Genetic Testing for Diagnosis and Management of Mental Health Conditions

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Section: Medicine
Place(s) of Service: Outpatient

I. 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 effects. Commercially available testing panels include several of these genes and are intended to aid in the diagnosis and treatment of mental health disorders.

For individuals who are evaluated for diagnosis or risk of a mental health disorder 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 health disorder 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 health disorder 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 undergone genetic testing to those who have not have shown that testing may be associated with differences in depression treatment outcomes. However, methodologic limitations limit the conclusions that can be drawn. Most studies are nonrandomized. One relevant RCT did not show a difference in patient
outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

II. Criteria

A. Genetic testing for mutations associated with mental health disorders is not covered in all situations, including but not limited to the following, as it is not known to be effective in improving health outcomes:

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

B. Genetic testing panels for mental health disorders, including but not limited to the Genecept Assay, STA2R test, the GeneSight Psychotropic panel, the Proove Opioid Risk assay, and the Mental Health DNA Insight panel are not covered for all indications as they are not known to be effective in improving health outcomes.

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>
<thead>
<tr>
<th>Table PG1. Nomenclature to Report on Variants Found in DNA</th>
</tr>
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<tbody>
<tr>
<td>Previous</td>
</tr>
<tr>
<td>Mutation</td>
</tr>
<tr>
<td>Variant</td>
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<tr>
<td>Familial variant</td>
</tr>
</tbody>
</table>
Table PG2. 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.

Coding
There is no specific CPT code for these testing panels. There are, however, specific codes for some of the component tests:

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81291</td>
<td>MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis; common variants (eg, 677T, 1298C)</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)</td>
</tr>
<tr>
<td>0032U</td>
<td>(catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G&gt;A (rs4680) variant (for the Catechol-O-Methyltransferase (COMT) Genotype)</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)</td>
</tr>
</tbody>
</table>

The remaining tests on the panel that are not currently codified in CPT would be reported with 1 unit of the unlisted molecular pathology code 81479.
III. Scientific Background: 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.

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 (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 (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 (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.

**Dopamine Receptors**
The DRD2 gene codes for a subtype of the dopamine receptor, called the D2 subtype. The activity of this receptor is modulated by G-proteins, which inhibit adenyl cyclase. These receptors are involved in a variety of physiologic functions related to motor and endocrine processes. The D2 receptor is the target of certain antipsychotic drugs. Mutations in this gene have been associated with schizophrenia and myoclonic dystonia. Polymorphisms of the DRD2 gene have been associated with addictive behaviors, such as smoking and alcoholism.

The DRD1 gene encodes another G-protein coupled receptor that interacts with dopamine to mediate some behavioral responses and modulate D2 receptor-mediated events. Polymorphisms of the DRD1 gene have been associated with nicotine dependence and schizophrenia.

The DRD4 gene encodes a dopamine receptor with a similar structure; DRD4 polymorphisms have been associated with risk-taking behavior and attention deficit hyperactivity disorder.

**Dopamine Transporter** (DAT1 or SLC6A3).
Similar to the SLC6A4 gene, the dopamine transporter gene (DAT1 or SLC6A3) encodes a transporter that mediates the active reuptake of dopamine from the synaptic spaces in the CNS. Polymorphisms in this gene are associated with Parkinson disease, Tourette syndrome, and addictive behaviors.
**Dopamine Beta-Hydroxylase.**
The dopamine beta-hydroxylase (DBH) protein encoded by this gene 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 (CACNA1C).**
This gene 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 polymorphisms of this gene have been most frequently studied in relation to cardiac disorders. Specific polymorphisms have been associated with Brugada syndrome and a subtype of long QT syndrome (Timothy syndrome).

**Ankyrin 3 (ANK3).**
Ankyrins are proteins that are components of the cell membrane and interconnect with the spectrin-based cell membrane skeleton. The ANK3 gene codes for the protein Ankyrin G, which has a role in regulating sodium channels in neurons. Alterations of this gene have been associated with cardiac arrhythmias such as Brugada syndrome. Polymorphisms of this gene have also been associated with bipolar disorder, cyclothymic depression, and schizophrenia.

