Genetic Testing for Mental Health Conditions

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.

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 1 or more psychotropic medications that are aimed at alleviating symptoms of the disorder. Although there are a wide variety of effective medications, treatment of psychiatric disease 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 psychiatric disorders is advancing rapidly and may substantially alter the way in which 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.

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 2 clinical situations:

1. Risk stratifying patients for one of several mental health conditions, including schizophrenia and related psychotic disorders, bipolar and related disorders, depressive disorders, obsessive-compulsive and related disorders, and substance-related and addictive disorders.
2. Predicting patients’ response to, dose requirement for, or adverse 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. Genes that have been implicated in mental health disorders or their treatments and that are included in currently available panels include the following:

Serotonin Transporter (SLC6A4)

This gene is responsible for coding the protein that clears serotonin metabolites (5-HT) from the synaptic spaces in the central nervous system (CNS). This protein is the principal target for many of the SSRIs. By inhibiting the activity of the SLC6A4 protein, the concentration of 5-HT in the synaptic spaces is increased. A common polymorphism in this gene consists of insertion or deletion of 44 base pairs in the serotonin-transporter-linked polymorphic region (5-HTTLPR). These polymorphisms have been studied in relation to a variety of psychiatric and nonpsychiatric conditions, including anxiety, obsessive compulsive disorder, and response to SSRIs.
Serotonin Receptor (5HT2C)
This gene codes for 1 of at least 6 subtypes of the serotonin receptor that is 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 and nefazodone, are direct antagonists of this receptor. There is also interest in developing agonists of the 5HT2C receptor as treatment for obesity and schizophrenia, but no such medications are commercially available at present.

The 5HT2A gene 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 (SULT4A1)
SULT4A1 encodes a protein that is involved in the metabolism of monoamines, particularly dopamine and norepinephrine.

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 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.

In addition, several labs offer genetic testing for individual genes, including MTFHR (GeneSight Rx and other laboratories), CYP450 genes, and SULT4A1.

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.

### Table 1:
**Genetic Panels for Mental Health Disorders – Polymorphisms Included**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphisms Included in Commercially Available Test Panels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genecept Assay</td>
</tr>
<tr>
<td>SULT4A1</td>
<td>X</td>
</tr>
<tr>
<td>SLC6A4 (serotonin transporter)</td>
<td>X</td>
</tr>
<tr>
<td>5HT2C (serotonin) receptor</td>
<td>X</td>
</tr>
<tr>
<td>5HT2A (serotonin) receptor</td>
<td></td>
</tr>
<tr>
<td>DRD1 (dopamine) receptor</td>
<td></td>
</tr>
<tr>
<td>DRD2 (dopamine) receptor</td>
<td>X</td>
</tr>
<tr>
<td>DRD4 (dopamine) receptor</td>
<td></td>
</tr>
<tr>
<td>DAT1 (dopamine) transporter</td>
<td></td>
</tr>
<tr>
<td>DBH (dopamine beta-hydroxylase)</td>
<td></td>
</tr>
<tr>
<td>CACNA1C (gated calcium channel)</td>
<td>X</td>
</tr>
<tr>
<td>Ankyrin 3</td>
<td>X</td>
</tr>
<tr>
<td>COMT (catechol O-) methyltransferase</td>
<td>X</td>
</tr>
<tr>
<td>MTHFR</td>
<td>X</td>
</tr>
<tr>
<td>GABA</td>
<td></td>
</tr>
<tr>
<td>OPRK1 (k-opioid) receptor</td>
<td></td>
</tr>
<tr>
<td>OPRM1 (µ opioid) receptor</td>
<td>X</td>
</tr>
<tr>
<td>CYP 450 genes</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>X</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>X</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>X</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>X</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>X</td>
</tr>
<tr>
<td>P2B6</td>
<td>X</td>
</tr>
<tr>
<td>UGT1A4</td>
<td></td>
</tr>
<tr>
<td>ABCB1</td>
<td></td>
</tr>
<tr>
<td>MC4R</td>
<td>X</td>
</tr>
<tr>
<td>ADRA2A</td>
<td>X</td>
</tr>
<tr>
<td>BDNF</td>
<td>X</td>
</tr>
<tr>
<td>GRIK1</td>
<td>X</td>
</tr>
</tbody>
</table>
II. Criteria

A. Genetic testing for mutations associated with mental health disorders (See Table 1) is not covered in all situations, including but not limited to the following, because it has not been shown to improve health outcomes:

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

B. Genetic testing panels for mental health disorders, including but not limited to the Genecept Assay, STA\textsuperscript{2}R test, the GeneSight Psychotropic panel, the Proove Opioid Risk assay, and the Mental Health DNA Insight panel is not covered for all indications because they have not been shown to improve health outcomes.

