Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Genetic Testing for Specified Conditions Using Testing Panels

Description/Background

MENTAL HEALTH DISORDERS

Mental health disorders cover a wide range of clinical phenotypes and are generally classified by symptomatology in systems such as the classification outlined in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). In addition to counseling and other forms of behavioral treatment, treatment commonly involves one or more psychotropic medications 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.

Pharmacogenomic Testing

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

Treatment decisions are currently based on the assessment of different factors that may influence the variability of drug effects: age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genes coding for drug-metabolizing enzymes, drug receptors, drug transporters, and molecules

involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

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

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

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

Serotonin Transporter
The serotonin transporter gene (*SLC6A4*) is responsible for coding the protein that clears serotonin metabolites (5-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), 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*)
The serotonin receptor gene (*5HT2C*) 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, e.g., 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 serotonin receptor gene (*5HT2A*) codes for another subtype of the serotonin receptor. Variations in the *5HT2A* gene have been associated with susceptibility to schizophrenia and obsessive compulsive disorder and response to certain antidepressants.

Sulfotransferase Family 4A, Member 1 (*SULT4A1*)
The sulfotransferase family 4A, member 1 gene (*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 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 *SCL6A4 gene,* 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 βeta-Hydroxylase (*DBH*)
The dopamine βeta-hydroxylase (*DBH*) gene encodes a protein that catalyzes the hydroxylase of dopamine to norepinephrine. It is primarily located in the adrenal medulla and in postganglionic sympathetic neurons. Variation in the *DBH* gene has been investigated as a modulator of psychotic symptoms in psychiatric disorders and in tobacco addiction.

Gated Calcium Channel (*CACNA1C*)
The gated calcium channel gene (*CACNA1C*) is responsible for coding of a protein that controls activation of voltage-sensitive calcium channels. Receptors for this protein are found widely throughout the body, including skeletal muscle, cardiac muscle, and in neurons in the CNS. In the brain, different modes of calcium entry into neurons determine which signaling pathways are activated, thus modulating excitatory cellular mechanisms. Associations of 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*)
The catechol *O*-methyltransferase gene (*COMT*) 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*)
The methylenetetrahydrofolate reductase gene (*MTHFR*) is a widely studied gene that codes for the protein that converts folic acid to methylfolate. Methylfolate is a precursor for the synthesis of norepinephrine, dopamine, and serotonin. It is a key step in the metabolism of homocysteine to methionine, and deficiency of MTHFR can cause hyperhomocysteinemia and homocystinuria. 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.

γ-Aminobutyric acid (GABA) A receptor
This gene encodes a ligand-gated chloride channel composed of five 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*)
CYP2D6, *CYP2C19*, *CYP3A4*, *CYP1A2*, *CYP2C9*, and *CYP2B6* code for hepatic enzymes that are members of the cytochrome p450 family and are responsible for the metabolism of a wide variety of medications, including many psychotropic agents. For each of these genes, polymorphisms exist that impact the rate of activity, which consequently affect drug metabolization rates. Based on the presence or absence of polymorphisms, patients can be classified as rapid metabolizers (RM), intermediate metabolizers (IM), and poor metabolizers (PM). Rapid metabolizers may not benefit from standard therapeutic doses because the drug is metabolized too quickly, resulting in subtherapeutic medication levels. Alternatively, poor metabolizers may require lower doses to avoid adverse events from an excess of medication in their system.

P-Glycoprotein Gene *(ABCB1)*
The *ABCB1* gene*,* also known as the *MDR1* gene, encodes P-glycoprotein which is involved in the transport of most antidepressants across the blood-brain barrier. *ABCB1* 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 *UGT1A4* 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. 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 STA^{2}R (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/Myriad, Inc.) 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 Opioid 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.

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

AltheaDx (San Diego, CA) offers a number of **IDgenetix**-branded tests, which include several panels focusing on polymorphisms that affect medication pharmacokinetics for a variety of disorders, including psychiatric disorders. Specific mutations included in the panel were not easily identified from the manufacturer's website.

In addition to the available panel tests, several labs offer genetic testing for individual genes, including *MTFHR (GeneSight Rx and other laboratories)*, *CYP450* genes, and *SULT4A1.*

Table A. Examples of Genetic Panels for Mental Health Disorders and Included Genes

Gene	Variants Included in Commercially Available Test Panels			
	Genecept Assay	GeneSightRx Psychotropic	Proove Opioid Risk	Mental Health DNA Insight
SULT4A1				
SLC6A4 (serotonin transporter)	X	X		X
5HT2C (serotonin receptor)	X	X		
5HT2A (sertonin receptor)	X			X
DRD1 (dopamine receptor)			X	
DRD2 (dopamine receptor)	X			
DRD4 (dopamine receptor)			X	
DAT1 (dopamine transporter)			X	
DBH (dopamine β-hydroxylase)			X	
CACNA1C	X			
ANK3	X			
COMT (catechol O-methyltranferase)	X			
MTHFR			X	
GABA			X	
OPRK1 (κ-opioid receptor)			X	
OPRM1 (μ-opioid receptor)	X			
CYP450 genes				
CYP2D6	X	X		X
CYP2C19	X	X		X
CYP3A4	X	X		X
CYP1A2	X	X		
CYP2C9	X	X		
CYP2B6	X	X		
P2B6				
UGT1A4				
ABCB1				
MC4R	X			
ADRA2A	X			
BDNF	X			
GRIK1	X			

Regulatory Status

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

Examples of commercially available panels include the following:

- Genecept™ Assay (Genomind);
- STA^{2}R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical Reference Laboratory). Specific variants included in the panel were not easily identified from the manufacturer's website.
- GeneSight® Psychotropic panel (Assurex Health/Myriad, Inc.);

- Mental Health DNA Insight™ panel (Pathway Genomics);
- IDgenetix-branded tests (AltheaDx).

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

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

Medical Policy Statement

Genetic testing for mutations associated with mental health disorders is considered experimental/investigational in all situations, including but not limited to the following:

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

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

*****See Government Regulations section for Medicare exception*

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81225	81226	81227	81230	81231	81291
81401	81479	0029U	0031U	0032U	0033U
0070U	0071U	0072U	0073U	0074U	0075U
0076U	0156U	0173U	0175U	0345U	

Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

TESTING FOR DIAGNOSIS OR RISK OF MENTAL HEALTH DISORDER

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

The following **PICOs** were used to select literature to inform this review.

Populations
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 (i.e., Diagnostic and Statistical Manual of Mental Disorders).

Outcomes
The primary outcome of interest is change in disease outcomes, which would result directly from changes in management that could be instituted because of earlier disease detection. Standardized outcome measures are available for many mental illnesses. Commonly used measures for the evaluation of depression in clinical trials are described in the next section.

Study Selection Criteria
Assessment of clinical utility of a genomic test cannot be made by a chain of evidence from clinical validity data alone. Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with or without the test. Because these are intervention studies, randomized controlled trials (RCTs)are needed. the preferred evidence is from randomized controlled trials.

- RCTs that reported the outcomes of pharmacogenetic testing to diagnose, assess the risk of developing, or to manage a mental health condition.
- evidence on outcomes, with emphasis on efficacy outcomes, as the main purpose of genetic testing in mental health conditions to achieve clinically meaningful improvement compared with standard of care (SOC).
- studies that reported only on adverse events, although for medications where adverse events tend to be mild, efficacy outcomes are of greater importance.

Review of Evidence
No randomized controlled trials evaluating the use of genetic test results to inform decisions on mental health diagnoses or management of patients with risk for mental health conditions were found. Multiple cohort and case control studies examined the association between different genetic markers with different mental health disorders.[1-8] However, those observational studies did not examine the effect of genetic testing on disease outcome among patients with risk for mental health conditions.

Section Summary: Testing for Diagnosis or Risk of Mental Health Disorder
No studies were identified that used genetic testing results to inform decisions on mental health diagnoses or management of patients with risk for mental health conditions. 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.

GENETIC TESTING TO INFORM MEDICATION SELECTION FOR PATIENTS WITH DEPRESSION

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition. The first step in assessing a medical test is to formulate the clinical context and purpose of the test.

Clinical Context and Test Purpose
The purpose of pharmacogenetic testing in patients with depression is to inform antidepressant selection in order to improve symptoms (i.e., clinical response) and, preferably, to achieve remission of depression.

Major Depressive Disorder (MDD) is a mood disorder characterized by pervasive sadness, lack of interest and enjoyment in most activities, feelings of low self-worth, sleep disturbance, over-or under-eating, suicidal thoughts, and suicide attempts. The goal of treatment is remission of depression. While response to treatment is defined as 50% or greater reduction of symptoms; the patient who has responded, but is not in remission, may still bear a considerable burden of depression. Moreover, the risk of recurrence is greater than when remission is achieved. The main categories of treatment for MDD are psychotherapy, pharmacotherapy, and brain stimulation therapies. These may be used in combination. First generation antidepressants are tricyclic antidepressants and monoamine oxidase inhibitors. Classes of second generation antidepressants are: selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and atypical agents.

Individuals who fail to achieve remission of MDD after 2 vigorous trials of antidepressant medications have a poor prognosis. The Sequenced Treatment Alternatives to Relieve Depression * (STAR*D) found that only about half of individuals reached remission after 2 treatments.[9] Individuals may stop treatment due to side effects of anti-depressants, which can include drowsiness; insomnia/agitation; orthostatic hypotension; QTc prolongation; gastrointestinal toxicity; weight gain; and sexual dysfunction.

