Test Specific Guidelines

GeneSight Psychotropic Test

MOL.TS.340.A
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Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
GeneSight Psychotropic	0345U

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 2019, roughly 19 million adults in the United States experienced at least one major depression episode in the previous year; this number represented 7.8% of all adults in the United States.[1] 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 2019, there were approximately 13.1 million adults in the United States with serious mental illness, representing 5.2% 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.[2] 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%.[3]

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.[4]

To find the optimal treatment approach, many clinicians try different antidepressants to maximize treatment response and reduce risk of recurrence. 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.[5]

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.[6]

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.

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.[7] Based on the composite phenotype measured for each patient, the GeneSight test has been proposed to assist clinicians in selecting psychotropic medication.[8] 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.[9]

GeneSight Psychotropic is a genetic panel that provides clinicians additional information about specific genetic variants to assist with decisions about drug selection regarding medications commonly prescribed to treat depression, anxiety, ADHD, and other psychiatric disorders. 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 15 genes that may affect an individual's response to ~56 antidepressant and antipsychotic (psychotropic) medications (including 5 pharmacodynamic genes and 9 pharmacokinetic genes).[10]

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)."[11]

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.[7]

Guidelines and Evidence

International Society of Psychiatric Genetics

A statement from the International Society of Psychiatric Genetics (2019) includes the following:[12]

"Pharmacogenetic testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care, enhancing rather than offering an alternative to standard protocols."

"We recommend HLA-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups. Evidence to support widespread use of other pharmacogenetic tests at this time is still inconclusive, but when pharmacogenetic testing results are already available, providers are encouraged to integrate this information into their medication selection and dosing decisions. Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial."

American Psychological Association

The American Psychological Association (2019) Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts does not include genetic or genomic testing in its recommendations regarding pharmacotherapy for treatment of depression.[13]

American Psychiatric Association

The American Psychiatric Association (APA, 2010) Practice Guideline for the Treatment of Patients with Major Depressive Disorder stated:[14]

"In time, genetic testing may help guide selection or dosing of antidepressants, but data are currently insufficient to justify the cost of such tests."

The APA (2018) Task Force for Biomarkers and Novel Treatments stated:[15]

"...at present there are insufficient data to support the widespread use of combinatorial pharmacogenetics testing in clinical practice..."

Food and Drug Administration (FDA)

In a 2018, the FDA released a safety communication regarding genetic tests claiming to predict response to specific medications, which included the following:[16]

For purposes of this safety communication, the product was defined as "genetic laboratory tests with claims to predict a patient's response to specific medications, that have not been reviewed by the FDA and may not be supported by clinical evidence. For example, genetic tests with claims to predict whether some medications used to treat depression may be less effective or have an increased chance of side effects."

"The FDA is alerting patients and health care providers that claims for many genetic tests to predict a patient's response to specific medications have not been reviewed by the FDA, and may not have the scientific or clinical evidence to support this use for most medications. Changing drug treatment based on the results from such a genetic test could lead to inappropriate treatment decisions and potentially serious health consequences for the patient."

"For example, the FDA is aware of genetic tests that claim results can be used to help physicians identify which antidepressant medication would have increased effectiveness or side effects compared to other antidepressant medications. However, the relationship between DNA variations and the effectiveness of antidepressant medication has never been established. The FDA is aware that health care providers may have made inappropriate changes to a patient's medication based on the results from genetic tests that claim to provide information on the personalized dosage or treatment regimens for some antidepressants."

"Be aware that most genetic tests that make claims about the effects of a specific medicine are not supported by enough scientific information or clinical evidence."

Selected Relevant Publications

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.[17-36]

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.[29]

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.

For the secondary endpoints of response and remission, the study results favored GeneSight-guided therapy over TAU. Statistically significant results were observed with a 50% improvement in remission rates (p=0.007) and a 30% increase in response rates (p=0.013) compared with TAU.

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.

Although significant improvements in the secondary endpoints were observed, no clinical conclusions can be drawn from these findings. Regarding endpoints in clinical trials, the FDA states "…a statistical conclusion cannot be made about the endpoints planned for the subsequent hypotheses, even if they have extremely small p-values. Suppose, for example, that in a study, the p-value for the first endpoint test in the sequence is p = 0.250, and the p-value for the second endpoint is p = 0.0001; despite the apparent "strong" finding for the second endpoint, no formal favorable statistical conclusion can be reached for this endpoint."[37] Therefore, despite the statistically significant findings, the improvements in GeneSight-guided treatment selection in response and remission rates in patients with MDD compared with TAU groups could still be due to random chance. Well-designed clinical trials, powered on the primary endpoints of remission and/or response would be needed to confirm these findings.

Results of this post-hoc analysis of the GUIDED trial data focused on patients who entered the study on medications with potential gene-drug interactions.[30]

While the findings reported significant improvements in symptoms (p=0.029), response rates (p=0.008), and remission rates (p=0.003) for these patients when subsequent therapy was guided by GeneSight compared with TAU, it is uncertain if the statistically significant results of the post-hoc analysis are directly attributed to use of GeneSight.

No conclusions can be drawn from post-hoc analyses of trials that have failed their primary endpoint.[37] Regarding post-hoc analyses, the FDA states "in the past, it was not uncommon, after the study was unblinded and analyzed, to see a variety of post hoc adjustments of design features (e.g., endpoints, analyses), usually plausible on their face, to attempt to elicit a positive study result from a failed study…." The FDA also concludes that "although post hoc analyses of trials that fail on their prospectively specified endpoints may be useful for generating hypotheses for future testing, they do not yield definitive results."[37]

To validate these findings, a prospective RCT with a different patient population would be necessary.

More recent publications describe results of a secondary analysis and a meta-analysis of previously published data, including from the GUIDED trial.[31-33,36]

Based on a comprehensive review of the best available and supporting peer-reviewed evidence, there is insufficient data to support the use of GeneSight Psychotropic testing to guide treatment selection in patients with major depressive disorder (MDD). There is also minimal evidence regarding the use of GeneSight to predict medication blood levels or health outcomes in patients with MDD.

Criteria

This test is 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.

Other Considerations

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 for Drug Toxicity and Response* clinical use guideline or a test-specific guideline to determine criteria for coverage.

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