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**Medical Policy Manual** Genetic Testing, Policy No. 53

# *Genetic Testing for Diagnosis and Management of Behavioral Health Conditions*

**Effective**: November 1, 2020

**Next Review:** August 2021
**Last Review:**

## 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, 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

## 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.

<u>Serotonin Transporter</u>

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.

<u>Serotonin Receptor</u>

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® 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).

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 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.

#### 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 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 PATIENTS WITH DEPRESSION INADEQUATELY CONTROLLED WITH MEDICATION FOR GENES ASSOCIATED WITH PHARMACOKINETICS AND PHARMACODYNAMICS

The purpose of pharmacogenetic testing in patients who are diagnosed with depression inadequately controlled with medication 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 patients with depression inadequately controlled with medication.

### 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, randomized controlled trials (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*.[2] Reviewers identified 294 studies meeting their inclusion criteria.

### 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.

Systematic Reviews

Of four systematic reviews identified that addressed general pharmacogenetic testing,[3-6] only one conducted a pooled analysis (Rosenblat [2018][6]), calculating risk ratios (RR) for response (defined as >50% decrease in HAMD) and remission (defined as HAMD <8). The RR for response was 1.4 (95% CI 1.1 to 1.6, p=0.0006) and the RR for remission was 1.7 (95% CI 1.1 to 2.8, p=0.02) in favor of guided treatment. Subgroup analyses of RCTs and open-label studies showed that both subgroups' results were significant in favor of guided treatment, though the effect was larger in the group of open-label studies. Quality assessment of the RCTs revealed several sources of bias and the funnel plot for the cohort studies indicated possible publication bias. Table 1 provides a list of included studies for each review and Table 2 summarizes characteristics and results of the reviews.

**Table 1. Comparison of Studies Included in Systematic Reviews**

| Study | Rosenblat (2017)[3] | Health Quality Canada (2017)[4] | Rosenblat (2018)[6] | Soloman (2019)[5]a |
|---|---|---|---|---|
| Berard (2017) | | | | X |
| Berm (2016) | | | | X |
| Bradley (2018) | | | X | |
| Brennan (2015) | X | | | |
| Fabbri (2018) | | | | X |
| Hall-Flavin (2012) | X | X | X | |
| Hall-Flavin (2013) | X | X | X | |
| Hodgson (2014) | | | | X |
| Hodgson (2015) | | | | X |
| Ng (2013) | | | | X |
| Penas-Lledo (2013) | | | | X |
| Rolla (2014) | | | | X |
| Singh (2015) | X | | X | |
| Taranu (2017) | | | | X |
| Torrellas (2017) | | | | X |
| Winner (2013) | X | X | X | |
| Winner (2015) | | X | | |
| Zastrozhin (2018) | | | | X |

[a] Review included 16 studies, 11 of which had patients with major depressive disorder (MDD); table includes only the 11 studies that had patients with MDD

**Table 2. Systematic Review Characteristics and Results**

| Study | Dates | Trials | Participants | N (range) | Design | Conclusions |
|---|---|---|---|---|---|---|
| Rosenblat (2017)[3] | through Oct 2015 | 5 | Patients with MDD | 1,081 (44 to 685) | 1 RCT, 4 nonrandomized comparative | Significant bias in all studies<br>Inconsistent findings reported among studies |
| Health Quality Canada (2017)[4] | through Feb 2016 | 4 | Patients with mood disorders, anxiety, or schizophrenia | 13,377 (51 to 13,048) | 1 RCT, 2 nonrandomized comparative, 1 case control | Improvements in response and patient/doctor satisfaction with guided treatment<br>No differences in remission between groups<br>Quality of studies was low or very low |
| Rosenblat (2018)[6] | Through Dec 2017 | 6 | Patients with MDD | 2,561 (23 to 335) | 4 RCTs, 2 cohort | Pooled response and remission rates favored guided treatment<br>RCTs had several sources of bias<br>Cohort studies may have publication bias |
| Soloman (2019)[5] | 2013 to 2018 | 16 | Studies on impact of *CYP2D6* and/or *CYP2C19* testing on response and adverse events | 4,027 (30 to 2,558) | 6 cohort, 3 post hoc analysis, 1 meta-analysis, 1 pre-post intervention | 4 studies reported no difference in antidepressant response between groups<br>6 studies reported greater antidepressant response in guided group<br>1 study reported inconclusive findings |