Pharmacogenomic testing is proposed to identify which antidepressant medications would be most effective or have the least side effects based on genetic variants that affect drug metabolism.

The following **PICOs** were used to select literature to inform this review.

Populations
Adult individuals who have a diagnosis of major depressive disorder who have had inadequate response to 2 or more trials of antidepressant therapy. MDD is defined by the presence of 5 or more of the symptoms below for a period of at least 2 weeks. At least 1 symptom must be: (1) lack of interest or enjoyment in most activities, almost every day; or (2) depressed mood almost every day for most of the day. And in addition at least 4 of the symptoms below must be present almost every day.

- Sleep disturbance, insomnia or excessive sleepiness
- Over-or under-eating with significant weight gain or loss
- Observable psychomotor agitation or retardation
- Fatigue or loss of energy
- Difficulty concentrating or making decisions
- Feelings of worthlessness or inappropriate guilt
- Thoughts of death or suicide, or suicide attempt

The symptoms are not attributable to another medical condition, or behavioral disorder or substance abuse.[10]

Interventions
Three commercially available pharmacogenetic tests for antidepressant selection are reviewed here: GeneSight®, NeuroIDgenetix®, and Neuropharmagen®. Each test has its own proprietary algorithm for assessing genes associated with drug pharmacokinetics and pharmacodynamics. Each of these tests also has a proprietary format for reporting results and categorizing likely responsiveness or intolerance to available antidepressants.

All are laboratory developed tests and not subject to U.S. Food and Drug Administration (FDA) regulation. However, recently, the FDA has raised concerns about pharmacogenetic tests that claim to predict medication response where drug labeling does not describe a predictive relationship between genetic variation and drug response. The FDA has reportedly reached out to firms marketing such tests, including tests of antidepressant response, with concerns about claims of clinical benefit.[11]

Comparators
The comparator is antidepressant drug selection without pharmacogenetic testing. At present there is no definitive algorithm for selecting next line treatment after failure to respond to initial treatment.

Outcomes

This evidence review assesses whether genetic testing for the management of depression is clinically useful. The balance of benefits and harms must be better when the test is used to manage the condition than when no test is used. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid adverse events.

There are standardized outcome measures for depression (e.g., Hamilton Rating Scale for Depression [HAM-D], Montgomery-Asberg Depression Rating Scale [MADRS], Patient Health Questionnaire 9 item [PHQ-9] and Beck's Depression Inventory [BDI]). Scoring for the HAM-D and MADRS are shown in Table 1.

HAM-D and MADRS are physician scored scales that rate the presence and intensity of attributes of depression. The HAM-D, introduced by Max Hamilton in 1960, is the progenitor of depression measurement scales. Attributes rated include depressive mood, guilt feelings, insomnia, suicidal ideas or attempts, work and activity. However, shortcomings of HAM-D are incomplete overlap with DSM criteria for MDD and weak item-level inter-rarer reliability.[12] None-the-less, HAM-D has moderate to high correlation with other depression scales. Various versions have been developed, intended to make the instrument easier to use. The 17-item HAM-D (HAM-D17) is the most commonly used instrument in trials of depression drugs.[13] The MADRS is the next most commonly used instrument in trials of depression drugs. Attributes scored include sadness, pessimism, inability to feel and suicidal thoughts. As with HAM-D, MADRS has incomplete overlap with DSM criteria for MDD. MADRS is reported to correlate to other depression scales, including the HAM-D17. MADRS is generally reported to be more sensitive to treatment related change and to have better inter-rater reliability than HAM-D17; perhaps because of its more uniform structure.[13]

The PHQ-9 is a self-administered scale used to assess depression based on the 9 criteria for depression outlined in the DSM-IV. It rates symptoms on a scale from "0" (not at all) to "3" (nearly every day) over a 2-week period.14 The criteria include: little interest in doing things, feeling down or depressed, difficulty with sleep, low energy levels, poor appetite or overeating, poor self-perception, difficulty concentrating, high or low speed of functioning, and thoughts of suicidality or self-harm. Cut-offs at scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression. The PHQ-9 has been extensively validated for accuracy in over 30 clinical studies.[15,]

Table 1: Measures of Depression in Adults

Outcome Measure	Description	Scale	Clinically Meaningful Difference
Hamilton Rating Scale for Depression	Physician scored. Rates presence and intensity of symptoms. Symptom domains include depressive mood, guilt, insomnia, suicidality, work and activity. The 17- item version is most common (HAM-D17).	0 to 7 normal (no depression); 8 to 13 mild depression; 14 to18 moderate depression; 19 to 22 severe depression; 23 or greater very severe depression	The goal of treatment is remission, typically defined as 7 or less. But 2 or less has been suggested as optimal. Response is 50% reduction from baseline.
Montgomery-Asberg Depression	Physician scored. Presence and intensity of symptoms. Symptom domains include sadness;	0 to 6 normal (no depression); 7 to 19 mild depression; 20 to 34	No consensus to define remission. Thresholds for remission have ranged from

Rating Scale	pessimism; inability to feel; suicidality	moderate depression; 35 to 59 severe depression; 60 or greater very severe depression	6 to 12 in trials.
Patient Health Questionnaire	Patient scored. Rates the presence and intensity of symptoms on 9 criteria for depression.	0 to 4 (no or minimal depression); 5 to 9 (mild depression); 10 to 14 (moderate depression); 15 to 19 (moderately severe depression); 20 to 27 (severe depression)	Remission is considered a score of less than 5. Response is 50% reduction from baseline.

Secondary endpoints are:

- Clinical Global Impression (CGI)
- Sheehan Disability Scale (SDS)

The CGI and SDS may supplement depression rating scales, by assessing severity of illness and functional impairment, respectively. However, the measurement properties of these instruments are not well characterized.

The CGI "asks that the clinician rate the patient relative to their experience with other patients with the same diagnosis, with or without collateral information." There are 3 components: Severity of Illness (CGI-S), Improvement (CGI-I), and the efficacy index, each rated on a scale of 1 to 7. Severity of Illness ranges from 1="not ill at all" to 7 "among the most extremely ill." A comparative meta-analysis of change in CGI in antidepressant trials found that, among double-blind trials, the CGI-S was more conservative than HAM-D and MADRS in showing change in severity of depression.[16] There is little evidence available on the validity and reliability of these measures.[13]

The SDS was developed as a simple tool to address the "desynchrony between psychiatric symptoms and disability": that some " very symptomatic patients who still functioned reasonably well socially and at work, while other patients with less severe and less frequent symptoms were quite disabled."[17] The SDS is a self-reported 3-item instrument used to assess the impact of symptoms on the individual's work, family and social life. Each item is scored on an 11 point scale with 0 indicating no impairment and 10 extreme impairment, with a score greater than 5 suggesting functional impairment. A study of 1001 primary care patients showed that almost half of patients with elevated SDS score had a psychiatric disorder diagnosis.16, No MICD has been set for assessing change in SDS score.[13]

Follow-up Duration
Typically, short term response for established classes of antidepressants is assessed in studies of 6-8 weeks duration, based on mechanism of pharmacologic response. As rapid-acting anti-depressants become available, a week or even less could be sufficient.

Maintenance, the ability of a treatment to reduce recurrence of MDD, is equally important. At least 6 months of follow up is typically required to assess the ability of an agent to reduce recurrence.

GeneSight® Test

GeneSight evaluates 14 total genes, this includes 9 pharmacokinetic genes and 5 pharmacodynamic genes. Based on results from the genotype test, the medications are categorized as either congruent ('use as directed' or 'use with caution') or incongruent ('use with increased caution and with more frequent monitoring') for a particular individual.

Review of Evidence

Systematic Reviews and Meta-Analyses

Brown et al. (2022) conducted a comprehensive meta-analysis that synthesized the findings of prospective randomized clinical trials (RCTs) and open-label trials investigating the efficacy of pharmacogenomic guided testing in achieving remission of depressive symptoms.[19] The meta-analysis revealed a favorable rate of remission among individuals who received therapy guided by pharmacogenomics compared to those receiving standard of care (SOC) treatment for depression. The analysis included a total of 13 trials, consisting of 10 RCTs and 3 open-label studies published through July 2022. Six of these included studies utilized the GeneSight test for guiding pharmacogenomic therapy. The analysis encompassed a sample of 4,767 individuals across these 13 trials, with individual study sample sizes ranging from 44 to 1,944 participants. With the exception of 2 trials, all studies exclusively enrolled individuals diagnosed with major depressive disorder (MDD). The majority of trials (69%) measured their primary endpoint at 8 weeks after baseline, although the range extended to 24 weeks. Remission was primarily assessed using the Hamilton Depression Rating Scale-17 (HDRS-17), while alternative rating scales were used in two trials. Notably, all studies included pharmacogenomic assessments of the *CYP2C19* and *CYP2D6* genes, although other genes tested varied across studies.

