

## Corporate Medical Policy

### Genetic Testing for Familial Hypercholesterolemia AHS – M2137

**File Name:** genetic\_testing\_for\_familial\_hypercholesterolemia  
**Origination:** 01/01/2019  
**Last Review:** 07/2024

#### Description of Procedure or Service

---

##### Definitions

Familial hypercholesterolemia (FH) is a genetic condition that results in premature atherosclerotic cardiovascular disease due to lifelong exposure to elevated low-density lipoprotein cholesterol (LDL-C) levels (Sturm et al., 2018). FH encompasses multiple clinical phenotypes associated with distinct molecular etiologies. The most common is an autosomal dominant disorder caused by mutations in one of three genes, low-density lipoprotein receptor (*LDLR*), *apolipoprotein B-100 (APOB)*, and proprotein convertase subtilisin-like kexin type 9 (*PCSK9*) (Ahmad et al., 2016; Goldberg et al., 2011). Rare autosomal recessive disease results from mutation in low-density lipoprotein receptor adaptor protein (*LDLRAP*) (Garcia et al., 2001).

Genetic counseling is strongly recommended for individuals pursuing genetic testing for familial hypercholesterolemia.

##### Related Policies:

Genetic Markers for Assessing Risk of Cardiovascular Disease AHS - M2180

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

#### Policy

---

**BCBSNC will provide coverage for genetic testing for familial hypercholesterolemia when it is determined the medical criteria or reimbursement guidelines below are met.**

#### Benefits Application

---

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore, member benefit language should be reviewed before applying the terms of this medical policy.

#### When Genetic Testing for Familial Hypercholesterolemia is covered

---

1. Genetic testing to establish a molecular diagnosis of familial hypercholesterolemia (FH) is considered medically necessary when **both** of the following criteria are met:
  - A. When FH is clinically suspected (based on clinical features, family history, physical exam, lipid levels, etc.) and a definitive diagnosis is required;
  - B. When the result of the test will directly impact the treatment being delivered to the individual.
2. For asymptomatic close blood relatives (see Note 1) of an individual affected with FH, genetic testing for a known familial mutation associated with FH is considered medically necessary.

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

## NOTES:

**Note 1:** Close blood relatives include 1st-degree relatives (e.g., parents, siblings, and children), 2nd-degree relatives (e.g., grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings), and 3rd-degree relatives (great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins), all of whom are on the same side of the family.

**Note 2:** For 2 or more gene tests being run on the same platform, please refer to AHS-R2162 Laboratory Procedures Medical Policy.

## When is Genetic Testing for Familial Hypercholesterolemia is not covered

---

For all other situations not described above, genetic testing to confirm a diagnosis of FH is considered not medically necessary.

## Policy Guidelines

---

### Background

Familial Hypercholesterolemia (FH) is considered the most common inherited cardiovascular disease, affecting up to one in 200 people. FH's signature clinical sign is extremely elevated levels of low-density lipoprotein (LDL) cholesterol, which often leads to early-onset atherosclerotic cardiovascular disease (ASCVD) (Rosenson & Durrington, 2023). FH likely accounts for up to 3% of myocardial infarctions for individuals under 60 (Youngblom et al., 2016). Although affected individuals have a 20-fold increased risk of premature ASCVD (Austin et al., 2004), early diagnosis and treatment with lipid-lowering drugs can reduce the risk of coronary heart disease (CHD) to rates comparable to the general population (Ahmad et al., 2016; Knowles et al., 2014; Versmissen et al., 2008).

The primary pathogenic mechanism of FH is the impairment of LDL-receptor mediated catabolism of LDL. Mutations in any of the three main genes (*APOB*, *LDLR*, *PCSK9*) typically cause this impairment, and mutations can be detected in up to 80% of patients with “definite” FH and up to 30% with “possible” FH. Of the three mutations, *LDLR* is the most common, composing 85-90% of the total mutations. *PCSK9* consists of 2-4% of the total, and *APOB* consists of 1-12%. The severity of clinical phenotype depends on the extent to which LDL metabolism is affected. *LDLR* mutations reduce the efficacy of LDL receptors to clear LDL particles, *APOB* mutations impair binding of LDL particles to the LDL receptor, and *PCSK9* mutations lead to decreased *LDLR* expression (fewer LDL receptors). Other factors (unrelated genetic conditions, diet, et al.) may affect LDL levels as well (Rosenson & Durrington, 2023). Several proprietary gene panels exist for assessment of FH. These typically include the three primary genes, but they may also include rarer genes, such as *LDLRAP* (Ambry, 2020; Invitae, 2020). Some panels intended for broader conditions, such as hyperlipidemia, may also include FH-related genes, such as BluePrint Genetics' 20 gene panel (BluePrint, 2022).

At least three current diagnostic criteria have been developed (Simon Broome, Dutch Lipid Clinic Network (DLCN), and the US Make Early Diagnosis to Prevent Early Death [MEDPED]). These criteria have been able to identify patients with FH-causing mutations with >80% sensitivity or specificity (Civeira, 2004; Marks et al., 2003; Williams et al., 1993). The Simon Broome and DLCN diagnostic criteria consider DNA-based evidence of mutations in any of *APOB*, *LDLR*, or *PCSK9* to be suitable evidence for a “definite” diagnosis of FH (Rosenson & Durrington, 2023).

However, <10% of FH cases are identified (O'Brien et al., 2014), despite an estimated prevalence of 1:200 to 1:500 (Ahmad et al., 2016; De Backer et al., 2015; Do et al., 2015; Nordestgaard et al., 2013). Ahmad et al. noted the heterogeneity of clinical application of FH diagnostic criteria, observing that the most commonly used formal criteria was Simon–Broome only (21%), followed by multiple diagnostic criteria (16%), MEDPED only (7%), DLCN only (1%), and other (0.5%) (Ahmad et al., 2016).

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

## *Clinical Utility and Validity*

Wald et al. (2016) assessed the efficacy and feasibility of child-parent screening for familial hypercholesterolemia in primary care practice. 10095 children provided capillary blood samples, and the authors measured their cholesterol. Children were considered positive for FH if their levels were at or above the 99.2% percentile (1.53 times the median level). 28 (0.3%) children were considered positive for FH, and 20 children were classified as carriers of an FH mutation. Another 17 children with levels under the 1.53 median were found to have an FH mutation. Overall, the mutation prevalence was 1/273 children (37/10095). The authors concluded that “Child-parent screening was feasible in primary care practices at routine child immunization visits. For every 1000 children screened, 8 persons (4 children and 4 parents) were identified as having positive screening results for familial hypercholesterolemia and were consequently at high risk for cardiovascular disease” (Wald et al., 2016).

Khera et al. (2016) evaluated the prevalence of an FH mutation among those with “severe” hypercholesterolemia and determined whether coronary artery disease (CAD) risk varies with mutation status. Three genes causative of FH (*LDLR*, *APOB*, and *PCSK9*) were sequenced in 26025 patients from seven case-control studies (5540 with CAD, 8577 controls without) and five prospective cohort studies (n = 11908). Out of the 20485 prospective cohort and CAD-free patients, 1386 were found to have LDL cholesterol levels of  $\geq 190$  mg/dL, and only 24 of these carried an FH mutation. Patients with LDL cholesterol  $\geq 190$  mg/dL and no FH mutation were found to have a 6-fold higher risk for CAD compared to patients with LDL  $< 130$  mg/dL, but patients with both LDL cholesterol  $\geq 190$  mg/dL and an FH mutation were found to have a 22-fold higher risk (Khera et al., 2016).

