Familial Hypercholesterolemia Genetic Testing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR Known Familial Mutation</td>
<td>81403</td>
</tr>
<tr>
<td>APOB Known Familial Mutation</td>
<td>81403</td>
</tr>
<tr>
<td>PCSK9 Known Familial Mutation</td>
<td>81403</td>
</tr>
<tr>
<td>LDLR Sequencing</td>
<td>81406</td>
</tr>
<tr>
<td>LDLR Deletion/Duplication</td>
<td>81405</td>
</tr>
<tr>
<td>APOB Targeted Mutation Analysis</td>
<td>81401</td>
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<tr>
<td>APOB Sequencing</td>
<td>81407</td>
</tr>
<tr>
<td>PCSK9 Sequencing</td>
<td>81406</td>
</tr>
</tbody>
</table>

What is familial hypercholesterolemia

Definition

Familial hypercholesterolemia (FH) is a genetic disorder characterized by very high levels of low-density lipoprotein (LDL) cholesterol.

- Familial hypercholesterolemia (FH) is a genetic disorder characterized by very high levels of low-density lipoprotein (LDL) cholesterol: usually >190 mg/dL in untreated adults. This leads to an increased risk for coronary heart disease (CHD), including heart attacks, at an early age.\(^1\)\(^2\)\(^3\)
  - Men with untreated FH have a 50% risk for a coronary event by age 50.\(^3\)\(^4\)
  - Women with untreated FH have a 30% risk for a coronary event by age 60.\(^3\)\(^4\)
- People with untreated FH have about a 20 fold increase for coronary heart disease.\(^3\)
- Early and aggressive LDL-lowering with high doses of potent statins or statin combination therapy significantly lowers CHD morbidity and mortality for people
with FH. Statins are contraindicated during pregnancy due to concerns for teratogenicity and should be discontinued prior to conception. Because there is considerable overlap between the LDL levels of those with FH and common multifactorial hypercholesterolemia, FH often goes undiagnosed until middle age, when much of the preventive value of cholesterol-lowering therapy is lost.

- For FH patients who are not adequately controlled with statin therapy, or with intolerance to statins, PCSK9 inhibitors (e.g. evolocumab, alirocumab) may be an effective alternative treatment.
- Less than 10% of people with FH are adequately treated.
- Various criteria for identifying FH clinically have been developed and are described below:

### Diagnosis: MEDPED criteria

**MEDPED criteria**

**Total Cholesterol (LDL), mg/dL**

<table>
<thead>
<tr>
<th>Patient's age</th>
<th>Patient has 1&lt;sup&gt;st&lt;/sup&gt; degree relative with FH</th>
<th>Patient has 2&lt;sup&gt;nd&lt;/sup&gt; degree relative with FH</th>
<th>Patient has 3&lt;sup&gt;rd&lt;/sup&gt; degree relative with FH</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>220 (155)</td>
<td>230 (165)</td>
<td>240 (170)</td>
<td>270 (200)</td>
</tr>
<tr>
<td>20</td>
<td>240 (170)</td>
<td>250 (180)</td>
<td>260 (185)</td>
<td>290 (220)</td>
</tr>
<tr>
<td>30</td>
<td>270 (190)</td>
<td>280 (200)</td>
<td>290 (210)</td>
<td>340 (240)</td>
</tr>
<tr>
<td>40+</td>
<td>290 (205)</td>
<td>300 (215)</td>
<td>310 (225)</td>
<td>360 (260)</td>
</tr>
</tbody>
</table>

### Diagnosis: Dutch criteria

Definitive FH: 8 points or more; Probable FH: 6-7 points; Possible FH: 3-5 points

<table>
<thead>
<tr>
<th>Points</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 point</td>
<td>First-degree relative with premature cardiovascular disease or LDL &gt;95th percentile, or personal history of premature peripheral or cerebrovascular disease or LDL 155-189 mg/dL</td>
</tr>
<tr>
<td>2 points</td>
<td>First-degree relative with tendinous xanthoma or corneal arcus, or first-degree relative age &lt;18 with LDL &gt;95th percentile, or personal history of coronary artery disease</td>
</tr>
<tr>
<td>3 points</td>
<td>LDL 190-249 mg/dL</td>
</tr>
</tbody>
</table>

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### Points Description

<table>
<thead>
<tr>
<th>Points</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 points</td>
<td>Corneal arcus in patient age &lt;45 years</td>
</tr>
<tr>
<td>5 points</td>
<td>LDL 250-329 mg/dL**</td>
</tr>
<tr>
<td>6 points</td>
<td>Tendon xanthoma</td>
</tr>
<tr>
<td>8 points</td>
<td>LDL ≥330 mg/dL**</td>
</tr>
</tbody>
</table>

**Note** **Please note that these are LDL level cut offs for untreated individuals.**

### Diagnosis: Simon Broome criteria

**Definitive FH**
- Total cholesterol (LDL): 290 (190) mg/dL in adults or 260 (155) mg/dL in pediatric patients and:
- DNA mutation

**Probable FH**
- Total cholesterol (LDL): 290 (190) mg/dL in adults or 260 (155) mg/dL in pediatric patients and:
- Tendon xanthoma in patient or in first-or second-degree relative

**Possible FH**
- Total cholesterol (LDL): 290 (190) mg/dL in adults or 260 (155) mg/dL in pediatric patients and:
- Family history of myocardial infarction (MI) at age <50 in second-degree relative or at age <60 in first-degree relative or family history of total cholesterol >290 mg/dL in first- or second-degree relative

### Prevalence

About 1 in 200-250 people worldwide have FH.\(^3\) The risk is much higher in some South African Afrikaner, Amish, Lebanese, and Finnish populations.\(^3\)

Approximately 1 in 300 to 500 people have heterozygous FH, which means they have one copy of the gene mutation.