MDD: major depressive disorder

An industry-funded meta-analysis by Brown (2020) included only studies of the GeneSight Psychotropic test.[7] The review included five articles reporting results of four studies: two RCTs (Winner [2013][8] and Greden [2019][9], described below) and two non-randomized prospective studies (Hall-Flavin [2012, 2013][10,11]). The authors noted that the test composition differed between some of the studies. The results of the pooled analysis favored the test-guided group for response (RR 1.40, 95% CI 1.17 to 1.67, p<0.001) and remission (RR 1.49, 95% CI 1.17 to 1.89, p=0.001). However, there was a substantial risk of bias reported for all of the included studies, including high performance bias and high recruitment bias, as well as industry sponsorship and involvement in study design, execution, and interpretation.

Randomized Controlled Trials

A multicenter randomized trial by Perlis (2020) evaluated the use of the Genecept Assay to guide treatment for major depressive disorder (MDD).[12] 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 Hamilton Depression Rating Scale (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.

Greden (2019) presented results for the Genomics Used to Improve DEpression Decisions (GUIDED) trial in which patients with MDD were randomized to receive treatment guided by results from a genotyping test (GeneSight®) or through standard physician assessment (Table 3).[9] GeneSight® evaluates eight genes (59 variants) in relation to 38 psychotropic medications and the potential for gene-drug interactions. Based on results from the genotype test, the medications are categorized as either congruent ('use as directed' or 'use with caution') or incongruent ('use with increased caution and with more frequent monitoring') for a particular patient. Primary outcome was symptom improvement, measured by change in HAMD. Secondary outcomes were response (>50% decrease in HAMD, Quick Inventory of Depressive Symptomatology [QIDS], or Patient Health Questionnaire [PHQ]) and remission (score of <7 HAMD, <5 QIDS, and <5 PHQ). At eight-weeks follow-up, the primary outcome was not statistically different, and the secondary outcomes were statistically different between the groups (Table 4). Patients taking incongruent medications prior to baseline and who switched to congruent medications by week eight experienced significant improvements in symptoms (33% versus 21%, p=0.002), response (29% versus 17%, p=0.04), and remission (21% versus 9%, p=0.007) compared with patients who remained on incongruent medications. Limitations of this study included a lack of explanation for the substantial proportion of patients who did not complete the eight-week assessment (18% in intervention group and 15% of controls). In addition, no intent-to-treat analysis was reported by study group. A post-hoc analysis of data from this trial reported similar results among patients over 65 years of age, with significantly higher response and remission in the test-guided group, but no significant difference in symptom improvement.[13]

Han (2018) conducted an RCT randomizing patients with MDD to receive antidepressants through standard physician assessment or guided by results from a genotyping test (Neuropharmagen®) (Table 3).[14] Neuropharmagen® analyzes 30 genes associated with drug metabolism and 59 medications used to treat MDD. Primary outcomes were change in HAMD and change in Frequency, Intensity, and Burden of Side Effects Ratings scores from baseline to eight-weeks follow-up. Secondary outcomes included changes in Patient Health Questionnaires, Clinical Global Impression-Severity, General Anxiety Disorder, and Sheehan Disability Scale. Patients whose treatment was guided by genotype testing experienced significantly larger improvements in all outcome measures except for Patient Health Questionnaire 15 compared with patients whose treatment was standard of care (Table 4). Blinding of outcome assessors was not reported.

