Introduction

Familial hypercholesterolemia (FH) is an inherited disorder that causes abnormally high levels of low-density lipoprotein levels (LDL), often called bad cholesterol, in the blood at any early age. The excess cholesterol forms thick, sticky, hard fatty clumps called plaque. The plaque builds up in the arteries clogging blood flow and may form clots that stop blood flow resulting in a heart attack or brain attack (stroke). If left untreated this disorder increases the risk of heart disease as well problems that are related to poor blood flow to the arms, legs, and feet. A definite diagnosis of FH may be required to qualify for specialty medications such as PCSK9 inhibitors. Genetic testing may be done when an individual has symptoms that are suspicious for FH and other diagnostic tests for the disorder are abnormal or uncertain. Genetic testing may be indicated for children whose parents have FH to determine their risk of developing the disorder. See Policy Criteria for more specific information.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
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<th><strong>Procedure</strong></th>
<th><strong>Coverage Criteria</strong></th>
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| **Confirm a diagnosis of familial hypercholesterolemia (FH)** | Genetic testing to confirm a diagnosis of heterozygous FH is considered investigational when criteria are not met. 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.  
  - Eligibility for specialty medicines (e.g., PCSK9 inhibitors) may require a definitive diagnosis of FH. The labeled indications for these agents state they are indicated for individuals with FH, although criteria for diagnosis are not given. In the key trials that led to Food and Drug Administration approval of these inhibitors, having a diagnosis of FH was 1 eligibility criterion. The diagnosis in these trials was based on clinical factors with or without genetic testing. (See Related Policy 5.01.558)  
AND  
- 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, see below).  
AND  
  - Alternative treatment considerations are in place for individuals who have an uncertain diagnosis of FH and a negative genetic test. |

**Notes:** 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 standardized diagnostic criteria are not met, it can be interpreted that the individual is in an “uncertain” category, 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-
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<td>Procedure</td>
<td>density lipoprotein &gt;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.</td>
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<td>• <strong>MEDPED Criteria.</strong> 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.</td>
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<td>See Evidence Review for more information about these tests.</td>
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<td><strong>Testing of adults who are close relatives of</strong></td>
<td><strong>Genetic testing of adults who are close relatives of individuals with FH to determine future risk of disease is considered investigational.</strong></td>
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<td><strong>individuals with FH</strong></td>
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<td><strong>Note:</strong></td>
<td>It is unlikely that screening of adults who are close relatives of an index case of FH will improve outcomes because management decisions will be made according to lipid levels and will not differ based on a diagnosis of FH. However, there are conditions under which testing of relatives will lead to improved outcomes, particularly when testing is performed as part of a formal cascade screening program. Cascade testing refers to a coordinated program of population screening intended to identify additional patients with FH. Cascade screening may involve a combination of lipid levels and genetic testing, or may be performed with genetic testing alone. Beginning with an index case, close relatives are screened. For patients who screen positive, all close relatives are then identified and screened. This process is repeated until no further close relative eligible for screening can be identified. While such programs exist in Western Europe, there are barriers to implementation in the United States, such as lack of an infrastructure to identify all individuals in the cascade and a lack of coordination for patients with different types of medical insurance.</td>
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<td><strong>Testing of children of</strong></td>
<td><strong>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:</strong></td>
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<td><strong>individuals with FH</strong></td>
<td>• A pathogenic mutation is present in a parent AND • General lipid screening is not recommended based on age or other factors</td>
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### Procedure

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<th>Coverage Criteria</th>
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| **Note:** 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 in the absence of a pathogenic mutation.  

