Policy Statement

Genetic testing for diagnosis and management of mental health disorders is considered **investigational** in all situations, including but not limited to the following:

- To confirm a diagnosis of a mental health disorder in an individual with symptoms
- To predict future risk of a mental health disorder in an asymptomatic individual
- To inform the selection or dose of medications used to treat mental health disorders, including but not limited to the following medications*:
  - Selective serotonin reuptake inhibitors
  - Selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
  - Tricyclic antidepressants
  - Antipsychotic drugs

Genetic testing panels for mental health disorders are considered **investigational** for all indications, including but not limited to the following:

- Genecept Assay
- GeneSight Psychotropic panel
- Mental Health DNA Insight panel
- Proove Opioid Risk assay
- STA²R test

Policy Guidelines

*Note: This policy does not address the use of Cytochrome P450 (CYP gene testing) for other drugs. See also Blue Shield of California Medical Policy: Cytochrome P450 Genotype-Guided Treatment Strategy

Genetics Nomenclature Update

The Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

<table>
<thead>
<tr>
<th>Table PG1. Nomenclature to Report on Variants Found in DNA</th>
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<tr>
<td><strong>Previous</strong></td>
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<tr>
<td>Mutation</td>
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<td>Familial variant</td>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
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<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
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</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

**Genetic Counseling**

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Coding**

There is no specific CPT code for these testing panels.

There are specific codes for some of the component tests:

- **81225**: CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
- **81291**: MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)

Effective January 1, 2018, the reference to CPY3A4 was removed from code 81401.

The following CPT codes include the testing for CYP3A4:

- **81230**: CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22) (effective 01/01/2018)
- **81231**: CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7) (effective 01/01/2018)

Effective January 1, 2018, there are specific PLA codes for 2 tests:

- **0032U**: COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant (for the Catechol-O-Methyltransferase (COMT) Genotype)
- **0033U**: HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (e.g., citalopram metabolism) gene analysis, common variants (i.e., HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G]) (for the Serotonin Receptor Genotype)

The remaining tests on the panel that are not currently codified in CPT would be reported with 1 unit of the following code:

- **81479**: Unlisted molecular pathology procedure
Description

Individual genes have been shown to be associated with the risk of psychiatric disorders and specific aspects of psychiatric drug treatment such as drug metabolism, treatment response, and risk of adverse events. Commercially available testing panels include several of these genes and are intended to aid in the diagnosis and management of mental health disorders.

Related Policies

- N/A

Benefit Application

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

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

Examples of commercially available panels include the following:

- Genecept™ Assay (Genomind)
- STA²R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical Reference Laboratory). Specific variants included in the panel were not easily identified from the manufacturer’s website
- GeneSight® Psychotropic panel (Assurex Health)
- Mental Health DNA Insight™ panel (Pathway Genomics)
- IDgenetix-branded tests (AltheaDx)

Also, many labs offer genetic testing for individual genes, including MTFHR (GeneSight Rx and other laboratories), 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.
Rationale

Background
Mental Health Disorders
Mental health disorders cover a wide range of clinical phenotypes and are generally classified by symptomatology in systems such as the classification outlined 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 mental 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 mental 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.

Drug Efficacy and Toxicity
Drug efficacy and toxicity vary 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 Mental Health Disorders
Below is a brief outline of genes that may be relevant to the diagnosis and management of mental health disorders, which are currently available in genetic testing panels.

ABCB1 Gene
Variants in the ABCB1 gene encode a P-glycoprotein efflux pump that is involved in the transport of various molecules (including antidepressant drugs), across the blood-brain barrier.

Serotonin Transporter
The serotonin transporter gene (SLC6A4) is responsible for coding the protein that clears serotonin metabolites (5-hydroxytryptamine) from the synaptic spaces in the central nervous system. This protein is the principal target for many of the selective serotonin reuptake inhibitors. 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. These variants have been studied in relation to a variety of psychiatric and nonpsychiatric conditions, including anxiety, obsessive-compulsive disorder, and response to selective serotonin reuptake inhibitors.
Serotonin Receptor
The serotonin receptor 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 a treatment for obesity and schizophrenia but such medications are not commercially available at present.

The serotonin receptor 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 various 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. Variants of the DRD2 gene have also been associated with addictive behaviors (e.g., smoking, 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.

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 central nervous system. Variants in this gene are associated with Parkinson disease, Tourette syndrome, and addictive behaviors.

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

Gated Calcium Channel
The gated calcium channel gene (CACNA1C) is responsible for coding of a protein that controls the 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 central nervous system. 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 (e.g., 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 gene, Val158Met, has been associated with alterations in emotional processing and executive function and has also been implicated in increased 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 the 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 (GABA) receptor gene encodes a ligand-gated chloride channel composed of five subunits that respond 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. OPRL1 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 affects 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 not benefit from standard therapeutic doses because the drug is metabolized too quickly, resulting in subtherapeutic medication levels. Alternately, poor 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 mental health disorders.

