

(204110)

<b>Medical Benefit</b>		<b>Effective Date:</b> 04/01/16	<b>Next Review Date:</b> 01/19
<b>Preauthorization</b>	Yes	<b>Review Dates:</b> 07/14, 01/15, 01/16, 01/17, 01/18	

**Preauthorization is required.**

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>Who are evaluated for diagnosis or risk of a mental illness</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic testing for risk of a mental illness</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Standard care</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Test accuracy</li> <li>Test validity</li> <li>Other test performance measures</li> <li>Change in disease status</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With a mental illness who are undergoing drug treatment</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Standard of care drug treatment</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Symptoms</li> <li>Change in disease status</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Health status measures</li> <li>Quality of life</li> <li>Treatment-related</li> </ul>

### 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.

### 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 trial did not show a difference in patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Policy

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:

- 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.
- In an affected individual to inform the selection or dose of medications used to treat mental health disorders.

Genetic testing panels for mental health disorders, including but not limited to the Genecept Assay, STA<sup>2</sup>R test, the GeneSight Psychotropic panel, the Proove Opioid Risk assay and the Mental Health DNA Insight panel, are considered **investigational** for all indications.

## 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 PG3. 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.

### **Medicare Advantage**

Genetic testing for mutations associated with mental health disorders with the GeneSight® Psychotropic panel, may be considered **medically necessary** when all of the following conditions are met:

- testing may only be ordered by licensed psychiatrists or neuropsychiatrists contemplating an alteration in neuropsychiatric medication for patients diagnosed with major depressive disorder (MDD) who are suffering with refractory moderate to severe depression (based upon DSM-V criteria) and
- the patient must have failed or currently be failing on at least one neuropsychiatric medication and
- the healthcare provider must be contemplating an alteration in neuropsychiatric medication treatment.

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

The 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 B-HYDROXYLASE

The dopamine  $\beta$ -hydroxylase (*DBH*) gene encodes a protein that catalyzes the hydroxylase of dopamine to norepinephrine. It is primarily located in the adrenal medulla and in postganglionic sympathetic neurons. Variation in 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.

#### $\gamma$ -AMINOBUTYRIC ACID A RECEPTOR

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

#### μ- AND κ-OPIOID RECEPTORS

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

#### CYTOCHROME P450 GENES

*CYP2D6*, *CYP2C19*, *CYP3A4*, *CYP1A2*, *CYP2C9*, and *CYP2B6* code for hepatic enzymes that are members of the cytochrome P450 family and are responsible for the metabolism of a wide variety of medications, including many psychotropic agents. For each of these genes, variants exist that affect the rate of enzyme activity 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.

#### **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);
- STA<sup>2</sup>R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical Reference Laboratory, Lenexa, KS). Specific variants included in the panel were not easily identified from the manufacturer's website.
- GeneSight® Psychotropic panel (Assurex Health, Mason, OH);
- Proove Opioid Risk panel (Proove Biosciences, Irvine, CA);
- Mental Health DNA Insight™ panel (Pathway Genomics, San Diego, CA);

- IDgenetix-branded tests (AltheaDx, San Diego, CA). 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 $\beta$ -hydroxylase)			X	
<i>CACNA1C</i> (gated calcium channel)	X			
<i>ANK3</i>	X			
<i>COMT</i> (catechol <i>O</i> -methyltransferase)	X		X	
<i>MTFHR</i>			X	
GABA			X	
<i>OPRK1</i> ( $\kappa$ -opioid receptor)			X	
<i>OPRM1</i> ( $\mu$ -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		
<i>CYP2B6</i>	X	X		
<i>P2B6</i>				
<i>UGT1A4</i>				
<i>ABCB1</i>				
<i>MC4R</i>	X			
<i>ADRA2A</i>	X			
<i>BDNF</i>	X			
<i>GRIK1</i>	X			

### Related Protocol

Cytochrome P450 Genotyping

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

## References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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