Braamskamp et al. (2017) performed a study assessing the effect of “two-year treatment with rosuvastatin on carotid intima-media thickness (IMT) in children with heterozygous familial hypercholesterolemia (HeFH). 197 children with HeFH were provided rosuvastatin for two years, and carotid IMT was assessed at baseline, one year, and two years. The authors noted that at baseline, carotid IMT was greater in HeFH than affected siblings, but rosuvastatin treatment resulted in “significantly less progression of increased carotid IMT in children with HeFH than untreated unaffected siblings”, even suggesting that “no difference in carotid IMT could be detected between the 2 groups after 2 years of rosuvastatin.” The authors concluded that “these findings support the value of early initiation of statin treatment for low-density lipoprotein cholesterol reduction in children with HeFH” (Braamskamp et al., 2017).

Elbitar et al. (2018) showed the identification new mutations in FH through use of exome sequencing of *LDLR*, *APOB*, *PCSK9*, and *APOE*. 13 French families with “autosomal dominant hypercholesterolemia” had an exome sequencing performed. Several new mutations were identified, such as “p.Arg50Gln mutation in the *APOB* gene, a p.Ala3396Thr mutation of *APOB*, and one patient with a severe phenotype carrying also a mutation in *PCSK9*: p.Arg96Cys.” The authors stated that this study provided the first known case of a compound heterozygote with a mutation in *APOB* and *PCSK9* and suggested that identifying these new mutations “lead to better diagnosis and treatment of ADH” (Elbitar et al., 2018).

Lee et al. (2019) performed a meta-analysis on the impact of genetic testing for FH on “1) diagnosis of 'definite familial hypercholesterolemia', 2) initiation and adherence of lipid-lowering therapy and 3) risk of ASCVD.” The authors included 56 studies. Genetic testing was found to have provided confirmation of FH in 28-80% of cases over clinical criteria alone. The authors also identified a 76751-individual cohort that indicated that an FH-causing variant was found in only 1.7%-2.5% of subjects with LDL  $> 190$  mg/dL. Molecular diagnosis was found to increase lipid-lowering therapy adherence (4181 definite FH subjects). A loss-of-function *LDLR* variant was found to increase risk of myocardial infarction by 6.77-fold, and even a milder pathogenic *LDLR* variant still increased risk by 4.4-fold. The authors concluded that “DNA sequencing confirms the diagnosis of FH but has a poor yield in unselected patients whose sole criterion is an elevated LDL-C. Initiation and adherence to treatment is improved. The risk of ASCVD is 4.4- to 6.8-fold increased in patients with an FH-causing variant compared with controls, depending on the severity of the DNA change” (Lee et al., 2019).

Trinder et al. (2019) evaluated the risk of premature (defined as  $< 55$  years old) cardiovascular events in patients with clinically diagnosed familial hypercholesterolemia. Monogenic (defined as mutations in *LDLR*,

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

*APOB*, or *PCSK9*, comprising up to 80% of cases) and polygenic causes of FH were compared. 626 patients were included, and both targeted sequencing and genetic variant analysis were performed to identify patients for both cohorts. Patients with polygenic scores above the 80th percentile were considered to have polygenic FH. Risk of several cardiovascular events (unstable angina, myocardial infarction, coronary revascularization, or stroke) were assessed. Monogenic causes of FH were associated with a 1.96-fold increase of CVD, whereas the polygenic cohort saw no significant increase compared to patients without any genetic cause of FH at all. The authors also found that an elevated low-density lipoprotein polygenic risk score increased the CVD risk for monogenic patients to 3.06-fold. The authors concluded that “genetic testing for FH provides important prognostic information that is independent of LDL-C levels” (Trinder et al., 2019).

Trinder et al. (2020) compared the risk of CVD events between three cohorts; monogenic FH (277 patients), polygenic FH (2379), and hypercholesterolemia with “undetermined cause” (2232). The authors defined polygenic FH as a “polygenic score >95th percentile based on 223 single-nucleotide variants.” The authors found that patients with monogenic FH were three times more likely than polygenic FH to experience a CVD event before age 55 (6.1% vs 2.0%) and that both genetically-based types of FH were more likely to experience a CVD event compared to patients with hypercholesterolemia of unknown cause. The authors concluded that “genetic determinants of LDL-C levels may impose additional risk of CVD” and that “understanding the possible genetic cause of hypercholesterolemia may provide important prognostic information to treat patients” (Trinder et al., 2020).

Sturm et al. (2021) conducted a cross-sectional study comparing limited-variant screening and comprehensive next-generation (NGS) genetic testing for diagnosing FH. In the patient cohort, the researchers found that the limited-variant screen would have only yielded a positive detection rate of 8.4%, compared to the 27.0% positive detection rate with the comprehensive test, meaning that 68.9% of individuals with a FH-associated gene would be missed by the limited screen. Individuals of self-reported Black/African American and Hispanic descent were more likely to be missed by the limited-variant screen. This demonstrates the need to conduct a full evaluation via genetic screening, and how it is a useful modality for diagnosing FH (Sturm et al., 2021).

Reeskamp et al. (2020) performed a study that investigated the role of NGS in clinical FH. For the diagnostic yield of NGS, the researchers stated that an “FH-causing genetic variant was identified in only 14.9% of FH patients with LDL-cholesterol levels of 5 mmol/L or greater;” the mutations being considered were from *LDLR* (80.2%), *APOB* (14.5%), or *PCSK9* (5.3%). “This percentage increased to more than 50% when patients were stratified according to either higher LDL-cholesterol levels or more stringent diagnostic FH criteria ascertained by the DLCN [Dutch Lipid Clinic Network] criteria; 4.8% of FH-mutation negative patients were heterozygous carriers of a pathogenic variant in a minor FH gene.” Though this study overall had a lower diagnostic yield using NGS in comparison to other studies, the researchers propose that “stringent use of clinical criteria algorithms is warranted to increase this yield” and thus maximize the clinical utility of NGS (Reeskamp et al., 2020).

Vallejo et al. (2021) conducted a cross-sectional assessment of 42,617 adults 18 years and older with a clinical or genetic diagnosis of heterozygous familial hypercholesterolaemia. The European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration provided a global registry of individuals with FH in World Health Organization regions. Cardiovascular risk factors varied by age and World Health Organization region. The authors found that, “among patients taking lipid-lowering medications, 2.7% had LDL cholesterol lower than 1.8 mmol/L; the use of combination therapy, particularly with three drugs and with proprotein convertase subtilisin-kexin type 9 inhibitors, was associated with a higher proportion and greater odds of having LDL cholesterol lower than 1.8 mmol/L.” In addition, the authors advocated for earlier detection and the use of combination therapies (as opposed to single-drug therapy) to achieve guideline-recommended LDL concentrations.

## Guidelines and Recommendations

### European Atherosclerosis Society (EAS)

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

Cuchel et al. (2014) published a position paper from the Consensus Panel on Familial Hypercholesterolemia of the EAS that stated that the diagnosis of homozygous familial hypercholesterolemia (HoFH) can be made on clinical or genetic criteria. The authors recommended genetic analysis should be considered to:

- Confirm the clinical diagnosis
- Facilitate testing of family members (reverse cascade screening) – still endorsed in 2023
- Assist in diagnosis where clinical presentation is borderline between that of HoFH and heterozygous FH

In 2023, the EAS provided updates to their clinical guidance for homozygous familial hypercholesterolaemia. In terms of the updated genetic criteria, EAS stated the following:

- “Genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* genes or  $\geq 2$  such variants at different loci”
- “Consider only variants reported as ‘pathogenic/likely pathogenic’ according to recognized criteria as a confirmed genetic diagnosis of HoFH.”

