

## Medical Coverage Policy | Genetic Testing for Diagnosis and Management of Mental Health Conditions



**EFFECTIVE DATE:** 10/01/2023

**POLICY LAST UPDATED:** 09/29/2023

### OVERVIEW

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.

The following tests are addressed in this policy:

- Genecept Assay (Genomind)
- GeneSight Psychotropic panel (Myriad Neuroscience)
- IDgenetix® (Castle Biosciences, Inc.) CPT code 0411U
- Mental Health DNA Insight panel (Pathway Genomics)
- Neuropharmagen (AB-Biotics)
- Proove Opioid Risk Assay (Proove Biosciences)
- Psychotropic Pharmacogenomics Gene Panel (Mayo Clinic)
- STA<sup>2</sup>R - SureGene Test for Antipsychotic and Antidepressant Response (SureGene)

### MEDICAL CRITERIA

#### Medicare Advantage Plans

**GeneSight® Psychotropic Panel - CPT code 0345U** (Code Effective 10/01/2022. For Dates of Service prior to 10/1/2022, CPT Code 81479 must be used)

The GeneSight® Psychotropic Panel may be considered medically necessary when ALL six (6) of the following criteria are met:

1. Individual has at least ONE of the following conditions:
  - A. Major Depressive Disorder (MDD); or,
  - B. Schizophrenia; or,
  - C. Schizophreniform disorder; or,
  - D. Bipolar disorder; or,
  - E. Social phobia, generalized; or,
  - F. Panic disorder [episodic paroxysmal anxiety]; or,
  - G. Anxiety disorders; or,
  - H. Post-traumatic stress disorder; or,
  - I. Obsessive-compulsive personality disorder; or,
  - J. Attention-deficit hyperactivity disorder; and,
2. Medication therapy is being considered or is already being administered; and,
3. Non-genetic factors are used to make preliminary drug selection; and,
4. Documentation that the test is required to define safe use of drug in the individual; and,
5. Must meet criteria A or B, below:
  - A. Initial Testing: Must meet ALL FIVE of the following criteria:

- 1) When medication therapy is being considered (has not already been administered), documentation must include that testing is required to define safe use of drug in the individual; and,
- 2) Medication is medically necessary, appropriate and approved for use with specific patient diagnosis; and,
- 3) Medication is known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable; and,
- 4) Selection of medication must be derived from clinical factors/necessity rather than from testing; and,
- 5) Test results are necessary for safe administration or dosing of medication; and,
- B. Additional Testing: Documented medical necessity for additional testing; and,
6. Must meet criteria A or B, below:
  - A. More than one gene is reasonable and necessary for the safe use of the drug being considered or in use; or,
  - B. More than one drug is in consideration or use that is associated with a gene-drug interaction

### **Psychotropic Pharmacogenomics Gene Panel – CPT Code 81479**

The Psychotropic Pharmacogenomics Gene Panel may be considered medically necessary when ALL six (6) of the following criteria are met:

1. Individual has at least ONE of the following conditions:
  - A. Schizophrenia; or,
  - B. Schizophreniform disorder; or,
  - C. Bipolar disorder; or,
  - D. Social phobia, generalized; or,
  - E. Panic disorder [episodic paroxysmal anxiety]; or,
  - F. Anxiety disorders; or,
  - G. Post-traumatic stress disorder; or,
  - H. Obsessive-compulsive personality disorder; or,
  - I. Attention-deficit hyperactivity disorder; and,
2. Medication therapy is being considered or is already being administered; and,
3. Non-genetic factors are used to make preliminary drug selection; and,
4. Documentation that the test is required to define safe use of drug in the individual; and,
5. Must meet criteria A or B, below:
  - A. Initial Testing: Must meet ALL FIVE of the following criteria:
    - 1) When medication therapy is being considered (has not already been administered), documentation must include that testing is required to define safe use of drug in the individual; and,
    - 2) Medication is medically necessary, appropriate and approved for use with specific patient diagnosis; and,
    - 3) Medication is known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable; and,
    - 4) Selection of medication must be derived from clinical factors/necessity rather than from testing; and,
    - 5) Test results are necessary for safe administration or dosing of medication; and,
  - B. Additional Testing: Documented medical necessity for additional testing; and,
6. Must meet criteria A or B, below:
  - A. More than one gene is reasonable and necessary for the safe use of the drug being considered or in use; or,
  - B. More than one drug is in consideration or use that is associated with a gene-drug interaction