**Catechol-O-Methyltransferase (COMT).**
This gene codes for the COMT enzyme that is responsible for the metabolism of the catecholamine neurotransmitters, dopamine, epinephrine and norepinephrine. COMT inhibitors, such as entacapone are currently used in the treatment of Parkinson disease. A polymorphism of the COMT gene, the Val158Met polymorphism, has been associated with alterations in emotional processing and executive function and has also been implicated in increasing susceptibility to schizophrenia.

**Methylenetetrahydrofolate Reductase (MTHFR).**
This 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 can cause hyperhomocysteinemia and homocystinuria. The MTHFR protein also plays a major role in epigenetics, through methylation of somatic genes. A number of polymorphism have been identified that result in altered activity of the MTHFR enzyme. These polymorphisms have been associated with a wide variety of clinical disorders, including vascular disease, neural tube defects, dementia, colon cancer, and leukemia.

**γ-Aminobutyric acid (GABA) A receptor.**
This gene encodes a ligand-gated chloride channel composed of 5 subunits that responds to GABA, a major inhibitory neurotransmitter. Mutations in the GABA receptor have been associated with several epilepsy syndromes.
μ- and κ-Opioid Receptors (*OPRM1* and *OPRK1*). 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. Polymorphisms 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, CYP2B6*). These 6 genes 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, polymorphisms exist that impact the rate of activity, and therefore the rapidity of elimination of drugs and their metabolites. Based on the presence or absence of polymorphisms, patients can be classified as rapid metabolizers (RM), intermediate metabolizers (IM), and poor metabolizers (PM).

P-Glycoprotein Gene (*ABCB1*)
This 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 polymorphisms 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 (*UGT1A4*)
The UDP-glucuronosyltransferase gene, UGT1A4, encodes an enzyme of the glucuronidation pathway that transforms small lipophilic molecules into water-soluble molecules. Polymorphisms 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 designed 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, such as the GeneSight panel, summarize 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 Act (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 US 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 mutations 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 mutations included in the panel were not easily identified from the manufacturer’s website.

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

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

RATIONALE
This evidence review was created in November 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through April 9, 2018.

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

TESTING FOR RISK OF MENTAL HEALTH DISORDER
For the first indication, this evidence review will assess whether genetic testing to determine the diagnosis or risk of mental illness is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

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

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

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

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

Patients
The relevant population of interest is asymptomatic individuals who would consider an intervention were a genetic variant detected.

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 (ie, Diagnostic and Statistical Manual of Mental Disorders).

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

Timing
Outcomes occur over the course of years.

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

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

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).
Evidence on the clinical validity of genetic testing for mental health disorders consists primarily of genome-wide association studies (GWAS) that correlate specific genetic variants with phenotypes and case-control studies that compared the odds ratio for genetic variants in individuals who had a clinical disorder with individuals who did not. In general, cross-sectional and case-control studies cannot be used to generate diagnostic characteristics such as sensitivity and specificity or clinically relevant risk prediction.

