

2.04.110	Genetic Testing for Mental Health Conditions		
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Policy Statement

Genetic testing for variants associated with mental health disorders (see Table 1) is considered **investigational** in **all** situations, including but not limited to the following:

- In an affected individual, to inform the selection or dose of medications used to treat mental health disorders.
- To confirm a diagnosis of a mental health disorder in an affected individual.
- To predict future risk of a mental health disorder in an asymptomatic individual.

Genetic testing panels for mental health disorders is 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

Genetics Nomenclature Update

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). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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 PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. 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.

The following 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)
- **81226:** CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
- **81291:** MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)

The following CPT code includes the testing for CYP3A4:

- **81401:** Molecular Pathology Procedure Level 2. CYP3A4 (cytochrome P450, family 3, subfamily A, polypeptide 4) (e.g., drug metabolism), common variants (e.g., *2, *3, *4, *5, *6).

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 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 treatment of mental health disorders.

Related Policies

- Cytochrome p450 Genotyping
- Genetic Testing for Inherited Thrombophilia

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 (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.

Examples of commercially available panels include the following:

- Genecept™ Assay (Genomind, Chalfont, PA);
- STA²R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical Reference Laboratory, Lenexa, KS). Specific variants included in the panel were not easily identified from the manufacturer's website.
- GeneSight® Psychotropic panel (Assurex Health, Mason, OH);
- Proove Opioid Risk panel (Proove Biosciences, Irvine, CA);
- Mental Health DNA Insight™ panel (Pathway Genomics, San Diego, CA);
- IDgenetix-branded tests (AltheaDx, San Diego, CA). Specific variants included in the panel were not easily identified from the manufacturer's website.

In addition, 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.

Table 1. Examples of Genetic Panels for Mental Health Disorders and Included Genes

Gene	Variants Included in Commercially Available Test Panels			
	Genecept Assay	GeneSightRx Psychotropic	Proove Opioid Risk	Mental Health DNA Insight
<i>SULT4A1</i>				
<i>SLC6A4</i> (serotonin transporter)	X	X		X
<i>5HT2C</i> (serotonin receptor)	X	X		
<i>5HT2A</i> (serotonin receptor)	X		X	X
<i>DRD1</i> (dopamine receptor)			X	
<i>DRD2</i> (dopamine receptor)	X			
<i>DRD4</i> (dopamine receptor)			X	
<i>DAT1</i> (dopamine transporter)			X	
<i>DBH</i> (dopamine β-hydroxylase)			X	
<i>CACNA1C</i> (gated calcium channel)	X			
<i>ANK3</i>	X			
<i>COMT</i> (catechol O-methyltransferase)	X		X	
<i>MTFHR</i>			X	
<i>GABA</i>			X	
<i>OPRK1</i> (κ-opioid receptor)			X	
<i>OPRM1</i> (μ-opioid receptor)	X			
<i>CYP450</i> genes				
<i>CYP2D6</i>	X	X		X
<i>CYP2C19</i>	X	X		X
<i>CYP3A4</i>	X	X		X
<i>CYP1A2</i>	X	X		
<i>CYP2C9</i>	X	X		

Gene	Variants Included in Commercially Available Test Panels	
CYP2B6	X	X
P2B6		
UGT1A4		
ABCB1		
MC4R	X	
ADRA2A	X	
BDNF	X	
GRIK1	X	

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.

Genes Relevant to Mental Health Disorders

Mental health disorders encompass a wide range of conditions: the *DSM-5* includes more than 300 disorders. However, currently available genetic testing for mental health disorders is primarily related to 2 clinical situations:

1. Risk-stratifying patients for one of several mental health conditions, including schizophrenia and related psychotic disorders, bipolar and related disorders, depressive disorders, obsessive-compulsive and related disorders, and substance-related and addictive disorders.
2. Predicting patients' response to, dose requirement for, or adverse events from one of several medications (or classes of medications) used to treat mental health conditions, including: typical and atypical antipsychotic agents, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors, and medications used to treat addiction (e.g., disulfiram).

Panels of genetic tests have been developed and proposed for use in the latter clinical situation. Genes implicated in prediction of mental health disorders or their response to treatment and included in currently available panels are outlined in the following sections.

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 (CNS). This protein is the principal target for many of the 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. These variants have been studied in relation to a variety of psychiatric and nonpsychiatric conditions, including anxiety, obsessive-compulsive disorder, and response to SSRIs.

Serotonin Receptor

The serotonin receptor gene (*5HT2C*) codes for one of at least 6 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 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 adenylyl 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. Variants of the *DRD2* gene have 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 *SCL6A4* 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 (*DBH*) gene encodes a protein that catalyzes the hydroxylation of dopamine to norepinephrine. It is primarily located in the adrenal medulla and in postganglionic sympathetic neurons. Variation in the *DBH* gene 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 (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 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 5 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 and, therefore, the rapidity of elimination of drugs and their metabolites. Based on the presence or absence of variants, patients can be classified as rapid metabolizers, intermediate metabolizers, and poor metabolizers.