When there is a clinical diagnosis of FH but no known pathogenic mutation in the family, it is necessary to test an index case to determine mutation status. Coverage of testing an index case to benefit family members depends on contract benefit language. |

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### Coding

Analyses related to this testing are listed under the following CPT tier 2 molecular pathology codes:

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| 81401 | 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)  
Includes: APOB (apolipoprotein B) (e.g., familial hypercholesterolemia type B), common variants (e.g., R3500Q, R3500W) |
| 81405 | 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)  
Includes: LDLR (low density lipoprotein receptor) (e.g., familial hypercholesterolemia), duplication/deletion analysis |
| 81406 | 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)  
Includes: LDLR (low density lipoprotein receptor) (e.g., familial hypercholesterolemia), full gene sequence  
PCSK9 (proprotein convertase subtilisin/kexin type 9) (e.g., familial hypercholesterolemia), full gene sequence |
The Ambry Genetics FHNExt panel, for example, includes all 4 of the analyses above so it would be reported with codes 81401, 81405, and 2 units of 81406.

Related Information

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Benefit Application

Recommendations indicate that, when possible, genetic testing for familial hypercholesterolemia is performed in an affected family member so that testing in unaffected, at-risk family members can focus on the mutation found in the affected family member. However, coverage for testing of the affected index case (proband) depends on the member’s contract.

Member’s contract must be reviewed and considered when determining coverage for testing. In some cases, coverage for testing the index case may be available through the unaffected, at-risk individual who will benefit from knowing the results of the genetic test.
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<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td><strong>Individuals:</strong>&lt;br&gt;- With signs and/or symptoms of familial hypercholesterolemia when definitive diagnosis is required for specialty medications</td>
<td>Interventions of interest are:&lt;br&gt;- Genetic testing to confirm the diagnosis of familial hypercholesterolemia</td>
<td>Comparators of interest are:&lt;br&gt;- Standard clinical workup without genetic testing</td>
<td>Relevant outcomes include:&lt;br&gt;- Test accuracy&lt;br&gt;- Test validity&lt;br&gt;- Other test performance measures&lt;br&gt;- Symptoms&lt;br&gt;- Change in disease status&lt;br&gt;- Morbid events</td>
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<tr>
<td><strong>Individuals:</strong>&lt;br&gt;- With signs and/or symptoms of familial hypercholesterolemia in other situations</td>
<td>Interventions of interest are:&lt;br&gt;- Genetic testing to confirm the diagnosis of familial hypercholesterolemia</td>
<td>Comparators of interest are:&lt;br&gt;- Standard clinical workup without genetic testing</td>
<td>Relevant outcomes include:&lt;br&gt;- Test accuracy&lt;br&gt;- Test validity&lt;br&gt;- Other test performance measures&lt;br&gt;- Symptoms&lt;br&gt;- Change in disease status&lt;br&gt;- Morbid events</td>
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<tr>
<td><strong>Individuals:</strong>&lt;br&gt;- Who are adults and have a close relative with a diagnosis of familial hypercholesterolemia</td>
<td>Interventions of interest are:&lt;br&gt;- Genetic testing to determine future risk of familial hypercholesterolemia</td>
<td>Comparators of interest are:&lt;br&gt;- Standard clinical workup without genetic testing</td>
<td>Relevant outcomes include:&lt;br&gt;- Test accuracy&lt;br&gt;- Test validity&lt;br&gt;- Other test performance measures&lt;br&gt;- Symptoms&lt;br&gt;- Change in disease status&lt;br&gt;- Morbid events</td>
</tr>
</tbody>
</table>
| **Individuals:**<br>- Who are children and have a close relative with a diagnosis of familial hypercholesterolemia | Interventions of interest are:<br>- Genetic testing to determine future risk of familial hypercholesterolemia | Comparators of interest are:<br>- Standard clinical workup without genetic testing | Relevant outcomes include:<br>- Test accuracy<br>- Test validity<br>- Other test performance measures<br>- Symptoms<br>- Change in disease status
Overview by Evidence Review Indications

**Indication 1:** Individuals with signs and/or symptoms of familial hypercholesterolemia when definitive diagnosis is required for specialty medications who are undergoing genetic testing to confirm the diagnosis of familial hypercholesterolemia.

The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

**Indication 2:** Individuals with signs and/or symptoms of familial hypercholesterolemia in all other situations who are undergoing genetic testing to confirm the diagnosis of familial hypercholesterolemia.

