Introduction

Genetic testing is done to see if there are changes in chromosomes, genes, or the proteins made by genes. There are many reasons to do a genetic test, such as to confirm or rule out a genetic condition, to determine the chance of developing or passing on a genetic disorder, or to see if a person has an increased risk of having health problems. When it comes to mental health, genetic tests generally try to determine if a person is at risk for a condition such as schizophrenia. Other mental health genetic tests try to find out a person's response to a certain drug or which dose to use for medications that might treat a mental health condition. To date, the medical studies on genetic testing for mental health or for managing drug dosing do not show that information from the test will change treatment or lead to better outcomes.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
<table>
<thead>
<tr>
<th>Testing</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing for mental health conditions</td>
<td>Genetic testing for diagnosis and management of mental health disorders is considered investigational in all situations, including but not limited to the following:</td>
</tr>
<tr>
<td></td>
<td>• To confirm a diagnosis of a mental health disorder in an affected individual.</td>
</tr>
<tr>
<td></td>
<td>• To predict future risk of a mental health disorder in an asymptomatic individual.</td>
</tr>
<tr>
<td></td>
<td>• To choose a medication or decide on its dose in order to treat mental health disorders in an affected individual.</td>
</tr>
<tr>
<td>Genetic panels for selecting medications or doses of medication</td>
<td>Genetic testing panels, including but not limited to the following tests, are considered investigational for selecting medications or doses of medications for the treatment of psychiatric or mental health symptoms or disorders:</td>
</tr>
<tr>
<td></td>
<td>• Ally Diagnostics Genetic Testing Panel</td>
</tr>
<tr>
<td></td>
<td>• Alpha Genomics Psychiatry/ADHD Panel</td>
</tr>
<tr>
<td></td>
<td>• Genecept Assay</td>
</tr>
<tr>
<td></td>
<td>• GeneSight Psychotropic Panel</td>
</tr>
<tr>
<td></td>
<td>• Genetic Technological Innovations Pharmacogenetic Testing</td>
</tr>
<tr>
<td></td>
<td>• IDgenetix-branded tests (NeurolDgenetix)</td>
</tr>
<tr>
<td></td>
<td>• Kailos Test for Antidepressants</td>
</tr>
<tr>
<td></td>
<td>• Luminex xTAG CYP2C19 assay</td>
</tr>
<tr>
<td></td>
<td>• Luminex xTAG CYP2D6 assay</td>
</tr>
<tr>
<td></td>
<td>• Mental Health Insight DNA</td>
</tr>
<tr>
<td></td>
<td>• Millennium Pharmacogenetic Testing</td>
</tr>
<tr>
<td></td>
<td>• Molecular Testing Labs Psychotropic Medication Panel</td>
</tr>
<tr>
<td></td>
<td>• PersonaGene Panel PsychiaGene</td>
</tr>
<tr>
<td></td>
<td>• PGXL Multi-Drug Panel</td>
</tr>
<tr>
<td></td>
<td>• PGxOne Plus Psychiatry</td>
</tr>
<tr>
<td></td>
<td>• PharmaRisk Basic</td>
</tr>
<tr>
<td></td>
<td>• PharmaRisk Psychiatric Panel</td>
</tr>
<tr>
<td></td>
<td>• Primex Expanded Pharmacogenomics Panel</td>
</tr>
<tr>
<td></td>
<td>• Progenity Informed PGx Pharmacogenetic Testing</td>
</tr>
<tr>
<td></td>
<td>• STA2R SureGene</td>
</tr>
<tr>
<td></td>
<td>• YouScript Panel</td>
</tr>
</tbody>
</table>
## Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
</tr>
<tr>
<td>0015U</td>
<td>Drug metabolism (adverse drug reactions), DNA, 22 drug metabolism and transporter genes, real-time PCR, blood or buccal swab, genotype and metabolizer status for therapeutic decision support (code terminated 1/1/18)</td>
</tr>
<tr>
<td>0032U</td>
<td>COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G&gt;A (rs4680) variant (new code effective 1/1/18)</td>
</tr>
<tr>
<td>0033U</td>
<td>HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T&gt;C], HTR2C rs3813929 [c.-759C&gt;T] and rs1414334 [c.551-3008C&gt;G]) (for the Serotonin Receptor Genotype) (new code effective 1/1/18)</td>
</tr>
<tr>
<td>81230</td>
<td>CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22) (new code effective 1/1/18)</td>
</tr>
<tr>
<td>81291</td>
<td>MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis; common variants (eg, 677T, 1298C)</td>
</tr>
<tr>
<td>81328</td>
<td>SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5) (new code effective 1/1/18)</td>
</tr>
<tr>
<td>81355</td>
<td>VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G&gt;A, c.173+1000C&gt;T)</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).
Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