A comprehensive review of the GWAS and case-control studies for all investigated genes and their variants is beyond the scope of this review. In a review of meta-analyses examining the association between specific genes and specific mental health disorders, Gatt et al (2015) reported that 134 genes (206 variants) have been identified as significantly associated risk factors for major depressive disorder, anxiety disorders, attention-deficit/hyperactivity disorder, schizophrenia, or bipolar disorder, with 13 genetic variants shared between 2 or more disorders. Examples of research in this area are summarized in Table1.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Evidence Details</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANK3, CACNA1C</td>
<td>Bipolar disorder</td>
<td>Croarkin (2017), case-control</td>
<td>Initial analysis showed associations with bipolar disorder; associations no longer significant after controlling for multiple comparisons</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>Kroibier (2012), meta-analysis</td>
<td>Initial analysis showed associations with depression; associations no longer significant after controlling for multiple comparisons</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td>Jiang (2015), meta-analysis</td>
<td>Variants associated with schizophrenia in both white and Asian populations</td>
</tr>
<tr>
<td>COMT</td>
<td>Schizophrenia</td>
<td>Zammit (2007), case-control</td>
<td>No association detected</td>
</tr>
<tr>
<td>DRD1, DRD2</td>
<td>Addictive behavior</td>
<td>Bai et al. (2008), case-control</td>
<td>DRD1 variants associated with alcohol dependence</td>
</tr>
<tr>
<td>DRD4, DAT1</td>
<td>(SLC6A3)</td>
<td>Huang (2008), case-control, Stapleton (2007), meta-analysis, Xu (2011), meta-analysis</td>
<td>DRD1 variants associated with tobacco dependence, DAT1 variant associated with successful smoking cessation, inconsistent results: some analyses found DAT1 variants associated with alcohol dependence and some analyses did not</td>
</tr>
<tr>
<td>Bipolar and unipolar disorders</td>
<td></td>
<td>Lopez Leon (2005), case-control, Zou (2012), meta-analysis</td>
<td>Association with bipolar and unipolar disorders found with 1 of 3 DRD2 variants tested, initial analysis showed associations with DRD4 variants, associations no longer significant after controlling for multiple comparisons</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td>Jonsson (2003), case-control, Liu (2014), meta-analysis, Pan (2014), meta-analysis, Zhu (2011), meta-analysis</td>
<td>DRD2 variants associated with schizophrenia in males only, DRD2 variants associated with schizophrenia in whites, but not in Asians, some DRD1 variants associated within increased risk and some DRD1 variants associated with decreased risk for schizophrenia</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Bipolar disorder</td>
<td>Hu (2015), meta-analysis</td>
<td>Variants marginally associated with bipolar disorder, particularly in Asian and black populations</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>Bousman (2014), cohort, Lizer (2011), case-control, Wu (2013), meta-analysis</td>
<td>One variant of several tested may indicate more severe prognosis in patients with depression, inconsistent results, with some analyses showing variants associated with depression, particularly in Asian populations, and other analyses did not</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td>Hu (2015), meta-analysis</td>
<td>Variants associated with schizophrenia, particularly in Asian and black populations, inconsistent results, with 1 variant associated with the combination of psychiatric conditions, but not with the individual conditions, and other variants not associated with the combination of individual conditions</td>
</tr>
<tr>
<td>Bipolar disorder, depression, schizophrenia combined</td>
<td></td>
<td>Peerbooms (2011), meta-analysis</td>
<td>Inconsistent results, with 1 variant associated with the combination of psychiatric conditions, but not with the individual conditions, and other variants not associated with the combination of individual conditions</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>Addictive behavior</td>
<td>Enoch (2011), case-control</td>
<td>Variant associated with alcohol and heroin/cocaine addiction, inconsistent results, with variants showing significant associations with some anxiety-related traits (e.g., neuroticism, fear), but no association with other traits (e.g., harm avoidance)</td>
</tr>
<tr>
<td>Bipolar and unipolar disorders</td>
<td></td>
<td>Lasty-Su (2005), meta-analysis</td>
<td>Variants associated with bipolar disorder, but not unipolar disorder, inconsistent results: when meta-analysis combined significance results, there was an association with the gene, stress, and developing depression; when meta-analysis combined raw data, no association detected, variant associated with depression in whites, no association in Asians</td>
</tr>
<tr>
<td>Depression</td>
<td>Karg (2011), meta-analysis, Kyohara (2010), meta-analysis, Risch (2009), meta-analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SULT4A1</td>
<td>Schizophrenia</td>
<td>Meltzer (2009), case series</td>
<td>All patients in series had schizophrenia; those with variant had worse symptom scores</td>
</tr>
</tbody>
</table>
Subsection Summary: Clinically Valid
The association between mental health disorders and individual gene variants is an area of active investigation. For tests included in currently available genetic testing panels, the largest body of evidence appears to be related to the role of SLC6A4 and various dopamine receptor gene (DRD1, DRD2, DRD4, DAT1) variants and multiple mental health disorders. For these and other gene variants, the association with disease risks appears to be relatively weak and not consistently demonstrated across studies. Studies have not been conducted to determine the diagnostic capability or precise risk prediction, but to determine whether the particular genotype of interest is associated with mental health disorders. Diagnostic characteristics of the genes or validated risk estimates in clinically relevant populations are not available.

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

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

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

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

There is no strong chain of indirect evidence supporting the clinical utility of any of the previously mentioned genes associated with disease risk. To determine clinical utility, evidence 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
No studies were identified that used genetic tests to diagnose a mental health condition to manage patients. 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
For indication 2, this evidence review will assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical uses of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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

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

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 study, which evaluated specific medication sequences.

