95% CI 0.48-15.8)	

HAM-D17: Hamilton Depression Rating Scale 17 item; OR: odds ratio

Table 4: Study Relevance Limitations: GeneSight

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Greden et al (2019)[19]	[1]Patients with mild depression excluded from per protocol analysis				[1]24-week follow-up was treatment arm only
Winner et al (2013)[18]	[2]MDD diagnostic criteria. Prior medication response not described				[1]Follow-up limited to 10 weeks

MDD: major depressive disorder
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 5: Study Design and Conduct Limitations: GeneSight

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Greden et al (2019)[19]	[4]Of 1799 patients randomized, 258 (14%) were excluded from the intent to treat cohort			[1,2]8 week response and remission results reported only for per protocol cohort No explanation for missing per protocol patients (15% of SOC group; 11% of test group)	[1]No description of power and sample size calculations	
Winner et al (2013)[18]						[4] Underpowered. 92N per arm required to detect remission or response

SOC: standard of care
The study limitations stated in this table are those notable in the current review; this is not a comprehensive

gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3.Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent-to-treat analysis (per protocol for non inferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

It is notable that the trial "A Three-arm, Parallel Group, Multicentre, Double-blind, Randomized Controlled Trial Evaluating the Impact of GeneSight Psychotropic and Enhanced-GeneSight Psychotropic, on Response to Psychotropic Treatment in Outpatients Suffering From a Major Depressive Disorder (MDD) and Having Had - Within the Current Episode - an Inadequate Response to at Least One Psychotropic Medication Included in GeneSight Psychotropic" (NCT02466477) has been reported as completed as of September 2019 with 542 participants. Results of this RCT have not been published.

Section Summary: GeneSight test
Evidence for the use of GeneSight test to inform antidepressant selection includes 2 published RCTs and an unpublished RCT. None of the trials provided adequate evidence. Greden et al 2019 reported potential supportive evidence on a relevant population. Both published studies have major limitations in design and conduct and in consistency and precision. The unpublished study raises further concerns about reporting and publication bias. The evidence is insufficient to permit conclusions on the health outcome – effects of managing antidepressant therapy with the GeneSight test.

NeuroIDgenetix test
Randomized Controlled Trials
Two RCTs reported results of antidepressant therapy selection, informed by NeuroIDgenetix test results compared to SOC—antidepressant therapy selected without gene test results.

Bradley et al (2018) conducted a double-blinded RCT in which 685 patients with depression and/or anxiety disorders were randomized to treatment guided by either NeuroIDgenetix or SOC (Table 6).[24,] Outcomes included HAM-D, the Hamilton Rating Scale for Anxiety (HAM-A), and adverse drug events. Trained and blinded clinicians conducted interviews using the HAM-D and HAM-A. Approximately 15% of randomized patients were lost to follow up over the 12 week period. Response results were only reported for 261 moderate and severe group of patients and remission results were reported for 93 severe group of patients. Response rates (p<.001; OR: 4.72 [1.93-11.52]) and remission rates (p<.02; OR: 3.54 [1.27-9.88]) were significantly higher in the NeuroIDgenetix-guided group as compared to the control group at 12 weeks. The frequency of adverse drug events did not differ statistically between groups. Study does not report clearly if the analysis was based on intention to treat population. Reporting is incomplete and suggestive of selective reporting.

Olson et al (2017) conducted an RCT in which patients with neuropsychiatric disorders were randomized to treatment guided by NeuroIDgenetix or SOC (see Table 6).[25,] A majority of the patients, 56% in the intervention group and 64% in the control group had a primary diagnosis of depression. Subgroup analyses by neuropsychiatric disorder were not conducted. Outcomes included Neuropsychiatric Questionnaire, Symbol Digit Coding test, and adverse drug events. The Neuropsychiatric Questionnaire is a computerized survey addressing symptoms of neuropsychoses, and the SCD assesses attention and processing speed, which is sensitive to

medication effects. The study did not report on response or remission of depression. There were no significant differences in Neuropsychiatric Questionnaire or Symbol Digit Coding scores between groups (see Table 7). However, the patients receiving SOC reported significantly more adverse events (53%) than patients receiving NeurolDgenetix-guided care (28%). The comparison of adverse drug events did not report the number of patients included in the analysis. ClinicalTrials.gov lists neurocognitive measures as co-primary outcomes, but these are not reported, suggestive of selective reporting.