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

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

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

Genes Relevant to Mental Health Disorders

Mental disorders encompass a wide range of conditions: the DSM-5 includes more than 300 different disorders. However, currently available genetic testing for mental health disorders is primarily related to several 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 effects from one of several medications (or classes of medications) used to treat mental health conditions, including: typical and atypical antipsychotic agents, serotonin and serotonin/norepinephrine reuptake inhibitors (SSRIs), and medications used to treat addiction, such as disulfiram.

Panels of genetic tests have been developed and have been proposed for use in the management of mental health disorders.

Commercially Available Genetic Tests

Several test labs market panels of tests or individual tests relevant for mental health disorders, which may include a variety of genes relevant to psychopharmacology or risk of mental illness. Some of the panels (eg, the GeneSight panel) provide an overall risk score or summary score. The following list includes many examples, but not necessarily all, of the available tests.

The Ally Diagnostics Genetic Testing Panel (Ally Clinical Diagnostics, Farmers Branch, Texas) is a panel to evaluate genes that may affect a patient’s response to medications for the treatment
of psychiatric or mental health symptoms or disorders. The panel includes three CYP450 tests, vitamin K epoxide reductase, and a non-specific molecular pathology procedure.

**The Alpha Genomix Psychiatry/ADHD Panel** Includes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A, ADRA2A, and COMT.

**The Genecept™ Assay** (Genomind, LLC, Chalfont, PA) is a genetic panel test that includes a range of genetic mutations and/or polymorphisms that have been associated with psychiatric disorders and/or response to psychotropic medication. The test consists of a group of individual genes, and the results are reported separately for each gene. There is no summary score or aggregate results derived from this test. The intent of the test is as a decision aid for treatment interventions, particularly in the choice and dosing of medications. However, guidance on specific actions that should be taken following specific results of the test is vague. Interpretation of the results and any management changes as a result of the test are left to the judgment of the treating clinician.

**GeneSight® Psychotropic** (Assurex Health, Mason, OH) is a genetic panel that provides information about genes that may affect a patient’s response to antidepressant and antipsychotic pharmacotherapy. According to the manufacturer’s website, following testing the treating provider receives a report with the most common medications for the patient’s diagnosed condition categorized by cautionary level, along with a report of the patient’s genetic variants. Details are not provided about the algorithm used by the manufacturer to generate risk levels.

**Genetic Technological Innovations** (DBA Vantari Genetics) offers genetic testing for drug metabolism, preconception and pregnancy, inherited conditions and inherited cancer. Their pharmacogenetic panel for drug metabolism includes CYP2C19, CYP2D6, MTHFR and CYP3A4.

**IDgenetix** (AltheaDx, (San Diego, CA) offers a number of IDgenetix-branded tests, which include several panels focusing on polymorphisms that affect medication pharmacokinetics for a variety of disorders, including psychiatric disorders. Specific mutations included in the panel were not easily identified from the manufacturer’s website. NeurolDgenetix (psychiatric) panel appears to include the following: CYP2D6, CYP2C19, Cyp2C9, HTR2A, and HTR2C.

**Luminex** Offers a genotyping assay which can aid clinicians in determining therapeutic strategy for drugs metabolized by cytochrome P450.

**Mental Health DNA Insight™** panel (Pathway Genomic, San Diego, CA) is a test intended to analyze DNA to genetic variants in relation to response to psychiatric medications.

**Molecular Testing Labs Psychotropic Medication Panel** (Molecular Testing Labs, Vancouver, WA) offers a genetic testing panel which their website describes as identifying “five different
categories of patients by the way they metabolize specific drugs”. The only specific gene mentioned is CYP2D6.

**Pathway Genomics** (San Diego, CA) offers the Mental Health DNA Insight™ panel, which is a single nucleotide polymorphism-based array test which evaluates a number of genes associated with the metabolism and efficacy of psychiatric medications.