Despite these recommendations, the EAS acknowledges that “genetic results can be potentially misunderstood or miscommunicated.” When there are privacy concerns for probands or parents, or limited access to testing, the EAS also states that screening of lipid levels is “acceptable” to identify family members with FH, as the LDL-C level/phenotype is what ultimately determines therapy (Cuchel et al., 2023).

Wiegman et al. (2015) published a position paper from the EAS regarding FH in children. In it, they state that “DNA testing establishes the diagnosis,” and that “detection of a pathogenic mutation, usually in the *LDLR* gene, is the gold standard for diagnosis of FH.” The EAS also observes that “It is best practice to first genetically test a phenotypically affected parent or a second-degree relative in the absence of a parent. If a mutation is identified, genetic testing and counselling should be offered to all family members” (Wiegman et al., 2015).

## European Society of Cardiology and European Atherosclerosis Society (ESC/EAS)

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) published an update in 2019. In it, they recommend that genetic testing should be performed to confirm clinically suspicious cases of FH. The EAS lists the following criteria as evidence for FH:

- “TC  $\geq 8$  mmol/L ( $\geq 310$  mg/dL) without treatment in an adult or adult family member (or  $>95$ th percentile by age and gender for country);
- Premature CHD in the patient or a family member;
- Tendon xanthomas in the patient or a family member; or
- Sudden premature cardiac death in a family member.”

The EAS also recommends that cascade testing be performed when a causative mutation is known in an index case of heterozygous FH. Moreover, “To improve risk assessment, the use of imaging techniques to detect asymptomatic atherosclerosis is recommended” (Mach et al., 2019).

## American Heart Association (AHA)

In 2015, the AHA released a scientific statement on FH that stated that “identification of all patients with FH is critical, but the optimal screening strategy has not been determined, and the complementary roles of genetic testing, family history, and LDL-C need to be further defined, particularly for children.” AHA noted that “In healthcare systems that are less cohesive such as the US system, genetic testing is controversial for individuals in confirming diagnosis, and implementing cascade screening will be more difficult. In most countries, genetic testing remains relatively expensive and has limited availability. A reduction in costs and improved efficiency of genetic testing is likely to increase its broader application in screening families for FH.” Regarding testing for family members of patients with FH, AHA stated that “Consenting family members should be offered a standard plasma lipid profile and a genetic test if the family mutation is known,

## Genetic Testing for Familial Hypercholesterolemia AHS – M2137

and DNA testing is available.” The AHA also recommended that “Genetic counseling for FH can help patients and their families complete their pedigree and understand the inheritance of FH and the personal and familial implications of the diagnosis” (Gidding et al., 2015).

For diagnosing FH, the AHA states that “genetic testing may offer additional insight regarding cardiac risk and diagnosis” and can confirm diagnosis, but “cannot be excluded in the absence of a causative mutation” (McGowan et al., 2019).

The American Heart Association also proposed new diagnostic criteria shown below (Gidding et al., 2015):

<b>ICD-10 Category</b>	<b>Clinical Criteria</b>	<b>With Genetic Testing Performed</b>
Heterozygous FH	LDL-C $\geq$ 160 mg/dL (4 mmol/L) for children and $\geq$ 190 mg/dL (5 mmol/L) for adults and with one first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C-raising gene defect (LDL receptor, <i>APOB</i> , or <i>PCSK9</i> )	<p>Presence of one abnormal LDL-C-raising (LDL receptor, <i>APOB</i> or <i>PCSK9</i>) gene defect</p> <p>Diagnosed as heterozygous FH if LDL-C-raising defect positive and LDL-C &lt;160 mg/dL (4 mmol/L)</p> <p>Occasionally, heterozygotes will have LDL-C &gt;400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes</p> <p>Presence of both abnormal LDL-C-raising (LDL receptor, <i>APOB</i> or <i>PCSK9</i>) gene defect(s) and LDL-C-lowering gene variant(s) with LDL-C &lt;160 mg/dL (4 mmol/L)</p>
Homozygous FH	LDL-C $\geq$ 400 mg/dL (10 mmol/L) and one or both parents having clinically diagnosed familial hypercholesterolemia, positive genetic testing for an LDL-C-raising (LDL receptor, <i>APOB</i> , or <i>PCSK9</i> ) gene defect, or autosomal-recessive FH	Presence of two identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-C-raising (LDL receptor, <i>APOB</i> or <i>PCSK9</i> ) gene defects; includes the rare autosomal-recessive type
	If LDL-C >560 mg/dL (14 mmol/L) or LDL-C >400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at <20 y of age, homozygous FH highly likely	Occasionally, homozygotes will have LDL-C <400 mg/dL (10 mmol/L)
Family history of FH	LDL-C level not a criterion; presence of a first-degree relative with confirmed FH	Genetic testing not performed

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

## American College of Cardiology/American Heart Association (ACC/AHA)

The 2018 statement (Sturm et al., 2018) on clinical genetic testing for familial hypercholesterolemia recommends:

### *Proband (index case)*

Genetic testing for FH should be offered to individuals of any age in whom a strong clinical index of suspicion for FH exists based on examination of the patient's clinical and/or family histories. This index of suspicion includes the following:

- “Children with persistent\* LDL-C levels  $\geq 160$  mg/dl or adults with persistent LDL-C levels  $\geq 190$  mg/dl without an apparent secondary cause of hypercholesterolemia and with at least 1 first-degree relative similarly affected or with premature CAD‡ or where family history is not available (e.g., adoption)”
- “Children with persistent\* LDL-C levels  $\geq 190$  mg/dl or adults with persistent LDL-C levels  $\geq 250$  mg/dl without an apparent secondary cause of hypercholesterolemia, even in the absence of a positive family history”

### *Genetic testing for FH may be considered in the following clinical scenarios:*

- “Children with persistent\* LDL-C levels  $\geq 160$  mg/dl (without an apparent secondary cause of hypercholesterolemia†) with an LDL-C level  $\geq 190$  mg/dl in at least 1 parent or a family history of hypercholesterolemia and premature CAD”
- “Adults with no pre-treatment LDL-C levels available but with a personal history of premature CAD and family history of both hypercholesterolemia and premature CAD”
- “Adults with persistent LDL-C levels  $\geq 160$  mg/dl (without an apparent secondary cause of hypercholesterolemia) in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD”

\*Two or more measurements, including assessment after intensive lifestyle modification

†Hypothyroidism, diabetes, renal disease, nephrotic syndrome, liver disease, medications.

If LDL-C values are unavailable, total cholesterol values  $\geq 320$ , 260, and 230 mg/dl (corresponding to LDL-C levels  $\geq 250$ , 190, and 160 mg/dl, respectively) could be used.

### *At-risk relatives*

Cascade genetic testing for the specific variant(s) identified in the FH proband (known familial variant testing) should be offered to all first-degree relatives. If first-degree relatives are unavailable, or do not wish to undergo testing, known familial variant testing should be offered to second-degree relatives. Cascade genetic testing should commence throughout the entire extended family until all at-risk individuals have been tested and all known relatives with FH have been identified.

They recommend that “Genetic testing for patients with suspected FH should, at a minimum, include analysis of *LDLR*, *APOB*, and *PCSK9*. This analysis should include for *LDLR* and *PCSK9* sequencing of all exons and exon/ intron boundaries, as well as *LDLR* deletion/duplication analysis, and for *APOB* the exons encoding the *LDLR* ligand-binding region... Larger, more inclusive, lipid disorder NGS panels are also available that provide evaluation of not only the main FH genes but also the genes causing conditions with phenotypic overlap previously described. These expanded panels should be considered to improve the diagnosis of patients with these ‘phenocopy’ conditions that may require specific therapies, and they should include the following genes: *LDLR*, *APOB*, *PCSK9*, *LDLRAP1*, *LIPA*, *ABCG5*, *ABCG8*, and *APOE*” (Sturm et al., 2018).