Commercially Available Genetic Tests
Several test labs market panels of tests or individual tests relevant for mental 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 et al (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.1 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 5 genes (CYP2C9, CYP2C19, CYP2D6, HLA-A, and HLA-B).

Literature Review
The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes in comparison with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

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

Testing For Diagnosis or Risk Of Mental Health Disorder
For the first indication, this evidence review will assess whether genetic testing to determine the diagnosis or risk of mental illness is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

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

**Clinical Context and Test Purpose**

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

The question addressed in this evidence review is: Does the use of testing for genes associated with increased risk of mental illness in patients who are currently asymptomatic improve the net health outcome?

The following PICO's were used to select literature to inform this review.

**Patients**

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

**Interventions**

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

**Comparators**

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

**Outcomes**

The primary outcome of interest is change in disease outcomes, which would result directly from changes in management that could be instituted because of earlier disease detection. For many mental illnesses, there are standardized outcome measures (e.g., Hamilton Rating Scale for Depression (for example, Hamilton Depression Rating Scale [HAMD] and Beck's Depression Inventory [BDI]).

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Evidence on the clinical validity of genetic testing for mental health disorders consists primarily of genome-wide association studies that correlate specific genetic variants with phenotypes and case-control studies that compared the odds ratio for genetic variants in individuals who had a clinical disorder with individuals who did not. 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 genome-wide association studies and case-control studies for all investigated genes and their variants is beyond the scope of this review. In a review of meta-analyses examining the association between specific genes and specific mental health disorders, Gatt et al (2015) reported that 134 genes (206 variants) have been identified as significantly associated risk factors for major depressive disorder, anxiety disorders, attention-
deficit/ hyperactivity disorder, schizophrenia, or bipolar disorder, with 13 genetic variants shared between 2 or more disorders.2

Subsection Summary: Clinically Valid
The association between mental 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 mental 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 mental health disorders. Diagnostic characteristics of the genes or validated risk estimates in clinically relevant populations are not available.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Although studies have suggested that there may be a number of genetic variants associated with increased risk of mental health disorders, estimates of the magnitude of the increased risk vary across studies. For the individual tests, results from genome-wide association studies and case-control studies are insufficient to determine clinical utility.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about 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 should demonstrate that testing for variants in these genes leads to changes in clinical management that improve outcomes.

Section Summary: Testing for Diagnosis or Risk of Mental Health Disorder
No studies were identified that used genetic testing results to inform decisions on mental health diagnoses or management of patients with risk for mental health conditions. There is no clear clinical strategy for how the associations of specific genes and mental health disorders would be used to diagnose a specific patient or to manage a patient at higher risk of a specific disorder.

Testing Patients with Depression Inadequately Controlled with Medication For Genes Associated with Pharmacokinetics and Pharmacodynamics
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

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

**Clinical Context and Test Purpose**

The purpose of pharmacogenetic testing in patients diagnosed with depression inadequately controlled with medication is to inform management decisions such as starting a particular drug, determining or adjusting a dose, or changing drugs when therapy fails.

The question addressed in this evidence review is: Does psychopharmacologic management aided by genetic testing improve the net health outcome compared with management guided by clinical symptoms alone in patients with depression inadequately controlled with medication?

The following PICOs were used to select literature to inform this review.

**Patients**

The relevant population of interest are individuals with depression inadequately managed with psychopharmacologic drugs.

**Interventions**

Interventions of interest include testing for genes (single or as part of a panel) associated with medication pharmacokinetics and/or pharmacodynamics.

**Comparators**

Currently, decisions about medication management for patients with mental illnesses are based on clinical response, potentially informed by studies such as the Sequenced Treatment Alternatives to Relieve Depression study, which evaluated specific medication sequences.

**Outcomes**

The primary outcome of interest is change in disease outcomes resulting from a more appropriate selection of specific drugs or doses for the patient's condition. Also, avoidance of adverse events is an important outcome. For many mental illnesses, there are standardized outcome measures (e.g., HAMD).

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Overview of Pharmacogenetics and Mental Health Disorders**

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 mental health disorders.

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 et al (2013), sponsored by Assurex, the manufacturer of the GeneSight Psychotropic panel, assessed the efficacy and safety of 26 antipsychotic and antidepressant medications associated with variants in 8
genes: CYP2D6, CYP2C19, CYP2C9, CYP1A2, CYP3A4, 2 serotonin receptor genes (HTR2C, HTR2A), and SLC6A4. Reviewers identified 294 studies meeting their inclusion criteria.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Management changes that might be made in response to genetic testing information include a selection of specific medications according to test results, discontinuation of medications, and changes in dosing of medications.