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 either 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. Examples of specific panels, and the genes included, are summarized in Table 1 in the Regulatory Status section.

Some of the panels (e.g., the GeneSight panel) provide an overall risk score or summary score.

Literature Review

See Appendix Table 1 for genetic testing categories.

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

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

Testing For Diagnosis or Risk of Mental Health Disorder

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 patients 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 increased risk of mental illness in patients who are currently asymptomatic associated improve health outcomes?

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

Patients

The relevant population of interest is asymptomatic individuals who would consider an intervention if a genetic variant were 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 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 general outcomes of interest are test accuracy and validity, other test performance measures, and change in disease status. 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 Depression Rating Scale [HAMD]).

Timing

Outcomes occur over the course of years.

Setting

Testing would generally occur in the primary care or mental health practice setting.

Analytic Validity

Genotyping of genes involved in mental health disorders can be done by single-nucleotide variant (SNV) microarrays, standard Sanger sequencing, or next-generation sequencing methods. Information on analytic validity of commercially available test panels is lacking. As a result, it is not possible to determine the analytic validity of the testing process. However, Sanger sequencing and next-generation sequencing are expected to generally have high analytic validity.

Clinical Validity***Genes Associated with Increased Disease Risk***

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

A comprehensive review of the GWAS and case-control studies for all investigated genes is beyond our scope. A 2015 review of meta-analyses examining the association between specific genes and specific mental health disorders 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.¹ Representative research in this area is discussed next.

Serotonin Transporter Gene

The *SLC6A4* gene that codes for the serotonin transport protein has been studied in relation to a number of psychiatric conditions. Published literature has reported associations between variants in this gene and anxiety, bipolar disorder, obsessive-compulsive disorder, and drug and alcohol dependence.²⁻⁴ However, these associations have not been reported consistently across studies.

In a meta-analysis of 26 studies, Sen et al (2004) reported that the overall association of *SLC6A4* variants with anxiety approached, but was not statistically significant ($p=0.09$).⁵ In a 2011 study and meta-analysis, Minelli et al also evaluated the association between variants in the *5-HTTLPR* gene and the nearby rs25531 locus and anxiety-related personality traits.⁶ In the first part of their study, 287 healthy volunteers underwent *5-HTTLPR* genotyping and personality trait assessment. There was no significant association between *5-HTTLPR* genotypes and anxiety-related scale score overall, but there was a significant association when the long allele was considered dominant ($p=0.02$). The Minelli meta-analysis selected studies that evaluated the association between *5-HTTLPR* variants and anxiety-related personality traits. While 50 articles met their inclusion criteria, the meta-analysis used data from 35 articles, after exclusions for insufficient data, significant deviation from Hardy-Weinberg equilibrium, and excessive ethnic heterogeneity. Reviewers found a significant association between the homozygosity for the *5-HTTLPR* short allele and higher scores for anxiety-related traits, but this association was not present when only studies using structured psychiatric screening were included.

In 2009 meta-analysis, Risch et al evaluated studies published through March 2009 that assessed the association between variants in the *5-HTTLPR* gene, stressful life events, and/or a diagnosis of depression.⁷ Reviewers included 14 studies (total $N=14,250$ participants). In the meta-analysis,

there was no association between 5-HTTLPR genotype (homozygous short, homozygous long, or heterogeneous) and depression (weighted odds ratio [OR], 1.05; 95% confidence interval [CI], 0.98 to 1.13). There was also no interaction between genotype and the effect of stressful life events on depression (weighted OR=1.01; 95% CI, 0.94 to 1.10).

In 2011, Karg et al reported results from another meta-analysis that evaluated the association between 5-HTTLPR variants and stressful life events and a diagnosis of depression.⁸ Using broader search criteria, reviewers included 54 studies (total N=40,749 patients). In their meta-analysis, conducted using the Liptak-Stouffer z score method to combine studies at the level of significance tests, weighted by study sample size, reviewers found a significant association between the presence of the 5-HTTLPR short allele and increased risk of developing depression under stress ($p<0.001$). When they confined analysis only to those studies used in the Risch meta-analysis, there was no significant association between 5-HTTLPR variants and depression.

In 2010, Kiyohara and Yoshimasu reported results from a meta-analysis of studies that assessed the association between 5-HTTLPR variants and depression.⁹ Reviewers included 22 studies, all case-control studies, published through March 2008 (total N=7919 patients). Analyses were stratified by ethnicity due to significant between-study heterogeneity in the frequency of the variant 5-HTTLPR allele. In pooled analysis, the homozygous short genotype was significantly associated with depression risk among whites (OR=1.41; 95% CI, 1.15 to 1.72), but not in Asians.