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

## National Lipid Association (NLA)

In 2011, the NLA released guidelines for screening, diagnosing, and managing familial hypercholesterolemia among pediatric and adult patients. This was last reaffirmed in August 2020. With regards to genetic testing/screening, the NLA stated the following:

- “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.”

On cascade screening, the NLA stated the following:

- “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-lowering treatment is begun in all those identified.”

However, in terms of diagnosis of FH, the NLA states:

- “Untreated fasting lipid levels at which FH may be suspected in children, adolescents and young adults (<20 years) are LDL cholesterol concentration  $\geq 160$  mg/dL or non-HDL cholesterol  $\geq 190$  mg/dL. These levels are supported by family studies of affected individuals.
- A second lipid profile should be performed to assess response to diet management, to account for regression to the mean, and to accurately classify those with levels close to classification thresholds” (Goldberg et al., 2011).

In 2015, the NLA published guidelines for the management of dyslipidemia (Jacobson et al., 2015) which was reaffirmed in August 2020:

“If LDL-C is  $\geq 190$  mg/dL, consider severe hypercholesterolemia phenotype, which includes familial hypercholesterolemia.”

The NLA also published a statement on genetic testing for dyslipidemia in 2020. This statement has been reaffirmed in June 2021. The FH-related recommendations are listed below:

- “Genetic testing is reasonable when heterozygous familial hypercholesterolemia is suspected but not definitively diagnosed based on clinical criteria alone.”
- “Cascade screening for FH either by lipid profile or genetic testing is recommended in all first-degree relatives (children and siblings) of an individual who has tested genetically positive for FH.”
- “Cascade testing [for general genetic dyslipidemias] should begin with first-degree relatives (parents, siblings, and children) and then extend to second- and third-degree relatives.”



# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

The Association also remarks that genetic testing for FH can predict clinical outcomes and that identifying specific mutations (such as *LDLR*) may guide targeted therapy in the future. No “polygenic risk scores” have been identified as a “gold standard” (Brown et al., 2020).

## **American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)**

The 2017 American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease include some items regarding FH. These guidelines include the following (Jellinger et al., 2017):

- For children at risk (such as family history) for FH,
  - screening should be at three years of age
  - repeated once between ages nine and 11 years
  - repeated again at age 18
- “Individuals should be screened for familial hypercholesterolemia (FH) when there is a family history of premature ASCVD...”
- Individuals should be screened if they have “Elevated cholesterol levels (total, non-HDL and/ or LDL) consistent with FH”
- The authors note, “While genetic testing may identify FH, it is not commonly used in the U.S. due to cost and lack of payer coverage” (Jellinger et al., 2017).

## **United States Preventive Services Task Force (USPSTF)**

According to the 2016 USPSTF guidelines, “Screening can detect FH in children, and lipid-lowering treatment in childhood can reduce lipid concentrations in the short term, with little evidence of harm. There is no evidence for the effect of screening for FH in childhood on lipid concentrations or cardiovascular outcomes in adulthood, or on the long-term benefits or harms of beginning lipid-lowering treatment in childhood” (Lozano et al., 2016).

In a 2023 screening recommendation, “The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for lipid disorders in children and adolescents 20 years or younger” (Barry et al., 2023).

## **National Institute for Health and Care Excellence (NICE)**

NICE published an update on FH in 2019, and their relevant recommendations include the following:

- “Carry out cascade testing using DNA testing to identify affected first- and second- and, when possible, third-degree biological relatives of people with a genetic diagnosis of FH.”
- “Healthcare professionals should consider a clinical diagnosis of homozygous FH in adults with a low-density lipoprotein cholesterol (LDL-C) concentration greater than 13 mmol/l and in children/young people with an LDL-C concentration greater than 11 mmol/l.”
- “Use the Simon Broome or Dutch Lipid Clinic Network (DLCN) criteria to make a clinical diagnosis of FH in primary care settings.”
- “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” (NICE, 2019).

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

## **Hyperlipidaemia Education and Atherosclerosis Research Trust United Kingdom (HEART UK)**

This guideline focuses on homozygous FH. For diagnosis of homozygous FH, HEART-UK recommends that mutation analysis “should be by comprehensive DNA sequencing of introns and exons of the *LDLR*, *APOB*, *PCSK9* and *LDLRAP1* gene loci [in an accredited laboratory]” (France et al., 2016).

## **International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel (IAS)**

The panel notes that in addition to the main three genes, mutations in *APOE* or *STAP1* may result in the heterozygous FH phenotype. However, the panel remarks that “...identification of a causative gene variant is not essential for either diagnosis or treatment decisions, since as mentioned these are more appropriately guided by the LDL-C and not by the genotype” (Santos et al., 2016).

New guidance from this society asserts that “Early detection of FH is fundamental to all models of care for FH... However, the best approach to detecting FH in primary care remains uncertain.” Nonetheless, they offer the following recommendations for the screening of FH:

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

Clinical recommendations	Class	Level
1. Multiple screening strategies (for example, selective, opportunistic and/or universal) should ideally be used to detect index cases with FH	1	B
2. Age-specific, sex-specific and country-specific LDL-cholesterol concentrations (estimated in plasma or serum) above the corresponding 95th percentiles for the population should preferably be used to screen for index cases with FH	1	B
3. Selective screening should be used to detect index cases among adults with premature ASCVD, mainly coronary artery disease, and a family history of premature ASCVD and/or hypercholesterolaemia	1	A
4. Opportunistic screening, such as an LDL-cholesterol concentration >4.9 mmol/l (≥190 mg/dl), should be used to detect cases in the community	1	B
5. Universal screening using age-specific and sex-specific criteria for LDL-cholesterol concentration should be considered initially to detect children and adolescents with FH, after which the diagnosis should be formally confirmed and reverse cascade testing offered to parents, as indicated	2	B
6. Cascade testing should be offered to all close relatives of an index case with definite FH and be carried out using phenotypic and genetic methods; if genetic testing is not feasible, LDL-cholesterol testing (based on appropriate age-specific and gender-specific thresholds) should be used	1	A
7. Genome-based population screening of adults may be considered for wider and more accurate detection of FH, but requires careful implementation	3	C
8. After initial detection of potential index cases, the diagnosis of FH should be formally confirmed using country-specific (or internationally accepted) phenotypic criteria and ideally with genetic testing	1	A
9. Children with suspected HoFH (for example, with physical stigmata), or at risk of FH (both parents known to have FH), should be tested as early as possible (at the newborn stage or by 2 years of age), with measurement of LDL-cholesterol concentrations, followed by genetic confirmation	1	B
10. Screening of children at risk of HeFH should be considered using LDL-cholesterol concentrations at or after the age of 5 years, or as early as 2 years in those with a strong family history of premature ASCVD, with confirmation of the diagnosis genetically, as indicated	2	B
11. Non-fasting samples may be considered when screening for FH; the Friedewald equation should be used with caution owing to the confounding effect of hypertriglyceridaemia on the estimation of LDL-cholesterol concentration	3	B
12. Patients with hypertriglyceridaemia > 4.5 mmol/l (>400 mg/dl), in whom FH is strongly suspected, should be re-screened for FH with a 12-h fasting sample and LDL-cholesterol concentration measured using a direct assay	1	A
13. In the absence of a direct assay for LDL-cholesterol concentration, the probability of FH should be reconsidered in patients with very severe hypertriglyceridaemia after therapeutic lowering of triglyceride concentrations to <4.5 mmol/l (<400 mg/dl), or by calculating LDL-cholesterol using a novel equation, if triglycerides are between 4.5 mmol/l and 10.0 mmol/l (400–850 mg/dl)	2	C
14. The effects of cholesterol-lowering medications and acute illness should be accounted for when phenotypically screening for FH; LDL-cholesterol concentrations should be adjusted for the use of statins, ezetimibe, PCSK9 inhibitors and other therapies, particularly if a reliable pretreatment value is unavailable; if the diagnosis of FH is in doubt, LDL-cholesterol measurement should be repeated after full recovery from acute illness	1	B

(Watts et al., 2023).

