Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the Blue Cross Blue Shield Association

Title: Genetic Testing for Diagnosis and Management of Mental Health Conditions

Related Policies:	▪ *Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders* ▪ *Cytochrome P450 Genotype-Guided Treatment Strategy* ▪ *Vagus Nerve Stimulation* ▪ *Deep Brain Stimulation*

Professional / Institutional
Original Effective Date: April 11, 2024
Latest Review Date: September 8, 2026
Current Effective Date: September 8, 2026

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are evaluated for diagnosis or risk of a mental illness	Interventions of interest are: • Genetic testing for risk of a mental illness	Comparators of interest are: • Standard of care	Relevant outcomes include: • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Populations	Interventions	Comparators	Outcomes
			• Treatment-related morbidity
Individuals: • Adults with major depressive disorder	Interventions of interest are: • GeneSight® testing guided drug treatment	Comparators of interest are: • Standard of care drug treatment	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • Adults with major depressive disorder	Interventions of interest are: • NeuroIDgenetix® testing guided drug treatment	Comparators of interest are: • Standard of care drug treatment	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • Adults with major depressive disorder	Interventions of interest are: • Neuropharmagen® testing guided drug treatment	Comparators of interest are: • Standard of care drug treatment	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With a mental health condition other than depression who are undergoing drug treatment	Interventions of interest are: • Genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics	Comparators of interest are: • Standard of care drug treatment	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

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.

OBJECTIVE

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

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 individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The primary goal of pharmacogenomic 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.

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-

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

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:

- OptimalRx Plus® (Dynacare plus; formerly known as Genecept® Assay);
- GeneSight® Psychotropic panel (Myriad genetics® formerly Assurex Health);
- Neuropharmagen (Precision Genetics).

Also, many labs offer genetic testing for individual genes, including *MTFHR* (GeneSight Rx and other laboratories), cytochrome P450 variants, and *SULT4A1.*

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

POLICY

A. Genetic testing for diagnosis and management of mental health disorders is considered **experimental / investigational** in all situations, including but not limited to the following:
   1. To confirm a diagnosis of a mental health disorder in an individual with symptoms.
   2. To predict future risk of a mental health disorder in an asymptomatic individual.
   3. 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.

B. Genetic testing panels for mental health disorders, including but not limited to the OptimalRx Plus (formerly the Genecept Assay), the GeneSight Psychotropic panel, and Neuropharmagen, are considered **experimental / investigational** for all indications.

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.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through May 26, 2026.

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. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

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

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

Comparators
The following practices are currently being used to make decisions about management of mental illness: diagnosis and risk assessment without genetic testing.

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

Outcomes
The general outcomes of interest are change in disease state, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

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 individuals 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

Randomized Controlled Trials
We did not find any RCT evaluating the use of genetic test results to inform decisions on mental health diagnoses or management of patients at 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 at risk for mental health conditions.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

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 at 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

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.

Populations
The relevant population of interest is adult individuals who have a diagnosis of major depressive disorder (MDD).

MDD is defined by the presence of 5 or more of the symptoms below during the same 2-week period. 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.[9,] 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 include: selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and atypical agents.

Individuals who fail to achieve remission of MDD after 2 vigorous trials of antidepressant 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.[10,] Individuals may stop treatment due to side effects of antidepressants, which can include drowsiness; insomnia/agitation; orthostatic hypotension; QTc prolongation; gastrointestinal toxicity; weight gain; and sexual dysfunction.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Interventions
The interventions being considered are commercially available pharmacogenetic tests to inform medication selection.

Two commercially available pharmacogenetic tests for antidepressant selection are reviewed here: GeneSight 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, 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 following practices are currently being used to make decisions about antidepressant drug selection: antidepressant selection without pharmacogenetic testing.

At present, there is no definitive algorithm for selecting next line treatment after failure to respond to initial treatment.

Outcomes
The general outcomes of interest are symptoms, change in disease state, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

There are standardized outcome measures for depression (eg, Hamilton Rating Scale for Depression [HAM-D], Montgomery-Asberg Depression Rating Scale [MADRS], Patient Health Questionnaire 9 item [PHQ-9], and Beck's Depression Inventory [BDI]). Scoring for the HAM-D, MADRS, and PHQ-9 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 the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for MDD and weak item-level inter-rarer reliability.[12,] Nonetheless, 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.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

The PHQ-9 is a self-administered scale used to assess depression based on the 9 criteria for depression outlined in the DSM-IV. It rates symptoms on a scale from "0" (not at all) to "3" (nearly every day) over a 2-week period.[14,] The criteria include: little interest in doing things, feeling down or depressed, difficulty with sleep, low energy levels, poor appetite or overeating, poor self-perception, difficulty concentrating, high or low speed of functioning, and thoughts of suicidality or self-harm. Cut-offs at scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression. The PHQ-9 has been extensively validated for accuracy in over 30 clinical studies.[15,]

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. The17-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.
Patient Health Questionnaire	Patient scored. Rates the presence and intensity of symptoms on 9 criteria for depression.	0 to 4 (no or minimal depression); 5 to 9 (mild depression); 10 to 14 (moderate depression); 15 to 19 (moderately severe depression); 20 to 27 (severe depression)	Remission is considered a score of less than 5. Response is 50% reduction from baseline.

Secondary endpoints are:

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

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

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

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.[16,] 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."[17,] 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.[18,] No minimally important clinical difference has been set for assessing change in SDS score.[13,]

Typically, short term response for established classes of antidepressants is assessed in studies of 6 to 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
GeneSight evaluates 14 genes in relation to more than 60 psychotropic medications and the potential for gene-drug interactions. Based on results from the genotype test, the medications are categorized as "Use as directed"; "Moderate gene-drug interaction"; "Significant gene-drug interaction" for a particular individual.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Systematic Reviews and Meta-Analyses

Albers et al (2025) published a meta-analysis of 6 studies (N=3532) comparing pharmacogenetic guided therapy (GeneSight) to unguided care in patients with MDD.[19,] A total of 4 studies (all summarized below) were RCTs and 2 studies were open-label. The primary outcome was measured at 8 weeks in most studies, although 1 study measured the primary endpoint at 10 weeks and another at 24 weeks. HAM-D17 was the outcome measure in all studies except Oslin et al (2022) which used PHQ-9. Patients with MDD whose care was guided by the pharmacogenetic test were 30% more likely to achieve response (risk ratio (RR), 1.30; 95% CI, 1.16 to 1.47; p<.001) and 41% more likely to achieve remission (RR, 1.41; 95% CI, 1.19 to 1.66; p<.001) compared to unguided care. The authors for no heterogeneity for response or remission. Results remained similar when the largest RCT (Oslin et al) was excluded due to its different study design (patients unblind and use of PHQ-9 as the primary endpoint) and when the 2 open-label trials were excluded.

Milosavljevic et al (2024) conducted a meta-analysis of 15 RCTs to evaluate the impact of pharmacogenomic guided therapy on antidepressant efficacy and tolerability in patients with MDD compared with treatment as usual.[20,] Trials were included if they measured MDD symptom severity using validated clinical scales and compared pharmacogenomic guided therapy to treatment as usual. Outcomes were assessed at 8 weeks of follow-up. Most trials involved adult participants, were predominantly female, and used commercial pharmacogenomic tools like GeneSight (n=5), Neuropharmagen (n=2), or Genecept (n=1). The authors reported a statistically significant improvement in antidepressant efficacy with pharmacogenomic-guided therapy, with patients experiencing a mean symptom reduction of 31.0% compared to 26.8% in treatment as usual (mean difference [MD], 3.4%; 95% CI, 1.6 to 5.2%), although the magnitude of effect was small. HAM-D score improvement was 0.75 points greater in the pharmacogenomic tested arm (95% CI, 0.30 to 1.21). Pharmacogenomic guidance yielded an 18% higher response rate (RR, 1.18; 95% CI, 1.05 to 1.33) and a 37% higher remission rate (RR, 1.37; 95% CI, 1.15 to 1.63). No significant differences were observed in discontinuation rates or side effect frequency scores. In a subgroup analysis of trials assessed as low risk of bias by the authors, these benefits lost statistical significance. Sensitivity analyses also revealed potential publication bias and inconsistency in some outcome reporting. While the effect on HAM-D reduction was statistically significant, it failed to reach a threshold for clinical significance (≥3 points), and the number needed to treat (NNT) for remission and response was 21, exceeding previously established thresholds for clinical meaningfulness (NNT ≤10).

