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 all 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, STA²R 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
- ABBC1 (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) and Next-generation Sequencing Panels 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, for Indications Other than Thrombophilia, Genetic Testing, Policy No. 65
6. Genetic Testing for Epilepsy, Genetic Testing, Policy No. 80

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

The efficacy and toxicity of psychopharmacotherapeutic drugs vary substantially across individuals. Due to these variances, choice of drug and dose are challenging, requiring close monitoring and adjustments, which prolong the time to optimal therapy. In some cases, serious adverse events may result.

Treatment decisions are currently based on the assessment of different factors that may influence the variability of drug effects: 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.

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

- Geneccept™ Assay (Genomind, Chalfont, PA);
- STA²R 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® Psychotropic panel (Assurex Health, Mason, OH);
- 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).

For evidence evaluating the clinical validity and clinical utility of genetic testing, separate sections of this report will summarize evidence on (1) genes associated with increased disease risk and (2) genes associated with medication pharmacokinetics and pharmacodynamics. The following is a summary of the key literature.

TESTING FOR DIAGNOSIS OR RISK OF BEHAVIORAL HEALTH DISORDER

The purpose of testing for genes 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.

A comprehensive review of the GWAS and case-control studies for all investigated genes and their variants is beyond the scope of this review. A 2015 review of meta-analyses examining the association between specific genes and specific behavioral health disorders reported that 134 genes (206 variants) have been identified as significantly associated risk factors for major depressive disorder, anxiety disorders, ADHD, schizophrenia, or bipolar disorder, with 13 genetic variants shared between two or more disorders.[^2] Examples of research in this area are summarized in Table 1.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Evidence</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANK3, CACNA1C</strong></td>
<td>Bipolar disorder</td>
<td>Croarkin (2017), case-control[3]</td>
<td>Initial analysis showed associations with bipolar disorder; associations no longer significant after controlling for multiple comparisons</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>Kloiber (2012), meta-analysis[4]</td>
<td>Initial analysis showed associations with depression; associations no longer significant after controlling for multiple comparisons</td>
</tr>
<tr>
<td><strong>COMT</strong></td>
<td>Schizophrenia</td>
<td>Zammit (2007), case-control[6]</td>
<td>No association detected</td>
</tr>
<tr>
<td><strong>DRD1, DRD2, DRD4, DAT1 (SLC6A3)</strong></td>
<td>Addictive behavior</td>
<td>Batel (2008), case-control[7]</td>
<td>DRD1 variants associated with alcohol dependence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Huang (2008), case-control[9]</td>
<td>DAT1 variant associated with successful smoking cessation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stapleton (2007), meta-analysis[10]</td>
<td>Inconsistent results: some analyses found DAT1 variants associated with alcohol dependence and some analyses did not</td>
</tr>
<tr>
<td></td>
<td>Bipolar and unipolar disorders</td>
<td>Lopez Leon (2005), case-control[12]</td>
<td>Association with bipolar and unipolar disorders found with one of three DRD2 variants tested Initial analysis showed associations with DRD4 variants; associations no longer significant after controlling for multiple comparisons</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>Jonsson (2003), case-control[14]</td>
<td>DRD2 variants associated with schizophrenia in in males only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pan (2014), meta-analysis[16]</td>
<td>Some DRD1 variants associated with increased risk and some DRD1 variants associated with decreased risk for schizophrenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zhu (2011), case-control[17]</td>
<td></td>
</tr>
<tr>
<td><strong>MTHFR</strong></td>
<td>Bipolar disorder</td>
<td>Hu (2015), meta-analysis[18]</td>
<td>Variants marginally associated with bipolar disorder, particularly in Asian and black populations</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>Bousman (2014), cohort[19]</td>
<td>One variant of several tested may indicate more severe prognosis in patients with depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lizer (2011), case-control[20]</td>
<td>Inconsistent results: some analyses showed variants associated with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wu (2013), meta-analysis[21]</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Disorder</td>
<td>Study</td>
<td>Clinical Utility</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>Schizophrenia, bipolar disorder, depression, schizophrenia combined</td>
<td>Hu (2015), meta-analysis[^18]</td>
<td>Variants associated with schizophrenia, particularly in Asian and black populations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peerbooms (2011), meta-analysis[^22]</td>
<td>Inconsistent results, with one variant associated with the combination of psychiatric conditions, but not with the individual conditions, and other variants not associated with the combination or individual conditions</td>
</tr>
<tr>
<td></td>
<td>SLC6A4</td>
<td>Enoch (2011), case-control[^23]</td>
<td>Variant associated with alcohol and heroin/cocaine addiction</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>Hariri (2002), case-control[^24]</td>
<td>Inconsistent results, with variants showing significant associations with some anxiety-related traits (e.g., neuroticism, fear), but not others (e.g., harm avoidance)</td>
</tr>
<tr>
<td></td>
<td>Bipolar and unipolar disorders</td>
<td>Lasky-Su (2005), meta-analysis[^27]</td>
<td>Variant associated with bipolar disorder, but not unipolar disorder</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>Karg (2011), meta-analysis[^28]</td>
<td>Inconsistent results: when meta-analysis combined significance results, there was an association with the gene, stress, and developing depression; when meta-analysis combined raw data, no association detected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kiyohara (2010), meta-analysis[^29]</td>
<td></td>
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<td></td>
<td></td>
<td>Risch (2009), meta-analysis[^30]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SULT4A1</td>
<td>Meltzer (2008), case series[^31]</td>
<td>All patients in series had schizophrenia; those with variant had worse symptom scores</td>
</tr>
</tbody>
</table>