Outcomes
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. Also, avoidance of adverse events is an important outcome. For many mental illnesses, there are standardized outcome measures (eg, HAMD).

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 (ie, how medications are absorbed, distributed, metabolized, or excreted) or pharmacodynamics (ie, medications’ effects on the body); thus, individual genetic differences may lead to variability in the effectiveness of medications used to treat mental health disorders.

A large body of evidence has shown that certain gene variants code for enzymes involved in the metabolism of antipsychotic and antidepressant medications. The evidence consists of systematic reviews, meta-analyses, RCTs, as well as case-control and cohort studies. The largest systematic review, by Altar et al (2013), sponsored by Assurex, the manufacturer of the GeneSight Psychotropic panel, assessed the efficacy and safety of 26 antipsychotic and antidepressant medications associated with variants in 8 genes: CYP2D6, CYP2C19, CYP2C9, CYP1A2, CYP3A4, 2 serotonin receptor genes (HTR2C, HTR2A), and SLC6A4. Reviewers identified 294 studies meeting their inclusion criteria. Table 2 summarizes additional studies investigating the association between genetic variants and medications for mental health conditions.
### Table 2. Evidence for Genes Associated With Response to Drug Treatment for Mental Health Conditions

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Evidence</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1</td>
<td>Depression</td>
<td>• Brodtka (2015), 15 cohort</td>
<td>Meta-analysis showed 2 of 6 variants associated with response to antidepressants and response to SSRI (fluoxetine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gex-Fabry (2008), 18 cohort</td>
<td>Cohort did not find association between variant and response to SSRIs (fluoxetine)</td>
</tr>
<tr>
<td>DRD1, DRD2, DRD4, DAT1 (SLC6A3)</td>
<td>Depression</td>
<td>• Yin (2015), 24 RCT</td>
<td>DRD4 variants associated with level of response to SSRIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DRD2 and DAT1 variants not associated with responses to SSRIs</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td>• Hwang (2007), 25 case-control</td>
<td>DRD1 variants associated with response to antipsychotic drugs among African American samples, but not among whites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Kaur (2017), 26 case-control</td>
<td>DRD2 variants associated with level of response to antipsychotic drugs</td>
</tr>
<tr>
<td>CYP2C19, CYP2D6</td>
<td>ADHD</td>
<td>• Friel (2015), 24 RCT</td>
<td>Patients with CYP2D6 variant metabolizer</td>
</tr>
<tr>
<td>CYP2C19, CYP3A44</td>
<td>Depression</td>
<td>• Ramoz (2009), 25 cohort</td>
<td>Status of ultra-rapid, extensive, and intermediate, have similar safety profiles when treated with SNRI (venlafaxine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gex-Fabry (2008), 25 cohort</td>
<td>CYP2D6 variant not associated with response to SNRI (venlafaxine)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td>• Llorente (2018), 25 cohort</td>
<td>Most studies reported variants not associated with response to antidepressants or remission rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lobello (2010), 26 meta-analysis</td>
<td>Most meta-analysis reported CYP2D6 variant not associated with response to SNRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serretti (2016), 27 case-control</td>
<td>Most consistent results, with some studies showing CYP2D6 variants associated with response to antipsychotic (risperidone) and 1 study reporting CYP2D6 variants associated with serum concentrations of antipsychotic drug (haloperidol), but not with clinical effects as measured by Schizophrenia Syndrome Scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tarantu (2017), 28 cohort</td>
<td>• CYP2D6 variants associated with antipsychotic-induced extrapyramidal side effects</td>
</tr>
<tr>
<td>OPRM1</td>
<td>Addictive behavior</td>
<td>• Chamorro (2012), 25 meta-analysis</td>
<td>Variant associated with response to opioid antagonist (naltrexone) in patients with alcohol dependence</td>
</tr>
<tr>
<td>SLC6A2</td>
<td>ADHD</td>
<td>• Ramoz (2009), 25 cohort</td>
<td>Variant associated with response to SNRI (fluoxetine)</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>Depression</td>
<td>• Yin (2015), 25 RCT</td>
<td>Variant associated with response to SSRIs</td>
</tr>
<tr>
<td></td>
<td>Addictive behavior</td>
<td>• Johnson (2011), 25 RCT</td>
<td>Variant associated with response to serotonin receptor antagonist (etondrol) measured by mean drinks per drinking day and percentage days abstinent</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td>• Lenze (2010), 25 RCT</td>
<td>Variant associated with level of response to SSRI (escitalopram)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td></td>
<td>• Biermacka (2012), 25 meta-analysis</td>
<td>Inconsistent results, with 1 study finding variant associated with antidepressant-induced mania and 1 study finding insufficient evidence due to heterogeneity between studies</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>• Daray (2010), 25 meta-analysis</td>
<td>RCT results showed response to SSRI (citalopram) and NARI (trazodone) similar irrespective of presence of variant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lewis (2011), 25 RCT</td>
<td>Meta-analysis results:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Parcelli (2012), 25 meta-analysis</td>
<td>• Among whites, variant may predict antidepressant response and remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Porzio (2015), 25 RCT</td>
<td>• Among Asians, variant did not predict antidepressant response or remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serpa (2015), 25 cohort</td>
<td>Cohort study results showed association between variants and response to SSRIs (escitalopram, sertraline, paroxetine, citalopram)</td>
</tr>
</tbody>
</table>