Systematic Reviews
Of 4 systematic reviews identified, only 1 conducted a pooled analysis (Rosenblatt [2018]), calculating risk ratios for response (defined as >50% decrease in HAMD) and remission (defined as HAMD <8). The risk ratio for a response was 1.4 (95% confidence interval [CI], 1.1 to 1.6, p=0.0006) and the risk ratio 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. Tables 1 provides a list of included studies for each review and Table 2 summarizes the characteristics and results of the reviews.

Table 1. Comparison of Studies Included in Systematic Reviews

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<tr>
<td>Taranu (2017)</td>
<td></td>
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<td>X</td>
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<tr>
<td>Tomellas (2017)</td>
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<tr>
<td>Winner (2013)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Winner (2015)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Zastrozhin (2018)</td>
<td></td>
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</tr>
</tbody>
</table>

a Review included 16 studies, 11 of which had patients with MDD; table includes only the 11 studies that had patients with MDD
Table 2. Systematic Review Characteristics and Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Rosenblat (2017)             | through Oct 2015           | 5      | Patients with MDD | 1081 (44 to 685) | 1 RCT, 4 nonrandomized comparative | • Significant bias was identified in all studies  
• Inconsistent findings reported among the studies |
| Health Quality Canada (2017) | 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  
• No differences in remission between guided and unguided groups  
• Quality of studies was low or very low |
| Rosenblat (2018)             | through Dec 2017           | 6      | Patients with MDD | 2561 (23-335)  | 4 RCTs, 2 cohort         | • Pooled response and remission rates in favor of guided treatment  
• RCTs had several sources of bias  
• Cohort studies may have publication bias |
| Soloman (2019)               | 2013 to 2018               | 16     | Studies that evaluated impact of CYP2D6 and/or CYP2C19 testing on response and adverse events (11 of 16 had patients with MDD) | 4027 (30 to 2558) | 6 cohort, 3 post hoc analysis, 1 meta-analysis, 1 pre-post intervention | • 4 studies reported no difference in antidepressant response between guided and unguided groups  
• 6 studies reported greater antidepressant response in guided group compared to unguided group  
• 1 study reported inconclusive results |

MDD: major depressive disorder; RCT: randomized controlled trial.

Randomized Controlled Trials

Greden et al (2019) presented results for the Genomics Used to Improve DEpression Decisions (GUIDED) trial in which patients with major depressive disorder (MDD) were randomized to receive treatment guided by results from a genotyping test (GeneSight) or through standard physician assessment (Table 3). GeneSight evaluates 8 genes (59 variants) in relation to 38 psychotropic medications and the potential for gene-drug interactions. Based on results from the genotype test, the medications are categorized as either congruent ('use as directed' or 'use with caution') or incongruent ('use with increased caution and with more frequent monitoring') for a particular patient. The primary outcome was symptom improvement, measured by a change in HAMD. Secondary outcomes were a 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 8 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 8 experienced significant improvements in symptoms (33% vs 21%, p=0.002), response (29% vs 17%, p=0.04), and remission (21% vs 9%, p=0.007) compared with patients who remained on incongruent medications.

Han et al (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). 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 Rating 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).

Bradley et al (2018) conducted an RCT in which 685 patients with depression and/or anxiety disorders were randomized to treatment guided by either NeuroIDgenetix or standard of care (Table 3). Outcomes included HAMD and the Hamilton Rating Scale for Anxiety (HAMA) and adverse drug events. Trained and blinded clinicians conducted interviews using the HAMD and HAMA. Changes in Hamilton scores are presented in Table 4. The frequency of adverse drug events did not differ statistically between groups.

Olson et al (2017) conducted an RCT in which patients with neuropsychiatric disorders were randomized to treatment guided by NeuroIDgenetix or standard of care (see Table 3). 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 4). However, the patients receiving standard of care reported significantly more adverse events (53%) than patients receiving NeuroIDgenetix-guided care (28%).

Perez et al (2017) conducted an RCT (AB-GEN trial) of patients diagnosed with major depressive disorder randomized to genotype-guided treatment (Neuropharmagen) or treatment as usual (see Table 3). 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 5 weeks (p=0.04) but not at 12 weeks (p=0.08). Menchon et al (2019) conducted post hoc subgroup analyses to determine which patients are most likely to benefit from genetic testing. 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 <5 years, were significantly more likely to respond to treatment.