For the diagnosis of FH, IAS offers the recommendations below.

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

Clinical recommendations	Class	Level
1. A diagnosis of HeFH or HoFH should be made, whenever possible, using genetic testing that identifies pathogenic variants (such as in <i>LDLR</i> , <i>APOB</i> , <i>PCSK9</i> or <i>LDLRAP1</i> ) 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	1	A
2. If genetic testing is not feasible, a clinical diagnosis of FH in adults should be made using country-specific or recognized phenotypic criteria (such as the Dutch Lipid Clinic Network, Simon Broome criteria, MED-PED, AHA, Canadian or Japanese criteria) for index cases (Supplementary Material 2)	1	A
3. A phenotypic diagnosis of FH in adults and children requires exclusion of, or correction for secondary causes of, high LDL-cholesterol concentrations (Supplementary Material 3); in the absence of an untreated value, LDL-cholesterol concentration should be adjusted for concurrent use of cholesterol-lowering medication; LDL-cholesterol concentrations should ideally be measured after fasting and on two occasions	1	A
4. Use of imaging-based detection of subclinical Achilles tendon xanthomas may be considered to increase the specificity and accuracy of the phenotypic diagnosis of FH in adults	3	B
5. A clinical diagnosis of FH in children and adolescents should be considered as highly probable in the presence of an untreated LDL-cholesterol concentration >4.9 mmol/l (>190 mg/dl), recorded on at least two occasions (fasting lipid profile, >2 weeks but <3 months apart), and a parental history of high LDL-cholesterol levels, premature ASCVD or a positive genetic test for FH	2	B
6. After exclusion of secondary causes of high LDL-cholesterol levels (Supplementary Material 3), a clinical diagnosis of FH in children and adolescents should be considered as probable in the presence of an untreated (a) LDL-cholesterol concentration > 4.9 mmol/l (>190 mg/dl; recorded on at least two occasions), even in the absence of a parental history of high LDL-cholesterol concentrations or premature ASCVD; (b) LDL-cholesterol concentration > 4.0 mmol/l (>160 mg/dl; recorded on at least two occasions), with a parental history of high LDL-cholesterol concentrations or premature ASCVD; (c) LDL-cholesterol concentration > 3.5 mmol/l (>135 mg/dl; recorded on at least two occasions), with a parent having a pathogenic gene variant for FH; (d) LDL-cholesterol concentration (recorded on at least two occasions) exceeding a country-specific LDL-cholesterol threshold (lower than the above) and a parental history of elevated LDL-cholesterol concentrations or premature ASCVD	2	B
7. Phenotypic criteria developed for making a diagnosis of HeFH in adult index cases (such as the Dutch Lipid Clinic Network criteria) should not be used in children or adolescents, or when undertaking cascade testing	1	A
8. After excluding secondary causes of high LDL-cholesterol levels (Supplementary Material 3), a clinical diagnosis of HoFH (that is, phenotypic HoFH) should be made in children and adults with an untreated LDL-cholesterol concentration > 10 mmol/l (>400 mg/dl; recorded on two occasions) in the presence of (a) physical stigmata (tendon or cutaneous xanthomas, arcus cornealis) before the age of 10 years and/or (b) untreated LDL-cholesterol concentrations consistent with HeFH in both parents; in the absence of genetic testing and a clear history of FH in both parents, sitosterolaemia and hypercholesterolaemia (cerebrotendinous xanthomatosis) should also be excluded	1	C
9. If cascade testing in the family is recommended, the diagnosis of FH in the proband or index case should ideally be confirmed genetically	1	A
10. The diagnosis of FH during phenotypic cascade testing should be made using age-specific, sex-specific and country-specific LDL-cholesterol concentrations, ideally measured after fasting and on two occasions	1	A

(Watts et al., 2023)

Finally, in asserting that “Genetic testing procedures should be standardized, including informed consent, pre-test and post-test genetic counselling, classification of variants, reporting and return of results, follow-up of family members for cascade testing, and shared decision-making”, IAS created the following table of recommendations:

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

Clinical recommendations	Class	Level
1. Genetic testing for FH should be offered to all individuals in whom there is a strong suspicion of FH based on clinical and/or family history (for example, phenotypic HoFH, definite or highly probable phenotypic HeFH in an adult, child or adolescent)	1	B
2. Genetic testing should be considered in individuals with a probable phenotypic diagnosis of HeFH	2	B
3. Genetic testing may be considered in individuals with a phenotypic diagnosis of possible HeFH, especially when there is incomplete information to establish a diagnosis and the genetic result affects clinical management	3	C
4. Genetic testing for FH should be carried out using an accredited method in a certified laboratory, using targeted next-generation sequencing of all exons and exon-intron boundaries of <i>LDLR</i> , <i>APOB</i> , <i>PCSK9</i> and <i>LDLRAP1</i> , and the exons in <i>APOB</i> that encode the LDLR ligand-binding region, as well as analysis for deletions and duplications in <i>LDLR</i>	1	A
5. Variants detected by genetic testing should be classified and reported according to contemporary standardized guidelines, for example, those of the ACMG, AMP or ClinGen FH Variant Curation Expert Panel	1	A
6. If a pathogenic or likely pathogenic variant is not detected, FH should not be excluded, particularly if the clinical phenotype is strongly suggestive of FH, because the condition may result from undetected genetic variants	1	A
7. Genetic counselling should be offered, before and after genetic testing, to all individuals suspected of having FH	1	B
8. Genetic counselling should at a minimum include obtaining a three-generation family medical history, risk and psychological assessment, family-based care, enabling of cascade testing, anticipatory guidance and psychological assessment	1	A
9. Pre-conception counselling should be offered to all couples, especially if both partners/parents are known, or suspected, to have FH	1	B
10. Prenatal or pre-implantation genetic testing should be offered if both partners/parents are known to have FH, counselling being particularly important in parents with HeFH who have previously had a child with HoFH	1	C
11. Polygenic scores for hypercholesterolaemia may be useful but are not yet fully standardized, so that they should be used with caution when assessing the differential diagnosis of FH in clinical practice	3	B
12. Cascade genetic testing is highly cost-effective and should be used after a disease-causing variant has been identified in the proband or index case	1	A
13. Pre-test and post-test genetic counselling should be offered to all at-risk relatives as an integral component of cascade testing	1	A
14. Cascade testing should be undertaken using both phenotypic and genotypic approaches (Fig. 1); if genetic testing is not available, a phenotypic approach (that is, a plasma or serum lipid profile, including the LDL-cholesterol concentration) should be used	1	A
15. Cascade genetic testing for the specific variant (variants) identified in the proband (that is, known familial variant testing) should initially be offered to all first-degree relatives; if first-degree relatives are unavailable, or do not wish to undergo testing, known familial variant testing should be offered to at-risk second-degree and then third-degree relatives, with sequential extension to the entire family until all at-risk individuals have been offered testing (Fig. 1)	1	A
16. At-risk children should be offered cascade genetic testing at the earliest opportunity (and more than once if not pursued at the first offer) if an FH-causing variant has been identified in a parent or other first-degree relative	1	A
17. When genetic testing is not feasible, the diagnosis of FH in at-risk relatives should be made phenotypically using age-specific, sex-specific and country-specific LDL-cholesterol concentrations (Fig. 1; Supplementary Material 4); clinical tools for diagnosing FH probands (such as the Dutch Lipid Clinic Network criteria and Simon Broome criteria) are not valid for this purpose. Phenotypic cascade testing should initially be offered to all first-degree relatives. If first-degree relatives are unavailable, or decline testing, phenotypic testing should next be offered to second-degree and then third-degree relatives, with sequential extension to the entire family until all at-risk individuals have been offered testing	1	A
18. 'Reverse' cascade testing (from child to parents) should be offered to parents after a child is identified as a proband with FH, such as after making a diagnosis following a clinical presentation or via a universal or newborn screening programme	1	B