The pooled risk ratio (RR) for remission, comparing pharmacogenomic guided therapy (n=2395) to unguided therapy (n=2372), was 1.41 (95% confidence interval [CI], 1.15 to 1.74), favoring guided therapy. The authors observed moderate to substantial heterogeneity between the studies (I^2=62%). Stratifying the analysis to only include RCTs (n=10) yielded a similar effect size for remission rates (RR, 1.45; 95% CI, 1.13 to 1.88), which remained statistically significant. However, when limiting the analysis to the open-label trials (n=3), the effect size was no longer statistically significant (RR, 1.26; 95% CI, 0.84 to 1.88). The authors also found that the number of prior antidepressant therapies and severity of depression symptoms had moderating effects on the RR for pharmacogenomic guided therapy, suggesting that as the severity and number of treatments increased, the RR for guided therapy also increased. No moderating effects were observed for age, sex, ancestry, or weeks to the primary endpoint. A subgroup analysis omitted the 6 GeneSight studies and found that the pooled RR for remission remained significant across the remaining trials (RR, 1.46; 95% CI, 1.02 to 2.09; p=.04).

To evaluate the risk of bias in the included studies, the authors employed the Cochrane Risk of Bias Tools, specifically Cochrane Risk of Bias version 2 for RCTs and Risk Of Bias In Non-randomized Studies of Interventions for open-label controlled studies. The majority of trials (n=10) were sponsored by industry, and 77% of them had published protocols prior to the

commencement of the study. Among the 10 included RCTs, low risk of bias was observed for attrition and selection, while high risk of bias was identified for performance. Blinding procedures varied across the studies, with participants being blinded in all RCTs, but treating physicians and, in 2 cases, outcome assessors were not blinded. One RCT was found to have a high risk of reporting bias due to selectively reporting outcomes for a subset of patients. Regarding the 3 open-label studies, low risk of bias was observed for pre-intervention selection, at-intervention information, and post-intervention confounding. However, the authors reported that post-intervention information and industry biases were high in 2 trials. Additionally, 1 trial exhibited a moderate risk of reporting bias, and 2 studies demonstrated post-intervention selection bias. Assessment of publication bias using funnel plot asymmetry and Egger's regression indicated no indication of publication bias. Although the authors found an increased likelihood of remission among individuals with depression who received pharmacogenomic guided therapy, the heterogeneity in study methodology, such as the variations in the genetic variants tested, poses challenges in making recommendations for a specific testing strategy.

Randomized Controlled Trials

Four randomized controlled trials compared response and remission with antidepressant therapy informed by GeneSight test results to antidepressant therapy selected without gene test results.[20-23] Due to limitations in these trials, discussed below, no conclusions can be drawn from these trials about the differential effect of treatment guided by GeneSight versus SOC.

The PRecision Medicine In MEntal Health Care (PRIME Care) RCT compared 24-week outcomes in adults with MDD who received either GeneSight-guided therapy or SOC.[20,] The study included 1,944 participants from 22 Veteran's Affairs medical centers who were randomly assigned to either pharmacogenomic-guided treatment (n=966) or SOC (n=978). Assessments were conducted at baseline and every 4 weeks until 24-weeks follow-up.

The authors reported a small and nonpersistent effect on the co-primary outcome of symptom remission. A significant difference in symptom remission rates on the PHQ-9 was reported favoring the GeneSight group at weeks 8 and 12, but no meaningful differences were detected at weeks 4, 18, or 24. The overall pooled effect over time for remission, however, remained favorable for the GeneSight group by a small margin (odds ratio [OR], 1.28; 95% CI, 1.05 to 1.5; p=.02) (Table 3). The other co-primary outcome, treatment initiation after pharmacogenomics testing, showed that more GeneSight-guided participants were likely to be prescribed an antidepressant in the first 30 days after testing (OR, 0.74; 95% CI, 0.6 to 0.92; p=.005). The pharmacogenomic-guided patients were less also likely to be classified as having no antidepressant and gene interaction compared to moderate or substantial interaction compared to SOC (OR, 2.08; 95% CI, 1.52 to 2.84; p=.005). The selection of genetic markers for antidepressant response has faced challenges due to the presence of confounding factors among the studied populations and large heterogeneity between studies, and we are unable to determine the clinical significance of the proprietary GeneSight algorithm used for predicted drug-gene interactions.[24,] The secondary outcomes of response rate (OR, 1.25; 95% CI, 1.07 to 1.46; p=.005) and symptom improvement (risk difference [RD], 0.56; 95% CI, 0.17 to 0.95; p=.005) on the PHQ-9 also demonstrated an overall pooled effect over time (Table 3).

Study relevance and design/conduct limitations are summarized in Tables 4 and 5. The PRIME trial exhibits a notable methodological limitation by lacking an intention-to-treat analysis. A

power calculation was performed, indicating that each treatment arm necessitated 1000 participants to detect a 5% disparity in the remission rate, accounting for an estimated 20% loss to follow-up and possessing 80% statistical power. The trial fell short of achieving the desired recruitment level, and by the conclusion of the 24-week follow-up period, approximately 22% (n=196) of the GeneSight group and 20% (n=172) of the SOC group were lost to follow-up, exacerbating the recruitment issue. In the PRIME trial, solely the outcome assessors were subject to blinding, while both the participants and their treating clinicians were informed of the treatment allocation. Consequently, the potential placebo effect within this trial remains uncertain.

Two similarly-designed RCTs (GUIDED[21,] and GAPP-MDD[22,]) compared 8-week outcomes in individuals who received treatment for MDD guided by GeneSight testing or SOC. In both GUIDED (N=1,799) and GAPP-MDD (N=437), the primary outcome was symptom improvement, measured by a change in HAM-D. Secondary outcomes were response and remission. Neither trial found a significant difference between GeneSight guided treatment and SOC in symptom improvement (Table 3). The GUIDED trial found treatment guided by GeneSight associated with a statistically significant benefit for response and remission compared with treatment as usual, while there were no significant differences between GeneSight and TAU groups in the GAPP-MDD trial for response or remission (Table 3).

The GUIDED trial randomized 1,799 individuals. After post-randomization exclusions, according to the text, 1,541 individuals remained, in what was labeled the intention to treat (ITT) cohort, but the ITT results reported in Figure 2 included only 1,299 participants. The publication text also describes a per protocol cohort that included 1,398 participants, yet only 1,167 of these participants are accounted for in the study results reported in Figure 1 of the text. The participant flow chart included in the Supplement describes missing data as occurring because of loss to follow-up, or study withdrawal due to inclusion/exclusion violations, HAM-D or Quick Inventory of Depressive Symptomatology (QIDS) scores, out of window visits, withdrawal of consent, or other reasons. Depending on the population (ITT or per protocol), up to one third of GUIDED randomized participants were missing from the reported results. The GAPP-MDD trial had similar limitations. The trial initially randomized 437 individuals, and the publication supplement indicates an ITT population of 363 individuals and a per protocol population of 202 individuals at 8 weeks. Reasons given for post-randomization exclusions were similar to those in the GUIDED trial: loss to follow-up, or study withdrawal due to inclusion/exclusion violations, QIDS score, withdrawal of consent or "other." The GAPP-MDD publication reported symptom improvement for 203 individuals in the ITT population and for 134 individuals in the per protocol population; data from 308 ITT and 196 per protocol individuals were reported for response and remission. Depending on the population (ITT or per protocol) and the outcome analyzed, data from 30% to 69% of randomized individuals were missing. In both trials, the post-randomization exclusions and analysis methods do not conform with definitions of intent-to-treat and there were no sensitivity analyses for the missing data provided.[24,25] In addition to these limitations, enrollment in the GAPP-MDD trial was stopped early due to a determination that it would not be possible to enroll enough participants to adequately power the trial. Although initially designed to enroll 570 participants, GAPP-MDD investigators revised that calculation based on results from the GUIDED trial, subsequently determining that a sample size of 4,000 would be required to achieve 90% power. Based on the recalculation, the GAPP-MDD results would have been powered at less than 25% probability to detect a difference between treatment groups even if the full, planned enrollment of 570 had been achieved.

A small RCT by Winner et al (2013) evaluated the effect of providing the GeneSight® test on the management of psychotropic medications used for major depressive disorder in a single outpatient psychiatric practice (see Table 2).[22] Fifty-one subjects were enrolled and randomized to treatment as usual or treatment guided by GeneSight® testing. All subjects underwent GeneSight® testing, though results were not given to the physicians in the treatment as a usual group until after study completion. At 10-week follow-up, treating physicians dose-adjusted subjects' medication regimens with the same likelihood in the GeneSight® group (53%) and the treatment as usual group (58%; p=0.66). However, patients in the GeneSight® group who were initially on a medication classified as "use with caution and with more frequent monitoring" were more likely than those with the same classification in the unguided group to have a medication change or dose adjustment (100% vs. 50% respectively; p=0.02). Depression outcomes, measured by the HAMD-17 score, did not differ significantly between groups at the 10-week follow-up (see Table 3). This trial's small size may have limited the ability to detect a significant effect, as the authors estimated that 92 patients per arm would be required; but the Gene Sight directed arm and the standard care arm included 26 and 25 patients, respectively.