A small RCT by Winner et al (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 (see Table 3). Fifty-one subjects were enrolled and randomized to treatment as usual or treatment guided by GeneSight testing. All subjects underwent GeneSight testing, though results were not given to the physicians in the treatment as usual group until after study completion. At 10-week follow-up, treating physicians dose-adjusted subjects' medication regimens with the same likelihood in 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 HAMD-17 score, did not differ significantly between groups at the 10-week follow-up (see Table 4). This trial's small size may have limited the ability to detect a significant effect.
### Table 3. Summary Characteristics of RCTs Assessing Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greden et al (2019)</td>
<td>U.S.</td>
<td>60</td>
<td>2014 to 2017</td>
<td>Patients with MDD based on QIDS assessment; inadequately controlled with medication</td>
<td>Treatment guided by GeneSight (n=681) SOC (n=717)</td>
</tr>
<tr>
<td>Han et al (2018)</td>
<td>Korea</td>
<td>2</td>
<td>NR</td>
<td>Patients with MDD using DSM-5 criteria; currently receiving antidepressant therapy at least 6 weeks with an inadequate response (CGI-I ≥ 3)</td>
<td>Treatment guided by Neuropharmagen (n=52) SOC (n=48)</td>
</tr>
<tr>
<td>Bradley et al (2018)</td>
<td>U.S.</td>
<td>20</td>
<td>2016</td>
<td>Patients with depression and/or anxiety disorders using DSM-5 criteria; either new to medication or inadequately controlled with medication</td>
<td>Treatment guided by NeuroIDgenetix (n=352) SOC (n=333)</td>
</tr>
<tr>
<td>Olson et al (2017)</td>
<td>U.S.</td>
<td>6</td>
<td>2015</td>
<td>Patients with ADHD, anxiety, depression, or psychosis; currently receiving antidepressants</td>
<td>Treatment guided by NeuroIDgenetix (n=178) SOC (n=59)</td>
</tr>
<tr>
<td>Perez et al (2017)</td>
<td>Spain</td>
<td>18</td>
<td>2014-2015</td>
<td>Patients with MDD using DSM-IV-TR criteria; either new to medication or inadequately controlled with medication</td>
<td>Treatment guided by Neuropharmagen (n=155) SOC (n=161)</td>
</tr>
<tr>
<td>Winner et al (2013)</td>
<td>U.S.</td>
<td>1</td>
<td>NR</td>
<td>Patients with major depressive disorder</td>
<td>Treatment guided by GeneSight (n=26) SOC (n=25)</td>
</tr>
</tbody>
</table>

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 Results of RCTs Assessing Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>HAMD change from baseline</th>
<th>≥50% decrease in HAMD, QIDS, or PHQ</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greden et al (2019)</td>
<td>8 weeks</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>GeneSight</td>
<td>-27.2%</td>
<td>26.0%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Standard of care</td>
<td>-24.4%</td>
<td>19.9%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Han et al (2018)</td>
<td>8 Weeks</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Neuropharmagen</td>
<td>-16.1 ± 6.8</td>
<td>-4.1 ± 5.3</td>
<td>-13.6 ± 6.8</td>
</tr>
<tr>
<td>Standard of care</td>
<td>-12.1 ± 8.2</td>
<td>-1.6 ± 5.9</td>
<td>-9.8 ± 7.8</td>
</tr>
<tr>
<td>Patients with anxiety or depression/anxiety</td>
<td>-27 (31)</td>
<td>-45 (33)</td>
<td>-51 (33)</td>
</tr>
<tr>
<td>NeuroIDgenetix</td>
<td>-34 (32)</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Standard of care</td>
<td>-7 (32)</td>
<td>0.05</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Percent Change in HAMD and HAMA Scores (SD)
Study | Outcomes
--- | ---
NeuroIDgenetix | -39 (32)
Standard of care | -26 (31)
Mean Neuropsychiatric Questionnaire<sup>a</sup>
Olson et al. (2017)<sup>11</sup> | 30 Days p 60 Days p 90 Days p
NeuroIDgenetix | 108
Standard of care | 113 NS 106 NS 95 NS
Percent Responder (PGI-I ≤2)
Perez et al. (2017)<sup>12</sup> | 4 Weeks p 8 Weeks p 12 Weeks p
Neuropharmagen | 28.5% 40.6% 47.8%
Standard of care | 32.0% NS 37.4% NS 36.1% 0.05
Percent Change in 17-Item HAMD Scores (SD)
Winner et al. (2013)<sup>14</sup> | 4 Weeks p 6 Weeks p 8 Weeks p
GeneSight | -28.3 (NR) -35.4 (NR) -30.8 (NR)
Standard of care | -19.8 (NR) 0.27 -18.5 (NR) 0.04 -20.7 (NR) 0.29

FIBSER: Frequency, Intensity, and Burden of Side Effects Ratings; HAMA: Hamilton Rating Scale for Anxiety; HAMD: Hamilton Rating Scale for Depression; NR: not reported; NS: not significant; PGI-I: Patient Global Impression of Improvement; PHQ: Patient Health Questionnaire; QIDS: Quick Inventory of Depressive Symptomatology; RCT: randomized controlled trial; SD: standard deviation.

<sup>a</sup> Estimated from graph.

