Protocol

Genetic Testing for Diagnosis and Management of Mental Health Conditions

(204110)

(Formerly Genetic Testing for Mental Health Conditions)

Medical Benefit		**Effective Date**: 04/01/16	**Next Review Date**: 01/20
Preauthorization	Yes	**Review Dates**: 07/14, 01/15, 01/16, 01/17, 01/18, 01/19	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are evaluated for diagnosis or risk of a mental illness	Interventions of interest are: • Genetic testing for risk of a mental illness	Comparators of interest are: • Standard care	Relevant outcomes include: • Test validity • Other test performance measures • Change in disease status
Individuals: • With a mental illness who are undergoing drug treatment	Interventions of interest are: • Genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics	Comparators of interest are: • Standard of care drug treatment	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity

DESCRIPTION

Individual genes have been shown to be associated with risk of psychiatric disorders and specific aspects of psychiatric drug treatment such as drug metabolism, treatment response, and risk of adverse events. Commercially available testing panels include several of these genes and are intended to aid in the diagnosis and management of mental health disorders.

SUMMARY OF EVIDENCE

For individuals who are evaluated for diagnosis or risk of a mental illness who receive genetic testing for risk of that disorder, the evidence includes various observational studies (case-control, genome-wide association study) evaluating the association between the mental illness of interest and candidate genes. Relevant outcomes are test validity, other test performance measures, and changes in disease status. Most studies have evaluated the association between genotype and mental health disorders without a clinical perspective; thus diagnostic characteristics and validated risk predictions among specific clinical populations are unknown. The associations are inconsistent across studies. There is no clear clinical strategy for how the associations of specific genes and mental health disorders would be used to diagnose a specific patient or to manage a patient at higher risk of a spe-

cific disorder. No studies were identified that evaluated whether testing for variants changed clinical management or affected health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

POLICY

Genetic testing for diagnosis and management of mental health disorders is considered **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 **investigational** for all indications.

POLICY GUIDELINES

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical protocol updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Genetic Counseling

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

MEDICARE ADVANTAGE

Genetic testing for mutations associated with mental health disorders with the GeneSight® Psychotropic panel, may be considered **medically necessary** when all of the following conditions are met:

- testing may only be ordered by licensed psychiatrists or neuropsychiatrists contemplating an alteration in neuropsychiatric medication for patients diagnosed with major depressive disorder (MDD) who are suffering with refractory moderate to severe depression (based upon DSM-V criteria) and
- the patient must have failed or currently be failing on at least one neuropsychiatric medication.

BACKGROUND

MENTAL HEALTH DISORDERS

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

behavioral treatment, treatment commonly involves one or more psychotropic medications aimed at alleviating symptoms of the disorder. Although there are a wide variety of effective medications, treatment of mental health disorders is characterized by relatively high rates of inadequate response. This often necessitates numerous trials of individual agents and combinations of medications to achieve optimal response.

Knowledge of the physiologic and genetic underpinnings of mental health disorders is advancing rapidly and may substantially alter the way these disorders are classified and treated. Genetic testing could be used in several ways, including stratifying patients' risks of developing a particular disorder, aiding diagnosis, targeting medication therapy, and optimally dosing medication.

Pharmacogenomic Testing

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

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

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

Genes Relevant to the Diagnosis and Management of Mental Health Disorders

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

ABCB1 Gene

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

Serotonin Transporter

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

Serotonin Receptor

The serotonin receptor gene (5HT2C) codes for one of at least six subtypes of the serotonin receptor that are involved in the release of dopamine and norepinephrine. These receptors play a role in controlling mood, motor function, appetite, and endocrine secretion. Alterations in functional status have been associated with affective disorders such as anxiety and depression. Certain antidepressants (e.g., mirtazapine, nefazodone) are direct

antagonists of this receptor. There is also interest in developing agonists of the 5HT2C receptor as a treatment for obesity and schizophrenia, but such medications are not commercially available at present.

