Clinical Policy Title: Pharmacogenomic tests for depression

Clinical Policy Number: 02.02.01

Effective Date: October 1, 2015
Initial Review Date: April 15, 2015
Most Recent Review Date: April 10, 2018
Next Review Date: April 2019

Related policies:

CP# 00.01.03 Genetic testing for cytochrome P450 polymorphisms.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of pharmacogenomic tests for psychiatric medications to be investigational/experimental and, therefore, not medically necessary, including but not limited to the use of GeneSightRx or PHARMAchip assay genotyping of CYP1A2, CYP2C9, CYP2C19, CYP2D6, HTR2A, and SCL6A4 to help guide administration of antidepressants and antipsychotics or SureGene (STA2R) for antipsychotic drug response.

Note: Because the U.S. Food and Drug Administration includes CYP2D6 metabolizer status for dosing, administration and determining drug response in the labels for several psychiatric medications, requests for testing of this genotype will be considered on a case by case basis.

Limitations:

None.

Alternative covered services:

Traditional medicinal management.
Background

Mental illnesses are very common; they affect 25 percent of U.S. adults at any one time, and more than half will be affected at some point. Mental conditions can also be debilitating. For example, depression is the leading cause of disability worldwide. While numerous medicines used to counter mental illness, many patients do not respond or experience adverse effects to first-line therapies (Gardner, 2014).

For decades, clinicians have recognized that all patients may not respond uniformly to the same dose of a given pharmaceutical agent. Drugs are approved by the U.S. Food and Drug Administration (FDA) for sale based upon the general health improvement across a population and individual variations are considered only if a subpopulation experiences significant adverse effects. As more of the human genetic makeup is understood, the goal of “personalized medicine” comes closer to realization. There is currently a limited number of genomic tests that can impact the physician selection of therapies and significantly impact the patient outcome.

There has been recognition of patterns of behavioral expression, suggesting an inherited predisposition in mental health. More exciting has been the hope that genomics can lead to improved selection of pharmacotherapy. Currently physician selection of antidepressants or antipsychotic medications has been largely based upon physician experience with that drug and not on knowledge of patient-specific medication impact.

Several commercially available genomic tests are currently on the market, with more to come. The intentions of these tests are to enhance positive predictors of medication-specific responders. By using genomic information, the hope is that targeted therapy will replace the current “trial-and-error” approach to medication selection.

Three genome-wide pharmacogenetics studies to evaluate genetic variation and ability to select the correct therapy in psychiatry have been active in Europe. They include the Genome-based Therapeutic Drugs for Depression (GENDEP) project, the Munich Antidepressant Response Signature (MARS) project, and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (GENDEP Investigators, 2013).

In addition, genetic testing presents the possibility of predicting whether an asymptomatic person is likely to develop particular diseases. However, while some genes that can predict a greater risk of mental health disorders, no genetic marker has yet been shown to be useful in prospectively identifying any specific psychiatric disorder (Dubovsky, 2016).

A 2010 sample of 80 American chief psychiatry residents showed 56 percent have received three or fewer hours of genomics training, and just 14 percent reported they understood the role a genetic counselor could play on a clinical team (Winner, 2010).

A guideline by the Clinical Pharmacogenetics Implementation Consortium includes evidence from published literature on CYP2D6 and CYP2C19 genotype-directed dosing of tricyclic antidepressants (Hicks, 2013).
Another guideline from the American College of Medical Genetics and Genomics provides general recommendations in genetic testing. These include 1) the lab must be accredited by the Clinical Laboratory Improvement Amendment; 2) a genetics expert must advise the patient on whether a test should be performed and how to interpret results; 3) patients should be fully informed on the risks of developing a disease; and 4) privacy must be assured and access to genetics testing data must be given to patients. These parameters do not specify mental health disorders (ACMGG, 2015).

Searches

Select Health of South Carolina searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on March 1, 2018. Search terms were: “pharmacogenomic testing,” “genetic testing,” “depression,” “mental health,” and psychiatric.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

Data on the ability of pharmacogenomic testing to predict outcomes of psychiatric medications on patients fail to produce consistent results. For example, one systematic review found only three trials that address first-episode psychoses, with conflicting results (Fond, 2015). Another issue is that much of the research has focused on major depressive disorder.

A systematic review on the predictability of effectiveness of schizophrenia drugs after pharmacogenomic testing noted that fewer than 200 studies investigating biomarkers exist, with only one clinically applicable (Prata, 2014). A meta-analysis failed to find an association between clozapine monotherapy with DRD1 rs4532 polymorphism and overall antipsychotic response (de Matos, 2015). A systematic review of risperidone for schizophrenia or bipolar disorder, based on 13 trials (10 not randomized or controlled), found elevated adverse effects in poor metabolizers; most outcomes were not significant, and authors recommended such testing not be used routinely (Cartwright, 2013).
A meta-analysis of 11 studies (n=1775) documented significantly higher response rates to antidepressants for major depressive disorder for three polymorphisms (rs6311 C>T, rs7997012 G>A, and rs6313 T>C) in some studies, and insignificantly higher responses in others (Lin, 2014). A review of seven studies (n=754) of eight genes found a response/fewer side effects from antidepressants for certain mutations (Kato, 2010).