(Watts et al., 2023)

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

## Canadian Cardiovascular Society (CCS)

In 2018, the CCS released a position statement on FH. With regards to genetic testing, screening and diagnosis of FH, the CCS included the following relevant recommendations:

- **Diagnosis of FH**
  - “We recommend that FH be defined using the DLCNC [Dutch Lipid Clinic Network Criteria], Simon Broome Registry, or FH Canada definition (Strong Recommendation, High-Quality Evidence).”
- **Screening for FH**
  - “We recommend that cascade screening (lipid profile) protocols be implemented at the local, provincial, and national level in Canada and offered to first-degree relatives of patients with FH (Strong Recommendation, Moderate-Quality Evidence).”
- **Genetics**
  - “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.”
- **ASCVD [atherosclerotic cardiovascular disease] and FH**
  - “We suggest that if available, genetic testing should be used to stratify the ASCVD risk in patients with FH (Weak Recommendation, Moderate-Quality Evidence).
    - Values and preferences. An FH-causing genetic variant increases ASCVD risk, beyond that associated with an elevated LDL-C level. Patients should be informed on the high lifetime risk of ASCVD associated with FH.”
- **Homozygous FH**
  - “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)” (Brunham et al., 2018).

## State and Federal Regulations, as applicable

### Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

## Billing/Coding/Physician Documentation Information

---

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81401, 81403, 81405, 81406, 81407, 81479*

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

---

- Ahmad, Z. S., Andersen, R. L., Andersen, L. H., O'Brien, E. C., Kindt, I., Shrader, P., Vasandani, C., Newman, C. B., deGoma, E. M., Baum, S. J., Hemphill, L. C., Hudgins, L. C., Ahmed, C. D., Kullo, I. J., Gidding, S. S., Duffy, D., Neal, W., Wilemon, K., Roe, M. T., . . . Knowles, J. W. (2016). US physician practices for diagnosing familial hypercholesterolemia: data from the CASCADE-FH registry. *J Clin Lipidol*, *10*(5), 1223-1229. <https://doi.org/10.1016/j.jacl.2016.07.011>
- Ambry. (2020). FHNNext®. <https://www.ambrygen.com/clinician/genetic-testing/13/cardiology/fhnnext>
- Austin, M. A., Hutter, C. M., Zimmern, R. L., & Humphries, S. E. (2004). Familial hypercholesterolemia and coronary heart disease: a HuGE association review. *Am J Epidemiol*, *160*(5), 421-429. <https://doi.org/10.1093/aje/kwh237>
- Barry, M. J., Nicholson, W. K., Silverstein, M., Chelmow, D., Coker, T. R., Davis, E. M., Donahue, K. E., Jaén, C. R., Li, L., Ogedegbe, G., Rao, G., Ruiz, J. M., Stevermer, J., Tsevat, J., & Underwood, S. M. (2023). Screening for Lipid Disorders in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. *Jama*, *330*(3), 253-260. <https://doi.org/10.1001/jama.2023.11330>
- Braamskamp, M., Langslet, G., McCrindle, B. W., Cassiman, D., Francis, G. A., Gagne, C., Gaudet, D., Morrison, K. M., Wiegman, A., Turner, T., Miller, E., Kusters, D. M., Raichlen, J. S., Martin, P. D., Stein, E. A., Kastelein, J. J. P., & Hutten, B. A. (2017). Effect of Rosuvastatin on Carotid Intima-Media Thickness in Children With Heterozygous Familial Hypercholesterolemia: The CHARON Study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label). *Circulation*, *136*(4), 359-366. <https://doi.org/10.1161/circulationaha.116.025158>
- Brown, E. E., Sturm, A. C., Cuchel, M., Braun, L. T., Duell, P. B., Underberg, J. A., Jacobson, T. A., & Hegele, R. A. (2020). Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. *J Clin Lipidol*. <https://doi.org/10.1016/j.jacl.2020.04.011>
- Brunham, L. R., Ruel, I., Aljenedil, S., Rivière, J. B., Baass, A., Tu, J. V., Mancini, G. B. J., Raggi, P., Gupta, M., Couture, P., Pearson, G. J., Bergeron, J., Francis, G. A., McCrindle, B. W., Morrison, K., St-Pierre, J., Henderson, M., Hegele, R. A., Genest, J., . . . Brophy, J. (2018). Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia: Update 2018. *Can J Cardiol*, *34*(12), 1553-1563. <https://doi.org/10.1016/j.cjca.2018.09.005>
- Civeira, F. (2004). Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis*, *173*(1), 55-68. <https://doi.org/10.1016/j.atherosclerosis.2003.11.010>
- Cuchel, M., Bruckert, E., Ginsberg, H. N., Raal, F. J., Santos, R. D., Hegele, R. A., Kuivenhoven, J. A., Nordestgaard, B. G., Descamps, O. S., Steinhagen-Thiessen, E., Tybjaerg-Hansen, A., Watts, G. F., Averna, M., Boileau, C., Borén, J., Catapano, A. L., Defesche, J. C., Hovingh, G. K., Humphries, S. E., . . . Chapman, M. J. (2014). Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*, *35*(32), 2146-2157. <https://doi.org/10.1093/eurheartj/ehu274>
- Cuchel, M., Raal, F. J., Hegele, R. A., Al-Rasadi, K., Arca, M., Averna, M., Bruckert, E., Freiberger, T., Gaudet, D., Harada-Shiba, M., Hudgins, L. C., Kayikcioglu, M., Masana, L., Parhofer, K. G., Roeters van Lennep, J. E., Santos, R. D., Stroes, E. S. G., Watts, G. F., Wiegman, A., . . . Ray, K. K. (2023). 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J*, *44*(25), 2277-2291. <https://doi.org/10.1093/eurheartj/ehad197>
- De Backer, G., Besseling, J., Chapman, J., Hovingh, G. K., Kastelein, J. J., Kotseva, K., Ray, K., Reiner, Z., Wood, D., & De Bacquer, D. (2015). Prevalence and management of familial hypercholesterolaemia in coronary patients: An analysis of EUROASPIRE IV, a study of the European Society of Cardiology. *Atherosclerosis*, *241*(1), 169-175. <https://doi.org/10.1016/j.atherosclerosis.2015.04.809>
- Do, R., Stitzel, N. O., Won, H. H., Jorgensen, A. B., Duga, S., Angelica Merlini, P., Kiezun, A., Farrall, M., Goel, A., Zuk, O., Guella, I., Asselta, R., Lange, L. A., Peloso, G. M., Auer, P. L., Girelli, D., Martinelli, N., Farlow, D. N., DePristo, M. A., . . . Kathiresan, S. (2015). Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature*, *518*(7537), 102-106. <https://doi.org/10.1038/nature13917>