III. Administrative Guidelines

GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO). The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

<table>
<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 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>
</tbody>
</table>
### Likely benign

<table>
<thead>
<tr>
<th>Likely benign</th>
<th>Likely benign change in the DNA sequence</th>
</tr>
</thead>
</table>

| Benign         | Benign change in the DNA sequence       |

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

### Genetic Counseling

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

### Coding

There are no specific CPT codes 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>
</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.

### IV. Scientific Background:

This policy has been updated periodically with literature reviews of the MEDLINE database. The most recent literature review was performed through April 25, 2017.

For evidence evaluating the clinical validity and clinical utility of genetic testing, separate sections of this report will summarize evidence on (1) genes associated with increased disease risk and (2) genes associated with medication pharmacokinetics and pharmacodynamics.
TESTING FOR RISK OF MENTAL HEALTH DISORDER

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

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

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

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

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

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

Outcomes
The general outcomes of interest are test accuracy and validity, other test performance measures, and change in disease status. The primary outcome of interest is change in disease outcomes, which would result directly from changes in management that could be instituted from earlier disease recognition. For many mental illnesses, there are standardized outcome measures (eg, Hamilton Depression Rating Scale).

Timing
Outcomes occur over the course of years.

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

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

Clinical Validity

Genes Associated with Increased Disease Risk

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

A comprehensive review of the GWAS and case control studies for all of these genes is beyond the scope of this policy. A 2015 review of meta-analyses examining the association between specific genes and specific mental health disorders reported that 134 genes (206 variants) have been identified as significantly associated risk factors for major depressive disorder, anxiety disorders, attention-deficit/hyperactivity disorder, schizophrenia, or bipolar disorder, with 13 genetic variants shared between 2 or more disorders. Some representative research in this area is discussed next.

Serotonin Transporter (SLC6A4) Gene

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

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

In 2009 meta-analysis, Risch et al evaluated studies published through March 2009 that assessed the association between polymorphisms in the 5-HTTLPR within the SLC6A4 gene and stressful life events and/or a diagnosis of depression. The authors included 14 studies that had a total of 14,250 participants. In a meta-analysis of published data, there was no association between 5-HTTLPR
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Genotype (homozygous short, homozygous long, or heterogeneous) and depression (weighted odds ratio [OR], 105; 95% confidence interval [CI], 0.98 to 1.13). There was also no interaction between genotype and the effect of stressful life events on depression (weighted OR=1.01; 95% CI, 0.94 to 1.10).

In 2010, Karg et al reported results from another meta-analysis that evaluated the association between 5-HTTLPR polymorphisms and stressful life events and a diagnosis of depression. Using broader search criteria, the authors included 54 studies that had a total of 40,749 patients. In their meta-analysis, conducted using the Liptak-Stouffer z score method to combine studies at the level of significance tests, weighted by study sample size, the authors found a significant association between the presence of the 5-HTTLPR short allele and increased risk of developing depression under stress (p<0.001). When they confined their analysis to only those studies used in the Risch et al meta-analysis, there was no significant association between 5-HTTLPR polymorphisms and depression.

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

**SULT4A1 Gene**
Based on a study targeting a polymorphism in the 5’ untranslated region of the SULT4A1 gene in 27 families with at least 2 siblings with schizophrenia or schizophrenia spectrum disorder, the SULT4A1 gene has been evaluated as a candidate gene for schizophrenia. Meltzer et al evaluated a panel of patients with schizophrenia or schizoaffective disorder and available DNA to determine the association between 3 SULT4A1 single nucleotide polymorphisms (SNPs) (rs138060, rs138097, and rs138110) and clinical symptoms and quality of life. Among 86 participants included, although all patients had a diagnosis of schizophrenia or schizoaffective disorder, the rs138060 SNP was significantly associated with worse symptoms scores. In addition, the rs138097 SNP was significantly associated with worse neuropsychological test performance.

