2.04.110	Genetic Testing for Diagnosis and Management of Mental Health Conditions		
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Section:	2.0 Medicine	**Page:**	Page 1 of 43

Policy Statement

I. Genetic testing for diagnosis and management of mental health disorders is considered **investigational** in all situations, including but not limited to the following:
   A. To confirm a diagnosis of a mental health disorder in an individual with symptoms
   B. To predict future risk of a mental health disorder in an asymptomatic individual
   C. To inform the selection or dose of medications used to treat mental health disorders, including but not limited to the following medications*:
      1. Selective serotonin reuptake inhibitors
      2. Selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
      3. Tricyclic antidepressants
      4. Antipsychotic drugs

II. Genetic testing panels for mental health disorders are considered **investigational** for **all** indications, including but not limited to the following:
   A. Genecept Assay
   B. GeneSight Psychotropic panel
   C. Mental Health DNA Insight panel
   D. Proove Opioid Risk assay
   E. STA^{2}R test

Note: For individuals enrolled in health plans subject to the Biomarker Testing Law (Health & Safety Code Section 1367.667 and the Insurance Code Section 10123.209), Centers for Medicare & Medicaid Services (CMS) Local Coverage Determination (LCD) may also apply. Please refer to the Medicare National and Local Coverage section of this policy and to MolDX: Pharmacogenomics Testing for reference.

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

Policy Guidelines

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

Coding
See the Codes table for details.

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.

Summary of Evidence

For individuals who are evaluated for diagnosis or risk of a mental illness who receive genetic testing for risk of that disorder, the evidence includes various observational studies (cohort, case-control, genome-wide association study). Relevant outcomes are changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Most studies evaluated the association between genotype and mental health disorders or gene-drug interactions among individuals at risk for mental health conditions. No studies were identified that evaluated whether testing for variants changed clinical management or affected health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult individuals with major depressive disorder (MDD) who receive GeneSight testing guided drug treatment, the evidence includes 4 randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The RCTs compared response (≥50% decrease in Hamilton Depression Rating Scale-17 [HAM-D17] or Patient Health Questionnaire-9 [PHQ-9]), remission (HAM-D17 ≤7 or PHQ-9 ≤5), and symptom improvement (mean % change in HAM-D17 or PHQ-9) with antidepressant therapy informed by GeneSight test results to antidepressant therapy selected without GeneSight test results (ie, standard of care [SOC]). The PRecision Medicine In MEntal Health Care (PRIME Care) trial did not find a statistically significant difference between GeneSight guided treatment and SOC in the primary outcome of remission at 24 weeks follow-up, but significant differences in the secondary outcome of symptom score improvement and treatment response were observed, favoring the GeneSight group. However, this trial had a high loss to follow-up (21%) and had inadequate participant recruitment based on a priori sample size estimation and power analysis. The GUIDED trial reported statistically significant improvements in response and remission in the GeneSight arm compared to SOC at 8 weeks among individuals with MDD. However, depending on the population (intention to treat [ITT] or per protocol), up to one-third of GUIDED randomized participants were missing from the reported results; the extent of missing data following randomization precludes conclusions on outcomes at 8 weeks. The GAPP-MDD trial, also comparing GeneSight guided treatment with SOC, found no statistically significant differences between groups in response, remission or symptom improvement at 8 weeks follow-up, although like the GUIDED trial, a high proportion (up to 69%) of randomized participants were excluded from outcome analysis and the study was not adequately powered to detect between-group differences. In the third trial, a small, single-center pilot study by Winner et al (2013), depression outcomes did not differ significantly between GeneSight-guided care and SOC groups at the 10-week follow-up, though the study was underpowered to detect significant differences in outcomes between study arms. All of these trials have major limitations in design and conduct and in consistency and precision, thus none provided adequate evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult individuals with MDD who receive NeuroIDgenetix testing guided drug treatment, the evidence includes 2 RCTs. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Bradley et al (2018) conducted a double-blind RCT among patients with MDD and reported statistically significant improvement in response (≥50% decrease in HAM-D17) in the NeuroIDgenetix arm (64% of 140) compared to SOC (46% of 121) at 12 weeks (p=.01) and significant improvement in remission (HAM-D17 ≤7) in the NeuroIDgenetix arm (35% of 40) compared to SOC (13% of 53) at 12 weeks (p=.02). There was evidence of reporting bias and, it was unclear if the analysis was based on ITT population; there was also high loss to follow-up (15%). In the RCT conducted by Olson et al (2017), among patients with neuropsychiatric disorders, those receiving SOC reported significantly more adverse events (53%) than those receiving NeuroIDgenetix-guided care (28%), however, the study did