The evidence is insufficient to determine the effects of the technology on health outcomes.

**Indication 3:** Individuals who are adults and have a close relative with a diagnosis of familial hypercholesterolemia who are undergoing genetic testing to determine future risk of familial hypercholesterolemia.

The evidence is insufficient to determine the effects of the technology on health outcomes.

**Indication 4:** Individuals who are children and have a close relative with a diagnosis of familial hypercholesterolemia who are undergoing genetic testing to determine future risk of familial hypercholesterolemia.

The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

**Summary**

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, much more common and more difficult to diagnose, is the focus of this evidence review. Genetic
testing for heterozygous FH can potentially improve the ability make a diagnosis of FH, and can identify asymptomatic relatives of affected individuals at risk for developing FH.

For individuals who have signs and/or symptoms of 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.

- 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.

**Epidemiology of Familial Hypercholesterolemia (FH)**

Familial Hypercholesterolemia encompasses a group of inherited genetic defects that causes severe elevations in LDL-C levels, as well as other lipid parameters. FH can be categorized as homozygous or heterozygous. 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.\(^1\) 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 patients and is present in childhood.\(^2,3\) Some populations such as Ashkenazi Jews and South Africans have a higher prevalence of FH, up to 1 in 100.\(^2\) For affected individuals, the burden of illness is high. Total cholesterol levels vary and can range from 350 to 550 mg/dL, which can result in premature coronary artery disease (CAD). 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.\(^3\)
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.4

- 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 (i.e., 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 (e.g., 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. 
  o 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.
  o Over 1500 different pathogenic mutations have been identified in this gene. 
• The APOB gene accounts for approximately 1% to 5% of FH cases.
  o Apolipoprotein B is a cofactor in the binding of LDL to the LDL receptor, and mutations in APOB lead to reduced clearance of LDL.
  o There are a limited number of mutations of this gene, allowing targeted testing.
• The PCSK9 gene accounts for approximately 0% to 3% of FH. 
  o This mutation results in increased PCSK9 levels, which impair the function of the LDL receptors leading to reduced clearance of LDL.
  o 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.

Clinical Evidence

This policy was developed in April 2016 with review of the literature covering the period through March 19, 2016.

Analytic Validity

No published evidence on the analytic validity of genetic testing for familial hypercholesterolemia (FH) was identified. Kassner et al reported that the analytic validity is “close to 100%,” but no empiric data were presented or referenced.

Clinical Validity
The clinical sensitivity is defined as the proportion of patients with FH who have a pathogenic mutation for FH, and the clinical specificity is defined as the proportion of patients without FH who do not have a pathogenic mutation for FH.

Five of the larger, more recent published studies of clinical validity were identified and are shown in Table 1.7-11 These cohorts included sample sizes ranging from 254 to 5430 patients with definite or suspected FH. These studies were conducted in different countries in Western Europe; no similar studies of US individuals were identified. All studies reported clinical sensitivity, and 1 study reported clinical specificity in an additional cohort of 40 unaffected individuals. 7 In some cases, the analysis was stratified by the clinical likelihood of FH prior to genetic testing using the Dutch Lipid Clinic Network (DLCN) criteria. Most patients in these studies were from referral centers in Europe and, therefore, may not be representative of the population seen in primary care.

The clinical sensitivity of these studies ranged from 34.5% to 66.5%, with 4 studies clustering in the 34.5% to 41.2% range. The fifth study that reported a substantially higher sensitivity of 66.5% included only patients with definite FH, unlike the other studies that included both definite and suspected FH cases. Two studies used the DLCN criteria to categorize individuals as definite, probable or possible FH.8,10 The proportion of individuals testing positive for FH varied by category. In the definite FH category, the sensitivity was 56.3% and 70.3%, respectively. This is in the same range as the Diakou study, which reported a sensitivity of 66.5% in patients with definite FH. In patients with probable or possible FH, the sensitivity was substantially lower (range, 10.8%-29.5%).