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

Sulfotransferase Family 4A, Member 1

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

Dopamine Receptors

The DRD2 gene codes for the D2 subtype of the dopamine receptor. The activity of this receptor is modulated by G proteins, which inhibit adenyl cyclase. These receptors are involved in various physiologic functions related to motor and endocrine processes. The D2 receptor is the target of certain antipsychotic drugs. Variants in this gene have been associated with schizophrenia and myoclonic dystonia. Variants of the DRD2 gene have also been associated with addictive behaviors (e.g., smoking, alcoholism).

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

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

Dopamine Transporter

Similar to the SCL6A4 gene, the dopamine transporter gene (DAT1 or SLC6A3) encodes a transporter that mediates the active reuptake of dopamine from the synaptic spaces in the central nervous system. Variants in this gene are associated with Parkinson disease, Tourette syndrome, and addictive behaviors.

Dopamine β*-Hydroxylase*

The dopamine β-hydroxylase (DBG) gene encodes a protein that catalyzes the hydroxylase of dopamine to norepinephrine. It is primarily located in the adrenal medulla and postganglionic sympathetic neurons. Variation in the DBH gene has been investigated as a modulator of psychotic symptoms in psychiatric disorders and tobacco addiction.

Gated Calcium Channel

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

Ankyrin 3

Ankyrins are protein components of the cell membrane and interconnect with the spectrin-based cell membrane skeleton. The ANK3 gene codes for the protein Ankyrin G, which has a role in regulating sodium channels in neurons. Alterations of this gene have been associated with cardiac arrhythmias (e.g., Brugada syndrome).

Variants of this gene have also been associated with bipolar disorder, cyclothymic depression, and schizophrenia.

Catechol O-Methyltransferase

The catechol O-methyltransferase gene (COMT) codes for the COMT enzyme, which is responsible for the metabolism of the catecholamine neurotransmitters, dopamine, epinephrine, and norepinephrine. COMT inhibitors (e.g., entacapone) are currently used to treat Parkinson disease. A variant of the COMT gene, Val158Met, has been associated with alterations in emotional processing and executive function and has also been implicated in increasing susceptibility to schizophrenia.

Methylenetetrahydrofolate Reductase

The methylenetetrahydrofolate reductase gene (MTHFR) is a widely studied gene that codes for the protein that converts folic acid to methylfolate. Methylfolate is a precursor for the synthesis of norepinephrine, dopamine, and serotonin. It is a key step in the metabolism of homocysteine to methionine, and deficiency of MTHFR protein can cause hyperhomocysteinemia and homocystinuria. The MTHFR protein also plays a major role in epigenetics, through methylation of somatic genes. A number of variants have been identified that alter the activity of the MTHFR enzyme. These variants have been associated with a wide variety of clinical disorders, including vascular disease, neural tube defects, dementia, colon cancer, and leukemia.

γ-Aminobutyric Acid A Receptor

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

μ- and κ-Opioid Receptors

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

Cytochrome P450 Genes

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

P-Glycoprotein Gene

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

UDP-Glucuronosyltransferase Gene

The UDP-glucuronosyltransferase gene (UGT1A4) encodes an enzyme of the glucuronidation pathway that trans-

forms small lipophilic molecules into water-soluble molecules. Variants in the UGT1A4 gene have been associated with variation in drug metabolism, including some drugs used for mental health disorders.

Commercially Available Genetic Tests

Several test labs market panels of tests or individual tests relevant for mental health disorders, which may include a variety of genes relevant to psychopharmacology or risk of mental illness. Some of the panels (e.g., the GeneSight panel) provide an overall risk score or summary score.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The tests discussed in this section are available under the auspices of the CIA. Laboratories that offer LDTs must be licensed by the CLIA 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);
- STA2R 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);
- Proove Opioid Risk panel (Proove Biosciences);
- 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.