not report the number of patients included in this analysis. The study did not describe the randomization procedure, and in clinicalTrials.gov, neurocognitive measures were listed as co-primary outcomes, which were not reported, suggesting possible selective reporting. None of these trials provided adequate evidence. The Olson et al (2017) study had major relevance limitations and both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult individuals with MDD who receive Neuropharmagen testing guided drug treatment, the evidence includes 2 RCTs. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The 2 RCTs compared response (≥50% decrease in HAM-D17) and remission (HAM-D17 ≤7) with antidepressant therapy informed by Neuropharmagen test results to antidepressant therapy selected without Neuropharmagen test results (ie, SOC). The single-blinded RCT by Han et al (2018) reported statistically significant improvement in response (72% of 52 vs. 44% of 48; p=.01) but no statistically significant improvement in remission (46% of 52 vs. 26% of 48; p=.07) in the Neuropharmagen arm compared to SOC at 8 weeks among patients with MDD. The study reported an early dropout of 25% in guided-care and 38% in the standard care arm and used the last observation carried forward (LOCF) approach in the ITT analysis of effectiveness. Use of LOCF assumes data are missing completely at random, which is unlikely to hold in this analysis. Also, the study did not report registration in any clinical trial database. The single-blinded RCT by Perez et al (2017) reported non-statistically significant improvement in response (45% of 141 vs. 40% of 139; p=.39) and remission (34% of 141 vs. 33% of 139; p=.87) in the Neuropharmagen arm compared to SOC at 12 weeks among individuals with MDD. Response and remission data were missing for 9% of individuals in the guided care group and 14% in the SOC group. None of these trials provided adequate evidence. Both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a mental illness other than depression who are undergoing drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a systematic review and meta-analysis and RCTs evaluating associations between specific genes and outcomes of drug treatment. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review and meta-analysis by Hartwell et al (2020) included 7 RCTs and reported no significant moderating effect of rs1799971, a single nucleotide polymorphism (SNP) that encodes a non-synonymous substitution (Asn40Asp) in the mu-opioid receptor gene, *OPRM1* on response to naltrexone treatment of alcohol use disorder. Bradley et al (2018) conducted a double-blind RCT among individuals with anxiety disorders and reported statistically significant improvement in response (≥50% decrease in Hamilton Rating Scale for Anxiety [HAM-A]) in the NeuroIDgenetix arm (63% of 82) compared to SOC (50% of 95) at 12 weeks among a moderate and severe group of patients (p=.04). There was evidence of reporting bias and, it was unclear if the analysis was based on the ITT population. Furthermore, among the randomized moderate and severe anxiety patients with only anxiety, 25% in the experimental arm and 17% in the SOC arm were lost to follow-up over the 12-week period. Skokou et al (2024) conducted a prospective RCT in adults with MDD, bipolar disorder, or schizophrenia and reported a statistically significant reduction in clinically relevant adverse drug reactions in the pharmacogenetic testing guided arm (10.4%) compared to standard care (19.1%) among patients with actionable genotypes (p=.049); however, this analysis included patients with MDD and provided no stratified analysis for bipolar disorder or schizophrenia. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Not applicable

Related Policies

- Cranial Electrotherapy Stimulation and Auricular Electrostimulation
- Deep Brain Stimulation
- Repetitive Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders

Benefit Application

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

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

SB 496
SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

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

Examples of commercially available panels include the following:

- Genecept™ Assay (Genomind);
- STA^{2}R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical Reference Laboratory). Specific variants included in the panel were not easily identified from the manufacturer's website.
- GeneSight® Psychotropic panel (Assurex Health);
- Mental Health DNA Insight™ panel (Pathway Genomics);
- IDgenetix-branded tests (AltheaDx).

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

AltheaDx offers a number of IDgenetix-branded tests, which include several panels focusing on variants that affect medication pharmacokinetics for a variety of disorders, including psychiatric disorders.

Rationale

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.

Literature Review

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.

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.

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 for a period of at least 2 weeks. At least 1 symptom must be: (1) lack of interest or enjoyment in most activities, almost every day; or (2) depressed mood almost every day for most of the day. In addition, at least 4 of the symptoms below must be present almost every day:

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

The symptoms are not attributable to another medical condition, or behavioral disorder or substance abuse.[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 are: selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and atypical agents.

Individuals who fail to achieve remission of MDD after 2 vigorous trials of 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.

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

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

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

Comparators
The 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 (e.g., 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.

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;	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.

Outcome Measure	Description	Scale	Clinically Meaningful Difference
	inability to feel; suicidality		
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.

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 8 genes (59 variants) in relation to 38 psychotropic medications and the potential for gene-drug interactions. Based on results from the genotype test, the medications are categorized as either congruent ('use as directed' or 'use with caution') or incongruent ('use with increased caution and with more frequent monitoring') for a particular individual.