Differences in the methodology of these studies may impact the reported sensitivities. The populations are from different countries and are comprised mostly of patients from tertiary referral centers. Different populations, especially those seen in primary care, may have different rates of mutations. The type and number of mutations tested for, and the methods of testing, also varied in these studies. For example, for LDLR gene mutations, some studies used a defined set of known pathogenic mutations while other studies searched for any mutations and reported both known and unknown mutations. There were also differences in the method for making a clinical diagnosis, and different diagnostic criteria may have resulted in different populations.

Table 1. Clinical Validity of Genetic Testing for FH

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Location</th>
<th>N</th>
<th>Genes Tested (Mutations)</th>
<th>Clinical Sensitivity</th>
<th>Clinical Specificity</th>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sample Size</th>
<th>Definitive FH</th>
<th>Probable FH</th>
<th>Possible FH</th>
<th>Unknown FH</th>
<th>Sensitivity</th>
</tr>
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</table>
| Diakou (2011)    | Greece      | 254         | LDLR (n=10)   | APOB (n=1)  | PSCK9 (n=1) | ARH (n=1)  | 66.5% (269/254)
|                  |             |             |               |             |             |            | 100% (40/40) |
| Hooper (2012)    | Australia   | 343         | LDLR (n=18)   | APOB (n=2)  | PSCK9 (n=1) |            | 70.3% (90/128) |
|                  |             |             |               |             |             |            | 29.5% (26/88) |
|                  |             |             |               |             |             |            | 10.8% (12/111) |
| Palacios (2012)  | Spain       | 5,430       | LDLR (any)    | APOB (n=1)  | PSCK9 (n=4) |            | --          |
|                  |             |             |               |             |             |            | --          |
|                  |             |             |               |             |             |            | 41.4% (2246/5430) |
| Taylor (2010)    | United Kingdom | 635    | LDLR (n=18)   | APOB (n=1)  | PSCK9 (n=1) |            | 56.3% (107/190) |
|                  |             |             |               |             |             |            | --          |
|                  |             |             |               |             |             |            | 28.4% (112/394) |
|                  |             |             |               |             |             |            | 34.5% (219/635) |
| Ticky (2012)     | Czech Republic | 2,239    | LDLR (any)    | APOB (n=1)  |             |            | --          |
|                  |             |             |               |             |             |            | --          |
|                  |             |             |               |             |             |            | 35.7% (800/2239) |

FH: familial hypercholesterolemia.

- Individuals with a clinical diagnosis of FH based on Williams's clinical criteria.
- Individuals with possible, probable, definite FH but not separated by category.
- Individuals with a high clinical suspicion for FH based on personal history, family history, and low-density lipoprotein levels.

**Section Summary: Clinical Validity**

Evidence on clinical validity includes cohorts of patients with definite or suspected FH tested for genetic mutations, and cohorts of unaffected patients tested for genetic mutations. Five moderate-to-large cohorts were reviewed, all from different countries in Europe. A wide range of clinical sensitivity was reported (range, 34.5%-66.5%). The sensitivity is higher in patients with definite FH (range, 50%-70%). In patients with probable or possible FH, the sensitivity is low (range, 10%-30%). Only 1 study reported clinical specificity, testing 40 unaffected individuals for pathogenic mutations, and no mutations were found.

**Clinical Utility**

**Diagnostic Testing**

There is no direct evidence on the clinical utility of genetic testing for FH. An indirect chain of evidence is thus constructed, and can provide evidence of clinical utility if all the links in the chain of evidence are intact. The elements contributing to the indirect chain of evidence are
derived from evidence review (see Related Medical Policies). The following series of questions represent the indirect chain of evidence on diagnostic testing for FH.

**Is FH a disorder with a high burden of illness and potentially preventable morbidity and mortality?**

- Yes. FH is a disorder with a high burden of illness and potentially preventable morbidity and mortality. Accelerated atherosclerotic disease in the absence of treatment leads to premature coronary artery disease (CAD) and increased morbidity and mortality for affected patients.