**CACNAIC and ANK3 Genes**
The CACNAIC gene has been studied most widely for its association with disorders of cardiac rhythm, such as long QT syndrome and Brugada syndrome. A lesser amount of research has reported associations of polymorphisms of this gene with schizophrenia and bipolar disorder.

In 2015, Jiang et al published a meta-analysis of studies evaluating the association between the CACNA1C SNP rs1006737 and schizophrenia risk in East Asian populations. The authors included 5 case-control studies in East Asian samples including 9432 cases with schizophrenia and 10,661 controls for their primary analysis. A second analysis was conducted for pooled East Asian and European populations, which included 2 additional candidate gene studies and 1 GWAS study in Europeans, for a total of 21,246 cases and 38,072 controls. In East Asian populations, the
rs1006737 SNP was significantly associated with risk of schizophrenia (allelic model: pooled OR=1.20 for A allele; p=4.39x10^{-6}). When the European studies were included, there was a stronger association between the CACNAIC polymorphism and schizophrenia risk (allelic model: pooled OR=1.12 for A allele; p=2.40x10^{-17}).

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

Subsequently, Croarkin et al (2017) also reported an association between CACNAIC and ANK3 polymorphisms in a series of 69 cases with early-onset bipolar disorder (aged 6-15 years), who were compared with 855 adults with bipolar disorder and 857 adult controls. A global risk score that included 8 variants (4 in CACNAIC, 3 in ANK3, and 1 in ODZ4) was associated with early-onset bipolar disorder (P=0.01), but not late-onset.

**COMT Genes**

For the COMT gene, polymorphisms have been reported to be associated with cognitive function, emotional processing, and other cognitive tasks. However, a more recent meta-analysis found no significant association between COMT genotype and several cognitive phenotypes. In addition, associations with specific psychiatric conditions such as schizophrenia are less certain.

**Dopamine Receptors and Transporter Genes**

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

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

Variants in the DRD2 gene have also shown associations with disorders other than schizophrenia. Zou et al reported results of a meta-analysis of studies that assessed the association between 3 DRD2 polymorphisms and mood disorders (bipolar disorder and unipolar depression). A total of 2157 cases and 3272 controls from 14 studies were included. A significant association was
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demonstrated between 1 polymorphism assessed (TaqI A1) and mood disorders (OR=1.84; 95% CI, 1.07 to 3.17; p=0.03).

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

For the DRD1 gene, case-control studies have linked polymorphisms to both increased and decreased risk of schizophrenia, along with addictive behaviors including smoking and alcohol dependence. A 2014 meta-analysis of studies evaluating the association between DRD1 polymorphisms and schizophrenia risk found that the rs5326 but not the rs4532 SNP was associated with schizophrenia.

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

MTHFR Gene

For psychiatric disease, Wu et al performed a meta-analysis of 26 GWAS evaluating the association of MTHFR variants with depression. Overall, there were low-strength associations between numerous MTHFR SNPs and depression, with odds ratios ranging from 1.15 to 1.42. On subgroup analysis, the associations were stronger for Asian populations. In whites, the associations were of marginal significance, and in elderly patients the associations were not statistically significant.

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

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

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

MTHFR mutations have also been associated with schizophrenia and bipolar disorder. Peerbooms et al conducted a systematic review and meta-analysis of case control studies evaluating associations between the MTHFR SNPs C677T and A1298C and schizophrenia, bipolar disorder, and unipolar depression. The analysis included 24 studies related to schizophrenia, 10 related to bipolar disorder, and 17 related to unipolar depression. The C677T SNP was significantly associated with all disorders combined (OR=1.26 comparing homozygotes; 95% CI, 1.09 to 1.46). The A1298C SNP was significantly associated with bipolar disorder (OR=2.03 comparing homozygotes; 95% CI, 1.07 to 3.86).

Section Summary: Clinical Validity of Genes Associated With Increased Disease Risk
The association between mental health disorders and individual gene polymorphisms is an area of active investigation. For tests that are 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 polymorphisms and multiple mental health disorders. For these and other gene polymorphisms, the association between genetic polymorphisms and disease risks appears to be relatively weak and is not consistently demonstrated across studies. Studies have not been conducted to determine the diagnostic capability or precise risk prediction, but to determine whether the particular genotype of interest is associated with mental health disorders. Diagnostic characteristics of the genes or validated risk estimates in clinically relevant populations are not available.