ADHD: attention deficit/hyperactivity disorder; NARI: norepinephrine reuptake inhibitor; RCT: randomized controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.
Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

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

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

Systematic Reviews
Rosenblat et al (2017)\textsuperscript{55} and Health Quality Canada (2017)\textsuperscript{56} conducted systematic reviews of RCTs and non-RCTs evaluating whether pharmacogenetics testing improves clinical outcomes for major depressive disorder. Study quality was assessed using the Newcastle-Ottawa Scale in Rosenblat and the GRADE system in Health Quality Canada. Overall, the studies were assessed as low quality, because many were open-label, nonrandomized, and industry-sponsored. Also, many of the estimates were imprecise. Pooled analyses were not conducted in either review. Key studies included in the reviews and trials published after the reviews are described below.

Randomized Controlled Trials
Bradley et al (2018) conducted an RCT in which 685 patients with depression and/or anxiety disorders were randomized to treatment guided by either NeuroIDgenetix or standard of care (see Table 3).\textsuperscript{57} Outcomes included HAMD and the Hamilton Rating Scale for Anxiety (HAMA) and adverse drug events. Trained and blinded clinicians conducted interviews using the HAMD and HAMA. Changes in Hamilton scores are presented in Table 4. The frequency of adverse drug events did not differ statistically between groups.

Olson et al (2017) conducted an RCT in which patients with neuropsychiatric disorders were randomized to treatment guided by NeuroIDgenetix or standard of care (see Table 3).\textsuperscript{58} Outcomes included Neuropsychiatric Questionnaire, Symbol Digit Coding test, and adverse drug events. The Neuropsychiatric Questionnaire is a computerized survey addressing symptoms of neuropsychoses, and the SCD assesses attention and processing speed, which is sensitive to medication effects. There were no significant differences in Neuropsychiatric Questionnaire or Symbol Digit Coding
scores between groups (see Table 4). However, the patients receiving standard of care reported significantly more adverse events (53%) than patients receiving NeuroIDgenetix-guided care (28%).

Perez et al (2017) conducted an RCT of patients diagnosed with major depressive disorder randomized to genotype-guided treatment (Neuropharmagen) or treatment as usual (see Table 3). The pharmacogenetics report from Neuropharmagen provided information on 50 drugs, highlighting gene-drug interactions and drug recommendations from the Food and Drug Administration and Clinical Pharmacogenetics Implementation Consortium. The primary outcome was Patient Global Impression of Improvement (PGI-I), which was collected by telephone interviewers blinded to treatment allocation group. A response was defined as a PGI-I of 2 or less. Percent responders differed nominally between groups (p=0.05) at the end of the 12-week study (see Table 4). Changes in 17-item HAMD (HAMD-17) scores were significant at 5 weeks (p=0.04) but not at 12 weeks (p=0.08).