RELATED PROTOCOL

Cytochrome p450 Genotyping

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Gatt JM, Burton KL, Williams LM, et al. Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. J Psychiatr Res. Jan 2015;60:1-13. PMID 25287955
2. Croarkin PE, Luby JL, Cercy K, et al. Genetic risk score analysis in early-onset bipolar disorder. J Clin Psychiatry. Nov/Dec 2017;78(9):1337-1343. PMID 28199072
3. Kloiber S, Czamara D, Karbalai N, et al. ANK3 and CACNA1C--missing genetic link for bipolar disorder and major depressive disorder in two German case-control samples. J Psychiatr Res. Aug 2012;46(8):973-979. PMID 22647524
4. Jiang H, Qiao F, Li Z, et al. Evaluating the association between CACNA1C rs1006737 and schizophrenia risk: A meta-analysis. Asia Pac Psychiatry. Sep 2015;7(3):260-267. PMID 25588813
5. Zammit S, Spurlock G, Williams H, et al. Genotype effects of CHRNA7, CNR1 and COMT in schizophrenia: interactions with tobacco and cannabis use. Br J Psychiatry. Nov 2007;191:402-407. PMID 17978319
6. Batel P, Houchi H, Daoust M, et al. A haplotype of the DRD1 gene is associated with alcohol dependence. Alcohol Clin Exp Res. Apr 2008;32(4):567-572. PMID 18341651
7. Du Y, Nie Y, Li Y, et al. The association between the SLC6A3 VNTR 9-repeat allele and alcoholism-a meta-analysis. Alcohol Clin Exp Res. Sep 2011;35(9):1625-1634. PMID 21554332
8. Huang W, Ma JZ, Payne TJ, et al. Significant association of DRD1 with nicotine dependence. Hum Genet. Mar 2008;123(2):133-140. PMID 18092181
9. Stapleton JA, Sutherland G, O'Gara C. Association between dopamine transporter genotypes and smoking cessation: a meta-analysis. Addict Biol. Jun 2007;12(2):221-226. PMID 17508996
10. Xu M, Lin Z. Genetic influences of dopamine transport gene on alcohol dependence: a pooled analysis of 13 studies with 2483 cases and 1753 controls. Prog Neuropsychopharmacol Biol Psychiatry. Jul 1 2011;35(5): 1255-1260. PMID 21078357
11. Lopez Leon S, Croes EA, Sayed-Tabatabaei FA, et al. The dopamine D4 receptor gene 48-base-pair-repeat polymorphism and mood disorders: a meta-analysis. Biol Psychiatry. May 1 2005;57(9):999-1003. PMID 15860340
12. Zou YF, Wang F, Feng XL, et al. Association of DRD2 gene polymorphisms with mood disorders: a meta-analysis. J Affect Disord. Feb 2012;136(3):229-237. PMID 21130502
13. Jonsson EG, Sillen A, Vares M, et al. Dopamine D2 receptor gene Ser311Cys variant and schizophrenia: association study and meta-analysis. Am J Med Genet B Neuropsychiatr Genet. May 15 2003;119B(1):28-34. PMID 12707934
14. Liu L, Fan D, Ding N, et al. The relationship between DRD2 gene polymorphisms (C957T and C939T) and schizophrenia: a meta-analysis. Neurosci Lett. Nov 7 2014;583:43-48. PMID 25240594
15. Pan Y, Yao J, Wang B. Association of dopamine D1 receptor gene polymorphism with schizophrenia: a meta-analysis. Neuropsychiatr Dis Treat. Jul 2014;10:1133-1139. PMID 25018632
16. Zhu F, Yan CX, Wang Q, et al. An association study between dopamine D1 receptor gene polymorphisms and the risk of schizophrenia. Brain Res. Oct 28 2011;1420:106-113. PMID 21955727
17. Hu CY, Qian ZZ, Gong FF, et al. Methylenetetrahydrofolate reductase (MTHFR) polymorphism susceptibility to schizophrenia and bipolar disorder: an updated meta-analysis. J Neural Transm. Feb 2015;122(2):307-320. PMID 24938371
18. Bousman CA, Potiriadis M, Everall IP, et al. Methylenetetrahydrofolate reductase (MTHFR) genetic variation and major depressive disorder prognosis: A five-year prospective cohort study of primary care attendees. Am J Med Genet B Neuropsychiatr Genet. Jan 2014;165(1):68-76. PMID 24123968