The purpose of the limitations tables (see Tables 5 and 6) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

<table>
<thead>
<tr>
<th>Table 5. Relevance Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>Greden (2019)&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Han (2018)&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bradley (2018)&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Olson (2017)&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Perez (2017)&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Winner (2013)&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ADHD: attention-deficit/hyperactivity disorder.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

<sup>c</sup> Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

<sup>d</sup> Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

<sup>e</sup> Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).
<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greden (2019)^8</td>
<td></td>
<td></td>
<td></td>
<td>1. No explanation of patients who did not complete the 8-week assessment (18% intervention group and 15% control group).</td>
<td>1. No description of power and sample size calculations.</td>
<td></td>
</tr>
<tr>
<td>Han (2018)^9</td>
<td>1. Subjects were blinded, but unknown if outcome assessors were blinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley (2018)^10</td>
<td></td>
<td></td>
<td></td>
<td>1. Approximately 15% of randomized patients were lost to follow-up. Figures 1 and 2 are unclear regarding how many patients were included.</td>
<td>1. No description of power and sample size calculations.</td>
<td></td>
</tr>
<tr>
<td>Olson (2017)^11</td>
<td>1. Randomization procedure not described</td>
<td></td>
<td></td>
<td>1. In the 3-month analyses, it appears that more than 30% of randomized patients were not included.</td>
<td>1. No description of power and sample size calculations.</td>
<td>1. Comparative statistics not reported for clinical or neurocognitive outcomes</td>
</tr>
</tbody>
</table>
2.04.110  Genetic Testing for Diagnosis and Management of Mental Health Conditions
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<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perez (2017)12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winner (2013)14</td>
<td></td>
<td></td>
<td></td>
<td>1. Missing follow-up visits: 7% intervention group and 11% control group; Missing phone interview (primary outcome): 12% intervention group and 11% control group.</td>
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</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

- **Allocation key:** 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
- **Blinding key:** 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
- **Selective Reporting key:** 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
- **Data Completeness key:** 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent-to-treat analysis (per protocol for noninferiority trials).
- **Power key:** 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
- **Statistical key:** 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

**Nonrandomized Comparative Studies**

Hall-Flavin et al (2013) presented 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 outpatient psychiatric practice.15 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, though only providers for 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.55 Subjects were followed for 8 weeks-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 HAMD-17 (p<0.001), the Quick Inventory of Depressive Symptomatology-Clinician Rated (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 Quick Inventory of Depressive Symptomatology-Clinician Rated than in the unguided patients (12.9% odds ratio, 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 et al (2012) compared outcomes for a group of patients who had major depression whose physicians received a GeneSight report with those of a historical control group of patients treated without the GeneSight report.62 Twenty-six subjects were included in the "unguided" group and 25 in the "guided" group. At 8 weeks of follow-up, patients in the guided group had a 31.2% lower Quick Inventory of Depression Symptomatology-Clinician Rated score compared with a 7.25% lower score in the unguided group (p=0.002); for HAMD-17 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 et al (2015)[6364] conducted pooled analyses of the 2, Hall-Flavin (2013, 2012) studies[6162] and the RCT by Winner (2013).60 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 HAMD-17 scores over 8 weeks than patients with "yellow" scores ("use with caution") or "green" scores ("use as directed"), or yellow/green for subjects prescribed cytochrome P450 2D6 (CYP2D6) substrate medications (p=0.001, p=0.01, p=0.002, respectively) and for subjects prescribed CYP2C19 substrate medications (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 et al (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.16, 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 1-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 hospital discharge (83.6% vs 62.1%, p=0.005) and lower HAMD scores at hospital discharge (scores extrapolated from the graph, 6 vs 8; p=0.02). This study was limited to hospitalized patients with the assessment of outcomes limited was to the time of hospital discharge.

Perlis et al (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.17 A total of 817 cases were matched to 2745 controls. A majority of the patients (60%) had MDD. Subgroup analyses on patients with MDD were 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 the number of psychotropic medications prescribed or mood-disorder related hospitalizations between the patients tested and not tested.

Noncomparative Studies
Brennan et al (2015) presented a case series of 685 patients who underwent testing with the Genecept Assay, with the results provided to participating clinicians.18 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 et al (2016) reported results of a retrospective series of psychiatric patients with a variety of diagnoses who underwent testing with a pharmacogenetic test (Neuropharmagen) marketed in Europe. Patients whose treatment was considered to follow the test recommendations were compared with those whose treatment did not. Criteria for determining whether a patient's treatment followed recommendations were complex. Outcomes were assessed by the treating psychiatrist who determined whether the patient improved over baseline, using the Clinical Global Impression-Severity scale. At 3-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.

Tonozzi et al (2018) surveyed and performed pharmacogenetic testing on patients with major depressive disorder or bipolar disorder who had been treated with psychotherapeutic medications (n=352). The survey asked patients about the effectiveness and side effects of medications taken in the last two years. Because most patients had been exposed to multiple medications, there were a total of 985 subject-medication events reported. The rate of agreement between self-reported efficacy and phenotype drug response (as indicated by genotype results) was 60%. The rate of agreement between self-reported side effects and phenotype drug response was 71%.

