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Medical Benefit		Effective Date: 04/01/16	Next Review Date: 01/21
Preauthorization	Yes	Review Dates: 07/14, 01/15, 01/16, 01/17, 01/18, 01/19, 01/20	

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: <ul style="list-style-type: none"> Who are evaluated for diagnosis or risk of a mental illness 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing for risk of a mental illness 	Comparators of interest are: <ul style="list-style-type: none"> Standard care 	Relevant outcomes include: <ul style="list-style-type: none"> Test validity Other test performance measures Change in disease status
Individuals: <ul style="list-style-type: none"> With depression inadequately controlled with drug treatment 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care drug treatment 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Morbid events Functional outcomes Health status measures Quality of life Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With a mental health condition other than depression who are undergoing drug treatment 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care drug treatment 	Relevant outcomes include: <ul style="list-style-type: none"> 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 the 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 specific disorder. No studies were identified that evaluated whether testing for variants changed clinical management or affected health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with depression who are inadequately controlled with drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a large number of observational studies evaluating associations between specific genes and outcomes of drug treatment, as well as six randomized controlled trials 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. The largest randomized trial did not find significant differences in the primary outcome of change in Hamilton Depression score among patients managed by results from a pharmacogenomic test compared with patients managed by the standard of care. The remaining trials reported inconsistent results, with some reporting significant improvements in Hamilton Depression and other depression measures, and other trials finding no difference among patients managed with pharmacogenomic tests vs. standard of care. 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.

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 studies evaluating associations between specific genes and outcomes of drug treatment, as well as a systematic review and observational studies. 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 of observational studies included patients with schizophrenia and reported associations between gene variants and treatment response; however, many of the studies were retrospective and had small sample sizes. No randomized controlled trials comparing health outcomes among patients undergoing guided and unguided management were identified. 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, STA²R 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.

Drug Efficacy and Toxicity

Drug efficacy and toxicity vary substantially across individuals. Because drugs and doses are typically adjusted, if needed, by trial-and-error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Multiple factors may influence the variability of drug effects, including 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 adenylyl 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 (DBH) gene encodes a protein that catalyzes the hydroxylation 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 the 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 increased 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 (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 affects 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 transforms 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.

Bousman et al (2018) addressed the issue of which genes and variants should be included on pharmacogenetic testing panels to best inform decisions on medication selection and dosing for patients with mental health conditions.¹ The authors created a network map of gene-drug interactions relevant to psychiatry based on the highest level of evidence from the following seven sources: the Pharmacogenomics Knowledgebase, the Clinical Pharmacogenetics Implementation Consortium, the Dutch Pharmacogenetics Working Group, the Food and Drug Administration, the European Medicines Agency, the Pharmaceuticals and Medical Devices Agency, and the Health Canada (Sante Canada). Based on the network map, the authors proposed a minimum gene and variant set for pharmacogenetic testing in psychiatry that includes 16 variants within five genes (CYP2C9, CYP2C19, CYP2D6, HLA-A, and HLA-B).

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);

- 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);
- 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 Genotype-Guided Treatment Strategy

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services 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. Bousman, CC, Maruf, AA, Müller, DD. Towards the integration of pharmacogenetics in psychiatry: a minimum, evidence-based genetic testing panel. *Curr Opin Psychiatry*, 2018 Oct 10;32(1). PMID 30299306.
2. 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.
3. 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.
4. 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.
5. 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.
6. Rosenblat, JJ, Lee, YY, McIntyre, RR. The effect of pharmacogenomic testing on response and remission rates in the acute treatment of major depressive disorder: A meta-analysis. *J Affect Disord*, 2018 Aug 28;241:484-491. PMID 30149336.