19. Lizer MH, Bogdan RL, Kidd RS. Comparison of the frequency of the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism in depressed versus nondepressed patients. J Psychiatr Pract. Nov 2011; 17(6):404-409. PMID 22108397
20. Wu YL, Ding XX, Sun YH, et al. Association between MTHFR C677T polymorphism and depression: An updated meta-analysis of 26 studies. Prog Neuropsychopharmacol Biol Psychiatry. Oct 1 2013;46:78-85. PMID 23831680
21. Peerbooms OL, van Os J, Drukker M, et al. Meta-analysis of MTHFR gene variants in schizophrenia, bipolar disorder and unipolar depressive disorder: evidence for a common genetic vulnerability? Brain Behav Immun. Nov 2011;25(8):1530-1543. PMID 21185933
22. Enoch MA, Gorodetsky E, Hodgkinson C, et al. Functional genetic variants that increase synaptic serotonin and 5-HT3 receptor sensitivity predict alcohol and drug dependence. Mol Psychiatry. Nov 2011;16(11):1139-1146. PMID 20838391
23. Hariri AR, Mattay VS, Tessitore A, et al. Serotonin transporter genetic variation and the response of the human amygdala. Science. Jul 19 2002;297(5580):400-403. PMID 12130784
24. Minelli A, Bonvicini C, Scassellati C, et al. The influence of psychiatric screening in healthy populations selection: a new study and meta-analysis of functional 5-HTTLPR and rs25531 polymorphisms and anxiety-related personality traits. BMC Psychiatry. Mar 31 2011;11:50. PMID 21453464
25. Sen S, Burmeister M, Ghosh D. Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. Am J Med Genet B Neuropsychiatr Genet. May 15 2004;127B(1):85-89. PMID 15108187
26. Lasky-Su JA, Faraone SV, Glatt SJ, et al. Meta-analysis of the association between two polymorphisms in the serotonin transporter gene and affective disorders. Am J Med Genet B Neuropsychiatr Genet. Feb 5 2005; 133B(1):110-115. PMID 15578606
27. Karg K, Burmeister M, Shedden K, et al. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Arch Gen Psychiatry. May 2011;68(5): 444-454. PMID 21199959
28. Kiyohara C, Yoshimasu K. Association between major depressive disorder and a functional polymorphism of the 5-hydroxytryptamine (serotonin) transporter gene: a meta-analysis. Psychiatr Genet. Apr 2010;20(2):49-58. PMID 20016401
29. Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA. Jun 17 2009;301(23):2462-2471. PMID 19531786
30. Meltzer HY, Brennan MD, Woodward ND, et al. Association of Sult4A1 SNPs with psychopathology and cognition in patients with schizophrenia or schizoaffective disorder. Schizophr Res. Dec 2008;106(2-3):258-264. PMID
31. Altar CA, Hornberger J, Shewade A, et al. Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy. Int Rev Psychiatry. Oct 2013;25(5):509-533. PMID 24151799
32. Breitenstein B, Bruckl TM, Ising M, et al. ABCB1 gene variants and antidepressant treatment outcome: A meta-analysis. Am J Med Genet B Neuropsychiatr Genet. Jun 2015;168B(4):274-283. PMID 25847751
33. Gex-Fabry M, Eap CB, Oneda B, et al. CYP2D6 and ABCB1 genetic variability: influence on paroxetine plasma level and therapeutic response. Ther Drug Monit. Aug 2008;30(4):474-482. PMID 18641553
34. Yin L, Zhang YY, Zhang X, et al. TPH, SLC6A2, SLC6A3, DRD2 and DRD4 polymorphisms and neuroendocrine factors predict SSRIs treatment outcome in the Chinese population with major depression. Pharmacopsychiatry. May 2015;48(3):95-103. PMID 25642918
35. Hwang R, Shinkai T, De Luca V, et al. Association study of four dopamine D1 receptor gene polymorphisms and clozapine treatment response. J Psychopharmacol. Sep 2007;21(7):718-727. PMID 17092969
36. Kaur G, Gupta D, Chavan BS, et al. Identification of genetic correlates of response to Risperidone: Findings of a multicentric schizophrenia study from India. Asian J Psychiatr. Oct 2017;29:174-182. PMID 28692863