SULT4A1 Gene

Based on a study targeting a variant in the 5' untranslated region of the *SULT4A1* gene in 27 families with at least 2 siblings with schizophrenia or schizophrenia spectrum disorder, the *SULT4A1* gene has been evaluated as a candidate gene for schizophrenia. Meltzer et al (2008) evaluated a panel of patients with schizophrenia or schizoaffective disorder and available DNA to determine the association between three *SULT4A1* SNVs (rs138060, rs138097, rs138110) and clinical symptoms and quality of life.¹⁰ Among 86 participants included, although all patients had a diagnosis of schizophrenia or schizoaffective disorder, the rs138060 SNV was significantly associated with worse symptom scores. In addition, the rs138097 SNV was significantly associated with worse neuropsychological test performance.

CACNA1C and ANK3 Genes

The *CACNA1C* gene has been studied most widely for its association with disorders of cardiac rhythm, such as long QT syndrome and Brugada syndrome. A lesser amount of research has reported associations of variants of this gene with schizophrenia and bipolar disorder.¹¹

In 2015, Jiang et al published a meta-analysis of studies evaluating the association between the *CACNA1C* SNV rs1006737 and schizophrenia risk in East Asian populations.¹² Reviewers included 5 case-control studies in East Asian samples including 9432 cases with schizophrenia and 10,661 controls for their primary analysis. A second analysis was conducted for pooled East Asian and European populations, which included 2 additional candidate gene studies and 1 GWAS study in Europeans, for a total of 21,246 cases and 38,072 controls. In East Asian populations, the rs1006737 SNV was significantly associated with risk of schizophrenia (allelic model: pooled OR=1.20 for A allele; $p=4.39\times10^{-6}$). When the European studies were included, there was a stronger association between the *CACNA1C* variant and schizophrenia risk (allelic model: pooled OR=1.12 for A allele; $p=2.40\times10^{-17}$).

Kloiber et al (2012) published results from 2 case-control studies evaluating the association between major depressive disorders and *CACNA1C* and *ANK3*.¹³ The first population consisted of 720 patients with depression and 542 patients without psychiatric disease. The second included 827 patients with recurrent depression and 860 patients without psychiatric disease. Several SNVs on both genes showed a statistical association with depression on initial analysis, but none remained significant after controlling for multiple comparisons. This evidence did not support a strong association between variants of these genes and depression.

Subsequently, Croarkin et al (2017) also reported an association between *CACNA1C* and *ANKK1* variants in a series of 69 cases with early-onset bipolar disorder (age range, 6-15 years), who were compared with 855 adults with bipolar disorder and 857 adult controls.¹⁴ A global risk score that included 8 variants (4 in *CACNA1C*, 3 in *ANKK1*, 1 in *ODZ4*) was associated with early-onset bipolar disorder ($p=0.01$), but not late-onset.

COMT Genes

For the *COMT* gene, variants have been reported to be associated with cognitive function, emotional processing, and other cognitive tasks.^{15,16} However, a 2008 meta-analysis found no significant association between *COMT* genotype and several cognitive phenotypes.¹⁷ In addition, associations with specific psychiatric conditions such as schizophrenia are less certain.¹⁸

Dopamine Receptors and Transporter Genes

The dopamine receptor genes (*DRD1*, *DRD2*, *DRD4*) and the dopamine transporter (*DAT1*) gene have been associated with mood disorders, schizophrenia, and substance abuse disorders.

For the *DRD2* gene, a meta-analysis of case-control studies that assessed for the presence of the *cys311* variant in patients with and without schizophrenia was published by Jonsson et al (2003).¹⁹ A total of 9152 individuals were included, 3707 individuals with schizophrenia and 5363 control patients without schizophrenia. Combined analysis showed a significant association of this allele with schizophrenia (OR=1.43; 95% CI, 1.16 to 1.78; $p<0.001$). A 2014 meta-analysis which included 13 articles ($n=3079$ schizophrenia cases, $n=3851$ controls), reported associations between the *DRD2* C957T variant and schizophrenia risk (for C vs T: OR=1.26; 95% CI, 1.09 to 1.46, $p=0.002$; Bonferroni and Benjamini-Hochberg corrected, $p=0.005$; for CC and CT vs TT: OR=1.47; 95% CI, 1.25 to 1.73; $p<0.001$; Bonferroni and Benjamini-Hochberg corrected, $p<0.001$).²⁰

Variants in the *DRD2* gene have also shown associations with disorders other than schizophrenia. Zou et al (2012) reported results of a meta-analysis of studies that assessed the association between three *DRD2* variants and mood disorders (bipolar disorder, unipolar depression).²¹ A total of 2157 cases and 3272 controls from 14 studies were included. A significant association was demonstrated between 1 variant assessed (Taq1A) and mood disorders (OR=1.84; 95% CI, 1.07 to 3.17; $p=0.03$).

For the *DRD4* gene, in another meta-analysis, Lopez Leon et al (2005) evaluated studies on the association between *DRD4* variants and mood disorders, including unipolar depression and bipolar disorder.²² Twelve studies that used a patient-control design and reported allele frequencies were included. *DRD4* variants were significantly associated with unipolar depression ($p<0.001$) and the combined group of unipolar depression and bipolar disorder ($p<0.001$).

