Pharmacogenomic Testing Panels for Major Depressive Disorder

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is major depressive disorder

Definition

Major depressive disorder (MDD) is a serious mental illness and one of the most
common mental disorders in the United States, carrying the heaviest burden of
disability among all mental and behavioral disorders. In 2016, roughly 16 million adults
in the United States experienced at least one major depression episode in the previous
year; this number represented 6.7% of all adults in the United States. A major
depressive episode can include a number of symptoms, including depressed mood,
insomnia or hypersomnia, change in appetite or weight, low energy, poor
concentration, and recurrent thoughts of death or suicide, among other symptoms.

• Although mental health disorders are common in the United States, the burden of
illness is concentrated among individuals with serious mental illness. In 2016, there
were approximately 10.4 million adults in the United States with serious mental
illness, representing 4% of all Americans. Serious mental illness (SMI) is defined as
a mental, behavioral, or emotional disorder resulting in serious functional
impairment, which substantially interferes with or limits one or more major life
activities. Serious mental illness can affect activities of daily living and may be
accompanied by fatigue, insomnia, sudden weight loss, depressed mood, among
other symptoms.

• Individuals with MDD experience high levels of recurrence; after recovery from one
episode, the estimated risk of recurrence over a two year period is 40%. With each
successive recurrence, the risk of a subsequent recurrence increases by 16%.

• Treatment for MDD generally consists of a combination of psychotherapy (ie,
cognitive behavioral therapy [CBT]) and pharmacotherapy (ie, antidepressants).
The goal of treatment for MDD is primarily enabling remission of symptoms and
restoring functioning.

• To find the optimal treatment approach, many clinicians try different antidepressants
to maximize treatment response and reduce risk of remission. However, this “trial
and error” approach is not always effective since the rates of remission are
relatively low and vary considerably across individuals. Consequences of treatment
failure include the continuation of disabling symptoms that adversely affect work
productivity, social functioning, and increase the risk of suicide.

• It is estimated that common genetic variants account for approximately 42.0% of
individual differences in antidepressant response. The phenotype of antidepressant
response is likely to be polygenic and involve a large number of SNPs with small
effect sizes.

• Pharmacogenomic testing has been developed to assist clinicians to predict those
medications that could yield the most optimal treatment response and/or predict the
lowest risk of side effects for an individual with mental health disorders, including
MDD.

• Although this guideline will focus on the use of the GeneSight Psychotropic for
management of major depressive disorder, it will apply broadly to
pharmacogenomic testing for mental and behavioral health disorders. The focus of
the guideline is guided by the preponderance of evidence (consisting of randomized
or nonrandomized studies with control groups) in the peer-review literature
available for the GeneSight test for the MDD disease indication.
Test information

- Researchers in the field of psychiatric pharmacogenomics have identified single nucleotide polymorphisms (SNPs) within genes that affect an individual's metabolism and response to anti-depressant medications.

- These SNPs have been combined into a medication decision support tool, GeneSight Psychotropic. Based on the composite phenotype measured for each patient, the GeneSight test has been proposed to assist clinicians in selecting psychotropic medication. Pharmacogenomic testing may be most useful in psychiatric patients who have treatment resistance, intolerable adverse effects, or the potential for experiencing adverse events or contraindications.

- GeneSight Psychotropic is a genetic panel that provides clinicians additional information about specific genetic variants to assist with decisions about drug selection regarding "psychotropic medications commonly prescribed to treat depression, anxiety, bipolar disorder, posttraumatic stress disorder (PTSD), obsessive compulsive disorder, schizophrenia and other behavioral health conditions." GeneSight tests for genetic variants in multiple pharmacokinetic and pharmacodynamic genes, which may impact drug tolerance and/or drug response. Specifically, the test currently analyzes 12 genes that may affect an individual's response to ~56 antidepressant and antipsychotic (psychotropic) medications (including 4 pharmacodynamic genes and 8 pharmacokinetic genes).