Brown et al (2022) conducted a comprehensive meta-analysis that synthesized the findings of prospective RCTs and open-label trials investigating the efficacy of pharmacogenomic guided testing in achieving remission of depressive symptoms.[11,] The meta-analysis revealed a favorable rate of remission among individuals who received therapy guided by pharmacogenomics compared to those receiving SOC treatment for depression. The analysis included a total of 13 trials, consisting of 10 RCTs and 3 open-label studies published through July 2022. Six of these included studies utilized the GeneSight test for guiding pharmacogenomic therapy. The analysis encompassed a sample of 4767 individuals across these 13 trials, with individual study sample sizes ranging from 44 to 1944 participants. With the exception of 2 trials, all studies exclusively enrolled individuals diagnosed with MDD. The majority of trials (69%) measured their primary endpoint at 8 weeks after baseline, although the range extended to 24 weeks. Remission was primarily assessed using the HAM-D17, while alternative rating scales were used in 2 trials. Notably, all studies included pharmacogenomic assessments of the cytochrome P450 (CYP)-

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

C19 and *CYP2D6* genes, although other genes tested varied across studies. The pooled RR for remission, comparing pharmacogenomic guided therapy (n=2395) to unguided therapy (n=2372), was 1.41 (95% CI, 1.15 to 1.74), favoring guided therapy. The authors observed moderate to substantial heterogeneity between the studies (I^2=62%). Stratifying the analysis to only include RCTs (n=10) yielded a similar effect size for remission rates (RR, 1.45; 95% CI, 1.13 to 1.88), which remained statistically significant. However, when limiting the analysis to the open-label trials (n=3), the effect size was no longer statistically significant (RR, 1.26; 95% CI, 0.84 to 1.88). The authors also found that the number of prior antidepressant therapies and severity of depression symptoms had moderating effects on the RR for pharmacogenomic guided therapy, suggesting that as the severity and number of treatments increased, the RR for guided therapy also increased. No moderating effects were observed for age, sex, ancestry, or weeks to the primary endpoint. A subgroup analysis omitted the 6 GeneSight studies and found that the pooled RR for remission remained significant across the remaining trials (RR, 1.46; 95% CI, 1.02 to 2.09; p=.04). To evaluate the risk of bias in the included studies, the authors employed the Cochrane Risk of Bias Tools, specifically Cochrane Risk of Bias version 2 for RCTs and Risk Of Bias In Non-randomized Studies of Interventions for open-label controlled studies. The majority of trials (n=10) were sponsored by industry, and 77% of them had published protocols prior to the commencement of the study. Among the 10 included RCTs, low risk of bias was observed for attrition and selection, while high risk of bias was identified for performance. Blinding procedures varied across the studies, with participants being blinded in all RCTs, but treating physicians and, in 2 cases, outcome assessors were not blinded. One RCT was found to have a high risk of reporting bias due to selectively reporting outcomes for a subset of patients. Regarding the 3 open-label studies, low risk of bias was observed for pre-intervention selection, at-intervention information, and post-intervention confounding. However, the authors reported that post-intervention information and industry biases were high in 2 trials. Additionally, 1 trial exhibited a moderate risk of reporting bias, and 2 studies demonstrated post-intervention selection bias. Assessment of publication bias using funnel plot asymmetry and Egger's regression indicated no indication of publication bias. Although the authors found an increased likelihood of remission among individuals with depression who received pharmacogenomic guided therapy, the heterogeneity in study methodology, such as the variations in the genetic variants tested, poses challenges in making recommendations for a specific testing strategy.

Randomized Controlled Trials

Four RCTs compared response and remission with antidepressant therapy informed by GeneSight test results to antidepressant therapy selected without gene test results (ie, SOC)(Table 2).[21,22,23,24,] Due to limitations in these trials, discussed below, no conclusions can be drawn from these trials about the differential effect of treatment guided by GeneSight versus SOC.

The PRecision Medicine In MEntal Health Care (PRIME Care) RCT compared 24-week outcomes in adults with MDD who received either GeneSight-guided therapy or SOC.[21,] The study included 1944 participants from 22 Veteran's Affairs medical centers who were randomly assigned to either pharmacogenomic-guided treatment (n=966) or SOC (n=978). Assessments were conducted at baseline and every 4 weeks until 24-weeks follow-up.

The authors reported a small and nonpersistent effect on the co-primary outcome of symptom remission. A significant difference in symptom remission rates on the PHQ-9 was reported favoring the GeneSight group at weeks 8 and 12, but no meaningful differences were detected at weeks 4, 18, or 24. The overall pooled effect over time for remission, however, remained

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

favorable for the GeneSight group by a small margin (odds ratio [OR], 1.28; 95% CI, 1.05 to 1.5; p=.02) (Table 3). The other co-primary outcome, treatment initiation after pharmacogenomics testing, showed that more GeneSight-guided participants were likely to be prescribed an antidepressant in the first 30 days after testing (OR, 0.74; 95% CI, 0.6 to 0.92; p=.005). The pharmacogenomic-guided patients were less also likely to be classified as having no antidepressant and gene interaction compared to moderate or substantial interaction compared to SOC (OR, 2.08; 95% CI, 1.52 to 2.84; p=.005). The selection of genetic markers for antidepressant response has faced challenges due to the presence of confounding factors among the studied populations and large heterogeneity between studies, and we are unable to determine the clinical significance of the proprietary GeneSight algorithm used for predicted drug-gene interactions.[25,] The secondary outcomes of response rate (OR, 1.25; 95% CI, 1.07 to 1.46; p=.005) and symptom improvement (risk difference [RD], 0.56; 95% CI, 0.17 to 0.95; p=.005) on the PHQ-9 also demonstrated an overall pooled effect over time (Table 3).

Study relevance and design/conduct limitations are summarized in Tables 4 and 5. The PRIME trial exhibits a notable methodological limitation by lacking an intention-to-treat analysis. A power calculation was performed, indicating that each treatment arm necessitated 1000 participants to detect a 5% disparity in the remission rate, accounting for an estimated 20% loss to follow-up and possessing 80% statistical power. The trial fell short of achieving the desired recruitment level, and by the conclusion of the 24-week follow-up period, approximately 22% (n=196) of the GeneSight group and 20% (n=172) of the SOC group were lost to follow-up, exacerbating the recruitment issue. In the PRIME trial, solely the outcome assessors were subject to blinding, while both the participants and their treating clinicians were informed of the treatment allocation. Consequently, the potential placebo effect within this trial remains uncertain.

Two similarly-designed RCTs (GUIDED[22,] and GAPP-MDD[23,]) compared 8-week outcomes in individuals who received treatment for MDD guided by GeneSight testing or SOC. In both GUIDED (N=1799) and GAPP-MDD (N=437), the primary outcome was symptom improvement, measured by a change in HAM-D. Secondary outcomes were response and remission. Neither trial found a significant difference between GeneSight guided treatment and SOC in symptom improvement (Table 3). The GUIDED trial found treatment guided by GeneSight associated with a statistically significant benefit for response and remission compared with treatment as usual, while there were no significant differences between GeneSight and TAU groups in the GAPP-MDD trial for response or remission (Table 3).