For the *DRD1* gene, case-control studies have linked variants to both increased and decreased risk of schizophrenia,²³ along with addictive behaviors including smoking and alcohol dependence.^{24,25} A 2014 meta-analysis of studies evaluating the association between *DRD1* variants and schizophrenia risk found that the rs5326 but not the rs4532 SNV was associated with schizophrenia.²⁶

For the *DAT1* gene (also known as *SLC6A3*), a number of studies have demonstrated an association between gene variants and addictive behaviors. For example, in a meta-analysis of 5 studies (total $N=2155$ patients), Stapleton et al (2007) found that a variable number tandem repeat alleles in the 3' untranslated region of the *DAT1* gene were associated with greater odds of smoking cessation (pooled OR=1.20; 95% CI, 1.01 to 1.43).²⁷ In another meta-analysis, Du et al (2011) found that variants in the 3' untranslated region of the *DAT1* gene were associated with alcoholism with a history of delirium tremens or alcohol withdrawal seizures, although no significant association was seen between variants and alcoholism in general.²⁸ In contrast, Xu and Lin (2011) performed a systematic review of 13 case-control studies evaluating the

association between variants in the 3' untranslated region of the *DAT1* gene and alcoholism and found no significant associations.²⁹

MTHFR Gene

For psychiatric disease, Wu et al (2013) performed a meta-analysis of 26 GWAS evaluating the association between *MTHFR* variants and depression.³⁰ Overall, there were low-strength associations between numerous *MTHFR* SNVs and depression (OR range, 1.15-1.42). On subgroup analysis, the associations were stronger for Asian populations. In whites, the associations were of marginal significance, and in elderly patients the associations were not statistically significant.

In another meta-analysis, Hu et al (2015) evaluated the association between *MTHFR* variants and risk of bipolar disorder or schizophrenia.³¹ In an analysis of 38 studies, reviewers found a significant association between the *MTHFR* C677T variant and schizophrenia (comparison, TT vs CT or CC; OR=1.34; 95% CI, 1.18 to 1.53). For bipolar disorder, there was a marginal association between the C677T variant and disease risk (comparison, TT vs CT or CC; OR=1.26; 95% CI, 1.00 to 1.59).

Since the publication of the Wu meta-analysis, Bousman et al (2014) conducted a prospective cohort study to evaluate the association between *MTHFR* genetic variants and prognosis of major depressive disorder.³² The study included 147 primary care attendees with major depression who underwent genotyping for 2 functional *MTHFR* variants (C677T rs1801133, A1298C rs1801131) and 7 haplotype-tagging SNVs and serial measures of depression. The C677T variant was significantly associated with symptom severity trajectory measured using the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire-9 ($p=0.038$). The A1298C variant and the haplotype-tagging SNVs were not associated with disease prognosis.

In contrast, Lizer et al (2011) conducted a case-control study with 156 subjects and found no significant differences in the frequency of various *MTHFR* C667T genotypes between depressed and nondepressed patients.³³

MTHFR variants have also been associated with schizophrenia and bipolar disorder. Peerbooms et al (2011) conducted a meta-analysis of case-control studies evaluating associations between the *MTHFR* depression.³⁴ The C677T SNV was significantly associated with all disorders combined (OR=1.26 vs homozygotes; 95% CI, 1.09 to 1.46). The A1298C SNV was significantly associated bipolar disorder (OR=2.03 vs homozygotes; 95% CI, 1.07 to 3.86).

Subsection Summary: Clinical Validity of Genes Associated with Increased Disease Risk

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 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.

Clinical Utility

Although studies have suggested that there may be a number of genetic variants associated with increased risk of mental health disorders and/or response to specific treatment, 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: Testing for Diagnosis or Risk of Mental Health Disorder

Most studies have evaluated the association between genotype and mental health disorders without a clinical perspective; thus diagnostic characteristics and validated risk predictions among specific clinical populations are unknown. The associations tend to be weak and would likely result in poor diagnostic characteristics. 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 For Genes Associated With Medication Pharmacokinetics and Pharmacodynamics**Clinical Context and Test Purpose**

The purpose of pharmacogenetic testing in patients who are being treated with or considered for therapy with a number of different medications used to treat mental illnesses is to inform a decision whether to start a particular drug, set or adjust dose, or change drugs when a therapy fails.

The question addressed in this evidence review is: Does psychopharmacologic management aided by genetic testing improve outcomes compared with management guided by clinical symptoms alone?

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

Patients

The relevant population of interest is individuals being managed with psychopharmacologic drugs.

Interventions

Interventions of interest include testing for genes associated with medication pharmacokinetics and/or pharmacodynamics, either singularly or as a panel.

Comparators

Currently decisions about medication management for mental illnesses are typically made based on clinical response, potentially informed by studies such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which evaluated specific medication sequences.