Clinical Utility
Although studies have suggested that there may be a number of genetic variants associated with increased risk of mental health disorders and/or response to specific treatment, estimates of the magnitude of the increased risk vary across studies. For the individual tests, results from GWAS and case-control studies are insufficient to determine clinical utility. There is no strong chain of indirect evidence supporting the clinical utility of any of the previously mentioned genes associated with disease risk. To determine clinical utility, evidence is needed showing that testing for variants in these genes leads to changes in clinical management that improve outcomes.

TESTING FOR GENES ASSOCIATED WITH MEDICATION PHARMACOKINETICS AND PHARMACODYNAMICS

Clinical Context and Test Purpose
The purpose of pharmacogenetic testing in patients who are being treated with or considered for therapy with a number of different medications used in the treatment of mental illnesses is to
inform a decision whether to start a particular drug or dose, make dose adjustments, or change
drugs when a therapy is not working.

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

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

**Patients**
The relevant population(s) of interest are 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 medications for mental illnesses are
typically made based on clinical response, with potentially informed by studies such as the
Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which evaluated specific
medication sequences.

**Outcomes**
The general outcomes of interest are test accuracy and validity, other test performance measures,
and change in disease status. The primary outcome of interest is change in disease outcomes
resulting from more appropriate selection of specific drugs or doses for the patients condition. In
addition, avoidance of adverse effects is an important outcome. For many mental illnesses, there
are standardized outcome measures (eg, Hamilton Depression Rating Scale).

**Timing**
Outcomes occur over the course of years.

**Setting**
Testing would generally occur in the setting of a primary care or mental health practitioner
practice.

**Overview of Pharmacogenetics and Mental Health Disorders**
Genetic polymorphisms 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. To distinguish genes that are predictive of
treatment response, versus those that are prognostic (predictive of outcome independent of
treatment), it is usually necessary for studies to evaluate outcomes in patients who are receiving
treatment and in patients not receiving treatment (or receiving an alternative treatment). A gene
that is predictive will result in a study demonstrating an interaction between genotype and
treatment. In many studies claiming to evaluate genotype and treatment response, only patients
receiving treatment have been evaluated.

Several studies have summarized the associations between multiple candidate genes and single or
multiple mental health disorders. Alter et al., in a study funded by Assurex, the manufacturer of the
GeneSight Psychotropic panel, conducted a systematic review to assess whether the efficacy
and/or adverse effects of 26 antipsychotic and antidepressant medications are associated with
polymorphisms in 8 genes: CYP2D6, CYP2C19, CYP2C9, CYP1A2, CYP3A4, 2serotonin receptor genes
(HTR2C, HTR2A), and SLC6A4. The authors reviewed 294 studies that met their inclusion criteria.
Thirty-two of the studies assessed associations between 5-HTR2C polymorphisms and various
aspects of mental health disease. These included drug response, remission, adverse drug reactions,
and evaluation of weight gain or metabolic syndrome in patients with psychiatric disorders (most
commonly schizophrenia or schizoaffective disorders). Significant associations between at least 1
HTR2C allele and metabolic syndrome were found in 6 of the 7 studies that evaluated metabolic
syndrome. Thirty-nine studies assessed the association between 5-HTR2A polymorphisms and
adverse events or drug efficacy; 5 of the 10 studies that evaluated antipsychotic-related adverse
events found a significant association between 5-HTR2A polymorphisms and adverse drug
reactions, including weight gain, tardive dyskinesia, extrapyramidal adverse effects, and
antipsychotic-induced Parkinsonism.

Seventy-four studies evaluated associations between the SLC6A4 gene and drug response,
remission, or adverse events (AEs), most commonly related to the use of SSRIs. Fifty-four studies
investigated the most frequently assessed polymorphism (5-HTTLPR “long”/”short”), with 29
studies showing a significant association with drug response or remission. Studies on a number of
p450 genes were also assessed and generally included associations of genotype with phenotypic
pharmacokinetic measures, including extensive metabolism (EM), intermediate metabolism (IM),
poor metabolism (PM), and ultrarapid metabolism (UM) status. The authors conclude that there is
substantial evidence of the association between polymorphisms and patient response to
psychotropic medications; however, questions remain about how to incorporate testing for
polymorphisms into clinical practice.