The GUIDED trial randomized 1799 individuals. After post-randomization exclusions, according to the text, 1541 individuals remained, in what was labeled the intention to treat (ITT) cohort, but the ITT results reported in Figure 2 included only 1299 participants. The publication text also describes a per protocol cohort that included 1398 participants, yet only 1167 of these participants are accounted for in the study results reported in Figure 1 of the text. The participant flow chart included in the Supplement describes missing data as occurring because of loss to follow-up, or study withdrawal due to inclusion/exclusion violations, HAM-D or Quick Inventory of Depressive Symptomatology (QIDS) scores, out of window visits, withdrawal of consent, or other reasons. Depending on the population (ITT or per protocol), up to one third of GUIDED randomized participants were missing from the reported results. The GAPP-MDD trial had similar limitations. The trial initially randomized 437 individuals, and the publication supplement indicates an ITT population of 363 individuals and a per protocol population of 202 individuals at 8 weeks. Reasons given for post-randomization exclusions were similar to those in the GUIDED trial: loss

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

to follow-up, or study withdrawal due to inclusion/exclusion violations, QIDS score, withdrawal of consent or "other." The GAPP-MDD publication reported symptom improvement for 203 individuals in the ITT population and for 134 individuals in the per protocol population; data from 308 ITT and 196 per protocol individuals were reported for response and remission. Depending on the population (ITT or per protocol) and the outcome analyzed, data from 30% to 69% of randomized individuals were missing. In both trials, the post-randomization exclusions and analysis methods do not conform with definitions of ITT and there were no sensitivity analyses for the missing data provided.[26,27,] In addition to these limitations, enrollment in the GAPP-MDD trial was stopped early due to a determination that it would not be possible to enroll enough participants to adequately power the trial. Although initially designed to enroll 570 participants, GAPP-MDD investigators revised that calculation based on results from the GUIDED trial, subsequently determining that a sample size of 4000 would be required to achieve 90% power. Based on the recalculation, the GAPP-MDD results would have been powered at less than 25% probability to detect a difference between treatment groups even if the full, planned enrollment of 570 had been achieved.

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).[24,] Fifty-one patients were enrolled and randomized to treatment as usual or treatment guided by GeneSight testing. All patients 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 patients' 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 SOC arm included 26 and 25 patients, respectively, in this pilot study for a larger trial.

Limitations of these studies are summarized in Tables 4 and 5.

Table 2. Summary Characteristics of RCTs Assessing GeneSight Test

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
Oslin et al (2022)[21,] (PRIME Care)	U.S.	22	2017-2021	Adult individuals with MDD; failure of at least 1 medication; 25% female; 69% White, 11% Hispanic, 18% Black, 3% Asian, 0.1% American	Treatment guided by GeneSight (n=966 randomized; n=754 at week 24)	SOC (n=978 randomized; n=775 at week 24)

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
				Indian/Alaska Native		
Greden et al (2019)[22,] (GUIDED)	U.S.	60	2014-2017	Individuals with MDD based on QIDS >11; failure of at least 1 medication; 71% female; 81% White, 15% Black, 2% Asian, 0.6% American Indian/Alaska Native, 0.1% Native Hawaiian/Pacific Islander, 2% other or multiple race/ethnicity	Treatment guided by GeneSight (n=681)* *Per protocol 1398 of 1799 randomized	SOC (n=717)* *Per protocol cohort is 1398 of 1799 randomized
Tiwari et al (2022)[23,] (GAPP-MDD)	Canada	8	2015-2018	Individuals with MDD, ≥11 on QIDS-C16 and total screening and baseline scores of ≥11 on QIDS-SR16, failure of at least 1 medication; 65% female, 84% White, 9% Asian, 3% Black, 2% Latin American, 3% other race/ethnicity	Treatment guided by standard GeneSight or enhanced GeneSight (standard GeneSight + 7 additional polymorphisms shown to have genetic variation associated with antipsychotic-induced weight gain; n=299 [n=147 standard GeneSight; n=152 enhanced GeneSight])	SOC (n=138)
Winner et al (2013)[24,]	U.S.	1	NR	Individuals with major	Treatment guided by	SOC (n=25)

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
				depressive disorder, HAM-D17 >14 (moderate); 80% female; 98% non-Hispanic White, 2% Black	GeneSight (n=26)	

HAM-D17: Hamilton Depression Rating Scale 17 item; MDD: major depressive disorder; NR: not reported; PRIME Care: PRecision Medicine In MEntal Health Care; QIDS: Quick Inventory of Depressive Symptomatology; QIDS-C16: 16-item Quick Inventory of Depressive Symptomatology (clinician rated); QIDS-SR16: 16-item Quick Inventory of Depressive Symptomatology (self rated); RCT: randomized controlled trial; SOC: standard of care.

Table 3. Summary of Results of RCTs Assessing GeneSight

Study	N	Response: ≥50% decrease in HAM-D17 or PHQ-9	Remission: HAM-D17 ≤7 or PHQ-9 ≤5	Symptom Improvement: mean % change in HAM-D17 or PHQ-9
Oslin et al (2022) [21,] (PRIME Care)		24 weeks		
GeneSight	754	32.1%	17.2%	5.4
SOC	787	27.5%	16%	4.8
Risk difference (95% CI); p-value		5.1 (0.6 to 9.6); p=.03	1.5 (-2.4 to 5.3); p=.45	0.65 (0.1 to 1.19); p=.02
Greden et al (2019)[22,] (GUIDED)		8 weeks		
GeneSight	ITT: PP: 560	ITT: 26.1% (SE 1.8) PP: 26.0% (SE 1.9)	ITT: 16.8% (SE 1.6) PP: 15.3% (SE 1.6)	ITT: 26.7% (SE1.3) PP: 27.2% (SE 1.3)
SOC	ITT: PP: 607	ITT: 19.8% (SE 1.5) PP: 19.9% (SE 1.6)	ITT: 11.4% (SE 1.3) PP: 10.1% (SE 1.2)	ITT: 23.5% (SE 1.2) PP: 24.4% (SE 1.2)
Risk difference (95% CI); p-value		ITT: MD 6.3; p=.007 PP: MD 6.1; p=.01	ITT: MD 5.4; p=.005 PP: MD 5.2; p=.007	ITT: MD 3.2; p=.07 PP: MD 2.8; p=.11
Tiwari et al (2022)[23,] (GAPP-MDD)		8 weeks		
GeneSight	ITT: 211 PP: 127	ITT: 25.1% (SE 3.0) PP: 30.3% (SE 4.1)	ITT: 16.4% (SE 2.7) PP: 15.7% (SE 3.4)	ITT: 23.8% (SE 2.4) PP: 27.6% (SE 2.6)

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Study	N	Response: ≥50% decrease in HAM-D17 or PHQ-9	Remission: HAM-D17 ≤7 or PHQ-9 ≤5	Symptom Improvement: mean % change in HAM-D17 or PHQ-9
SOC	ITT: 97 PP: 69	ITT: 21.9% (SE 4.2) PP: 22.7% (SE 5.1)	ITT: 9.7% (SE 2.9) PP: 8.3% (SE 3.3)	ITT: 17.8% (SE 3.6) PP: 22.7% (SE 3.6)
Risk difference (95% CI); p-value		ITT: MD 3.3; p=.54 PP: MD 7.6; p=.26	ITT: MD 6.7; p=.10 PP: MD 7.4; p=.13	ITT: MD 6.0; p=.17 PP: MD 4.9; p=.27
Winner et al (2013)[24,]		10 weeks		
GeneSight	26	36%	20%	
SOC	25	20.8%	8.3%	
OR (95% CI); p-value		2.14 (95% CI, 0.59 to 7.79)	2.75 (95% CI, 0.48 to 15.8)	

CI: confidence interval; HAM-D17: Hamilton Depression Rating Scale 17 item; ITT: intention to treat; MD: mean difference; OR: odds ratio; PHQ-9: Physician Health Questionnaire 9 item; PP: per protocol; PRIME Care: PRecision Medicine In MEntal Health Care; SE: standard error; SOC: standard of care.