## Commercial Products

Not applicable

## PRIOR AUTHORIZATION

### Medicare Advantage Plans

Prior authorization is required for the GeneSight® Psychotropic Panel (CPT code 0345U). Prior authorization is also required when there is no specific CPT code for the services in this policy and an Unlisted CPT code should be used (See Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Prior authorization is obtained via the online tool for participating providers. See the Related Policies section.

### Commercial Products

Prior authorization is required when there is no specific CPT code for the services in this policy and an Unlisted CPT code should be used (See Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Prior authorization is obtained via the online tool for participating providers. See the Related Policies section.

**Note:** Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

## POLICY STATEMENT

### Medicare Advantage Plans and Commercial Products

The following test(s) are covered:

- IDgenetix® - CPT code 0411U (New Code Effective 10/01/2023. For Dates of Service prior to 10/01/2023, CPT code 81479 must be used)

### Medicare Advantage Plans

GeneSight® Psychotropic panel and Psychotropic Pharmacogenomics gene panel will be considered medically necessary when the medical criteria listed above are met.

The following tests are not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- Genecept Assay (Genomind)
- Mental Health DNA Insight Panel (Pathway Genomics)
- Neuropharmagen (AB-Biotics)
- Proove Opioid Risk Assay (Proove Biosciences)
- STA<sup>2</sup>R - SureGene Test for Antipsychotic and Antidepressant Response (SureGene)

## Commercial Products

The following tests are not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- Genecept Assay (Genomind)
- GeneSight Psychotropic panel (Assurex Health)
- Mental Health DNA Insight Panel (Pathway Genomics)
- Neuropharmagen (AB-Biotics)
- Proove Opioid Risk Assay (Proove Biosciences)
- STA<sup>2</sup>R - SureGene Test for Antipsychotic and Antidepressant Response (SureGene)

## COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for laboratory tests or not medically necessary/not covered benefits/coverage.

## BACKGROUND

This policy assesses whether genetic testing for the diagnosis and 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 patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes compared to managing the condition with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug.

Therefore, assessment of clinical utility of a pharmacogenetic test cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the use of the pharmacogenomic test to make management decisions alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype. 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, the preferred evidence is from randomized controlled trials.

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 CLIA. Laboratories that offer LDTs must be licensed by 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<sup>TM</sup> Assay (Genomind)
- GeneSight<sup>®</sup> Psychotropic panel (Assurex Health)
- IDgenetix<sup>®</sup> (Castle Biosciences, Inc.)
- Mental Health DNA Insight<sup>TM</sup> panel (Pathway Genomics)
- Neuropharmagen (AB-Biotics)
- Proove Opioid Risk Assay (Proove Biosciences)
- Psychotropic Pharmacogenomics gene panel (Mayo Clinic)

- STA2R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical Reference Laboratory)

### Commercial Plans

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 patients 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 that the technology results in an improvement in the net health outcome.

