Genetic Testing for Diagnosis and Management of Behavioral Health Conditions

Effective: December 1, 2025

Next Review: August 2026
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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Genetic testing has been proposed as method to evaluate risk of having a behavioral health disorder and to guide the selection of medication for such disorders.

MEDICAL POLICY CRITERIA

Note: Please see Cross References for policies related to:

- Genetic testing for *CYP450* genes not related to behavioral health
- Genetic testing for methionine metabolism enzymes, including MTHFR
- Chromosomal microarray analysis (CMA) and next-generation sequencing panels for autism spectrum disorder

I. Genetic testing for diagnosis and management of behavioral health disorders is considered **investigational** in <u>all</u> situations, including but not limited to the following:

   A. To confirm a diagnosis of a behavioral health disorder in an individual with symptoms.

   B. To predict future risk of a behavioral health disorder in an asymptomatic individual.

C. To inform the selection or dose of medications used to treat behavioral health disorders, including but not limited to selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and antipsychotic drugs.

II. Genetic testing panels for behavioral health disorders, including but not limited to the Genecept Assay, STA^{2}R test, the GeneSight® Psychotropic panel, the Proove Opioid Risk assay, and the Mental Health DNA Insight panel, are considered **investigational** for all indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

BEHAVIORAL HEALTH DISORDERS

Behavioral health conditions considered in this policy include schizophrenia and related psychotic disorders, bipolar and related disorders, depressive disorders, anxiety disorders, hyperactivity disorders, obsessive-compulsive and related disorders, and substance-related and addictive disorders.

GENES COMMONLY TESTED FOR BEHAVIORAL HEALTH DISORDERS

- *5HT2A*
- *5HT2C*
- *5-HTTLPR*
- *ABCB1* (*MDR1*)
- *ANK3*
- *CACNA1C*
- *COMT*
- *DAT1/SLC6A3*
- *DBH*
- *DRD1*
- *DRD2*
- *HTR2A*
- *HTR2C*
- *OPRK1*
- *OPRM1*
- *SLC6A4*
- *SULT4A1*
- *UGT1A4*
- *CYP450 genes (*see GT10, Cytochrome p450 Genotyping)
- *MTHFR (see GT65, Genetic Testing for Methionine Metabolism Enzymes, including MTHFR, for Indications Other than Thrombophilia*

CROSS REFERENCES

1. Cytochrome p450 and VKORC1 Genotyping for Treatment Selection and Dosing, Genetic Testing, Policy No. 10
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Chromosomal Microarray Analysis (CMA) or Copy Number Analysis for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies, Genetic Testing, Policy No. 58
4. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
5. Genetic Testing for Methionine Metabolism Enzymes, Including MTHFR, Genetic Testing, Policy No. 65
6. Genetic Testing for Epilepsy, Genetic Testing, Policy No. 80
7. Investigational Gene Expression, Biomarker, and Multianalyte Testing, Laboratory, Policy No. 77

BACKGROUND

BEHAVIORAL HEALTH DISORDERS

Behavioral health disorders cover a wide range of clinical phenotypes and are generally classified by symptomatology, as in the American Psychiatric Association's Diagnostic and

Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). In addition to counseling and other forms of behavioral treatment, treatment commonly involves one or more psychotropic medications aimed at alleviating symptoms of the disorder. Although there are a wide variety of effective medications, treatment of behavioral health disorders is characterized by relatively high rates of inadequate response. This often necessitates numerous trials of individual agents and combinations of medications to achieve optimal response.

Knowledge of the physiologic and genetic underpinnings of behavioral health disorders is advancing rapidly and may substantially alter the way these disorders are classified and treated. Genetic testing could be used in several ways, including stratifying patients' risks of developing a particular disorder, aiding diagnosis, targeting medication therapy, and optimally dosing medication.

Pharmacogenetic Testing

Drug efficacy and toxicity substantially across individuals. Because drugs and doses are typically adjusted, if needed, by trial-and-error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Multiple factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genes coding for drug-metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

Pharmacogenomics studies how an individual's genetic inheritance affects the body's response to drugs. It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse events, and decrease medical costs.

Genes Relevant to the Diagnosis and Management of Behavioral Health Disorders

Below is a brief outline of genes that may be relevant to the diagnosis and management of behavioral health disorders, which are currently available in genetic testing panels.