Table 2. Summary Characteristics of RCTs Assessing GeneSight® Test

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
Oslin et al (2022) (PRIME Care)	U.S.	22	2017-2021	Adult individuals with MDD; failure of at least 1 medication; 25% female; 69% White, 11% Hispanic, 18% Black, 3% Asian, 0.1% American Indian/Alaska Native	Treatment guided by GeneSight (n=966 randomized; n=754 at week 24)	SOC (n=978 randomized; n=775 at week 24)
Greden et al (2019)	U.S.	60	2014-2017	Patients with MDD based on QIDS assessment; failure of at least 1 medication; 71% female; 81% White, 15% Black, 2% Asian, 0.6% American Indian/Alaska Native, 0.1% Native Hawaiian/Pacific Islander, 2% other or multiple race/ethnicity	Treatment guided by GeneSight® (n=681)* *Per protocol 1398 of 1799 randomized	SOC (n=717)* *Per protocol cohort is 1398 of 1799 randomized
Tiwari et al (2022)	Canada	8	2015-2018	Individuals with MDD, ≥11 on QIDS-C16 and total screening and baseline scores of ≥11 on QIDS-SR16, failure of at least 1 medication; 65% female, 84% White, 9% Asian, 3% Black, 2% Latin American, 3% other race/ethnicity	Treatment guided by standard GeneSight or enhanced GeneSight (standard GeneSight + 7 additional polymorphisms shown to have genetic variation associated	SOC (n=138)

					with antipsychotic-induced weight gain; n=299 [n=147 standard GeneSight; n=152 enhanced GeneSight])	
Winner et al (2013)	U.S.	1	NR	Patients with major depressive disorder, HAM D-17>14 (moderate); 80% female; 98% non-Hispanic White, 2% Black	Treatment guided by GeneSight® (n=26)	SOC (n=25)

HAM-D17: Hamilton Depression Rating Scale 17 item; MDD: major depressive disorder; NR: not reported; QIDS: Quick Inventory of Depressive Symptomatology; QIDS-C16: 16-item Quick Inventory of Depressive Symptomatology (clinician rated);QIDS-SR16: 16-item Quick Inventory of Depressive Symptomatology (self-rated); RCT: randomized controlled trial; SOC: standard of care.

Table 3. Summary of Results of RCTs Assessing GeneSight®

Study	**N**	**Response: ≥50% decrease in HAM-D17**	**Remission: HAM-D17 ≤7**	**Symptom Improvement: mean % change in HAM-D17**
Oslin et al (2022) (PRIME Care)		24 weeks		
GeneSight	754	32.1%	17.2%	5.4
SOC	787	27.5%	16	4.8
Risk difference (95% CI); p-value		5.1 (0.6 to 9.6); p=.03	1.5 (-2.4 to 5.3); p=.45	0.65 (0.1 to 1.19); p=.02
Greden et al (2019)		8 weeks		
GeneSight	ITT: PP: 560	ITT: 26.1% (SE 1.8) PP: 26.0% (SE 1.9)	ITT: 16.8% (SE 1.6) PP: 15.3% (SE 1.6)	ITT: 26.7% (SE1.3) PP: 27.2% (SE 1.3)
SOC	ITT: PP: 607	ITT: 19.8% (SE 1.5) PP: 19.9% (SE 1.6)	ITT: 11.4% (SE 1.3) PP: 10.1% (SE 1.2)	ITT: 23.5% (SE 1.2) PP: 24.4% (SE 1.2)
Risk difference (95% CI); p-value		ITT: MD 6.3; p=.007 PP: MD 6.1; p=.01	ITT: MD 5.4; p=.005 PP: MD 5.2; p=.007	ITT: MD 3.2; p=.07 PP: MD 2.8; p=.11
Tiwari et al (2022)		8 weeks		
GeneSight	ITT: 211 PP: 127	ITT: 25.1% (SE 3.0) PP: 30.3% (SE 4.1)	ITT: 16.4% (SE 2.7) PP: 15.7% (SE 3.4)	ITT: 23.8% (SE 2.4) PP: 27.6% (SE 2.6)
SOC	ITT: 97 PP: 69	ITT: 21.9% (SE 4.2) PP: 22.7% (SE 5.1)	ITT: 9.7% (SE 2.9) PP: 8.3% (SE 3.3)	ITT: 17.8% (SE 3.6) PP: 22.7% (SE 3.6)
HR/Diff/OR/RR (95% CI); p-value		ITT: MD 3.3; p=.54 PP: MD 7.6; p=.26	ITT: MD 6.7; p=.10 PP: MD 7.4; p=.13	ITT: MD 6.0; p=.17 PP: MD 4.9; p=.27
Winner et al (2013)[-]		10 weeks		
GeneSight	26	36%	20%	
SOC	25	20.8%	8.3%	

Risk difference (95% CI); p-value		OR 2.14 (95% CI 0.59-7.79)	OR 2.75 (95% CI 0.48-15.8)	

CI: Confidence interval; HAM-D17: Hamilton Depression Rating Scale 17 item; ITT: intention to treat; MD: mean difference; OR: odds ratio; PP: per protocol; SE: standard error; SOC: standard of care.

Table 4. Study Relevance Limitations: GeneSight®

Study	Population	Intervention	Comparator	Outcomes	Duration of Follow-Up
Oslin et al (2022) (PRIME Care)	1. Patients with mild depression excluded from per protocol analysis				
Greden et al (2019)	[1]Patients with mild depression excluded from per protocol analysis				[1]24-week follow-up was treatment arm only
Tiwari et al (2022)	1. Patients with mild depression excluded from per protocol analysis				
Winner et al (2013)	2.MDD diagnostic criteria. Prior medication response not described				1.Follow-up limited to 10 weeks

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 5. Study Design and Conduct Limitations: GeneSight®

Study	Allocations	Blinding	Selective Reporting	Data Completeness	Power	Statistical
Oslin et al (2022) (PRIME Care)		2. Single blinding only (no blinding of patient or treating clinician)		1. Of 1,944 randomized individuals, data were reported for 1,819 at four weeks follow-up and 1,541 at 24 weeks follow-up		4. Underpowered; n=1000 per arm required to detect remission
Greden et al (2019)				1,2Of 1,799 randomized individuals, data were reported for 1,299 in the ITT population and 1,167 in the per protocol population		

Tiwari et al (2022)				1. Of 437 randomized individuals, data were reported for up to 308 (70%) in the ITT population and 196 (45%) in the per protocol population		
Winner et al (2013)						[4] Underpowered. N=92 per arm required to detect remission or response

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3.Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent-to-treat analysis (per protocol for non-inferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: GeneSight® test

Evidence for the use of GeneSight test to inform antidepressant selection includes 4 RCTs. None of the trials provided adequate evidence, and all have major limitations in design and conduct, and in consistency and precision.

NeuroIDgenetix® Test

Randomized Controlled Trials

Two randomized controlled trials reported results of antidepressant therapy selection, informed by NeuroIDgenetix® test results compared to standard of care —antidepressant therapy selected without gene test results.

Bradley et al (2018) conducted a double-blinded RCT in which 685 individuals with depression and/or anxiety disorders were randomized to treatment guided by either NeuroIDgenetix® or standard of care (Table 6).[27] Outcomes included HAMD and the Hamilton Rating Scale for Anxiety (HAMA) and adverse drug events. Trained and blinded clinicians conducted interviews using the HAMD and HAMA. Approximately 15% of randomized individuals were lost to follow up over the 12 week period. Response results were only reported for 261 moderate and severe group of individuals and remission results were reported for 93 severe group of individuals. Response rates ($p<0.001$; OR: 4.72 [1.93-11.52]) and remission rates ($p<0.02$; OR: 3.54 [1.27-9.88]) were significantly higher in the NeuroIDgenetix®-guided group as compared to the control group at 12 weeks. The frequency of adverse drug events did not differ statistically between groups. Study does not report clearly if the analysis was based on intention to treat population. Reporting is incomplete, and suggestive of selective reporting.

Olson et al (2017) conducted an RCT in which individuals with neuropsychiatric disorders were randomized to treatment guided by NeuroIDgenetix® or standard of care (see Table 6).[28] A majority of the individuals, 56% in the intervention group and 64% in the control group had a

primary diagnosis of depression. Subgroup analyses by neuropsychiatric disorder were not conducted. Outcomes included Neuropsychiatric Questionnaire, Symbol Digit Coding test, and adverse drug events. The Neuropsychiatric Questionnaire is a computerized survey addressing symptoms of neuropsychoses, and the SCD assesses attention and processing speed, which is sensitive to medication effects. The study did not report on response or remission of depression. There were no significant differences in Neuropsychiatric Questionnaire or Symbol Digit Coding scores between groups (see Table 7). However, the individuals receiving standard of care reported significantly more adverse events (53%) than individuals receiving NeuroIDgenetix®-guided care (28%). The comparison of adverse drug events did not report the number of individuals included in the analysis. ClinicalTrials.gov lists neurocognitive measures as co-primary outcomes, but these are not reported, suggestive of selective reporting.