Outcomes

The general outcomes of interest are test accuracy and validity, other test performance measures, and change in disease status. The primary outcome of interest is change in disease outcomes resulting from more appropriate selection of specific drugs or doses for the patient's condition. In addition, avoidance of adverse effects is an important outcome. For many mental illnesses, there are standardized outcome measures (e.g., HAM-D).

Timing

Outcomes occur over the course of years.

Setting

Testing would generally occur in the primary care or mental health practice setting.

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. To distinguish genes predictive of treatment response, versus those prognostic (predictive of outcome independent of treatment), it is usually necessary for studies to evaluate outcomes in patients receiving treatment and in patients not receiving treatment (or receiving an alternative treatment). A gene that is predictive will result in

a study demonstrating an interaction between genotype and treatment. In many studies claiming to evaluate genotype and treatment response, only patients receiving treatment have been evaluated.

Several studies have summarized the associations between multiple candidate genes and single or multiple mental health disorders. Altar et al (2013), in a study funded by Assurex, the manufacturer of the GeneSight Psychotropic panel, conducted a systematic review to assess whether the efficacy and/or adverse events of 26 antipsychotic and antidepressant medications are associated with variants in 8 genes: *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP1A2*, *CYP3A4*, 2 serotonin receptor genes (*HTR2C*, *HTR2A*), and *SLC6A4*.³⁵ Reviewers selected 294 studies meeting their inclusion criteria. Thirty-two studies assessed associations between 5-*HTR2C* variants and various aspects of mental health disease. They included drug response, remission, adverse drug reactions, and evaluation of weight gain or metabolic syndrome in patients with psychiatric disorders (most commonly schizophrenia or schizoaffective disorders). Significant associations between at least one *HTR2C* allele and metabolic syndrome were found in 6 of the 7 studies that evaluated metabolic syndrome. Thirty-nine studies assessed the association between 5-*HTR2A* variants and adverse events or drug efficacy; 5 of the 10 studies that evaluated antipsychotic-related adverse events found a significant association between 5-*HTR2A* variants and adverse drug reactions, including weight gain, tardive dyskinesia, extrapyramidal adverse events, and antipsychotic-induced Parkinsonism.

Seventy-four studies evaluated associations between the *SLC6A4* gene and drug response, remission, or adverse events, most commonly related to the use of selective serotonin reuptake inhibitor (SSRIs). Fifty-four studies investigated the most frequently assessed variant (5-HTTLPR long/ short), with 29 studies showing a significant association with drug response or remission. Studies on a number of *p450* genes were also assessed and generally included associations between genotype and phenotypic pharmacokinetic measures, including extensive metabolism, intermediate metabolism, poor metabolism, and ultrarapid metabolism status. Reviewers concluded that there was substantial evidence of the association between variants and patient response to psychotropic medications; however, questions remained about how to incorporate testing for variants into clinical practice.

In a 2015 study not included in the Altar systematic review, Yin et al assessed the association between *SLC6A2*, *SLC6A3*, *DRD2*, and *DRD4* variants and response to SSRI therapy in a clinical trial of 229 patients undergoing treatment for depression.³⁶ The *DRD4* gene rs1800544 variant differed significantly between drug responders and nonresponders ($p < 0.05$), with no significant association with response seen for the other genotypes. In a 2014 trial comparing outcomes for 137 patients with depression randomized to antidepressant therapy ($n=97$) or to interpersonal counseling ($n=40$), *SLC6A4* genotypes (AA genotype and A allele) were associated with response rates to antidepressants in the antidepressant group ($p=0.015$ and $p=0.005$, respectively).³⁷

Analytic Validity

No studies were identified specifically addressing analytic validity of commercially available tests for mental health panels or specific genes.

Clinical Validity

Antipsychotic Response

Dopamine Receptor Genes

A number of studies have evaluated variants in the *DRD1* and *DRD2* genes and response to treatment for schizophrenia. Zhang et al (2010) reported results from a meta-analysis evaluating the association between *DRD2* variants and response to antipsychotic agents among patients with schizophrenia.³⁸ Reviewers identified 6 studies evaluating the role of the -141insC or -141delC variant ($n=687$ patients). There was a significantly lower response rate to antipsychotics for patients who were deletion carriers compared with Ins/Ins groups (pooled OR=0.65; 95% CI, 0.43 to 0.97; $p=0.03$). Eight studies evaluated the association between a different variant (TaqA1)

and antipsychotic response (N=748 patients). There was no significant association between the TaqA1 variant and antipsychotic response in pooled analysis.

Studies investigating the relation between variants in the *DRD1* gene and antipsychotic response have not consistently reported a significant association.^{23,39}

Antidepressant Response

Serotonin Transporter (SLC6A4) Gene

Variants in the *SLC6A4* gene and the 5-HTTLPR region have been associated with variability in response to SSRIs and other antidepressant medications for different mental health disorders, including depression, bipolar disorder, and generalized anxiety disorder.