Serotonin Transporter

The serotonin transporter gene, *SLC6A4,* is responsible for coding the protein that clears serotonin (5-hydroxytryptamine) metabolites from the synaptic spaces in the central nervous system (CNS). This protein is the principal target for many of the selective serotonin reuptake inhibitors (SSRIs). By inhibiting the activity of the *SLC6A4* protein, the concentration of 5-hydroxytryptamine in the synaptic spaces is increased. A common variant in this gene consists of insertion or deletion of 44 base pairs in the serotonin-transporter-linked polymorphic region (*5-HTTLPR*). These variants have been studied in relation to a variety of psychiatric and nonpsychiatric conditions, including anxiety, obsessive-compulsive disorder, and response to SSRIs.

Serotonin Receptor

The gene *5HT2C* codes for one of at least six subtypes of the serotonin receptor that are involved in the release of dopamine and norepinephrine. These receptors play a role in controlling mood, motor function, appetite, and endocrine secretion. Alterations in functional status have been associated with affective disorders such as anxiety and depression. Certain antidepressants (e.g., mirtazapine, nefazodone) are direct antagonists of this receptor. There is also interest in developing agonists of the 5HT2C receptor as treatment for obesity and schizophrenia, but such medications are not commercially available at present.

The gene *5HT2A* codes for another subtype of the serotonin receptor. Variations in the *5HT2A* gene have been associated with susceptibility to schizophrenia and obsessive-compulsive disorder and response to certain antidepressants.

Sulfotransferase Family 4A, Member 1

The sulfotransferase family 4A, member 1, gene (*SULT4A1*) encodes a protein involved in the metabolism of monoamines, particularly dopamine and norepinephrine.

Dopamine Receptors

The *DRD2* gene codes for the D2 subtype of the dopamine receptor. The activity of this receptor is modulated by G proteins, which inhibit adenyl cyclase. These receptors are involved in a variety of physiologic functions related to motor and endocrine processes. The D2 receptor is the target of certain antipsychotic drugs. Variants in this gene have been associated with schizophrenia and myoclonic dystonia, as well as addictive behaviors, such as smoking and alcoholism.

The *DRD1* gene encodes another G protein–coupled receptor that interacts with dopamine to mediate some behavioral responses and to modulate D2 receptor–mediated events. Variants of the *DRD1* gene have been associated with nicotine dependence and schizophrenia.

The *DRD4* gene encodes a dopamine receptor with a similar structure; *DRD4* variants have been associated with risk-taking behavior and attention-deficit/hyperactivity disorder (ADHD).

Dopamine Transporter

Similar to the *SLC6A4* gene, the dopamine transporter gene (*DAT1* or *SLC6A3*) encodes a transporter that mediates the active reuptake of dopamine from the synaptic spaces in the CNS. Variants in this gene are associated with Parkinson disease, Tourette syndrome, and addictive behaviors.

Dopamine β-Hydroxylase

The dopamine β-hydroxylase gene (*DBH*) encodes a protein that catalyzes the hydroxylase of dopamine to norepinephrine. It is primarily located in the adrenal medulla and in postganglionic sympathetic neurons. Variation in *DBH* has been investigated as a modulator of psychotic symptoms in psychiatric disorders and in tobacco addiction.

Gated Calcium Channel

The gated calcium channel gene (*CACNA1C*) is responsible for coding of a protein that controls activation of voltage-sensitive calcium channels. Receptors for this protein are found widely throughout the body, including skeletal muscle, cardiac muscle, and in neurons in the

CNS. In the brain, different modes of calcium entry into neurons determine which signaling pathways are activated, thus modulating excitatory cellular mechanisms. Associations of variants of this gene have been most frequently studied in relation to cardiac disorders. Specific variants have been associated with Brugada syndrome and a subtype of long QT syndrome (Timothy syndrome).

Ankyrin 3

Ankyrins are protein components of the cell membrane and interconnect with the spectrin-based cell membrane skeleton. The *ANK3* gene codes for the protein ankyrin G, which has a role in regulating sodium channels in neurons. Alterations of this gene have been associated with cardiac arrhythmias, such as Brugada syndrome. Variants of this gene have also been associated with bipolar disorder, cyclothymic depression, and schizophrenia.

Catechol O-Methyltransferase

The catechol O-methyltransferase gene (*COMT*) codes for the COMT enzyme, which is responsible for the metabolism of the catecholamine neurotransmitters, dopamine, epinephrine, and norepinephrine. COMT inhibitors (e.g., entacapone) are currently used to treat Parkinson disease. A variant of the COMT protein, Val158Met, has been associated with alterations in emotional processing and executive function and has also been implicated in increasing susceptibility to schizophrenia.