**Are there some cases in which the diagnosis cannot be made by standard clinical workup without genetic testing?**

- Yes. There are cases in which the diagnosis cannot be made by standard clinical workup without genetic testing. There is an overlap in cholesterol levels between individuals with FH and those with other types of hypercholesterolemia. Therefore cholesterol levels cannot always distinguish between FH and non-FH. Family history of premature CAD may or may not be apparent for all individuals, leading to a substantial number of cases in which the diagnosis is uncertain based on family history and cholesterol levels.

**Can genetic testing make the diagnosis of FH with certainty in patients with an uncertain clinical diagnosis?**

- Yes. For patients with an uncertain diagnosis of FH, genetic testing can confirm the diagnosis in a substantial proportion of patients. Identification of a known pathogenic mutation has a high specificity for FH and therefore will confirm the disorder with a high degree of certainty. On the other hand, the sensitivity for identifying a pathogenic mutation is suboptimal and therefore a negative genetic test will not rule out FH.

**Does establishment of a definitive diagnosis of FH lead to management changes?**

Two situations are considered here: (1) a definitive diagnosis of FH is required to establish eligibility for specialty medications and (2) all other situations.

- A definitive diagnosis of FH is required to establish eligibility for specialty medications
  - Yes. When a definitive diagnosis is required, genetic testing may be necessary. For patients who are in an uncertain category by clinical criteria, a positive genetic test will confirm the diagnosis of FH. These patients will then be eligible for specialty medications (e.g., PCSK9 inhibitors) and these medications will be initiated in patients who have uncontrolled lipid levels despite treatment with statins and/or other agents.

- All other situations
No. Following a definitive diagnosis of FH, it is unlikely that management changes occur that improve outcomes. Treatment of hyperlipidemia is primarily based on LDL levels, and the presence of FH does not affect treatment decisions apart from the LDL level. All patients with FH will have indications for statin treatment, and many will have indications for additional interventions based on the LDL response to statins.

- It is possible that clinicians may intensify treatment following a diagnosis of FH, such as switching to a more potent statin, increasing the statin dose, or referral to a lipid specialist. However, these types of management changes have not been documented in the literature and have an uncertain impact on health outcomes.

Do management changes that occur result in improved health outcomes?

- A definitive diagnosis of FH is required to establish eligibility for specialty medications

  - Yes. Management changes that occur as a result of genetic testing are initiation of effective medications (e.g., PCSK9 inhibitors). In patients who have uncontrolled lipid levels despite treatment with standard medications, these drugs have been demonstrated to improve outcomes.\textsuperscript{12,13}

- All other situations

  - No. It is uncertain whether management changes occur as a result of genetic testing in other situations, therefore, it is not possible to conclude that management changes occur that improve outcomes.

Testing Individuals for Future Risk of Disease

There is no direct evidence on the clinical utility of genetic testing for FH. An indirect chain of evidence is thus constructed, and can provide evidence of clinical utility if all the links in the chain of evidence are intact. The elements contributing to the indirect chain of evidence are derived from evidence review (see Related Medical Policies). The following series of questions represent the indirect chain of evidence for testing asymptomatic individuals to determine future risk of disease.

Is FH a disorder with a high burden of illness and potentially preventable morbidity and mortality?

- Yes. FH is a disorder with a high burden of illness and potentially preventable morbidity and mortality. Accelerated atherosclerotic disease in the absence of treatment leads to premature CAD and increased morbidity and mortality for affected patients.
When there is a known pathogenic mutation in the family, is risk stratification by genetic testing superior to risk stratification from standard workup alone (serum LDL levels)?

- Yes. The presence of a pathogenic mutation in the family allows for targeted testing in relatives. Targeted testing for a known pathogenic mutation has positive and negative predictive values, both approaching 100%. Risk stratification by lipid levels is less accurate because lipid levels for patients with FH overlap with lipid levels for patients with non-FH, and therefore some errors will be made in assigning a diagnosis.