- Per a 2018 publication, "The combinatorial pharmacogenomic test (GeneSight Psychotropic, Assurex Health, OH, USA) included 65 alleles and variants across 12 genes: CYP1A2 (15 alleles), CYP2B6 (4 alleles), CYP2C9 (6 alleles), CYP2C19 (9 alleles), CYP2D6 (17 alleles and duplication), CYP3A4 (4 alleles), UGT1A4 (2 alleles), UGT2B15 (2 alleles), HTR2A (2 alleles), the long and short 5HTTLPR variants of the SLC6A4 serotonin transporter gene (2 alleles), HLA-A (*3101 associated SNP rs1061235) and HLA-B (1 allele)."

- Results of the GeneSight Psychotropic are detailed in a report provided to the clinician, describing the most common medications for the patient’s diagnosed condition categorized by cautionary level. Each medication is placed into one of three color-coded categories: "Use as Directed" in green, "Moderate Gene-Drug Interaction" in yellow, or "Significant Gene-Drug Interaction" in red.

- Additional pharmacogenomic panels or individual tests address treatment of mental health disorders, and are marketed by different labs or manufacturers. A few specific tests included in each panel are listed below:
  - Genecpt™ Assay (Genomind)
  - SureGene Test for Antipsychotic and Antidepressant Response (STA2R)
  - Proove Opioid Risk panel (Proove Biosciences)
  - Mental Health DNA Insight™ panel (Pathway Genomics)
  - IDgenetix-branded tests
Guidelines and evidence

• The best available published evidence does not currently support the use of pharmacogenomic testing using the GeneSight Psychotropic test to aid in the treatment of the psychiatric disorders, specifically MDD.\textsuperscript{11-21}

• In a large (\(n=1799\)), blinded, multicenter randomized controlled trial (RCT), the Genomics Used to Improve Depression Decisions (GUIDED) trial evaluated the effect of the GeneSight Psychotropic test compared with usual care on treatment selection in patients with major depressive disorder (MDD), who had failed at least one adequate medication trial. Patients were randomized to either treatment as usual (TAU) or GeneSight guided groups.\textsuperscript{22}

  o For the primary endpoint, there were no statistically significant differences between GeneSight and TAU for the change in depression symptoms at 8 weeks. Also, there were no statistically significant differences in the mean number of side effects between the two groups at 8 weeks.

  o For the secondary endpoints of response and remission, the study results favored GeneSight-guided therapy over TAU. Response and remission significantly improved in the GeneSight-guided therapy arm versus TAU.

  o The lack of significant differences observed between groups for the primary endpoint indicate that a meaningful benefit of GeneSight to guide treatment and improve symptoms of MDD relative to usual care was not demonstrated.

  o Although significant improvements in the secondary endpoints were observed, additional well-designed clinical trials, powered on the primary endpoints of remission and/or response, are needed to confirm these findings.

  o Results of a post-hoc analyses suggest that GeneSight may have clinical utility to guide changes in treatment from less to more optimal drug therapies. However, these findings need to be replicated in a well-designed trial with a pre-specified subgroup analysis before the clinical utility of the GeneSight test can be established with certainty.

  o The study has a few notable limitations:
      - There appears to be considerable attrition. It is not clear if the sample size estimation included a specified dropout rate in the statistical plan.
The primary endpoint was evaluated in the per-protocol (PP) population, rather than the intent-to-treat (ITT) population, which may have introduced selection bias. The PP approach did not appear to account for loss to follow-up. The ITT population should include all patients who were randomized into study groups.

Clinicians in the guided GeneSight arm were not required to adhere to the test result, and the number and basis of treatment decisions made in this arm were not reported.

The results of post-hoc analyses should be interpreted cautiously since hypotheses are typically generated after the analysis has been completed and results are subject to bias.

- No specific evidence-based U.S. testing guidelines were identified. However, the American Psychiatric Association (APA) Task Force for Novel Biomarkers and Treatments, a component of the APA Council on Research, stated that there is insufficient data to support the widespread use of pharmacogenomic tests in clinical practice to guide antidepressant treatment.

Criteria

- These tests are considered investigational and/or experimental.
  - Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
  - In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

Billing and reimbursement considerations

- Due to these tests typically being performed as gene panels and reported out as associated risks using proprietary algorithms, individual CPT codes will also not be reimbursed under this guideline.
- If single gene testing is being requested and performed to determine an individual’s response to a specific medication (e.g. CYP2D6, CYP2C19, etc), please see either the pharmacogenomic testing clinical use guideline or a test-specific guideline to determine criteria for coverage.
References