Methylenetetrahydrofolate Reductase

The methylenetetrahydrofolate reductase gene (*MTHFR*) is a widely studied gene that codes for the protein that converts folic acid to methylfolate. Methylfolate is a precursor for the synthesis of norepinephrine, dopamine, and serotonin. It is a key step in the metabolism of homocysteine to methionine, and deficiency of MTHFR protein can cause hyperhomocysteinemia and homocystinuria. The MTHFR protein also plays a major role in epigenetics, through methylation of somatic genes. A number of variants have been identified that alter activity of the MTHFR enzyme. These variants have been associated with a wide variety of clinical disorders, including vascular disease, neural tube defects, dementia, colon cancer, and leukemia.

γ-Aminobutyric Acid A Receptor

The γ-aminobutyric acid A (GABA) receptor gene encodes a ligand-gated chloride channel composed of five subunits that responds to GABA, a major inhibitory neurotransmitter. Variants in the GABA receptor gene have been associated with several epilepsy syndromes.

μ- and κ-Opioid Receptors

OPRM1 encodes the μ-opioid receptor, which is a G protein–coupled receptor that is the primary site of action for commonly used opioids, including morphine, heroin, fentanyl, and methadone. Variants in the *OPRM1* gene have been associated with differences in dose requirements for opioids. *OPRK1* encodes the κ-opioid receptor, which binds the natural ligand dynorphin and a number of synthetic ligands.

Cytochrome P450 Genes

CYP2D6, *CYP2C19*, *CYP3A4*, *CYP1A2*, *CYP2C9*, and *CYP2B6* code for hepatic enzymes

that are members of the cytochrome P450 family and are responsible for the metabolism of a wide variety of medications, including many psychotropic agents. For each of these genes, variants exist that affect the rate of enzyme activity, which consequently affect drug metabolism rates. Based on the presence or absence of variants, patients can be classified as rapid metabolizers, intermediate metabolizers, and poor metabolizers. Rapid metabolizers may require lower doses to avoid adverse events from an excess of medication in their system.

P-Glycoprotein Gene

The *ABCB1* gene, also known as the *MDR1* gene, encodes P-glycoprotein, which is involved in the transport of most antidepressants across the blood-brain barrier. *ABCB1* variants have been associated with differential response to antidepressants that are substrates of P-glycoprotein, but not to antidepressants that are not P-glycoprotein substrates.

UDP-Glucuronosyltransferase Gene

The UDP-glucuronosyltransferase gene (*UGT1A4*) encodes an enzyme of the glucuronidation pathway that transforms small lipophilic molecules into water-soluble molecules. Variants in the *UGT1A4* gene have been associated with variation in drug metabolism, including some drugs used for behavioral health disorders.

REGULATORY STATUS

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

Commercially Available Genetic Tests

Several test labs market either panels of tests or individual tests relevant for behavioral health disorders, which may include a variety of genes relevant to psychopharmacology or risk of mental illness. Some of the panels (e.g., the GeneSight® panel) provide an overall risk score or summary score.

Bousman (2018) addressed the issue of which genes and variants should be included on pharmacogenetic testing panels to best inform decisions on medication selection and dosing for patients with mental health conditions. The authors created a network map of gene-drug interactions relevant to psychiatry based on the highest level of evidence from the following seven sources: the Pharmacogenomics Knowledgebase, the Clinical Pharmacogenetics Implementation Consortium, the Dutch Pharmacogenetics Working Group, the Food and Drug Administration, the European Medicines Agency, the Pharmaceuticals and Medical Devices Agency, and the Health Canada (Sante Canada). Based on the network map, the authors proposed a minimum gene and variant set for pharmacogenetic testing in psychiatry that includes 16 variants within five genes (*CYP2C9*, *CYP2C19*, *CYP2D6*, *HLA-A*, and *HLA-B*).

Examples of commercially available panels include, but are not limited to, the following:

- Genecept™ Assay (Genomind, Chalfont, PA);
- STA^{2}R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical

Reference Laboratory, Lenexa, KS). Specific variants included in the panel were not easily identified from the manufacturer's website.
- GeneSight® panel (Myriad Genetics, Salt Lake City, UT);
- Proove Opioid Risk panel (Proove Biosciences, Irvine, CA);
- Mental Health DNA Insight™ panel (Pathway Genomics, San Diego, CA);
- IDgenetix-branded tests (AltheaDx, San Diego, CA).
- INFINITI® Neural Response Panel, PersonalizeDx Labs

In addition, many labs offer genetic testing for individual genes, including *MTFHR*, *CYP450* variants, and *SULT4A1*.

