Medical Policy Reference Manual
Medical Policy

11.01.073 Genetic Testing

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Description

Genetic tests are laboratory tests or studies that identify changes in human deoxyribonucleic acid (DNA), chromosomes, genes, or proteins, and can confirm or rule out a suspected genetic condition and identify a person's chance of developing and passing on a genetic disorder. Genetic testing includes the analysis of single genes, a panel of genes or the entire exome or genome. Test selection depends on the indication for testing and includes tests used to guide intervention or treatment selection in symptomatic or asymptomatic individuals; tests that identify individuals at risk for future disorders; tests that predict disease prognosis; and tests that predict response to treatment.

CareFirst Genetic Testing Program scope includes the following:

- Genetic Testing for Hereditary Cardiac Disease
- Genetic Testing for Hereditary Cancer Susceptibility
- Genetic Testing for Reproductive Carrier Screening
- Genetic Testing for Single-Gene and Multifactorial Conditions
- Pharmacogenetic Testing and Testing for Thrombotic Disorders
- Molecular Testing of Solid and Hematologic Tumors and Malignancies
- Whole Exome and Whole Genome Sequencing

The Genetic Testing Program scope does not include:

- Human Leukocyte Antigen (HLA) Testing
- Cologuard® (refer to CareFirst Medical Policy Operating Procedure # 2.03.011A)
- Preimplantation Genetic Testing (refer to CareFirst Medical Policy # 4.02.007)
- Circulating Tumor Cell Testing (refer to CareFirst Medical Policy # 11.01.076)
- Inpatient genetic testing

*****Prior Authorization is required for ALL Genetic Testing Services within the program scope noted above. *****

Genetic testing services must be preauthorized. Providers should submit preauthorization requests online at provider.carefirst.com or call (844) 377-1277.

Policy

CareFirst Blue Cross Blue Shield defers to AIM Specialty Health's Clinical Appropriateness Guidelines for the following genetic testing services:

- Single Gene and Multifactorial Conditions Genetic Testing
- Genetic Testing for Hereditary Cardiac Disease
- Hereditary Cancer Susceptibility Genetic Testing
- Reproductive Carrier Screening and Prenatal Diagnosis Genetic Testing
- Somatic and Hematologic Tumors Genetic Testing
- Pharmacogenomic and Thrombophilia Genetic Testing
- Chromosomal Microarray Analysis, Whole Exome and Whole Genome Sequencing

A molecular genetic test is covered when the test meets appropriate use criteria as outlined in the AIM Clinical Appropriateness Guidelines available at: http://aimspecialtyhealth.com/CG-GeneticTesting.html

Pretest genetic counseling is <u>required</u> for tests described in the following AIM Guidelines:

- Single Gene and Multifactorial Conditions Genetic Testing
- Genetic Testing for Hereditary Cardiac Disease
- Hereditary Cancer Susceptibility Genetic Testing
- Reproductive Carrier Screening and Prenatal Diagnosis Genetic Testing
- Somatic and Hematologic Tumors Genetic Testing
- Pharmacogenomic and Thrombophilia Genetic Testing
- Chromosomal Microarray Analysis, Whole Exome and Whole Genome Sequencing

Genetic Counseling must be performed by one of the below genetic experts:

- A board-certified or board-eligible medical geneticist not employed by a commercial genetic testing laboratory*
- An American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counselor not employed by a commercial genetic testing laboratory*
- A genetic nurse who a) is credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), and b) is not employed by a commercial genetic testing laboratory*

**A physician, genetic counselor or genetic nurse employed by a laboratory that operates within an integrated, comprehensive health care delivery system is not considered to be an employee of a commercial genetic testing laboratory for the purpose of this policy.*

A molecular genetic test that <u>does not meet the criteria</u> as described above is considered not medically necessary, and therefore not covered.

CareFirst <u>does not</u> defer to AIM Specialty Health's Clinical Appropriateness Guidelines for the following assays: GeneSight Psychotropic®, Genomind Professional PGx Express™.

Coverage based on CareFirst criteria for the above-named assays is as follows:

<u>GeneSight Psychotropic®</u>:

The GeneSight® Psychotropic assay, to assist with psychotropic medication selection and management in patients with major depressive disorder is considered medically necessary for patients with at least one prior failed psychiatric medication trial.