**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 direct 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 gene (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.

**TESTING FOR GENES ASSOCIATED WITH MEDICATION PHARMACOKINETICS AND PHARMACODYNAMICS**

The purpose of pharmacogenetic testing in patients who are diagnosed with a behavioral health disorder is to inform management decisions, such as whether to start a particular drug, set or adjust dose, or change drugs when a therapy fails.

Genetic variants may alter medications' pharmacokinetics (i.e., how medications are absorbed, distributed, metabolized, or excreted) or pharmacodynamics (i.e., medications' effects on the body); thus, individual genetic differences may lead to variability in the effectiveness of medications used to treat behavioral health disorders.

**Clinical Validity**

A large body of evidence has shown that certain gene variants code for enzymes involved in the metabolism of antipsychotic and antidepressant medications. The evidence consists of systematic reviews, meta-analyses, RCTs, as well as case-control and cohort studies. The largest systematic review, by Altar (2013), sponsored by Assurex, the manufacturer of the GeneSight Psychotropic panel, assessed the efficacy and safety of 26 antipsychotic and antidepressant medications are associated with variants in eight genes: CYP2D6, CYP2C19, CYP2C9, CYP1A2, CYP3A4, two serotonin receptor genes (HTR2C, HTR2A), and SLC6A4.[32] Reviewers identified 294 studies meeting their inclusion criteria. Table 2 summarizes additional studies investigating the association between genetic variants and medications for mental health conditions.