In a 2015 study not included in the Altar systematic review, Yin et al assessed the association
between SLC6A2, SLC6A3, DRD2, and DRD4 polymorphisms and response to selective serotonin
reuptake inhibitor (SSRI) therapy in a clinical trial of 229 patients undergoing treatment for
depression. DRD4 gene rs1800544 polymorphism differed significantly between drug responders
and nonresponders (p<0.05), with no significant association with response seen for the other
genotypes. In a 2014 trial comparing outcomes for 137 patients with depression randomized to
antidepressant therapy (n=97) or interpersonal counseling (n=40), SL6A4 genotypes (AA genotype
and A allele) were associated with response rates to antidepressants in the antidepressant group
(p=0.015 and p=0.005, respectively).

**Clinical Validity**

**Antipsychotic Response**
Dopamine Receptor Genes

A number of studies have evaluated polymorphisms in the dopamine receptor genes (DRD1, DRD2) and response to treatment for schizophrenia. Zhang et al reported results from a systematic review and meta-analysis of the association between DRD2 polymorphisms and response to antipsychotic agents among patients with schizophrenia. The authors identified 6 studies that evaluated the role of the -141C Ins/Del polymorphism (N=687 patients). There was a significantly lower response rate to antipsychotics for patients who were Del carriers compared with Ins/Ins groups (pooled OR=0.65; 95% CI, 0.43 to 0.97; p=0.03). Eight studies were identified that evaluated the association between a different polymorphism (TaqA1) and antipsychotic response (N=748 patients). There was no significant association between the TaqA1 polymorphism and antipsychotic response in pooled analysis.

Studies investigating the relationship between polymorphisms in the DRD1 gene and antipsychotic response have not consistently reported a significant association.

Antidepressant Response

Serotonin Transporter (SLC6A4) Gene

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

A number of studies have associated SLC6A4 polymorphisms with antidepressant response. In a 2011 systematic review and meta-analysis, Porcelli et al evaluated the role of the 5-HTTLPR polymorphisms in predicting antidepressant response. The authors identified 33 publications that compared outcomes after antidepressant use for either major depressive disorder or bipolar disorder, 28 of which were used in an analysis of SSRI response, and 8 in an analysis of other antidepressants. The 5-HTTLPR “long” allele was associated with remission when homozygous “long” patients were compared with homozygous “short” patients (for all antidepressant classes: OR=1.37; 95% CI, 1.09 to 1.72; p=0.007; for SSRIs only: OR=1.48; 95% CI, 1.12 to 1.96; p=0.005).

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

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

Research has also evaluated the association between SCL6A4 polymorphisms and antidepressant adverse effects. In a systematic review and meta-analysis, Daray et al evaluated the role of 5-HTTLPR polymorphisms and antidepressant-induced mania, a complication of antidepressant therapy that can be seen in patients with bipolar disorder.(37) Previous studies had reported that the “long” and “short” forms of this gene were associated with different rates of antidepressant-induced mania. In the authors’ meta-analysis, based on 6 studies that met their inclusion criteria, the “short” form of the gene was associated with an increased risk of antidepressant induced mania (combined risk ratio, 1.35; 95% CI, 1.04 to 1.76).

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

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

**ABCB1 Gene**

Polymorphisms in the ABCB1 gene, encoding a P-glycoprotein efflux pump that is involved in the transport of various molecules (including antidepressant drugs), across the blood-brain barrier, have been associated with response to antidepressant treatment. In 2015, Breitenstein et al reported results of a meta-analysis of 16 pharmacogenetic studies (total N=2695 patients) evaluating the association between ABCB1 variants and antidepressant treatment outcomes for patients with major depression. Six ABCB1 SNPs were evaluated: rs2032583, rs2235015, rs2235040, rs1045662, rs2032582, and rs1128503. Two SNPs (rs2032583, rs2235015) were significantly associated with treatment response among 485 inpatients after Bonferroni correction (n=485 and p=1.5×10^-5 for rs2032583; n=195 and p=3.0×10^-4 for rs2235015).

**Addiction Response**

**Opioid Receptor Genes**

Several studies have evaluated the role of polymorphisms in the opioid receptor gene (OPRM1) and response to the opioid antagonist naltrexone for the treatment of alcohol dependence. Chamorro et al conducted a systematic review and meta-analysis to assess the relationship between the A118G polymorphism in the OPRM1 gene and response to treatment with naltrexone in patients with alcohol dependence. The authors included 6 studies among patients with alcohol dependence.
Naltrexone-treated patients who were homozygous for the A allele had a higher rate of relapse than those carrying the G allele (summary OR=1.97; 95% CI, 1.06 to 3.66; p=0.03).