Table 6: Summary Characteristics of RCTs Assessing NeurolDgenetix

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
Bradley et al (2019)[24]	U.S.	20 Psychiatry and primary care settings	2016	Patients with depression and/or anxiety disorders using either HAM-D17 or HAM-A score ≥18 (moderate and severe) were included in efficacy analysis; either new to medication or inadequately controlled with medication	Treatment guided by NeurolDgenetix (n=352)	SOC (n=333)
Olson et al (2017)[25]	U.S.	6	2015	Patients with ADHD, anxiety, depression, or psychosis; currently receiving antidepressants	Treatment guided by NeurolDgenetix (n=178)	SOC (n=25)

ADHD: attention deficit hyperactivity disorder; HAM-A: Hamilton Anxiety Rating Scale; HAM-D17: Hamilton Depression Rating Scale 17 item; SOC: standard of care

Table 7: Summary of Results of RCTs Assessing NeurolDgenetix

Study	N	Outcome			
		Response ≥50% decrease in HAM-D17		Remission: HAM-D17 ≤7	
Bradley et al (2019)[24]		12 weeks	p	12 weeks	p
NeurolDgenetix	140 (moderate/severe)	64%		NR	
Standard Care	121 (moderate/severe)	46%	.01	NR	
NeurolDgenetix	40 (severe)			35%	
Standard Care	53 (severe)			13%	.02
		≤1 Adverse Drug Event		≥2 Adverse Drug Events	
Olson et al (2017)[25]		10 weeks			
NeurolDgenetix	NR	28%		5%	
Standard Care	NR	53%	.001	24%	.001

HAM-D17: Hamilton Depression Rating Scale 17 item; NR; not reported

Table 8: Study Relevance Limitations: NeurolDgenetix

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Bradley et al (2019)[24]					
Olson et al (2017)[25]	[2] No description of criteria used to determine mental health condition diagnosis. [4] Majority of patients with depression (57%); remaining with ADHD, anxiety, or psychosis			[1] Adverse drug events. Did not report response or remission	

ADHD: attention deficit hyperactivity disorder
The study limitations stated in this table are those notable in the current review; this is not a comprehensive

gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 9: Study Design and Conduct Limitations: NeuroIDgenetix

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Bradley et al (2019)[24,]			[2] In the clinicaltrials.gov listing, reduction of adverse drug events was listed as the primary outcome, but was not reported as primary outcome Remission not reported for moderate/sever, only severe	[1] Approximately 15% of randomized patients were lost to follow-up over the 12 week trial. Analysis does not appear to be intent to treat.	[1]No description of power and sample size calculations	
Olson et al (2017)[25,]	[1] Randomization procedure not described		[2] In the clinicaltrials.gov listing, change in Neuropsychiatric Questionnaire and Symbol Digit Coding at 4 months were listed as coprimary outcomes. Four month results not reported	[1] In the 3-month analyses, it appears that more than 30% of randomized patients were not included. [6] Unclear if analysis was intention-to-treat	[1] No description of power and sample size calculations	[1] Comparative statistics not reported for clinical or neurocognitive outcomes

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3.Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent-to-treat analysis (per protocol for non inferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: NeuroIDgenetix Test
Evidence for the use of NeuroIDgenetix test to inform antidepressant selection includes 2 RCTs, one reporting response and remission as outcomes and another reporting adverse events as outcome. None of the trials provided adequate or supportive evidence in terms of relevance, design and conduct or consistency and precision. Both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to permit conclusions on the health outcome – effects of managing antidepressant therapy with the NeuroIDgenetix test.