**Table 2. Evidence for Genes Associated with Response to Drug Treatment for Behavioral Health Conditions**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Evidence</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1</td>
<td>Depression</td>
<td>• Breitenstein (2015), meta-analysis[33]</td>
<td>• Meta-analysis showed two of six variants associated with response to antidepressants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gex-Fabry (2008), cohort[34]</td>
<td>• Cohort did not find association between variant and response to SSRI (paroxetine)</td>
</tr>
<tr>
<td>DRD1, DRD2, DRD4</td>
<td>Depression</td>
<td>• Yin (2015), RCT[35]</td>
<td>• DRD4 variants associated with level of response to SSRIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• DRD2 and DAT1 variants not associated with response to SSRIs</td>
</tr>
<tr>
<td>Gene/Phenotype</td>
<td>Disorder</td>
<td>Studies</td>
<td>Additional Information</td>
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<tr>
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<tr>
<td>DAT1 (SLC6A3)</td>
<td>Schizophrenia</td>
<td>Hwang (2007), case-control</td>
<td>DRD1 variants associated with response to antipsychotic drugs among African American samples, but not among whites</td>
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<td></td>
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<td>Kaur (2017), case-control</td>
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<td>Zhang (2010), meta-analysis</td>
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<tr>
<td>CYP450 (CYP2D6, CYP2C19, CYP3A4)</td>
<td>ADHD</td>
<td>Fijal (2015), RCT</td>
<td>Patients with CYP2D6 variant metabolizer status of ultrarapid, extensive, and intermediate have similar safety profiles when treated with SNRI (atomoxetine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ramoz (2009), cohort</td>
<td>CYP2D6 variant not associated with response to SNRI (atomoxetine)</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>Gex-Fabry (2008), cohort</td>
<td>Most studies reported variants not associated with response to antidepressants or remission rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lloret-Linares (2018), cohort</td>
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<tr>
<td></td>
<td></td>
<td>Lobello (2010), meta-analysis</td>
<td>Meta-analysis reported CYP2D6 variant associated with response to SNRI (venlafaxine)</td>
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<td></td>
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<td>Serretti (2009), case-control</td>
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<tr>
<td></td>
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<td>Taranu (2017), cohort</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>Almoguera (2013), case series</td>
<td>Inconsistent results, with some studies showing CYP2D6 variants associated with response to antipsychotic (risperidone) and one study reporting CYP2D6 variants associated with serum concentrations of antipsychotic drug (haloperidol), but not with clinical effects as measured by Schizophrenia Syndrome Scale</td>
</tr>
<tr>
<td></td>
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<td>Crescenti (2008), case-control</td>
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<td>Kaur (2017), case-control</td>
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<td></td>
<td></td>
<td>Panagiotidis (2007), case series</td>
<td></td>
</tr>
<tr>
<td>OPRM1</td>
<td>Addictive behavior</td>
<td>Chamorro (2012), meta-analysis</td>
<td>Variant associated with response to opioid antagonist (naltrexone) in patients with alcohol dependence</td>
</tr>
<tr>
<td>SLC6A2</td>
<td>ADHD</td>
<td>Ramoz (2009), cohort</td>
<td>Variant associated with response to SNRI (atomoxetine)</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>Yin (2015), RCT</td>
<td>Variants not associated with response to SSRIs</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>Addictive behavior</td>
<td>Johnson (2011), RCT</td>
<td>Variant associated with response to serotonin receptor antagonist (ondansetron) measured by mean drinks per drinking day and percentage days abstinent</td>
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<tr>
<td>Anxiety</td>
<td>• Lenze (2010), RCT[^{49}]</td>
<td>• Variant associated with level of response to SSRI (escitalopram)</td>
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<tr>
<td>Bipolar disorder</td>
<td>• Biernacka (2012), meta-analysis[^{50}] • Daray (2010), meta-analysis[^{51}]</td>
<td>• Inconsistent results, with one study finding variant associated with antidepressant-induced mania and one study finding insufficient evidence due to heterogeneity between studies</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>• Lewis (2011), RCT • Porcelli (2012), meta-analysis[^{52}] • Seripa (2015), cohort[^{53}]</td>
<td>• RCT results showed response to SSRI (citalopram) and NARI (reboxetine) similar irrespective of presence of variant • Meta-analysis results showed that among whites, variant may predict antidepressant response and remission, but not among Asians. • Cohort study results showed association between variants and response to SSRIs (escitalopram, sertraline, paroxetine, citalopram)</td>
<td></td>
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</table>

ADHD: attention deficit/hyperactivity disorder, NARI: norepinephrine reuptake inhibitor, RCT: randomized controlled trial, SNRI: serotonin-norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor

**Clinical Utility**

Management changes that might be made in response to genetic testing information include selection of specific medications according to test results, discontinuation of medications, and changes in dosing of medications. However, management changes made in response to genetic testing information are not well-defined and may vary according to the judgment of the treating clinician. Currently, there are no specific recommended changes in management linked to specific test results, making it difficult to assess whether test results lead to improvements in health outcomes.