Systematic Reviews and Meta-Analyses

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.[19,] 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% confidence interval [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 (risk ratio [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.[20,] 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)-*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 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 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 Indian/Alaska Native	Treatment guided by GeneSight (n=966 randomized; n=754 at week 24)	SOC (n=978 randomized; n=775 at week 24)	
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 depressive disorder, HAM-D17 >14 (moderate); 80% female; 98% non-Hispanic White, 2% Black	Treatment guided by GeneSight (n=26)	SOC (n=25)	

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)
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				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
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.
[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 predictivevalues); 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 1,944 randomized individuals, data were reported for 1,819 at four weeks follow-up and 1,541 at 24 weeks follow-up		4. Underpowered; n=1000 per arm required to detect remission
Greden et al (2019)[22,] (GUIDED)				1,2. Of 1,799 randomized individuals, data were reported for 1,299 in the ITT population and 1,167 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 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.

NeuroIDgenetix test

Randomized Controlled Trials

Two RCTs reported results of antidepressant therapy selection, informed by NeuroIDgenetix test results compared to antidepressant therapy selected without Neuropharmagen 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 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%	Treatment guided by NeuroIDgenetix (n=352)	SOC (n=333)

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
				female; 63% White, 18% Black, 16% Hispanic, 1% Asian, 1% other race/ethnicity		
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

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 reported for moderate/severe, only severe	1. Approximately 15% of randomized patients were lost to follow-up over the 12 week trial Analysis does not appear to be intent to treat	1. No description of power and sample size calculations	
Olson et al (2017)[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

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 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; race/ethnicity not reported	Treatment guided by Neuropharmagen (n=52)	SOC (n=48)
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%	Treatment guided by Neuropharmagen (n=155)	SOC (n=161)

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
				female; 92% White, 5% Latin American, 2% other race/ethnicity		

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.
[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		

Study	Allocations[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
				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

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).

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 contolled trial; SOC: standard of care.

Table 15. Summary of Results of RCTs Assessing NeuroIDgenetix

Study	N	Outcomes			
		Response ≥50% decrease in HAM-A 17		Remission: HAM-A17 ≤7	
Bradley et al (2019)[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 contolled 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.	

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 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 *HTR2*A are not yet supported for clinical use in antidepressant prescribing. Dosing recommendations for SSRIs based 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.

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
***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 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.	Consider a 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.
***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	Initiate therapy with recommended starting dose.	Moderate	

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
	with *CYP2D6* normal metabolizers. Higher plasma concentrations may increase the probability of side effects.			
***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-desmethylvenlafaxine: venlafaxine ratio in *CYP2D6* intermediate metabolizers.	No action recommended based on genotype for venlafaxine because of minimal evidence regarding the impact on efficacy or side effects.	No recommendation	

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
***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.
***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	Initiate 50% of starting dose (e.g., 5 mg) and titrate to the maximum recommended dose	Moderate	Drug–drug interactions and other patient characteristics (e.g., age, renal function,

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
	with *CYP2D6* normal metabolizers. Higher plasma concentrations may increase the probability of side effects.	of 10 mg or consider a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2D6.*		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 active compounds when compared with *CYP2C19* normal metabolizers. Lower plasma concentrations decrease the probability of clinical benefit.	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.*	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.
***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	Consider a clinically appropriate antidepressant not predominantly metabolized	Strong	Per the FDA warning, citalopram 20 mg/day is the maximum recommended dose

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
	with *CYP2C19* normal and intermediate metabolizers. Higher plasma concentrations may increase the probability of side effects.	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.		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, 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 plasma concentrations	Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with *CYP2C19* normal	Moderate	*CYP2B6* metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should be considered when

Dosing recommendations for paroxetine based on *CYP2D6* phenotype				
	may increase the probability of side effects.	metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*.		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.
***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.
***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.

Phenotype	*CYP2D6* ultrarapid or rapid metabolizer	*CYP2D6* normal metabolizer	*CYP2D6* intermediate metabolizer	*CYP2D6* poor metabolizer	*CYP2D6* indeterminate metabolizer
***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 select a clinically appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*.	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 appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*.	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 appropriate alternative antidepressant not predominantly metabolized by *CYP2C19*.	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 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."