Approximately one in 1 million people have homozygous FH, which means they have 2 copies of the gene mutation. This is much more severe than heterozygous FH.\(^4\) People with this type of FH typically have severe coronary heart disease by their mid-20s; the rate of death or the need for surgical treatment of heart problems by the teenage years is high.\(^3\)
Cause

Most cases of FH are caused by mutations in one of three genes: LDLR, APOB, PCSK9. However, mutations in these genes only account for approximately 60%-80% of FH.

There are likely other genes that are not known at the present time that make up the remaining 20%-40% of cases of FH. Therefore, a negative genetic test does not rule out a diagnosis of FH.

Inheritance

FH is an autosomal dominant condition, meaning that only one gene mutation is needed to cause the condition.

A person with heterozygous FH has a 50% chance to pass the mutation to each child.

Although not included in this guideline, it is important to note that there is an autosomal recessive form of hypercholesterolemia which is caused by mutations in the LDLRAP1 gene. There is also a milder autosomal dominant form, Familial Combined Hyperlipidemia, which is usually caused by mutations in the LPL gene.

Test information

- A clinical diagnosis of FH is suspected based on some combination of personal and family history of very high cholesterol, premature CHD, and cholesterol deposits, such as tendon xanthomas and corneal arcus. At least three organizations have attempted to define clinical diagnostic criteria for FH, but all criteria have recognized limitations. The three different criteria are described above.
- Genetic testing for FH can confirm a diagnosis of FH, particularly in borderline clinical cases.
- Laboratories may offer evaluation of the LDLR, APOB, or PCSK9 genes individually, as panels, or with reflex options.
  - **LDLR**: Over 1000 mutations have been characterized so sequence analysis is required. Major gene deletions and rearrangements account for an estimated 9% of LDLR mutations and require specialized deletion testing to detect them.
  - **APOB**: FH-causing APOB mutations are primarily found in a limited region of the gene, with the R3500Q mutation being most common. Laboratory testing may be done by targeted mutation analysis for a limited number of APOB mutations or sequencing of the gene region where these mutations are generally found. According to GeneReviews, as of 2016 there has been only one reported case of a deletion in APOB causing FH.
  - **PCSK9**: “Gain of function mutations in PCSK9 cause fewer than 5% of cases in most studies.” According to GeneReviews, as of 2016 there have been no deletions or duplications reported in PCSK9 that cause FH.
• Once a mutation is found in an affected person, single-site testing should be offered to at-risk family members to allow for appropriately early intervention.\textsuperscript{15,16}

**Genetic testing for FH**

Proportion of FH attributed to each gene.

**Molecular Genetic Testing for FH**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Proportion of FH Attributed to Mutations in Gene\textsuperscript{3}</th>
<th>Test Method\textsuperscript{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR</td>
<td>60%-80%</td>
<td>Sequence Analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/Duplication</td>
</tr>
<tr>
<td>APOB</td>
<td>1%-5%</td>
<td>Targeted Analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sequencing Analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/Duplication</td>
</tr>
<tr>
<td>PCSK9</td>
<td>0%-3%</td>
<td>Targeted Analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sequencing Analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/Duplication</td>
</tr>
<tr>
<td>Unknown</td>
<td>20%-40%</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Guidelines and evidence**

**Guidelines and evidence - genetic testing**

• A Journal of the American College of Cardiology Scientific Expert Panel (2018) statement on clinical genetic testing for FH states:\textsuperscript{17}
  
  o “Because FH is common yet underdiagnosed, it is expected that genetic testing will facilitate the diagnosis of FH, the initiation and intensity of recommended lipid-lowering therapy (LLT), and the identification of affected relatives, thus reducing the burden of cardiovascular disease in families with FH.”

• Evidence-based guidelines by the National Institute for Clinical Excellence of UK (NICE, 2008 (reaffirmed 2016)) support genetic testing for FH as follows:\textsuperscript{16}
  
  o “A diagnosis of FH should be made using the Simon Broome criteria, which include a combination of family history, clinical signs (specifically tendon xanthomata), cholesterol concentration and DNA testing (see appendix E of the NICE guideline).”
o "Healthcare professionals should offer people with a clinical diagnosis of FH a DNA test to increase the certainty of their diagnosis and to aid diagnosis among their relatives."

o "Healthcare professionals should inform all people who have an identified mutation diagnostic of FH that they have an unequivocal diagnosis of FH even if their LDL-C concentration does not meet the diagnostic criteria (see appendix E)."

o "In a family where a DNA mutation is identified, not all family members may have inherited the mutation. When DNA testing has excluded FH in a member of a family, healthcare professionals should manage the person's coronary heart disease risk as in the general population."

o "In families in which a mutation has been identified, the mutation and not LDL-C concentration should be used to identify affected relatives. This should include at least the first- and second- and, when possible, third-degree biological relatives."

o "In children at risk of FH because of one affected parent, the following diagnostic tests should be carried out by the age of 10 years or at the earliest opportunity thereafter."