A number of studies have associated *SLC6A4* variants with antidepressant response. In a 2012 meta-analysis, Porcelli et al (2012) evaluated the role of the 5-HTTLPR variants in predicting antidepressant response.⁴⁰ They identified 33 publications that compared outcomes after antidepressant use for major depressive disorder or bipolar disorder, 28 of which were used in an analysis of SSRI response, and 8 in an analysis of other antidepressants. The 5-HTTLPR long allele was associated with remission when homozygous "long" patients were compared with homozygous "short" patients (for all antidepressant classes: OR=1.37; 95% CI, 1.09 to 1.72; p=0.007; for SSRIs only: OR=1.48; 95% CI, 1.12 to 1.96; p=0.005).

Studies on the role of *SLC6A4* variants in antidepressant response not included in the Porcelli meta-analysis have reported mixed findings. For example, in an analysis of data from 125 patients enrolled in a randomized controlled trial (RCT) comparing the SSRI escitalopram to placebo in the treatment of generalized anxiety disorder in older adults, Lenze et al (2010) evaluated two *SLC6A4*-related variants, the 5-HTTLPR short/long variant and the rs25531G>A SNV.⁴¹ Patients who did not have the combination of 5-HTTLPR long rs25531 had no significant improvement with escitalopram, while those with other haplotypes had moderate improvement. In another prospective study, Seripa et al (2015) evaluated the association between *SLC6A4* variants and response to treatment with SSRIs (sertraline, paroxetine, citalopram) in 234 subjects with late-life major depressive disorder.⁴² Patients considered to be treatment responders were more likely to have the rs4795541-S allele (gene frequency, 0.436 vs 0.321; p=0.023). In an additive regression model predicting treatment response, the single S-allele dose-additive effect was associated with an odds of 1.74 (95% CI, 1.12 to 2.69). Tomita et al (2014) reported opposite degrees of association between plasma paroxetine concentrations and treatment response on the basis of 5-HTTLPR genotype among 51 patients with major depressive disorder.⁴³ Among patients with 2 short alleles, paroxetine concentration correlated negatively with improvement in depressive symptoms after 6 weeks, while, for patients with 1 or 2 long alleles, paroxetine concentration correlated positively with improvement in depressive symptoms after 6 weeks.

By contrast, in an analysis of data from a randomized trial comparing the SSRI citalopram (n=258) to the norepinephrine uptake inhibitor reboxetine (n=262), Lewis et al (2011) found no differences in treatment response for patients with different 5-HTTLPR genotype.⁴⁴ In a regression to predict Beck Depression Inventory score at 6 weeks following enrollment, the coefficient for the interaction term (treatment group by genotype) was 0.50 (95% CI, -2.04 to 3.03; p=0.70), indicating no significant moderation of treatment effect by 5-HTTLPR genotype.

Research has also evaluated the association between *SLC6A4* variants and antidepressant adverse effects. In a 2010 systematic review and meta-analysis, Daray et al assessed the role of 5-HTTLPR variants and antidepressant-induced mania, a complication of antidepressant therapy seen in patients with bipolar disorder.⁴⁵ Previous studies had reported that the long and short allelic forms of this gene were associated with different rates of antidepressant-induced mania. In the meta-analysis, based on 6 studies, the short allelic form of the gene was associated with an increased risk of anti-depressant-induced mania (combined relative risk, 1.35; 95% CI, 1.04 to 1.76).

In contrast, a 2012 systematic review and meta-analysis that used more stringent inclusion criteria, Biernacka et al found no significant association between *5-HTTLPR* variants and antidepressant-induced mania.⁴⁶

The *SCL6A4* variant has been associated with response to ondansetron, a 5-HT(3) receptor antagonist, among patients with alcohol dependence.⁴⁷

ABCB1 Gene

Variants in the *ABCB1* gene, encoding a P-glycoprotein efflux pump that is involved in the transport of various molecules (including antidepressant drugs), across the blood-brain barrier, have been associated with response to treatments with antidepressants. In 2015, Breitenstein et al reported results of a meta-analysis of 16 pharmacogenetic studies (total N=2695 patients) evaluating the association between *ABCB1* variants and antidepressant treatment outcomes for patients with major depression.⁴⁸ Six *ABCB1* SNVs were evaluated: rs2032583, rs2235015, rs2235040, rs1045642, rs2032582, and rs1128503. Two SNVs (rs2032583, rs2235015) were significantly associated with treatment response among 485 inpatients after Bonferroni correction (n=485 and $p=1.5 \times 10^{-5}$ for rs2032583; n=195 and $p=3.0 \times 10^{-4}$ for rs2235015).

Addiction Response

Opioid Receptor Genes

Several studies have evaluated the role of variants in the μ -opioid receptor gene (*OPRM1*) and response to the opioid antagonist naltrexone for the treatment of alcohol dependence. Chamorro et al (2012) conducted a systematic review and meta-analysis to assess the relation between the A118G SNV in the *OPRM1* gene and response to use naltrexone for alcohol dependence.⁴⁹ Reviewers selected 6 studies. Naltrexone-treated patients homozygous for the A allele had a higher rate of relapse than those with the G allele (summary OR=1.97; 95% CI, 1.06 to 3.66; $p=0.03$).