Neuropharmagen Test
Systematic Review and Meta-analysis
Vilches et al (2019) conducted a meta-analysis with the aim to assess the clinical utility of Neuropharmagen in the treatment management of depressive patients.[26.] The study included 2 RCTs and a multicenter, retrospective, observational study.[27.28.29.] Evidence from both RCTs are discussed below.

Randomized Controlled Trials
Han et al (2018) conducted a randomized, single-blind clinical trial among patients with MDD to evaluate the effectiveness of Neuropharmagen test guided antidepressant treatment (n=52) compared to receiving antidepressants through standard physician assessment (n=48) (Table 10).[27.] Neuropharmagen analyzes 30 genes associated with drug metabolism and 59 medications used to treat MDD. Primary endpoint was change in HAM-D17 score from baseline to 8 weeks follow-up. Response rate (at least 50% reduction in HAM-D17 score from baseline), remission rate (HAM-D17 score ≤7 at the end of treatment) as well as the change of total score of Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER) from baseline to end of treatment were also investigated (Table 4). The intention-to-treat (ITT) population consisted of all patients who had at least 1 post-treatment assessment for effectiveness during the study. The effectiveness evaluation was based on the analyses with ITT on last observation carried forward (LOCF). The mean change of HAM-D17 score was significantly different between 2 groups favoring guided arm by −4.1 point of difference (p=.010) at the end of treatment. The response rate (71.7 % vs. 43.6%, p=.014) were also significantly higher in the guided arm than in standard care arm at the end of treatment, while the remission rate was numerically higher in the guided arm than in standard care arm without statistical difference (45.5% vs. 25.6%, p=.071). The study reported early dropout of 25% in guided-care and 38% in standard care arm. The reason for early dropout associated with adverse events was higher in standard care arm (n=9, 50.0%) than in guided care arm (n=4, 30.8%). The effectiveness evaluation was based on the analyses with ITT on LOCF. Use of LOCF assumes data are missing completely at random (MCAR).[30.] The distribution of reasons for termination among early dropouts indicates that the assumption of MCAR is unlikely to hold in this analysis. Study did not report registration in any clinical trial database.

Perez et al (2017) conducted a single-blind RCT (AB-GEN trial) of patients diagnosed with MDD randomized to genotype-guided treatment (Neuropharmagen) or treatment as usual (see Table 10).[28.] The pharmacogenetics report from Neuropharmagen provided information on 50 drugs, highlighting gene-drug interactions and drug recommendations from the U.S. Food and Drug Administration and Clinical Pharmacogenetics Implementation Consortium. The primary outcome was Patient Global Impression of Improvement (PGI-I), which was collected by telephone interviewers blinded to treatment allocation group. A response was defined as a PGI-I of 2 or less. Percent responders differed nominally between groups (p=.05) at the end of the 12-week study (see Table 11). Changes in HAM-D17 scores were significant at 5 weeks (p=.04) but not at 12 weeks (p=.08). Response and remission rates were calculated post-hoc based on the HAM-D17 (single-blinded). There was no significant difference in response (45.4% vs. 40.3%, p=.39) or remission (34.0% vs. 33.1%, p=.87) between guided care and standard care arms at 12 weeks. However, response and remission data were missing for 9% patients in the guided care group and 14% of the standard care group.