Table 4. Study Relevance Limitations: GeneSight

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Oslin et al (2022) [21,] (PRIME Care)	1. Patients with mild depression excluded from per protocol analysis				
Greden et al (2019)[22,] (GUIDED)	1. Patients with mild depression excluded from per protocol analysis				1. 24-week follow-up was treatment arm only
Tiwari et al (2022)[23,] (GAPP-MDD)	1. Patients with mild depression excluded from per protocol analysis				
Winner et al (2013)[24,]	2. MDD diagnostic criteria. Prior medication response not described				1. Follow-up limited to 10 weeks

MDD: major depressive disorder; PRIME Care: PRecision Medicine In MEntal Health Care.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

[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]
Oslin et al (2022) [21,] (PRIME Care)		2. Single blinding only (no blinding of patient or treating clinician)		1. Of 1944 randomized individuals, data were reported for 1,819 at 4 weeks follow-up and 1541 at 24 weeks follow-up		4. Underpowered; n=1000 per arm required to detect remission
Greden et al (2019)[22,] (GUIDED)				1,2. Of 1799 randomized individuals, data were reported for 1299 in the ITT population and 1167 in the per protocol population		
Tiwari et al (2022)[23,] (GAPP-MDD)				1. Of 437 randomized individuals, data were reported for up to 308 (70%) in the ITT population and 196 (45%) in the per protocol population		
Winner et al (2013)[24,]						4. Underpowered; n=92 per arm required to detect remission or response

ITT: intention to treat; PRIME Care: PRecision Medicine In MEntal Health Care; 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

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

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: GeneSight test

Evidence for the use of GeneSight test to inform antidepressant selection includes 4 RCTs. None of the trials provided adequate evidence, and all have major limitations in design and conduct and in consistency and precision. Multiple meta-analyses have reviewed pharmacogenetic tests for antidepressant selection including a 2025 meta-analysis limited to GeneSight studies. Although this meta-analysis found positive response and remission results with use of GeneSight, the limitations of the RCTs included in the analysis remains.

NEUROIDGENETIX TEST

Randomized Controlled Trials

Two RCTs reported results of antidepressant therapy selection, informed by NeuroIDgenetix test results compared to antidepressant therapy selected without pharmacogenetic test results (ie, SOC).

Bradley et al (2018) conducted a double-blinded RCT in which 685 individuals with depression and/or anxiety disorders were randomized to treatment guided by either NeuroIDgenetix or SOC (Table 6).[28,] 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 individuals in the moderate and severe group and remission results were reported for 93 individuals in the severe group. Response rates (OR, 4.72; 95% CI, 1.93 to 11.52; p<.001) and remission rates (OR, 3.54; 95% CI, 1.27 to 9.88; p<.02) 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 ITT population. Reporting is incomplete and suggestive of selective reporting.

Olson et al (2017) conducted an RCT in which individuals with neuropsychiatric disorders were randomized to treatment guided by NeuroIDgenetix or SOC (see Table 6).[29,] A majority of the individuals, 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 Symbol Digit Coding test 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 individuals receiving SOC reported significantly more adverse events (53%) than patients receiving NeuroIDgenetix-guided

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

care (28%). The comparison of adverse drug events did not report the number of individuals included in the analysis. ClinicalTrials.gov lists neurocognitive measures as co-primary outcomes, but these are not reported, suggestive of selective reporting.

Limitations of these studies are summarized in Tables 8 and 9.

Table 6. Summary Characteristics of RCTs Assessing NeuroIDgenetix

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
Bradley et al (2018)[28,]	U.S.	20	2016	Individuals 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; 73% female; 63% White, 18% Black, 16% Hispanic, 1% Asian, 1% other race/ethnicity	Treatment guided by NeuroIDgenetix (n=352)	SOC (n=333)
Olson et al (2017)[29,]	U.S.	6	2015	Individuals with ADHD, anxiety, depression, or psychosis; currently receiving antidepressants	Treatment guided by NeuroIDgenetix (n=178)	SOC (n=25)

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

Table 7. Summary of Results of RCTs Assessing NeuroIDgenetix

Study	N	Outcome			
		Response ≥50% decrease in HAM-D17		Remission: HAM-D17 ≤7	
Bradley et al (2018)[28,]		12 weeks	p	12 weeks	p
NeuroIDgenetix	140 (moderate/severe)	64%		NR	
SOC	121 (moderate/severe)	46%	.01	NR	
NeuroIDgenetix	40 (severe)			35%	
SOC	53 (severe)			13%	.02
		≤1 Adverse Drug Event		≥2 Adverse Drug Events	
Olson et al (2017)[29,]		10 weeks			
NeuroIDgenetix	NR	28%		5%	
SOC	NR	53%	.001	24%	.001

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

HAM-D17: Hamilton Depression Rating Scale 17 item; NR; not reported; RCT: randomized controlled trial; SOC: standard of care.

Table 8. Study Relevance Limitations: NeuroIDgenetix

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Bradley et al (2018)[28,]					
Olson et al (2017)[29,]	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 (2018)[28,]			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	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	

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
			reported for moderate/severe, only severe			
Olson et al (2017)[29,]	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 ITT	1. No description of power and sample size calculations	1. Comparative statistics not reported for clinical or neurocognitive outcomes

ITT: intention 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.

Section Summary: NeuroIDgenetix test

Evidence for the use of NeuroIDgenetix test to inform antidepressant selection includes 2 RCTs, 1 reporting response and remission as outcomes and another reporting adverse events as the 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.

Neuropharmagen Test

Neuropharmagen evaluates more than 60 genetic polymorphisms in 26 genes providing information for 62 psychotropic drugs.

Randomized Controlled Trials

Han et al (2018) conducted a randomized, single-blind clinical trial among individuals 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).[30,] Neuropharmagen analyzes 30 genes associated with drug metabolism and 59 medications

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

used to treat MDD. The 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. The ITT population consisted of all individuals who had at least 1 post-treatment assessment for effectiveness during the study. The effectiveness evaluation was based on ITT analysis with last observation carried forward (LOCF). The mean change of HAM-D17 score was significantly different between the 2 groups favoring the guided arm by a −4.1 point of difference (p=.010) at the end of treatment. The response rate (71.7 % vs. 43.6%; p=.014) was also significantly higher in the guided arm than in the SOC arm at the end of treatment, while the remission rate was numerically higher in the guided arm than in the SOC arm without statistical difference (45.5% vs. 25.6%; p=.071). The study reported an early dropout of 25% in the guided-care and 38% in the SOC arms. The reason for early dropout associated with adverse events was higher in the SOC arm (n=9, 50.0%) than in the guided care arm (n=4, 30.8%). The effectiveness evaluation was based on ITT analyses with LOCF. Use of LOCF assumes data are missing completely at random (MCAR).[31,] The distribution of reasons for termination among early dropouts indicates that the assumption of MCAR is unlikely to hold in this analysis. The study did not report registration in any clinical trial database.

Perez et al (2017) conducted a single-blind RCT (AB-GEN trial) of individuals diagnosed with MDD randomized to genotype-guided treatment (Neuropharmagen) or treatment as usual (see Table 10).[32,] The pharmacogenetics report from Neuropharmagen provided information on 50 drugs, highlighting gene-drug interactions and drug recommendations from the FDA 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 SOC arms at 12 weeks. However, response and remission data were missing for 9% of patients in the guided care group and 14% in the SOC group.

Limitations of these studies are summarized in Tables 12 and 13.

Table 10. Summary Characteristics of RCTs Assessing Neuropharmagen

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
Han et al (2018)[30,]	Korea	2	NR	Individuals with MDD using DSM-5 criteria; currently receiving antidepressant therapy at least 6 weeks with an inadequate response (CGI-I >3); 75% female;	Treatment guided by Neuropharmagen (n=52)	SOC (n=48)

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
				race/ethnicity not reported		
Perez et al (2017)[32,]	Spain	18	2014-2015	Individuals with MDD using DSM-IV-TR criteria; either new to medication or inadequately controlled with medication; 64% female; 92% White, 5% Latin American, 2% other race/ethnicity	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; RCT: randomzied controlled trial; SOC: standard of care; TR: text revision.

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)[30,]		8 weeks	p		p
Neuropharmagen	52	71.7%		45.5%	
SOC	48	43.6%	.01	25.6%	.07
Perez et al (2017)[32,]		12 weeks		12 weeks	
Neuropharmagen	141	45.4%		34.0%	
SOC	139	40.3%	.39	33.1%	.87
		OR 1.23 (95% CI 0.77 to 1.98)		OR 1.04 (95% CI 0.64 to 1.71)	

CI: confidence interval; HAM-D17: Hamilton Depression Rating Scale 17 item; OR: odds ratio; RCT: randomized controlled trial; SOC: standard of care.

