Genetic Testing for Heterozygous Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is an inherited disorder characterized by markedly elevated low-density lipoprotein levels, physical exam signs of cholesterol deposition, and premature cardiovascular disease. FH can be either homozygous or heterozygous. Heterozygous FH is much more common and more difficult to diagnose. Genetic testing for heterozygous FH can potentially improve the ability to make a diagnosis of FH, and can identify asymptomatic relatives of affected individuals at risk for developing FH.

Homozygous FH is an extremely rare disorder that arises from biallelic mutations in a single gene, and has a prevalence of between 1:160,000 and 1:1,000,000. Individuals with homozygous FH have extreme elevations of LDL, develop coronary artery disease (CAD) in the second or third decade, and are generally diagnosed easily.

Heterozygous FH is more common and has an estimated prevalence between 1 in 200 to 1 in 500 individuals. Some populations such as Ashkenazi Jews and South Africans have higher prevalence of up to 1 in 100. For affected individuals, the burden of illness is high. The average age for presentation with CAD is in the fourth decade for males and the fifth decade for females, and there is a 30% to 50% increase in risk for individuals in the fifth and sixth decades, respectively.

Regulatory Status

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). 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.

As of 2015, the following labs offered genetic testing for familial hypercholesterolemia in the United States:

- Ambry Genetics (CA)
- Correlagen Diagnostics (MA)
- Athena Diagnostics (MA)
- Mayo Clinic (MN)
- Baylor College of Medicine (TX)
- Progenika Biopharma (MA)
- Prevention Genetics (WI)
- ARUP Laboratories (UT).
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***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing for heterozygous familial hypercholesterolemia when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Heterozygous Familial Hypercholesterolemia is covered

Genetic testing to confirm a diagnosis of familial hypercholesterolemia (FH) may be considered medically necessary when a definitive diagnosis is required as an eligibility criterion for specialty medications and when the following criteria are met:

- Genetic testing is targeted to individuals who are in an uncertain category according to clinical criteria (personal and family history, physical exam, lipid levels); AND
- Alternative treatment considerations are in place for individuals who have an uncertain diagnosis of FH and a negative genetic test.

Genetic testing of children of individuals with FH to determine future risk of disease may be considered medically necessary when the following criteria are met:

- A pathogenic mutation is present in a parent; AND
- General lipid screening is not recommended based on age or other factors.

When Genetic Testing for Heterozygous Familial Hypercholesterolemia is not covered

Genetic testing to confirm a diagnosis of heterozygous FH is considered investigational in all other situations.

Genetic testing of adults who are close relatives of individuals with FH to determine future risk of disease is considered investigational.

Policy Guidelines

For individuals who have signs and/or symptoms of familial hypercholesterolemia (FH) and who receive genetic testing to confirm the diagnosis of FH, the evidence consists of case series and cross-sectional studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, change in disease status, and morbid events. No published empiric evidence on analytic validity was identified; however, there are claims in the literature that the analytic validity approaches 100%. For clinical validity, there are large samples of individuals with FH who have been systematically tested for FH mutations. In these cohorts of patients, the clinical sensitivity ranges from 50% to 70% for those with definite FH. For suspected FH, the sensitivity...
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is lower, ranging from 10% to 30%. There is scant evidence on clinical specificity. False positives are expected to be low for known pathogenic mutations, but the false-positive rate is unknown for novel mutations or for variants of unknown significance. Direct evidence for clinical utility is lacking. Clinical utility of genetic testing was evaluated through an indirect chain of evidence in the following situations.

• **A definitive diagnosis of FH is required to establish eligibility for specialty medications.** An indirect chain of evidence demonstrates that clinical utility is present. For patients who are in an uncertain diagnostic category, a positive genetic test can confirm the diagnosis of FH and establish eligibility for specialty medications. Specialty medications (eg, PCSK9 inhibitors) have known efficacy in patients with FH and uncontrolled lipid levels despite treatment with statins and/or other medications. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

• **All other situations.** Clinical utility of testing for diagnosis cannot be demonstrated through an indirect chain of evidence in other situations. No changes in management occur as a result of establishing a definitive diagnosis with genetic testing compared to standard clinical evaluation. For adolescents and adults, measurement of lipid levels is indicated, and management decisions will be made primarily on lipid levels and will not differ in the presence of FH. Therefore, an improvement in health outcomes cannot be demonstrated. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a close relative with a diagnosis of FH who receive genetic testing to determine future risk of FH, the evidence consists of case series and cross-sectional studies. Relevant outcomes include test accuracy and validity, other test performance measures, symptoms, change in disease status, and morbid events. No published empiric evidence on analytic validity was identified; however, there are claims in the literature that the analytic validity approaches 100%. For clinical validity, there are large samples of individuals with FH who have been systematically tested for FH mutations. In these cohorts, the clinical sensitivity ranges from 50% to 70% for individuals with definite FH. For suspected FH, the sensitivity is lower, ranging from 10% to 30%. There is scant evidence on clinical specificity. False positives are expected to be low for known pathogenic mutations, but the false-positive rate is unknown for novel mutations or for variants of unknown significance. Direct evidence for clinical utility is lacking. Clinical utility was evaluated through an indirect chain of evidence in the following situations.

• **Adults.** Clinical utility cannot be demonstrated through an indirect chain of evidence. While targeted genetic testing is superior to standard risk stratification for determining future risk of disease, it is unlikely that management changes will occur as a result of genetic testing. Adults who are close relatives of individuals with FH will have their lipid levels tested, and management decisions for adults are made primarily by low-density lipoprotein levels and will not differ for patients with a diagnosis of FH. The evidence is insufficient to determine the effects of the technology on health outcomes.

• **Children.** Clinical utility can be demonstrated through an indirect chain of evidence. Targeted genetic testing is superior to standard risk stratification for determining future risk of disease. Recommendations for children of affected individuals who have a pathogenic mutation include screening at earlier ages and initiation of treatment with statins earlier than they would be the case absent a pathogenic mutation. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
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Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81401, 81405, 81406

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Medical Director Review, 5/2016


Policy Implementation/Update Information

7/1/16       New policy developed. Medical Director review 6/1/2016. Policy effective on 7/1/2016. (jd)
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8/30/16    Specialty Matched Consultant Advisory Panel review 7/2016. Medical Director review 7/2016. (jd)

12/30/16   Minor revisions to description section. No change to policy statement/intent. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.