Table 6: Summary Characteristics of RCTs Assessing NeuroIDgenetix®

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
Bradley et al (2018)	U.S.	20 Psychiatry and primary care settings	2016	Individuals with depression and/or anxiety disorders using either HAM D-17 or HAM A score≥18 (moderate and severe) were included in efficacy analysis. Either new to medication or inadequately controlled with medication	Treatment guided by NeuroIDgenetix® (n=352)	SOC (n=333)
Olson et al (2017)	U.S.	6	2015	Individuals with ADHD, anxiety, depression, or psychosis; currently receiving antidepressants	Treatment guided by NeuroIDgenetix® (n=178)	SOC (n=25)

Table 7. Summary of Results of RCTs Assessing NeuroLDgenetix®

Study	N	Outcome			
		Response ≥50% decrease in HAM-D17		Remission: HAM-D17≤7	
Bradley et al (2018)		12 weeks	p	12 weeks	p
NeuroIDgenetix®	140 (moderate/severe)	64%		NR	
Standard Care	121 (moderate/severe)	46%	0.01	NR	
NeuroIDgenetix®	40 (severe)			35%	
Standard Care	53 (severe)			13%	0.02
		≤1 Adverse Drug Event		≥2 Adverse Drug Events	
Olson et al (2017)		10 weeks			
NeuroIDgenetix®	NR	28%		5%	
Standard Care	NR	53%	0.001	24%	0.001

Table 8. Study Relevance Limitations: NeurolDgenetix®

Study	Population	Intervention	Comparator	Outcomes	Duration of Follow-Up
Bradley et al (2018)					
Olson et al (2017)	[2] No description of criteria used to determine mental health condition diagnosis. [4] Majority of individuals with depression (57%); remaining with ADHD, anxiety, or psychosis			[1] Adverse drug events. Did not report response or remission	

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 9. Study Design and Conduct Limitations: NeurolDgenetix®

Study	Allocations	Blinding	Selective Reporting	Data Completeness	Power	Statistical
Bradley et al (2018)[24]			2. In the clinicaltrials.gov listing, reduction of adverse drug events was listed as the primary outcome, but was not reported as primary outcome Remission not reported for moderate/sever, only severe	1. Approximately 15% of randomized individuals were lost to follow-up over the 12 week trial. Analysis does not appear to be intent to treat.	1.No description of power and sample size calculations	
Olson et al (2017)	1. Randomization procedure not described		2. In the clinicaltrials.gov listing, change in Neuropsychiatric Questionnaire and Symbol Digit Coding at 4 months were listed	1. In the 3-month analyses, it appears that more than 30% of randomized individuals were not included.	1.No description of power and sample size calculations	1. Comparative statistics not reported for clinical or neurocognitive outcomes

			as coprimary outcomes. Four month results not reported	6. Unclear if analysis was intention-to-treat		

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3.Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent-to-treat analysis (per protocol for non-inferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: NeuroIDgenetix® test

Evidence for the use of NeuroIDgenetix® test to inform antidepressant selection includes 2 RCTs, one reporting response and remission as outcomes and another reporting adverse events as outcome. None of the trials provided adequate or supportive evidence in terms of relevance, design and conduct or consistency and precision. Both studies have major limitations in design and conduct and in consistency and precision.

Neuropharmagen® Test

Systematic Review and Meta-analysis

Vilches et al (2019) conducted a meta-analysis with the aim to assess the clinical utility of Neuropharmagen® in the treatment management of depressive individuals.[29] The study included 2 RCTs and a multicenter retrospective observational study.[30-32] Evidence from both the RCTs are discussed below.

Han et al (2018) conducted a randomized single-blind clinical trial among individuals with MDD to evaluate the effectiveness of Neuropharmagen® test guided antidepressant treatment (N=52) compared to receiving antidepressants through standard physician assessment (N=48) (Table 10).[30] Neuropharmagen® analyzes 30 genes associated with drug metabolism and 59 medications used to treat MDD. Primary endpoint was change in HAMD-17 score from baseline to 8 weeks follow-up. Response rate (at least 50% reduction in HAMD-17 score from baseline), remission rate (HAMD-17 score ≤7 at the end of treatment) as well as the change of total score of Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER) from baseline to end of treatment were also investigated. (Table 4). The intention-to-treat (ITT) population consisted of all individuals who had at least 1 post-treatment assessment for effectiveness during the study. The effectiveness evaluation was based on the analyses with ITT on last observation carried forward. The mean change of HAMD-17 score was significantly different between 2 groups favoring guided arm by −4.1 point of difference (p=0.010) at the end of treatment. The response rate (71.7 % vs. 43.6%, p=0.014) were also significantly higher in the guided arm than in standard care arm at the end of treatment, while the remission rate was numerically higher in the guided arm than in standard care arm without statistical difference (45.5% vs. 25.6%, p=0.071). The study reported early dropout of 25% in guided-care and 38% in in standard care arm. The reason for early dropout associated with adverse events was higher in standard care arm (n=9, 50.0%) than in guided care arm (n=4, 30.8%). The effectiveness evaluation was based on the analyses with ITT on last observation carried forward (LOCF). Use of LOCF assumes data are missing completely at random (MCAR).[33] The

distribution of reasons for termination among early dropouts indicates that the assumption of MCAR is unlikely to hold in this analysis. Study did not report registration in any clinical trial database.

Perez et al (2017) conducted a single-blind RCT (AB-GEN trial) of individuals diagnosed with major depressive disorder randomized to genotype-guided treatment (Neuropharmagen®) or treatment as usual (see Table 10).[31] The pharmacogenetics report from Neuropharmagen® provided information on 50 drugs, highlighting gene-drug interactions and drug recommendations from the U.S. Food and Drug Administration and Clinical Pharmacogenetics Implementation Consortium. The primary outcome was Patient Global Impression of Improvement (PGI-I), which was collected by telephone interviewers blinded to treatment allocation group. A response was defined as a PGI-I of 2 or less. Percent responders differed nominally between groups (p=0.05) at the end of the 12-week study (see Table 11). Changes in 17-item HAMD (HAMD-17) scores were significant at 5 weeks (p=0.04) but not at 12 weeks (p=0.08). Response and remission rates were calculated post-hoc based on the HDRS-17 (single-blinded). There was no significant difference in response (45.4% vs. 40.3%, p=0.39) or remission (34.0% vs. 33.1%, p=0.87) between guided care and standard care arms at 12 weeks. However, response and remission data were missing for 9% individuals in the guided care group and 14% of the standard care group.

Table 10. Summary Characteristics of RCTs Assessing Neuropharmagen®

Study	Country	Sites	Dates	Participants	Interventions	
					Active	Comparator
Han et al (2018)	Korea	2	NR	Individuals with MDD using DSM-5 criteria; currently receiving antidepressant therapy at least 6 weeks with an inadequate response (CGI-I >3)	Treatment guided by Neuropharmagen® (n=52)	SOC (n=48)
Perez et al (2017)	Spain	18	2014-2015	Individuals with MDD using DSM-IV-TR criteria; either new to medication or inadequately controlled with medication	Treatment guided by Neuropharmagen® (n=155)	SOC (n=161)

Table 11. Summary of Results of RCTs Assessing Neuropharmagen®

Study	N	Outcomes			
		Response ≥50% decrease in HAM-D17		Remission: HAM-D17≤7	
Han et al (2018)		8 weeks	p		p
Neuropharmagen®	52	71.7%		45.5%	
Standard Care	48	43.6%	0.01	25.6%	0.07
Perez et al (2017)		12 weeks		12 weeks	
Neuropharmagen®	141	45.4%		34.0%	
Standard Care	139	40.3%	0.39	33.1%	0.87
		OR = 1.23 (95%CI: 0.77 – 1.98)		OR = 1.04 (95%CI: 0.64 – 1.71)	

Table 12. Relevance Limitations: Neuropharmagen®

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of

					Follow-Up[e]
Han et al (2018)					
Perez et al (2017)					

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 13. Study Design and Conduct Limitations: Neuropharmagen®

Study	Allocations[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Han et al (2018)		3. Subjects were blinded, but unknown if outcome assessors were blinded	1. Not registered	1. High loss to follow-up or missing data 2. Inadequate handling of missing data. LOCF may not be the most appropriate approach		
Perez et al (2017)		3. Subjects were blinded, outcome (HDRS-17) assessed by treating physicians		1.Response and remission data were missing for 9% individuals in the guided care group and 14% of the standard care group.		

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3.Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent-to-treat analysis (per protocol for non-inferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: Neuropharmagen® Test

Evidence for the use of Neuropharmagen® test to inform antidepressant selection for individuals who have failed 2 or more courses of antidepressant therapy includes 2 RCTs. Han et al (2018) provided adequate evidence for 'Response' on a relevant population. Both studies have major limitations in design and conduct and inconsistency and precision.

Genetic Testing to Inform Medication Selection for Individuals with a Mental Illness other than Depression

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

The following **PICO** was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with a mental illness other than depression inadequately managed with psychopharmacologic drugs.

Interventions
Interventions of interest include testing for genes (single or as part of a panel) associated with medication pharmacokinetics and/or pharmacodynamics.

Comparators
Currently, decisions about medication management for individuals with mental illnesses are based on clinical response, potentially informed by studies such as the Sequenced Treatment Alternatives to Relieve Depression study, which evaluated specific medication sequences.

Outcomes
This evidence review assesses whether genetic testing for the management of mental health conditions is clinically useful. To make a clinical management decision that improves the net health outcome; the balance of benefits and harms must be better when the test is used to manage the condition than when another test or no test is used. The net health outcome can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The primary outcome of interest is change in disease outcomes resulting from a more appropriate selection of specific drugs or doses for the patient's condition. Also, avoidance of adverse events is an important outcome.

Systematic Review
Hartwell et al (2020) conducted a systematic review and meta-analysis of the moderating effect of rs1799971, a single nucleotide polymorphism (SNP) that encodes a non-synonymous substitution (Asn40Asp) in the mu-opioid receptor gene, *OPRM1* on response to naltrexone treatment of alcohol use disorder. The meta-analysis included 7 RCTs (659 subjects randomly assigned to receive naltrexone and 597 received placebo).[34] Of the 5 alcohol consumption outcomes considered, there was a nominally significant moderating effect of the Asn40Asp SNP only on drinks per day (d = −0.18, 95% CI=−0.32 to −0.03, P = 0.02). However, the effect was not significant when multiple comparisons were taken into account. There was no statistically significant heterogeneity (I^2 = 33.8%, P = 0.18).