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

- Elbitar, S., Susan-Resiga, D., Ghaleb, Y., El Khoury, P., Peloso, G., Stitzel, N., Rabes, J. P., Carreau, V., Hamelin, J., Ben-Djoudi-Ouadda, A., Bruckert, E., Boileau, C., Seidah, N. G., Varret, M., & Abifadel, M. (2018). New Sequencing technologies help revealing unexpected mutations in Autosomal Dominant Hypercholesterolemia. *Sci Rep*, 8(1), 1943. <https://doi.org/10.1038/s41598-018-20281-9>
- France, M., Rees, A., Datta, D., Thompson, G., Capps, N., Ferns, G., Ramaswami, U., Seed, M., Neely, D., Cramb, R., Shoulders, C., Barbir, M., Pottle, A., Eatough, R., Martin, S., Bayly, G., Simpson, B., Halcox, J., Edwards, R., . . . Soran, H. (2016). HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. *Atherosclerosis*, 255, 128-139. <https://doi.org/10.1016/j.atherosclerosis.2016.10.017>
- Garcia, C. K., Wilund, K., Arca, M., Zuliani, G., Fellin, R., Maioli, M., Calandra, S., Bertolini, S., Cossu, F., Grishin, N., Barnes, R., Cohen, J. C., & Hobbs, H. H. (2001). Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science*, 292(5520), 1394-1398. <https://doi.org/10.1126/science.1060458>
- Gidding, S. S., Champagne, M. A., de Ferranti, S. D., Defesche, J., Ito, M. K., Knowles, J. W., McCrindle, B., Raal, F., Rader, D., Santos, R. D., Lopes-Virella, M., Watts, G. F., & Wierzbicki, A. S. (2015). The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. *Circulation*, 132(22), 2167-2192. <https://doi.org/10.1161/cir.0000000000000297>
- Goldberg, A. C., Hopkins, P. N., Toth, P. P., Ballantyne, C. M., Rader, D. J., Robinson, J. G., Daniels, S. R., Gidding, S. S., de Ferranti, S. D., Ito, M. K., McGowan, M. P., Moriarty, P. M., Cromwell, W. C., Ross, J. L., & Ziajka, P. E. (2011). Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*, 5(3 Suppl), S1-8. <https://doi.org/10.1016/j.jacl.2011.04.003>
- Invitae. (2020). *Invitae Familial Hypercholesterolemia Panel*. <https://www.invitae.com/en/physician/tests/02401/>
- Jacobson, T. A., Ito, M. K., Maki, K. C., Orringer, C. E., Bays, H. E., Jones, P. H., McKenney, J. M., Grundy, S. M., Gill, E. A., Wild, R. A., Wilson, D. P., & Brown, W. V. (2015). National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. *J Clin Lipidol*, 9(2), 129-169. <https://doi.org/10.1016/j.jacl.2015.02.003>
- Jellinger, P. S., Handelsman, Y., Rosenblit, P. D., Bloomgarden, Z. T., Fonseca, V. A., Garber, A. J., Grunberger, G., Guerin, C. K., Bell, D. S. H., Mechanick, J. I., Pessah-Pollack, R., Wyne, K., Smith, D., Brinton, E. A., Fazio, S., & Davidson, M. (2017). AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. *Endocr Pract*, 23(Suppl 2), 1-87. <https://doi.org/10.4158/ep171764.appgl>
- Khera, A. V., Won, H. H., Peloso, G. M., Lawson, K. S., Bartz, T. M., Deng, X., van Leeuwen, E. M., Natarajan, P., Emdin, C. A., Bick, A. G., Morrison, A. C., Brody, J. A., Gupta, N., Nomura, A., Kessler, T., Duga, S., Bis, J. C., van Duijn, C. M., Cupples, L. A., . . . Kathiresan, S. (2016). Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. *J Am Coll Cardiol*, 67(22), 2578-2589. <https://doi.org/10.1016/j.jacc.2016.03.520>
- Knowles, J. W., O'Brien, E. C., Greendale, K., Wilemon, K., Genest, J., Sperling, L. S., Neal, W. A., Rader, D. J., & Khoury, M. J. (2014). Reducing the burden of disease and death from familial hypercholesterolemia: a call to action. *Am Heart J*, 168(6), 807-811. <https://doi.org/10.1016/j.ahj.2014.09.001>
- Lee, S., Akioyamen, L. E., Aljenedil, S., Riviere, J. B., Ruel, I., & Genest, J. (2019). Genetic testing for familial hypercholesterolemia: Impact on diagnosis, treatment and cardiovascular risk. *Eur J Prev Cardiol*, 26(12), 1262-1270. <https://doi.org/10.1177/2047487319829746>
- Lozano, P., Henrikson, N. B., Dunn, J., Morrison, C. C., Nguyen, M., Blasi, P. R., Anderson, M. L., & Whitlock, E. P. (2016). Lipid Screening in Childhood and Adolescence for Detection of Familial Hypercholesterolemia: Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama*, 316(6), 645-655. <https://doi.org/10.1001/jama.2016.6176>
- Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, L., Chapman, M. J., De Backer, G. G., Delgado, V., Ference, B. A., Graham, I. M., Halliday, A., Landmesser, U., Mihaylova, B., Pedersen, T. R., Riccardi, G., Richter, D. J., Sabatine, M. S., Taskinen, M.-R., . . . Group, E. S. C. S. D. (2019). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J*, 41(1), 111-188. <https://doi.org/10.1093/eurheartj/ehz455>
- Marks, D., Thorogood, M., Neil, H. A., & Humphries, S. E. (2003). A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis*, 168(1), 1-14.



# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

- McGowan, M. P., Hosseini Dehkordi, S. H., Moriarty, P. M., & Duell, P. B. (2019). Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. *Journal of the American Heart Association*, 8(24), e013225. <https://doi.org/10.1161/JAHA.119.013225>
- NICE. (2019). *Familial hypercholesterolaemia: identification and management*. <https://www.nice.org.uk/guidance/cg71/chapter/Recommendations>
- Nordestgaard, B. G., Chapman, M. J., Humphries, S. E., Ginsberg, H. N., Masana, L., Descamps, O. S., Wiklund, O., Hegele, R. A., Raal, F. J., Defesche, J. C., Wiegman, A., Santos, R. D., Watts, G. F., Parhofer, K. G., Hovingh, G. K., Kovanen, P. T., Boileau, C., Averna, M., Boren, J., . . . Tybjaerg-Hansen, A. (2013). Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*, 34(45), 3478-3490a. <https://doi.org/10.1093/eurheartj/ehf273>
- O'Brien, E. C., Roe, M. T., Fraulo, E. S., Peterson, E. D., Ballantyne, C. M., Genest, J., Gidding, S. S., Hammond, E., Hemphill, L. C., Hudgins, L. C., Kindt, I., Moriarty, P. M., Ross, J., Underberg, J. A., Watson, K., Pickhardt, D., Rader, D. J., Wilemon, K., & Knowles, J. W. (2014). Rationale and design of the familial hypercholesterolemia foundation CAscade SCReening for Awareness and DEtection of Familial Hypercholesterolemia registry. *Am Heart J*, 167(3), 342-349.e317. <https://doi.org/10.1016/j.ahj.2013.12.008>
- Reeskamp, L. F., Tromp, T. R., Defesche, J. C., Grefhorst, A., Stroes, E. S., Hovingh, G. K., & Zuurbier, L. (2020). Next-generation sequencing to confirm clinical familial hypercholesterolemia. *Eur J Prev Cardiol*, 2047487320942996. <https://doi.org/10.1177/2047487320942996>
- Rosenson, R., & Durrington, P. (2023, December 10). *Familial hypercholesterolemia in adults: Overview*. <https://www.uptodate.com/contents/familial-hypercholesterolemia-in-adults-overview>
- Santos, R. D., Gidding, S. S., Hegele, R. A., Cuchel, M. A., Barter, P. J., Watts, G. F., Baum, S. J., Catapano, A. L., Chapman, M. J., Defesche, J. C., Folco, E., Freiburger, T., Genest, J., Hovingh, G. K., Harada-Shiba, M., Humphries, S. E., Jackson, A. S., Mata, P., Moriarty, P. M., . . . Yamashita, S. (2016). Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol*, 4(10), 850-861. [https://doi.org/10.1016/s2213-8587\(16\)30041-9](https://doi.org/10.1016/s2213-8587(16)30041-9)
- Sturm, A. C., Knowles, J. W., Gidding, S. S., Ahmad, Z. S., Ahmed, C. D., Ballantyne, C. M., Baum, S. J., Bourbon, M., Carrié, A., Cuchel, M., Ferranti, S. D. d., Defesche, J. C., Freiburger, T., Hershberger, R. E., Hovingh, G. K., Karayan, L., Kastelein, J. J. P., Kindt, I., Lane, S. R., . . . Foundation, C. b. t. F. H. (2018). Clinical Genetic Testing for Familial Hypercholesterolemia. *Journal of the American College of Cardiology*, 72(6). <https://doi.org/10.1016/j.jacc.2018.05.044>
- Sturm, A. C., Truty, R., Callis, T. E., Aguilar, S., Esplin, E. D., Garcia, S., Haverfield, E. V., Morales, A., Nussbaum, R. L., Rojahn, S., Vatta, M., & Rader, D. J. (2021). Limited-Variant Screening vs Comprehensive Genetic Testing for Familial Hypercholesterolemia Diagnosis. *JAMA Cardiology*, 6(8).
- Trinder, M., Francis, G. A., & Brunham, L. R. (2020). Association of Monogenic vs Polygenic Hypercholesterolemia With Risk of Atherosclerotic Cardiovascular Disease. *JAMA Cardiology*, 5(4), 390-399. <https://doi.org/10.1001/jamacardio.2019.5954>
- Trinder, M., Li, X., DeCastro, M. L., Cermakova, L., Sadananda, S., Jackson, L. M., Azizi, H., Mancini, G. B. J., Francis, G. A., Frohlich, J., & Brunham, L. R. (2019). Risk of Premature Atherosclerotic Disease in Patients With Monogenic Versus Polygenic Familial Hypercholesterolemia. *J Am Coll Cardiol*, 74(4), 512-522. <https://doi.org/10.1016/j.jacc.2019.05.043>
- Versmissen, J., Oosterveer, D. M., Yazdanpanah, M., Defesche, J. C., Basart, D. C., Liem, A. H., Heeringa, J., Witteman, J. C., Lansberg, P. J., Kastelein, J. J., & Sijbrands, E. J. (2008). Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *Bmj*, 337, a2423. <https://doi.org/10.1136/bmj.a2423>
- Wald, D. S., Bestwick, J. P., Morris, J. K., Whyte, K., Jenkins, L., & Wald, N. J. (2016). Child-Parent Familial Hypercholesterolemia Screening in Primary Care. *N Engl J Med*, 375(17), 1628-1637. <https://doi.org/10.1056/NEJMoal602777>
- Watts, G. F., Gidding, S. S., Hegele, R. A., Raal, F. J., Sturm, A. C., Jones, L. K., Sarkies, M. N., Al-Rasadi, K., Blom, D. J., Daccord, M., de Ferranti, S. D., Folco, E., Libby, P., Mata, P., Nawawi, H. M., Ramaswami, U., Ray, K. K., Stefanutti, C., Yamashita, S., . . . Santos, R. D. (2023). International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia. *Nat Rev Cardiol*. <https://doi.org/10.1038/s41569-023-00892-0>
- Wiegman, A., for the European Atherosclerosis Society Consensus, P., Gidding, S. S., for the European Atherosclerosis Society Consensus, P., Watts, G. F., for the European Atherosclerosis Society Consensus, P., Chapman, M. J., for the European Atherosclerosis Society Consensus, P., Ginsberg, H. N., for the European

# Genetic Testing for Familial Hypercholesterolemia AHS – M2137

Atherosclerosis Society Consensus, P., Cuchel, M., for the European Atherosclerosis Society Consensus, P., Ose, L., for the European Atherosclerosis Society Consensus, P., Averna, M., for the European Atherosclerosis Society Consensus, P., Boileau, C., for the European Atherosclerosis Society Consensus, P., Borén, J., . . . Ginsberg, H. N. (2015). Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*, 36(36), 2425-2437. <https://doi.org/10.1093/eurheartj/ehv157>

Williams, R. R., Hunt, S. C., Schumacher, M. C., Hegele, R. A., Leppert, M. F., Ludwig, E. H., & Hopkins, P. N. (1993). Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol*, 72(2), 171-176.

Youngblom, E., Pariani, M., & Knowles, J. W. (2016). Familial Hypercholesterolemia [Text]. *GeneReviews*. <https://www.ncbi.nlm.nih.gov/books/NBK174884/>

Specialty Matched Consultant Advisory Panel review 7/2020

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel review 7/2021

Medical Director review 7/2021

Medical Director review 10/2022

Medical Director review 11/2023

Medical Director review 7/2024

## Policy Implementation/Update Information

---

- 1/1/2019 BCBSNC will provide coverage for genetic testing for familial hypercholesterolemia when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)
- 8/13/19 Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019. (jd)
- 10/29/19 No change to policy statements. Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)
- 12/10/19 Reviewed by Avalon 3rd Quarter 2019 CAB. Added Related Policies to Description section and “Note” to When Not Covered section of policy. Medical Director review 11/2019. (jd)
- 7/28/20 Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)
- 8/11/20 Minor revision to “Last Review” date for clarification. (jd)
- 11/10/20 Reviewed by Avalon 3<sup>rd</sup> Quarter 2020 CAB. Background, policy guidelines, and references updated. Related policies section revised. When Not Covered section, statement 1 revised removing “investigational” and replacing with “not medically necessary”. CPT code 81479 removed and 81407 added to the Billing/Coding section. Medical Director review 10/2020. (jd)

## Genetic Testing for Familial Hypercholesterolemia AHS – M2137

- 9/7/21 Specialty Matched Consultant Advisory Panel review 7/2021. Medical Director review 7/2021. (jd)
- 11/16/21 Reviewed by Avalon 3<sup>rd</sup> Quarter 2021 CAB. Policy guidelines and references updated. Medical Director review 10/2021. (jd)
- 12/30/22 Reviewed by Avalon 3<sup>rd</sup> Quarter 2022 CAB. Background, Policy Guidelines, and References updated. Related policies section revised. When Covered section, criteria 2 stating “Genetic testing of children of individuals with FH to determine future risk of disease is considered medically necessary when a known pathogenic mutation is present in a parent” removed and replaced with “Genetic testing for a known familial mutation associated with FH is considered medically necessary in asymptomatic close relatives (i.e., first-, second-, or third-degree relative) of an affected individual”. CPT code 81403 removed and 81479 added to the Billing/Coding section. Medical Director review 10/2022. (tm)
- 12/5/23 Reviewed by Avalon 3<sup>rd</sup> Quarter 2023 CAB. Background, Policy Guidelines, and References updated. New Note 1 added to When Covered section, Not Covered section edited for clarity, no change to policy statement. CPT code 81403 added to Billing/Coding section. Medical Director review 11/2023. (tm)
- 9/4/24 Reviewed by Avalon 2<sup>nd</sup> Quarter 2024 CAB. Updated Policy Guidelines and References. Note 2 in When Covered section updated to now read: “For 2 or more gene tests being run on the same platform, please refer to AHS-R2162 Laboratory Procedures Medical Policy.” No change to policy statement. Medical Director review 7/2024. (tm)

---

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.