  - Cascade screening for FH has been evaluated in a national screening program from the Netherlands. This program was initiated at a time when cholesterol screening was recommended for the general population. The addition of cascade screening for FH led to more than 9000 additional individuals diagnosed with FH. The rate of statin use increased in this population from an estimate of 39% prior to initiation of the program to 85% after full implementation. While cascade screening is likely to improve outcomes, it requires an infrastructure that allows access to the entire population, and is not likely to be feasible when only a limited population is available for screening. As a result of these barriers, cascade screening has not been used in the United States.

Does the presence of a pathogenic mutation indicate high risk for clinical disease (high penetrance)?

- Yes. Penetrance for all of the known pathogenic mutations is greater than 90%. Therefore, the presence of a pathogenic mutation in an asymptomatic individual indicates a very high likelihood of developing clinical disease.

Is there a presymptomatic phase during which preventive strategies can be implemented?

- Yes. FH has a reasonably long presymptomatic phase in which preventive strategies can be implemented. Because the development of atherosclerotic disease is gradual and cumulative, preventive strategies initiated during the presymptomatic phase have the potential to reduce the burden of atherosclerotic disease.

Does the presence of a pathogenic mutation lead to management changes?

Two situations are considered here: (1) adults and (2) children.

- Adults
  - No. Following a definitive diagnosis of FH, it is unlikely that management changes will improve outcomes. In adults, treatment of hyperlipidemia is based on LDL levels, and the presence of FH does not affect treatment decisions apart from the LDL level. All patients
with FH will have indications for statin treatment, and many will have indications for additional interventions based on the LDL response to statins.

- Children
  - Yes. For children, screening for hyperlipidemia will begin at different ages if FH is present in the family, and treatment with statins will begin earlier than if FH was not diagnosed. For the general population, lipid screening should begin at approximately 10 years of age. However, for children of individuals with FH, screening should begin sooner, and management changes, consisting of lifestyle modifications and/or medications, should begin as soon as possible.

**Do management changes that occur as a result of genetic testing lead to improved health outcomes?**

- Adults
  - No. It is uncertain whether management changes occur as a result of genetic testing in other situations, therefore, it is not possible to conclude that management changes will improve outcomes.

- Children
  - Yes. Management changes that occur in children are primarily initiation of effective medications (e.g., statins, PCSK9 inhibitors). These medications are known to decrease cardiovascular events in patients with hypercholesterolemia; therefore, initiation of these medications in patients at high risk of atherosclerotic disease will improve outcomes.

**Section Summary: Clinical Utility**

There is a lack of direct evidence for clinical utility; therefore indirect chains of evidence are used to determine whether testing has clinical utility. For diagnostic genetic testing, when a definitive diagnosis of FH is required to establish eligibility for specialty medications, the links in the chain of indirect evidence are intact and clinical utility is demonstrated. In other situations, there are gaps in the chain of indirect evidence that preclude conclusions on clinical utility. For this indication, genetic testing can confirm the presence of FH in some individuals who have an uncertain clinical diagnosis, but treatment decisions are made primarily on LDL levels and the establishment of definite FH will not change treatment recommendations. It is possible that some types of management changes are undertaken after a diagnosis of FH, such as intensification of medication treatment or referral to a lipid specialist, but these management changes have an uncertain impact on outcomes.
For testing individuals to determine future risk of disease, in adults there gaps in the chain of indirect evidence that preclude conclusions on clinical utility. Genetic testing is superior to standard risk stratification, but treatment decisions are made primarily on LDL levels and the establishment of definite FH will not change treatment recommendations. For children, an indirect chain of evidence establishes that clinical utility is present. Screening will begin at different ages for children at risk for FH compared to the general population, and treatment with statins will be initiated earlier once a diagnosis of FH is made. Therefore, for children of individuals with a known pathogenic mutation in the family, targeted genetic testing will improve outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

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<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
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<td>Ongoing</td>
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NCT: national clinical trial

Summary of Evidence

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.

- **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.

