I. POLICY

Genetic testing for mutations associated with mental health disorders (see Table 1) is considered investigational in all situations. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Genetic testing panels for mental health disorders, including but not limited to the Genecept Assay, STA2R test, the GeneSight Psychotropic panel, and the Proove Narcotic Risk assay, are considered investigational for all indications. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-reference:

MP-2.234 Cytochrome p450 Genotyping
MP-2.323 General Approach to Evaluating the Utility of Genetic Panels
MP-2.253 General Testing for Inherited Thrombophilia

II. PRODUCT VARIATIONS

\[N\] = No product variation, policy applies as stated
\[Y\] = Standard product coverage varies from application of this policy, see below

\[N\] Capital Cares 4 Kids
\[N\] PPO
\[N\] HMO
\[N\] SeniorBlue HMO
\[N\] SeniorBlue PPO

\[N\] Indemnity
\[N\] SpecialCare
\[N\] POS
\[N\] FEP PPO
III. DESCRIPTION/BACKGROUND

Psychiatric 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 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 in order 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. Better understanding of these factors may lead to an improved ability to target medications to the specific underlying abnormalities, with potential improvement in the efficiency and efficacy of treatment.

Genes Relevant to Mental Health Disorders

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

1. Risk stratifying patients for one of several mental health conditions, including schizophrenia and related psychotic disorders, bipolar and related disorders, depressive disorders, obsessive-compulsive and related disorders, and substance-related and addictive disorders.

2. Predicting patients’ response to, dose requirement for, or adverse effects from one of several medications (or classes of medications) used to treat mental health conditions, including: typical and atypical antipsychotic agents, serotonin and serotonin/norepinephrine reuptake inhibitors, 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 serotonin reuptake inhibitors (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), leading to the terminology of the
long (L) and short (S) variants of this gene. 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 one 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.

Serotonin Receptor (5HT2A). 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 (DRD1, DRD2, DRD4). 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 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, this gene product 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’s disease, Tourette syndrome, and addictive behaviors.

Dopamine Beta-Hydroxylase (DBH). The dopamine beta-hydroxylase protein encoded by this gene catalyzes the hydroxylation of dopamine to norepinephrine. It is primarily located in the adrenal medulla and in postganglionic sympathetic neurons. Variation in the DBH gene has been investigated as a modulator of psychotic symptoms in psychiatric disorders and in tobacco addiction.
Gated Calcium Channel (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’s 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 homocysteinuria.

The MTHFR protein also plays a major role in epigenetics, through methylation of somatic genes. A number of polymorphisms 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.

gamma-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.

mu and kappa Opioid Receptors (OPRM1 and OPRK1). OPRM1 encodes the mu 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 kappa opioid receptor, which binds the natural ligand dynorphin and a number of synthetic ligands.
Cytochrome P450 genes (CYP2D6, CYP2C19, CYP3A4, CYP1A2). These 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).

Commercially Available Genetic Tests
Several tests labs market either panels of tests or individual tests designed relevant for mental health disorders. The specific tests included in each panel are summarized in Table 1.

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

The STA2R (SureGene Test for Antipsychotic and Antidepressant Response, SureGene, LLC, Louisville, KY) is another genetic panel that provides information about medication response, adverse event likelihood, and drug metabolism. According to the manufacturer’s website, the test is recommended for initial medication selection, for patients who have poor efficacy, tolerability, or satisfaction with existing medications, and in cases of severe treatment failure.(1)

GeneSight® Psychotropic (Assurex Health, Mason, OH) is a genetic panel that provides information about genes that may affect a patient’s response to antidepressant and antipsychotic pharmacotherapy. According to the manufacturer’s website, following testing, the treating provider receives a report with the most common medications for the patient’s diagnosed condition categorized by cautionary level, along with a report of the patient’s genetic variants.(2) Details are not provided about the algorithm used by the manufacturer to generate risk levels.

The Proove Narcotic Risk panel (Proove Biosciences, Irvine, CA) is a panel to evaluate genes involved in the development of substance abuse or dependence and in response to medical therapy for substance abuse or dependence.

In addition to the available panel tests, several labs offer genetic testing for individual genes, including MTFHR, CYP450 genes, and SULT4A1.
Table 1: Genetic Panels for Mental Health Disorders – Polymorphisms Included

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genecept Assay (Genomind)</th>
<th>SULT4A1 (PSQL Laboratories)</th>
<th>MTHFR (PSQL Laboratories, AssureRx Health)</th>
<th>STA2R (SureGene, LLC)</th>
<th>GeneSightRx Psychotropic (AssureRx Health)</th>
<th>Promea Narcotic Risk (Promea Biotechnology)</th>
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Regulatory Status
The Genecept Assay, STA2R test, the GeneSight Psychotropic panel and the GeneSight MTFHR tests are laboratory-developed tests that are not subject to U.S. Food and Drug Administration (FDA) approval. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).
IV. RATIONALE

Analytic Validity
Information on analytic validity of the test is lacking. No published studies were identified that specifically evaluated the analytic validity of the test as performed commercially. There was no information identified in the published literature or from the manufacturer’s website concerning the genetic testing methods used for analysis. As a result, it is not possible to determine the analytic validity of the testing process.