Bradley (2018) published an industry-funded trial that randomized 685 patients with depression and/or anxiety to equal groups that received either the NeuroIDgenetix® test or standard care.[15] 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 NeuroIDgenetix®

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. There were a number of limitations to this study, including a loss of approximately 15% of patients to follow-up. In the listing for this study on clinicaltrials.gov, the primary outcome was listed as the reduction of adverse drug events, however this is not mentioned in the publication. It was also unclear if the analysis was intent-to-treat.

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 (see Table 4). Changes in 17-item HAMD (HAMD-17) scores were significant at five weeks (p=0.04) but not at 12 weeks (p=0.08). Menchon (2019) conducted post hoc subgroup analyses to determine which patients are most likely to benefit from genetic testing.[17] Results from the subgroup analyses comparing responders between the guided group and standard of care group showed that younger patients (<60 years), patients with moderate or severe depression, and patients with a diagnosis of depression for less than five years, were significantly more likely to respond to treatment.

Olson (2017) conducted an RCT in which patients with neuropsychiatric disorders were randomized to treatment guided by NeuroIDgenetix® or standard of care.[18] 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 (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.[8] 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.

**Table 3. Summary Characteristics of RCTs Assessing Depression**

| Study | Country (# of Sites) | Dates | Participants | Interventions | |
|---|---|---|---|---|---|
| | | | | Active | Comparator |
| Greden (2019)[9] | U.S. (60) | 2014 to 2017 | Patients with MDD (QIDS assessment) inadequately controlled with medication | Treatment guided by GeneSight® (n=681) | SOC (n=717) |
| Han (2018) | Korea (2) | NR | Patients with MDD (DSM-5 criteria) currently receiving antidepressant therapy (≥6 weeks) with inadequate response (CGI-I ≥3) | Treatment guided by Neuropharmagen® (n=52) | SOC (n=48) |
| Bradley (2018) | U.S. (20) | 2016 | Patients with depression and/or anxiety disorders (DSM-5 criteria) new to medication or inadequately controlled with medication | Treatment guided by NeuroIDgenetix® (n=352) | SOC (n=333) |
| Olson (2017) | U.S. (6) | 2015 | Patients with ADHD, anxiety, depression, or psychosis currently receiving antidepressants | Treatment guided by NeuroIDgenetix® (n=178) | SOC (n=59) |
| Perez (2017) | Spain (18) | 2014 to 2015 | Patients with MDD (DSM-IV-TR criteria) new to medication or inadequately controlled with medication | Treatment guided by Neuropharmagen® (n=155) | SOC (n=161) |
| Winner (2013) | U.S. (1) | NR | Patients with MDD | Treatment guided by GeneSight® (n=26) | SOC (n=25) |

ADHD: attention-deficit/hyperactivity disorder; CGI-I: Clinical Global Impression – Improvement; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders; MDD: major depressive disorder; NR: not reported; QIDS: Quick Inventory of Depressive Symptomatology; RCT: randomized controlled trial; SOC: standard of care.