A small RCT by Winner et al (2013) evaluated the effect of providing the GeneSight test on the management of psychotropic medications used for major depressive disorder in a single outpatient psychiatric practice (see Table 3). Fifty-one subjects were enrolled and randomized to treatment as usual or treatment guided by GeneSight testing. All subjects underwent GeneSight testing, though results were not given to the physicians in the treatment as usual group until after study completion. At 10-week follow-up, treating physicians dose-adjusted subjects’ medication regimens with the same likelihood in the GeneSight group (53%) and the treatment as usual group (58%; p=0.66). However, patients in the GeneSight group who were initially on a medication classified as “use with caution and with more frequent monitoring” were more likely than those with the same classification in the unguided group to have a medication change or dose adjustment (100% vs 50% respectively; p=0.02). Depression outcomes, measured by the HAMD-17 score, did not differ significantly between groups at the 10-week follow-up (see Table 4). This trial’s small size may have limited the ability to detect a significant effect.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Active Interventions</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradley et al</td>
<td>U.S.</td>
<td>20</td>
<td>2016</td>
<td>Patients with depression and/or anxiety disorders</td>
<td>Treatment guided by NeuroIDgenetix</td>
<td>SOC (n=333)</td>
</tr>
<tr>
<td>Olson et al</td>
<td>U.S.</td>
<td>6</td>
<td>2015</td>
<td>Patients with ADHD, anxiety, depression, or psychosis</td>
<td>Treatment guided by NeuroIDgenetix</td>
<td>SOC (n=59)</td>
</tr>
<tr>
<td>Perez et al</td>
<td>Spain</td>
<td>18</td>
<td>2014-2015</td>
<td>Patients with MDD according to DSM-IV-TR</td>
<td>Treatment guided by Neuropharmagen</td>
<td>SOC (n=161)</td>
</tr>
<tr>
<td>Winner et al</td>
<td>U.S.</td>
<td>1</td>
<td>NR</td>
<td>Patients with major depressive disorder</td>
<td>Treatment guided by GeneSight</td>
<td>SOC (n=26)</td>
</tr>
</tbody>
</table>

ADHD: attention-deficit/hyperactivity disorder; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders; MDD: major depressive disorder; NR: not reported; RCT: randomized controlled trial; SOC: standard of care.
Two comparative, nonrandomized studies compared clinical outcomes in patients with and without genetic testing. Hall-Flavin et al (2013) presented results from an open-label, nonrandomized comparative trial to evaluate the effects of providing the GeneSight pharmacogenomics test results to inform the management of psychotropic medications used for major depressive disorder in outpatient psychiatric practice. Patients with major depressive disorder were enrolled and grouped consecutively into a “guided” group (n=113) or “unguided” group (n=114). All subjects had DNA samples collected and sent for the GeneSight test, though only providers for the “guided” group received results. Based on results from patients’ genotypes for CYP2D6, CYP2C19, CYP1A2, SLC6A4, and HTR2A, the test generates a “proprietary interpretive report” that includes recommendations for “use as directed,” “use with caution,” or “use with caution and with more frequent monitoring” for each of 26 antidepressant and antipsychotic agents. Subjects were followed for 8 weeks; 93 patients in the unguided group and 72 patients in the guided group completed follow-up (27% drop out rate). Reviewers found a greater reduction in symptoms in the guided group than in the unguided group for: HAMD-17 (p<0.001), the Quick Inventory of Depressive Symptomatology- Clinician Rated ( p<0.001), and the Patient Health Questionnaire (p=0.002). Patients in the guided group had higher rate of remission (26.4%) as measured by the Quick Inventory of Depression Symptomatology- Clinician Rated than in the unguided patients (12.9%; odds ratio,2.42; 95% CI, 1.09 to 5.39; p=0.03). Patients in the guided group who were initially on a medication classified as “use with caution and with more frequent monitoring” were more likely (93.8%) than those with the same classification in the unguided group (55%) to have a medication change or dose adjustment during the study period (p=0.01). In an earlier nonrandomized pilot study, Hall-Flavin et al (2012) compared outcomes for a group of patients who had major depression whose physicians received a GeneSight report with those of a
historical control group of patients treated without the GeneSight report. Twenty-six subjects were included in the “unguided” group and 25 in the “guided” group. At 8 weeks of follow-up, patients in the guided group had a 31.2% lower Quick Inventory of Depression Symptomatology®Clinician Rated score compared with a 7.25% lower score in the unguided group (p=0.002); for HAMD-17 scores, the guided group had a 30.8% lower score while the unguided group had 18.2% lower score (p=0.04).