Tanner et al (2018) presented results of the Individualized Medicine Pharmacogenetics Assessment and Clinical Treatment study. The open-label prospective study conducted pharmacogenetic testing (GeneSight) on patients with MDD (n=1871) and measured BDI at baseline and at 8 to 12 weeks. Results of the combinatorial pharmacogenetic testing of 8 genes and 33 medications were shared with the patients' healthcare providers. The primary outcome was symptom improvement (percent change in BDI). Secondary outcomes included a response (≥50% decrease in BDI from baseline) and remission (BDI score ≤10). Medications are categorized as either congruent ('use as directed' or 'use with caution') or incongruent ('use with increased caution and with more frequent monitoring'). Patients experienced a mean 27.9% decrease in BDI compared with baseline, with rates of response and remission of 25.7% and 15.2%, respectively.

Section Summary: Testing Patients with Depression Inadequately Controlled by Medication for Genes Associated with Pharmacokinetics and Pharmacodynamics
Six RCTs testing three different genetic panels were identified. After 8 to 12 weeks of follow-up, several trials reported significant improvements in outcomes such as HAMD and HAMA scores, Neuropsychiatric Questionnaires, and remission measures, among patients whose clinicians were guided by information from genetic tests. However, results in other trials did not show differences between test-guided and unguided groups. Limitations of the RCTs included analyses that were not an intent-to-treat and large loss to follow-up. In addition, only four of the six RCTs reported results using the HAMD scale. Nonrandomized studies have reported significant improvements in outcomes among patients receiving guided treatment, but weaknesses in the studies such as large loss to follow-up, no comparison group, and small sample sizes 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 improved clinical outcomes.

Testing Patients with a Mental Illness other than Depression Inadequately Controlled with Medication for Genes Associated With Pharmacokinetics And Pharmacodynamics
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.
The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Clinical Context and Test Purpose**
The purpose of pharmacogenetic testing in patients diagnosed with a mental illness other than depression is to inform management decisions such as starting a particular drug, determining or adjusting a dose, or changing drugs when therapy fails.

The question addressed in this evidence review is: Does psychopharmacologic management aided by genetic testing improve the net health outcome compared with management guided by clinical symptoms alone in patients with a mental illness other than depression inadequately controlled with medication?

The following PICOs were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with a mental illness other than depression inadequately managed with psychopharmacologic drugs.

**Interventions**
Interventions of interest include testing for genes (single or as part of a panel) associated with medication pharmacokinetics and/or pharmacodynamics.

**Comparators**
Currently, decisions about medication management for patients with mental illnesses are based on clinical response, potentially informed by studies such as the Sequenced Treatment Alternatives to Relieve Depression study, which evaluated specific medication sequences.

**Outcomes**
The primary outcome of interest is change in disease outcomes resulting from a more appropriate selection of specific drugs or doses for the patient's condition. Also, avoidance of adverse events is an important outcome.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). See Table 1 above, Evidence for Genes Associated With Mental Health Conditions.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Management changes that might be made in response to genetic testing information include a selection of specific medications according to test results, discontinuation of medications, and changes in dosing of medications.
No RCTs were identified to provide direct evidence for the use of pharmacogenetic testing in patients with mental health conditions other than depression.

**Systematic Review**
Routhieaux et al (2018) conducted a systematic review to evaluate the clinical value of pharmacogenetic testing in patients with schizophrenia or bipolar disorder. 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.

**Noncomparative Studies**
Brandl et al (2014) tested 184 patients with obsessive-compulsive disorder for CYP2D6 and CYP2C19 variants and conducted structured patient interviews regarding response to antidepressant treatments. 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.

He et al (2017) tested 78 patients with panic disorder for CYP2C19 variants to assess the impact of variants on response to escitalopram treatment. Diagnosis was based on DSM-5 criteria. Panic Disorder Severity Score and HAMA assessments were conducted pre- and posttreatment. 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 a 40% reduction in Panic Disorder Severity Score and 50% reduction in HAMA. Poor metabolizers experienced higher reductions in Panic Disorder Severity Score and HAMA compared with intermediate and extensive metabolizers at weeks 2 and 4. By week eight, there were no differences in response to treatment among the three metabolizer groups.

Conley et al (2019) described the use of pharmacogenomic testing to manage patients with schizophrenia (n=40), bipolar disorder (n=9), and MDD (n=3). The clinical outcome of interest was the Cross-Cutting Symptom Measure developed by the American Psychiatric Association, which evaluates overall mental health symptoms, as well as changes in medication. After 6 months of follow-up, 73% of the patients had undergone medication changes from baseline, most commonly in dosage, followed by a change in the total number of medications prescribed. Total Cross-Cutting Symptom Measure scores significantly improved, though individual domain scores were not statistically different at follow-up.

**Section Summary: Testing Patients with Mental Health Conditions other than Depression**

**Inadequately Controlled by Medication for Genes Associated with Pharmacokinetics and Pharmacodynamics**
Evidence for the use of pharmacogenetic testing in patients with mental health conditions other than depression is limited to observational studies. While some of the studies have reported associations between certain genes and response to treatment, many of the studies had small sample sizes and most were retrospective studies. RCTs showing changes in medication management based on pharmacogenetic testing are needed.