**Table 4. Summary of Results of RCTs Assessing Depression**

| Study | Treatment Group | Outcomes | | |
|---|---|---|---|---|
| Greden (2019)[9] | | HAMD change from baseline, 8 weeks | ≥50% decrease in HAMD, QIDS, or PHQ, 8 weeks | Remission (p-value) |
| | GeneSight® | -27.2% | 26.0% | 15.3% |
| | Standard of care | -24.4% (p=0.11) | 19.9% (p=0.01) | 10.1% (p=0.007) |
| Han (2018)[14] | | HAMD change from baseline, 8 weeks | FIBSER change from baseline, 8 weeks | PHQ-9, 8 weeks |
| | Neuropharmagen® | -13.1 ±6.8 | -4.1 ±5.3 | -13.6 ±6.8 |
| | Standard of care | -12.1 ±8.2 (p=0.01) | -1.6 ±5.9 (p=0.03) | -9.8 ±7.8 (p=0.01) |
| Bradley (2018)[15] | Patients with anxiety or depression/anxiety | % change in HAMD and HAMA scores (SD), 4 weeks | % change in HAMD and HAMA scores (SD), 8 weeks | % change in HAMD and HAMA scores (SD), 12 weeks |
| | NeuroIDgenetix® | -27 (31) | -45 (33) | -51 (33) |
| | Standard of care | -34 (32) (p=0.05) | -37 (33) (p=0.02) | -44 (33) (p=0.06) |
| Olson (2017)[18] | | Mean Neuropsychiatric Questionnaire,[a] 30 days | Mean Neuropsychiatric Questionnaire,[a] 60 days | Mean Neuropsychiatric Questionnaire,[a] 90 days |
| | NeuroIDgenetix® | 108 | 100 | 92 |
| | Standard of care | 113 (NS) | 106 (NS) | 95 (NS) |
| Perez (2017) | | % responders (PGI-I ≥2), 4 weeks | % responders (PGI-I ≥2), 8 weeks | % responders (PGI-I ≥2), 12 weeks |
| | Neuropharmagen® | 28.5 | 40.6 | 47.8 |
| | Standard of care | 32.0 (NS) | 37.4 (NS) | 36.1 (0.05) |
| Winner (2013) | | % change in 17-item HAMD scores, 4 weeks | % change in 17-item HAMD scores, 6 weeks | % change in 17-item HAMD scores, 8 weeks |
| | GeneSight® | -28.3 | -35.4 | -30.8 |
| | Standard of care | -19.8 (p=0.27) | -18.5 (p=0.04) | -20.7 (p=0.29) |

FIBSER: Frequency, Intensity, and Burden of Side Effects Ratings; HAMA: Hamilton Rating Scale for Anxiety; HAMD: Hamilton Rating Scale for Depression; NS: not significant; PGI-I: Patient Global Impression of Improvement; PHQ: Patient Health Questionnaire; QIDS: Quick Inventory of Depressive Symptomatology.
[a] Estimated from graph

Nonrandomized Studies

Perlis (2018) conducted a propensity-score matched case control analysis using a large claims database, comparing health care utilization among patients with a mood or anxiety disorder

who received and did not receive genetic testing for pharmacological variants.[19] A total of 817 cases were matched to 2,745 controls. A majority of the patients (60%) had MDD. Subgroup analyses on patients with MDD was not provided. Six-month follow-up analyses reported that patients who underwent genetic testing experienced 40% fewer all-cause emergency room visits and 58% fewer all-cause hospitalizations. There were no significant differences in number of psychotropic medications prescribed or mood-disorder related hospitalizations between the patients tested and not tested.

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.[11] 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.[3] 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.[10] 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 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]).[20] 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.[21] 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.[22] The majority of patients had a mood disorder diagnosis: 43% depression, 29% anxiety, and 17% bipolar disorder. Subgroup analyses by diagnosis were not presented. Eighty-seven percent of patients showed improvement (defined as very much improved, much improved, or minimally improved in the Clinical Global Impressions – Improvement scale), and 62% showed very much or much improved status.

Espadeler (2016) reported the results of a retrospective series of psychiatric patients with a variety of diagnoses who underwent testing with a pharmacogenetic test (Neuropharmagen®) marketed in Europe.[23] 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, using the Clinical Global Impression – Severity scale. 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). Results from subgroup analyses by psychiatric diagnosis were consistent with the overall outcomes.

Section Summary

Six RCTs testing three different genetic panels were identified. After 8 to 12 weeks of follow-up, several trials reported significant improvements in Hamilton Rating Scale for Depression (HAMD) and Hamilton Rating Scale for Anxiety (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.

