Genetic Testing for Heterozygous Familial Hypercholesterolemia

Introduction

Familial hypercholesterolemia (FH) is an inherited disorder that causes abnormally high levels of low-density lipoprotein (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, and as a result, the arteries can become clogged or clots can form. These clogged arteries and clots can then cause high blood pressure, heart attacks, and strokes. If left untreated, familial hypercholesterolemia can also cause 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.
## Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Confirm a diagnosis of familial hypercholesterolemia (FH)** | 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 (see Additional Information) 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) (see Additional Information)  
  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.  |
| **Testing of children of individuals with FH** | 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 (see Additional Information):  
  - A pathogenic variation is present in a parent  
  AND  
  - General lipid screening is not recommended based on age or other factors  

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

<table>
<thead>
<tr>
<th>Service</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing of adults who are close relatives of</strong></td>
<td>Genetic testing of adults who are close relatives of individuals with FH to determine future risk of disease is considered investigational.</td>
</tr>
</tbody>
</table>
Service | Investigational
--- | ---
individuals with FH | investigational (see Additional Information).

Note: See additional information below.

Additional Information

To confirm a diagnosis of familial hypercholesterolemia (FH)

- 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. Here are some examples of certain criteria not being met:
  - Dutch Lipid Clinic Criteria. A score of 8 or greater on the Dutch Lipid Clinic Network 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-degree or a second-degree relative.
  - Make Early Diagnosis Prevent Early Death (MEDPED) Diagnostic 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.

  Note: See Evidence Review for more information about these tests.

- Eligibility for specialty medicines (eg, 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 served as an eligibility criterion. The diagnosis in these trials was based on clinical factors with or without genetic testing.

Testing of adults who are close relatives of individuals with FH
Additional Information

- 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; conversely, cascade screening 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; additionally, there exists a lack of coordination for patients with different types of medical insurance.

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
</tbody>
</table>
| 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) (eg, familial hypercholesterolemia type B), common variants (eg, 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) (eg, 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) (eg, familial hypercholesterolemia), full gene sequence  
PCSK9 (proprotein convertase subtilisin/kexin type 9) (eg, familial |
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

#### Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

### Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benignchange in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, 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 be performed in an affected family member so that testing in unaffected, at-risk family members can focus on the variant found in the affected family member. However, coverage for testing of the affected index case (proband) depends contract benefit language.

Specific contract language 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.
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, which is more common and more difficult to diagnose, is the focus of this medical policy. 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.

Familial Hypercholesterolemia

Familial hypercholesterolemia can be categorized as homozygous or heterozygous. Homozygous FH is an extremely rare disorder that arises from biallelic variants in a single gene, and the disorder 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 patients and is present in childhood. Some populations, such as Ashkenazi Jews and South Africans, have a higher prevalence of FH, up to 1 in 100. For affected individuals, the burden of illness is high. Patients with FH and increased LDL cholesterol (>190 mg/dL) have a 3 times higher risk of CAD than those with increased LDL cholesterol alone. The average age for presentation with CAD is in the fourth decade for men and the fifth decade for women, and there is a 30% to 50% increase in risk for men and women in the fifth and sixth decades, respectively. Increased risk of CAD is associated with a higher rate of death associated with cardiovascular causes in patients with homozygous and heterozygous FH.

Diagnosis

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.⁶

- **Make Early Diagnosis Prevent Early Deaths Diagnostic Criteria**
  - 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 his/her 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 Network 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 Register Criteria**
  - Using these criteria, a definite diagnosis of FH is made based on a total cholesterol greater than 290 mg/dL in adults (or LDL >190 mg/dL) together with tendinous xanthoma in the individual or in 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-degree or a second-degree relative.
**Treatment**

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 the standard treatment of hypercholesterolemia. There may be more differences in children, for whom the presence of a pathogenic variant 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.³ 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.⁷

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.³ 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.³ 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.

**Genetic Markers for 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 variants associated with FH.

- The LDL receptor gene (LDLR) is the most common variant identified, accounting for between 60% and 80% of FH.⁶
  - 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 variants have been identified in this gene.\(^1,6\) Characterization of the frequency and spectrum of variants is ongoing.\(^8\)

- The APOB gene accounts for approximately 1% to 5% of FH cases.\(^1\)
  - Apolipoprotein B is a cofactor in the binding of LDL to the LDL receptor, and variants in APOB lead to reduced clearance of LDL.
  - There are a limited number of variants of this gene, allowing targeted testing.

- The PCSK9 gene accounts for approximately 0% to 3% of FH.\(^1\)
  - This variant 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 variants, allowing targeted testing.

Penetrance for all FH genes is 90% or higher.\(^1\) Therefore, nearly all patients found to have a pathogenic variant 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 of Evidence

For individuals who have signs and/or symptoms of FH when a definitive diagnosis is required to establish eligibility for specialty medications or who have signs and/or symptoms of FH undergoing lipid lowering therapy 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. For clinical validity, there are large samples of individuals with FH who have been systematically tested for FH variants. In these cohorts of patients, the clinical sensitivity ranges from 30% to 70% for those with definite FH. For suspected FH, the sensitivity is lower, ranging from 1% to 30%. Clinical specificity ranges from 99% to 100%. False-positives are expected to be low for known pathogenic variants, but the false-positive rate is unknown for novel variants or for variants of unknown significance. Direct evidence for clinical utility is lacking. The clinical utility of genetic testing was evaluated using a chain of evidence in the following situations:
• **When a definitive diagnosis of FH is required to establish eligibility for specialty medications.** A 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 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 a chain of evidence. 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 are adults or children and 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 validity, other test performance measures, symptoms, change in disease status, and morbid events. For clinical validity, there are large samples of individuals with FH who have been systematically tested for FH variants. In these cohorts of patients, the clinical sensitivity ranges from 30% to 70% for individuals with definite FH. For suspected FH, the sensitivity is lower, ranging from 1% to 30%. Clinical specificity ranges from 99% to 100%. False-positives are expected to be low for known pathogenic variants, but the false-positive rate is unknown for novel variants or for variants of unknown significance. Direct evidence for clinical utility is lacking. Clinical utility was evaluated using a chain of evidence in the following situations.