37. Zhang JP, Lencz T, Malhotra AK. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. Am J Psychiatry. Jul 2010;167(7):763-772. PMID 20194480
38. Fijal BA, Guo Y, Li SG, et al. CYP2D6 predicted metabolizer status and safety in adult patients with attention-deficit hyperactivity disorder participating in a large placebo-controlled atomoxetine maintenance of response clinical trial. J Clin Pharmacol. Oct 2015;55(10):1167-1174. PMID 25919121
39. Ramoz N, Boni C, Downing AM, et al. A haplotype of the norepinephrine transporter (Net) gene Slc6a2 is associated with clinical response to atomoxetine in attention-deficit hyperactivity disorder (ADHD). Neuropsychopharmacology. Aug 2009;34(9):2135-2142. PMID 19387424
40. Lloret-Linares C, Bosilkovska M, Daali Y, et al. Phenotypic Assessment of Drug Metabolic Pathways and PGlycoprotein in Patients Treated With Antidepressants in an Ambulatory Setting. J Clin Psychiatry. Mar/Apr 2018;79(2). PMID 29570971
41. Lobello KW, Preskorn SH, Guico-Pabia CJ, et al. Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. J Clin Psychiatry. Nov 2010;71(11):1482-1487. PMID 20441720
42. Serretti A, Calati R, Massat I, et al. Cytochrome P450 CYP1A2, CYP2C9, CYP2C19 and CYP2D6 genes are not associated with response and remission in a sample of depressive patients. Int Clin Psychopharmacol. Sep 2009;24(5):250-256. PMID 19593158
43. Taranu A, Colle R, Gressier F, et al. Should a routine genotyping of CYP2D6 and CYP2C19 genetic polymorphisms be recommended to predict venlafaxine efficacy in depressed patients treated in psychiatric settings? Pharmacogenomics. May 2017;18(7):639-650. PMID 28480819
44. Almoguera B, Riveiro-Alvarez R, Lopez-Castroman J, et al. CYP2D6 poor metabolizer status might be associated with better response to risperidone treatment. Pharmacogenet Genomics. Nov 2013;23(11):627-630. PMID 24026091
45. Crescenti A, Mas S, Gasso P, et al. Cyp2d6*3, *4, *5 and *6 polymorphisms and antipsychotic-induced extrapyramidal side-effects in patients receiving antipsychotic therapy. Clin Exp Pharmacol Physiol. Jul 2008; 35(7):807-811. PMID 18346175
46. Panagiotidis G, Arthur HW, Lindh JD, et al. Depot haloperidol treatment in outpatients with schizophrenia on monotherapy: impact of CYP2D6 polymorphism on pharmacokinetics and treatment outcome. Ther Drug Monit. Aug 2007;29(4):417-422. PMID 17667795
47. Chamorro AJ, Marcos M, Miron-Canelo JA, et al. Association of micro-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis. Addict Biol. May 2012;17(3):505-512. PMID 22515274
48. Johnson BA, Ait-Daoud N, Seneviratne C, et al. Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking. Am J Psychiatry. Mar 2011;168(3):265-275. PMID 21247998
49. Lenze EJ, Goate AM, Nowotny P, et al. Relation of serotonin transporter genetic variation to efficacy of escitalopram for generalized anxiety disorder in older adults. J Clin Psychopharmacol. Dec 2010;30(6):672-677. PMID 21105279
50. Biernacka JM, McElroy SL, Crow S, et al. Pharmacogenomics of antidepressant induced mania: a review and meta-analysis of the serotonin transporter gene (5HTTLPR) association. J Affect Disord. Jan 2012;136(1-2):e21-29. PMID 21680025
51. Daray FM, Thommi SB, Ghaemi SN. The pharmacogenetics of antidepressant-induced mania: a systematic review and meta-analysis. Bipolar Disord. Nov 2010;12(7):702-706. PMID 21040287
52. Lewis G, Mulligan J, Wiles N, et al. Polymorphism of the 5-HT transporter and response to antidepressants: randomised controlled trial. Br J Psychiatry. Jun 2011;198(6):464-471. PMID 21263010
53. Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. Eur Neuropsychopharmacol. Apr 2012;22(4):239-258. PMID 22137564