**Cytochrome p450 Genes**

A large amount of research has been conducted on the cytochrome P450 genes, with variants associated with altered drug metabolism for a wide variety of medications. A review of specific associations between these variations and metabolism of some psychiatric medications is discussed in related evidence review (Cytochrome p450 Genotyping).

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

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

**Clinical Utility**

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

**Systematic Reviews**

Rosenblat et al (2017) reported on a systematic review of clinical trials and cost-effectiveness studies evaluating whether pharmacogenetics testing improves clinical outcomes for major depressive disorder. The review identified 5 studies, 3 nonrandomized comparative studies (Hall-Flavin et al [2013], Hall-Flavin et al [2012], Brennan et al [2015], which are described below), 1 RCT (Winner et al [2013], described below), and an additional industry-sponsored RCT (Singh et al [2015]) comparing a pharmacokinetic report-guided medication-management group with standard management. No pooled analyses were conducted. As described below, one nonrandomized comparative study of the Genecept assay showed improvements depression ratings for patients being treated in the guided-treatment group (Hall-Flavin et al [2013]), and another showed higher rates of remission with guided treatment (Hall-Flavin et al [2012], while a small RCT showed no difference between genotype-guided treatment and standard treatment (Winner et al). As described below, in a noncomparative study evaluating the Genecept assay about 40% of patients had a response or remission. Finally, in a double-blind RCT which randomized patients to a genotype-guided medication strategy (n=74) or an unguided strategy (n=74), patients with major
depressive disorder were followed for 12 months. Those in the genotype-guided group had a higher remission rate (72% vs 28%, OR 2.52, 95% CI 1.71 to 3.73, P<0.0001).

**Randomized Controlled Trials**
A small 2013 RCT by Winner et al evaluated the effect of providing the GeneSight test on the management of psychotropic medications used for major depressive disorder in a single outpatient psychiatric practice. Fifty-one subjects were enrolled and randomized to a treatment as usual group or a GeneSight testing-guided group. All subjects underwent GeneSight testing and report preparation as described for the Hall-Flavin study previously discussed. At 10-week follow-up, treating physicians changed, augmented, or dose-adjusted subjects’ medication regimens with the same likelihood for the GeneSight group and the treatment as usual group (53% vs 58% respectively; χ²=0.19; 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; χ²=5.09; p=0.02). Depression outcomes, measured by the HAMD-17 score, did not differ significantly at the 10-week follow-up between groups. This study’s small size may have limited its ability to detect a significant effect.

**Nonrandomized Studies**
Two comparative, nonrandomized studies from the same research group compared clinical outcomes in patients with and without genetic testing. In 2013, Hall-Flavin et al reported results from an open-label, nonrandomized comparative trial to evaluate the effects of providing the GeneSight pharmacogenomics test results on the management of psychotropic medications used for major depressive disorder in an outpatient psychiatric practice. Two hundred twenty-seven patients with major depressive disorder were enrolled and grouped consecutively into a “guided” group (n=113) or “unguided” group (n=114). All subjects had DNA samples collected and sent for the GeneSight test. Based on results from patients’ genotypes for CYP2D6, CYP2C19, CYP1A2, SLC6A4, and HTR2A, the test generates a “proprietary interpretive report” that includes recommendations for “use as directed,” “use with caution,” or “use with caution and with more frequent monitoring” for each of 26 antidepressant and antipsychotic agents. Providers for patients in the “guided” group received the results from the GeneSight test report. Subjects were followed for 8 weeks; 93 patients in the unguided group and 72 patients in the guided group completed follow-up. In an analysis of those who completed follow-up, the authors found a greater reduction in symptoms for the guided group than in the unguided group for the depression measures used: Hamilton Rating Scale for Depression (HAMD-17; F=22.4, p<0.001), the Quick Inventory of Depressive Symptomatology–Clinician Rated (QIDS-C16; F=29.7, p<0.001), and the Patient Health Questionnaire (F=7.07, p=0.002). Patients in the guided group had a higher rated of remission (26.4%) as measured by the QIDS-C16 than in the unguided patients (12.9%; OR=2.42; 95% CI, 1.09 to 5.39; p=0.03). Patients in the guided group who were initially on a medication classified as “use with caution and with more frequent monitoring” were more likely (93.8%) than those with the same classification in the unguided group (55%) to have a medication change or dose adjustment during the study period (χ² test, 6.35; p=0.01).