Clinical Validity
Evidence on the clinical validity of genetic testing for mental health disorders consists primarily of genome-wide association 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 to individuals without the disorder. There were no studies of clinical validity that identified evaluated defined groups of patients (eg, patients with schizophrenia; patients with depression and nonresponse to serotonin reuptake inhibitors (SSRIs)) and reported the sensitivity and specificity of the panel results for those patients. Therefore it is not possible to estimate the clinical sensitivity and specificity of the test as a diagnostic test for specific patient groups.
A comprehensive review of the genome-wide association studies (GWAS) and case control studies for all of these genes is beyond the scope of this policy. However, some of the representative literature in this area is discussed below.

Genes Associated with Increased Disease Risk
Serotonin Transporter (SLC6A4) Gene and Risk of Multiple Mental Health Disorders. The SLC6A4 gene that codes for the serotonin transport protein has been studied in relation to a number of psychiatric conditions. Published literature has reported associations between variants in this gene and anxiety, bipolar disorder, and obsessive-compulsive disorder, and drug and alcohol dependence. (3-5). 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).(6) In a 2011 study and systematic review/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.(7) 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). In the Minelli et al meta-analysis, the authors 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
authors 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 systematic review and 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. (8) 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 genotype (homozygous short, homozygous long, or heterogeneous) and depression (weighted odds ratio [OR]; 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 systematic review and meta-analysis that evaluated the association between 5-HTTLPR polymorphisms and stressful life events and a diagnosis of depression. (9) 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=0.00002). 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.(10) The authors included 22 studies, all case-control studies, published through March 2008 that included a total of 7,919 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 Caucasians (OR 1.41, 95% CI 1.15 to 1.72), but not in Asians.

SULT4A1 Gene and Risk of Schizophrenia and Related Disorders. 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 three SULT4A1 SNPs (rs138060, rs138097, and rs138110) and clinical symptoms and quality of life.(11) Among 86 participants included, although all patients had a diagnosis of schizophrenia or schizoaffective disorder, the rs138060 SNP was significantly associated with worse Brief Psychiatric Rating Scale total and anxiety/depression scores and higher SCALE for the Assessment of Positive Symptoms total scores. In addition, the rs138097 SNP was significantly associated with worse neuropsychological test performance.
CACNAIC and ANK3 Genes and Risk of Multiple Mental Health Disorders. 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.(12).

Kloiber et al. published results from 2 case-control studies evaluating the association of major depressive disorders with CACNAIC and ANK3.(13) 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 single-nucleotide polymorphisms (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.

COMT Genes and Risk of Multiple Mental Health Disorders. 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 and Risk of Multiple Mental Health Disorders. 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).

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 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, (21) along with addictive behaviors including smoking and alcohol dependence. (22, 23)

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 systematic review and 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). (24) In another systematic review and 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. (25) 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. (26)

MTHFR Gene and Risk of Depression, Bipolar Disorder, and Schizophrenia The MTHFR gene has been widely studied for nonpsychiatric conditions such as hyperhomocysteinemia and thrombophilia. A review of evidence on the association between this gene and thrombophilia is included in MPRM policy 2.04.82 (Genetic Testing for Inherited Thrombophilia).

For psychiatric disease, Wu et al performed a meta-analysis of 26 GWAS evaluating the association of MTHFR variants with depression. (27) 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.

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. (28) 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 non-depressed patients. (29)

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. (30) 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 bipolar disorder (OR=2.03 comparing homozygotes; 95% CI, 1.07 to 3.86).

Section Summary
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.

Genes Associated with Medication Pharmacokinetics and Pharmacodynamics
Medications are a mainstay of treatment for many 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); in turn, inter-individual differences in pharmacokinetics and pharmacodynamics may lead to variability in the clinical effectiveness of medications used to treat mental health disorders.

Overview – Pharmacogenetics and Mental Health Disorders. 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, 2 serotonin receptor genes (HTR2C, HTR2A), and SLC6A4. (31) 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.