Use of the GeneSight® Psychotropic assay for all other indications including but not limited to: anxiety, bipolar disorder, post-traumatic stress disorder (PTSD), obsessive compulsive disorder, and schizophrenia is considered not medically necessary, and therefore not covered.

<u>Genomind Professional PGx Express™</u>:

The Genomind assay, to assist with psychotropic medication selection and management in patients with major depressive disorder is considered medically necessary for patients with at least one prior failed psychiatric medication trial.

Use of the Genomind Professional PGx Express™ assay for all other indications including but not limited to: anxiety, bipolar disorder, post-traumatic stress disorder (PTSD), obsessive compulsive disorder, and schizophrenia is considered not medically necessary, and therefore not covered.

Policy Guidelines

<u>Rationale:</u>
GeneSight Psychotropic®

GeneSight® Psychotropic, a pharmacogenomic assay, uses proprietary algorithm to analyze up to 12 genes to identify genetically appropriate FDA-approved psychotropic medications for the treatment of major depressive disorder. The test is suitable for patients with major depressive disorder who have failed at least one psychiatric medication. GeneSight places patient-specific results for each medication into one of three color-coded categories (green, yellow and red). Categorization of these results assists prescribing providers with the selection and dosage of genetically appropriate medications to increase the likelihood of response and reduce the risk of adverse events.

GeneSight Psychotropic® is certified under the Clinical Laboratory Improvement Amendments (CLIA) of 1988, and therefore does not require approval from the Food and Drug Administration (FDA). Direct evidence on the analytical validation of the marketed version is lacking and no studies could be found that directly assessed the clinical validity of the current marketed version of the test. Indirect evidence on clinical validity were reported in three clinical utility studies (Hall-Flavin et al., 2012; Hall-Flavin et al., 2013; Winner et al., 2013). Genotyping results were provided by these studies, but test accuracy, sensitivity, specificity, or positive predictive values were not reported. Hall-Flavin et al. (2012) prospectively evaluated the potential benefit of utilizing a pharmacogenomics test report to guide the selection and dosing of psychotropic medication in an outpatient psychiatric practice (N=22). Patients were non-randomly assigned to one of two possible groups (guided group: use of pharmacogenomic testing to guide medication decisions; and unguided group: treatment decisions are unguided by pharmacogenomic test results). Patients in the guided medication group experienced significantly (P=0.002) more reduction in depressive symptoms compared to patients in the unguided group. Significantly more patients (21.4%) in the unguided group were prescribed medications in the red category versus 5.9% for patients in the guided group (P=0.02). An open-label study by Hall-Flavin et al. (2013) (N=227) examined modifications to medication management in patients whose pharmacotherapy was guided by a 5-gene pharmacogenomics test versus unguided with an 8-week follow up period. The majority (76.8%) of patients in the guided group had a change medication management compared to 44.1% of patients in the unguided group (P<0.0001). Remission rates were highest among patients in the guided intervention group (P=0.03). Overall, patients in the guided group experienced greater percent improvement in depression scores compared with the unguided group. Winner et al. (2012), retrospectively evaluated healthcare utilization in relation to an interpretive pharmacogenomic test and reporting system for 96 patients with a DSM-IV-TR diagnosis of anxiety or depression. All subjects were on at least one antidepressant or antipsychotic medication therapy. Patients whose medications fell into the red category (‘use with caution and frequent monitoring’) had the highest utilization of total healthcare visits, general medical visits, three times more medical absence days and four times more disability claims than patients in the yellow (‘use with caution’) and green (‘use as directed’) groups. A prospective, randomized, double-blinded study by Winner et al. (2013), evaluated the benefit of the GeneSight (five-gene version) for the management of psychotropic medications in the treatment of major depression at an outpatient psychiatric practice. Patients were either randomized to the treatment as usual (n=25) or the pharmacogenomic-informed (GeneSight) group (n=26). Depression severity was assessed by blinded study raters at baseline (within two days of enrollment), 4, 6 and 10 weeks after baseline assessment. Patients in the GeneSight group reported more improvement in depressive symptoms compared to the TAU group (30.8% versus 20.7%, p=0.28). Patients in the TAU group whose medications at baseline fell into the red category had very little improvement (0.8%) in depressive symptoms at week 10. Whereas 33.1% of patients in the GeneSight group who started on a red category medication experienced an improvement in depressive symptoms (P=0.06). Although the findings appear promising, they must be interpreted with caution because the differences between with two groups were generally not of statistical significance (at weeks 4 and 10). However, at 6 weeks follow up, the GeneSight group experienced significantly more improvement in depressive symptoms compared to the TAU group (35.4% versus 18.5%, P=0.04).