Table 12. Study Relevance Limitations: Neuropharmagen

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Han et al (2018)[30,]					
Perez et al (2017)[32,]					

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.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

[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)[30,]		3. Patients 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		
Perez et al (2017)[32,]		3. Patients were blinded, outcome (HAM-D17) assessed by treating physicians		1. Response and remission data were missing for 9% patients in the guided care group and 14% of the SOC group.		

HAM-D17: Hamilton Depression Rating Scale 17 item; LOCF: last observation carried forward; 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.

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.

GENETIC TESTING TO INFORM MEDICATION SELECTION FOR PATIENTS WITH A MENTAL ILLNESS OTHER THAN DEPRESSION

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Clinical Context and Test Purpose

The purpose of pharmacogenetic testing in individuals 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 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 individuals with mental illnesses are based on clinical response, potentially informed by studies such as the STAR*D study, which evaluated specific medication sequences.

Outcomes

The primary outcome of interest is change in disease outcomes resulting from a more appropriate selection of specific drugs or doses for the 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 patients randomly assigned to receive naltrexone and 597 received placebo).[33,] 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).

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Randomized Controlled Trials

Bradley et al (2018) conducted a double-blind RCT in which 685 individuals with depression and/or anxiety disorders were randomized to treatment guided by either NeuroIDgenetix or SOC (Tables 14 to 17).[28,] 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 SOC 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). The study does not report clearly if the analysis was based on the 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 (2018)[28,]	U.S.	20	2016	Individuals 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; 73% female; 63% White, 18% Black, 16% Hispanic, 1% Asian, 1% other race/ethnicity	Treatment guided by NeuroIDgenetix (n=352)	SOC (n=333)

HAM-A: Hamilton Anxiety Rating Scale; HAM-D17: Hamilton Depression Rating Scale 17 item; RCT: randomzied controlled trial; SOC: standard of care.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

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)[28,]		12 weeks	p	12 weeks	p
NeuroIDgenetix	82 (moderate/severe)	63%		NR	
SOC	95 (moderate/severe)	50%	.04	NR	

HAM-A: Hamilton Anxiety Rating Scale; NR: not reported; RCT: randomzied controlled trial; SOC: standard of care.

Table 16. Study Relevance Limitations: NeuroIDgenetix

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Bradley et al (2019)[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. 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)[28,]			2. In the clinicaltrials.gov listing, reduction of adverse drug events was listed as the primary outcome, but was not reported as primary outcome. Also, anxiety remission was listed as a secondary outcome but was not reported.	1. Approximately 25% of randomized patients were lost to follow-up or were not included in the outcome analysis at 12 weeks. Analysis does not appear to be ITT.	1. No description of power and sample size calculations.	

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

ITT: intention 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 individuals 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.[34,] Study reported better treatment outcomes with disulfiram pharmacotherapy of cocaine dependence among individuals 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.[35,] 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.

Skokou et al (2024) conducted the prospective, multicenter PREPARE RCT to evaluate preemptive pharmacogenomic testing in 1,076 adults with MDD (n = 494), bipolar disorder (n = 252), or schizophrenia (n = 330), grouped into a single cohort. [36,] The primary outcome was the occurrence of clinically relevant adverse drug reactions of grade 2 or higher. Among patients with actionable genotypes (n=262), clinically relevant adverse drug reactions occurred in 10.4% of those in the pharmacogenomic guided arm versus 19.1% in the control arm (Odds Ratio [OR] 0.48, 95% CI 0.23 to 0.98; p=.049). Secondary outcomes in the total study population favored the pharmacogenomic guided arm, including fewer hospitalizations (OR 0.46, 95% CI 0.34 to 0.61; p<.001), but no significant differences in the rate of readmission or reduced polypharmacy. Outcomes were not stratified by disease group, and the effect of pharmacogenomic testing on bipolar disorder and schizophrenia cannot be assessed.

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 individuals with mental health conditions other than depression includes a meta-analysis on alcohol use disorder, an RCT on MDD, bipolar disorder or schizophrenia, 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

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

alcohol use. The single available trials did not provide adequate or supportive evidence effect of pharmacogenetic testing on managing moderate to severe anxiety or bipolar disorder or schizophrenia. The studies had major limitations in design, conduct, precision, or stratification by relevant disease groups.

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 a 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.[37,]

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.

American Psychiatric Association
In 2024, the American Psychiatric Association (APA) Workgroup on Biomarkers and Novel Treatments reviewed the evidence on pharmacogenomic tools for treating depression.[38,] Despite a growing number of RCTs,11 new clinical trials and 5 meta-analyses since publication of the APA's earlier report in 2018, the workgroup found the overall evidence lacking to support the use of pharmacogenomic tools for treatment selection in major depressive disorder. Most trials either failed to show effectiveness, were methodologically flawed, lacked adequate blinding, or relied on treatment-as-usual control groups that often lacked clarity or did not reflect best practices. The APA panel emphasized that no current pharmacogenomic algorithm has been demonstrated to reliably predict antidepressant efficacy or side effect risk. While some subgroup or post hoc analyses have suggested benefit for certain patients (e.g., those with significant gene-drug interactions), the panel states that these findings are not robust enough to inform clinical practice. Meta-analyses suggesting modest benefits also fail to correct for these limitations. Accordingly, the APA Workgroup recommends that pharmacogenomic testing remain experimental and suggests that future research focus on blinded, well-controlled trials to assess its utility.

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.[39,] The panel consists of experts from the U. S., Europe, and Asia.

In 2023, the CPIC conducted a systematic literature review on the influence of *CYP2D6*, *CYP2C19, CYP2B6, SLC6A4,* and *HTR2A* genotyping on selective serotonin reuptake inhibitor (SSRI) therapy.[40,] The CPIC concluded that *SLC6A4* and *HTR*2A are not yet supported for clinical use in antidepressant prescribing. Dosing recommendations for SSRIs based

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

on *CYP2D6*, *CYP2C19*, and *CYP2B6* phenotypes that classified patients as ultrarapid metabolizers, rapid metabolizers, intermediate metabolizers, poor metabolizers, or indeterminant metabolizers are presented in Tables 18 and 19. However, the CPIC noted that individuals on an effective and stable dose of SSRIs would not benefit from dose modifications based on 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.

Table 18. Dosing Recommendations for Antidepressants Based on *CYP2D6*, *CYP2C19, and CYP2B6* Phenotype[40,]

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
Phenotype	**Implications**	**Recommendation**	**Class of recommendation**	**Considerations**
CYP2D6 ultrarapid metabolizer	Increased metabolism of paroxetine to less active compounds when compared with *CYP2D6* normal metabolizers. Lower plasma concentrations decrease the probability of clinical benefit. The extent to which ultrarapid metabolizers phenoconvert to normal, intermediate, or poor metabolizers due to paroxetine autoinhibition of *CYP2D6* is unclear.	Select alternative drug not predominantly metabolized by *CYP2D6.*	moderate	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy.
CYP2D6 rapid metabolizer	Normal metabolism of paroxetine to less active compounds. Paroxetine-associated phenoconversion of normal metabolizers to intermediate or poor metabolizers due to *CYP2D6* autoinhibition may occur and is dose-dependent and greater at steady state concentrations.	Initiate therapy with recommended starting dose.	strong	
CYP2D6 intermediate metabolizer	Reduced metabolism of paroxetine to less active compounds when compared with *CYP2D6* normal metabolizers when	Consider a lower starting dose and slower titration schedule as compared with	optional	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
	starting treatment or at lower doses. Higher plasma concentrations may increase the probability of side effects. Paroxetine-associated phenoconversion of intermediate metabolizers to poor metabolizers due to *CYP2D6* autoinhibition may occur and is dose-dependent and greater at steady-state concentrations.	normal metabolizers.		function) should be considered when adjusting dose or selecting an alternative therapy.
CYP2D6 poor metabolizer	Greatly reduced metabolism when compared with *CYP2D6* normal metabolizers. Higher plasma concentrations may increase the probability of side effects. The impact of paroxetine-associated autoinhibition of *CYP2D6* is minimal in poor metabolizers.	Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose as compared with normal metabolizers.	moderate	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy.
Dosing recommendations for fluvoxamine based on *CYP2D6* phenotype				
CYP2D6 ultrarapid metabolizer	No data available for *CYP2D6* ultrarapid metabolizers.	No recommendation due to lack of evidence.	No recommendation	
CYP2D6 normal metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong	
CYP2D6 intermediate metabolizer	Reduced metabolism of fluvoxamine to less active compounds when compared with *CYP2D6* normal metabolizers. Higher plasma concentrations may increase the probability of side effects.	Initiate therapy with recommended starting dose.	Moderate	