For adult patients with major depressive disorder (MDD) who receive GeneSight testing guided drug treatment, the evidence includes 3 randomized controlled trials (RCTs). Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The RCTs compared response ( $\geq 50\%$  decrease in Hamilton Depression Rating Scale 17 item (HAM-D17)) and remission ( $\text{HAM-D17} \leq 7$ ), and symptom improvement (Mean % change in HAM-D17) with antidepressant therapy informed by GeneSight test results to antidepressant therapy selected without GeneSight test results (standard of Care (SOC)). The Genomics Used to Improve Depression Decisions (GUIDED) trial reported statistically significant improvement in response (26% of 560 vs. 20% of 607,  $p=.01$ ) and remission (15% of 560 vs. 10% of 607,  $p=.007$ ) in the GeneSight arm compared to SOC at 8 weeks among patients with MDD. However, depending on the population (intention to treat [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 Genomic Applications Partnership Program - Major Depressive Disorder (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 patients with MDD who receive Neuropharmagen testing guided drug treatment, the evidence includes 2 RCTs. 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 ( $\geq 50\%$  decrease in HAM-D17) and remission ( $\text{HAM-D17} \leq 7$ ) with antidepressant therapy informed by Neuropharmagen test results to antidepressant therapy selected without Neuropharmagen test results (i.e. SOC). The single-blinded RCT by Han et al (2018) reported statistically significant improvement in response (72% of 52 vs. 44% of 48;  $p=.01$ ) but no statistically significant improvement in remission (46% of 52 vs. 26% of 48;  $p=.07$ ) in the Neuropharmagen arm compared to SOC at 8 weeks among patients 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 the ITT analysis of effectiveness. Use of LOCF assumes data are missing completely at random, 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 non-statistically significant improvement in response (45% of 141 vs. 40% of 139;  $p=.39$ ) and remission (34% of 141 vs. 33% of 139;  $p=.87$ ) in the Neuropharmagen arm compared to SOC at 12 weeks among patients with MDD. Response and remission data were missing for 9% of patients in the guided care group and 14% in the SOC 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 that the technology results in an improvement in the net health outcome.

### **IDgenetix®**

IDgenetix® is a pharmacogenomic tests that analyze clinically important genetic variations in DNA. The results can inform physicians about genes that may impact how a particular patient metabolizes or responds to certain medications.

### **Medicare Advantage Plans**

GeneSight® Psychotropic panel and Psychotropic Pharmacogenomics Gene Panel are pharmacogenomic tests that analyze clinically important genetic variations in DNA. The results can inform physicians about genes that may impact how a particular patient metabolizes or responds to certain medications. GeneSight® Psychotropic panel and Psychotropic Pharmacogenomics Gene Panel may be considered medically necessary when medical criteria are met in testing for drug selection in the treatment of mental health conditions.

### **Documentation Requirements**

The medical record must clearly reflect the following:

- The patient has a diagnosis for which pharmacologic therapy is reasonable and necessary, and the drug or drugs that the clinician is considering using must be reasonable and necessary for the treatment of the patient's diagnosis.
- The clinician has made an initial personalized decision for the patient based on the patient's diagnosis, the patient's other medical conditions, other medications the patient is taking, professional judgement, clinical science and basic science pertinent to the drug (e.g. mechanism of action, side effects), the patient's past medical history and when pertinent family history and the patient's preferences and values.
- The provider performing the service must have a record of what drug(s) is/are being considered and for what indication(s).

### **CODING**

The following CPT code is covered for Medicare Advantage Plans and Commercial Products:

IDgenetix®

**0411U** Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 (New Code Effective 10/01/2023; for Dates of Service prior to 10/01/2023, CPT code 81479 (Unlisted molecular pathology procedure) should be filed)

The following CPT code is covered for Medicare Advantage Plans when criteria is met and not medically necessary for Commercial Products:

GeneSight® Psychotropic Panel

**0345U** Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 (Code: Effective 10/01/2022. For Dates of Service prior to 10/1/2022, Unlisted CPT code 81479 must be used.)

While there may be specific CPT codes for some of the components of the GeneSight® Psychotropic panel testing, claims for the entire panel must be filed with CPT code 0345U or 81479 according to the Dates of Service outlined above.

### **Medicare Advantage Plans and Commercial Products**

\*For all other testing referenced in this policy:

There is not a specific CPT code, therefore, claims should be filed with Unlisted CPT code **81479**.

## 81479 Unlisted molecular pathology procedure

While there may be specific CPT codes for some of the components of the panel testing in this policy, claims for the entire panel must be filed with the Unlisted CPT code noted above.

