Medical Policy
Genetic Testing for Heterozygous Familial Hypercholesterolemia

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Policy Number: 796
BCBSA Reference Number: 2.04.139
NCD/LCD: N/A

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

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 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.

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.

The definition of an "uncertain" diagnosis of familial hypercholesterolemia (FH) is not standardized. However, available diagnostic tools provide guidance on when a diagnosis is and is not definitive. When FH is suspected and evaluated against standardized diagnostic criteria, it can be interpreted that the individual is in an "uncertain" category when criteria for a definitive diagnosis are not met, as follows:
• Dutch Lipid Clinic Criteria. A score of 8 or greater on the Dutch Lipid Clinic criteria is considered definitive FH. Scores between 3 and 7 are considered “possible” or “probable” FH. The latter 2 categories can be considered to represent “uncertain” FH.

• Simon Broome Criteria. A definitive diagnosis of FH is made based on a total cholesterol level greater than 290 mg/dL in adults (or low-density lipoprotein >190 mg/dL), together with either positive physical exam findings or a positive genetic test. Probable FH, which can be interpreted as “uncertain” FH, is diagnosed using the same cholesterol levels, plus family history of premature coronary artery disease or total cholesterol of at least 290 mg/dL in a first- or a second-degree relative.

• MEDPED Criteria. These criteria provide a yes/no answer for whether an individual has FH, based on family history, age, and cholesterol levels. An individual who meets criteria for FH can be considered to have definitive FH; however, there is no “possible” or “probable” category that allows assignment of an “uncertain” category.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th>Commercial Managed Care (HMO and POS)</th>
<th>No</th>
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<tbody>
<tr>
<td></td>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
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<tr>
<td></td>
<td>Medicare HMO BlueSM</td>
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<td></td>
<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
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<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
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Epidemiology of Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is an inherited disorder characterized by markedly elevated low-density lipoprotein (LDL) levels, physical exam signs of cholesterol deposition, and premature cardiovascular disease. FH can be categorized as homozygous or heterozygous 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, with 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 men and women in the fifth and sixth decades, respectively.

Diagnosis of FH

The diagnosis of FH relies on elevated LDL levels in conjunction with a family history of premature CAD and physical exam signs of cholesterol deposition. There is wide variability in cholesterol levels for patients with FH, and considerable overlap in levels between patients with FH and patients with non-FH. Physical exam findings can include tendinous xanthomas, xanthelasma, and corneal arcus, but these are not often helpful in making a diagnosis. Xanthelasma and corneal arcus are common in the elderly population and therefore not specific. Tendinous xanthomas are relatively specific for FH but are not sensitive findings. They occur mostly in patients with higher LDL levels and treatment with statins likely delays or prevents the development of xanthomas.

Because of the variable cholesterol levels, and the low sensitivity of physical exam findings, there are a considerable number of patients in whom the diagnosis is uncertain. For these individuals, there are a number of formal diagnostic tools for determining the likelihood of FH.

- Make Early Diagnosis Prevent Early Deaths Program Diagnostic Criteria (MEDPED)
  - This tool relies on a combination of total cholesterol levels, age, and family history. For example, a 20-year-old individual who has no family history is diagnosed with FH if total cholesterol is 270 mg/dL or higher. A 25-year-old individual with a first-degree relative who has FH is diagnosed with FH if total cholesterol is 240 mg/dL or higher.
  - Genetic testing is not considered as part of the diagnostic workup with this tool.

- Dutch Lipid Clinic Criteria
  - This tool assigns points for family history, CAD in the individual, physical exam signs of cholesterol deposition, LDL levels, and results of genetic testing. The diagnosis of definite FH is made when the score is 8 or higher and probable FH when the score is 6 to 8.
  - The diagnosis can be made with or without genetic testing. A positive genetic test is given 8 points, which is the highest for any criterion and indicates that a positive genetic test alone is sufficient to make a definitive diagnosis.

- Simon Broome Registry Criteria
  - Using these criteria, a definite diagnosis of FH is made based on total cholesterol is greater than 290 mg/dL in adults (or LDL >190 mg/dL) together with tendinous xanthoma in the individual or a first-degree relative.
  - A definite diagnosis can also be made using cholesterol levels and a positive genetic test.
  - Probable FH is diagnosed by cholesterol levels and either a family history of premature CAD, or a family history of total cholesterol 290 mg/dL or higher in a first- or a second-degree relative.

Treatment of FH

Treatment of FH is generally similar to that for non-FH, and is based on LDL levels. Treatment may differ in that the approach to treating FH is more aggressive (ie, treatment may be initiated sooner and a higher intensity medication regimen may be used). In adults, there are no specific treatment guidelines that indicate treatment for FH differs from standard treatment of hypercholesterolemia. There may be more
differences in children, for whom the presence of a pathogenic mutation may impact the timing of starting medications.

As with other forms of hypercholesterolemia, statins are the mainstay of treatment for FH. However, because of the degree of elevated LDL in many patients with FH, statins will not be sufficient to achieve target lipid levels. Additional medications can be used in these patients. Ezetimibe inhibits absorption of cholesterol from the gastrointestinal tract, and is effective for reducing LDL levels by up to 25% in patients already on statins. The IMPROVE-IT trial randomized patients with acute coronary syndrome to a combination of ezetimibe plus statins versus statins alone, and reported that cardiovascular events were reduced for patients treated with combination therapy.

The PCSK9 inhibitors are the most recently approved drugs for hyperlipidemia. These medications have potent LDL-lowering properties and have been tested in patients with FH. When added to statins, these drugs can result in additional LDL reduction of 30% to 70% and have been reported to reduce the incidence of nonfatal myocardial infarction. Other antilipid medications (eg, bile acid sequestrants, niacin) are effective at reducing LDL levels but have not demonstrated efficacy in reducing cardiovascular events when added to statins. For patients who continue to have elevated LDL levels despite maximum medical treatment, lipid apheresis is an option.

Genetics of FH
FH is generally inherited as an autosomal dominant condition. The primary physiologic defect in FH is impaired ability to clear LDL from the circulation, resulting in elevated serum levels. Three genes have been identified as harboring mutations associated with FH.

- The LDL receptor gene (LDLR) is the most common mutation identified, accounting for between 60% and 80% of FH.
  - The LDL receptor binds LDL thus allowing removal of LDL from the circulation. A defect in the LDL receptor leads to reduced clearance of LDL.
  - Over 1500 different pathogenic mutations have been identified in this gene.
- The APOB gene accounts for approximately 1% to 5% of FH cases.
  - Apolipoprotein B is a cofactor in the binding of LDL to the LDL receptor, and mutations in APOB lead to reduced clearance of LDL.
  - There are a limited number of mutations of this gene, allowing targeted testing,
- The PCSK9 gene accounts for approximately 0% to 3% of FH.
  - This mutation results in increased PCSK9 levels, which impair the function of the LDL receptors leading to reduced clearance of LDL.
  - There are a limited number of known pathogenic mutations, allowing targeted testing.
  - Penetrance for all FH genes is 90% or higher. Therefore, nearly all patients found to have a pathogenic mutation will eventually develop clinical disease. There is some degree of variable clinical expressivity that might be mediated by both environmental factors such as diet and exercise, and unknown genetic factors that modify gene expression.

Summary
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 includes 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 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 (e.g., 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 includes 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.

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.

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.

### Policy History

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<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>11/2017</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
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### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines
References