Table 10: Summary Characteristics of RCTs Assessing Neuropharmagen

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
Han et al (2018)[27.]	Korea	2	NR	Patients with MDD using DSM-5 criteria; currently receiving antidepressant therapy at least 6 weeks with an inadequate response (CGI-I >3)	Treatment guided by Neuropharmagen (n=52)	SOC (n=48)
Perez et al (2017)[28.]	Spain	18	2014-2015	Patients with MDD using DSM-IV-TR criteria; either new to medication or inadequately controlled with medication	Treatment guided by Neuropharmagen (n=155)	SOC (n=161)

CGI-I: Clinical Global Impression-Improvement; DSM: Diagnostic and Statistical Manual of Mental Disorders; MDD: major depressive disorder; NR: not reported; SOC: standard of care

Table 11: Summary of Results of RCTs Assessing Neuropharmagen

Study	N	Outcomes			
		Response ≥50% decrease in HAM-D17		Remission: HAM-D17 ≤7	
Han et al (2018)[27.]		8 weeks	p		p
Neuropharmagen	52	71.7%		45.5%	
Standard Care	48	43.6%	.01	25.6%	.07
Perez et al (2017)[28.]		12 weeks		12 weeks	
Neuropharmagen	141	45.4%		34.0%	
Standard Care	139	40.3%	0.39	33.1%	0.87
		OR 1.23 (95% CI 0.77 – 1.98)		OR 1.04 (95% CI 0.64 – 1.71)	

HAM-D17: Hamilton Depression Rating Scale 17 item; OR: odds ratio

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Han et al (2018)[27.]					
Perez et al (2017)[28.]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 13: Study Design and Conduct Limitations: Neuropharmagen

Study	Allocations[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Han et al (2018)[27.]		[3]Subjects were blinded, but unknown if outcome assessors were blinded	[1] Not registered	[1] High loss to follow-up or missing data [2] Inadequate handling of missing data. LOCF may not be the most appropriate approach		

Study	Allocations[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Perez et al (2017)[28.]		[3] Subjects were blinded, outcome (HAM-D17) assessed by treating physicians		Response and remission data were missing for 9% patients in the guided care group and 14% of the standard care group.		

HAM-D17: Hamilton Depression Rating Scale 17 item; LOCF: last observation carried forward
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3.Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent-to-treat analysis (per protocol for non inferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: Neuropharmagen Test
Evidence for the use of Neuropharmagen test to inform antidepressant selection for patients with MDD includes 2 RCTs. Han et al (2018) provided adequate evidence for 'Response' on a relevant population. Both studies have major limitations in design and conduct and inconsistency and precision. The evidence is insufficient to permit conclusions on the health outcome – effects of managing antidepressant therapy with the Neuropharmagen test.

Genetic Testing to Inform Medication Selection for Patients with a Mental Illness other than Depression

Clinical Context and Test Purpose
The purpose of pharmacogenetic testing in patients diagnosed with a mental illness other than depression is to inform management decisions such as starting a particular drug, determining or adjusting a dose, or changing drugs when therapy fails.

The question addressed in this evidence review is: Does psychopharmacologic management aided by genetic testing improve the net health outcome compared with management guided by clinical symptoms alone in patients with a mental illness other than depression?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with a mental illness other than depression.

Interventions
Interventions of interest include testing for genes (single or as part of a panel) associated with medication pharmacokinetics and/or pharmacodynamics.

Comparators
Currently, decisions about medication management for patients with mental illnesses are based on clinical response, potentially informed by studies such as the Sequenced Treatment Alternatives to Relieve Depression study, which evaluated specific medication sequences.

Outcomes
This evidence review assesses whether genetic testing for the 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 outcome of interest is change in disease outcomes resulting from a more appropriate selection of specific drugs or doses for the patient's condition. Also, avoidance of adverse events is an important outcome.

Study Selection Criteria
Assessment of clinical utility of a genomic test cannot be made by a chain of evidence from clinical validity data alone. 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, RCTs are needed.

- We sought RCTs that reported the outcomes of pharmacogenetic testing to diagnose, assess the risk of developing, or to manage a mental health condition.
- We sought evidence on outcomes, with emphasis on efficacy outcomes, as the main purpose of genetic testing in mental health conditions to achieve clinically meaningful improvement compared with SOC.
- We also included studies that reported only on adverse events, although for medications where adverse events tend to be mild, efficacy outcomes are of greater importance.