Cytochrome P450 Genes

A large amount of research has been conducted on the cytochrome *P450* genes, with variants associated with altered drug metabolism for a variety of medications. A review of specific associations between these variations and metabolism of some psychiatric medications is discussed in Blue Shield of California Medical Policy: Cytochrome p450 Genotyping.

Section Summary: Clinical Validity of Genes Associated With Medication Pharmacokinetics and Pharmacodynamics

Genetic variants appear to have some association with response to medication, particularly for *SLC6A4* variants and response to antidepressants and for opioid receptor genes and response to naltrexone treatment. However, because many studies did not include untreated patients or patients treated with alternative therapies, one cannot determine from many of these studies whether the identified genes are predictive of treatment response or are simply prognostic factors (predictive of outcome independent of treatment).

Clinical Utility

Management changes that might be made in response to genetic testing information include selection of specific medications according to test results, discontinuation of medications, and changes in dosing of medications. However, management changes made in response to genetic testing information are not well-defined and may vary according to the judgment of the treating clinician. Currently, there are no specific recommended changes in management linked to specific test results, making it difficult to assess whether test results lead to improvements in health outcomes. Without a compelling chain of evidence supporting clinical utility, direct evidence, in terms of comparisons of outcomes for patients managed with and without the results of genetic testing, is necessary to determine clinical utility.

Systematic Reviews

Rosenblat et al (2017) reported on a systematic review of clinical trials and cost-effectiveness studies evaluating whether pharmacogenetics testing improves clinical outcomes for major depressive disorder.⁵⁰ Reviewers identified 5 studies, 3 nonrandomized comparative studies (Hall-Flavin et al [2013],⁵¹ Hall-Flavin et al [2012],⁵² Brennan et al [2015],⁵³ which are described below), 1 RCT (Winner et al [2013],⁵⁴ described below), and an additional industry-sponsored RCT (Singh [2015]⁵⁵) comparing a pharmacokinetic report-guided medication management group with standard management. No pooled analyses were conducted. As described below, 1 nonrandomized comparative study of the Genecept assay showed improvements in depression ratings for patients treated in the guided-treatment group (Hall-Flavin et al [2013]⁵¹), and another showed higher rates of remission with guided treatment (Hall-Flavin et al [2012],⁵² while a small RCT showed no difference between genotype-guided treatment and standard treatment (Winner et al).⁵⁴ As described below, in a 2015 noncomparative study evaluating the Genecept assay, about 40% of patients had a response or remission.⁵³ Finally, in a double-blind RCT that randomized patients to a genotype-guided medication strategy (n=74) or to an unguided strategy (n=74), patients with major depressive disorder were followed for 12 months. Those in the genotype-guided group had a higher remission rate (72% vs 28%; OR=2.52; 95% CI, 1.71 to 3.73; p<0.001).

Randomized Controlled Trials

A small 2013 RCT by Winner et al 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.⁵⁴ 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 HAM-D-17 score, did not differ significantly between groups at the 10-week follow-up. This trial's small size may have limited the ability to detect a significant effect.

Nonrandomized Studies

Two comparative, nonrandomized studies from the same research group compared clinical outcomes in patients with and without genetic testing. In 2013, Hall-Flavin et al 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.⁵¹ Two hundred twenty-seven 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. 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.⁵⁰ Providers for patients in the "guided" group received the results from the GeneSight test report. Subjects were followed for 8 weeks—93 patients in the unguided group and 72 patients in the guided group completed follow-up. In analysis of those who completed follow-up, reviewers found a greater reduction in symptoms in the guided group than in the unguided group for the depression measures used: HAM-D-17 (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 rates 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 et al (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.⁵² 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 QIDS-C16 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 ($p=0.04$).

While both Hall-Flavin studies provide some evidence that a genotype report may be associated with differences in depression treatment outcomes, study limitations (including small sizes, nonrandomized designs, and loss to follow-up) make generalizations of their results difficult.

Altar et al (2015) reported the results of pooled analyses from the 3 studies previously described (Hall-Flavin et al [2013], Hall-Flavin et al [2012], Winner et al [2013]).⁵⁶ 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 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.

In 2014, Breitenstein et al 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.⁵⁷ In this study, 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 (e.g., pay attention to sufficient dosing, consider changing to a medication not a substrate of the P-glycoprotein encoded by the *ABCB1* gene for subjects who had 2 T alleles of the rs2032583 SNV and 2 G alleles of the rs2235015 SNV). 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%, $p=0.005$, 1-sided) and lower HAMD scores at the time of hospital discharge (scores extrapolated from graph, 6 vs 8; $p=0.02$, 1-sided). This study was limited to hospitalized patients with assessment of outcomes limited to the time of hospital discharge.