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

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[1] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

This evidence review is focused primarily on clinical validity and utility.

TESTING FOR DIAGNOSIS OR RISK OF BEHAVIORAL HEALTH DISORDER

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

Clinical Validity

Evidence on the clinical validity of genetic testing for behavioral health disorders consists primarily of genome-wide association studies (GWAS) that correlate specific genetic variants with phenotypes and case-control studies that report on the odds ratio for genetic variants in individuals with a clinical disorder compared with individuals without the disorder. In general, cross-sectional and case-control studies cannot be used to generate diagnostic characteristics such as sensitivity and specificity or clinically relevant risk prediction.

Clinical Utility

Although studies have suggested that there may be genetic variants that are associated with increased risk of behavioral health disorders, estimates of the magnitude of the increased risk vary across studies. For the individual tests, results from GWAS and case-control studies are insufficient to determine clinical utility. There is no strong chain of indirect evidence supporting the clinical utility of any of the previously mentioned genes associated with disease risk. To determine clinical utility, evidence is needed showing that testing for variants in these genes leads to changes in clinical management that improve outcomes.

Section Summary

The association between behavioral health disorders and individual gene variants is an area of active investigation. For tests included in currently available genetic testing panels, the largest body of evidence appears to be related to the role of *SLC6A4* and various dopamine receptor genes (*DRD1*, *DRD2*, *DRD4*, *DAT1*) variants and multiple behavioral health disorders. For these and other gene variants, the association with disease risks appears to be relatively weak and not consistently demonstrated across studies. Studies have not been conducted to determine the diagnostic capability or precise risk prediction, but to determine whether the particular genotype of interest is associated with behavioral health disorders. Diagnostic characteristics of the genes or validated risk estimates in clinically relevant populations are not available.

No studies were identified that used genetic tests to diagnose a behavioral health condition to manage patients. There is no clear clinical strategy for how the associations of specific genes and behavioral 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

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

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

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

Assessment of clinical utility of a genomic test cannot be made by a chain of evidence from clinical validity data alone. Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with or without the test. Because these are intervention studies, randomized controlled trials (RCTs) are needed.

Systematic Reviews

Milosavljevic (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.[3] 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 eight 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 of 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).

A meta-analysis by Fares-Otero (2025) focused on three RCTs that evaluated functional outcomes, as measured by the Sheehan Disability Scale/Inventory.[4] In the random-effect analysis, pharmacogenomic-guided antidepressant treatment significantly decreased SDS/I-measured functional disability compared to standard treatment by 2.85 points on average (MD −2.85, 95 % CI −5.44 to −0.26, p=0.031); with substantial heterogeneity (I^2 = 70.46), but this difference became non-significant following Hartung-Knapp adjustment of p-values. The authors noted that the overall certainty of the evidence was very low, in part due to risk of bias and high heterogeneity.

Brown (2020) 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.[5] The meta-analysis revealed a favorable rate of remission among individuals who received therapy guided by pharmacogenomics compared to those receiving standard of care (SOC) treatment for depression. The analysis included a total of 13 trials: 10 RCTs and three 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 4,767 individuals across these 13 trials, with individual study sample sizes ranging from 44 to 1,944 participants. With the exception of two trials, all studies exclusively enrolled individuals diagnosed with MDD. The majority of trials (69%) measured their primary endpoint at eight weeks after baseline, although the range extended to 24 weeks. Remission was primarily assessed using

the Hamilton Depression Rating Scale-17 (HDRS-17), while alternative rating scales were used in two trials. Notably, all studies included pharmacogenomic assessments of the *CYP2C19* and *CYP2D6* genes, although other genes tested varied across studies.

The pooled risk ratio (RR) for remission, comparing pharmacogenomic guided therapy (n=2395) to unguided therapy (n=2,372), was (RR 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 six 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=0.04).

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 (RoB2) for RCTs and Risk Of Bias In Non-randomized Studies of Interventions (ROBINS I) 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 two 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 three 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 two trials. Additionally, one trial exhibited a moderate risk of reporting bias, and two 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.

GeneSight® Test

Randomized Controlled Trials

Four RCTs compared response and remission with antidepressant therapy informed by GeneSight® test results to SOC—antidepressant therapy selected without gene test results.[6-9] 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.[6] The study included 1,944 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 four 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 nine-item Physician Health Questionnaire (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=0.02). 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% C, 0.6 to 0.92; p=0.005). 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=0.005). 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. The secondary outcomes of response rate (OR 1.25, 95% CI 1.07 to 1.46, p=0.005) and symptom improvement (risk difference [RD] 0.56, 95% CI 0.17 to 0.95, p=0.005) on the PHQ-9 also demonstrated an overall pooled effect over time.