Randomized Controlled Trials
Bradley et al (2018) conducted a double-blinded RCT in which 685 individuals with depression and/or anxiety disorders were randomized to treatment guided by either NeuroIDgenetix® or

standard of care (Table 14).[27] Among the participants, 115 in the experimental arm and 120 in the standard of care arm had only anxiety. Outcomes included percent reduction in Hamilton Rating Scale for Anxiety (HAM-A) and response (50% reduction in HAM-A) rate. Trained and blinded clinicians conducted interviews using the HAMA. Response results were only reported for 224 moderate and severe anxiety (Anxiety Only HAM-A≥18) group of individuals (109 in the experimental arm and 115 in the standard of care arm). Among the randomized moderate and severe anxiety individuals with only anxiety, 25% in the experimental arm and 17% in the standard care arm were lost to follow up over the 12 week period. Response rate was significantly higher in the NeuroIDgenetix®-guided group as compared to the control group at 12 weeks (63% vs. 50%, p=0.04). Study does not report clearly if the analysis was based on intention to treat population. Reporting is incomplete, and suggestive of selective reporting.

Table 14. Summary Characteristics of RCTs Assessing NeuroIDgenetix®

Study	Country	Sites	Dates	Participants	Intervention	
					Active	Comparator
Bradley et al (2019)	U.S.	20 Psychiatry and primary care settings	2016	Individuals with depression and/or anxiety disorders using either HAM D-17 or HAM A score≥18 (moderate and severe) were included in efficacy analysis. Either new to medication or inadequately controlled with medication	Treatment guided by NeuroIDgenetix® (n=352)	SOC (n=333)

Table 15. Summary of Results of RCTs Assessing NeuroIDgenetix®

Study	N	Outcomes			
		Response ≥50% decrease in HAM-A 17		Remission: HAM-A 17≤7	
Bradley et al (2019)		12 weeks	p	12 weeks	p
NeuroIDgenetix®	82 (moderate/severe)	63%		NR	
Standard Care	95 (moderate/severe)	50%	0.04	NR	

Table 16. Study Relevance Limitations: NeuroIDgenetix®

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Bradley et al (2019)					

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 17. Study Design and Conduct Limitations: NeuroIDgenetix®

Study	Allocations[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Bradley et al (2019)[24]			2. In the clinicaltrials.gov listing, reduction of adverse drug events was listed as the primary outcome, but was not reported as primary outcome Also, Anxiety remission was listed as a secondary outcome but was not reported.	1. Approximately 25% of randomized individuals were lost to follow-up or were not included in the outcome analysis at 12 week. Analysis does not appear to be intent to treat.	1. No description of power and sample size calculations	

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3.Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent-to-treat analysis (per protocol for non-inferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Kampangkaew et al (2019) conducted a study among cocaine and opioid codependent individuals randomized into disulfirum (n=32) and placebo (n=35) groups for 12 weeks of treatment and evaluated the role of SLC6A3 (DAT1) 40 bp 3′-untranslated region variable number tandem repeat variant in moderating disulfirum efficacy for cocaine dependence.[35] Study reported better treatment outcomes with disulfirum pharmacotherapy of cocaine dependence among individuals with genetically higher dopamine transporter (DAT) levels compared to those with lower DAT levels.

Naumova et al (2019) conducted a randomized pharmacodynamic investigation to evaluate the effect of DRD4 exon 3 polymorphism on child behaviors in response to treatment of ADHD with methylphenidate.[36] In this 2-week prospective within-subject, placebo-controlled, crossover trial there was significant interaction between DRD4 genotype and treatment when the ‘child’s behavior was evaluated by the parents (P = 0.035, effect size of 0.014), driven by a better treatment response in children homozygous for long 7-repeat allele.

Section Summary: Genetic Testing to Inform Medication Selection for Individuals with a Mental Illness other than Depression Inadequately Controlled with Medication
Evidence for the use of pharmacogenetic testing in individuals with mental health conditions other than depression includes a meta-analysis on alcohol use disorder and an RCT on anxiety disorder. The meta-analysis found no significant effect of Asn40Asp on the response to naltrexone treatment of heavy drinking or AUD. The single available trial did not provide adequate or supportive evidence effect of pharmacogenetic testing on managing moderate to severe anxiety. The study had major limitations in design and conduct and precision.

No other studies performed a direct intervention study. Jukic et al (2019) conducted a retrospective cohort study using patient data from a routine therapeutic drug monitoring database and showed that *CYP2D6* genetic variability had significant effect on risperidone and aripiprazole exposure and treatment and lower doses should be administered to CYP2D6 poor metabolizer's to avoid overdosing and dose-dependent side-effects.[37]

SUMMARY OF EVIDENCE

For individuals who are evaluated for diagnosis or risk of a mental illness who receive genetic testing for risk of that disorder, the evidence includes various observational studies (cohort, case-control, genome-wide association study). Relevant outcomes are changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Most studies evaluated the association between genotype and mental health disorders or gene-drug interactions among individuals with risk for mental health conditions. No studies were identified that evaluated whether testing for variants changed clinical management or affected health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For adult individuals with MDD who receive GeneSight testing guided drug treatment, the evidence includes 3 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The RCTs compared response (≥50% decrease in HAM-D17), remission (HAM-D17 ≤7), and symptom improvement (mean % change in HAM-D17) with antidepressant therapy informed by GeneSight test results to antidepressant therapy selected without GeneSight test results (i.e., SOC). The GUIDED trial reported statistically significant improvements in response and remission in the GeneSight arm compared to SOC at 8 weeks among individuals with MDD. However, depending on the population (ITT or per protocol), up to one-third of GUIDED randomized participants were missing from the reported results; the extent of missing data following randomization precludes conclusions on outcomes at 8 weeks. The GAPP-MDD trial, also comparing GeneSight guided treatment with SOC, found no statistically significant differences between groups in response, remission or symptom improvement at 8 weeks follow-up, although like the GUIDED trial, a high proportion (up to 69%) of randomized participants were excluded from outcome analysis and the study was not adequately powered to detect between-group differences. In the third trial, a small, single-center pilot study by Winner et al (2013), depression outcomes did not differ significantly between GeneSight-guided care and SOC groups at the 10-week follow-up, though the study was underpowered to detect significant differences in outcomes between study arms. All of these trials have major limitations in design and conduct and in consistency and precision, thus none provided adequate evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult individuals with major depressive disorder who have had inadequate response to antidepressant therapy who receive NeuroIDgenetix® testing guided drug treatment, the evidence includes 2 randomized controlled trials (RCT). Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Bradley *et al* (2018) conducted a double-blind RCT among individuals with MDD and reported statistically significant improvement in response (≥50% decrease in HAM-D17) in the NeuroIDgenetix® arm (64% of 140) compared to SOC (46% of 121) at 12 weeks (p=0.01) and significant improvement in remission (HAMD-17≤7) in the NeuroIDgenetix® arm (35% of 40) compared to SOC (13% of 53) at 12 weeks

(p=0.02). There was evidence of reporting bias and it was unclear if the analysis was based on intention-to-treat population and there was high loss to follow-up (15%). In the RCT conducted by Olson *et al* (2017), among individuals with neuropsychiatric disorders those receiving SOC reported significantly more adverse events (53%) than those receiving NeuroIDgenetix® guided care (28%), however, the study did not report the number of individuals included in this analysis. The study did not describe the randomization procedure and in ClinicalTrials.gov neurocognitive measures were listed as co-primary outcomes, which were not reported, suggesting possible selective reporting. None of these trials provided adequate evidence. The Olson et al (2017) study had major relevance limitations and both the studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine the effects of the technology on health outcomes.

For adult individuals with major depressive disorder who have had inadequate response to antidepressant therapy who receive Neuropharmagen® testing guided drug treatment, the evidence includes 2 randomized controlled trials (RCT). Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The 2 RCTs compared response (≥50% decrease in HAM-D17) and remission (HAMD-17≤7) with antidepressant therapy informed by Neuropharmagen ® test results to standard of care (SOC)—antidepressant therapy selected without Neuropharmagen ® test results. The single-blinded RCT by Han *et al* (2018) reported statistically significant improvement in response (72% of 52 vs. 44% of 48, p=0.01) and not statistically significant improvement in remission (46% of 52 vs. 26% of 48, p=0.07) in the Neuropharmagen® arm compared to SOC at 8 weeks among individuals with MDD. The study reported early dropout of 25% in guided-care and 38% in the standard care arm and used last observation carried forward (LOCF) approach in intention to treat analysis of effectiveness. Use of LOCF assumes data are missing completely at random (MCAR), which is unlikely to hold in this analysis. Also, the study did not report registration in any clinical trial database. The single-blinded RCT by Perez *et al* (2017) reported statistically not significant improvement in response (45% of 141 vs. 40% of 139, p=0.39) and remission (34% of 141 vs. 33% of 139, p=0.87) in the Neuropharmagen® arm compared to SOC at 12 weeks among individuals with MDD. Response and remission data were missing for 9% individuals in the guided care group and 14% of the standard care group. None of these trials provided adequate evidence. Both studies have major limitations in design and conduct and in consistency and precision. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a mental illness other than depression who are undergoing drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a systematic review and meta-analysis and RCTs evaluating associations between specific genes and outcomes of drug treatment. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review and meta-analysis by Hartwell *et al* (2020) included 7 RCTs and reported no significant moderating effect of rs1799971, a single nucleotide polymorphism (SNP) that encodes a non-synonymous substitution (Asn40Asp) in the mu-opioid receptor gene, *OPRM1* on response to naltrexone treatment of alcohol use disorder. Bradley *et al* (2018) conducted a double-blind RCT among individuals with anxiety disorders and reported statistically significant improvement in response (≥50% decrease in HAM-A17) in the NeuroIDgenetix® arm (63% of 82) compared to SOC (50% of 95) at 12 weeks among moderate and severe group of individuals (p=0.04). There was evidence suggesting selective reporting, as anxiety remission

was not reported and contrary to the listing in clinicaltrials.gov adverse drug events was not reported as the primary outcome. It was unclear if the analysis was based on intention-to-treat population and among the randomized moderate and severe anxiety individuals with only anxiety, 25% in the experimental arm and 17% in the standard care arm were lost to follow up over the 12 week period. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 18.