### Practice Guidelines and Position Statements

**National Lipid Association Expert Panel**

Recommendations on the diagnosis and screening for FH were developed by the National Lipid Association Expert Panel on Familial Hypercholesterolemia and published in 2011. The following recommendations relevant to genetic testing were included:

- “Formal clinical diagnosis of FH can be made by applying any one of several validated sets of criteria [U.S. Make Early Diagnosis Prevent Early Death (MEDPED), Dutch Lipid Clinic Network, Simon-Broome Registry]. It should be noted that LDL [low-density lipoprotein] cholesterol cut points usually vary with age...

- Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when diagnosis is uncertain.

- Identification of a causal mutation may provide additional motivation for some patients to implement appropriate treatment.

- Importantly, a negative genetic test does not exclude FH, since approximately 20% of clinically definite FH patients will not be found to have a mutation despite an exhaustive search using current methods...

- Cascade screening involves testing lipid levels in all first-degree relatives of diagnosed FH patients.

- As cascade screening proceeds, newly identified FH cases provide additional relatives who should be considered for screening.
• Cascade screening is the most cost-effective means of finding previously undiagnosed FH patients and is also cost-effective in terms of cost per year of life saved. General population screening of a young population (before age 16) is similarly cost-effective in terms of cost per year of life saved, given that effective cholesterol treatment is begun in all those identified.”

**American College of Cardiology and American Heart Association**

The American College of Cardiology and American Heart Association task force recommendations on the treatment of blood cholesterol to reduce atherosclerotic disease in adults (follow-up report to Adult Treatment Recommendations from the National Cholesterol Education Panel) were published in 2013. 17 These recommendations do not mention genetic testing. Treatment recommendations are based on LDL levels and clinical factors, and there are no separate treatment recommendations for individuals with FH.

**National Heart, Lung, and Blood Institute**

Recommendations from an expert panel on cardiovascular health and risk reduction in children and adolescents were published in 2011. 15 The report contained the following recommendations:

• “The evidence review supports the concept that early identification and control of dyslipidemia throughout youth and into adulthood will substantially reduce clinical CVD risk beginning in young adult life. Preliminary evidence in children with heterozygous FH with markedly elevated LDL-C indicates that earlier treatment is associated with reduced subclinical evidence of atherosclerosis. (Grade B)

• TC and LDL-C levels fall as much as10-20% or more during puberty.(Grade B) Based on this normal pattern of change in lipid and lipoprotein levels with growth and maturation, age 10 years (range age 9-11 years) is a stable time for lipid assessment in children. (Grade D) For most children, this age range will precede onset of puberty.”

**U.S. Preventive Services Task Force Recommendations**

The U.S. Preventive Services Task Force (USPSTF) published recommendations for lipid disorders in adults in 2008. 18 This publication does not make specific recommendations for genetic testing for FH. An update of this report is currently in progress in 2016.
A draft evidence review on Lipid Screening in Children and Adolescents for Detection of Familial Hypercholesterolemia was posted on the USPSTF website in 2016. This draft report states that genetic screening for FH and cascade screening of relatives are beyond the scope of the report.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**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)
- ARUP Laboratories (UT)
- Athena Diagnostics (MA)
- Baylor College of Medicine (TX)
- Correlagen Diagnostics (MA)
- Mayo Clinic (MN)
- Prevention Genetics (WI)
- Progenika Biopharma (MA)


History

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<td>8/9/16</td>
<td>New policy, add to Genetic Testing section. Policy created with a literature review through March 19, 2016. Genetic testing to confirm a diagnosis of Familial Hypercholesterolemia (FH) may be considered medically necessary when a definitive diagnosis of FH may be required for eligibility for specialty medications and criteria are met. FH testing is investigational when criteria are not met. Genetic testing to determine future risk of disease may be considered medically necessary in children when criteria are met. Genetic testing to determine future risk of disease in adults is investigational when criteria are not met.</td>
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  - Qualified interpreters
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U.S. Department of Health and Human Services

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