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 1,000 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[7] and GAPP-MDD[8]) compared eight-week outcomes in individuals who received treatment for MDD guided by GeneSight® testing or SOC. In both GUIDED (n=1,799) 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. 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.

The GUIDED trial randomized 1,799 individuals. After post-randomization exclusions, according to the text, 1,541 individuals remained, in what was labeled the intention to treat (ITT) cohort, but the ITT results reported in Figure 2 included only 1,299 participants. The publication text also describes a per protocol cohort that included 1,398 participants, yet only 1,167 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 eight 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 intent-to-treat and there were no sensitivity analyses for the missing data provided.[10, 11] 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 4,000 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 (2013) evaluated the effect of providing the GeneSight® test on the management of psychotropic medications used for MDD in a single outpatient psychiatric practice.[9] Fifty-one subjects were enrolled and randomized to treatment as usual or to treatment guided by GeneSight® testing. All subjects underwent GeneSight® testing and report preparation as described for the Hall-Flavin studies previously discussed. At 10-week follow-up, treating physicians changed, augmented, or dose-adjusted subjects' medication regimens with the same likelihood for the GeneSight® group (53%) and the treatment as usual group (58%, p=0.66). 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=0.02). Depression outcomes, measured by the Hamilton Depression Rating Scale (HAM-D17) score, did not differ significantly between groups at the 10-week follow-up. Patient loss to follow-up as not reported. This trial's small size may have limited the ability to detect a significant effect, as the authors estimated that 92 patients per arm would be required. The GeneSight® directed arm and the standard care arm included 26 and 25 patients, respectively, in this pilot study for a larger trial.

Table 1. Summary Characteristics of RCTs Assessing the GeneSight® Test

Study	Country (# of Sites)	Dates	Participants	Interventions	
				Active	Comparator
Oslin (2022)[6]	U.S.	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)
Tiwari (2022)[8] (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)
Greden (2019)[7]	U.S. (60)	2014 - 2017	Patients 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 1,398 of 1,799 randomized	SOC (n=717)* *Per protocol 1,398 of 1,799 randomized
Winner (2013)[9]	U.S. (1)	NR	Patients with MDD, 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; NR: not reported; QIDS: Quick Inventory of Depressive Symptomatology; RCT: randomized controlled trial; SOC: standard of care

Table 2. Summary of Results of RCTs Assessing the GeneSight® Test

Study	Treatment Group	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 (2022)[6]		24 weeks		
	GeneSight®	32.1%	17.2%	5.4
	Standard of	27.5%	16%	4.8
	Risk Difference (95% CI), p-	5.1 (0.6 to 9.6), p=0.03	1.5 (-2.4 to 5.3), p=0.45	0.65 (0.1 to 1.19), p=0.02
Tiwari (2022)[8]		8 weeks		
	GeneSight®	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)
	Standard of care	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)
	HR/Diff/OR/RR (95% CI), p-value	ITT: MD 3.3, p=0.54 PP: MD 7.6, p=0.26	ITT: MD 6.7, p=0.10 PP: MD 7.4, p=0.13	ITT: MD 6.0, p=0.17 PP: MD 4.9, p=0.27
Greden (2019)[7]		8 weeks		
	GeneSight®	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)
	Standard of care	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=0.007 PP: MD 6.1, p=0.01	ITT: MD 5.4, p=0.005 PP: MD 5.2, p=0.007	ITT: MD 3.2, p=0.07 PP: MD 2.8, p=0.11
Winner (2013)[9]		10 weeks		
	GeneSight®	36%	20%	
	Standard of care	20.8%	8.3%	

Study	Treatment Group	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
	Risk difference (95% CI), p-value	OR 2.14 (95% CI 0.59 to 7.79)	OR 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: Patient Health Questionnaire 9 item; PP: per protocol; SE: standard error.

Section Summary: GeneSight® Test

Evidence for the use of GeneSight® test to inform antidepressant selection for patients includes four 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 SOC—antidepressant therapy selected without gene test results.