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
CYP2D6 poor metabolizer	Greatly reduced metabolism of fluvoxamine to less active compounds when compared with *CYP2D6* normal metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 25–50% lower starting dose and slower titration schedule as compared with normal metabolizers.	Optional	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy.
Dosing recommendations for venlafaxine based on *CYP2D6* phenotype				
CYP2D6 ultrarapid metabolizer	Increased metabolism of venlafaxine to the active metabolite O-desmethylvenlafaxine (desvenlafaxine) and increased O-desmethylvenlafaxine: venlafaxine ratio as compared with *CYP2D6* normal metabolizers. There is insufficient evidence supporting the clinical impact of increased O-desmethylvenlafaxine: venlafaxine ratio in *CYP2D6* ultrarapid metabolizers.	No action recommended based on genotype for venlafaxine because of minimal evidence regarding the impact on efficacy or side effects.	No recommendation	
CYP2D6 normal metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong	
CYP2D6 intermediate metabolizer	Decreased metabolism of venlafaxine to active metabolite O-desmethylvenlafaxine (desvenlafaxine) and decreased O-desmethylvenlafaxine: venlafaxine ratio as compared with *CYP2D6* normal metabolizers. There is insufficient evidence supporting the clinical impact of the decreased O-	No action recommended based on genotype for venlafaxine because of minimal evidence regarding the impact on efficacy or side effects.	No recommendation	

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
	desmethylvenlafaxine: venlafaxine ratio in *CYP2D6* intermediate metabolizers.			
CYP2D6 poor metabolizer	Decreased metabolism of venlafaxine to the active metabolite O-desmethylvenlafaxine (desvenlafaxine) and greatly decreased O-desmethylvenlafaxine: venlafaxine ratio as compared with *CYP2D6* normal and intermediate metabolizers. The clinical impact of increased venlafaxine and decreased O-desmethylvenlafaxine: venlafaxine ratio in *CYP2D6* poor metabolizers is unclear, but *CYP2D6* PM genotype has been associated with adverse effects.	Consider a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2D6.*	Optional	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy.
Dosing recommendations for vortioxetine based on *CYP2D6* phenotype				
CYP2D6 ultrarapid metabolizer	Increased metabolism of vortioxetine to inactive compounds when compared with CYP2D6 normal metabolizers. Lower plasma concentrations decrease the probability of clinical benefit.	Select alternative drug not predominantly metabolized by *CYP2D6*. If vortioxetine use is warranted, initiate therapy at standard starting dose and titrate to maintenance dose based on efficacy and side effects. Increasing the target maintenance dose by 50% or more may be needed for efficacy.	Optional	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
CYP2D6 normal metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong	
CYP2D6 intermediate metabolizer	Reduced metabolism of vortioxetine to less active compounds when compared with *CYP2D6* normal metabolizers. Higher plasma concentrations may increase the probability of side effects.	Initiate therapy with recommended starting dose.	Moderate	
CYP2D6 poor metabolizer	Greatly reduced metabolism of vortioxetine to inactive compounds when compared with *CYP2D6* normal metabolizers. Higher plasma concentrations may increase the probability of side effects.	Initiate 50% of starting dose (e.g., 5 mg) and titrate to the maximum recommended dose of 10 mg or consider a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2D6.*	Moderate	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy.
Dosing recommendations for citalopram and escitalopram based on *CYP2C19* phenotype				
CYP2C19 ultrarapid metabolizer	Increased metabolism of citalopram and escitalopram to less active compounds when compared with *CYP2C19* rapid and normal metabolizers. Lower plasma concentrations decrease the probability of clinical benefit.	Consider a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*. If citalopram or escitalopram are clinically appropriate, and adequate efficacy is not achieved at standard maintenance dosing, consider titrating to a higher maintenance dose.	Strong	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy.
CYP2C19 rapid metabolizer	Increase in metabolism of citalopram and escitalopram to less	Initiate therapy with recommended starting dose. If	Optional	Drug–drug interactions and other patient

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
	active compounds when compared with *CYP2C19* normal metabolizers. Lower plasma concentrations decrease the probability of clinical benefit.	patient does not adequately respond to recommended maintenance dosing, consider titrating to a higher maintenance dose or switching to a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2C19.*		characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy.
CYP2C19 normal metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong	
CYP2C19 intermediate and likely intermediate metabolizers	Reduced metabolism when compared with *CYP2C19* normal metabolizers. Higher plasma concentrations may increase the probability of side effects.	Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than normal metabolizers.	Moderate	Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy.
CYP2C19 poor and likely poor metabolizers	Reduced metabolism of citalopram and escitalopram to less active compounds when compared with *CYP2C19* normal and intermediate metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a clinically appropriate antidepressant not predominantly metabolized by *CYP2C19*. If citalopram or escitalopram are clinically appropriate, consider a lower starting dose, slower titration schedule, and 50% reduction of the standard maintenance dose as compared with normal metabolizers.	Strong	Per the FDA warning, citalopram 20 mg/day is the maximum recommended dose in *CYP2C19* poor metabolizers due to the risk of QT prolongation. FDA product labeling additionally cautions that citalopram dose should be limited to 20 mg/day in patients with hepatic impairment, those taking a *CYP2C19* inhibitor

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
				, and patients greater than 60 years of age.
Dosing recommendations for sertraline based on *CYP2C19* phenotype				
CYP2C19 ultrarapid metabolizer	Small increase in metabolism of sertraline to less active compounds when compared with *CYP2C19* normal metabolizers.	Initiate therapy with recommended starting dose.	Strong	*CYP2B6* metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered.
CYP2C19 rapid metabolizer	Small increase in metabolism of sertraline to less active compounds when compared with normal metabolizers.	Initiate therapy with recommended starting dose.	Strong	*CYP2B6* metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered.
CYP2C19 normal metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong	*CYP2B6* metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered.
CYP2C19 intermediate and likely intermediate metabolizers	Reduced metabolism of sertraline to less active compounds when compared with CYP2C19 normal metabolizers.	Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than *CYP2C19* normal metabolizers.	Moderate	
CYP2C19 poor and likely poor metabolizers	Greatly reduced metabolism of sertraline to less active compounds when compared with *CYP2C19* normal metabolizers. Higher	Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose	Moderate	*CYP2B6* metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
	plasma concentrations may increase the probability of side effects.	as compared with *CYP2C19* normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2C19.*		function) should be considered when adjusting dose or selecting an alternative therapy.
Dosing recommendations for sertraline based on *CYP2B6* phenotype				
CYP2B6 ultrarapid metabolizer	Increase in metabolism of sertraline to less active compounds when compared with *CYP2B6* normal metabolizers.	Initiate therapy with recommended starting dose.	Moderate	*CYP2C19* metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered.
CYP2B6 rapid metabolizer	Small increase in metabolism of sertraline to less active compounds when compared with *CYP2B6* normal metabolizers.	Initiate therapy with recommended starting dose.	Strong	*CYP2C19* metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered.
CYP2B6 normal metabolizer	Normal metabolism of sertraline to less active compounds.	Initiate therapy with recommended starting dose.	Strong	*CYP2C19* metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered.
CYP2B6 intermediate metabolizers	Reduced metabolism of sertraline to less active compounds when compared with *CYP2B6* normal metabolizers.	Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than *CYP2B6* normal metabolizers.	Optional	*CYP2C19* metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
CYP2B6 poor metabolizers	Greatly reduced metabolism of sertraline to less active compounds when compared with *CYP2B6* normal metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a lower starting dose, slower titration schedule, and 25% reduction of standard maintenance dose as compared with *CYP2B6* normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2B.*	Optional	*CYP2C19* metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy.