Systematic Review
Hartwell et al (2020) conducted a systematic review and meta-analysis of the 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. The meta-analysis included 7 RCTs (659 subjects randomly assigned to receive naltrexone and 597 received placebo).[31] Of the 5 alcohol consumption outcomes considered, there was a nominally significant moderating effect of the Asn40Asp SNP only on drinks per day (d=−0.18, 95% CI=−0.32 to −0.03, p=.02). However, the effect was not significant when multiple comparisons were taken into account. There was no statistically significant heterogeneity (I^2=33.8%, p=.18).

Randomized Controlled Trials
Bradley et al (2018) conducted a double-blinded RCT in which 685 patients with depression and/or anxiety disorders were randomized to treatment guided by either NeuroIDgenetix or SOC (Table 14).[24] Among the participants, 115 in the experimental arm and 120 in the SOC arm had only anxiety. Outcomes included percent reduction in HAM-A and response (50% reduction in HAM-A) rate. Trained and blinded clinicians conducted interviews using the HAM-A. Response results were only reported for 224 moderate and severe anxiety (Anxiety Only HAM-A ≥18) group of patients (109 in the experimental arm and 115 in the SOC arm). 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. Response rate was significantly higher in the NeuroIDgenetix-guided group as compared to the control group at 12 weeks (63% vs. 50%, p=.04). Study does not report clearly if the analysis was based on ITT population. Reporting is incomplete and suggestive of selective reporting.

Table 14: Summary Characteristics of RCTs Assessing NeuroIDgenetix

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
Bradley et al (2019)[24.]	U.S.	20 Psychiatry and primary care settings	2016	Patients with depression and/or anxiety disorders using either HAM D-17 or HAM-A score ≥18 (moderate and severe) were included in efficacy analysis. Either new to medication or inadequately controlled with medication	Treatment guided by NeuroIDgenetix (n=352)	SOC (n=333)

HAM-A: Hamilton Anxiety Rating Scale; HAM-D17: Hamilton Depression Rating Scale 17 item; SOC: standard of care

Table 15: Summary of Results of RCTs Assessing NeuroIDgenetix

Study	N	Outcomes			
		Response ≥50% decrease in HAM-A 17		Remission: HAM-A17 ≤7	
Bradley et al (2019)[24.]		12 weeks	p	12 weeks	p
NeuroIDgenetix	82 (moderate/severe)	63%		NR	
Standard Care	95 (moderate/severe)	50%	.04	NR	

HAM-A: Hamilton Anxiety Rating Scale; NR: not reported

Table 16: Study Relevance Limitations: NeuroIDgenetix

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Bradley et al (2019)[24.]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 17: Study Design and Conduct Limitations: NeuroIDgenetix

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Bradley et al (2019)[24.]			[2] In the clinicaltrials.gov listing, reduction of adverse drug events was listed as the primary outcome, but was	[1] Approximately 25% of randomized patients were lost to follow-up or were not included in the	[1] No description of power and sample size calculations	

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
			not reported as primary outcome Also, anxiety remission was listed as a secondary outcome but was not reported.	outcome analysis at 12 weeks. Analysis does not appear to be intent to treat.		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3.Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent-to-treat analysis (per protocol for non inferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Kampangkaew et al (2019) conducted a study among cocaine and opioid codependent patients randomized into disulfiram (n=32) and placebo (n=35) groups for 12 weeks of treatment and evaluated the role of SLC6A3 (DAT1) 40 bp 3′-untranslated region variable number tandem repeat variant in moderating disulfiram efficacy for cocaine dependence.[32] Study reported better treatment outcomes with disulfiram pharmacotherapy of cocaine dependence among patients with genetically higher dopamine transporter (DAT) levels compared to those with lower DAT levels.