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04615234	Towards Precision Medicine in Psychiatry: Clinical Validation of a Combinatorial Pharmacogenomic Approach (PANDORA)	300	Mar 2023
NCT04909749[a]	CDDOM Oneome Rightmed Depression Study	350	Jun 2023
NCT04500301	Pharmacogenomic Testing to Personalize Supportive Oncology	120	Feb 2024
NCT05669391	Pharmacogenomics on Individualized Precise Treatment of Patients With Depression	120	Dec 2026
Unpublished			
NCT02573168a	A Three-arm, Parallel Group, Multicentre, Double-blind, Randomized Controlled Trial Evaluating the Impact of GeneSight Psychotropic and Enhanced-GeneSight Psychotropic, on Change in Weight Following Antipsychotic Treatment in Patients Suffering From Disorders Indicated for Antipsychotic Utilization	103	Sep 2020
NCT04207385	Accurate Clinical Study of Medication in Patients With Depression Via Pharmacogenomics (PGx) and Therapeutic Drug Monitoring (TDM) of Venlafaxine	160	Nov 2021 (status unknown)
NCT03749629	Comparative Effectiveness of Pharmacogenomics for Treatment of Depression	201	Mar 2022

NCT: national clinical trial
[a] Denotes industry-sponsored or cosponsored trial

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

Clinical Pharmacogenetics Implementation Consortium

The CPIC was established in 2009 to develop practice guidelines on the use of genetic laboratory results to inform prescribing decisions.[37] The panel consists of experts from the United States, Europe, and Asia.

The CPIC (2015) conducted a systematic literature review on the influence of *CYP2D6* and *CYP2C19* genotyping on selective serotonin reuptake inhibitor (SSRI) therapy.[38] The CPIC provided dosing recommendations for SSRIs based on phenotypes that classified individuals as ultra-rapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. However, CPIC noted that individuals on an effective and stable dose of SSRIs would not benefit from dose modifications based on *CYP2D6* and *CYP2C19* genotype results.

Additionally, CPIC asserted that genetic testing is only one factor among several clinical factors that should be considered when determining a therapeutic approach.

The CPIC (2016) conducted a systematic literature review of the influence of *CYP2D6* and *CYP2C19* genotype on the dosing of tricyclic antidepressants.[39] Dosing recommendations for tricyclic antidepressants were provided, based on patient classifications of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. CPIC noted that the most appropriate use of genotype-based dosing is when initiating therapy with a tricyclic. For individuals already on tricyclics who have had doses adjusted based on plasma concentrations, response, or side effects, genetic testing is not as helpful.

Table 18. Dosing Recommendations for Antidepressants Based on CYP2D6 and CYP2C19 Phenotype[37]

Recommendations for TCAs				
Phenotype	**Implications**	**Recommendation**	**Class of recommendation for amitriptyline and nortripyline**	**Class of recommendation for other TCAs[a]**
CYP2D6 ultrarapid metabolizer	Increased metabolism to less active compound results in lower plasma concentrations of active drug and decreased probability of drug effectiveness.	Avoid TCA due to potential lack of efficacy. If TCA warranted, consider higher dose with monitoring to guide dose adjustments.	strong	optional
CYP2D6 rapid metabolizer	Normal metabolism of TCAs	Initiate TCA with recommended steady-state dose.	strong	strong
CYP2D6 intermediate metabolizer	Reduced metabolism to less active compound results in higher plasma concentrations of active drug and increased probability of side effects.	Consider 25% reduced starting dose with monitoring to guide dose adjustments.	moderate	optional
CYP2D6 poor metabolizer	Greatly reduced metabolism to less active compound results in higher plasma concentrations of active drug and increased probability of side effects.	Avoid TCA due to potential side effects. If TCA is warranted, consider 50% reduced starting dose with monitoring to guide dose adjustments.	strong	optional
Recommendations for Tertiary Amines Amytriptyline, Clomipramine, Doxepin, Imipramine, and Trimipramine				

Phenotype	Implications	Recommendation	Class of recommendation for amitriptyline	Class of recommendation for other tertiary amine TCAs
CYP2C19 ultrarapid and rapid metabolizer	Increased metabolism of tertiary amines to secondary amines may affect efficacy and side effects	Avoid tertiary amines due to potential sub-optimal response. Consider secondary amines. If tertiary amines warranted, use monitoring to guide dose adjustments.	optional	optional
CYP2C19 normal metabolizer	Normal metabolism of tertiary amines	Initiate tertiary amine with recommended steady-state dose.	strong	strong
CYP2C19 intermediate metabolizer	Reduced metabolism of tertiary amines	Initiate tertiary amine with recommended steady-state dose.	strong	optional
CYP2C19 poor metabolizer	Greatly reduced metabolism of tertiary amines to secondary amines may affect efficacy and side effects	Avoid tertiary amines due to potential sub-optimal response. Consider secondary amines. If tertiary amines warranted, consider 50% reduced starting dose with monitoring to guide dose adjustments.	moderate	optional

[a] There is less clinical and pharmacokinetic evidence to support genotype-guided dose adjustments for TCAs other than amitriptyline or nortriptyline, though it may be reasonable to apply the same recommendations.
TCA: tricyclic antidepressants.

Table 19. Dosing Recommendations for Amitriptyline Based on Both CYP2D6 and CYP2C19 Phenotypes[a,b]

Phenotype	*CYP2D6* ultrarapid metabolizer	*CYP2D6* normal metabolizer	*CYP2D6* intermediate metabolizer	*CYP2D6* poor metabolizer
CYP2C19 ultrarapid or rapid metabolizer	Avoid amitryptyline. (optional)	Consider alternative drug. (optional)	Consider alternative drug. (optional)	Avoid amitryptyline. (optional)
CYP2C19 normal metabolizer	Avoid amitryptyline. If amitryptyline is warranted, consider higher target dose, (strong)	Initiate therapy with recommended starting dose. (strong)	Consider 25% reduction of recommended starting dose. (moderate)	Avoid amitryptyline. If amitryptyline is warranted, consider 50% reduction of recommended starting dose. (strong)
CYP2C19 intermediate metabolizer	Avoid amitryptyline. (optional)	Initiate therapy with recommended starting dose. (strong)	Consider 25% reduction of recommended starting dose.(optional)	Avoid amitryptyline. If amitryptyline is warranted, consider 50% reduction of recommended starting dose. (optional)
CYP2C19 poor metabolizer	Avoid amitryptyline. (optional)	Avoid amitryptyline. If amitryptyline is warranted, consider	Avoid amitryptyline. (optional)	Avoid amitryptyline. (optional)

		50% reduction of recommended starting dose. (moderate)		

[a] classification of recommendation appears in parenthesis after every recommendation
[b] Recommendations from studies focused on amitryptyline; however, since tricyclic antidepressants have comparable pharmacokinetic properties, these guidelines may apply to other tertiary amines.

International Society of Psychiatric Genetics[38,39]

In 2019, The International Society of Psychiatric Genetics (ISPG) issued recommendations on the use of pharmacogenetic testing in the management of psychiatric disorders, and in 2020 published the evidence review used to inform the recommendations.[40,41] The recommendations state: "we recommend HLA-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups. Evidence to support widespread use of other pharmacogenetic tests at this time is still inconclusive, but when pharmacogenetic testing results are already available, providers are encouraged to integrate this information into their medication selection and dosing decisions. Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial."