CYP: cytochrome P450

Table 19. Dosing Recommendations for Sertraline Based on *CYP2C19* and *CYP2B6* phenotypes

Phenotype	***CYP2D6* ultrarapid or rapid metabolizer**	***CYP2D6* normal metabolizer**	***CYP2D6* intermediate metabolizer**	***CYP2D6* poor metabolizer**	***CYP2D6* indeterminate metabolizer**
CYP2C19 ultrarapid or rapid metabolizers	Initiate therapy with recommended starting dose. If patient does not adequately respond to recommended maintenance dosing, consider titrating to a higher maintenance dose or switching to a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2C19* or *CYP2B6*.	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Phenotype	***CYP2D6*** **ultrarapid or rapid metabolizer**	***CYP2D6*** **normal metabolizer**	***CYP2D6*** **intermediate metabolizer**	***CYP2D6*** **poor metabolizer**	***CYP2D6*** **indeterminate metabolizer**
CYP2C19 normal metabolizers	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose.	Consider a lower starting dose, slower titration schedule, and 25% reduction of standard maintenance dose as compared with *CYP2B6* normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2B6*.	Initiate therapy with recommended starting dose.
CYP2C19 intermediate metabolizers Or *CYP2C19* likely intermediate metabolizers	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose.	Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose.	Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with *CYP2B6* normal metabolizers.	Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose.
CYP2C19 poor metabolizers Or *CYP2C19* likely poor metabolizers	Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with *CYP2C19* normal metabolizers or	Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with *CYP2C19* normal metabolizers	Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with *CYP2C19* normal metabolizers or select a clinically	Select an alternative antidepressant not primarily metabolized by *CYP2C19* or *CYP2B6*.	Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with *CYP2C19* normal metabolizers or select a clinically

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Phenotype	*CYP2D6* ultrarapid or rapid metabolizer	*CYP2D6* normal metabolizer	*CYP2D6* intermediate metabolizer	*CYP2D6* poor metabolizer	*CYP2D6* indeterminate metabolizer
	select a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*.	or select a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*.	appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*.		appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*.
CYP2C19 indeterminate	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose.	Consider a lower starting dose, slower titration schedule, and 25% reduction of standard maintenance dose as compared with *CYP2B6* normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2B6*.	No recommendation.

CYP: cytochrome P450.

International Society of Psychiatric Genetics

In 2019, The International Society of Psychiatric Genetics (ISPG) issued recommendations on the use of pharmacogenetic testing in the management of psychiatric disorders, and in 2020 published the evidence review used to inform the recommendations.[41,42,] The recommendations state: "we recommend HLA [human leukocyte antigen]-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups. Evidence to support widespread use of other pharmacogenetic tests at this time is still inconclusive, but when pharmacogenetic testing results are already available, providers are encouraged to integrate this information into their medication selection and dosing decisions. Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial."

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

The ISPG also included the following considerations regarding pharmacogenetic testing:

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

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

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

Table 20. Summary of Key Trials

NCT Number	Title	Enrollment	Completion Date
Ongoing			
NCT04507555	Pharmacist Guided Pre-emptive Pharmacogenetic Testing in Antidepressant Therapy	190	Dec 2025
NCT06929533	Pharmacogenomics-Supported Psychotropic Prescribing Trial (PGx-SUPPORT): A Pilot Study on Inpatient Mental Health Units in Manitoba	200	Dec 2030
NCT06729541	Development and Application of Precision Treatment Strategies for Patients with Depression, Bipolar Disorder, and Schizophrenia: a Multicenter Randomized Controlled Trial	600	Dec 2026
NCT04797364	Pharmacogenetic-Supported Prescribing in Kids	6000	Dec 2026
NCT06907784	Phoenix Trial - A Pilot Randomised Controlled Trial Of Pre-Emptive Pharmacogenomics In Acute Care Settings With Health Economic Evaluations	2000	Sep 2026
NCT06210321	Randomised Controlled Study of the Efficacy and Acceptability of a Pharmacogenetic Test in the Management of Patients Treated With Escitalopram.	240	Oct 2025
Unpublished			
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 (completed)
NCT04207385	Accurate Clinical Study of Medication in Patients With Depression Via Pharmacogenomics (PGx) and Therapeutic Drug Monitoring (TDM) of Venlafaxine	160	Nov 2021 (status unknown)
NCT03749629	Comparative Effectiveness of Pharmacogenomics for Treatment of Depression (CEPIO-D)	201	Mar 2022 (completed)
NCT04909749[a]	CDDOM Oneome Rightmed Depression Study	350	Jun 2023 (status unknown
		70	Dec 2023 (completed)
NCT03674138	Pharmacogenomic-Guided Antidepressant Drug Prescribing in Cancer Patients	99	Oct 2024 (completed)

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

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
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) (List separately in addition to code for primary procedure)
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)
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) (List separately in addition to code for primary procedure)
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) (List separately in addition to code for primary procedure)
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) (List separately in addition to code for primary procedure)
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
0345U	Psychiatry (e.g., depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

CPT/HCPCS	
0392U	Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug [Medication Management Neuropsychiatric Panel by RCA Laboratory Services LLC DBA GENETWORx]
0411U	Psychiatry (e.g., depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
0434U	Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes
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)
81418	Drug metabolism (e.g., pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
81479	Unlisted molecular pathology procedure (use for genes listed in an active code)

REVISIONS	
Posted 03-12-2024 Effective 04-11-2024	Policy added to the bcbsks.com web site.
08-27-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section
10-01-2024	Updated Coding Section ▪ 0476U, 0477U, 0517U, 0518U, 0519U, and 0520U (eff. 10-01-2024)
08-26-2025	Updated Description Section
	Updated Rationale Section
	Updated References Section
01-01-2026	Updated Coding Section ▪ Removed Deleted code 0033U (eff. 01-01-2026)
07-01-2026	Updated Coding Section ▪ Removed Deleted codes 0029U and 0031U (eff. 07-01-2026)
09-08-2026	Updated Description Section
	Updated Policy Section ▪ Statement B: • Removed:"STA^{2}R test", "the Proove Opioid Risk assay", "and the Mental Health DNA Insight panel" • Added:"OptimalRx Plus (formerly" the Genecept Assay), "and Neuropharmagen"
	Updated Rationale Section

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

REVISIONS	
	Updated Coding Section ▪ Removed Codes: 0032U, 0476U-0520U, 81291
	Updated Reference Section