7. Solomon, HH, Cates, KK, Li, KK. Does obtaining CYP2D6 and CYP2C19 pharmacogenetic testing predict antidepressant response or adverse drug reactions?. *Psychiatry Res*, 2018 Dec 17;271:604-613. PMID 30554109.
8. Greden, JJ, Parikh, SS, Rothschild, AA, Thase, MM, Dunlop, BB, DeBattista, CC, Conway, CC, Forester, BB, Mondimore, FF, Shelton, RR, Macaluso, MM, Li, JJ, Brown, KK, Gilbert, AA, Burns, LL, Jablonski, MM, Dechairo, BB. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. *J Psychiatr Res*, 2019 Jan 25;111:59-67. PMID 30677646.
9. Han, CC, Wang, SS, Bahk, WW, Lee, SS, Patkar, AA, Masand, PP, Mandelli, LL, Pae, CC, Serretti, AA. A Pharmacogenomic-based Antidepressant Treatment for Patients with Major Depressive Disorder: Results from an 8-week, Randomized, Single-blinded Clinical Trial. *Clin Psychopharmacol Neurosci*, 2018 Nov 24;16(4). PMID 30466219.
10. 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.
11. Olson MC, Maciel A, Garipey 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.
12. 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.
13. Menchón, JJ, Espadaler, JJ, Tuson, MM, Saiz-Ruiz, JJ, Bobes, JJ, Vieta, EE, Pérez, VV. Patient characteristics driving clinical utility in psychiatric pharmacogenetics: a reanalysis from the AB-GEN multicentric trial. *J Neural Transm (Vienna)*, 2018 May 8;126(1). PMID 29728861.
14. 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.
15. 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.
16. 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.
17. Perlis, RR, Mehta, RR, Edwards, AA, Tiwari, AA, Imbens, GG. Pharmacogenetic testing among patients with mood and anxiety disorders is associated with decreased utilization and cost: A propensity-score matched study. *Depress Anxiety*, 2018 May 8;35(10). PMID 29734486.
18. 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.
19. 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.
20. Tonozzi, TT, Braunstein, GG, Kammesheidt, AA, Curran, CC, Golshan, SS, Kelsoe, JJ. Pharmacogenetic profile and major depressive and/or bipolar disorder treatment: a retrospective, cross-sectional study. *Pharmacogenomics*, 2018 Sep 13;19(15). PMID 30207201.
21. Tanner, JJ, Davies, PP, Voudouris, NN, Shahmirian, AA, Herbert, DD, Braganza, NN, Gugila, AA, Dechairo, BB, Kennedy, JJ. Combinatorial pharmacogenomics and improved patient outcomes in depression: Treatment by primary care physicians or psychiatrists. *J Psychiatr Res*, 2018 Aug 7;104:157-162. PMID 30081389.
22. Routhieaux, MM, Keels, JJ, Tillery, EE. The use of pharmacogenetic testing in patients with schizophrenia or bipolar disorder: A systematic review. *Ment Health Clin*, 2018 Nov 7;8(6). PMID 30397571.

23. Brandl, EE, Tiwari, AA, Zhou, XX, Deluce, JJ, Kennedy, JJ, Müller, DD, Richter, MM. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. *Pharmacogenomics J.*, 2013 Apr 3;14(2). PMID 23545896.
24. He, QQ, Yuan, ZZ, Liu, YY, Zhang, JJ, Yan, HH, Shen, LL, Luo, XX, Zhang, YY. Correlation between cytochrome P450 2C19 genetic polymorphism and treatment response to escitalopram in panic disorder. *Pharmacogenet. Genomics*, 2017 Jun 15;27(8). PMID 28614176.
25. Conley, VV, Daack-Hirsch, SS, Halbmaier, KK, Shaw, LL. Bringing Personalized Medicine to a PACT Program: A Quality Improvement Project. *J Am Psychiatr Nurses Assoc*, 2019 Jan 29;1078390319826687:1078390319826687. PMID 30688546.
26. 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.
27. 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.
28. 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.
29. 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.
30. Nurnberger, JJ, Austin, JJ, Berrettini, WW, Besterman, AA, DeLisi, LL, Grice, DD, Kennedy, JJ, Moreno-DeLuca, DD, Potash, JJ, Ross, DD, Schulze, TT, Zai, GG. What Should a Psychiatrist Know About Genetics? Review and Recommendations From the Residency Education Committee of the International Society of Psychiatric Genetics. *J Clin Psychiatry*, 2018 Dec 15;80(1). PMID 30549495.