**Systematic Reviews**

Rosenblat (2017)\[^{54}\] and Health Quality Ontario (2017)\[^{55}\] conducted systematic reviews of randomized and nonrandomized clinical trials evaluating whether pharmacogenetics testing improves clinical outcomes for major depressive disorder.\[^{54}\] Study quality was assessed using the Newcastle-Ottawa Scale in Rosenblat (2017) and the GRADE system in Health Quality Ontario (2017). Overall, the studies were assessed as low quality, because many were open-label, nonrandomized, and industry-sponsored. Also, many of the estimates were imprecise. Pooled analyses were not conducted in either review. Key studies included in the reviews and trials published since the reviews are described below.

**Randomized Controlled Trials**

Bradley (2018) published an industry-funded trial that randomized 685 patients with depression and/or anxiety to equal groups that received either the NeurolDgenetix® test or standard care.\[^{56}\] 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. In the NeurolDgenetix® group, test results were provided before the first study visit. Depression and anxiety symptom data were collected at 4-, 8-, and 12-week follow-up visits, using HAM-A and HAM-D17.
interviews. Medication changes and prescription use was tracked at all visits. Depression was classified by HAM-D17 score as normal (0 to 7), mild (8 to 17), moderate (18 to 24), or severe (>24). Anxiety score classifications had the same cutoff points for the HAM-A instrument. Only patients with moderate or severe disorders (HAM scores 18 and above) were included in the efficacy analysis. Remission was defined as a HAM score of ≤7. There were 579 patients (84.5%) that completed the study. Remission rates for depression were significantly higher in the experimental group (35%, n = 140) than in the control group (13%, n =121) (p=0.01). Response rates (50% reduction in HAM-A scores) were reported for anxiety patients instead of remission rates, and these were slightly higher in the experimental group (63% vs. 50%, p=0.04 at 12-week follow-up). Medication changes were also higher in the experimental group (81% vs. 64% at two-week visit). These changes corresponded with the test recommendation 70% of the time in the test group. Rates of adverse events were very low and not different between groups.

Another industry-sponsored RCT was published by Pérez (2017), evaluating the Neuropharmagen® panel in 316 adults diagnosed with major depressive disorder at multiple centers in Spain.[57] For study inclusion, patients had to have Clinical Global Impression-Severity (CGI-S) scores ≥4 at both screening and randomization visits, and either a requirement for medication de novo or a medication change for depression, as determined by the provider. Patients were assessed at 6- and 12-week follow-up visits and the primary outcome variable, the Patient Global Impression of Improvement (PGI-I) scale, was collected during telephone interviews at 4, 8, and 12 weeks by blinded interviewers. Additional measures were collected by treating (unblinded) psychiatrists, including the HAM-D17, the Sheehan Disability Inventory (SDI), and the Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER). Medication response was defined as scores ≤ 2 on the PGI-I by phone. Of the 316 patients (155 in test group and 161 controls) that were randomized, 280 completed the 12-week follow-up. The primary outcome, sustained response within the study period, did not differ between the test and control groups, although the test group had a higher responder rate at 12 weeks (47.8% vs 36.1%, p=0.0476). Among individuals that reported baseline side effects burden, the test group had higher odds than the control group of reporting better tolerability at 6 and 12 weeks.

Olson (2017) conducted an RCT in which patients with neuropsychiatric disorders were randomized to treatment guided by NeuroIDgenetix® or standard of care.[58] 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 (see Table 5). However, the patients receiving standard of care reported significantly more adverse events (53%) than patients receiving NeuroIDgenetix®-guided care (28%).

A small RCT by Winner (2013) evaluated the effect of providing the GeneSight® test on the management of psychotropic medications used for major depressive disorder in a single outpatient psychiatric practice.[59] 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. This trial’s small size may have limited the ability to detect a significant effect.