In an earlier nonrandomized pilot study, Hall-Flavin et al (2012) compared outcomes for a group of patients with major depression whose physicians received a GeneSight report to 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 QIDS-C16 score compared with a 7.25% lower score in the unguided group (p=0.002); for HAMD-17 scores, the guided group had a 30.8% lower score while the unguided group had 18.2% lower score (p=0.04).

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

Altar et al reported the results of pooled analyses from the 3 studies previously described (Hall-Flavin et al [2013], Hall-Flavin et al [2012], Winner et al [2013]). Patients who received a “red” score on the basis of the GeneSight algorithm (“use with increased caution and with more frequent monitoring”) had less improvement in HAMD-17 scores over 8 weeks than patients with “yellow” scores (“use with caution”) or “green” scores (“Use as directed”), or yellow/green for subjects prescribed medications that are cytochrome P450 2D6 (CYP2D6) substrates (p=0.001, p=0.01, p=0.002, respectively) and for subjects prescribed medications that are CYP2C19 substrates (p=0.003, p=0.02, p=0.004, respectively). None of the single genes included in the GeneSight panel was individually associated with positive or negative treatment outcomes.

In 2014, Breitenstein et al reported results of a small nonrandomized comparative study assessing whether genotyping of the ABCB1 gene in clinical practice was associated with changes in medication management in outcomes among 58 patients hospitalized with depression. In this study, patients and matched controls were selected from the Munich Antidepressant Response Signature (MARS) 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 (eg, pay attention to sufficient dosing, consider changing to a medication not a substrate of the P-glycoprotein encoded by the ABCB1 gene for subjects who had 2 T alleles of the rs2032583 SNP and 2 G alleles of the rs2235015 SNP). The 58 patients who had ABCB1 genotyping were compared with a matched sample of historical controls enrolled before genotyping was implemented. Patients who received ABCB1 genotyping had higher remission rates at the time of hospital discharge (83.6% vs 62.1%, p=0.005, 1-sided) and lower HAMD scores at the time of hospital discharge (scores extrapolated from graph, 6 vs 8; p=0.02, 1-sided). This study was limited to hospitalized patients with assessment of outcomes limited to the time of hospital discharge.

In 2015, Brennan et al reported results of a case series of 685 patients who underwent testing with the Genecept assay. Approximately 70% and 29% of patients had primary diagnoses of a mood or an anxiety disorder, respectively. Eighty-seven percent of patients showed improvement (defined as very much improved, much improved, or minimally improved), and 62% showed very much or much improved status.
In 2016, Espadeler et al reported the results of a retrospective series of psychiatric patients who underwent testing with a pharmacogenetic test (Neuropharmagen) marketed in Europe. Patients whose treatment was considered by the authors to follow the test recommendations were compared to those whose treatment did not. Criteria for determining whether a patient’s treatment followed recommendations were very complex. For example, the test provides 4 types of information on up to 39 different drugs. An example of not following the test recommendation is whether a patient’s treatment included a medication with a red alert, indicating increased risk of adverse drug reaction. Outcomes were assessed by the treating psychiatrist who determined whether the patient improved over baseline. At 3-month follow-up, 93% (83/89) patients whose treatment followed the recommendations had improved compared with 82% (76/93) those whose treatment did not (p=0.019). This study did not directly evaluate use of genetic testing, because all patients had testing. Certain patients had treatment judged not to be concordant with the recommendations. It cannot be determined why they received the specific treatment or whether they would have had worse outcomes regardless.

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

SUMMARY OF EVIDENCE
For individuals who are evaluated for diagnosis or risk of a mental 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.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS
No guidelines or statements were identified.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

<table>
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<th>Trial Name</th>
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<th>Completion Date</th>
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<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>1200</td>
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<tr>
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<td>Six-month Study of the Genecept Assay vs. Treatment as Usual to Evaluate Efficacy of Using Assay Guided Treatment in Outpatient Adults With Treatment Resistant Depression</td>
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<td>NCT01555021</td>
<td>Pharmacogenomics for Antidepressant Guidance and Education</td>
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<td>Dec 2014 (unknown)</td>
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NCT: national clinical trial.
V. 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 Hawaii’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. 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.

VI. References