Bradley (2018) published an double-blindd trial that randomized 685 patients with depression and/or anxiety to equal groups that received either the NeuroIDgenetix® test or SOC.[12] Eligible participants were either “new to treatment”, defined as taking medication less than six weeks, or “inadequately controlled”, defined as lack of medication efficacy or discontinuation of treatment due to intolerability or adverse events. Outcomes included HAM-D, the Hamilton Rating Scale for Anxiety (HAM-A), and adverse drug events. Trained and blinded clinicians conducted interviews using the HAM-D and HAM-A. Approximately 15% of randomized patients were lost to follow up over the 12-week period. Response results were only reported for 261 moderate and severe group of patients and remission results were reported for 93 severe group of patients. Response rates (OR 4.72, 95% CI 1.93 to 11.52, p<0.001) and remission rates (OR 3.54, 95% CI 1.27 to 9.88, p<0.02) were significantly higher in the test-guided group as compared to the control group at 12 weeks. The frequency of adverse drug events did not differ statistically between groups. Study does not report clearly if the analysis was based on intention to treat population. Reporting was incomplete and suggestive of selective reporting.

Olson (2017) conducted an RCT in which patients with neuropsychiatric disorders were randomized to treatment guided by NeuroIDgenetix® or SOC.[13] A majority of the patients, 56% in the intervention group and 64% in the control group, had a primary diagnosis of depression. Subgroup analyses by neuropsychiatric disorder were not conducted. Outcomes included Neuropsychiatric Questionnaire, Symbol Digit Coding test, and adverse drug events. The Neuropsychiatric Questionnaire is a computerized survey addressing symptoms of neuropsychoses, and the SCD assesses attention and processing speed, which is sensitive to medication effects. There were no significant differences in Neuropsychiatric Questionnaire or Symbol Digit Coding scores between groups. However, the patients 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 patients included

in the analysis. ClinicalTrials.gov lists neurocognitive measures as co-primary outcomes, but these are not reported, suggestive of selective reporting.

Table 3. Summary Characteristics of RCTs Assessing the NeuroIDgenetix® Test

Study	Country (# of Sites)	Dates	Participants	Interventions	
				Active	Comparator
Bradley (2018)[12]	U.S. (20)	2016	Patients with depression and/or anxiety disorders using either HAM-D17 or HAM-A score ≥18 (moderate and severe) were included in efficacy analysis; either new to medication or inadequately controlled with medication; 73% female; 63% White, 18% Black, 16% Hispanic, 1% Asian, 1% other race/ethnicity	Treatment guided by NeuroIDgenetix® (n=352)	SOC (n=333)
Olson (2017)[13]	U.S. (6)	2015	Patients 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; SOC: standard of care.

Table 4. Summary of Results of RCTs Assessing the NeuroIDgenetix® Test

Study	N	Outcomes	
		Response ≥50% decrease in HAM-D17	Remission: HAM-D17 ≤7
Bradley (2018)[12]		12 weeks	12 weeks
NeuroIDgenetix®	140 (moderate/severe)	64%	NR
SOC	121 (moderate/severe)	46% (p=0.01)	NR
NeuroIDgenetix®	40 (severe)		35%
SOC	53 (severe)		13% (p=0.02)
		≤1 Adverse Drug Event	≤2 Adverse Drug Event
Olson (2017)[13]		10 weeks	10 weeks
NeuroIDgenetix®	NR	28%	5%
SOC	NR	53% (p=0.001)	24% (p=0.001)

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

Section Summary: NeuroIDgenetix® Test

Evidence for the use of NeuroIDgenetix® test to inform antidepressant selection includes two RCTs, one reporting response and remission as outcomes and another reporting adverse

events as outcome. None of the trials provided adequate or supportive evidence in terms of relevance, design and conduct or consistency and precision. Both studies have major limitations in design and conduct and in consistency and precision.

Neuropharmagen® Test

Systematic Reviews

Vilches (2019) conducted a meta-analysis with the aim to assess the clinical utility of Neuropharmagen® in the management of patients with depression.[14] The study included two RCTs and a multicenter, retrospective, observational study.[15-17] Evidence from both RCTs is discussed below.