REFERENCES

1. Koyama E, Zai CC, Bryushkova L, et al. Predicting risk of suicidal ideation in youth using a multigene panel for impulsive aggression. Psychiatry Res. Mar 2020; 285: 112726. PMID 31870620
2. Ghafouri-Fard S, Taheri M, Omrani MD, et al. Application of Single-Nucleotide Polymorphisms in the Diagnosis of Autism Spectrum Disorders: A Preliminary Study with Artificial Neural Networks. J Mol Neurosci. Aug 2019; 68(4): 515-521. PMID 30937628
3. Ran L, Ai M, Wang W, et al. Rare variants in SLC6A4 cause susceptibility to major depressive disorder with suicidal ideation in Han Chinese adolescents and young adults. Gene. Feb 05 2020; 726: 144147. PMID 31629822
4. Wan L, Zhang G, Liu M, et al. Sex-specific effects of methylenetetrahydrofolate reductase polymorphisms on schizophrenia with methylation changes. Compr Psychiatry. Oct 2019; 94: 152121. PMID 31476590
5. Zhu D, Yin J, Liang C, et al. CACNA1C (rs1006737) may be a susceptibility gene for schizophrenia: An updated meta-analysis. Brain Behav. Jun 2019; 9(6): e01292. PMID 31033230
6. Schröter K, Brum M, Brunkhorst-Kanaan N, et al. Longitudinal multi-level biomarker analysis of BDNF in major depression and bipolar disorder. Eur Arch Psychiatry Clin Neurosci. Mar 2020; 270(2): 169-181. PMID 30929061
7. Chen X, Wang M, Zhang Q, et al. Stress response genes associated with attention deficit hyperactivity disorder: A case-control study in Chinese children. Behav Brain Res. May 02 2019; 363: 126-134. PMID 30707907
8. Zhang L, Hu XZ, Benedek DM, et al. Genetic predictor of current suicidal ideation in US service members deployed to Iraq and Afghanistan. J Psychiatr Res. Jun 2019; 113: 65-71. PMID 30904785
9. DSM-5 Criteria for Major Depressive Disorder. MD Calc. https://www.mdcalc.com/calc/10195/dsm-5-criteria-major-depressive-disorder. Accessed May 26, 2026.
10. Gaynes BN, Warden D, Trivedi MH, et al. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr Serv. Nov 2009; 60(11): 1439-45. PMID 19880458
11. Browin VK. DNA test for antidepressants raises questions from FDA. Bloomberg. August 14 2019. https://www.bloomberg.com/news/articles/2019-08-14/dna-test-for-depression-drugs-raise-fda-doubts-cratering-myriad?in_source=embedded-checkout-banner. Accessed May 26, 2026.
12. Rohan KJ, Rough JN, Evans M, et al. A protocol for the Hamilton Rating Scale for Depression: Item scoring rules, Rater training, and outcome accuracy with data on its application in a clinical trial. J Affect Disord. Aug 2016; 200: 111-8. PMID 27130960
13. CADTH Common Drug Reviews. Aripiprazole (Abilify): Depression, Major Depressive Disorder (MDD). Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, Copyright (c) CADTH 2016.; 2016.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

14. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. Sep 2001; 16(9): 606-13. PMID 11556941
15. Costantini L, Pasquarella C, Odone A, et al. Screening for depression in primary care with Patient Health Questionnaire-9 (PHQ-9): A systematic review. J Affect Disord. Jan 15 2021; 279: 473-483. PMID 33126078
16. Spielmans GI, McFall JP. A comparative meta-analysis of Clinical Global Impressions change in antidepressant trials. J Nerv Ment Dis. Nov 2006; 194(11): 845-52. PMID 17102709
17. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. Jun 1996; 11 Suppl 3: 89-95. PMID 8923116
18. Leon AC, Olfson M, Portera L, et al. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med. 1997; 27(2): 93-105. PMID 9565717
19. Albers RE, Dyer MP, Kucera M, et al. Meta-analysis of Response and Remission Outcomes With a Weighted Multigene Pharmacogenomic Test for Adults With Depression. J Clin Psychopharmacol. Nov-Dec 2025; 45(6): 570-579. PMID 40901805
20. Milosavljević F, Molden PE, Ingelman-Sundberg PM, et al. Current level of evidence for improvement of antidepressant efficacy and tolerability by pharmacogenomic-guided treatment: A Systematic review and meta-analysis of randomized controlled clinical trials. Eur Neuropsychopharmacol. Apr 2024; 81: 43-52. PMID 38340605
21. Oslin DW, Lynch KG, Shih MC, et al. Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder: The PRIME Care Randomized Clinical Trial. JAMA. Jul 12 2022; 328(2): 151-161. PMID 35819423
22. Greden JF, Parikh SV, Rothschild AJ, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res. Apr 2019; 111: 59-67. PMID 30677646
23. Tiwari AK, Zai CC, Altar CA, et al. Clinical utility of combinatorial pharmacogenomic testing in depression: A Canadian patient- and rater-blinded, randomized, controlled trial. Transl Psychiatry. Mar 14 2022; 12(1): 101. PMID 35288545
24. Winner JG, Carhart JM, Altar CA, et al. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med. Nov 2013; 16(89): 219-27. PMID 24229738
25. Noordam R, Avery CL, Visser LE, et al. Identifying genetic loci affecting antidepressant drug response in depression using drug-gene interaction models. Pharmacogenomics. Jun 2016; 17(9): 1029-40. PMID 27248517
26. International Conference on Harmonization. Statistical principles for clinical trials: E9. 1998. https://www.fda.gov/media/71336/download. Accessed May 26, 2026.
27. Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. Int J Epidemiol. Oct 1992; 21(5): 837-41. PMID 1468842
28. Bradley P, Shiekh M, Mehra V, et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility. J Psychiatr Res. Jan 2018; 96: 100-107. PMID 28992526
29. Olson MC, Maciel A, Gariepy JF, et al. Clinical Impact of Pharmacogenetic-Guided Treatment for Patients Exhibiting Neuropsychiatric Disorders: A Randomized Controlled Trial. Prim Care Companion CNS Disord. Mar 16 2017; 19(2). PMID 28314093
30. Han C, Wang SM, Bahk WM, et al. A Pharmacogenomic-based Antidepressant Treatment for Patients with Major Depressive Disorder: Results from an 8-week, Randomized, Single-

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

blinded Clinical Trial. Clin Psychopharmacol Neurosci. Nov 30 2018; 16(4): 469-480. PMID 30466219
31. Lachin JM. Fallacies of last observation carried forward analyses. Clin Trials. Apr 2016; 13(2): 161-8. PMID 26400875
32. Pérez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. BMC Psychiatry. Jul 14 2017; 17(1): 250. PMID 28705252
33. Hartwell EE, Feinn R, Morris PE, et al. Systematic review and meta-analysis of the moderating effect of rs1799971 in OPRM1, the mu-opioid receptor gene, on response to naltrexone treatment of alcohol use disorder. Addiction. Aug 2020; 115(8): 1426-1437. PMID 31961981
34. Kampangkaew JP, Spellicy CJ, Nielsen EM, et al. Pharmacogenetic role of dopamine transporter (SLC6A3) variation on response to disulfiram treatment for cocaine addiction. Am J Addict. Jul 2019; 28(4): 311-317. PMID 31087723
35. Naumova D, Grizenko N, Sengupta SM, et al. DRD4 exon 3 genotype and ADHD: Randomised pharmacodynamic investigation of treatment response to methylphenidate. World J Biol Psychiatry. Jul 2019; 20(6): 486-495. PMID 29182037
36. Skokou M, Karamperis K, Koufaki MI, et al. Clinical implementation of preemptive pharmacogenomics in psychiatry. EBioMedicine. Mar 2024; 101: 105009. PMID 38364700
37. Jukic MM, Smith RL, Haslemo T, et al. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. Lancet Psychiatry. May 2019; 6(5): 418-426. PMID 31000417
38. Baum ML, Widge AS, Carpenter LL, et al. Pharmacogenomic Clinical Support Tools for the Treatment of Depression. Am J Psychiatry. Jul 01 2024; 181(7): 591-607. PMID 38685859
39. Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. Feb 2014; 15(2): 209-17. PMID 24479687
40. Bousman CA, Stevenson JM, Ramsey LB, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants. Clin Pharmacol Ther. Jul 2023; 114(1): 51-68. PMID 37032427
41. International Society of Psychiatric Genetics. Genetic Testing and Psychiatric Disorders: A Statement from the International Society of Psychiatric Genetics. Accessed May 26, 2026.
42. Bousman CA, Bengesser SA, Aitchison KJ, et al. Review and Consensus on Pharmacogenomic Testing in Psychiatry. Pharmacopsychiatry. Jan 2021; 54(1): 5-17. PMID 33147643

OTHER REFERENCES

1. Blue Cross and Blue Shield of Kansas Behavioral Health Liaison Committee, February 2025.
2. Blue Cross and Blue Shield of Kansas Family Medicine Liaison Committee, February 2025.
3. Blue Cross and Blue Shield of Kansas Pediatric Liaison Committee, April 2025.
4. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee, June 2025.

Current Procedural Terminology © American Medical Association. All Rights Reserved.
Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information