Naumova el al (2019) conducted a randomized pharmacodynamic investigation to evaluate the effect of DRD4 exon 3 polymorphism on child behaviors in response to treatment of attention deficit hyperactivity disorder (ADHD) with methylphenidate.[33] In this 2-week prospective within-subject, placebo-controlled, crossover trial there was significant interaction between DRD4 genotype and treatment when the child's behavior was evaluated by the parents (p=.035, effect size of 0.014), driven by a better treatment response in children homozygous for long 7-repeat allele.

Section Summary: Genetic Testing to Inform Medication Selection for Patients with a Mental Illness other than Depression Inadequately Controlled with Medication
Evidence for the use of pharmacogenetic testing in patients with mental health conditions other than depression includes a meta-analysis on alcohol use disorder and an RCT on anxiety disorder. The meta-analysis found no significant effect of Asn40Asp on the response to naltrexone treatment of heavy drinking or alcohol use. The single available trial did not provide adequate or supportive evidence effect of pharmacogenetic testing on managing moderate to severe anxiety. The study had major limitations in design and conduct and precision. The evidence is insufficient to permit conclusions on the health outcome – effects of managing mental health conditions other than depression using pharmacogenetic testing.

No other studies performed a direct intervention study. Jukic et al (2019) conducted a retrospective cohort study using patient data from a routine therapeutic drug monitoring database and showed that CYP2D6 genetic variability had significant effect on risperidone and aripiprazole exposure and treatment and lower doses should be administered to CYP2D6 poor metabolizers to avoid overdosing and dose-dependent side-effects.[34]

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 that the technology results in an improvement in the net health outcome.

For adult patients with MDD who receive GeneSight 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 GeneSight test results to SOC—antidepressant therapy selected without GeneSight test results. The Genomics Used to Improve DEpression Decisions (GUIDED) trial by Greden et al (2019) reported statistically significant improvement in response (26% of 560 vs. 20% of 607, p=.01) and remission (15% of 560 vs. 10% of 607, p=.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 pilot study by Winner et al (2013), depression outcomes did not differ significantly between guided care and SOC groups at the 10-week follow-up and the study was underpowered to detect significant differences in outcomes between study arms. None of these trials provided adequate evidence. Both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult patients 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 among moderate and severe group of patients (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 among severe group of patients only (p=.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 were not reported as the primary outcome. It was unclear if the analysis was based on ITT 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 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 patients 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 SOC—antidepressant therapy selected without Neuropharmagen test results. The single-blinded RCT by Han et al (2018) reported statistically significant improvement in response (72% of 52 vs. 44% of 48, p=.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 standard care arm and used 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=.39) and remission (34% of 141 vs. 33% of 139, p=.87) in the Neuropharmagen arm compared to SOC at 12 weeks among patients with MDD. Response and remission data were missing for 9% of 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 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 patients 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 moderate and severe group of patients (p=.04). There was evidence suggesting selective reporting, as anxiety remission was not reported and, contrary to the listing in clinicaltrials.gov, adverse drug events were not reported as the primary outcome. It was unclear if the analysis was based on ITT 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 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.[35] 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.[36] 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.[37] Dosing recommendations for tricyclic antidepressants were provided, based on patient classifications of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers (Tables 18 and 19).

Table 18. Dosing Recommendations for Antidepressants Based on *CYP2D6* and *CYP2C19* Phenotype[37]

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	Avoid tertiary amines due to potential sub-optimal	optional	optional

Recommendations for Tricyclic Antidepressants				
	tertiary amines to secondary amines may affect efficacy and side effects	response. Consider secondary 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.
TCA: tricyclic antidepressants.

Table 19. 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.

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.[38] 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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 20.