### RELATED POLICIES

Genetic Testing Services

Proprietary Laboratory Analyses (PLA)

### PUBLISHED

Provider Update, January 2023, September 2023

Provider Update, February 2022

Provider Update, March 2021

Provider Update, February 2020

Provider Update, January 2019

### REFERENCES

1. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Pharmacogenomics Testing, CGS Administrators, LLC (L38394)
2. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Pharmacogenomics Testing, CGS Administrators, LLC (A58324)
3. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Pharmacogenomics Testing, Noridian Healthcare Solutions, LLC (L38335)
4. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Pharmacogenomics Testing, Noridian Healthcare Solutions, LLC (A57384)
5. Koyama E, Zai CC, Bryushkova L, et al. Predicting risk of suicidal ideation in youth using a multigene panel for impulsive aggression. *Psychiatry Res.* Mar 2020;285: 112726. PMID 31870620
6. Ghafouri-Fard S, Taheri M, Omrani MD, et al. Application of Single-Nucleotide Polymorphisms in the Diagnosis of Autism Spectrum Disorders: A Preliminary Study with Artificial Neural Networks. *J Mol Neurosci.* Aug 2019; 68(4): 515-521. PMID 30937628
7. Ran L, Ai M, Wang W, et al. Rare variants in SLC6A4 cause susceptibility to major depressive disorder with suicidal ideation in Han Chinese adolescents and young adults. *Gene.* Feb 05 2020; 726: 144147. PMID 31629822
8. Wan L, Zhang G, Liu M, et al. Sex-specific effects of methylenetetrahydrofolate reductase polymorphisms on schizophrenia with methylation changes. *Compr Psychiatry.* Oct 2019; 94: 152121. PMID 31476590
9. Zhu D, Yin J, Liang C, et al. CACNA1C (rs1006737) may be a susceptibility gene for schizophrenia: An updated meta-analysis. *Brain Behav.* Jun 2019; 9(6):e01292. PMID 31033230
10. Schroter K, Brum M, Brunkhorst-Kanaan N, et al. Longitudinal multi-level biomarker analysis of BDNF in major depression and bipolar disorder. *Eur Arch Psychiatry Clin Neurosci.* Mar 2020; 270(2): 169-181. PMID 30929061
11. Chen X, Wang M, Zhang Q, et al. Stress response genes associated with attention deficit hyperactivity disorder: A case-control study in Chinese children. *BehavBrain Res.* May 02 2019; 363: 126-134. PMID 30707907
12. Zhang L, Hu XZ, Benedek DM, et al. Genetic predictor of current suicidal ideation in US service members deployed to Iraq and Afghanistan. *J Psychiatr Res.* Jun2019; 113: 65-71. PMID 30904785
13. Gaynes BN, Warden D, Trivedi MH, et al. What did STAR\*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv.* Nov 2009; 60(11): 1439-45. PMID 19880458
14. Bonin L. Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis. 2021; [https://www.uptodate.com/contents/pediatric-unipolar-depression-epidemiology-clinical-features-assessment-and-diagnosis?topicRef=1231&source=related\\_link](https://www.uptodate.com/contents/pediatric-unipolar-depression-epidemiology-clinical-features-assessment-and-diagnosis?topicRef=1231&source=related_link). Accessed June 4, 2022.
15. Source Bloomberg news, August 14 2019.

