Familial Hypercholesterolemia Genetic Testing

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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.

Procedures addressed by this guideline	Procedure codes
APOB common variants	81401
APOB sequence analysis	81407
FH known familial mutation analysis	81403
FH multigene panel	81479
LDLR sequence analysis	81406
LDLR deletion/duplication analysis	81405
PCSK9 sequence analysis	81406

Criteria

Introduction

Requests for familial hypercholesterolemia (FH) genetic testing are reviewed using these criteria.

Known Familial Mutation Testing for Familial Hypercholesterolemia

- 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 that would detect the familial mutation, and
  - LDLR, APOB, or PCSK9 mutation identified in 1st, 2nd or 3rd degree biological relative, AND

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- Diagnostic Testing:
  - LDL cholesterol of >120 mg/dL in the absence of treatment, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

LDLR Full Sequence and Deletion/Duplication Analysis

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

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, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

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, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

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

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 Dutch or Simon Broome criteria is not medically necessary.

What is familial hypercholesterolemia?

Definition

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

Prevalence

About 1 in 200-250 individuals worldwide have heterozygous FH (they have 1 FH-causing mutation), but may be higher in certain ethnicities.[1]

Approximately one in 160,000-400,000 individuals have homozygous FH (they have 2 FH-causing mutations). This is much more severe than heterozygous FH.[2] Individuals 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.[1]

Symptoms

FH is a genetic disorder characterized by very high levels of low-density lipoprotein (LDL) cholesterol: usually >190 mg/dL in untreated adults and >130 mg/dl in untreated children/adolescents.[1] This leads to an increased risk for coronary heart disease (CHD), including heart attacks, at an early age.[1,3,4]

- Men with untreated FH have a 50% risk for a coronary event by age 50.[1,2]
- Women with untreated FH have a 30% risk for a coronary event by age 60.[1,2]

Individuals with untreated FH have about a 22 fold increased risk for coronary artery disease.[1]

Cause

Most cases of FH are caused by mutations in one of three genes: LDLR, APOB, PCSK9.[1] However, mutations in these genes only account for approximately 60%-80% of FH.[1]

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.[1]

Inheritance

FH is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

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.[1]

Diagnosis

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.[4] Several organizations have attempted to define clinical diagnostic criteria for FH with the Dutch Lipid Clinic Network and Simon Broom criteria being most widely used, but all criteria have recognized limitations.[5-8]

Genetic testing for FH can confirm a diagnosis of FH, particularly in borderline clinical cases.[4,9,10]

MEDPED criteria[6]

Table gives required cholesterol levels and family history for diagnosing FH.

Total Cholesterol (LDL), mg/dL

Patient's age	Patient has 1st degree relative with FH	Patient has 2nd degree relative with FH	Patient has 3rd degree relative with FH	General population
<20	220 (155)	230 (165)	240 (170)	270 (200)
20-29	240 (170)	250 (180)	260 (185)	290 (220)
30-39	270 (190)	280 (200)	290 (210)	340 (240)
40 or older	290 (205)	300 (215)	310 (225)	360 (260)

Dutch criteria[6]

Definitive FH: Greater than 8 points; Probable FH: 6-8 points; Possible FH: 3-5 points; Unlikely FH <3 points

Points	Description
1 point	First-degree relative with premature* cardiovascular disease or LDL >95th percentile, or personal history of premature peripheral or cerebrovascular disease or LDL 155-189 mg/dL**
2 points	First-degree relative with tendinous xanthoma and/or corneal arcus, or first-degree relative age <18 with LDL >95th percentile, or personal history of coronary artery disease
3 points	LDL 190-249 mg/dL**
4 points	Corneal arcus in patient age <45 years
5 points	LDL 250-329 mg/dL**
6 points	Tendon xanthoma
8 points	LDL ≥330 mg/dL**

Note * Premature: less than 55 years in men; less than 60 years in women

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

Simon Broome criteria[5]

Definitive FH

- Total cholesterol (LDL cholesterol): 290 (190) mg/dL or higher in adults or 260 (155) mg/dL or higher in pediatric patients and tendon xanthoma in patient or in first-or second-degree relative, or
- DNA mutation

Probable 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

Management

Early and aggressive LDL-lowering with high doses of potent statins or statin combination therapy significantly lowers CHD morbidity and mortality for individuals with FH.[11,12] Statins are contraindicated during pregnancy due to concerns for teratogenicity and should be discontinued prior to conception.[1] Due to 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.[13]

The US Food and Drug Administration (FDA) has approved several medications for FH homozygous and heterozygous mutation carriers.[14] However, there have been no guidelines recommending that genetic testing should be performed for the sole purpose of treatment decisions in the absence of a clinical suspicion of FH.