The ISPG also included the following considerations regarding pharmacogenetic testing:

- Common genetic variants alone are not sufficient to cause psychiatric disorders such as depression, bipolar disorder, substance dependence, or schizophrenia. Genotypes from large numbers of common variants can be combined to produce an overall genetic risk score which can identify individuals at higher or lower risk, but at present it is not clear that this has clinical value.
- There is growing evidence that rare, pathogenic variants with large effects on brain function play a causative role in a significant minority of individuals with psychiatric disorders and may be a major cause of illness in some families. Identification of known pathogenic variants may help diagnose rare conditions that have important medical and psychiatric implications for individual patients and may inform family counseling. Identification of de novo mutations and copy number variants (CNVs) may also have a place in the management of serious psychiatric disorders. CNV testing may also prove useful for persons requesting counseling on familial risk. While the Committee did not reach consensus on widespread use of CNV testing in adult-onset disorders, most agreed that such tests may have value in cases that present atypically or in the context of intellectual disability, autism spectrum disorder, learning disorders, or certain medical syndromes.
- Professional counseling can play an important role in the decision to undergo genetic testing and in the interpretation of genetic test results. We recommend that diagnostic or genome-wide genetic testing should include counseling by a professional with expertise in both mental health and the interpretation of genetic tests. Consultation with a medical geneticist is recommended, if available, when a recognized genetic disorder is identified or when findings have reproductive or other broad health implications.
- Whenever genome-wide testing is performed, the possibility of incidental (secondary) findings must be communicated in a clear and open manner. Procedures for dealing with such findings should be made explicit and should be agreed with the patient or

study participant in advance. The autonomy of competent individuals regarding preferences for notification of incidental findings should be respected.
- Genetic test results, like all medical records, are private data and must be safeguarded against unauthorized disclosure with advanced encryption and computer security systems.
- We advocate the development and dissemination of education programs and curricula to enhance knowledge of genetic medicine among trainees and mental health professionals, increase public awareness of genetics and genetic testing, and reduce stigma.
- Expanded research efforts are needed to identify relevant genes and clarify the proper role of genetic testing and its clinical utility in psychiatric care.
- Pharmacogenetic testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care.

Government Regulations
National:
No NCD on this topic.

Local:
Local Coverage Determination (LCD): MoPath: GeneSight® Assay for Refractory Depression (L38435) WPS Insurance Corporation For services performed on or after 08/24/23.

Coverage Indications, Limitations
This is a limited coverage policy for pharmacogenomics testing (PGx) including single gene, multi-gene panels, and combinatorial tests. These tests are generally covered (with a few exceptions) as described in further detail below to improve safety in the use of specific medications by avoiding potentially harmful medications, doses and/or adverse reactions known to occur with certain genotypes.

PGx testing is considered reasonable and necessary in limited circumstances as described below as an adjunctive personalized medicine decision-making tool once a treating clinician has narrowed treatment possibilities to specific medications under consideration for use, or is already using a specified medication, based on other clinical considerations including the patient's diagnosis, the patient's other medical conditions, other medications, professional judgement, clinical science and basic science pertinent to the drug, and the patient's preferences and values.

PGx tests must demonstrate analytical validity, clinical validity, and clinical utility to be considered reasonable and necessary for coverage. This is demonstrated through a required technical assessment of the test. PGx Tests are considered germline tests and must adhere to other relevant germline testing policies published by this contractor.

It is understood that some panel/combinatorial tests may include content that has demonstrated clinical utility and some that has not. In such circumstances, this contractor may provide coverage for the components of tests that have demonstrated clinical utility when used in the proper clinical context described below.

Clinical Indications
PGx tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A and B).

The selection of the medications in question must be derived from clinical factors/necessity rather than from a PGx test. Once the putative therapeutic agents are selected, and those agents are known to have gene-drug interactions as identified above, then a PGx test may be considered reasonable and necessary when the result of that test is necessary for the physician's decision-making process regarding safely administering or dosing the drug. PGx testing is not considered reasonable and necessary merely on the basis of a patient having a particular diagnosis. Unless the record reflects that the treating clinician has already considered non-genetic factors to make a preliminary drug selection, PGx testing is not considered reasonable and necessary.

This LCD does not address (provides neither coverage nor non-coverage criteria) PGx testing for anticoagulation dosing, which is addressed by the National Coverage Determination (NCD) 90.1.

Coverage Information:
The clinical record must clearly show the use of or intent to prescribe a drug that has known drug-gene interactions that require a PGx test to be ordered to define the safe use of that drug in that patient.

If a treating clinician orders a single gene test or a test for a particular allele(s), but as a matter of operational practicality, the laboratory tests that single gene or allele on a platform that looks for variants in other genes/alleles as well, that particular test done in that particular instance is considered a single gene/ allele test for coverage purposes. In this scenario the provider may bill for the component of the test that was reasonable and necessary (in this example, the single gene test).

A multi-gene panel is considered reasonable and necessary if more than one single gene on that panel would be considered reasonable and necessary for safe use of the medication in question or if multiple drugs are being considered (each fulfilling the criteria of actionable gene-drug interactions identified above) that have different relevant genes. Additionally, a gene panel must contain at a minimum all the necessary relevant gene/allele content required for their indicated use to meet clinical utility requirements. Such minimum criteria are determined by experts including relevant associations such as the Association for Molecular Pathology and are considered during the technical assessment. A multi-gene panel is not considered reasonable and necessary if only a single gene on the panel is considered reasonable and necessary.

If two or more single genes are tested, rather than a multi-gene panel, then the record must reflect that a clinician individually ordered each gene, and each single gene must individually be reasonable and necessary at the time they are ordered.

The ordering provider of a PGx test is restricted to providers who have the licensure, qualifications, and necessary experience / training to both diagnose the condition being treated and also to prescribe medications (the provider must be able to do both) for the condition either independently or in an arrangement as required by all the applicable state laws.

Noncovered Indications
PGx testing is not covered when a treating clinician is not considering treatment with a medication that has an actionable drug-gene interaction, or when the use of a medication with a drug-gene interaction is not reasonable and necessary.

Proposed Local Coverage Determination (LCD) DL36398: MolDX: *CYP2C19, CYP2D6, CYP2C9* and *VKORC1* Genetic Testing. Wisconsin Physicians Service Insurance Corp. (WPS), for services performed on or after 02/01/2019. Retired on or after 11/28/2019. L35698: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing. Effective 07/01/2020. Retired 07/25/2020.

CYP2C19
Covered Indications
In summary, genetic testing of the CYP2C19 gene is considered medically necessary for patients with ACS undergoing PCI who are initiating or reinitiating Clopidogrel (Plavix) therapy.

Non-covered Indications
Genetic testing for the CYP2C19 gene is considered investigational at this time for the following medications including but not limited to:

- Amitriptyline
- Clopidogrel for indications other than above
- Proton pump inhibitors

- Selective serotonin reuptake inhibitors
- Warfarin

CYP2D6

I. **Covered Indications**
In summary, genetic testing of the *CYP2D6* gene is considered medically necessary to guide medical treatment and/or dosing for individuals for whom initial therapy is planned with:
    - Amitriptyline or nortriptyline for treatment of depressive disorders
    - Tetrabenazine doses greater than 50 mg/day or re-initiation of therapy with doses greater than 50 mg/day.

Non-covered Indications
There is insufficient evidence to demonstrate that genetic testing for the *CYP2D6* gene improves clinical outcomes. Consequently, genetic testing for the *CYP2D6* gene is considered investigational including but not limited to the following medications:

- Antidepressants other than those listed above
- Antipsychotics
- Codeine

- Donepezil
- Galantamine
- Tamoxifen

CYP2C9
Pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness by any method, and is therefore covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who:

- Have not been previously tested for CYP2C9 or VKORC1 alleles; and
- Have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and
- Are enrolled in a prospective, randomized, controlled clinical study when that study meets the following standards.

Non-covered Indications
All other coverage for genetic testing for the CYP2C9 gene is considered investigational at this time. There is currently no proven clinical utility related to any medication, including but not limited to:

- Celecoxib
- Fluorbiprofen
- Flovoxamine

VKORC1
Pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness by any method, and is therefore covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who:

- Have not been previously tested for *CYP2C9* or *VKORC1* alleles; and
- Have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and
- Are enrolled in a prospective, randomized, controlled clinical study when that study meets the standards as outlined in NCD 90.1 - Pharmacogenomic Testing to Predict Warfarin Responsiveness.

Non-covered Indications
Genetic testing for the VKORC1 gene is considered investigational at this time for all other medications.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing and Counseling
- Genetic Testing for Cytochrome P450 Polymorphisms

- Genetic Testing for Inherited Thrombophilia

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through September 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/15	6/16/15	7/16/15	Joint policy established 12/16/15: title changed from "Genetic Testing for Mental Health Conditions" to "Genetic Testing for Specified Conditions."
9/1/16	6/21/16	6/21/16	Routine policy maintenance. No change in policy status.
9/1/17	6/20/17	6/20/17	Updated rationale, added references #56 and 57. Updated CMS information. No changes in policy status.
11/1/18	8/21/18	8/21/18	Rationale reorganized, references 2, 36, 40, 43, 55-59 added. Policy statement changed to specify drugs used to treat mental health conditions. The intent of the policy was not changed.
1/1/19	10/16/18	10/16/18	Added codes 81227, 81230, 81231, and 0031U. Code 0028U deleted as of 10/01/18.
1/1/20	10/15/19		Rationale updated, references 8, 9 and 25 added. No change in policy status.
1/1/21	10/20/20		Rationale rearranged, CMS section updated, references 1, 3, 6, 14 and 26 added. No change in policy status.
1/1/22	10/19/21		Routine policy maintenance, no change in policy status.
1/1/23	10/18/22		Discussed GeneSight® testing, new literature send in by Myriad. Updated rationale, added reference #19. No change in policy status.
1/1/24	10/17/23		Updated rationale, references added. Added codes 0029U, 0032U, 0033U, 0070U-0076U, 0156U, 0173U, 0175U, 0345U the policy as E/I. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR SPECIFIED CONDITIONS USING TESTING PANELS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.