In 2015, Brennan et al reported results of a case series of 685 patients who underwent testing with the Genecept assay.⁵³ Approximately 70% and 29% of patients had primary diagnoses of a mood or an anxiety disorder, respectively. Eighty-seven percent of patients showed improvement (defined as very much improved, much improved, or minimally improved), and 62% showed very much or much improved status.

In 2016, Espadeler et al reported the results of a retrospective series of psychiatric patients who underwent testing with a pharmacogenetic test (Neuropharmagen) marketed in Europe.⁵⁸ 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. For example, the test provides 4 types of information on up to 39 different drugs. An example of not following the test recommendation is whether a patient’s treatment included a medication with a red alert, indicating increased risk of adverse drug reaction. Outcomes were assessed by the treating psychiatrist who determined

whether the patient improved over baseline. 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 ($p=0.019$). This study did not directly evaluate use of genetic testing, because all patients had testing. Certain patients had treatment judged not to be concordant with the recommendations. It cannot be determined why they received the specific treatment or whether they would have had worse outcomes regardless.

Section Summary: Clinical Utility

A limited number of studies have evaluated clinical outcomes associated with genetic testing panels for mental health disorders, primarily using the GeneSight pharmacokinetic test, with other studies using other tests. One small RCT did not show a difference in treatment outcomes. Nonrandomized studies have provided evidence that a genotype report may be associated with differences in depression treatment outcomes; however, weaknesses in the studies limit the conclusions that can be drawn. Additional studies in larger number of patients with randomization and blinded outcome assessment will be needed to confirm findings that genotyping may be associated with improved clinical outcomes.

Summary of Evidence

For individuals who are evaluated for diagnosis or risk of a mental illness who receive genetic testing for risk of that disorder, the evidence includes various observational studies (case-control, genome-wide association study) evaluating the relation between the mental illness of interest and candidate genes. Relevant outcomes are test accuracy and validity, other test performance measures, and changes in disease status. Most studies have evaluated the association between genotype and mental health disorders without a clinical perspective; thus diagnostic characteristics and validated risk predictions among specific clinical populations are unknown. The associations tend to be weak and would likely result in poor diagnostic characteristics. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a mental illness who are undergoing drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a large number of observational studies assessing specific genes and outcomes of drug treatment, and a limited number of studies comparing outcomes for patients who have undergone genetic testing with those who have not. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Some studies comparing patients who have had and have not had genetic testing have shown that testing may be associated with differences in depression treatment outcomes. However, methodologic shortcomings limit the conclusions that can be drawn. Most studies are nonrandomized. One relevant randomized controlled trials did not show a difference in patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information**Practice Guidelines and Position Statements**

No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02109939 ^a	A 12-Week, Randomized, Double-Blind, Controlled Evaluation Followed by an Open-Label 12-Week Follow-up Period of the Impact of GeneSight Psychotropic on Response to Psychotropic Treatment in Outpatients Suffering From a Major Depressive Disorder (MDD) and Having Had - Within the Current Episode - an Inadequate Response to at Least One Psychotropic Medication Included in GeneSight Psychotropic	1200	Jun 2017
Unpublished			
NCT01426516 ^a	Six-month Study of the Genecept Assay vs. Treatment as Usual to Evaluate Efficacy of Using Assay Guided Treatment in Outpatient Adults With Treatment Resistant Depression	100	Jun 2014 (terminated)
NCT01555021	Pharmacogenomics for Antidepressant Guidance and Education	200	Dec 2014 (unknown)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Appendix

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.110

Category	Addressed
1. Testing of an affected individual's germline to benefit the individual	
1a. Diagnostic	X
1b. Prognostic	X
1c. Therapeutic	X
2. Testing cancer cells from an affected individual to benefit the individual	
2a. Diagnostic	
2b. Prognostic	
2c. Therapeutic	
3. Testing an asymptomatic individual to determine future risk of disease	X
4. Testing of an affected individual's germline to benefit family members	
5. Reproductive testing	
5a. Carrier testing: preconception	
5b. Carrier testing: prenatal	
5c. In utero testing: aneuploidy	
5d. In utero testing: familial variants	
5e. In utero testing: other	
5f. Preimplantation testing with in vitro fertilization	

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Documentation for Clinical Review

- No records required

Coding

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.

Type	Code	Description
CPT®	0032U	COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant (Code effective 1/1/2018)
	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]) (Code effective 1/1/2018)
	81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
	81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
	81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
	81401	Molecular Pathology Procedure Level 2
	81479	Unlisted molecular pathology procedure
HCPCS	None	
ICD-10 Procedure	None	

Policy History

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

Effective Date	Action	Reason
03/01/2016	BCBSA Medical Policy Adoption	Medical Policy Committee
08/01/2016	Policy revision without position change	Medical Policy Committee
08/01/2017	Policy revision without position change	Medical Policy Committee
05/01/2018	Coding update	Administrative Review

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

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 governmental 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)
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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. Please call (800) 541-6652 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.