Only 10% of individuals with FH have been identified, and more than 80% of those are not adequately treated.[4]

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.[4, 15-18]

Survival

Individuals with untreated FH have a much higher risk of dying from a coronary event than those in the general population.[2]

Adequate treatment with statins and other medications significantly decreases morbidity and mortality.[1] In one study, survival to age 39 in those treated since childhood was 100%, while in their affected parents, the survival rate was 93%.[19]

Test information

Introduction

Testing for FH may include known familial mutation analysis, targeted or full single gene sequence analysis, deletion/duplication analysis, and/or multigene panels.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Over 1000 LDLR mutations have been characterized so sequence analysis is required. Major gene deletions and rearrangements account for an estimated 15% of mutations and require specialized deletion testing to detect them.[1]

APOB mutations are primarily found in a limited region of the gene, with the R3500Q mutation being most common.[1] 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.[1] Deletions and duplications of APOB are not commonly reported in individuals with FH.[1]

Mutations in PCSK9 are the least common genetic cause of FH with less than 5% of cases being attributed.[20] Whole-gene duplications have been reported to cause FH in 2 families.[1]

The proportion of FH attributed to each gene and recommended testing differs. See the Table: Molecular Genetic Testing for FH.

Molecular Genetic Testing for FH

Gene	Proportion of FH Attributed to Mutations in Gene[1]	Test Method[1]
LDLR	>50%	Sequence Analysis Deletion/Duplication
APOB	~5-10%	Targeted Analysis Sequencing Analysis
PCSK9	<1%	Targeted Analysis Sequencing Analysis Deletion/Duplication
Unknown	20%-40%	NA

Guidelines and evidence

Canadian Cardiovascular Society

The Canadian Cardiovascular Society (CCS, 2018) published an updated position statement that stated the following:[21]

- "We recommend that genetic testing be offered, when available, to complement a diagnosis of FH and enable cascade screening (Strong Recommendation, High-Quality Evidence)."
- "The decision to request genetic screening should be made by the treating physician after discussion with the patient."
- "We suggest that if available, genetic testing should be used to stratify the ASCVD risk in patients with FH (Weak Recommendation, Moderate-Quality Evidence)."

- “We recommend that patients with HoFH be referred to a specialized lipid clinic and undergo complete evaluation for genetic analysis, presence of ASCVD, and aggressive lipid-lowering therapies, including consideration for extracorporeal LDL-C removal, lomitapide, and PCSK9 inhibitors (Strong Recommendation, Moderate-Quality Evidence).”

Cardiac Society of Australia and New Zealand

Consensus-based guidelines from The Cardiac Society of Australia and New Zealand (CSANZ, 2016) stated:[9]

- “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.”

European Atherosclerosis Society

The European Atherosclerosis Society Consensus Panel (2015) stated the following: [22]

- “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.”

International Atherosclerosis Society

The International Atherosclerosis Society (2023) evidence-based guidelines stated the following with regard to diagnosis of FH:[4]

- "A diagnosis of HeFH [heterozygous FH] or HoFH [homozygous FH] should be made, whenever possible, using genetic testing that identifies pathogenic variants (such as in LDLR, APOB, PCSK9 or LDLRAP1) that impair the LDL-receptor pathway; such testing is particularly important when phenotypic features are less obvious, such as in children, and for planning long-term care and cascade testing of family members. Conversely, if the phenotype strongly suggests FH and a pathogenic or likely pathogenic variant is not detected, FH should not be excluded."
- "The value of early detection derives from the premise that the burden of ASCVD [atherosclerotic cardiovascular disease] owing to genetically elevated plasma LDL-cholesterol concentrations in FH begins at birth and accumulates over time and that initiation of treatment in childhood can cost-effectively prevent coronary events, improve quality of life and reduce mortality."

National Institute for Health and Care Excellence

Evidence-based guidelines by the National Institute for Health and Care Excellence (NICE, 2019) supported genetic testing for FH as follows:[16]

- "Use the Simon Broome or Dutch Lipid Clinic Network (DLCL) criteria to make a clinical diagnosis of FH in primary care settings. This should be done by a healthcare professional competent in using the criteria."
- "Refer the person to an FH specialist service for DNA testing if they meet the Simon Broome criteria for possible or definite FH, or they have a DLCN score greater than 5."
- "Healthcare professionals should offer all people with FH a referral to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing."
- "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 ..."
- "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."
- "In children aged 0–10 years at risk of FH because of 1 affected parent, offer a DNA test at the earliest opportunity. If testing of a child at risk has not been undertaken by the age of 10 years, offer an additional opportunity for a DNA test."

National Lipid Association

The National Lipid Association expert panel on Familial Hypercholesterolemia (NLA, 2011) made the following recommendations regarding genetic testing:[20]

- "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."

In a statement on genetic testing in dyslipidemia (2020), the NLA stated:[10]

- "Patients with severe primary hypercholesterolemia, and suspected to have FH, are at high risk of ASCVD; the precise genotype is not predictive in an individual patient."
- "Intensity of treatment should be guided by LDL-C elevation rather than the underlying genotype."

- "Prospective studies are needed to determine whether genetic testing for FH in addition to routine lipid profile testing will alter cardiovascular outcomes by identifying the appropriate LDL-C–lowering therapy based on a patient's gene mutations."

Selected Relevant Publication

A Journal of the American College of Cardiology Scientific Expert Panel (2018) statement on clinical genetic testing for FH stated:[17]

- "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."

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for familial hypercholesterolemia testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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