**Nonrandomized Studies**

Two comparative, nonrandomized studies compared clinical outcomes in patients with and without genetic testing. Hall-Flavin (2013) reported results from an open-label, nonrandomized comparative trial to evaluate the effects of providing the GeneSight® pharmacogenomics test results to inform the management of psychotropic medications used for major depressive disorder in an outpatient psychiatric practice.[60] Patients with major depressive disorder were enrolled and grouped consecutively into a “guided” group (n=113) or “unguided” group (n=114). All subjects had DNA samples collected and sent for the GeneSight® test, but only providers in the “guided” group received results. Based on results from patients’ genotypes for CYP2D6, CYP2C19, CYP1A2, SLC6A4, and HTR2A, the test generates a “proprietary interpretive report” that includes recommendations for “use as directed,” “use with caution,” or “use with caution and with more frequent monitoring” for each of 26 antidepressant and antipsychotic agents.[54] Subjects were followed for eight weeks, and 93 patients in the unguided group and 72 patients in the guided group completed follow-up (27% drop out rate). Reviewers found a greater reduction in symptoms in the guided group than in the unguided group for: HAM-D17 (\( p<0.001 \)), the Quick Inventory of Depressive Symptomatology–Clinician Rated (QIDS-C16, \( p<0.001 \)), and the Patient Health Questionnaire (\( p=0.002 \)). Patients in the guided group had a higher rate of remission (26.4%) as measured by the QIDS-C16 than in the unguided patients (12.9%, OR 2.42, 95% CI 1.09 to 5.39, \( p=0.03 \)). Patients in the guided group who were initially on a medication classified as “use with caution and with more frequent monitoring” were more likely (93.8%) than those with the same classification in the unguided group (55%) to have a medication change or dose adjustment during the study period (\( p=0.01 \)).

In an earlier nonrandomized pilot study, Hall-Flavin (2012) compared outcomes for a group of patients with major depression whose physicians received a GeneSight® report to those of a historical control group of patients treated without the GeneSight® report.[61] Twenty-six subjects were included in the “unguided” group and 25 in the “guided” group. At eight weeks of follow-up, patients in the guided group had a 31.2% lower QIDS-C16 score compared with a 7.25% lower score in the unguided group (\( p=0.002 \)), for HAM-D17 scores, the guided group had a 30.8% lower score while the unguided group had a 18.2% lower score (\( p=0.04 \)).

To address the issue of small sample sizes, Altar (2015) published pooled analyses from the three studies previously described (Hall-Flavin [2013], Hall-Flavin [2012], Winner [2013]).[62] Included in the pooled analyses were 119 patients receiving GeneSight®-guided treatment and 139 receiving usual care. Patients who received a “red” score on the basis of the GeneSight® algorithm (“use with increased caution and with more frequent monitoring”) had less improvement in HAM-D17 scores over eight weeks than patients with “yellow” scores (“use with caution”) or “green” scores (“Use as directed”), or yellow/green for subjects prescribed medications that are cytochrome P450 2D6 (CYP2D6) substrates (\( p=0.001, p=0.01, p=0.002 \), respectively) and for subjects prescribed medications that are CYP2C19 substrates (\( p=0.003, p=0.02, p=0.004 \), respectively). None of the single genes included in the GeneSight® panel
was individually associated with positive or negative treatment outcomes. The odds for clinical response, defined as a 50% or greater decrease in HAMD score, was significant, favoring the patients receiving GeneSight®-guided treatment (2.3, 95% CI 1.3 to 3.9). The odds ratio for clinical remission, defined as achieving a score of 7 or less on the HAMD score, was not significant (1.8, 95% CI 0.9 to 3.4).

Breitenstein (2014) reported results of a small nonrandomized comparative study assessing whether genotyping of the \(ABCB1\) gene in clinical practice was associated with changes in medication management in outcomes among 58 patients hospitalized with depression.\(^{[63]}\) Patients and matched controls were selected from the Munich Antidepressant Response Signature project, a naturalistic study designed to identify factors that help to predict and improve treatment response in affective disorders. \(ABCB1\) genotyping was implemented into the study’s protocol in 2008, and genotype results were provided to treating physicians with a one-page letter outlining potential strategies based on genotype. The 58 patients who had \(ABCB1\) genotyping were compared with a matched sample of historical controls enrolled before genotyping was implemented. Patients who received \(ABCB1\) genotyping had higher remission rates at the time of hospital discharge (83.6% vs. 62.1%, \(p=0.005\), one-sided) and lower HAM-D17 scores at the time of hospital discharge (scores extrapolated from graph, 6 vs. 8, \(p=0.02\), one-sided). This study was limited to hospitalized patients with assessment of outcomes limited to the time of hospital discharge.