**The PersonaGene panel** Uses next generation sequencing to test for metabolism of common drugs for pain management, cardiology, psychiatry and urology. Although this large panel encompassing four specialties, all of the mutations tested are within the CYP450 family.

**The PGXL Multi-Drug Panel** Includes CYP2D6, CYP2C9, CYP2C190, CYP1A2, CYP3A4, CYP3A5, SLC6A4, OPRM1, VKORC1, SLCO1B1, SULT24A1, Factor II, Factor V, MTHFR and COM.

**The PharmaRisk Basic Panel** Is described by OptimumMeds as a test that “analyzes the genes that metabolize many commonly prescribed medications used in all clinical practices including: internal medicine, cardiology, geriatrics, psychiatry and chronic pain management.” The test analyzes 55 genetic markers across 4 genes – CYP2C19, CYP2C9, CYP2D6 and VKORC1.

**The PharmaRisk Psychiatric Panel** Includes CYP2D6, OPRM1, CYP2C9, COMT, DRD2, CYP2B6, CYP2C19, CYP1A2, UGT2B15.

**Progenity Informed PGx genetic testing panels** – there are 3 panels: ADHD (4 mutations), Depression (7 mutations) and Psychotropic (7 mutations) - and each panel tests a variety of CYP450 genes, MTHFR, etc.

**The STA2R** (SureGene Test for Antipsychotic and Antidepressant Response, SureGene, LLC, Louisville, KY) is another genetic panel that provides information about medication response, adverse event likelihood, and drug metabolism. According to the manufacturer’s website, the test is recommended for initial medication selection, for patients who have poor efficacy, tolerability, or satisfaction with existing medications, and in cases of severe treatment failure. Specific mutations included in the panel were not easily identified from the manufacturer’s website.

In addition to the available panel tests, several labs offer genetic testing for individual genes, including MTFHR, CYP450 genes, and SULT4A1.
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 management of mental health disorders.

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 in order 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 potentially be used in several ways including stratifying patients’ risks of developing a particular disorder, aiding diagnosis, targeting medication therapy, and optimally dosing medication.

**Pharmacogenomic Testing**

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

Treatment decisions are currently based on the assessment of different factors that may influence the variability of drug effects: age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genes
coding for drug-metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

Pharmacogenomics studies how an individual’s genetic inheritance affects the body’s response to drugs. It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse events, and decrease medical costs.

**Genes Relevant to the Diagnosis and Management of Mental Health Disorders**

Below is a brief outline of genes that may be relevant to the diagnosis and management of mental health disorders, which are currently available in genetic testing panels.

**ABCB1 Gene**

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

**Serotonin Transporter**

The serotonin transporter gene (*SLC6A4*) is responsible for coding the protein that clears serotonin metabolites (5-hydroxytryptamine) from the synaptic spaces in the central nervous system. This protein is the principal target for many of the selective serotonin reuptake inhibitors. By inhibiting the activity of the SLC6A4 protein, the concentration of 5-hydroxytryptamine in the synaptic spaces is increased. A common variant in this gene consists of insertion or deletion of 44 base pairs in the serotonin-transporter-linked polymorphic region. These variants have been studied in relation to a variety of psychiatric and nonpsychiatric conditions, including anxiety, obsessive-compulsive disorder, and response to selective serotonin reuptake inhibitors.
**Serotonin Receptor**

The serotonin receptor gene (*SHT2C*) 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 (eg, mirtazapine, nefazodone) are direct antagonists of this receptor. There is also interest in developing agonists of the 5HT2C receptor as a treatment for obesity and schizophrenia, but such medications are not commercially available at present.

The serotonin receptor gene (*SHT2A*) codes for another subtype of the serotonin receptor. Variations in the 5HT2A gene have been associated with susceptibility to schizophrenia and obsessive-compulsive disorder and response to certain antidepressants.

**Sulfotransferase Family 4A, Member 1**

The sulfotransferase family 4A, member 1, gene (*SULT4A1*) encodes a protein involved in the metabolism of monoamines, particularly dopamine and norepinephrine.