  - A DNA test if the family mutation is known.
  - LDL-C concentration measurement if the family mutation is not known. When excluding a diagnosis of FH a further LDL-C measurement should be repeated after puberty because LDL-C concentrations change during puberty."

- The European Atherosclerosis Society Consensus Panel (2015) states the following: 18

  o "Given the proven atherogenicity of LDL-C in experimental models and in humans with FH, with evidence that exposure to even moderate hypercholesterolaemia increases the long-term risk of a new CHD event, and given the lifelong benefit of genetically determined low LDL-C concentrations, there is an urgent need to identify and treat FH early to maximize therapeutic benefit…. Detection of a pathogenic mutation, usually in the LDLR gene, is the gold standard for diagnosis of FH."

- Consensus-based guidelines from The Cardiac Society of Australia and New Zealand (CSANZ, 2013) state: "Although the clinical picture of FH will be clear-cut in many instances, the diagnostic criteria suggest that genetic testing can provide certainty of diagnosis in some cases where confounding factors such as borderline cholesterol levels, inconclusive family histories or tendon injuries have resulted in a diagnostic dilemma." 11

- The National Lipid Association expert panel on Familial Hypercholesterolemia (2011) 14 made the following recommendations regarding genetic testing:
“Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when the 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.”

**Guidelines and evidence - drug treatment**

- The US Food and Drug Administration approved the following PCSK9 inhibitors as treatment for FH. However, there have been no guidelines recommending that genetic testing should be performed for the sole purpose of treatment decisions (i.e. PCSK9 inhibitors) in the absence of a clinical suspicion of FH:

  - “Praluent (alirocumab) injection in adult patients with heterozygous familial hypercholesterolemia or patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol.”  
  
    [19](#)

  - “Repatha (evolocumab) injections for use in additional to diet and maximally-tolerated statin therapy in adult patients with heterozygous hypercholesterolemia, homozygous hypercholesterolemia, or clinical atherosclerotic cardiovascular disease, such as heart attacks or strokes, who require additional lowering of LDL cholesterol.”  
  
    [20](#)

**Criteria**

**LDLR, APOB, PCSK9 Known Familial Mutation Testing**

- **Clinical Consultation:**
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- **Previous Genetic Testing:**
  - No previous genetic testing of LDLR, APOB, or PCSK9, and
  - LDLR, APOB, or PCSK9 mutation identified in 1\textsuperscript{st}, 2\textsuperscript{nd} or 3\textsuperscript{rd} degree biological relative, AND

- **Diagnostic Testing:**
  - LDL cholesterol of >120 mg/dL in the absence of treatment
LDLR Full Sequence and Deletion/Duplication Analysis

• Clinical Consultation:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by
    the Health Plan policy), AND
• Previous Testing:
  o No previous LDLR sequencing or deletion/duplication testing, and
  o No known LDLR, APOB, or PCSK9 mutation in the family, AND
• Diagnostic Testing:
  o Member meets the MEDPED criteria or either the Dutch criteria or the Simon
    Broome criteria for possible or probable FH, and
  o Genetic testing is necessary because there is uncertainty in the clinical
    diagnosis

APOB Targeted Mutation Analysis or Full Sequence Analysis

• Criteria for LDLR sequencing and deletion/duplication analysis is met, AND
• No previous full sequence analysis of APOB, AND
• No mutations detected in full sequencing or deletion/duplication testing of LDLR or
  PCSK9 sequencing, if previously performed

PCSK9 Full Sequence Analysis

• Criteria for LDLR sequencing and deletion/duplication analysis is met, AND
• No previous genetic testing for PCSK9, AND
• No mutations detected in full sequencing or deletion/duplication analysis of LDLR or
  APOB sequencing, if previously performed

LDLR, APOB, PCSK9 Multigene Panels

FH multi-gene panels, limited to testing for LDLR, APOB, and PCSK9, will be
reimbursed when the following criteria are met:

• Clinical Consultation:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by
    the Health Plan policy), AND
• Previous Testing:
o No previous LDLR, APOB, or PCSK9 sequencing or deletion/duplication testing, and
o No known LDLR, APOB, or PCSK9 mutation in the family, AND

- Diagnostic Testing:
  o Member meets the MEDPED criteria or either the Dutch criteria or the Simon Broome criteria for possible or probable FH, and
  o Genetic testing is necessary because there is uncertainty in the clinical diagnosis

Exclusions

Genetic testing for the sole purpose of treatment decisions (i.e. PCSK9 inhibitors) in the absence of a clinical suspicion supported by either the MEDPED, Dutch, or Simon Broome criteria is considered investigational and/or experimental.

References