Alternatives to the GeneSight® Psychotropic assay include single-gene testing and medication selection without pharmacogenomic testing. Studies have showed that patients whose medication selection was guided by pharmacogenomics testing with the GeneSight® assay experienced an improvement in depressive symptoms compared to patients whose pharmacotherapy was unguided. Although preliminary findings are promising, further well-designed studies are needed to confirm these findings.

Genomind Professional PGx Express™

The Genomind Professional PGx Express™ Assay contains a panel of 24 genes that are used to inform prescriptions of psychiatric drugs. A report is generated for this test that includes genetic implications for 130 mental health medications. Traditionally, optimizing mental health medication has involved a cumbersome trial-and-error process. Using this pharmacogenomic test to guide medication selection is suggested to shorten the process of identifying effective medications for individual patients.

In 2015 a study was conducted by Brennan et al. to study the impact of treatments guided by Genomind on patient outcomes. This was an unblinded prospective analysis of psychiatric patients and clinicians who utilized the Genomind Genecept Assay. Each patient who participated in this study had a report displaying their likely responsiveness to medication provided to their physician. Clinicians completed surveys within one week of receiving the test results and three months after receiving test results. Patients completed assessments of depression, anxiety, medication side effects, and quality of life at baseline, one month, and three months. Results demonstrated a substantial proportion of individuals receiving pharmacogenetic testing showed clinically significant improvements on measures of symptoms, adverse effects, and quality of life. Of the patients studied 87% showed clinically measurable improvement. Importantly, this study did not contain a comparison group in which Genomind report results were not considered when making

treatment decisions. This means the proportion of treatment outcomes that can be attributed to test results is unable to be determined.

In 2017 the data from the Brennan et al., 2015 study was analyzed with a focus on a subset of participants with variants of SLC6A4 (the serotonin transporter gene) and MTHFR (the gene encoding methylenetetrahydrofolate reductase). Individuals with these variants whose subsequent treatment was consistent with the assay-guided treatment per the Genomind Genecept Assay tended to fare better on several self-reported outcomes than those individuals whose subsequent treatment was discordant with the assay. Specifically, individuals with SLC6A4 variants and assay-guided treatment reported significantly better quality of life outcomes.

Genetic information is increasingly being used in clinical psychiatry to guide treatment decisions. Genomind panels and reports provide an important option for clinicians who are seeking to optimize medical treatment for patients.

******At its sole discretion, CareFirst may cover emerging technologies that have been proven to be safe; have promising initial trial results; and have medical benefit and a strong potential to improve the net health outcomes***.

Update 2020:
A search of the peer-reviewed literature was performed for the period of March 2017 through March 2019. Findings in the recent literature do not change the medically necessary indication in the policy section.

Update 2021:
Genomind is a provider of phamacogenomic testing to guide psychiatric medication selection. Studies have suggested that consideration of Genomind test results when prescribing medication to treat depression is associated with better patient outcomes.

Update 2021b:
AIM Specialty Health's Clinical Appropriateness Guidelines will be followed for ExoDx Prostate (IntelliScore), Oncotype DX, and EndoPredict.

Benefit Applications

Note: For FEP, check the Member's contract for benefits.

Provider Guidelines

Genetic testing services must be preauthorized. Providers should submit preauthorization requests online at provider.carefirst.com or call (844) 377-1277.

Cross References to Related Policies and Procedures

4.02.007	Preimplantation Genetic Testing, Policy
11.01.076	Circulating Tumor Cell Testing, Policy

References

The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own and may or may not be in agreement with those of CareFirst.

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