Randomized Controlled Trials

Han (2018) conducted an RCT randomizing patients with MDD to receive antidepressants through standard physician assessment or guided by results from the Neuropharmagen® test.[15] 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 eight 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 intention-to-treat population consisted of all patients who had at least one post-treatment assessment for effectiveness during the study. The effectiveness evaluation was based on the intention-to-treat analysis with intention-to-treat on last observation carried forward (LOCF). The mean change of HAM-D17 score was significantly different between two groups favoring guided arm by −4.1 point of difference (p=0.010) at the end of treatment. The response rate (71.7 % vs. 43.6%, p=0.014) was also significantly higher in the guided arm than in standard care arm at the end of treatment, while the remission rate was numerically higher in the guided arm than in standard care arm without statistical difference (45.5% vs. 25.6%, p=0.071). The study reported early dropout of 25% in guided-care and 38% in standard care arm. The reason for early dropout associated with adverse events was higher in standard care arm (n=9, 50.0%) than in guided care arm (n=4, 30.8%). The effectiveness evaluation was based on the intention-to-treat analysis with LOCF. Use of LOCF assumes data are missing completely at random.[18] The distribution of reasons for termination among early dropouts indicates that the assumption of randomness is unlikely to hold in this analysis. Study did not report registration in any clinical trial database.

Another industry-sponsored RCT (AB-GEN trial) was published by Pérez (2017), evaluating the Neuropharmagen® panel in 316 adults diagnosed with MDD at multiple centers in Spain.[16] The pharmacogenetics report from Neuropharmagen® provided information on 50 drugs, highlighting gene-drug interactions and drug recommendations from the Food and Drug Administration and Clinical Pharmacogenetics Implementation Consortium. The primary outcome was Patient Global Impression of Improvement (PGI-I), which was collected by telephone interviewers blinded to treatment allocation group. A response was defined as a PGI-I of 2 or less. Percent responders differed nominally between groups (p=0.05) at the end of the 12-week study. Changes in HAMD-17 scores were significant at five weeks (p=0.04) but not at 12 weeks (p=0.08). 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=0.39) or remission (34.0% vs. 33.1%, p=0.87) between guided care and standard

care arms at 12 weeks. However, response and remission data were missing for 9% patients in the guided care group and 14% of the standard care group.

Table 5. Summary Characteristics of RCTs Assessing the Neuropharmagen® Test

Study	Country (# of Sites)	Dates	Participants	Interventions	
				Active	Comparator
Han (2018)[15]	Korea (2)	NR	Patients with MDD (DSM-5 criteria) currently receiving antidepressant therapy (≥6 weeks) with inadequate response (CGI-I ≥3); 75% female; race/ethnicity not reported	Treatment guided by Neuropharmagen® (n=52)	SOC (n=48)
Perez (2017)[16]	Spain (18)	2014 to 2015	Patients with MDD (DSM-IV-TR criteria) new to medication or inadequately controlled with medication; 64% female; 92% White, 5% Latin American, 2% other race/ethnicity	Treatment guided by Neuropharmagen® (n=155)	SOC (n=161)

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

Table 6. Summary of Results of RCTs Assessing the Neuropharmagen® Test

Study	N	Outcomes	
		Response ≥50% decrease in HAM-D17	Remission: HAM-D17 ≤7
Han (2018)[15]		8 weeks	8 weeks
Neuropharmagen®	52	71.7%	45.5%
SOC	48	43.6% (p=0.01)	25.6% (p=0.07)
Perez (2017)[16]		12 weeks	12 weeks
Neuropharmagen®	141	45.4%	34.0%
SOC	139	40.3% (p=0.39)	33.1% (p=0.871)
		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.

Section Summary: Neuropharmagen® Test

Evidence for the use of Neuropharmagen® test to inform antidepressant selection for patients with MDD includes two RCTs. One trial provided adequate evidence for 'Response' on a relevant population. Both studies have major limitations in design and conduct and inconsistency and precision.

Genecept Assay™

Randomized Controlled Trials

A multicenter randomized trial by Perlis (2020) evaluated the use of the Genecept Assay™ to guide treatment for MDD.[19] Study participants (n=304) and raters were blinded, while

unblinded clinicians used test results to guide treatment in the assay-guided group, but not in the control group. The primary outcome of the study was change in the HAMD after eight weeks of follow-up. Over 90% of patients in both groups completed the study, and no significant differences were found for the primary outcome, or for remission or response between groups.

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

Systematic Reviews

Hartwell (2020) conducted a systematic review and meta-analysis of the moderating effect of rs1799971, a single nucleotide polymorphism that encodes a non-synonymous substitution (Asn40Asp) in the mu-opioid receptor gene, *OPRM1*, on response to naltrexone treatment of alcohol use disorder.[20] The meta-analysis included seven RCTs (659 subjects randomly assigned to receive naltrexone and 597 received placebo). Of the five alcohol consumption outcomes considered, there was a nominally significant moderating effect of the Asn40Asp polymorphism only on drinks per day (d=−0.18, 95% CI=−0.32 to −0.03, p=0.02). However, the effect was not significant when multiple comparisons were taken into account. There was no statistically significant heterogeneity (I^2=33.8%, p=0.18).