In a systematic review of 30 studies, changes in the gene promoter polymorphism 5-HTTLPR (a predictor of anti-depressant response) within the SLC6A4 gene (that codes for serotonin transport protein) were tested. In Caucasians significant links were found in response rates (p = 0.004) and remission rates (p = 0.004) in the group assigned to selective serotonin reuptake inhibitors. In Asians, a significant association was only observed for remission (p = 0.04) (Porcelli, 2012).

A meta-analysis of 14 studies assessed the interaction between stressful life events and the serotonin transporter gene on depression. The number of stressful life events was significantly associated with depression (OR, 1.41; 95% CI, 1.25-1.57). However, no association was observed between the 5-HTTLPR genotype and depression (OR, 1.05; 95% CI, 0.98-1.13), or between the combination of genotype and stressful life events on depression (OR, 1.01; 95% CI, 0.94-1.10) (Risch, 2009).

A review of four studies (n=215), conducted by industry, documented combinatorial pharmacogenomic testing using the GeneSight Psychotropic Test that analyzes how genes are affected by drugs commonly prescribed for mental health conditions was significantly more likely to predict if an antidepressant would be considered “use as directed,” “use with caution,” or “use with increased caution and with more frequent monitoring.” Tests of multiple mutations yielded significantly better predictability (Altar, 2015a). The same group compared depressed patients with or without GeneSight testing in four studies (n=258), and found a 2.3-fold greater clinical response and 53 percent greater improvement in symptoms, both significant (Altar, 2015b). GeneSight use was linked with a greater reduction of depression symptoms (p<.001) in a randomized trial of 227 patients (Hall-Flavin, 2013).

A sample of 3,330 persons tested for genome-wide analyses found preliminary support for the hypothesis that recurrent major depressive disorder with the FH+ subset mutation helps predict episodes of the condition, but cautioned that larger cohorts are needed to replicate results (Ferentinos, 2014).

The three European studies (GENDEP, MARS, and STAR*D) attempted to predict the ability of genetic testing for polymorphisms for depression treatment in a meta-analysis of 2,256 individuals of Northern European descent. No such reliable predictors were identified, except for a modest link in patients treated with citalopram or escitalopram in the first two weeks of treatment (GENDEP, 2013). A 2013 meta-analysis found no major effect of any single gene variant in antidepressant efficacy (Niitsu, 2013).

A recent review reported greater improvement in predicting antidepressant outcomes after testing, but two were industry-sponsored, two were not randomized, and one lacked a control group. Another recent study followed 46 adolescents with major depressive disorder for one year, and concluded no relationship was found between genetic variants in fluoxetine (Prozac) transportation and remission or recovery (Blazquez, 2016).
A review of combined pharmacogenomics testing for major depression concluded that testing improved treatment response by 70 percent versus treatment as usual; the article’s lead author is a physician director of a small business (Hornberger, 2015).

Genetic analysis was performed in a study of 2023 persons suffering from depression who were assigned a score of suicide attempt likelihood. No single nucleotide polymorphism was associated with suicidal behavior at the genome-wide level of significance, while seven polymorphisms demonstrated significance (Schosser, 2011).

A prospective, randomized study assigned 237 outpatients with neuropsychiatric disorders into groups in which the clinician knew and did not know the pharmacogenomics test results. After 90 days, 28 percent of the group with known genomic results had at least one adverse drug event, significantly lower (p=.001) than the 53 percent figure for those with no known genomic test results (Olson, 2017).

Policy updates:

A total of six peer-reviewed references were added to, and four removed from, this policy in March, 2018.

A total of one guideline/other and 10 peer-reviewed references were added to this policy in the 2017 update.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Blazquez (2016) | **Key points:**  
  - One year follow-up of 46 adolescents with major depressive disorder.  
  - Remission was 69.5%, recovery 56.5%.  
  - No relationship found between ABCB1 and remission or recovery.  
  - Significant association found between ABCB1 and suicide attempts.  
  - Conclusion: Other factors like stress, family support, and other genetic factors are likely to be involved in major depressive disorder outcomes. |
| Ferentinos (2014) | **Key points:**  
  - Recurrent major depressive disorder believed to increase risk of shift to bipolar.  
  - 1,966 and 1,364 cases of major depressive disorder with presence/absence of family history of the disease.  
  - Genome-wide analyses produced no genome-wide significant findings.  
  - Two mutations most closely associated with link of elevated episodes.  
  - FH+ subset at STIM1 (calcium channel signaling gene) part of a link with highly recurrent major depressive disease, but needs replication in larger cohorts. |
| Niitsu (2013) | **Key points:**  
  - Meta-analysis from three major reviews. |
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| major depression | • The findings suggested the BDNF Val66Met as the best single candidate involved in antidepressant response, with a selective effect on SSRI treatment.  
• Our overall results supported no major effect of any single gene variant on AD efficacy. |
| GENDEP (2013) | **Key points:**  
• A meta-analysis was performed on data from three genome-wide pharmacogenetic studies (the Genome-Based Therapeutic Drugs for Depression [GENDEP] project, the Munich Antidepressant Response Signature [MARS] project, and the Sequenced Treatment Alternatives to Relieve Depression [STAR*D] study), which included 2,256 individuals of Northern European descent with major depressive disorder.  
• There were no reliable predictors of antidepressant treatment outcome, although they did identify modest, direct evidence that common genetic variation contributes to individual differences in antidepressant response. |

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local coverage determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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