**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 RCTs comparing outcomes for patients who received treatment guided by genetic testing with patients who received standard of care treatment. The 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 the 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 vs 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. The 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 RCTs 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.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**Clinical Pharmacogenetics Implementation Consortium**

The CPIC (2009) was established to develop practice guidelines on the use of genetic laboratory results to inform prescribing decisions. The panel consists of experts from the U.S., Europe, and Asia.

The CPIC (2015) conducted a systematic literature review on the influence of CYP2D6 and CYP2C19 genotyping on selective serotonin reuptake inhibitor (SSRI) therapy. The CPIC provided dosing recommendations for SSRIs based on phenotypes that classified patients as ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. However, CPIC noted that patients on an effective and stable dose of SSRIs would not benefit from dose modifications based on CYP2D6 and CYP2C19 genotype results. Additionally, CPIC asserted that genetic testing is only one factor among several clinical factors that should be considered when determining a therapeutic approach.

The CPIC (2016) conducted a systematic literature review of the influence of CYP2D6 and CYP2C19 genotype on the dosing of tricyclic antidepressants. Dosing recommendations for tricyclic antidepressants were provided, based on patient classifications of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers (Table 7 and 8).
### Table 7. Dosing Recommendations for Antidepressants Based on CYP2D6 and CYP2C19 Phenotype

#### Recommendations for Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications</th>
<th>Recommendation</th>
<th>Class of recommendation for amitriptyline and nortriptyline</th>
<th>Class of recommendation for other TCAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 ultra rapid metabolizer</td>
<td>Increased metabolism to less active compound results in lower plasma concentrations of active drug and decreased probability of drug effectiveness.</td>
<td>Avoid TCA due to potential lack of efficacy. If TCA warranted, consider higher dose with monitoring to guide dose adjustments.</td>
<td>strong</td>
<td>optional</td>
</tr>
<tr>
<td>CYP2D6 rapid metabolizer</td>
<td>Normal metabolism of TCAs</td>
<td>Initiate TCA with recommended steady-state dose.</td>
<td>strong</td>
<td>strong</td>
</tr>
<tr>
<td>CYP2D6 intermediate metabolizer</td>
<td>Reduced metabolism to less active compound results in higher plasma concentrations of active drug and increased probability of side effects.</td>
<td>Consider 25% reduced starting dose with monitoring to guide dose adjustments.</td>
<td>moderate</td>
<td>optional</td>
</tr>
<tr>
<td>CYP2D6 poor metabolizer</td>
<td>Greatly reduced metabolism to less active compound results in higher plasma concentrations of active drug and increased probability of side effects.</td>
<td>Avoid TCA due to potential side effects. If TCA is warranted, consider 50% reduced starting dose with monitoring to guide dose adjustments.</td>
<td>strong</td>
<td>optional</td>
</tr>
</tbody>
</table>

#### Recommendations for Tertiary Amines Amtriptyline, Clomipramine, Doxepin, Imipramine, and Trimipramine

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications</th>
<th>Recommendation</th>
<th>Class of recommendation for amitriptyline</th>
<th>Class of recommendation for other tertiary amine TCAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 ultra rapid and rapid metabolizer</td>
<td>Increased metabolism of tertiary amines to secondary amines may affect efficacy and side effects</td>
<td>Avoid tertiary amines due to potential sub-optimal response. Consider secondary amines. If tertiary amines warranted, use monitoring to guide dose adjustments.</td>
<td>optional</td>
<td>optional</td>
</tr>
<tr>
<td>CYP2C19 normal metabolizer</td>
<td>Normal metabolism of tertiary amines</td>
<td>Initiate tertiary amine with recommended steady-state dose.</td>
<td>strong</td>
<td>strong</td>
</tr>
<tr>
<td>CYP2C19 intermediate metabolizer</td>
<td>Reduced metabolism of tertiary amines</td>
<td>Initiate tertiary amine with recommended steady-state dose.</td>
<td>strong</td>
<td>optional</td>
</tr>
<tr>
<td>CYP2C19 poor metabolizer</td>
<td>Greatly reduced metabolism of tertiary amines</td>
<td>Avoid tertiary amines due to potential sub-</td>
<td>moderate</td>
<td>optional</td>
</tr>
</tbody>
</table>
### Recommendations for Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CYP2D6 ultrarapid metabolizer</th>
<th>CYP2D6 normal metabolizer</th>
<th>CYP2D6 intermediate metabolizer</th>
<th>CYP2D6 poor metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 ultrarapid or rapid metabolizer</td>
<td>Avoid amitriptyline, (optional)</td>
<td>Consider alternative drug, (optional)</td>
<td>Consider alternative drug, (optional)</td>
<td>Avoid amitriptyline, (optional)</td>
</tr>
<tr>
<td>CYP2C19 normal metabolizer</td>
<td>Avoid amitriptyline. If amitriptyline is warranted, consider higher target dose, (strong)</td>
<td>Initiate therapy with recommended starting dose, (strong)</td>
<td>Consider 25% reduction of recommended starting dose, (moderate)</td>
<td>Avoid amitriptyline. If amitriptyline is warranted, consider 50% reduction of recommended starting dose, (strong)</td>
</tr>
<tr>
<td>CYP2C19 intermediate metabolizer</td>
<td>Avoid amitriptyline, (optional)</td>
<td>Initiate therapy with recommended starting dose, (strong)</td>
<td>Consider 25% reduction of recommended starting dose, (optional)</td>
<td>Avoid amitriptyline. If amitriptyline is warranted, consider 50% reduction of recommended starting dose, (optional)</td>
</tr>
<tr>
<td>CYP2C19 poor metabolizer</td>
<td>Avoid amitriptyline, (optional)</td>
<td>Avoid amitriptyline. If amitriptyline is warranted, consider 50% reduction of recommended starting dose, (moderate)</td>
<td>Avoid amitriptyline, (optional)</td>
<td>Avoid amitriptyline. (optional)</td>
</tr>
</tbody>
</table>