**Dopamine Receptors**

The *DRD2* gene codes for the D2 subtype of the dopamine receptor. The activity of this receptor is modulated by G proteins, which inhibit adenyl cyclase. These receptors are involved in various physiologic functions related to motor and endocrine processes. The D2 receptor is the target of certain antipsychotic drugs. Variants in this gene have been associated with schizophrenia and myoclonic dystonia. Variants of the *DRD2* gene have also been associated with addictive behaviors (eg, 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 central nervous system. 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 hydroxylase of dopamine to norepinephrine. It is primarily located in the adrenal medulla and postganglionic sympathetic neurons. Variation in the **DBH** gene has been investigated as a modulator of psychotic symptoms in psychiatric disorders and tobacco addiction.

**Gated Calcium Channel**

The gated calcium channel gene (**CACNA1C**) is responsible for coding of a protein that controls activation of voltage-sensitive calcium channels. Receptors for this protein are found widely throughout the body, including skeletal muscle, cardiac muscle, and in neurons in the central nervous system. In the brain, different modes of calcium entry into neurons determine which signaling pathways are activated, thus modulating excitatory cellular mechanisms. Associations of variants of this gene have been most frequently studied in relation to cardiac disorders. Specific variants have been associated with Brugada syndrome and a subtype of long QT syndrome (Timothy syndrome).

**Ankyrin 3**

Ankyrins are protein components of the cell membrane and interconnect with the spectrin-based cell membrane skeleton. The **ANK3** gene codes for the protein Ankyrin G, which has a role in regulating sodium channels in neurons. Alterations of this gene have been associated with cardiac arrhythmias (eg, 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 (eg, 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 the activity of the MTHFR enzyme. These variants have been associated with a wide variety of clinical disorders, including vascular disease, neural tube defects, dementia, colon cancer, and leukemia.

**γ-Aminobutyric Acid A Receptor**

The γ-aminobutyric acid A (GABA) receptor gene encodes a ligand-gated chloride channel composed of 5 subunits that respond to GABA, a major inhibitory neurotransmitter. Variants in the GABA receptor gene have been associated with several epilepsy syndromes.

**μ- and κ-Opioid Receptors**

OPRM1 encodes the μ-opioid receptor, which is a G protein–coupled receptor that is the primary site of action for commonly used opioids, including morphine, heroin, fentanyl, and methadone. Variants in the OPRM1 gene have been associated with differences in dose requirements for opioids. OPRK1 encodes the κ-opioid receptor, which binds the natural ligand dynorphin and a number of synthetic ligands.
Cytochrome P450 Genes

*CYP2D6, CYP2C19, CYP3A4, CYP1A2, CYP2C9,* and *CYP2B6* code for hepatic enzymes that are members of the cytochrome P450 family and are responsible for the metabolism of a wide variety of medications, including many psychotropic agents. For each of these genes, variants exist that affect the rate of enzyme activity, which consequently affect drug metabolization rates. Based on the presence or absence of variants, patients can be classified as rapid metabolizers, intermediate metabolizers, and poor metabolizers. Rapid metabolizers may not benefit from standard therapeutic doses because the drug is metabolized too quickly, resulting in subtherapeutic medication levels. Alternatively, poor metabolizers may require lower doses to avoid adverse events from an excess of medication in their system.

P-Glycoprotein Gene

The *ABCB1* gene, also known as the *MDR1* gene, encodes P-glycoprotein, which is involved in the transport of most antidepressants across the blood-brain barrier. *ABCB1* variants have been associated with differential response to antidepressants that are substrates of P-glycoprotein, but not to antidepressants that are not P-glycoprotein substrates.

UDP-Glucuronosyltransferase Gene

The UDP-glucuronosyltransferase gene (*UGT1A4*) encodes an enzyme of the glucuronidation pathway that transforms small lipophilic molecules into water-soluble molecules. Variants in the *UGT1A4* gene have been associated with variation in drug metabolism, including some drugs used for mental health disorders.