Dopamine Receptor Genes and Antipsychotic Response. 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. (32) 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. (21, 33)

Serotonin Transporter (SLC6A4) Gene and Antidepressant Response. 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 SCL6A4 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. (34) 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 SCL6A4 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. (35) 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 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. (36) In a regression to predict Beck Depression Inventory Score at 6 weeks following enrollment, the coefficient for the interaction term treatment group and 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 later systematic review and meta-analysis that used more stringent inclusion criteria, Biernacka et al found no significant association between 5-HTTLPR polymorphisms and antidepressant-induced mania. (38)

The SCL6A4 polymorphism has been associated with response to ondansetron, a 5-HT(3) receptor antagonist, among patients with alcohol dependence. (39)

Opioid Receptor Genes and Response to Treatment for Addiction. Several studies have evaluated the role of polymorphisms in the mu 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. (40) 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 MPRM policy 2.04.38 Cytochrome p450
Genotyping. For selection and/or dosing of all psychiatric medications included in that policy review, genetic testing for cytochrome p450 variants is considered investigational.

**Section Summary**

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.

**Clinical Utility**

Studies suggest that there may be a number of genetic variants associated with increased risk of mental health disorders and/or response to specific treatment, although estimates of the magnitude of the increased risk and findings of significance are variable across studies. For the individual tests, results from GWAS and case control studies are insufficient to determine clinical utility. To determine clinical utility, evidence is needed that testing for variants in these genes leads to changes in clinical management that improve outcomes. Given that many of the available genetic tests for mental health disorders are offered as panels, there are two relevant questions that address the clinical utility of genetic testing for mental health disorders. First, does testing for specific genetic variants lead to changes in management that improve health outcomes? Second, does a testing strategy that relies on a panel of tests lead to improved health outcomes compared with a strategy that relies on testing for variants individually?

**Does genetic testing for mental health disorders lead to improved health outcomes?**

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, these management changes are not well-defined and may vary according to the judgment of the treating clinician. Additionally, genetic testing could potentially allow more accurate diagnosis of mental health disorders, particularly if a patient’s symptoms are consistent with more than one disorder, allowing better targeting of therapy. Currently, there are no specific recommended changes in management that are linked to specific test results, making it difficult to assess whether a particular management change based on test results leads to improvements in health outcomes.

Two comparative, nonrandomized studies from the same research group compared clinical outcomes in patients with genetic testing versus patients without genetic testing. In 2013, Hall-Flavin et al reported results from an open-label, nonrandomized comparative trial to evaluate the effect of providing the GeneSight pharmacogenomics test results and report on the management of psychotropic medications used for major depressive disorder in an outpatient psychiatric practice. (41) 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 included 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 report 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 patients who completed follow up, the authors found a greater reduction in symptoms for the guided group compared with 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<0.0001), and the Patient Health Questionnaire (PHQ-9; F=7.07, p=0.002). Patients in the guided group had a higher rate of remission as measured by the QIDS-C16 than the unguided patients (26.4% vs 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 that was 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 during the study period (93.8% vs 55%, χ²= 6.35; p=0.01).

In an earlier nonrandomized pilot study, Hall-Flavin et al compared outcomes for a group of patients with major depression whose physicians received a GeneSight report to a historical control group of patients who were treated without the GeneSight report. (42) Twenty-six subjects were included in the “unguided” group and 25 were included in the “guided” group. At 8 weeks of follow up, patients in the guided group had a reduction in their QIDS-C16 score of 31.2% compared with a 7.25%, reduction in the unguided group (p=0.002), and a reduction in their HAMD17 score of 30.8%, compared with a 18.2% reduction in the unguided group (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, their limitations, including small sizes, nonrandomized designs, and loss to follow up, make generalization of their results difficult.

One small RCT was published in 2012 by Winner et al, but this publication was not likely powered to detect differences in clinical outcomes. This trial evaluated the effect of providing the GeneSight pharmacogenomics test and report on the management of psychotropic medications used for major depressive disorder in a single outpatient psychiatric practice. (43) 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 weeks of 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.

Results of a survey of clinicians who have used the test are reported on the Genomind website. (44) A description of the methodology for this survey is not provided, therefore it is not possible to evaluate such factors as selection of the population or the survey response rate. Survey results were reported for 132 clinicians who used the test in the treatment of 545 patients. Clinicians reported that their treatment decisions were influenced by the test (definitely yes or probably yes) in 87% of cases. For patients in whom decisions were influenced, 76% of the treatment decisions involved a change in medication. Clinicians also reported that confidence in their treatment decisions were increased (definitely yes or probably yes) in 93% of the cases.

Section Summary
A limited number of studies have evaluated clinical outcomes associated with genetic testing panels for mental health disorders, primarily using the GeneSight pharmacokinetic test. These studies provide some 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. The clinical utility of genetic panels and individual genetic tests for mental health disorders other than the GeneSight test has not been evaluated.