The ISPG also included the following considerations regarding pharmacogenetic testing:

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National and Local Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Local coverage guidance for California is provided by the Molecular Diagnostic Services Program (MolDx) in the document MolDX: Pharmacogenomics Testing and the associated Billing and Coding: MolDX: Pharmacogenomics Testing. MolDx considers pharmacogenomic testing, including to guide treatment mental health conditions, medically necessary, appropriate, and approved for use in the patient's condition and there is a known gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A and B). As noted above in Table 18, CYP2D6, CYP2C19 and CYP2B6 have CPIC recommendations to guide dosing of

drugs to treat mental health conditions and are covered by MolDx for those indications. MolDx states that the following multigene panels are covered for specific intended uses:

Test Name	Company	Intended Use
GENESIGHT	Assurex Health	Major Depressive Disorder (MDD) or Neuropsychiatric
Genomind Professional PGx Express™	Genomind, Inc.	Neuropsychiatric
NeuroIDgenetix	AltheaDx	Major Depressive Disorder (MDD) or Neuropsychiatric
Neuropharmagen	Precision Molecular Solutions	Neuropsychiatric
PGXPSYCH	PHD Laboratory LLC	Neuropsychiatric
Psychotropic Pharmacogenomics Gene Panel	Mayo Clinic Laboratories	Neuropsychiatric

Ongoing and Unpublished Clinical Trials

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

Table 20. Summary of Key Trials

NCT Number	Title	Enrollment	Completion Date
Ongoing			
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	Jul 2025
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			
NCT04615234	Towards Precision Medicine in Psychiatry: Clinical Validation of a Combinatorial Pharmacogenomic Approach (PANDORA)	300	Mar 2023 (status unknown)
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
NCT04500301	Pharmacogenomic Testing to Personalize Supportive Oncology	120	Feb 2024 (completed)
NCT04500301	Pharmacogenomic Testing to Personalize Supportive Oncology	120	Feb 2024 (completed)

NCT Number	Title	Enrollment	Completion Date
NCT03674138	Pharmacogenomic-Guided Antidepressant Drug Prescribing in Cancer Patients	300	Oct 2024 (completed)
NCT05669391	Pharmacogenomics on Individualized Precise Treatment of Patients With Depression	120	Dec 2026 (completed)

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

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Documentation for Clinical Review

- No records required

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
	0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7)
	0032U	COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant

Type	Code	Description
	0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (e.g., citalopram metabolism) gene analysis, common variants (i.e., HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])
	0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, common and select rare variants (i.e., *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
	0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
	0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene)
	0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
	0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans)
	0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5′ gene duplication/multiplication)
	0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 3′ gene duplication/ multiplication)
	0156U	Copy number (e.g., intellectual disability, dysmorphology), sequence analysis
	0173U	Psychiatry (i.e., depression anxiety) genomic analysis panel includes variant analysis of 14 genes
	0175U	Psychiatry (e.g., depression anxiety); genomic analysis panel variant analysis of 15 genes
	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
	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)

Type	Code	Description
	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
HCPCS	None	

Policy History

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

Effective Date	Action
03/01/2016	BCBSA Medical Policy Adoption
08/01/2016	Policy revision without position change
08/01/2017	Policy revision without position change
05/01/2018	Coding update
11/01/2018	Policy title change from Genetic Testing for Mental Health Conditions Policy revision without position change
08/01/2019	Policy revision without position change
03/01/2020	Coding Update.
08/01/2020	Annual review. Policy Guidelines updated. Coding update
09/01/2020	No change to policy statement. Literature review updated.
09/01/2021	Annual review. No change to policy statement. Literature review updated.
03/01/2022	Coding Update.
09/01/2022	Annual review. No change to policy statement. Literature review updated.
11/01/2022	Coding Update.
03/01/2023	Coding Update.
09/01/2023	Annual review. No change to policy statement. Literature review updated. Coding Update.
10/01/2023	Coding Update.
10/01/2025	Policy reactivated. Previously archived from 02/01/2024 to 09/30/2025

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.

- This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
- Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
- The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Genetic Testing for Diagnosis and Management of Mental Health Conditions 2.04.110** **Policy Statement:** I. Genetic testing for diagnosis and management of mental health disorders is considered **investigational** in all situations, including but not limited to the following: A. To confirm a diagnosis of a mental health disorder in an individual with symptoms B. To predict future risk of a mental health disorder in an asymptomatic individual C. To inform the selection or dose of medications used to treat mental health disorders, including but not limited to the following medications*: 1. Selective serotonin reuptake inhibitors 2. Selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors 3. Tricyclic antidepressants 4. Antipsychotic drugs II. Genetic testing panels for mental health disorders are considered **investigational** for **all** indications, including but not limited to the following: A. Genecept Assay B. GeneSight Psychotropic panel C. Mental Health DNA Insight panel D. Proove Opioid Risk assay E. STA^{2}R test Note: For individuals enrolled in health plans subject to the Biomarker Testing Law (Health & Safety Code Section 1367.667 and the Insurance Code Section 10123.209), Centers for Medicare & Medicaid Services (CMS) Local Coverage Determination (LCD) may also apply. Please refer to the

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	Medicare National and Local Coverage section of this policy and to MolDX: Pharmacogenomics Testing for reference.