16. Rohan KJ, Rough JN, Evans M, et al. A protocol for the Hamilton Rating Scale for Depression: Item scoring rules, Rater training, and outcome accuracy with data on its application in a clinical trial. *J Affect Disord.* Aug 2016; 200: 111-8. PMID 27130960
17. CADTH Common Drug Reviews. Aripiprazole (Abilify): Depression, Major Depressive Disorder (MDD). Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, Copyright (c) CADTH 2016.; 2016.
18. Spielmans GI, McFall JP. A comparative meta-analysis of Clinical Global Impressions change in antidepressant trials. *J Nerv Ment Dis.* Nov 2006; 194(11): 845-52. PMID 17102709
19. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol.* Jun 1996; 11 Suppl 3: 89-95. PMID 8923116
20. Leon AC, Olfson M, Portera L, et al. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatry Med.* 1997; 27(2): 93-105. PMID 9565717
21. Brown L, Vranjkovic O, Li J, et al. The clinical utility of combinatorial pharmacogenomic testing for patients with depression: a meta-analysis. *Pharmacogenomics.* Jun 2020; 21(8): 559-569. PMID 32301649
22. Jokic M, Vandersluis S, Higgins C, et al. Multi-gene Pharmacogenomic Testing That Includes Decision-Support Tools to Guide Medication Selection for Major Depression: A Health Technology Assessment. *Ont Health Technol Assess Ser.* 2021; 21(13): 1-214. PMID 34484487
23. Tiwari AK, Zai CC, Altar CA, et al. Clinical utility of combinatorial pharmacogenomic testing in depression: A Canadian patient- and rater-blinded, randomized, controlled trial. *Transl Psychiatry.* Mar 14 2022; 12(1): 101. PMID 35288545
24. Greden JF, Parikh SV, Rothschild AJ, et al. 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.* Apr 2019; 111: 59-67. PMID 30677646
25. 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): 219-27. PMID 24229738
26. International Conference on Harmonization. Statistical principles for clinical trials: E9. 1998. <https://www.fda.gov/media/71336/download>. Accessed June 8, 2022.
27. Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *Int J Epidemiol.* Oct 1992; 21(5): 837-41. PMID 1468842
28. 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
29. 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
30. Vilches S, Tuson M, Vieta E, et al. Effectiveness of a Pharmacogenetic Tool at Improving Treatment Efficacy in Major Depressive Disorder: A Meta-Analysis of Three Clinical Studies. *Pharmaceutics.* Sep 02 2019; 11(9). PMID 31480800
31. Han C, Wang SM, Bahk WM, et al. A Pharmacogenomic-based Antidepressant Treatment for Patients with Major Depressive Disorder: Results from an 8-week, Randomized, Single-blinded Clinical Trial. *Clin Psychopharmacol Neurosci.* Nov 30 2018; 16(4): 469-480. PMID 30466219
32. 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
33. Espadaler J, Tuson M, Lopez-Ibor JM, et al. Pharmacogenetic testing for the guidance of psychiatric treatment: a multicenter retrospective analysis. *CNS Spectr.* Aug 2017; 22(4): 315-324. PMID 27098095
34. Lachin JM. Fallacies of last observation carried forward analyses. *Clin Trials.* Apr 2016; 13(2): 161-8. PMID 26400875
35. Hartwell EE, Feinn R, Morris PE, et al. Systematic review and meta-analysis of the moderating effect of rs1799971 in OPRM1, the mu-opioid receptor gene, on response to naltrexone treatment of alcohol use disorder. *Addiction.* Aug 2020; 115(8): 1426-1437. PMID 31961981



36. Kampangkaew JP, Spellicy CJ, Nielsen EM, et al. Pharmacogenetic role of dopamine transporter (SLC6A3) variation on response to disulfiram treatment for cocaine addiction. *Am J Addict.* Jul 2019; 28(4): 311-317. PMID 31087723
37. Naumova D, Grizenko N, Sengupta SM, et al. DRD4 exon 3 genotype and ADHD: Randomised pharmacodynamic investigation of treatment response to methylphenidate. *World J Biol Psychiatry.* Jul 2019; 20(6): 486-495. PMID 29182037
38. Jukic MM, Smith RL, Haslemo T, et al. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. *Lancet Psychiatry.* May 2019; 6(5): 418-426. PMID 31000417
39. 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): 209-17. PMID 24479687
40. 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): 127-34. PMID 25974703
41. 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.* Jul 2017; 102(1): 37-44. PMID 27997040
42. International Society of Psychiatric Genetics. Genetic Testing and Psychiatric Disorders: A Statement from the International Society of Psychiatric Genetics. Accessed June 3, 2022.
43. Bousman CA, Bengesser SA, Aitchison KJ, et al. Review and Consensus on Pharmacogenomic Testing in Psychiatry. *Pharmacopsychiatry.* Jan 2021; 54(1): 5-17. PMID 33147643

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