Routhieaux (2018) conducted a systematic review to evaluate the clinical value of pharmacogenetic testing in patients with schizophrenia or bipolar disorder.[21] The literature search, conducted through April 2017, identified 18 articles for inclusion. Quality assessment of the studies was not discussed. Twelve of the 18 studies focused on the effect of genetic variants on mood stabilizers and/or psychotic response. Due to the variety of genes and medications across the studies, pooled analyses were not possible. While correlations were reported between certain genetic variants and medication response, the research was unclear on the type of therapeutic recommendations that could be made based on pharmacogenetic testing in patients with schizophrenia.

Randomized Controlled Trials

The trial published by Bradley (2018), described above, randomized 685 patients with depression and/or anxiety disorders to treatment guided by either NeuroIDgenetix® or SOC.[12] Among the participants, 115 in the experimental arm and 120 in the SOC arm had only anxiety. Outcomes included percent reduction in HAM-A and response (50% reduction in HAM-A) rate. Trained and blinded clinicians conducted interviews using the HAM-A. Response results were only reported for 224 moderate and severe anxiety (Anxiety Only HAM-A ≥18) group of patients (109 in the experimental arm and 115 in the SOC arm). Among the randomized moderate and severe anxiety patients with only anxiety, 25% in the experimental arm and 17% in the standard care arm were lost to follow up over the 12-week period. Response rate was significantly higher in the NeuroIDgenetix-guided group as compared to the control group at 12 weeks (63% vs. 50%, p=0.04). Study does not report clearly if the analysis was based on ITT population. Reporting is incomplete and suggestive of selective reporting.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY

The American Academy of Child & Adolescent Psychiatry (AACAP) published a position statement with the following recommendations in 2020:[22]

- Clinicians avoid using pharmacogenetic testing to select psychotropic medications in children and adolescents.
- Future high-quality prospective studies to assess the clinical significance of pharmacodynamic and combinatorial pharmacogenomic testing in children and adolescents.

AMERICAN PSYCHIATRIC ASSOCIATION

The American Psychiatric Association (APA) Council of Research Workgroup on Biomarkers and Novel Treatments published a position statement on the use of pharmacogenetic tools for depression treatment selection in 2024.[23] After an evaluation of the evidence for various pharmacogenomic clinical support tools, including the GeneSight®, NeuroIDgenetix®, Genecept™, and others, the authors concluded that “the evidence does not support the use of currently available combinatorial PGx 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. The authors additionally commented that “the variants chosen for use in PGx tools, and the algorithms by which they are combined, have not been shown to be predictive of clinical efficacy or side effects.”

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.[24, 25] The recommendations state: "we recommend HLA-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.

SUMMARY

There is not enough research to show that genetic testing to confirm a diagnosis of a behavioral health disorder, predict future risk of a behavioral health disorder, or inform the selection or dose of medications used to treat behavioral health disorders, can improve health outcomes for patients. In addition, there are no clinical guidelines based on research that recommend genetic testing for these purposes. Therefore, genetic testing, including panel testing, for behavioral health disorders is considered investigational.

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CODES

NOTE: There are no codes specific to testing for these indications, but the codes in this Medical Policy represent some that are likely to be used for this testing.

Codes	Number	Description
CPT	0032U	COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant
	0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])
	0173U	Psychiatry (ie, depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes

Codes	Number	Description
	0175U	Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes
	0345U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
	0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
	0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
	0349U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions
	0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
	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 (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
	0419U	Neuropsychiatry (eg, depression, anxiety), genomic sequence analysis panel, variant analysis of 13 genes, saliva or buccal swab, report of each gene phenotype
	0423U	Psychiatry (eg, depression, anxiety), genomic analysis panel, including variant analysis of 26 genes, buccal swab, report including metabolizer status and risk of drug toxicity by condition
	0434U	Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes
	0438U	Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted genedrug interactions
	0476U	Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis and reported phenotypes
	0477U	Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis, including impacted gene-drug interactions and reported phenotypes
	0533U	Drug metabolism (adverse drug reactions and drug response), genotyping of 16 genes (ie, ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP2C, CYP2D6, CYP3A5, CYP4F2, DPYD, G6PD, GGCX, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1), reported as metabolizer status and transporter function
	81418	Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis

Codes	Number	Description
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Date of Origin: *February 2018*