Brennan (2015) reported results of a case series of 685 patients who underwent testing with the Genecept assay, with the results provided to participating clinicians.\(^{[64]}\) Approximately 70% and 29% of patients had primary diagnoses of a mood or an anxiety disorder, respectively. Eighty-seven percent of patients showed improvement (defined as very much improved, much improved, or minimally improved), and 62% showed very much or much improved status.

Espadeler (2016) reported the results of a retrospective series of psychiatric patients who underwent testing with a pharmacogenetic test (Neuropharmagen®) marketed in Europe.\(^{[65]}\) Patients whose treatment was considered to follow the test recommendations were compared to those whose treatment did not. Criteria for determining whether a patient’s treatment followed recommendations were very complex. Outcomes were assessed by the treating psychiatrist who determined whether the patient improved over baseline. At three-month follow-up, 93% (83/89) patients whose treatment followed the recommendations had improved compared with 82% (76/93) those whose treatment did not (\(p=0.019\)).

**Section Summary**

Four RCTs testing three different genetic panels were identified. After 8 to 12 weeks of follow-up, the largest RCT showed significant improvements in HAMD and HAMA scores among patients whose clinicians were guided by information from genetic tests. However, results in the remaining three trials did not show differences between test-guided and -unguided groups. Nonrandomized studies have reported significant improvements in outcomes among patients receiving guided treatment, but weaknesses in the studies limit the conclusions that can be drawn. Additional studies including larger numbers of patients with randomization and blinded outcome assessment will be needed to confirm findings that genotyping may be associated with sustained improvements in clinical outcomes.

**SUMMARY OF EVIDENCE**
For individuals who are evaluated for diagnosis or risk of a behavioral illness who receive genetic testing for risk of that disorder, the evidence includes various observational studies (case-control, genome-wide association study) evaluating the association between the behavioral health disorder of interest and candidate genes. Relevant outcomes are test validity, other test performance measures, and changes in disease status. Most studies have evaluated the association between genotype and behavioral health disorders without a clinical perspective; thus, diagnostic characteristics and validated risk predictions among specific clinical populations are unknown. The associations are inconsistent across studies. 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. No studies were identified that evaluated whether testing for variants changed clinical management or affected health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a behavioral health disorder who are undergoing drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a large number of observational studies assessing specific genes and outcomes of drug treatment, as well as four RCTS and several observational studies comparing outcomes for patients who received treatment guided by genetic testing with patients who received standard of care treatment. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. A large RCT showed that patients receiving treatment guided by genetic test results experienced significant improvements in mental health scores; however, the remaining RCTs showed no difference in mental health outcomes. Observational studies comparing patients who have had and have not had genetic testing reported that testing may be associated with differences in depression treatment outcomes, though methodologic shortcomings, such as lack of randomization, small sample sizes, and large loss to follow-up limit the conclusions that can be drawn. The evidence is insufficient to determine the effects of the technology on health outcomes.

**PRACTICE GUIDELINE SUMMARY**

No clinical practice guidelines were identified that provided recommendations for genetic testing for behavioral health disorders.

**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.

**REFERENCES**


54. Rosenblat, JD, Lee, Y, McIntyre, RS. Does Pharmacogenomic Testing Improve Clinical Outcomes for Major Depressive Disorder? A Systematic Review of Clinical Trials and


**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.

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GT53 | 21
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<td>HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T&gt;C], HTR2C rs3813929 [c.-759C&gt;T] and rs1414334 [c.551-3008C&gt;G])</td>
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<td>Pain management (opioid-use disorder) genotyping panel, 16 common variants (ie, ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder</td>
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*Date of Origin: February 2018*