To address the issue of small samples sizes, Altar et al (2015) conducted pooled analyses of the 2 Hall-Flavin (2013, 2012) studies and the RCT by Winner (2013). Included in the pooled analyses were 119 patients receiving GeneSight-guided treatment and 139 receiving usual care. Patients who received a “red” score on the basis of the GeneSight algorithm (“use with increased caution and with more frequent monitoring”) had less improvement in HAMD-17 scores over 8 weeks than patients with “yellow” scores (“use with caution”) or “green” scores (“use as directed”), or yellow/green for subjects prescribed cytochrome P450 2D6 (CYP2D6) substrate medications (p=0.001, p=0.01, p=0.002, respectively) and for subjects prescribed CYP2C19 substrate medications (p=0.003, p=0.02, p=0.004, respectively). None of the single genes included in the GeneSight panel was individually associated with positive or negative treatment outcomes. The odds for clinical response, defined as a 50% or greater decrease in HAMD score, was significant, favoring the patients receiving GeneSight-guided treatment (2.3; 95% CI, 1.3 to 3.9). The odds ratio for clinical remission, defined as achieving a score of 7 or less on the HAMD score, was not significant (1.8; 95% CI, 0.9 to3.4).

Breitenstein et al (2014) reported on 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. Patients and matched controls were selected from the Munich Antidepressant Response Signature project, a naturalistic study designed to identify factors that help to predict and improve treatment response in affective disorders. ABCB1 genotyping was implemented into the study’s protocol in 2008, and genotype results were provided to treating physicians with a 1-page letter outlining potential strategies based on genotype. The 58 patients who had ABCB1 genotyping were compared with a matched sample of historical controls enrolled before genotyping was implemented. Patients who received ABCB1 genotyping had higher remission rates at hospital discharge (83.6% vs 62.1%, p=0.005) and lower HAMD scores at hospital discharge (scores extrapolated from the graph, 6 vs 8; p=0.02). This study was limited to hospitalized patients with assessment of outcomes limited was to the time of hospital discharge.

Retrospective Studies
Brennan et al (2015) presented a case series of 685 patients who underwent testing with the Genecept Assay, with the results provided to participating clinicians. 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.
Espadeler et al (2016) reported on the results of a retrospective series of psychiatric patients who underwent testing with a pharmacogenetic test (Neuropharmagen) marketed in Europe. Patients whose treatment was considered to follow the test recommendations were compared with those whose treatment did not. Criteria for determining whether a patient’s treatment followed recommendations were complex. Outcomes were assessed by the treating psychiatrist who determined whether the patient improved over baseline. 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).

Section Summary: Clinically Useful
Four RCTs testing 3 different genetic panels were identified. After 8 to 12 weeks of follow-up, the largest RCT showed significant improvements in HAMD and HAMA scores among patients whose clinicians were guided by information from genetic tests. However, results in the remaining 3 trials did not show differences between test-guided and -unguided groups. Nonrandomized studies have reported significant improvements in outcomes among patients receiving guided treatment, but weaknesses in the studies such as large loss to follow-up, no comparison group, and small sample sizes limit the conclusions that can be drawn. Additional studies including larger numbers of patients with randomization and blinded outcome assessment will be needed to confirm findings that genotyping may be associated with improved clinical outcomes.

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, morbidity 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.

SUPPLEMENTAL INFORMATION
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. 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. 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.”

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 5. 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>A Research in Pharmacogenomics and Accurate Medication of Risperidone</td>
<td>800</td>
<td>Dec 2018</td>
</tr>
<tr>
<td></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></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></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></td>
<td>Pharmacogenomic Testing in Major Depressive Disorder</td>
<td>206</td>
<td>May 2021</td>
</tr>
<tr>
<td>Unpublished</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></td>
<td>Pharmacogenetic Testing on an Outpatient Population with a Depression Diagnosis (PGX-AMS)</td>
<td>84</td>
<td>Apr 2017 (completed)</td>
</tr>
<tr>
<td></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></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></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.
* Denotes industry-sponsored or cosponsored trial.

IV. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawai‘i’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. Medicare defines medical necessity as health care services or supplies needed to
diagnose or treat an illness, injury, condition, disease, or its symptoms and that meet accepted standards of medicine. This definition applies only to Medicare Advantage (PPO and HMO) plans.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

V. References