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 association between the mental illness of interest and candidate genes. Relevant outcomes are test validity, other test performance measures, and changes in disease status. Most studies have evaluated the association between genotype and mental health disorders without a clinical perspective; thus diagnostic characteristics and validated risk predictions among specific clinical populations are unknown. The associations are inconsistent across studies. There is no clear clinical strategy for how the
associations of specific genes and mental health disorders would be used to diagnose a specific patient or to manage a patient at higher risk of a specific disorder. No studies were identified that evaluated whether testing for variants changed clinical management or affected health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a 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, as well as 4 RCTs and several observational studies comparing outcomes for patients who received treatment guided by genetic testing with patients who received standard of care treatment. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. A large RCT showed that patients receiving treatment guided by genetic test results experienced significant improvements in mental health scores; however, the remaining RCTs showed no difference in mental health outcomes. Observational studies comparing patients who have had and have not had genetic testing reported that testing may be associated with differences in depression treatment outcomes, though methodologic shortcomings such as lack of randomization, small sample sizes, and large loss to follow-up limit the conclusions that can be drawn. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 3.

**Table 3. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03302364</td>
<td>A Research in Pharmacogenomics and Accurate Medication of Risperidone</td>
<td>800</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT03270891</td>
<td>Pharmacoeconomic Testing in Primary Care for the Treatment of Depression and Anxiety</td>
<td>120</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>NCT02573168</td>
<td>Pharmacogenomic Decision Support with GeneSight Psychotropic to Guide the Treatment of Schizophrenia/Schizoaffective Disorder</td>
<td>531</td>
<td>Sep 2020</td>
</tr>
<tr>
<td>NCT02466477</td>
<td>Pharmacogenomic Decision Support with GeneSight Psychotropic to Guide the Treatment of Major Depressive Disorder</td>
<td>570</td>
<td>Nov 2020</td>
</tr>
<tr>
<td>NCT03228953</td>
<td>Pharmacogenomic Testing in Major Depressive Disorder</td>
<td>206</td>
<td>May 2021</td>
</tr>
<tr>
<td>NCT02474680</td>
<td>Evaluation of Pharmacogenetic Testing in a Mental Health Population and Economic Outcomes (PGx-TIME)</td>
<td>84</td>
<td>Jan 2017 (completed)</td>
</tr>
<tr>
<td>NCT02443584</td>
<td>Pharmacogenetic Testing on an Outpatient Population with a Depression Diagnosis (PGX-AMG)</td>
<td>84</td>
<td>Apr 2017 (completed)</td>
</tr>
<tr>
<td>NCT02497027</td>
<td>Pharmacogenetic Testing in an Outpatient Population of Patients with Depression (PGx-UPA)</td>
<td>83</td>
<td>Apr 2017 (completed)</td>
</tr>
<tr>
<td>NCT02109939</td>
<td>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</td>
<td>1303</td>
<td>Jun 2017 (completed)</td>
</tr>
<tr>
<td>NCT02855580</td>
<td>Integrating Pharmacogenomic Testing into a Child Psychiatry Clinic (PGX)</td>
<td>71</td>
<td>Jul 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*a Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

**Clinical Pharmacogenetics Implementation Consortium**

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was established in 2009 to develop practice guidelines on the use of genetic laboratory results to inform prescribing decisions.\(^6\) The panel consists of experts from the United States, Europe, and Asia.

CPIC (2015) conducted a systematic literature review on the influence of \(CYP2D6\) and \(CYP2C19\) genotyping on selective serotonin reuptake inhibitor (SSRI) therapy.\(^6\) The CPIC provided dosing
recommendations for SSRIs based on phenotypes that classified patients as ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. However, CPIC noted that patients on an effective and stable dose of SSRIs would not benefit from dose modifications based on CYP2D6 and CYP2C19 genotype results. Additionally, CPIC asserted that genetic testing is only 1 factor among several clinical factors that should be considered when determining a therapeutic approach.

CPIC (2016) conducted a systematic literature review of the influence of CYP2D6 and CYP2C19 genotype on the dosing of tricyclic antidepressants. Dosing recommendations for tricyclic antidepressants were provided, based on patient classifications of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. CPIC noted that the most appropriate use of genotype-based dosing is when initiating therapy with a tricyclic. For patients already on tricyclics who have had doses adjusted based on plasma concentrations, response, or side effects, genetic testing is not as helpful.

**Evaluation of Genomic Applications in Practice and Prevention**

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

**Medicare National Coverage**

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

**Regulatory Status**

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

Also, many labs offer genetic testing for individual genes, including *MTFHR* (GeneSight Rx and other laboratories), *CYP450* variants, and *SULT4A1*.