Do panels of genetic tests for mental health disorders offer incremental benefits compared with testing for individual genes?
A framework for determining the clinical utility of genetic panels is provided in MPRM policy 2.04.92 (General Approach to Evaluating the Utility of Genetic Panels). According to the classification of panels in that policy, the panels evaluated in this policy are classified as a panel intended to assess risk for multiple conditions. The criteria to be used for evaluating panels in this category are as follows:
- Clinical utility has been established for at least one component of the panel.
- Test is performed in a CLIA-approved laboratory.
- Analytic validity of the panel approaches that of direct sequencing
- Panel offers substantial advantages (efficiency of work-up, cost) over sequential analysis of individual genes.
- The impact of ancillary information is well-defined.

The genetic testing panels reviewed do not meet the majority of these criteria. Most importantly, clinical utility has not been established for any of the individual tests for their intended purpose in this assay. In addition, the analytic validity of the test is unknown. The testing methods are not well-described, so there is uncertainty as to whether the efficiency of testing is improved by use of this panel. Finally, the impact of ancillary information is not well-defined. It is not known how the results of various tests might be combined to determine overall risk, nor is it known how unexpected results may impact treatment decisions and health outcomes. It is also unknown as to how the results of genetic variants that indicate increased risk for nonpsychiatric conditions, such
as variants in the CACNA1C gene that may denote an increased risk of cardiac disorders, will impact patient management and outcomes.

Ongoing Clinical Trials
A search of ClinicalTrials.gov using each test name as a key word identified the following randomized, controlled trials that are currently enrolling patients:

- PAGE trial (NCT01555021). The Pharmacogenomics for Antidepressant Guidance and Education trial is an RCT that is currently recruiting patients admitted to an inpatient psychiatric facility with treatment-resistant depression, as defined by a failure of at least one prior trial of antidepressant medication. Treatment guided by results of the Genecept Assay will be compared with usual care over a 6-month period. The primary outcome measure is the change in the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) at 6 months. Secondary outcomes include change in treatment decisions based on Genecept results, treatment adherence, and medication adverse effects. Planned enrollment is for 200 patients with an estimated completion date of December 2013.

- PAGE-1_AG1 trial (NCT01426516). The Pharmacogenomics for Antidepressant Guidance and Education 1 trial is an RCT that is currently recruiting patients with treatment-resistant depression, as defined by a failure of at least one prior trial of antidepressant medication. Treatment guided by results of the Genecept Assay will be compared to usual care over a 6-month period. The primary outcome measure is the change in the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) at 6 months. Secondary outcomes include change in treatment decisions based on Genecept results, quality of life, cost and patient/provider satisfaction. Planned enrollment is for 100 patients with an estimated completion date of

- Impact of GeneSight Psychotropic on Response to Psychotropic Treatment in Outpatients Suffering From a Major Depressive Disorder (MDD) and Having Had an Inadequate Response to at Least One Psychotropic Medication Included in GeneSight Psychotropic (RCT) (NCT02109939). This is a double-blind RCT designed to compare treatment guided by the GeneSight Psychotropic testing report with treatment as usual among adults with major depression. The primary outcome measure is the HAM-D17 score at 12 weeks postenrollment. Planned enrollment is for 300 subjects with an estimated completion date of February 2016.

Summary
Panels of multiple genetic tests have been developed to aid the diagnosis and treatment of mental health disorders. Genes included in the panels have shown some association with psychiatric disorders or with the pharmacokinetics of psychotropic medications. The analytic validity of these assays cannot be determined due to a lack of information on the testing methods. The available evidence on clinical validity consists of genome-wide association studies and case-control studies that indicate a correlation between variants of these genes and clinical factors. This evidence shows low-strength associations with a variety of psychiatric and nonpsychiatric conditions. Often the evidence for an association is not consistently reported across all studies, and in many cases, there are correlations of the same genetic variants with
other nonpsychiatric disorders. There are also a range of associations reported for response to certain medications and alterations in pharmacokinetics. Evidence on clinical utility is lacking. Management changes that occur as a result of this assay are ill-defined, with uncertain impact on clinical outcomes. In addition, it is not well-understood how unexpected results or unknown variants are handled and whether these type of results have an impact on diagnostic work-up, treatment decisions, and health outcomes. Due to these deficiencies in the evidence base, genetic testing panels for mental health disorders are considered investigational for all indications.

Practice Guidelines and Position Statements
None identified.

Medicare National Coverage
None.

V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.
VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

There is no specific CPT code for this testing panel

Investigational when used for Genecept Assay

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There are specific codes for some of the component tests:

Investigational; therefore not covered: Genetic testing panels for mental health disorders, including but not limited to the Genecept Assay, STA2R test, the GeneSight Psychotropic panel, and the Proove Narcotic Risk assay

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IX. REFERENCES


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X. POLICY HISTORY

| MP- 2.264 | CAC 5/20/14. New policy BCBSA adopted. Genetic testing for mental health conditions is considered investigational for all indications. Policy coded. |

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