Table 20. Summary of Key Trials

NCT Number	Title	Enrollment	Completion Date
Ongoing			
NCT04207385	Accurate Clinical Study of Medication in Patients With Depression Via Pharmacogenomics (PGx) and Therapeutic Drug Monitoring (TDM) of Venlafaxine	160	Nov 2021
NCT03952494	Individualizing Antidepressant Treatment Using Pharmacogenomics and EHR-driven Clinical Decision Support	500	Mar 2023
NCT03749629	Comparative Effectiveness of Pharmacogenomics for Treatment of Depression (CEPIO-D)	400	Feb 2022
NCT03674138	Pharmacogenomic-Guided Antidepressant Drug Prescribing in Cancer Patients	99	Oct 2022
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
Unpublished			
NCT02466477[a]	A Three-arm, Parallel Group, Multicentre, Double-blind, Randomized Controlled Trial Evaluating the Impact of GeneSight Psychotropic and Enhanced-GeneSight Psychotropic, on Response to Psychotropic Treatment in Outpatients Suffering From a Major Depressive Disorder (MDD) and Having Had - Within the Current Episode - an Inadequate Response to at Least One Psychotropic Medication Included in GeneSight Psychotropic	542	Sep 2019
NCT03591224[a]	Pharmacogenomic Testing to Optimize Antidepressant Drug Therapy	213	Dec 2019
NCT02573168[a]	A Three-arm, Parallel Group, Multicentre, 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	103	Sep 2020
NCT03228953	Impact of Comprehensive Pharmacogenomic Testing on the Treatment of Major Depressive Disorder	206	May 2021 (status unknown)

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

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
	0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7)
	0032U	COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant
	0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (e.g., citalopram metabolism) gene analysis, common variants (i.e., HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])
	0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, common and select rare variants (i.e., *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
	0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
	0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene)
	0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)

Type	Code	Description
	0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans)
	0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5' gene duplication/multiplication)
	0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 3' gene duplication/ multiplication)
	0156U	Copy number (e.g., intellectual disability, dysmorphology), sequence analysis
	0173U	Psychiatry (i.e., depression anxiety) genomic analysis panel includes variant analysis of 14 genes
	0175U	Psychiatry (e.g., depression anxiety); genomic analysis panel variant analysis of 15 genes
	0291U	Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score ***(Code effective 1/1/2022)***
	0292U	Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score ***(Code effective 1/1/2022)***
	0293U	Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score ***(Code effective 1/1/2022)***
	81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
	81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
	81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22)
	81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7)
	81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/01/2016	BCBSA Medical Policy Adoption
08/01/2016	Policy revision without position change
08/01/2017	Policy revision without position change
05/01/2018	Coding update
11/01/2018	Policy title change from Genetic Testing for Mental Health Conditions Policy revision without position change

Effective Date	Action
08/01/2019	Policy revision without position change
03/01/2020	Coding Update.
08/01/2020	Annual review. Policy Guidelines updated. Coding update
09/01/2020	No change to policy statement. Literature review updated.
09/01/2021	Annual review. No change to policy statement. Literature review updated.
03/01/2022	Coding Update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. 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 covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Genetic Testing for Diagnosis and Management of Mental Health Conditions 2.04.110 **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*: o Selective serotonin reuptake inhibitors o Selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors o Tricyclic antidepressants o Antipsychotic drugs Genetic testing panels for mental health disorders are considered **investigational** for **all** indications, including but not limited to the following: • Genecept Assay • GeneSight Psychotropic panel • Mental Health DNA Insight panel • Proove Opioid Risk assay • STA²R test	**Genetic Testing for Diagnosis and Management of Mental Health Conditions 2.04.110** **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: I. To confirm a diagnosis of a mental health disorder in an individual with symptoms II. To predict future risk of a mental health disorder in an asymptomatic individual III. To inform the selection or dose of medications used to treat mental health disorders, including but not limited to the following medications*: A. Selective serotonin reuptake inhibitors B. Selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors C. Tricyclic antidepressants D. Antipsychotic drugs Genetic testing panels for mental health disorders are considered **investigational** for **all** indications, including but not limited to the following: I. Genecept Assay II. GeneSight Psychotropic panel III. Mental Health DNA Insight panel IV. Proove Opioid Risk assay V. STA²R test