*classification of recommendation appears in parenthesis after every recommendation

Recommendations from studies focused on amitriptyline; however, since tricyclic antidepressants have comparable pharmacokinetic properties, these guidelines may apply to other tertiary amines.

### Evaluation of Genomic Applications in Practice and Prevention

The EGAPP Working Group (2007) commissioned the Agency for Healthcare Research and Quality to conduct a systematic review on CYP450 testing in patients receiving SSRIs. Based on results from the review, EGAPP "found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are complete."

### International Society of Psychiatric Genetics

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

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

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

**Ongoing and Unpublished Clinical Trials**
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 9.

<table>
<thead>
<tr>
<th>Table 9. Summary of Key Trials</th>
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<tbody>
<tr>
<td>NCTNo.</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td><strong>Ongoing</strong></td>
</tr>
<tr>
<td>NCT03302364</td>
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<td>NCT03228953</td>
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<td>NCT03537547</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
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<tr>
<td>NCT02855580</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

**References**


7. Solomon, HH, Cates, KK, Li, KK. Does obtaining CYP2D6 and CYP2C19 pharmacogenetic testing predict antidepressant response or adverse drug reactions?. Psychiatry Res, 2018 Dec 17;271:604-613. PMID 30554109.


**Documentation for Clinical Review**

- No records required
This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0156U</td>
<td>Copy number (e.g., intellectual disability, dysmorphology), sequence analysis (Code effective 1/1/2020)</td>
</tr>
<tr>
<td></td>
<td>0029U</td>
<td>Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLC01B1, VKORC1 and rs12777823)</td>
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<tr>
<td></td>
<td>0031U</td>
<td>CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7)</td>
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<tr>
<td></td>
<td>0032U</td>
<td>COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G&gt;A (rs4680) variant</td>
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<tr>
<td></td>
<td>0033U</td>
<td>HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (e.g., citalopram metabolism) gene analysis, common variants (i.e., HTR2A rs7997012 [c.614-2211T&gt;C], HTR2C rs3813929 [c.-759C&gt;T] and rs1414334 [c.551-3008C&gt;G])</td>
</tr>
<tr>
<td></td>
<td>0071U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure) (Code effective 10/1/2018)</td>
</tr>
<tr>
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<td>0072U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene) (Code effective 10/1/2018)</td>
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<tr>
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<td>0073U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure) (Code effective 10/1/2018)</td>
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<td>0074U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans) (Code effective 10/1/2018)</td>
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<td>0075U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5' gene duplication/multiplication) (Code effective 10/1/2018)</td>
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<td>0076U</td>
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<td>81225</td>
<td>CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)</td>
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</table>
### Type Code Description

<table>
<thead>
<tr>
<th>Type</th>
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<tbody>
<tr>
<td></td>
<td>81230</td>
<td>CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22)</td>
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<td></td>
<td>81231</td>
<td>CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7)</td>
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<tr>
<td></td>
<td>81291</td>
<td>MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)</td>
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<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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### HCPCS

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<th>Description</th>
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### Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>03/01/2016</td>
<td>BCBSA Medical Policy Adoption</td>
</tr>
<tr>
<td>08/01/2016</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>08/01/2017</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>05/01/2018</td>
<td>Coding update</td>
</tr>
<tr>
<td>11/01/2018</td>
<td>Policy title change from Genetic Testing for Mental Health Conditions to Genetic Testing for Diagnosis and Management of Mental Health Conditions Policy revision without position change</td>
</tr>
<tr>
<td>08/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>03/01/2020</td>
<td>Coding update</td>
</tr>
</tbody>
</table>

### Definitions of Decision Determinations

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

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state government is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.
Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

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

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