• **Adults.** Clinical utility cannot be demonstrated through a 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 a chain of evidence. Targeted genetic testing is superior to standard risk stratification for determining future risk of disease. It is recommended that children of individuals who have a pathogenic variant initiate screening
at an earlier age; further, the affected children should begin treatment with statins as early as possible. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01524289</td>
<td>Study to Assess the Tolerability and Efficacy of Anacetrapib Co-administered With Statin in Participants With Heterozygous Familial Hypercholesterolemia (MK-0859-020) (REALIZE)</td>
<td>306</td>
<td>Oct 2018</td>
</tr>
<tr>
<td>NCT03253432</td>
<td>IN-TANDEM Familial Hypercholesterolemia Pilot Study</td>
<td>400</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01960244</td>
<td>Study of Awareness and Detection of Familial Hypercholesterolemia (CASCADE-FH)</td>
<td>5000</td>
<td>Oct 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial  
a Denotes industry-sponsored trial

**Practice Guidelines and Position Statements**

Migliara et al (2017) conducted a systematic review of guidelines on genetic testing and patient management of individuals with familial hypercholesterolemia (FH). The literature search, conducted through April 2017, identified 10 guidelines for inclusion. Three of the guidelines were developed within the United States: those by the National Lipid Association, International FH Foundation, and American Association of Clinical Endocrinologists and American College of Endocrinology. Guidance from the National Institute for Health and Care Excellence was also included in the review. The quality of the guidelines was assessed using the Appraisal of Guidelines for Research and Evaluation II) instrument, with guideline quality ranging from average to good. Most guidelines agreed that genetic testing follows cholesterol testing, physical findings distinctive of FH, and highly suggestive family history of FH. Universal
screening for FH was not recommended. This review highlighted the importance of genetic testing for FH in children, because aggressive treatment at an earlier age may prevent premature coronary heart disease.

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. The report contained the following recommendations (see Table 4).

Table 4. Recommendations on Cardiovascular Health and Risk Reduction in Children and Adolescents

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“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.”</td>
<td>B</td>
</tr>
<tr>
<td>“TC and LDL-C levels fall as much as 10–20% or more during puberty.”</td>
<td>B</td>
</tr>
<tr>
<td>“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. For most children, this age range will precede onset of puberty.”</td>
<td>D</td>
</tr>
</tbody>
</table>

CVD: cardiovascular disease; FH: familial hypercholesterolemia; GOE: grade of evidence; LDL-C: low-density lipoprotein cholesterol; TC: triglycerides.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2008) published recommendations for lipid disorders in adults which was archived in 2013. This publication did not make specific recommendations for genetic testing for FH.

A Task Force evidence report, conducted by Lozano et al (2016), evaluated lipid screening in children and adolescents to detect familial hypercholesterolemia. This report stated that genetic screening for FH was beyond the scope of the report. Further, the report stated that “because implementing this approach [cascade screening] in the United States would require
new infrastructure, cascade screening is outside of the purview of U.S. primary care and beyond the scope of this review.”

**Medicare National Coverage**

There is no national coverage determination.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**References**


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/01/16</td>
<td>New policy, add to Genetic Testing section. Approved August 9, 2016. 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>
</tr>
</tbody>
</table>

**Disclaimer**: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope**: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):

"يجب إن هذا الإشعار معقول. قد يكون هذا الإشعار معقول مهماً، ونعد أن تكون قد تسر على مصلحة Premera Blue Cross. العملية التي نتيسر على فتح النصوص على هذا الإشعار. مع المجازحة. ونحتاج إلى إحرازه في تواريخ محددة للعثور على معلومات الصحية والمساعدة في دفع التكاليف. يتحدى مصلحة هذه المعلومات والمساعدة بذلك دون كيد أي كلمة. إن مصلحة 800-722-1471 (TTY: 800-842-5357) لن تخطأ.

中文 (Chinese):

本通知有重要的讯息。本通知可能有关於您透过 Premera Blue Cross 提交的 申请或保险的重要讯息。本通知可能有重要日期，您可能需要在截止日期之前采取行动，以保留您的健康保险或者费用补贴。您有权免费以您的母语得到本讯息和帮助。请拨电话 800-722-1471 (TTY: 800-842-5357)。

Oromo (Cushite):


Deutsche (German):


Italiano (Italian):

日本語 (Japanese): この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補足情報に関する重要な情報が含まれている場合があります。この通知には記載されている可能性がある重要な日付をご確認ください。健康保険や無料サポートを維持するためには、特定の日または時刻以降に行動を取りなければならないうえがあります。役のある言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。


Русский (Russian): Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В этом уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish): Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).


Український (Ukrainian): Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).