54. Seripa D, Pilotto A, Paroni G, et al. Role of the serotonin transporter gene locus in the response to SSRI treatment of major depressive disorder in late life. J Psychopharmacol. May 2015;29(5):623-633. PMID 25827644
55. Rosenblat JD, Lee Y, McIntyre RS. Does pharmacogenomic testing improve clinical outcomes for major depressive disorder? A systematic review of clinical trials and cost-effectiveness studies. J Clin Psychiatry. Jun 2017;78(6):720-729. PMID 28068459
56. Health Quality Ontario (HQO). Pharmacogenomic testing for psychotropic medication selection: a systematic review of the Assurex GeneSight Psychotropic Test. Ont Health Technol Assess Ser. Apr 2017;17(4):1-39. PMID 28515818
57. Bradley P, Shiekh M, Mehra V, et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility. J Psychiatr Res. Jan 2018;96:100-107. PMID 28992526
58. Olson MC, Maciel A, Gariepy JF, et al. Clinical impact of pharmacogenetic-guided treatment for patients exhibiting neuropsychiatric disorders: a randomized controlled trial. Prim Care Companion CNS Disord. Mar 16 2017;19(2). PMID 28314093
59. Perez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. BMC Psychiatry. Jul 14 2017; 17(1):250. PMID 28705252
60. Winner JG, Carhart JM, Altar CA, et al. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med. Nov 2013; 16(89):219-227. PMID 24229738
61. Hall-Flavin DK, Winner JG, Allen JD, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenet Genomics. Oct 2013; 23(10):535-548. PMID 24018772
62. Hall-Flavin DK, Winner JG, Allen JD, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. 2012;2:e172. PMID 23047243
63. Altar CA, Carhart JM, Allen JD, et al. Clinical validity: Combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes. Pharmacogenomics J. Oct 2015;15(5):443-451. PMID 25686762
64. Altar CA, Carhart J, Allen JD, et al. Clinical utility of combinatorial pharmacogenomics-guided antidepressant therapy: evidence from three clinical studies. Mol Neuropsychiatry. Oct 2015;1(3):145-155. PMID 27606312
65. Breitenstein B, Scheuer S, Pfister H, et al. The clinical application of ABCB1 genotyping in antidepressant treatment: a pilot study. CNS Spectr. Apr 2014;19(2):165-175. PMID 23880209
66. Brennan FX, Gardner KR, Lombard J, et al. A naturalistic study of the effectiveness of pharmacogenetic testing to guide treatment in psychiatric patients with mood and anxiety disorders. Prim Care Companion CNS Disord. Oct 2015;17(2). PMID 26445691
67. Espadaler J, Tuson M, Lopez-Ibor JM, et al. Pharmacogenetic testing for the guidance of psychiatric treatment: a multicenter retrospective analysis. CNS Spectr. Apr 21 2016:1-10. PMID 27098095
68. Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. Feb 2014;15(2):209-217. PMID 24479687
69. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. Aug 2015;98(2):127-134. PMID 25974703
70. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. Dec 20 2016;102(1):37-44. PMID 27997040

71. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Genet Med. Dec 2007;9(12):819-825. PMID 18091431
72. CGS Administrators, LLC, (Jurisdiction 15-Kentuckey, Ohio) Local Coverage Determination (LCD): MolDX: GENESIGHT® Assay for Refractory Depression (L35443), Revision Effective Date for services performed on or after 03/08/2018.