AltheaDx offers a number of IDgenetix-branded tests, which include several panels focusing on variants that affect medication pharmacokinetics for a variety of disorders, including psychiatric disorders.

References


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/09/13</td>
<td>New Policy. New policy developed with literature review through September 30, 2013. The Genecept™ assay is investigational for all indications.</td>
</tr>
<tr>
<td>05/23/14</td>
<td>Update Related Policies. Add 12.04.509 and removed 12.04.82 as it was deleted.</td>
</tr>
<tr>
<td>08/11/14</td>
<td>Annual Review. Policy updated with literature review through April 14, 2014. Policy expanded to include other genetic testing panels for mental health disorders; title of policy changed to “Genetic Testing Panels for Mental Health Conditions.” Rationale extensively revised. References 1, 2, 7-11, 19-26, 28-8 added. Policy statement changed to indicate that individual genetic tests (as mutations or genetic variations) and genetic testing panels for mental health disorders are investigational.</td>
</tr>
<tr>
<td>09/10/14</td>
<td>Minor update. New test added to Policy Statement for genetic testing panels: Primex Expanded Pharmacogenomics Panel.</td>
</tr>
<tr>
<td>03/24/15</td>
<td>Minor update. New test added to investigational Policy statement for genetic testing panels: Frontier Toxicology PGx Pharmacogenomic Testing.</td>
</tr>
<tr>
<td>04/24/15</td>
<td>Minor update: Alpha Genomix Psychiatry/ADHD Panel and PGXL Multi-Drug Panel added to investigational Policy statement for genetic testing panels.</td>
</tr>
<tr>
<td>07/14/15</td>
<td>Annual Review. Policy number changed from 12.04.110 to 12.04.515 due to the addition of several local plan tests to the Policy Statement, Description and Reference</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>10/19/15</td>
<td>Update Related Policies. Remove 12.04.509 as it was archived.</td>
</tr>
<tr>
<td>05/01/16</td>
<td>Annual Review, approved April 12, 2016. Added rationale and references for CYP450 for use in review of mental health conditions/medications. References 51-93 added. No change in policy statements.</td>
</tr>
<tr>
<td>10/07/16</td>
<td>Coding update. Reference codes removed from Description section; these were informational only. CPT codes 81355 and 81479 added to the Coding section.</td>
</tr>
<tr>
<td>02/14/17</td>
<td>Policy moved into new format; no change to policy statements. References missing in error adding to Reference section.</td>
</tr>
<tr>
<td>08/01/17</td>
<td>Annual Review. Policy approved on July 25, 2017. No changes to policy statement.</td>
</tr>
<tr>
<td>10/01/17</td>
<td>Coding update. Added new CPT code 0015U (effective 8/1/17).</td>
</tr>
<tr>
<td>01/23/18</td>
<td>Coding update. Added new CPT code 81328 (new code effective 1/1/18).</td>
</tr>
<tr>
<td>01/30/18</td>
<td>Coding update, added note that CPT code 0015U was terminated 1/1/18.</td>
</tr>
<tr>
<td>09/01/18</td>
<td>Annual Review, approved August 10, 2018. Policy updated with literature review through April 2018; references 32, 35, 37-44, and 68-70 added. Policy statements unchanged. Title changed from “Genetic Testing for Mental Health Conditions” to “Genetic Testing for Diagnosis and Management of Mental Health Conditions.” Minor editing to lab name examples as some have gone out of business. Added CPT codes 0033U, 81230, and 81231. Removed CPT code 81401.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a customer service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
• Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  • Qualified sign language interpreters
  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in any other way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4355, Fax 425-918-5992. TTY 800-842-5357
Email AppealsDepartmentinquines@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at:
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申訴或稱屈的重要訊息。本通知可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。


Kreyòl ayisyen (Creole): Avi sila a gen Enfòmasyon Enpòtan lodann. Avi sila a kapat genyen enfòmasyon enpòtand konspès aplikasyon w lan osawa konspèt kouvètì asirans lan atravè Premera Blue Cross. Kapat genyen dat ki enpòt linya a avi sila a. Ou ka gen pou paan kék akson avan se taat dim po pou ka bwin kouvètì asirans sante la w la osawa pou yo k a ede w avèk depans yo. Se dwa w pou resewa enfòmasyon san a a asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