## TESTING PATIENTS WITH A MENTAL ILNESS OTHER THAN DEPRESSION INADEQUATELY CONTROLLED WITH MEDICATION FOR GENES ASSOCIATED WITH PHARMACOKINETICS AND PHARMACODYNAMICS

### Systematic Reviews

Routhieaux (2018) conducted a systematic review to evaluate the clinical value of pharmacogenetic testing in patients with schizophrenia or bipolar disorder.[24] 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.

### Nonrandomized Studies

Conley (2019) described the use of pharmacogenomics testing to manage patients with schizophrenia (n=40), bipolar disorder (n=9), and MDD (n=3).[25] The clinical outcome of interest was the Cross-Cutting Symptom Measure (CCSM) developed by the American Psychiatric Association, which evaluates overall mental health symptoms, as well as changes in medication. After six months of follow-up, 73% of the patients had undergone medication changes from baseline, most commonly in dosage, followed by a change in total number of medications prescribed. Total CCSM scores significantly improved, though individual domain scores were not statistically different at follow-up.

He (2017) tested 78 patients with panic disorder for *CYP2C19* variants to assess the impact of variants on response to escitalopram treatment.[26] Diagnosis was based on DSM-5 criteria. Panic Disorder Severity Score (PDSS) and HAMA assessments were conducted pre- and post-treatment. Pharmacogenetic testing categorized the patients into poor metabolizers (n=8), intermediate metabolizers (n=36), and extensive metabolizers (n=34). Response to treatment was defined as 40% reduction in PDSS and 50% reduction in HAMA. Poor metabolizers experienced higher reductions in PDSS and HAMA compared with intermediate and extensive metabolizers at weeks two and four. By week eight, there were no differences in response to treatment among the three metabolizer groups.

Brandl (2014) tested 184 patients with obsessive compulsive disorder for *CYP2D6* and *CYP2C19* variants and conducted structured patient interviews regarding response to antidepressant treatments.[27] No significant associations were detected between *CYP2D6* and *CYP2C19* metabolizer status and treatment response to various antidepressant medications. However, patients with *CYP2D6* variants had undergone more medication trials than those without *CYP2D6* variants, suggesting inadequate responses or intolerable side effects among patients with variants

## SUMMARY OF EVIDENCE

For individuals with depression who are inadequately controlled with drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a large number of observational studies evaluating associations between specific genes and outcomes of drug treatment, as well as six

randomized controlled trials 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. The largest randomized trial did not find significant differences in the primary outcome of change in HAMD score among patients managed by results from a pharmacogenomic test compared with patients managed by standard of care. The remaining trials reported inconsistent results, with some reporting significant improvements in HAMD and other depression measures, and other trials finding no difference among patients managed with pharmacogenomic tests versus standard of care. 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.

For individuals with a mental illness other than depression who are undergoing drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes studies evaluating associations between specific genes and outcomes of drug treatment, as well as a systematic review and observational studies. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review of observational studies included patients with schizophrenia and reported associations between gene variants and treatment response; however, many of the studies were retrospective and had small sample sizes. No randomized controlled trials comparing health outcomes among patients undergoing guided and unguided management were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

## PRACTICE GUIDELINE SUMMARY

### INTERNATIONAL SOCIETY OF PSYCHIATRIC GENETICS

In 2018, the International Society of Psychiatric Genetics published a review and recommendations from its Residency Education Committee regarding genetic issues relevant to psychiatric training programs.[28] The Committee only recommends genetic testing as part of a diagnostic workup for patients with autism spectrum disorders or intellectual disability. Regarding pharmacogenetic testing, the Committee states that the "efficacy of these pharmacogenomic profiles requires further investigation in controlled studies."

## 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]) |
| | 0078U | 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 |
| | 0173U | Psychiatry (ie, depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes |
| | 0175U | Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes |
| | 81479 | Unlisted molecular pathology procedure |
| HCPCS | None | |

***Date of Origin:*** *February 2018*